

Oral Allergy Syndrome (Pollen-Food Allergy Syndrome)

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Oral allergy syndrome (OAS) or pollen-food allergy syndrome (PFS) is a hypersensitivity reaction to plant-based foods, manifesting most commonly with pruritus of the lips, tongue, and mouth. Unlike simple food allergy, OAS requires prior sensitization to a cross-reacting inhalant allergen rather than direct sensitization to a specific food protein. In this review, we summarize the clinical features and pathophysiology of OAS and provide an overview of known pollen-food associations.

Oral allergy syndrome (OAS) or pollen-food allergy syndrome (PFS) is a hypersensitivity reaction to specific foods due to prior sensitization to plant inhalant allergens. The relationship between seasonal allergies and food hypersensitivity was first noted in the 1940s.¹ The term *oral allergy syndrome* was coined by Amlot et al² in 1987 to describe oral mucosal symptoms that occasionally spread to the entire body in patients with food hypersensitivity and a positive skin test to inhalants or foods.² Approximately 20% to 70% of patients sensitized to pollen allergens experience OAS symptoms after eating raw fruits, vegetables, nuts, or certain spices.^{3–6} The incidence of sensitization to plant foods is highest in those with birch pollen allergy.⁷ With the increasing prevalence of pollen allergies,^{8,9} the prevalence of OAS allergy is projected to rise. The syndrome should be suspected in patients who present with characteristic symptoms immediately after ingestion of raw fruits, nuts, vegetables, and spices. Oral allergy syndrome occurs in patients with a history of atopy, and it is thus an important phenomenon to recognize in these predisposed individuals.^{6,10,11}

Oral allergy syndrome is triggered by a cross-reaction between allergens in pollen and allergens in fresh fruits and vegetables.^{12,13} Nonplant foods, such as cow's milk, egg, or seafood, do not cause OAS. The literature is replete with reports of systemic reactions to cooked foods such as bird meat,¹⁴ chicken,¹⁵ pork,¹⁶ salami,¹⁷ as well as sensitization via mite allergens,¹⁷ attributed to OAS in the

absence of a history of pollen allergy.^{18,19} Several authors have argued that these cases should not be included under the heading of OAS.^{12,19–21} Although some plant allergens that induce OAS are resistant to heating, most are heat-labile. Because digestive enzymes in the gastrointestinal tract readily break down the food allergens, most commonly in fruits, vegetables, and nuts, the symptoms of OAS are typically limited to the oropharynx, although systemic reactions may rarely occur. To avoid confusion between this unique food allergy syndrome and food allergies unrelated to inhalant allergens, the term *pollen-food allergy syndrome* was adopted to refer to this syndrome.^{12,13}

Oral allergy syndrome is distinct from simple food allergies. In food allergies, a reaction develops after direct sensitization to food proteins rather than cross-reactivity between food proteins and inhalant allergens. Moreover, food allergies can be caused by plant or nonplant foods and tend to occur in response to substances that are relatively stable and able to survive gastrointestinal processing and/or cooking. In addition, food allergies more commonly result in systemic allergic reactions including anaphylaxis.

Dermatologists, allergists, and pediatricians manage a large number of patients with atopy and seasonal allergies who may also experience OAS. These patients can usually identify the fruits and vegetables that cause their symptoms. It is important for the practicing clinician to recognize these symptoms and educate those affected to avoid offending foods and mitigate rare but potential progression to more severe systemic allergic reactions.^{22,23} Although no case-controlled studies have been performed on the impact of food avoidance on the natural history of PFAS, identifying and avoiding foods that trigger symptoms will improve patient outcomes by lessening symptoms and increase patient safety in those with more severe allergic reactions.^{24,25} In addition, although dietary restriction can negatively impact patient quality of life,²⁶ avoidance of foods that trigger symptoms remains the key in the management of OAS symptoms, particularly in those patients presenting with more severe allergic reactions.

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The authors have no funding or conflicts of interest to declare.

Supported in part by funding from the Carl J. Herzog Foundation.

DOI: 10.1097/DER.0000000000000087

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TABLE 1. Association of Specific Fruits and Nuts With Specific Aeroallergens

Fruit or Nut	Birch	Ragweed	Mugwort	Grass	References
Almond*	+				28
Apple	+		+	+	27,28,39,112,123,124
Apricot*	+				28,125
Banana		+			28
Cantaloupe		+			28
Cherry*	+				28,39,125
Chestnut	+			+	98,126
Currant				+	127
Date palm	+			+	128
Fig	+			+	129
Grape	+			+	130
Hazelnut	+				28,131
Honeydew		+			28
Jackfruit	+				32
Kiwi	+	+		+	28,132
Mango			+		39,133
Melon	+	+		+	77,133
Nectarine/orange	+			+	24,30,115
Peach*	+	+	+	+	28,39,125,133,134
Pear	+				28,39
Peanut	+				103
Pistachio	+			+	135
Plum*	+				28,125
Prune	+				28
Walnut	+				28,39
Watermelon		+	+	+	28,39,136

*Fruits or nuts that have been identified as having higher risk for progression to systemic reactions.³⁹

Case Studies

A 12-year-old Asian boy presented with a pruritic eruption that occurred within 5 minutes after eating a red apple.²⁷ While he was eating the apple, his hard palate started to itch, and shortly thereafter, he developed a rash around his mouth. His medical history was significant for atopic dermatitis during infancy, contact urticaria to eggplant, and seasonal allergies relieved with antihistamines. On physical examination, there were confluent urticarial erythematous patches in a perioral distribution.

A 32-year-old man presented to the Allergy and Immunology Outpatient Clinic with a chief complaint of worsening atopic dermatitis.²⁸ His medical history was also significant for a history of perennial allergic rhinoconjunctivitis that worsened each winter and anaphylaxis to seafood, particularly lobster. He also complained of itching of his lips and throat as well as difficulty breathing after ingestion of fresh fruits, such as peaches, pears, plums, and cherries, and tree nuts including walnuts, cashews, and pistachios. His symptoms usually began 5 to 15 minutes after he ingested these foods and led him to avoid these and other fresh fruits and nuts. Skin testing showed strongly positive reactions to extracts of grasses, birch, and ragweed.

A 42-year-old lady was referred to the maxillofacial department by her general dental practitioner with a 9-month history of recurrent painful oral ulcerations.²⁹ The pain was described as a stinging sensation on the left side of the oral cavity, her preferred side for chewing when eating. Occasionally, this was accompanied by an itchy sensation causing her to rub the areas resulting in blisters/ulcers. The onset of symptoms occurred on immediate contact with raw fruits or vegetables, including apples, melon, and raw potato. Skin prick testing with fresh fruit revealed allergies to raw apples, raw potatoes, peanuts, almonds, hazelnuts, grass, and tree pollen.

Symptoms

Symptoms of OAS usually occur within minutes of exposure to the offending fruits or vegetables and last from minutes to hours.²⁸ Symptoms are typically limited to the oropharynx and are usually mild and transient. The most common symptom is oral-pharyngeal pruritus,³⁰ especially of the lips and the palate region³¹; although rarely, there may also be oral and perioral angioedema.²⁷ Patients typically describe itching or tingling in the lips or mouth, oral burning and swelling, or throat tightness after ingestion of fresh fruits or vegetables.^{2,32,33} Although rare, the most frequent extra-oral symptoms include facial rash and nasal and otic pruritus.³¹ Occasionally, mucosal vesicles or blistering along the oral cavity, conjunctivitis, congestion, or coryza also occur.^{28,34} Physical examination may reveal tongue swelling,³⁵ uvular edema,³⁶ erythema and swelling of the lips,³⁷ a perioral urticarial eruption,²⁷ and facial³⁸ and periorbital²⁸ edema.

Five percent of patients have OAS progress to a more generalized allergic reaction with systemic symptoms including nausea, vomiting, abdominal pain, upper respiratory obstruction, or even anaphylaxis.¹² There are currently no predictive metrics to accurately determine which patients are at risk for progression from

TABLE 2. Association of Specific Vegetables With Specific Aeroallergens

Vegetable	Birch	Ragweed	Mugwort	Grass	References
Avocado			+		137
Carrot*	+	+	+	+	28,39,133,138
Celery*	+	+	+	+	23,28,39,133
Cucumber		+			28,102
Eggplant				+	139
Fennel*	+	+	+		28,39,102,133
Mushroom				+	140
Parsley	+		+		28,39,133
Parsnip	+				28
Peppers		+	+		28,39,133
Potato	+				28
Soybean	+				103,141–143
Spinach	+				38
Tomato*				+	28,39,60
Zucchini		+			24,122

*Vegetables that have been identified as having higher risk for progression to systemic reactions.³⁹

TABLE 3. Association of Specific Spices and Flowers With Specific Aeroallergens

Spice or Flower	Birch	Ragweed	Mugwort	Grass	References
Aniseed			+		133
Caraway seed			+		133
Chamomile		+	+	+	28
Chicory	+				145
Coriander		+	+		28,39,133
Dandelion		+			28
Mustard*			+		133
Sunflower			+		28

*Spices or flowers that have been identified as having higher risk for progression to systemic reactions.³⁹

typical OAS to systemic illness, although consumption of certain foods such as apricot, lentil, peach, and tomato have been implicated in elevating the risk in susceptible patients.³⁹ Risk factors for systemic reactions include a history of systemic reaction to food, a

positive skin prick test to commercial antigen, and prior reaction to peaches or tree nuts.¹² However, oral itching after consumption of tree nuts should not be exclusively attributed to OAS because similar symptoms may herald severe systemic reactions associated with simple food allergy.¹²

Inhalant Allergens and Triggers

Oral allergy syndrome has been reported in response to a variety of fruits, nuts, vegetables, flowers, and spices which have been summarized, along with their most commonly associated pollinoses, in Table 1 to 3. Most studies referenced are case reports that do not indicate the botanical source of the pollen or document the part of the food (peel, pulp, seed, stem, leaf) to which the reaction occurred. Reactions can develop from small doses of triggering allergen. In some instances, OAS reactions have been reported in response to intimate or casual contact with someone who had consumed or handled the trigger.^{36,40} A wide variety of pollens can lead to initial sensitization and subsequent OAS.

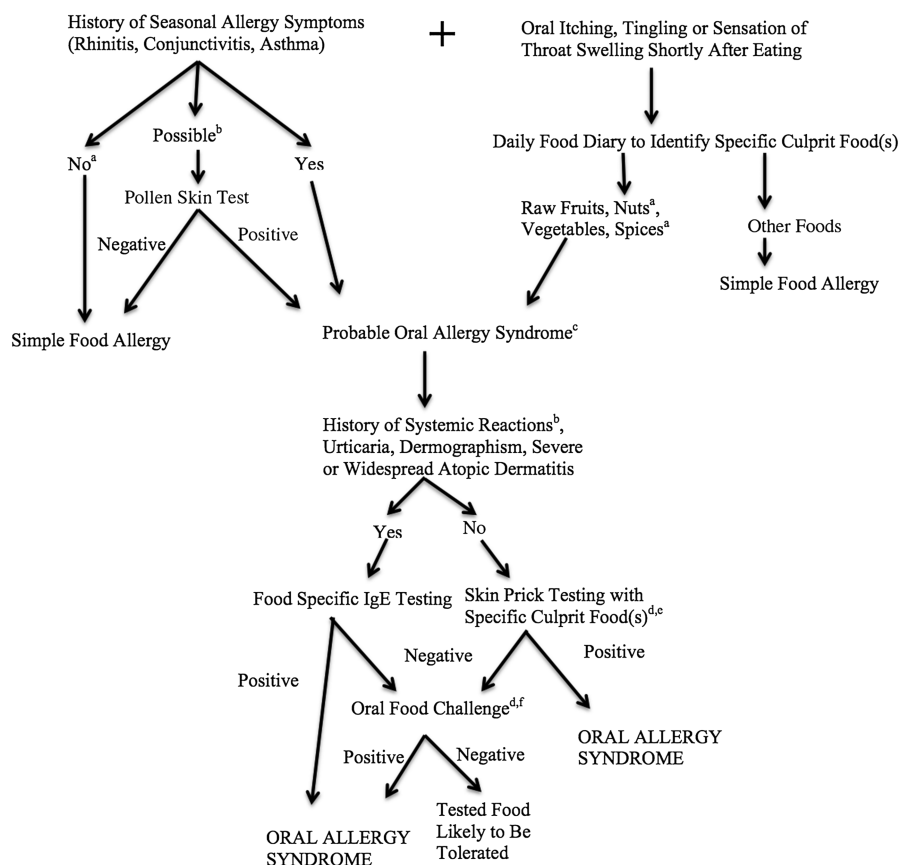


Figure 1. Approach to diagnosis of OAS. Referral to an allergist is indicated if there are oropharyngeal symptoms and no seasonal allergies or if there is a history of reaction to peanuts, tree nuts, or mustard (a). Confirmation of pollen sensitization either by skin testing (most accurate) or by IgE immunoassays is necessary if it is unclear if the patient has pollen allergy or if there are any systemic symptoms (b). Extensive evaluation may not be necessary if symptoms are mild and limited to oropharynx (c). Skin testing and oral food challenge should be performed by an allergist with training in management of serious allergic reactions (d). Medications that may interfere with skin testing (ie, antihistamines, steroids, omalizumab, tricyclic antidepressants, and high-dose methotrexate) should be discontinued before skin testing (e). CAST-ELISA is an alternative in vitro test to assess food allergy in lieu of the oral food challenge in patients with a history of anaphylaxis (f).⁷

TABLE 4. Classification of PR Proteins and Examples of Their Function⁵⁵

Family	Member Type	Properties
PR-1	Tobacco PR-1a	Antifungal
PR-2	Tobacco PR-2	β -1,3,-glucanase
PR-3	Tobacco P, Q	Chitinase, class I, II, IV, V, VI, VII
PR-4	Tobacco "R"	Chitinase, class I, II
PR-5*	Tomato S	Thaumatococcal
PR-6	Tomato inhibitor I	Proteinase inhibitor
PR-7	Tomato P69	Endoprotease
PR-8	Cucumber chitinase	Chitinase, class III
PR-9	Tobacco "lignin forming peroxidase"	Peroxidase
PR-10*	Parsley "PR1"	Ribonuclease
PR-11	Tobacco "class V" chitinase	Chitinase, class I
PR-12	Radish Rs-AFP3	Defensin
PR-13	Arabidopsis THI2.1	Thionin
PR-14*	Barley LTP4	LTP
PR-15	Barely OxOa (germiin)	Oxalate oxidase
PR-16	Barley OxOLP	Oxalate oxidase-like
PR-17	Tobacco PRp27	Unknown

*PR families most commonly implicated in IgE cross-reactivity resulting in OAS. Reproduced from Sels J, et al. *Plant pathogenesis-related (PR) proteins: a focus on PR peptides*. *Plant Physiol Biochem* 2008;46(11):941–950, Copyright 2014, Elsevier Masson SAS. All rights reserved.

Common pollinoses include birch,³⁹ ragweed, mugwort, grass,³³ and Japanese cedar.⁴¹

Diagnosis

The diagnosis of OAS relies on a history of oropharyngeal symptoms associated with ingestion of specific raw fruits or vegetables and pollen-associated allergies.⁴² Skin prick testing with the most allergenic part of the suspected fresh food (peel vs pulp) gives the most practical and reproducible results.^{43,44} Skin prick testing with commercial extracts has been found to be less reliable than direct inoculation with the offending agent in fresh form.⁴⁵ Radioallergosorbent testing is more sensitive than skin prick testing with commercial extracts but is less sensitive than skin prick testing with fresh extracts.²⁸ CAST-ELISA (cellular antigen stimulation test in combination with enzyme-linked immunoabsorbent assay) is more specific diagnostically for allergy to celery, hazelnut, and carrot when compared to commercial skin prick tests and allergen-specific IgE analysis.⁴⁶ The CAST-ELISA is a method for assessing IgE- and non-IgE-mediated allergies.⁴⁷ The test measures sulfidoleukotriene release by sensitized leukocytes after specific allergen stimulation.⁴⁷ The released leukotrienes are measured by an ELISA test. A concentration of sulfidoleukotrienes greater than 200 pg/mL above the spontaneous production level is a positive result.⁴⁸ Component-resolved diagnosis using microarray techniques has also been used in the diagnosis of IgE-mediated allergens, yet its utility in discriminating between sensitization versus real allergy is questionable.⁴⁹ Nonetheless, it is a useful tool

to analyze cross-reactivity in patients with multiple sensitizations to plant foods and pollens.^{50–52} However, a reliable and thorough patient history and understanding of the pollen-food associations are generally adequate for clinical diagnosis in most instances. It is important to identify those cases associated with systemic symptoms that need more extensive evaluation (Fig 1).

Pathogenesis

Oral allergy syndrome is a type I immediate hypersensitivity reaction mediated by IgE induced by sensitization to pollen. Sensitization to pollen leads to subsequent development of

TABLE 5. Families of PR Proteins Commonly Implicated in IgE Cross-reactivity Resulting in OAS

Protein Family	Pollen Allergy	Associated Foods Causing OAS	References
PR-5	Plane	Peach	52
PR-10	Birch	Chestnut	28,65,147–149
		Apple	
		Cherry	
		Hazelnut	
		Peach	
		Pear	
		Apricot	
		Celery	
		Carrot	
		Parsley	
		Potato	
PR-14	Mugwort	Peach, cabbage	3,61,121,133,150–152
		Plane	3,153
		Ragweed	133
		Grass, Parietaria	28,154
		Fennel-peach	155
		Celery	23
		Melon	77
		Apple	78
		Pear	78
		Carrot	78
Profilin	Birch	Potato	78
		Melon	77
		Timothy grass	77
		Ragweed	81
		Ryegrass	79
		Apple	
		Birch-mugwort	80
		Wheatgrass	157
		Date palm ¹⁵⁶	73,156
		Watermelon	
LTP	Mugwort	Tomato	
		Banana	
		Pineapple	
		Orange	
		Chestnut	158
LTP	Artemisia	Peach, Wheat	159

TABLE 6. Heat-Labile and Heat-Stable Allergens in Raw Foods Implicated in OAS

Heat-Labile Allergens*	Heat-Stable Allergens	Heat-Stable and Heat-Labile Allergens
Kiwi ⁹²	Peach ¹⁶⁰	Apple ^{43,99,161,162}
Fig ¹⁶³	Orange ¹⁶⁴	Hazelnut ⁶²
Asparagus ^{165,166}	Cherry ^{100,167}	Peanut ^{96,168}
Soybean ⁹³	Melon ¹⁶⁹	Tomato ¹⁷⁰
Carrot ^{101†}	Walnut ⁶²	Celery ^{162,171}
	Pecan ⁶²	
	Pistachio ⁶²	
	Chamomile ¹⁴⁴	
	Wheat ¹⁷²	
	Barley ¹⁷³	
	Rice ¹⁷⁴	

*Heat sensitivity testing performed in in vitro setting under specific controlled conditions.

†LTP Dau C 3, another protein present in carrots, may be heat-stable.

cross-reactivity to food allergens. Cross-reactivity develops as a consequence of shared epitopes in the primary and tertiary structures of pollen and food allergens.^{13,18,53} Pollen-specific IgE antibodies are able to recognize homologous dietary allergens that share the same epitopes. The IgE allergen complexes bind to the surface of mucosal mast cells and basophils, triggering the localized release of histamine, which results in the symptoms of OAS.²⁸

The antigenic proteins implicated in OAS have recently been classified. Many plants have developed pathogenesis-related (PR) or pathogen-response proteins to protect against pathogen invasion.²⁸ The PR proteins have been classified into 17 families based on similarities in their physiologic properties, biological activity, and amino acid sequence (Table 4).^{54,55} The ribosome-inactivating proteins (PR-10), lipid transfer proteins (LTPs) (PR-14), and thaumatinlike proteins (TLPs) (PR-5) share significant homology with proteins found in various fruits and vegetables. These families of PR proteins are commonly implicated in IgE cross-reactivity resulting in OAS (Table 5).

The PR-10 proteins are the most important family of PR proteins associated with pollen-food allergy syndrome. The major birch allergen Bet v 1 is a member of this family of proteins. Birch was one of the first pollen allergies associated with hypersensitivity to various fruits and vegetables.⁵⁶ A major antigenic protein in apples, Mal d 1, cross-reacts with Bet v 1 (Table 1, 5). Other fruits and vegetables with homologous proteins to Bet v 1 include the following: cherry, apricot, pear, peach, hazelnut, celery, carrot, parsley, and potato (Table 1, 2, 5).^{28,43} Consumption of these foods in birch-allergic individuals can lead to the symptoms of OAS. Patients with atopic dermatitis who are sensitized to birch pollen may experience a worsening of their eczema after consumption of birch pollen-related foods.^{57,58} Oropharyngeal reactions caused by foods that are related to birch pollen are more prevalent in central and northern Europe where birch trees are common.⁵⁹

Lipid transfer proteins comprise the PR-14 family of proteins and can be found in tomatoes, peaches, apples, apricot, plum,

cherry, almonds, and grapes.^{28,60} Lipid transfer proteins are cross-reacting antigens responsible for OAS triggered by consumption of apples and peaches in patients without birch or grass pollen allergy.²⁸ Art v 3, the mugwort pollen LTP, has been shown to cross-react with peach LTP Pru p 3 and is involved in the mugwort/peach-associated allergy (Table 1, 2, 5).³ However, this family of proteins may also cause allergy to fruits in the absence of pollen allergy.⁶¹ The LTP microarray immunoassay data suggest that peach LTP (Pru p 3) acts as the principal primary sensitizer of food-pollen allergies and as the main gateway to polysensitization to LTPs.⁵⁰ Lipid transfer proteins are particularly heat-stable and resistant to digestive enzymes, unlike most allergens causing OAS.^{12,62,63} Stability allows the allergen to reach the gastrointestinal immune system in an immunogenic and allergenic conformation, allowing sensitization and induction of systemic symptoms.⁶⁴ Consequently, this family of proteins is more likely to cause severe systemic reactions, including urticaria, angioedema, dyspnea, and anaphylaxis.^{12,28,51,65} The conserved IgE-binding conformation is probably the most important factor contributing to the observation that LTP-reactive patients have a higher incidence of severe systemic reactions than classic birch-related food allergic proteins.⁶¹ Often, severe allergic reactions to LTP food allergens are triggered by physical exercise and nonsteroidal anti-inflammatory medications.⁵¹ Lipid transfer proteins are dominant allergens in the Mediterranean region and cause severe and systemic symptoms in this region at a higher rate than seen in central Europe.^{3,59,66}

The PR-5 group of proteins has been recognized as a fairly new family of cross-reactive allergens.⁶⁷ Allergens within the PR-5 group of proteins share homology with thaumatins, intensely sweet proteins first isolated from the tropical plant *Thaumatococcus daniellii*, native to West Africa.⁶⁷ Mal d 2, the minor allergen of apple, was the first TLP described as a plant food allergen.⁶⁸ Pru av 2⁶⁹ (a major allergen of cherry), Cup a 3⁷⁰ (from *Cupressus arizonica* pollen), Jun a 3⁷¹ (from mountain cedar), and Man z TLP2⁶⁷ (from sapodilla plum) have also been shown to be homologous to the TLPs (Table 5). Further research is needed to understand the cross-reactivity of TLPs with other foods and pollens.

Profilin, an actin-binding protein ubiquitously present in eukaryotic cells, has also been associated with pollen- and plant-associated food allergies.⁷² The prevalence of skin sensitization to date-pollen-profilin has been estimated to be between 10% and 30% in pollen-allergic patients in Europe.⁷³ In 1 study, over 50% of patients sensitized to profilins experienced oral allergy symptoms with plant-derived foods.⁷³ However, clinical pollen-food allergy in profilin-sensitized patients may be independent of the level of specific IgE.^{74,75} The first profilin identified was Bet v 2, an allergen in birch pollen. IgE antibodies in birch pollen-food-allergic individuals cross-react with Bet v 2 homologous proteins from apple, pear, melon, carrot, celery, and potato (Table 1, 2, 5).^{28,76–78} Similarly, patients with allergies to grass pollen profilin may have OAS in response to eating peaches and apples that contain these profilin proteins.⁷⁹ Patients who are

sensitized to profilin tend to also be sensitized to mugwort and ragweed pollen in addition to birch and grass pollen.⁷³ Profilin has been implicated in the mugwort-celery-spice syndrome and ragweed-melon allergy (Table 2, 3, 5).^{80,81} Fruit allergy to melon, watermelon, tomato, banana, pineapple, and orange may be considered a marker of profilin hypersensitivity (Table 5).⁷³ Profilin sensitization in pollen-allergic individuals is common in southern Europe with prevalence rates of 6% in Spain's Mediterranean coast,¹¹ 21% in Portugal,⁸² and 30% in Italy.⁷³

Treatment

Avoidance of known food triggers is generally the primary treatment for OAS.^{28,83} Avoidance of all other fresh fruits and vegetables in the same plant family, or those known to cross-react with the same pollen, may be excessively restrictive and felt to be unnecessary in most cases of OAS. Although some have suggested systematic oral challenges of fruits and vegetables that are either in the same plant family or antigenically linked to the known trigger,⁸⁴ this process can be expensive and time consuming. Patients may be cautioned about the symptoms of a potentially more serious allergic reaction and maintain a list of potential cross-reactants. Patients should be alerted to proceed with caution when consuming potentially allergenic foods and be cognizant of symptoms that suggest progression to a systemic reaction (Table 1–3).

Although exclusion diets have been successful in the treatment of simple food allergies in some adults (~1/3),⁸⁵ with reports of food allergies being eliminated after strict avoidance for 2 years,^{86,87} food avoidance does not seem to have a role in OAS because the latter is due to cross-reaction to pollen rather than food protein. Oral allergy syndrome tends to be perennial, perhaps due to continued exposure to the corresponding and cross-reacting aeroallergens.⁸⁸ Moreover, peeling the suspect foods may not provide adequate protection because the flesh may contain the provocative allergen or become contaminated during handling. However, antihistamines have been reported useful when taken before eating raw fruits and vegetables.⁸⁹

Allergens in OAS typically are labile and therefore heat sensitive. Cooking suspect food is therefore 1 potential solution.⁹⁰ Steam cooking kiwi for 5 minutes at 100°C has been reported to increase tolerance of kiwi in kiwi-allergic children with OAS (Table 1).⁹¹ Industrial homogenization of kiwi involving a 4-step heating process of scalding for 5 minutes at 90°C, heat treatment for 15 seconds at 115°C, stabilization for 15 seconds at 110°C, and pasteurization for 21 minutes at 65°C was also shown to eliminate kiwi sensitivity.⁹¹ Other studies have demonstrated that thermal stability of allergenic proteins in kiwi is strongly dependent on the pH.⁹² The antigenicity of soybean products increases at 5 minutes of boiling and gradually decreases as the duration of boiling approaches 60 minutes.⁹³ However, diagnostic accuracy is vital in this setting because those experiencing other types of food allergy may not be protected by this exercise. Thermal processing of fruits has not been uniformly effective in

decreasing their allergenicity. The disulfide bond-stabilized structure of the LTP molecule makes these proteins extremely resistant to heat denaturation.⁶⁴ In addition, many foods contain both heat-stable LTPs and heat-labile PR-10 proteins (Table 6), and therefore, whether or not heating the food will result in clinical resolution of symptoms depends on which protein the patient is allergic to. Component-resolved microarray immunoassay is promising in identifying specific IgE to individual allergens, but the low sensitivity of the assay limits its utility.⁹⁴ Roasted peanuts are apparently more allergenic than raw peanuts (Table 1). Roasting raw peanuts at 55°C for 10 days was shown to increase the IgE-binding activity of 2 major peanut allergens Ara h 1 and Ara h 2 as compared with raw peanuts.⁹⁵ Higher allergenicity was also demonstrated with commercially roasted peanuts as compared with raw and boiled peanuts.⁹⁶ More recently, autoclaving roasted peanuts at 138°C for 15 and 30 minutes has been demonstrated to produce a significant decrease of IgE-binding capacity of peanut allergens, although further studies are needed to confirm the clinical relevance of these findings.⁹⁷ Hazelnuts roasted at 140°C for 40 minutes have also been shown to cause OAS in certain hazelnut-allergic patients (Table 1).⁹⁸ In addition, in a subset of patients, those with OAS-like symptoms but without an aeroallergen sensitization, IgE reactivity to Mal d 3, an LTP from apple, has been shown via radioallergosorbent testing to remain unchanged despite moderate (90°C, 20 minutes) thermal treatment.⁹⁹ In addition, the nonspecific LTP, Pru av 3, in cherries has been shown to retain a much higher allergenic potency after thermal processing (Table 1).¹⁰⁰ Recombinant cherry allergens were heated at increments of 20°C, 40°C, 70°C, and 100°C during CD spectroscopy.¹⁰⁰ In this subset of patients, therefore, heating is ineffective for prophylaxis. In addition, consumption of cooked birch-related fruits by patients with birch pollen allergy and atopic dermatitis has been implicated in flaring eczema.¹⁰¹ In patients with birch pollen allergy and atopic dermatitis, cooked birch-related food allergens trigger a cellular response that is not dependent on IgE binding.¹⁰¹ Cooked birch-related food allergens lose the capacity to bind IgE but retain their ability to activate Bet v 1-specific T-cells as native proteins and trigger atopic dermatitis.¹⁰¹

Although pollen immunotherapy^{102–104} may be efficacious in certain patients, the results are variable. A subset of birch-allergic patients with apple allergy experienced a decrease in OAS symptoms after subcutaneous injection of birch pollen extract or regular consumption of increasing amounts of the fresh apple.^{105–108} In addition, daily dosing of sublingual birch pollen extract solution was found to be efficacious in lessening pollen-induced allergic rhinitis and symptoms of OAS in birch-allergic patients.¹⁰⁹ Sublingual recombinant Mal d 1 (apple PR-10 protein) and subcutaneous injection of birch pollen extract have also been shown to induce immune responses characteristic of allergen tolerance in patients with birch allergy.^{110,111} However, many patients do not experience improvement in their OAS symptoms, and oral food tolerance, if induced, may be only transient after immunotherapy.^{112–114} Further characterization of IgE epitopes

of fruit allergens and greater analysis of IgE and T-cell cross-reactivity may lead to successful immunotherapies in the future.^{115–117}

Ideally, the specific allergens causing symptoms should be easily identified in any patient; however, this is not always feasible. Fruits and vegetables may contain more than 1 allergenic protein, often from different antigenically distinct families. Individual sensitization profiles to these proteins may also vary due to dietary habits and pollinoses in each geographical area.¹¹⁸ In northern and central Europe, allergic reactions to plant foods are associated with birch pollen allergens Bet v 1 homologs and profilins.³ In North America, important aeroallergens include birch, rye grass, Bermuda grass, and ragweed.¹¹⁹ In southern Europe, allergy to fruits of the Rosaceae family is attributed to grass pollen sensitization rather than to birch pollen.⁷⁹ In the Mediterranean area, LTPs are dominant allergens, whereas LTP allergy is rarely reported in central and northern Europe.^{3,61} Olive and Salsola pollen are largely responsible for cross-sensitizations with foods in Mediterranean regions.^{3,61,120} In northern China, exposure to mugwort LTP Art v 3 has been implicated in causing peach allergy,¹²¹ whereas in southern Europe, peach allergy is attributed to primary sensitization to peach LTP Pru p 3.¹²² Geography greatly contributes to the diagnostic complexity of pollen-food syndrome.

For patients with symptoms related to nuts, more restrictive and cautious recommendations should be suggested to prevent potentially more serious or generalized hypersensitivity reactions. Similarly, allergy to peaches and other LTP food allergens, which have also been implicated in more severe reactions, should also raise the level of caution.¹² Patients with allergic rhinitis and classic OAS to other fruits and vegetables can be reassured that their symptoms are not likely to progress to anaphylaxis. Understanding the pathogenesis, triggers, management, and prognosis of OAS can enable early intervention and potentially lessen the morbidity associated with the disease.

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