FOOD ALLERGY: ADVERSE REACTIONS TO FOODS AND FOOD ADDITIVES

Third Edition

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Oral Allergy Syndrome

Elide Anna Pastorello
Claudio Ortolani

Definition

Oral allergy syndrome (OAS) is the clinical term used to refer to food allergy symptoms involving the mouth and the pharynx (1, 2). The name of the syndrome focuses on the need for direct contact of the oral mucosa with the offending food to trigger local symptoms, usually in the form of oral itching, lip swelling, and labial angioedema, but occasionally also glottal edema. OAS symptoms arise immediately (within 1–5 min) after the culprit food(s) comes in contact with the oral mucosa. Symptoms recur regularly after each new exposure to the culprit food(s) (2). OAS is an IgE-mediated food allergy that can be diagnosed in patients by positive allergy tests such as specific IgEs, skin tests, etc. During the last few years, OAS has been defined as a distinct condition by clinical studies using double-blind placebo-controlled oral food challenges (DBPCFCs), and by studies that identified several allergens involved in this syndrome.

The first reports of oral symptoms associated with food allergy date back more than 50 years (3, 4). Today OAS constitutes a true clinical syndrome with complex characteristics. OAS occurs primarily in atopic subjects—with or without pollenosis—who are sensitized to fruits and vegetables, especially when consumed raw. In many cases oral symptoms appear first and are then followed by more complex symptoms that may include other organs or systems or are generalized (5). Occasionally, more severe conditions such as anaphylactic shock or glottal edema may be associated with oral symptoms (5–9). For these reasons, OAS should not be considered a minor clinical syndrome localized to the oropharynx, but rather as a condition that could involve more severe and even life-threatening symptoms.

OAS is used as a synonym for the association between fruit-and-vegetable allergy and tree-pollen allergy, especially in the case of birch-tree allergy, i.e., the pollen-food allergy syndrome (10). However, OAS is often present in subjects who are not allergic to pollens; for example, it is found in subjects allergic to Prunoideae, particularly in the Mediterranean area (6, 11), and in subjects allergic to latex (*Hevea brasiliensis*) in the so-called latex-fruit allergy syndrome, which in turn may or may not be associated with allergy to pollens (12–14).

Oral allergy symptoms provoked by foods of animal origin (such as milk, eggs, shrimp, etc.) (1, 15–17) occur less frequently. In contrast, oral symptoms provoked by plant-origin foods almost always involve OAS, to the point that it is known as the most characteristic sign of plant-origin food allergy. One important question is whether the term oral allergy syndrome should be used only to refer to a clinical entity characterized by an IgE-mediated allergic sensitization to plant-origin foods, or should it include all the oropharyngeal manifestations of food allergy? Although many authors seem to share the former position, many observations of OAS associate the allergy to animal-origin foods, suggesting caution when considering the culprit food to diagnose OAS.

Epidemiology

Few studies have addressed the prevalence of OAS, and all of them concerned plant-origin food OAS. A recent study evaluated food allergy and intolerance data gathered by questionnaire from 1537 subjects who were randomly sampled

and cross-sectionally stratified for age and sex (17). Of the reported allergic reactions, 659 (42.9%) were thought to be caused by OAS. The frequency of occurrence of OAS varied according to the culprit food: 72.3% for walnuts, 68% for apple and related fruits, 62.9% for Prunoideae, 94.5% for tomato, 43.6% for other vegetables, 24.4% for citrus fruits, 37.7% for other fruits, 30.3% for peanuts, 28.6% for soy, 20% for milk, 13.6% for fish, 8.3% for spices, and 25% for wine. OAS was caused most frequently by fruits and nuts; moreover, ingestion of these foods was most often associated with systemic reactions.

Adults develop OAS to fresh fruits and vegetables more frequently than children. A study from Israel found that fruits and vegetables were the most common sources of food allergy for patients over the age of 10 (18). The association between OAS and pollen allergy has been widely described. Two studies determined OAS prevalence in subjects allergic to pollens. A study from Switzerland (19) reported that approximately 35% of patients allergic to pollens shared allergic symptoms and positive skin prick tests (SPT) to fresh fruits and vegetables. Pastorello et al (20) observed a prevalence of 25% of OAS among 300 patients allergic to pollens. Allergy to fruits and vegetables occurred most frequently in subjects with hay fever from birch allergy. Studies conducted in subjects allergic to birch pollen found different prevalences of OAS in different European countries: 35% in Finland, 63% in Sweden, 75% in Austria, and 59% in Italy (20–23).

Fruit allergy also often occurs in subjects allergic to rubber latex. In one study, 27% of latex-allergic subjects had positive skin tests for latex, and 14% of these showed local oral symptoms (24). Another study found that 13 (52%) of 25 patients allergic to latex showed symptoms after eating some fruits (13). A third study reported that 69.1% of latex-allergic subjects had positive IgEs for some associated fruits, and that 42.5% had allergic reactions after eating these fruits (14).

Allergy to fruits and vegetables can occur in the absence of pollen allergy, albeit less commonly. Ortolani et al (2) found that 21% of subjects allergic to fruits and vegetables were not allergic to pollens. Fernandez-Rivas et al (6) found 15% of subjects allergic to fruits and vegetables were not allergic to pollens. Cuesta-Harranz et al (25) reported that 17% of subjects allergic to peach did not have any associated allergy to pollen.

Symptoms

Typically, symptoms occur immediately after the culprit food comes into contact with the oral mucosa. The rapidity of the reaction is one of the peculiar characteristics of OAS, and it is one of the most valuable diagnostic elements in determining a given food's role in provoking symptoms. A study of the time of occurrence of symptoms after food ingestion showed that most patients had symptoms within 5 minutes of food contact, and in only three (7%) of 43 patients did symptoms appear after 30 minutes (2). DBPCFC studies further confirmed the rapidity of onset of symptoms for two other foods: a few minutes for hazelnut (26) and within 30 minutes for cantaloupe (9). Oral symptoms are immediate and arise in the lining of the lips, the oropharynx, and the gastrointestinal tract, which comes into direct contact with the offending food (Table 13–1). Symptoms consist of intra-oral and lip irritation, angioedema, papulae, and, more rarely, blisters, which appear within a few minutes after contact with the culprit food. Systemic symptoms such as urticaria, rhinitis, asthma, and occasionally even anaphylactic shock, may appear after contact with the culprit food associated to the local symptoms (Table 13–2).

It seems appropriate to classify OAS symptoms into four levels of increasing severity: level 1, oral mucosa symptoms only; level 2, oral mucosa plus gastrointestinal symptoms; level 3, oral mucosa symptoms plus systemic symptoms (urticaria, rhinoconjunctivitis, or asthma); and level 4, oral mucosa symptoms plus life-threatening problems (glottal edema, anaphylactic shock) (27). This classification of symptoms shows the evolving pathway of this syndrome. Local symptoms clearly prevail, as has been well documented by studies on patients with allergic reactions to fresh fruits and vegetables (5, 28–30). In a study of 90 patients suffering from ragweed allergic rhinitis and allergy to melon and banana, Anderson et al (28) found that all the subjects experienced oropharyngeal symptoms. Similarly, Eriksson et al (29) reported that

Table 13–1.
Skin-Mucosal Contact Provoked Symptoms Observed in 706 OAS Patients (5)

Symptoms	*Number of Patients*	*%*
Oral only	596	84.4
Oral + gastrointestinal	67	9.5
Gastrointestinal only	29	4.1

Table 13–2.
Systemic Symptoms Associated with Oral/Gastrointestinal Contact Symptoms Observed in 706 OAS Patients (5)

Symptoms	*Number of Patients*	*%*
Urticaria/angioedema	191	27.0
Rhinitis	63	8.9
Asthma	50	7.1
Conjunctivitis	25	3.5
Anaphylactic shock	15	2.1

199 (78%) of 255 patients allergic to birch and related foods (e.g., apple, peach, cherry, pear, and carrot) complained of symptoms localized in the oral mucosa. Ortolani et al reported that local symptoms occurred in 219 (83.6%) of 262 patients allergic to fresh fruits and vegetables (2). In a subsequent study on a larger population, the same authors found that 663 (93.9%) of 706 patients had local oral symptoms (5) (Table 13–1).

The clinical features of OAS have emerged from a series of studies published in the last few years in Europe. These studies applied DBPCFC to diagnose allergy to fruits and vegetables (9, 26, 31, 32). These studies, carried out on adults, showed that oral symptoms (level 1) were the most common clinical manifestation elicited by the following plant-origin culprit foods: carrot, celery, hazelnut, melon (Table 13–3). In a small percentage of subjects, OAS appeared to be associated with gastrointestinal symptoms (level 2); in 21% of cases it was associated with the following systemic symptoms: cutaneous (9.5%), rhino-conjunctival (6.3%) and asthmatic (3.2%). These extra-oral symptoms observed in these 126 DBPCFC positive patients were self-limiting and slight, probably because of a patient selection regime that excluded severe cases.

The most severe local symptom of OAS is glottal edema. This symptom appears particularly frequently in allergy to celery, a vegetable known to induce severe allergic reactions (33). In a study of 262 patients with OAS from fresh fruit and vegetables, Ortolani et al observed 62 cases (26%) of glottal edema after ingestion of several fresh foods (2). In a subsequent study, the same authors reported that 98 (13.9%) of 706 OAS patients presented at least one well-documented episode of glottal edema (5).

In some cases, OAS may rapidly evolve to a generalized anaphylactic reaction with respiratory difficulty, generalized urticaria, angioedema, and hypotension. Ortolani et al (5) found that 15 (2.1%) of 706 patients with OAS had anaphylactic shock after ingesting one of the following foods: peach, apricot, walnut, cherry, tomato, apple, hazelnut, or pear. One study examined the prevalence of severe reactions in OAS and reported six (23%) severe anaphylactic reactions occurring after oral symptoms in 26 patients (7). The foods responsible for these severe reactions were banana, apple, plum, nectarine, cherry, apricot, strawberry, grape, carrot, and peanut. Two (10.5%) anaphylactic shock reactions were also reported in 19 patients allergic to cantaloupe (9). Subjects allergic only to peach but who had no pollen allergy appeared to have a higher frequency of severe allergic reactions, compared to subjects who were allergic to peach and pollen both. One study showed that 36% of subjects allergic to peach but without pollenosis had at least one anaphylactic shock episode, in contrast to only 9% of subjects allergic to both peach and pollen (6). It seems that sensitization to lipid transfer protein (LTP) allergens is responsible for the severity of symptoms occurring in these subjects. LTP allergen sensitivity is also associated with severe reactions reported in corn and hazelnut allergy (34, 35). A high association between OAS and systemic anaphylaxis has also been reported in children (e.g., 3 [38%] of 8 children with OAS had systemic anaphylaxis) (8).

Table 13–3.
Symptom Distribution in 126 DBPCFC-positive Patients (9, 26, 31, 32)

Symptoms	*Number of patients*	*%*
OAS alone (grade 1)	100	79
OAS+ gastrointestinal (grade 2)	7	5
OAS+ systemic (grade 3)	21	16
skin	12	9.5
rhino-conjunctive	8	6.3
asthma	4	3.2
OAS + life threatening*	0	0

* exclusion criterion for DBPCFC.

Clusters of Hypersensitivity

Sensitization to some fruits or vegetables may be significantly associated with sensitization to other foods belonging to the same botanical family, as well as with sensitization to botanically unrelated foods. Clinically this phenomenon has been defined as "cluster of hypersensitivity" (36).

Several clusters have been observed since the first reports of this disease. For example, in 1984 Eriksson (36) reported the following clusters based on a long list of case studies:

1. Hazelnut, walnut, brazil nut, almond, with desert almond, as well as nuts combined with apple and stone fruits.
2. Stone fruits in combination with apple and pear.
3. Apple and pear.
4. Kiwi fruit and avocado.
5. Potato and carrot.
6. Parsley and celery.

Other "clusters" have also been described: celery, carrot, mugwort, and spices (37); apple, carrot, and potato (38); fennel and celery (2); cherry and apple (2); melon, watermelon, and tomato (2); fennel, celery, and carrot (39); lettuce and carrot (40); tomato and peanut (41); and, celery, cucumber, carrot, and watermelon (42). Moreover, Pastorello et al (11) performed oral open food challenges to check for clinical cross-reactivity in members of the Prunoideae subfamily such as peach, apricot, plum, and cherry, and found high cross-reactivity between these fruits.

During recent years, it has become increasingly evident that the presence of common allergens, or allergens with a similar molecular structure but belonging to different foods, may influence allergic cross-reactivity. This finding might help explain the clustering of allergy-provoking foods. The most common clusters in OAS are: 1) birch-fruit syndrome due to cross-reactivity between Bet v 1 homologous proteins (PR-10); 2) latex-fruit syndrome due to PR-2, β-1,3-glucanase, and PR-3 class 1 chitinase sensitization; and 3) LTP-PR 14 sensitization.

Many past observations support the existence of three syndromes and can be encompassed by them. Birch-fruit syndrome is characterized by allergy to birch and hazel pollen associated with food allergy toward apple, pear, celery, carrot, parsley, potato, hazelnut, and less frequently, cherry and apricot (10, 21, 29). Latex-fruit syndrome is characterized by allergy to latex and to avocado, banana, chestnut, fig, kiwi (13, 14), tomato, and potato (43). LTP syndrome is characterized by allergy to peach with cross-reactivity extended to other Prunoideae such as cherry, apricot, plum, apple (Mal d 3), and corn (11, 27, 34, 44).

Association With Rhinitis or Asthma Due to Pollen Allergy

In many cases, OAS to fresh fruits and vegetables is associated with allergy to pollens. The association with birch pollen allergy has been confirmed, and other associations have been described involving pollens from grasses, ragweed, and mugwort (Table 13–4) (45, 46). Hay fever often occurs before OAS with a significant difference in the timing of occurrence (2). One study using immunoblot inhibition with the major allergen of birch, Bet v 1, showed that sensitization to pollen causes sensitization to fruits and vegetables. Sensitization to birch pollen is certainly the main reason that OAS develops toward birch-related foods (e.g., apple, hazelnut, carrot, celery, etc.). Mugwort's pollen allergy may be associated with food allergy toward celery, carrot, and spices (47). Grass pollen allergy was found to be related to food allergy to tomato, melon, watermelon, and orange (2, 41). The association between kiwi fruit allergy and grass pollen allergy was reported in Italy (5), whereas kiwi fruit allergy has been described in association with birch pollen allergy only in Scandinavia and the US (48, 49). In the US, an association between ragweed allergy and allergy to melon and banana has been re-

Table 13–4.
Associations Between Pollinosis and Allergy to Fresh Fruits and Vegetables

Author	*Year*	*Pollen*	*Fruit/Vegetable*
Tuft, Blumstein (3)	1942	Birch	Apple
Juhlin-Danfelt (4)	1948	Birch	Apple, hazelnut
Anderson et al (28)	1970	Ragweed	Melon, banana
Eriksson (29)	1978	Birch	Apple, hazelnut, carrot, potato
Wüthrich (45)	1981	Mugwort	Celery
Pauli et al (46)	1982	Mugwort	Celery
Wüthrich (37)	1985	Mugwort	Celery, carrot, spices
Pauli et al (47)	1985	Birch, mugwort	Celery
Enberg et al (30)	1987	Ragweed	Watermelon, gourd family
Ortolani et al (5)	1988	Grass	Tomato, melon, watermelon
De Martino et al (41)	1988	Grass	Tomato, peanut
Ebner et al (21)	1991	Birch	Apple
Ortolani et al (5)	1992	Birch	Celery, fennel

ported (28). Ragweed allergy has also been found to be associated with allergy to members of the gourd family (i.e., watermelon, cantaloupe, honeydew, zucchini, and cucumber) (30). A common finding of all these studies is a statistically significant relationship between the presence of allergy symptoms to fresh fruits and vegetables and high levels of specific IgE to related pollens. In a study by Enberg et al (30), only those patients with the highest radioallergosorbent test (RAST) levels to ragweed presented symptoms to fruits of the gourd family. Similarly, Eriksson et al (50) found that high levels of birch-specific IgE antibodies in serum were closely related to the occurrence of allergy to fruits and vegetables. Finally, Ebner et al (21) confirmed a higher incidence of apple allergy in subjects with high levels of birch-specific IgE compared to subjects with lower IgE values.

Etio-pathogenesis

OAS is a true IgE-mediated food allergy. When this syndrome is suspected, diagnosis is based on specific tests that demonstrate the presence of IgE mechanisms. If these tests are negative, an irritant mechanism due to enzymatic components or the acidic nature of certain foods may be involved instead. The route of sensitization to plant-origin foods has not yet been determined. Only in OAS associated with pollen allergy are we almost certain that the primary sensitization is toward pollens, and that food allergy is a consequence. Kazemi-Shirazi et al (51) demonstrated that in subjects with birch pollen allergy and OAS to apple, all the allergenic epitopes are on Bet v 1, the major pollen allergen, whereas only a few of them are represented on its homologous counterpart in apple, Mal d 1. Moreover, the cross-reactivity between apple and birch pollen, which causes OAS, is not only serologic but also at the level of allergen-specific T helper cells (52). On the basis of this observation the authors hypothesized that, in early infancy, contact with the implicated foods could prime T cells that could then react with pollens. In latex-fruit syndrome, the primary sensitization is still unknown, and in LTP syndrome it seems to be due to peach LTP, because in all crosswise inhibition experiments performed with pollen, peach LTP was the strongest inhibitor (53).

Localization of symptoms to the oral mucosa is another unsolved issue. Amlot et al (1) suggested that local oral symptoms are caused by a high concentration of mast cells in the oropharyngeal mucosa. This condition would lead to a stronger interaction between the allergens that are rapidly released from the fruit or vegetable and specific IgE on the cell surface. This interaction, in turn, might explain the early onset of OAS symptoms. Local oral symptoms are also caused by a high concentration of allergens on the oral mucosa that are rapidly released from the culprit fruit or vegetable as they come in contact with the saliva of the allergic subject. This kind of reaction resembles that seen with pollens, which react in their intact form with IgE antibodies bound to mast cells in the mucosa of the upper and lower airways. An alternative hypothesis is that the high concentration of T cells in the oropharyngeal lymphoid tissue might have a food-specific T cell response. For example, in birch-fruit syndrome, a positive birch pollen-specific T cell response was found only in the injured skin of patients reacting with atopic eczema following ingestion of birch-related foods in DBPCFC experiments (54).

Allergens

During recent decades, a number of allergenic proteins of plant-origin foods have been characterized. In several cases, descriptions of allergens with homologous sequences in different allergenic sources were the key to understanding the molecular basis of the cross-reactivity so common in OAS (55). The presence of such similar components in pollens and foods is the main cause of the three previously mentioned clinical syndromes. The allergens responsible for these syndromes will be described below.

Birch-Fruit Syndrome

The major allergens of birch, Bet v 1 and Bet v 2, are proteins that share significant amino acid sequences with other proteins that are widespread in the vegetable kingdom, especially in apple, pear, hazelnut, carrot, celery, potatoes, parsley, and beans. The association between OAS to two or more of these foods and birch hay fever, now known as "birch-fruit syndrome," is due to the cosensitization to these proteins in different sources (56, 57). Bet v 1 and its apple homolog, Mal d 1, are proteins with a molecular mass of 17 kilodaltons (kDa) (58). These proteins share 64.5% of their amino acid sequence identity, and this homology explains why

about 70% of birch-allergic patients are also allergic to apple. Other Bet v 1-homologous allergens are Api g 1 in celery, Pyr c 1 in pear, Dau c 1 in carrot, Pru ar 1 in apricot, Pru a 1 in cherry, and Cor a 1 in hazelnut (10). The involvement of allergens such as Mal d 1, Api g 1, and Dau c 1 has been confirmed by the IgE reactivity of the sera of subjects positive at DBPCFC with the relevant food items (31, 32, 59). Pastorello et al (35) demonstrated the clinical importance of hazelnut's major allergen, which is an allergen with 72% amino acid sequence identity to Bet v 1 (60). In a multi-center study within the framework of an EU project, we found that in 67 subjects with a positive DBPCFC result for hazelnut, the most important allergen was an 18 kDa protein entirely cross-reacting with Bet v 1 (35). All these patients developed OAS, showing that this allergen was the basis of their symptoms (26). In inhibition experiments with sera from the same patients, we demonstrated that this allergen is destroyed by roasting the hazelnuts and is thus quite labile (35). All these Bet v1 homologous allergens are proteins belonging to group n.10 of the pathogenesis-related (PR) protein family (61), being thus named PR-10. These are plant-defense proteins that plants express (through regulation of their mRNAs) in response to different environmental, chemical, or biological attacks. As shown by Son et al (62) the amino acid serine-112 in Mal d 1 and Bet v 1 is essential for both IgE binding and cross-reactivity between them. It is interesting to observe that this SER 112 is conserved in all reported sequences of PR-10.

Another important cross-reacting allergen of birch with foods is Bet v 2, which belongs to the profilin family. These actin-binding proteins regulate cellular movement and are ubiquitous in nature (63). Profilin is the 12 kDa actin-binding protein first identified as an allergen in birch pollen and now found in several important allergenic sources. It is particularly important in celery, where it is also involved in the celery-mugwort-spices syndrome (64). Bet v 2 homologs are present in apple, pear, celery, carrot, and potatoes. Although the in vitro cross-reactivity of the various profilins is well recognized, their clinical role has never been satisfactorily demonstrated.

Other allergens also seem to be important in the cross-reactivity between birch and related foods. For example Karamloo et al (65) described a 33 kDa protein in birch, Bet v 5, where it behaves as a minor allergen belonging to a family of isoflavone reductase-related proteins. Bet v 5 showed a high degree of cross-reactivity with pear, a well-known birch-related food (65). In our study of hazelnut allergens (35) we found three other major allergens at 32 kDa, 35 kDa, and 47 kDa (represented respectively by a 2 S albumin, a legumin, and a sucrose-binding protein) that were totally inhibited by preincubation with birch pollen extract; this showed indirectly the presence of cross-reactive structures in birch that could be either cross-reacting carbohydrate determinants or new cross-reacting allergens.

Lipid Transfer Protein Syndrome

In the Mediterranean area, IgE-mediated allergic reactions to several plant-origin foods are not associated with pollen hypersensitivity but are due to sensitization to molecules belonging to the LTP family. These ubiquitous proteins (66) are present in homologous forms in many fruits and vegetables and cause a specific sensitization that is at the basis of some severe systemic reactions. LTPs are defense proteins up-regulated in some plants in response to infection by various fungal pathogens (67). For this reason they have been included in the PR protein family, forming group n. 14 that is thus named PR-14 (10). We first identified an LTP as the major allergen of peach, Pru p 3 (Fig. 13–1 and Fig. 13–2). This is a 91 amino acid molecule with a mass of 9.2 kDa characterized by a structure typical for all known LTPs containing eight strictly conserved cysteine residues (27). It was especially resistant to heating and acid treatment, which may explain the in vivo stability demonstrated by this allergen. In fact, the only technological treatments found to decrease the amount of peach major allergen were chemical (lye) peeling of fruits and juice ultrafiltration (68). By studying peach-allergic patients we found that the LTP major allergen was the only one recognized by the IgE antibodies of subjects allergic to peach but not allergic to pollen (27). Furthermore, as in a previous study (11) we confirmed an in vivo and in vitro IgE cross-reactivity between peach, apricot, plum, and cherry. After we discovered the important role played by LTP allergen in peach, we tested IgE-binding LTP proteins in these other allergenic sources, and found that LTPs were also the major allergens in plum (Pru s 3) and apricot (Pru ar 3), and that both were highly homologous to peach LTP major allergen (69, 70) (Table 13–5 and Table 13–6). From apricot we purified a second LTP with a lower molecular weight (7 kDa), a sequence homologous to Pru ar 3 but

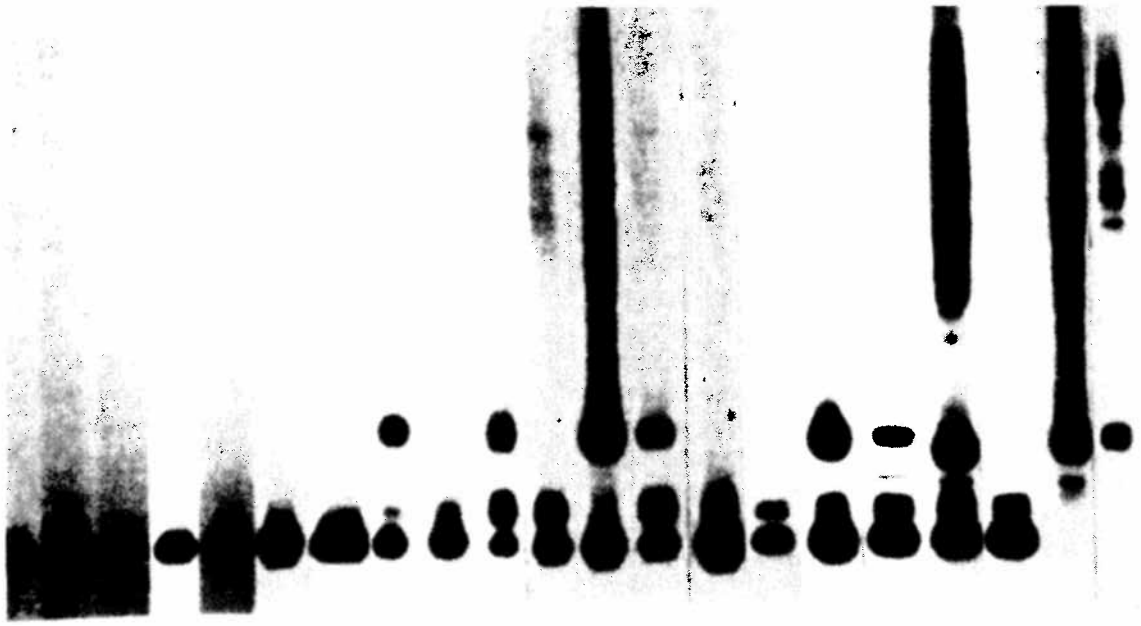

Figure 13–1. Autoradiographs of IgE-immunoloblot analysis of peach extract with sera from 21 patients, presenting specific IgE to peach. The molecular weight of some of the allergens are given. Patients 1 to 19 presented OAS to peach. (Reprinted from Pastorello EA, et al. *J Allergy Clin Immunol 1994;94:699–707.*)

with no IgE binding activity (71). As we found for peach, the LTP major allergens in apricot and plum were the only allergens recognized by IgE antibodies of subjects not allergic to pollen. Another LTP was also found to be a major allergen of cherry (72). After comparing IgE binding to cherry in Italian and German patients, we found that only Italian patients were sensitized to this allergen (72). Similarly, in a previous study we showed that Italian patients allergic to apple but not to birch were sensitized only to an LTP allergen having a high percentage of homology with peach LTP (44). Almost all of these patients were allergic to peach and to other fruits of the Rosaceae family. It is interesting that patients allergic to apple but not to birch have never been described in northern and middle Europe, whereas they are usually observed in Spain, where a specific reactivity only to

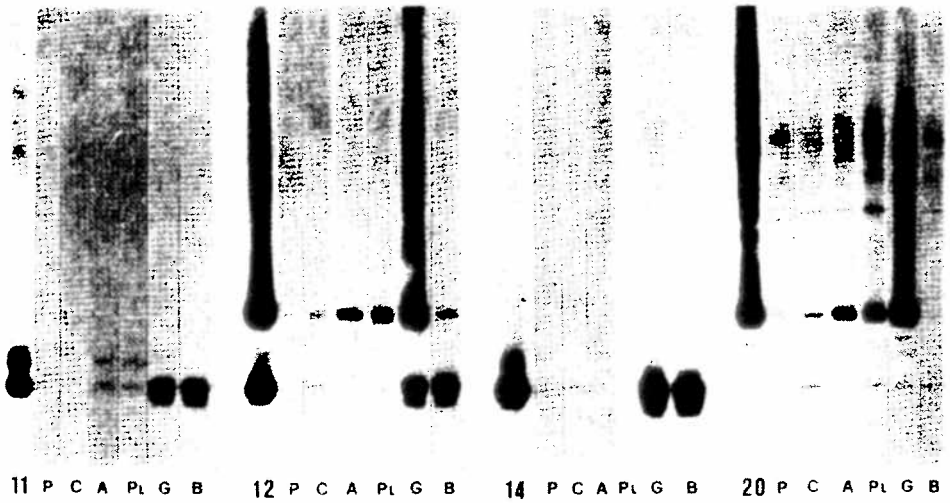

Figure 13–2. Immunoblotting inhibition in the sera of four patients. P, peach; C, cherry; A, apple; PL, plum; G, grass; B, birch. (Reprinted from Pastorello EA, et al. *J Allergy Clin Immunol 1994;94:699–707.*)

Table 13–5.
Amino Acid Sequence Alignment of Peach, Apricot, Plum, and Cherry 9 kDa Major Allergens

Peach	**ITCGQVSS▮LAPCI▮YVRGGGAVPPACCNG**
Apricot	**ITCGQVSS▮LAPCI▮YVRGGGAVPPACCNG**
Plum	**ITCGQVSS▮LAPCI▮YV▮GGGAVPPACCNG**
Cherry	**▮TCGQVSS▮LAPCI▮YVRGGGAVPPACCNG**
Peach	**IRNVNNLARTTPDR▮AACNCLKQLS▮S▮PG**
Apricot	**IRNVNNLARTTPDRR▮ACNCLKQLSGSI▮G**
Plum	**IRN▮NNLARTT▮DRRAACNCLKQLSGSIPG**
Cherry	**IRN▮NNLA▮TT▮R▮AACNCLKQLS▮S▮PG**
Peach	**VNPNNAAALPGKCGV▮IPYKIS▮▮TNCATVK**
Apricot	**VNPNNAAALPGKCGVNIPYKISASTNCATVK**
Plum	**VNPNNAAALPGKCGVN▮PYKISASTNCATVK**
Cherry	**VN▮NNAAALPGKCGVNVPYKIS▮STNCATVK**

Major allergen molecules in these fruits are: peach (prunus persica), Pru p 3; apricot (prunus armeniaca), Pru ar 3; plum (prunus domestica), Pru d 3; and cherry (prunus avium), Pru a 3.

the LTP allergen is also reported (73). The reason for this specific sensitization in Italian and Spanish patients needs to be elucidated. Table 13–5 depicts the alignment of LTP amino acid sequences for the most relevant members of the Rosaceae family, and Table 13–6 shows the degree of homology with peach LTP (74). Spanish authors recently confirmed the cross-reactivity among fruits of Rosaceae family by DBPCFC (75).

An LTP is also the major allergen of maize, as we demonstrated in a population of subjects with anaphylactic reactions to maize that were or were not associated with OAS to peach (34) (Fig. 13–3). It was interesting to observe that the cross-reactivity between maize and peach LTPs was higher than that between maize and wheat LTPs (Fig. 13–4 and Fig. 13–5); this cross-reactivity may explain the higher observed frequency of allergic reactions to maize with peach than to maize with wheat. These results strongly support the clinical role of LTPs as allergens that cause both localized and severe systemic reactions to multiple, apparently unrelated foods. This seems a particular clinical entity that can be classified as "LTP syndrome."

Latex-Fruit Syndrome

Latex allergens are represented by several proteins responsible for occupational allergic reactions and for anaphylactic reactions arising especially in patients with spina bifida (76). Some latex allergens also cross-react with a number of fruits in the latex-fruit syndrome (14). The main allergen involved in this syndrome is hevein, Hev b 6.02 (77), which is the most allergenic component of the latex protein prohevein. Prohevein is also a latex allergen called Hev b 6.01 (78), and is the latex-allergenic component implicated in occupational allergic reactions, as shown by the demonstration of a general sensitization to it in health care workers with allergies. The latex component implicated in sensitization of patients with spina bifida is Hev b 1 (79). Prohevein, an important defense protein of *Hevea brasiliensis* (80), is a protein of 187 amino acid residues with a molecular weight of 20 kDa. It has two domains that may be processed by post-translational modifications into an amino-terminal domain, i.e., the previously mentioned Hev b 6.02, the allergenic hevein of 4.7 kDa; and a carboxy-terminal domain of 14 kDa, named Hev b 6.03 (79). Hev b 6.02 is much more allergenic than Hev b 6.03 because of its higher chemical stability due to seven disulfide bridges (78). Several food allergenic sources, such as avocado, chestnut, and banana, contain proteins homologous to Hev b 6.02 (81–85) (Table 13–7).

Hevein and its homologous allergens belong to class 1 of the family of plant chitinases (86), defense proteins widely distributed throughout the plant kingdom (87). These are basic proteins with

Table 13–6.
Degree of Homology of 9 kDa Major Allergens of Apricot, Plum, Cherry, and Apple with Peach 9 kDa Major Allergen

Organism	*Taxonomy*			*Percent Identity with Peach Major Allergen*
APRICOT NLT1	Dicotyledoneae	Rosales	Rosaceae	89%
(*Prunus armeniaca*)	Dicotyledoneae	Rosales	Rosaceae	87%
PLUM NLT1	Dicotyledoneae	Rosales	Rosaceae	87.9%
(*Prunus domestica*)				
CHERRY	Dicotyledoneae	Rosales	Rosaceae	75.8%
(*Prunus avium*)				
APPLE	Dicotyledoneae	Rosales	Rosaceae	84%
(*Malus domestica*)				

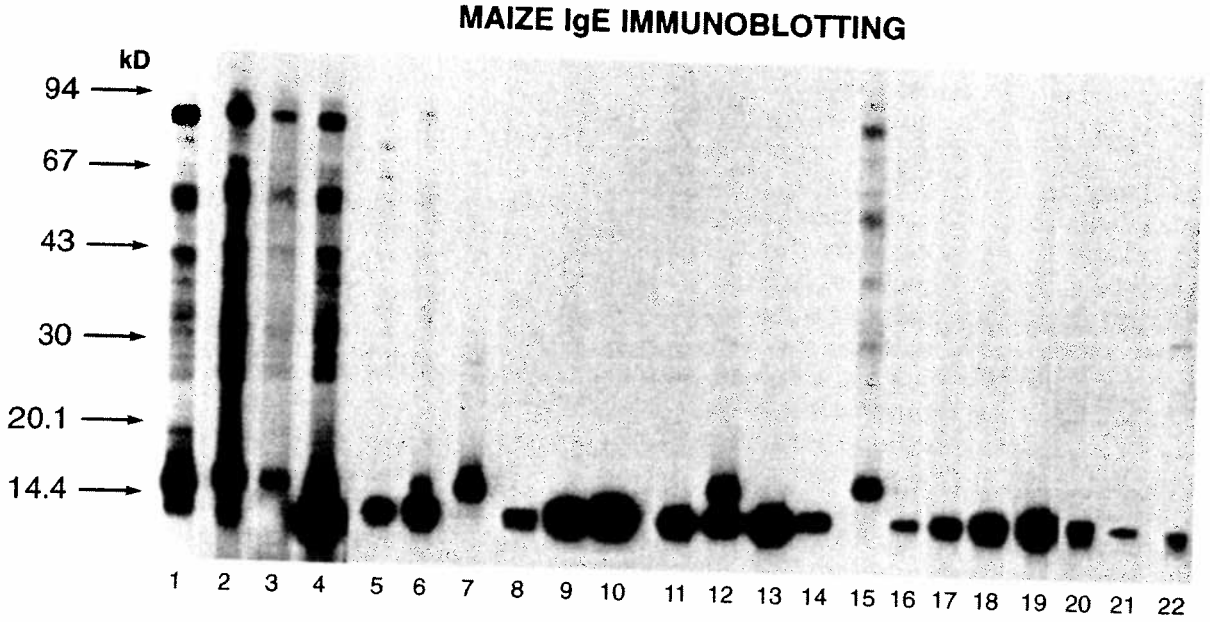

Figure 13–3. IgE immunoblotting of maize extract with the sera from 22 patients with severe systemic reactions upon ingestion of maize. (Reprinted from Pastorello EA, et al. *J Allergy Clin Immunol* 2000;106:744–51.)

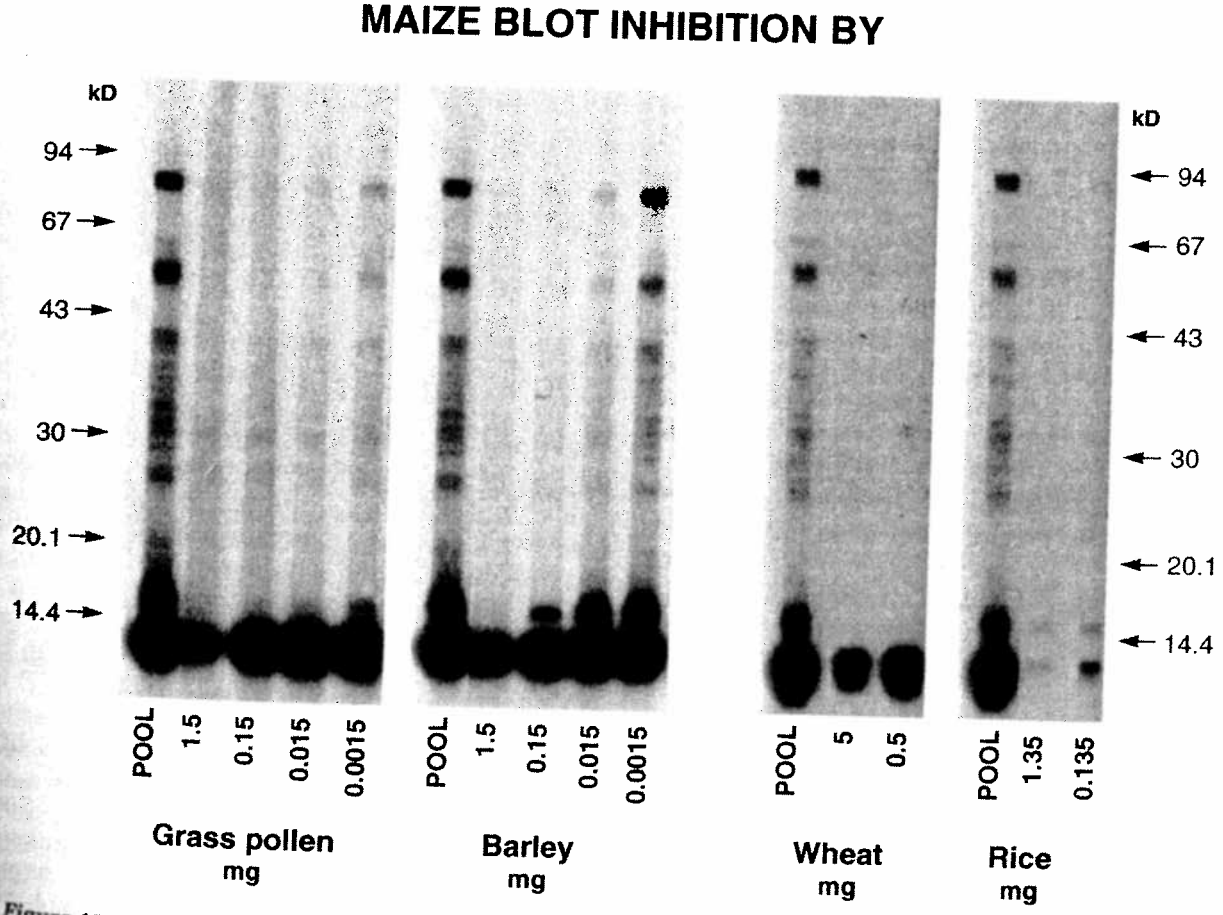

Figure 13–4. Inhibition of maize IgE immunoblotting (pool) by different amounts of grass pollen, barley wheat, and rice. (Reprinted from Pastorello EA, et al. *J Allergy Clin Immunol* 2000;106:744–51.)

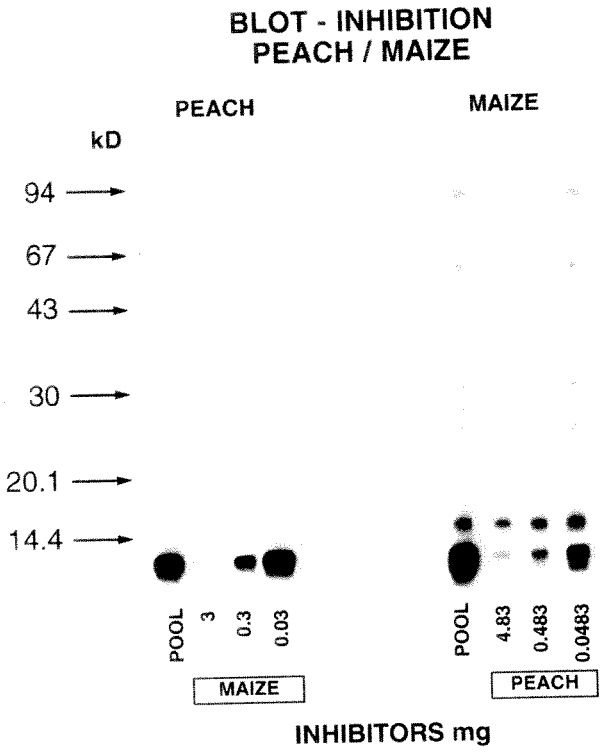

Figure 13–5. Inhibition of IgE immunoblotting of the purified maize 9 kDa protein by peach row extract and inhibition of peach row extract IgE immunoblotting by maize crude extract. The protein at 9 kDa was also completely inhibited in both experiments. (Reprinted from Pastorello EA, et al. *J Allergy Clin Immunol* 2000;106: 744–51.)

a cysteine-rich domain that is responsible for the chitin binding function. It is interesting that other plant foods, such as green beans, contain class 1 chitinases, but they are not cross-reactive with latex, probably because they are consumed after cooking and the allergenic activity is destroyed by heating (81). Allergenic cross-reactivity has been demonstrated between latex and fruits such as kiwi, papaya, mango, and passion fruit; class 1 chitinases may be the relevant cross-reactive components, but this has not been demonstrated finitively (86).

Other plant-origin foods may cause OAS; k fruit is an especially common allergenic sou Several proteins of kiwi are allergenic but its j jor allergen is actinidin, a proteolytic enzym 30 kDa belonging to the thiol protease family (Bromelin of pineapple and papain of papaya a belong to this family, which may cause allerge cross-reactivity. The major mite allergens De 1 and Der f 1 are also thiol proteases, but cr reactivity with plant-origin foods has never b described.

Table 13–7.
Allergens Homologous to Hev b 6.02

Allergens	*Fruits*	*Molecular Weight*	*% Homology*
Pers a 1 (82)	Avocado	32 kDa	70%
Cas s 1 (83)	Chestnut	32 kDa	71%
Bra r 1 (84)	*Brassica rapa*	18.7 kDa	70%
Major allergen (85)	Banana	32 kDa 34 kDa	—

Diagnosis

Diagnosis of OAS is based on the gener accepted procedure for the diagnosis of I mediated food allergy (90–93). Because of its p ticular features, however, OAS requires a slig different diagnostic approach.

The clinical history plays a substantial rol the diagnosis. In most cases, an association is s between contact of the food with the oral muc and the occurrence of symptoms. The rapid pearance of symptoms (within 30 minutes) a oral contact pinpoints the food as the causal ag The diagnosis becomes especially clear w symptoms are always manifested after each c tact with a particular food.

Other elements of the clinical history r support a diagnosis of OAS, such as localizat of the symptoms to the mouth, lips, pharynx, glottis, and the coexistence of allergic rhin The diagnosis is strengthened by known asso tions between food and pollen allergy (e.g., bi and apple, or mugwort and celery). Skin tests allergen-specific IgE titers can be used to con the clinical history; however, their low overall curacy makes them unsatisfactory for formula a definitive diagnosis by themselves.

Recent studies have reported the accurac skin tests and antigen-specific IgE in serum c pared to the gold standard, i.e., DBPCFC, in tients who have OAS to plant-origin foods (T 13–8). SPTs with commercial extracts for ca have low sensitivity and, consequently, l specificity; in contrast, SPTs with natural fo show 100% sensitivity and 0 specificity. S larly, high sensitivity and low specificity was for skin tests for both commercial and nat hazelnut, and for celery when an Allergopha extract was used. When a Stallèrgenes extract

Table 13–8.
Performance of SPT and CAP

	Sensitivity	*Specificity*	*PPV*	*NPV*
Carrot (31)				
Commercial SPT	0.26	1.00		
Raw SPT	0.1	0.00		
CAP	0.9	0.5		
Hazelnut (26)				
Commercial SPT	1.00	0.05	0.93	0.04
Raw SPT	0.88	0.27	0.94	0.15
CAP	0.75	0.18	0.92	0.05
Celery (32)				
Commercial SPT				
Stallergenes	0.48	0.88	0.96	0.19
Allergopharma	0.86	0.13	0.87	0.11
Raw SPT	0.96	0.0		
CAP	0.73	0.38	0.88	0
Melon (9)				
Raw SPT	0.79	0.38	0.42	0.77

used for celery, however, sensitivity was insufficient and the specificity was good. In general, clinical assay Pharmacia (CAP) measurements have been unsatisfactory for the foods reported in the table and for the studies in question; good sensitivity was reported only for carrot. Diagnostic sensitivity and positive predictive value (PPV) of SPTs and specific IgE determinations are sufficient, but these tests produce poor specificity and negative predictive value (NPV).

Cross-reactivity between allergenic molecules that share common epitopes in different foods is common in patients who are allergic to plant-origin foods, making the results of the skin tests and in vitro tests unreliable. These subjects are allergic to a certain food, but can test positive to many other foods even if they tolerate them (i.e., false-positive results). The large number of false-positive results obtained with conventional diagnostic procedures such as SPT and/or in vitro tests, makes these tests useless for the diagnosis of OAS. Lack of standardization of the allergenic extracts used in these methods is at fault. Moreover, lectins in vegetables are theoretically capable of giving false-positive results in vitro because of specific bonds with the solid phase (94).

Diagnostic sensitivity of SPT and specific IgE determinations are sometimes also poor because they yield many false negative results. This outcome has become evident in clinical studies where patient selection for DBPCFC was based exclusively on histories, not on SPT and specific IgE results. With these "inclusive criteria," patients with negative conventional tests were not excluded by the DBPCFC. Two studies listed in Table 13–8 (celery [28] and hazelnut [29]) adhered to these "inclusive criteria"; the diagnostic sensitivity of CAP for celery was 73% and for hazelnut 75%, while NPV for celery was 0% and for hazelnut 0.05%.

This result is partly due to insufficient knowledge of the chemical structures or components of the main allergens of plant-origin foods. The above study on hazelnut allergy (26) described four new hazelnut allergens—three major and one minor—all of which are important in sustaining symptoms. These allergens had not been known previously, and hazelnut diagnostic extracts had not considered them in the standardization.

Another cause of false-negative responses is the lability of some food allergens. These allergens lose their allergenicity during the preparation of the extract. Many patients suffering from severe OAS can eat a cooked version of the offending food without developing any symptoms. In a study of 70 patients with positive SPTs to birch and/or mugwort pollens and celery, 66 (94%) patients gave a positive SPT to raw celery but only 25 (36%) reacted to the cooked vegetable (95). In patients with a DBPCFC positive to cooked celery, this vegetable remains allergenic even after extended thermal treatment (76.07 minutes at 100°C) (96). Loss of allergenicity can occur during the preparation of commercial extracts (97–99). Fresh foods—particularly fresh apple—have been proposed as coating material for the RAST disk (100). RAST prepared by this technique showed concordance with both clinical history and skin tests. Björkstén et al (99) increased apple RAST diagnostic sensitivity to 90% by inhibiting reactions with phenolic compounds during apple extract preparation.

Another factor influencing the sensitivity of SPT with fresh fruits and vegetables is ripeness. Allergenic potency may increase during maturation of the fruit or vegetable, as shown in Golden Delicious apples by Vieths et al (101). This increase in the allergenic properties of the mature apples is due to an 18 kDa allergen. In another study, Vieths et al showed that the different allergenic potencies of 16 apple strains were related to the occurrence of this 18 kDa allergen (102).

The role of some single allergenic proteins is further highlighted by studies on hazelnut and brazil nuts (26, 103) showing that some allergens are related to the presence of symptoms.

In conclusion, are the SPT and/or antigen-specific IgE levels useless or do they play a role? On the contrary—we suggest that they be per-

formed as part of the diagnostic workup. In fact, positive SPT, in vitro, and antigen-specific IgE results are useful to confirm a diagnostic suspicion of IgE-mediated food allergy, especially when the history is clear, e.g., when symptoms occur regularly after the contact with a certain food. Although the SPT with fresh foods is impractical and has a low diagnostic specificity that generates many false positive results, it can be useful to consolidate the history-based possibility of food allergy. A positive test can suffice for concluding the diagnostic procedure in these cases. However, a negative SPT with fresh foods, especially if it is negative for all the tested foods, forces one to reconsider the correct diagnosis and re-evaluate the etiology of the symptoms.

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