Pollen-food allergy syndrome (PFAS): An overview

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Eastern Food Allergy & Comorbidity Conference

FAIT PROGRAM
Food Allergy Immunotherapy

Objectives

- 1) Review the pathogenesis and epidemiology of pollen-food allergy syndrome (PFAS)
- 2) Discuss recent consensus recommendations for management of PFAS

Case: 13 yo male

- As a preschooler, had atopic dermatitis and asthma which was outgrown at school age
- Since ~7 yo, has had spring/summer nasal and eye symptoms, managed with non-sedating oral antihistamines as needed
- In the past 3 years, has had localized itching in the mouth/throat with apple, peach, & plum

Pathogenesis and epidemiology of PFAS

OAS vs PFAS

- Oral allergy syndrome (OAS)
  - First proposed in 1987
  - Used to describe the symptoms of allergy to various foods in patients sensitized to aeroallergens
- Pollen-food allergy syndrome (PFAS)
  - Used in 1995
  - Better characterizes the pathogenesis and avoids confusion re: possible symptoms

Carlson G, Coop C. Ann Allergy Asthma Immunol. 2019 Oct

Common PFAS allergens

Table 6
Common clinically relevant PFAS allergens

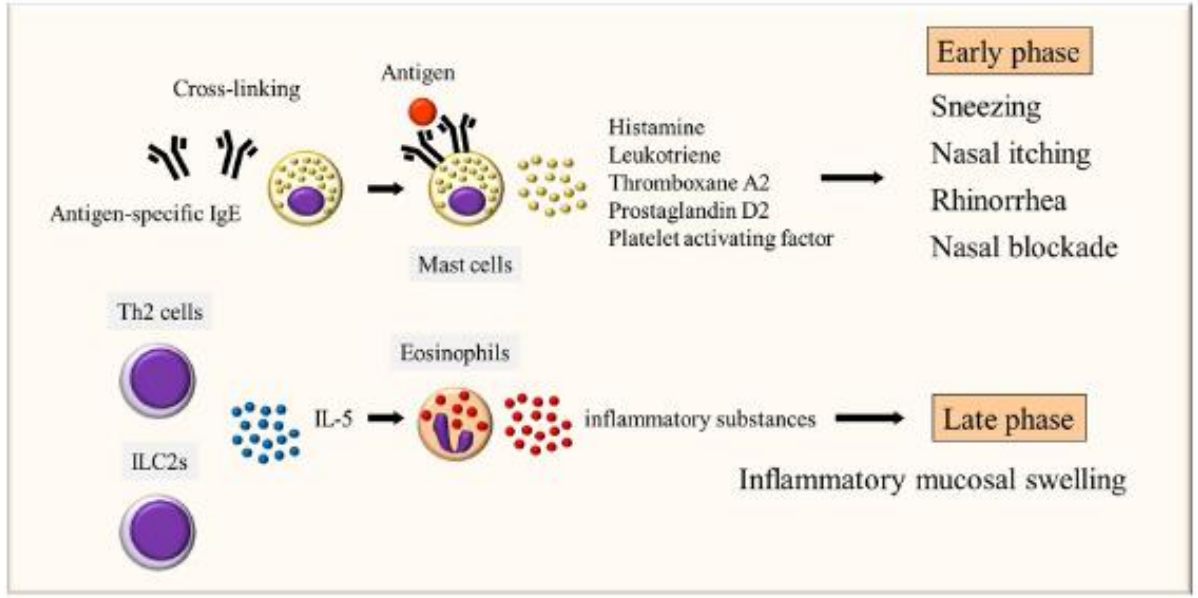
Relevant PFAS allergens	
Primary sensitization	Cross-reactive allergens
Profilin examples:	Kiwi (Act d 9)
Birch	Pineapple (Ana c 1)
Mugwort	Celery (Api g 4)
Ragweed	Peanut (Ara h 5)
	Carrot (Dau c 4)
	Soy (Gly m 3)
	Apple (Mal d 4)
	Banana (Mus a 1)
	Peach (Pru p 4)
PR-10 proteins examples	Peach (Pru p 1)
Birch (Bet v 1)	Apple (Mal d 1)
Oak (Que a 1)	Peanut (Ara h 8)
	Hazelnut (Cor a 1)
	Soy (Gly m 4)
	Celery (Api g 1)
LTP examples	Kiwi (Act d 10)
Ragweed (Amb a 6)	Peanut (Ara h 9)
Mugwort (Art v 3)	Hazelnut (Cor a 8)
	Latex (Hev b 12)
	Walnut (Jug r 3)
	Apple (Mal d 3)
	Wheat (Tri a 14)
	Peach (Pru p 3)

- Sensitization to aeroallergen followed by cross-reactivity
- Profilins & PR-10 (pathogenesis-related proteins)
  - Labile proteins easily denatured
  - Symptoms with fresh forms, but able to tolerate cooked/processed forms
  - Generally non-anaphylactic
- Lipid transfer proteins
  - Proteins resistant to heat/digestion
  - Severe, anaphylactic reactions possible
  - Well described in Southern Europe

Carlson G, Coop C. Ann Allergy Asthma Immunol. 2019 Oct

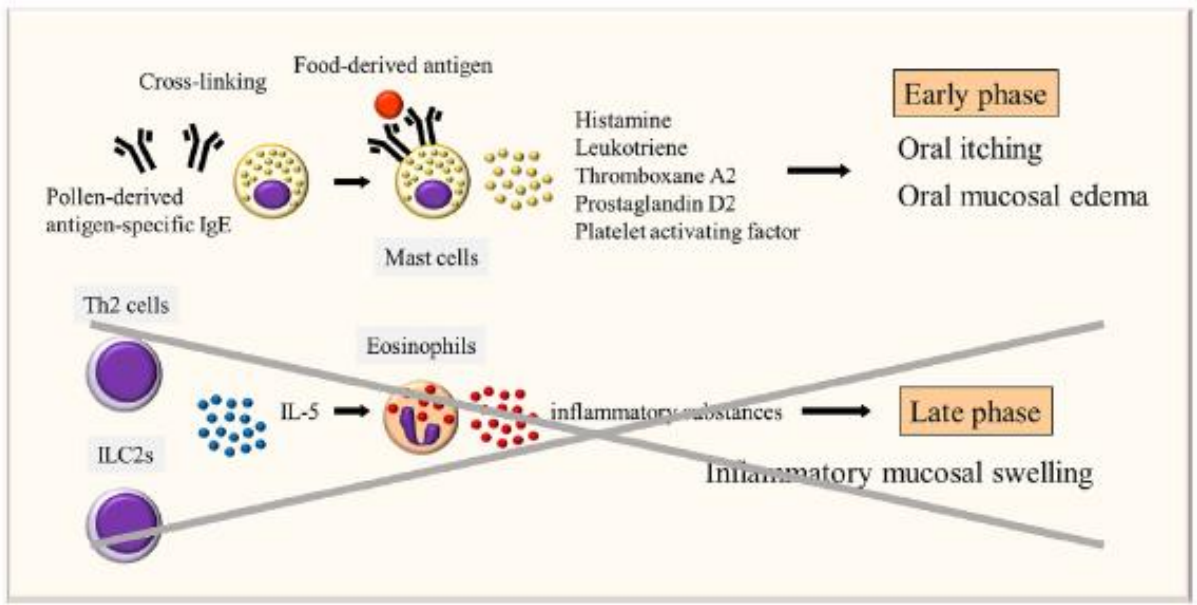
(A) Allergic rhinitis

Nasal mucosa



(B) Pollen-food allergy syndrome

Oral mucosa



Kato Y et al. Allergol Int. 2025 Jan

Epidemiology

- Estimates of PFAS prevalence vary according to geographic region
  - E.g.) 4.7-20% of children and 13-53.8% of adults
- Another method for estimating prevalence
  - Allergic rhinitis ~20-50% of population
  - 47-70% of patients with pollen allergy experience PFAS
  - Therefore estimated prevalence PFAS ~9.4-35%
- PFAS generally a low risk condition
  - Estimated 3% have systemic symptoms without oral symptoms, and 1.7% have anaphylaxis
  - E.g.) LTP (Pru p 3) in peach well described in Spain

Carlson G, Coop C. Ann Allergy Asthma Immunol. 2019 Oct
Kato Y et al. Allergol Int. 2025 Jan

Diagnosis

- Index of suspicion for symptoms with fruits, vegetables, legumes
- Confirm sensitization to pollen associated with the causative food
- Prick to prick SPT with raw food
  - When booking patient can ask them to bring in the raw food
- Component testing
  - Individual component tests
  - vs Multiplex arrays: ImmunoCAP ISAC or AllergyExplorer (ALEX) not universally available and possible clinically irrelevant sensitization
    - To be cost effective ISAC would have to replace at least 13 single IgE tests

Carlson G, Coop C. Ann Allergy Asthma Immunol. 2019 Oct
Kato Y et al. Allergol Int. 2025 Jan
Westwood M et al. Health Technol Assess. 2016 Sep

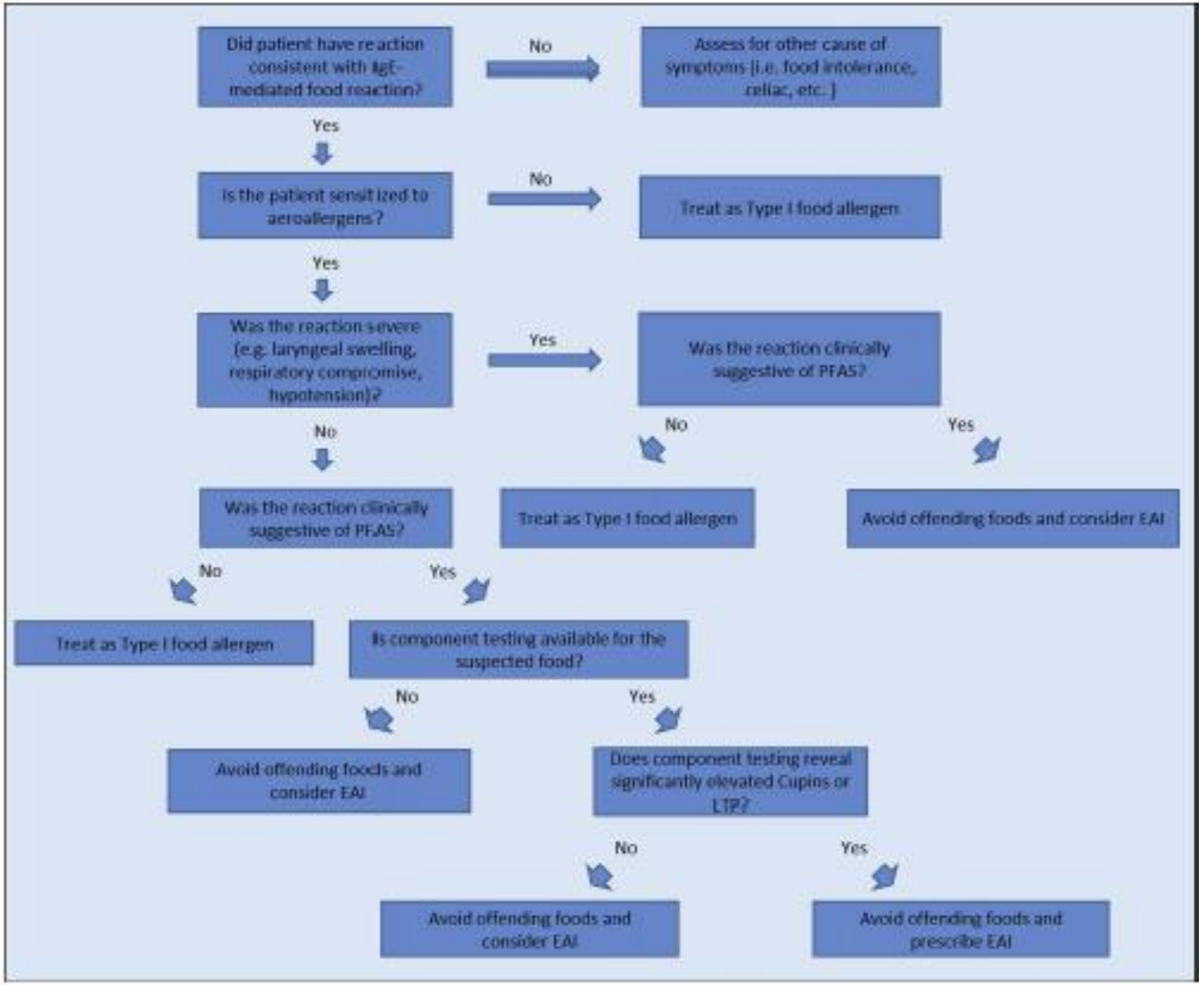


Figure 1. Algorithm for the approach to PFAS.

Carlson G, Coop C. Ann Allergy Asthma Immunol. 2019 Oct

Table 1
A compilation of LTP components for foods and aeroallergens

Prolamin (LTP)			
Aeroallergen		Foods	
Indian hemp	Can s 3	Almond	Pru du 3
London plane tree	Pla a 3	Apple	Mal d 3
Mugwort	Art v 3	Apricot	Pru ar 3
Oriental plane	Pla or 3	Asparagus	Aspa o 1
Para rubber tree (latex)	Hev b 12	Banana	Mus a 3
Short ragweed	Amb a 6	Cabbage	Bra o 3
		Celery	Api g 2, 6
		Cherry	Pru av 3
		Chestnut	Cas s 8
		Grape	Vit v 1
		Green bean	Pha v 3
		Hazelnut	Cor a 8
		Kiwi	Act c 10, Act d 10
		Lemon	Cit l 3
		Lentil	Len c 3
		Lettuce	Lac s 1
		Mulberry	Mor n 3
		Olive	Ole e 7
		Orange	Cit s 3
		Pea	Pis s 3
		Peach	Pru p 3
		Peanut	Ara h 9, 16, 17
		Plum	Pru d 3
		Pomegranate	Pun g 1
		Raspberry	Rub i 3
		Strawberry	Fra a 3
		Sunflower	Hel a 3
		Tangerine	Cit r 3
		Tomato	Sola i 3, 6, 7
		Walnut	Jug r 3
		Wheat	Tri a 14
		Yellow mustard	Sin a 3

Table 4
A compilation of PR-10 components for foods and aeroallergens

PR-10			
Aeroallergen		Foods	
Alder	Aln g 1	Apple	Mal d 1
Beech	Fag s 1	Apricot	Pru ar 1
Birch	Bet v 1	Carrot	Dau c 1
Hornbeam	Car b 1	Celery	Api g 1
White Oak	Que a 1	Cherry	Pru av 1
		Chestnut	Cas s 1
		Hazelnut	Cor a 1
		Kiwi	Act c 8, Act d 8, 11
		Mungbean	Vig r 1
		Peanut	Ara h 8
		Pear	Pyr c 1
		Raspberry	Rub i 1
		Soybean	Gly m 4
		Strawberry	Fra a 1
		Tomato	Sola l 4
		Walnut	Jug r 5

Table 5
A compilation of profilin components for foods and aeroallergens

Profilin family			
Aeroallergen		Foods	
Bermuda grass	Cyn d 12	Almond	Pru du 4
Birch	Bet v 2	Apple	Mal d 4
Burning bush	Koc s 2	Banana	Mus a 1
Date palm	Pho d 2	Barley	Hor v 12
Lambsquarter	Che a 2	Carrot	Dau c 4
Mesquite	Pro j 2	Celery	Api g 4
Mugwort	Art v 4	Cherry	Pru av 4
Para rubber tree (latex)	Hev b 8	Chili/bell pepper	Cap a 2
Pellitory-of-the-wall	Par j 3	Hazelnut	Cor a 2
Needle brush	Aca f 2	Kiwi	Act d 9
Pigweed	Ama r 2	Lupine	Lup a 5
Ragweed	Amb a 8	Lychee	Lit c 1
Russian thistle	Sal k 4	Muskmelon	Cuc m 2
Storage mite	Tyr p 36	Olive	Ole e 2
Timothy grass	Phl p 12	Orange	Cit s 2
		Peach	Pru p 4
		Peanut	Ara h 5
		Pear	Pyr c 4
		Pineapple	Ana c 1
		Rice	Ory s 12
		Soybean	Gly m 3
		Strawberry	Fra a 4
		Sunflower	Hel a 2
		Tomato	Sola l 1
		Walnut	Jug r 7
		Watermelon	Citr l 2
		Wheat	Tri a 12
		Yellow mustard	Sin a 4

Carlson G, Coop C. Ann Allergy Asthma Immunol. 2019 Oct

Could a similar phenomenon exist for shrimp?

TABLE I. Demographic data, clinic history, OFC symptoms, SPT, and sIgE results of patients

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis	3 y	6 y	12 y	5 y
Age at OFC	17 y	36 y	41 y	41 y
Atopic conditions	Asthma, allergic rhinitis	Asthma, allergic rhinitis	Allergic rhinitis	Allergic Rhinitis
History of reaction	Lip swelling and itching	Throat swelling, difficulty swallowing	Lip and throat itching, tingling, and swelling	Lip and throat itching and swelling
Symptoms during OFC	Itchy throat	Difficulty swallowing	Itchy and tingling sensation of lips	Itchy lips and throat; nausea
Skin prick test (SPT) to shrimp	Negative	Positive	Positive	Positive
Skin prick to prick to fresh shrimp	Positive	Not done	Negative	Positive
Skin prick to prick to cooked shrimp	Negative	Negative	Negative	Positive
SPT to house dust mite	Positive	Positive	Positive	Negative

- "Mite shrimp allergy syndrome"?
- A hypothetical condition extrapolated from PFAS
- Primary sensitization to heat labile arginine kinase protein in dust mite, followed by cross-reactivity in shrimp
- Oropharyngeal symptoms only
- More research needed

Tuano KTS, Davis CM. J Allergy Clin Immunol Pract. 2018 Nov-Dec

Recent consensus recommendations for management of PFAS

American Academy of Allergy Asthma & Immunology

An International Delphi Consensus on the Management of Pollen-Food Allergy Syndrome: A Work Group Report of the AAAAI Adverse Reactions to Foods Committee

Taha Al-Shaikhly, MBChB, FACAAI, FAAAAI[a], Amanda Cox, MD[b], Anna Nowak-Wegrzyn, MD, PhD[c,d], Antonella Cianferoni, MD, PhD[e], Constance Katelaris, MBBS, PhD[f], Didier G. Ebo, MD, PhD[g,h], George N. Konstantinou, MD, PhD, MS, MCArmy[i], Hannelore Brucker, MD[j], Hyeon-Jong Yang, MD, PhD[k], Jennifer L.P. Protudjer, PhD[l,m], José Laerte Boechat, MD, PhD[n], Joyce E. Yu, MD[o], Julie Wang, MD[b], Karen S. Hsu Blatman, MD[p], Lukasz Blazowski, PhD[q,r], Mahesh Padukudru Anand, MBBS, DNB[s], Manish Ramesh, MBBS, PhD[t], Maria J. Torres, MD, PhD[u], Mark Holbreich, MD[v], Richard Goodman, PhD[w], Richard L. Wasserman, MD, PhD[x], Russell Hopp, DO[y], Sakura Sato, MD[z], and Isabel Skypala, PhD, RD[aa] *Hershey and Philadelphia, Pa; New York and Bronx, NY; Olsztyn, Rabka-Zdroj, and Rzeszow, Poland; Sydney, Australia; Antwerp and Ghent, Belgium; Thessaloniki, Greece; Minneapolis, Minn; Seoul, Republic of Korea; Winnipeg, Man, Canada; Porto, Portugal; Lebanon, NH; Mysore, Karnataka, India; Málaga, Spain; Indianapolis, Ind; Lincoln and Omaha, Neb; Dallas, Texas; Kanagawa, Japan; and London, United Kingdom*

J Allergy Clin Immunol Pract. 2024 Dec

Delphi consensus process

- International panel of 25 experts (allergists, scientists, dietitians)
- Conducted electronically on REDCap
- RAND/UCLA methodology
- Consensus if median appropriateness/agreement level at least 8 (scale of 1-9), & DI (disagreement index) < 1
- After 2 Delphi rounds, consensus on 14 revised statements

TABLE I. Round 2 Delphi exercise

Statement	Appropriateness, median	DI
Individuals with PFAS may benefit from education about the mechanistic basis of their PFAS.	9	0
Reactions in PFAS are mostly benign and limited to the oropharynx, although, rarely, more severe symptoms may occur.	9	0.050
Certain foods associated with PFAS (nuts, soy milk, smoothies/fresh juices), especially if consumed rapidly or in large amounts might rarely trigger systemic symptoms.	9	0.132
Certain factors have been reported to increase the severity of PFAS symptoms including medications (eg. PPIs, NSAIDs), bariatric surgery, uncontrolled asthma, fasting, and exercise)	8	0.132
Individuals with PFAS limited to oral symptoms may choose to avoid only the raw forms of the responsible fruit/vegetable.	9	0.132
Patients with PFAS limited to oral symptoms may choose to continue to ingest the responsible fruit and vegetable if well-cooked but are cautioned that roasting may not eliminate the risk of reaction with nuts.	9	0.132
Lighter cooking methods (eg, steaming or stir-frying) may be insufficient to fully denature the allergens relevant to PFAS.	8	0.132
Patients should be educated on the higher allergen contents in the peels and seeds of fruits but are cautioned peeling and removing the seeds is usually insufficient to prevent symptoms of PFAS.	9	0.132
Patients with PFAS characterized by systemic reactions (ie, symptoms extending beyond the oropharynx) should strictly avoid the responsible fruits and vegetables.	9	0.132
When possible, modifiable risk factors for systemic reactions should be identified and mitigated in patients with PFAS to decrease the risk of life-threatening anaphylaxis.	9	0
Mild symptoms of PFAS limited to oropharynx often resolve without treatment; a nonsedating antihistamine can be used for uncomfortable symptoms.	9	0
PFAS with a history of systemic reaction (defined as having symptoms that extend beyond the oropharynx) may be at a higher risk for future severe reactions. An emergency treatment plan and a prescription of EAI should be offered.	9	0
Individuals with PFAS limited to the oropharynx and who have risk factors for systemic reactions (PPI or β-blockers use, gastric bypass surgery, or asthma) benefit from a shared decision-making approach when discussing the need for an EAI.	9	0.132
Pollen AIT via subcutaneous or sublingual route is not proven to alleviate symptoms of PFAS. PFAS is not an indication for pollen AIT.	9	0.132

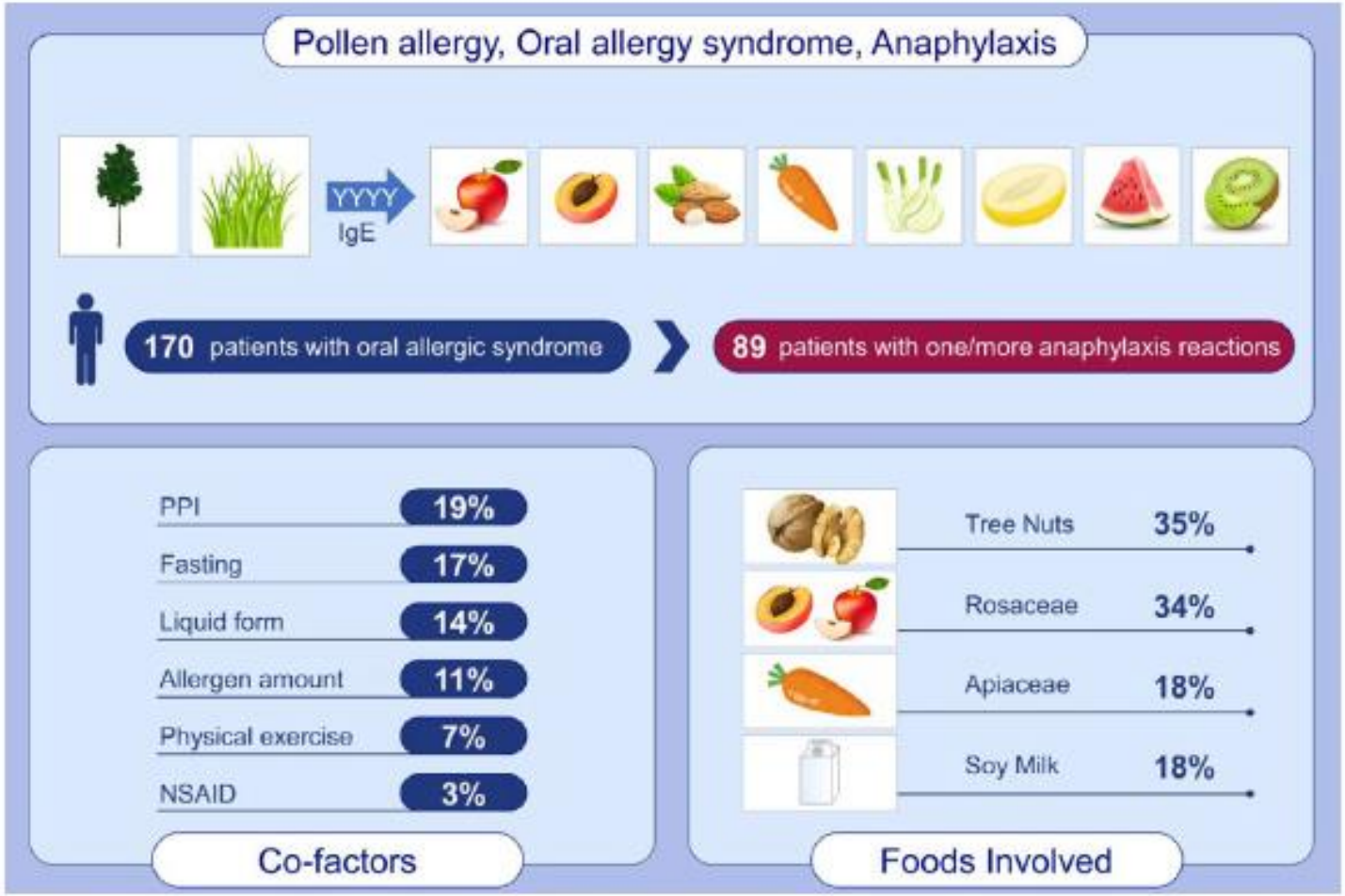
Categories of recommendations

Patient education

- **Statement 1.** Individuals with PFAS may benefit from education about the mechanistic basis of their PFAS.
- **Statement 2.** Reactions in PFAS are mostly benign and limited to the oropharynx, although, rarely, more severe symptoms may occur.
- **Statement 3.** Certain foods associated with PFAS (nuts, soy beverages, smoothies/fresh juices), especially if consumed rapidly or in large amounts, might rarely trigger systemic symptoms.

Patient education, cont’d

- **Statement 4.** Certain factors have been reported to increase the severity of PFAS symptoms including medications (eg, proton pump inhibitors [PPIs], nonsteroidal anti-inflammatory drugs [NSAIDs]), bariatric surgery, uncontrolled asthma, fasting, and exercise).



GRAPHICAL ABSTRACT

Hypersensitivity to labile plant-food allergens (PR-10 and profilin) secondary to pollen allergy frequently causes oral allergy syndrome. Labile allergens may become dangerous when the raw foods are ingested in excessive amounts or in liquid form. Other cofactors include therapy with proton pump inhibitors and fasting. The most frequently involved foods are as follows: tree nuts, *Rosaceae*, *Apiaceae*, *and* soy milk. Abbreviations: NSAID, non- steroidal anti- inflammatory drugs; PPI, proton pump inhibitors; PR- 10, pathogenesis- related proteins group 10

Asero R et al. Allergy. 2021 May

Dietary avoidance and food processing

- **Statement 5.** Individuals with PFAS limited to oral symptoms may choose to avoid only the raw forms of the responsible fruit/vegetable.
- **Statement 6.** Patients with PFAS limited to oral symptoms may choose to continue to ingest the responsible fruit and vegetable if well-cooked but are cautioned that roasting may not eliminate the risk of reaction with nuts.
- **Statement 7.** Lighter cooking methods (eg, steaming or stirfrying) may be insufficient to fully denature the allergens relevant to PFAS.

Dietary avoidance and food processing, cont’d

- **Statement 8.** Patients should be educated on the higher allergen content in the peels and seeds of fruits but cautioned that peeling and removing the seeds are usually insufficient means for preventing symptoms of PFAS.
- **Statement 9.** Patients with PFAS characterized by systemic reactions (ie, symptoms extending beyond the oropharynx) should strictly avoid the responsible fruits and vegetables.

Treatment of acute reactions

- **Statement 10.** When possible, modifiable risk factors for systemic reactions should be identified and mitigated in patients with PFAS to decrease the risk of life-threatening anaphylaxis.
- **Statement 11.** Mild symptoms of PFAS limited to the oropharynx often resolve without treatment; a nonsedating antihistamine can be used for uncomfortable symptoms.

Treatment of acute reactions, cont'd

- **Statement 12.** PFAS with a history of systemic reaction (defined as having symptoms that extend beyond the oropharynx) may be at a higher risk for future severe reactions. An emergency treatment plan and a prescription of an EAI (epinephrine autoinjector) should be offered.
- **Statement 13.** Individuals with PFAS limited to the oropharynx and who have risk factors for systemic reactions (PPI or beta-blockers use, gastric bypass surgery, or asthma) benefit from a shared decision-making approach when discussing the need for an EAI.

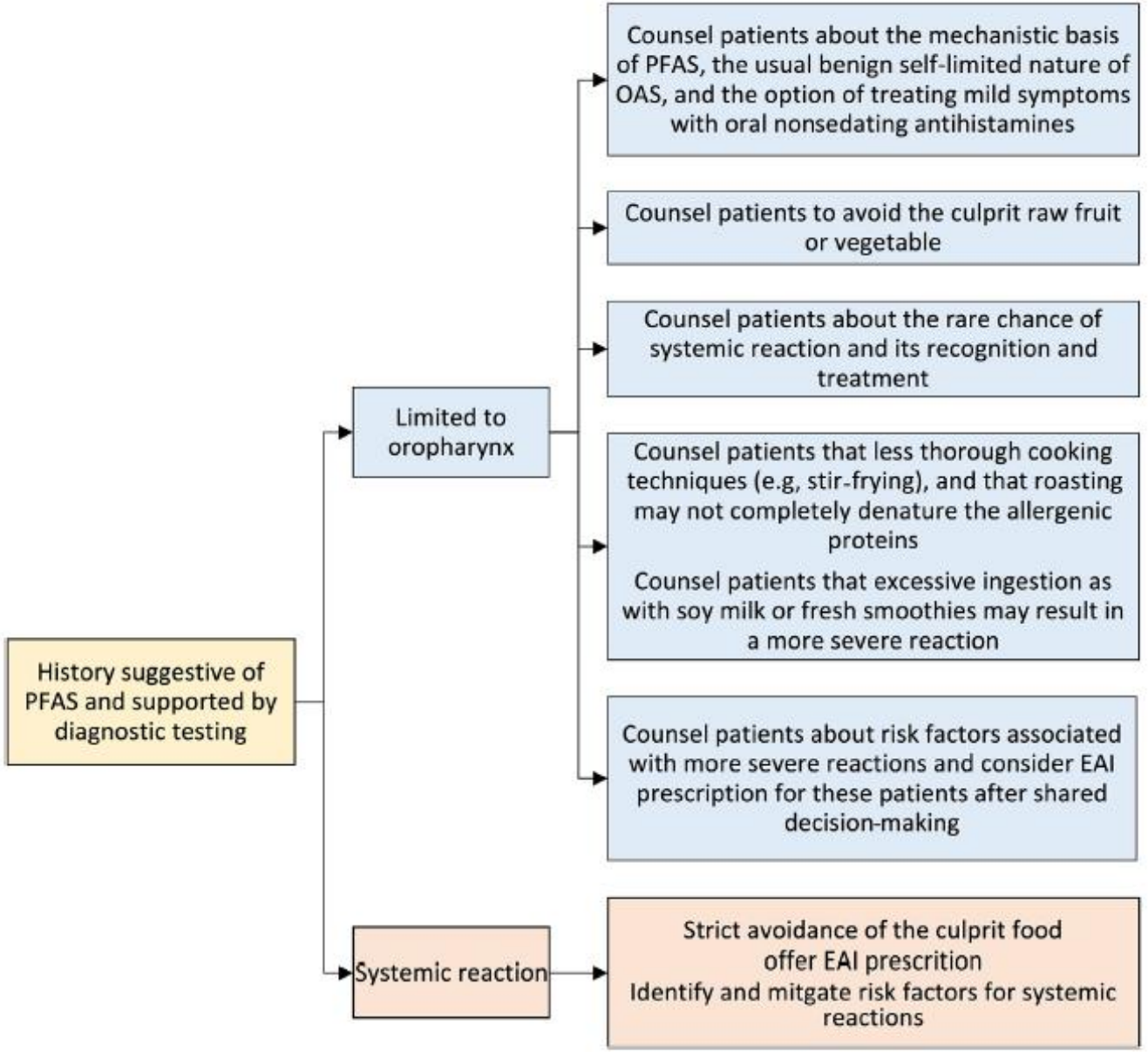


FIGURE 1. Approach for managing patients with PFAS. *OAS,* Oral allergy syndrome.

Immunotherapy for PFAS

- **Statement 14.** Pollen AIT via subcutaneous or sublingual route is not proven to alleviate symptoms of PFAS. PFAS is not an indication for pollen AIT.

Other treatment considerations **not** reaching consensus

- Individuals with PFAS may be offered oral immunotherapy only in a research capacity.
  - Appropriateness 7, DI 0.164
- Omalizumab might be offered to patients with PFAS as a treatment strategy.
  - Appropriateness 5, DI 1.290

Table 5
Efficacy of AIT for birch pollinosis-related apple allergy.

First author	Year	Material used for AIT	Method	Term (months)	Number	Effectiveness (N, %)
Asero R	1998	Birch pollen extract	SCIT	36	49	41 (84%)
Hansen	2004	Birch pollen extract	SCIT	48	15	6 (40%)
		Birch pollen extract	SLIT	48	11	5 (45%)
			(Placebo)	48	14	6 (43%)
Kinaciyan T	2007	Birch pollen extract	SLIT	12	15	2 (13%)
Mauro M	2011	Birch pollen extract	SCIT	12	8	5 (63%)
		Birch pollen extract	SLIT	12	7	3 (43%)
Kopac P	2012	Apple	OIT	8	27	17 (63%)
			(Placebo)	8	13	0 (0%)
Kinaciyan T	2018	Recombinant Mal d 1	SLIT	4	20	14 (70%)
		Recombinant Bet v 1	SLIT	4	16	7 (44%)
			(Placebo)	4	19	8 (42%)
van der Valk JPM	2020	Birch pollen extract	SCIT	24	8	4 (50%)
			(Before AIT)		8	3 (38%)
Nothegger B	2021	Apple	OIT	8	16	13 (81%)

Kato Y et al. Allergol Int. 2025 Jan

Outcomes of apple oral immunotherapy in pollen food allergy syndrome

Desie Dijkema, MSc,[a] Mirte C. Ruitenbeek, BSc,[a] Kirsten Weerstand-Noor, BSc,[a]
Hanneke N. G. Oude Elberink, MD, PhD,[b] and Annick A. J. M. van de Ven, MD, PhD[b,c] *Groningen, The Netherlands*

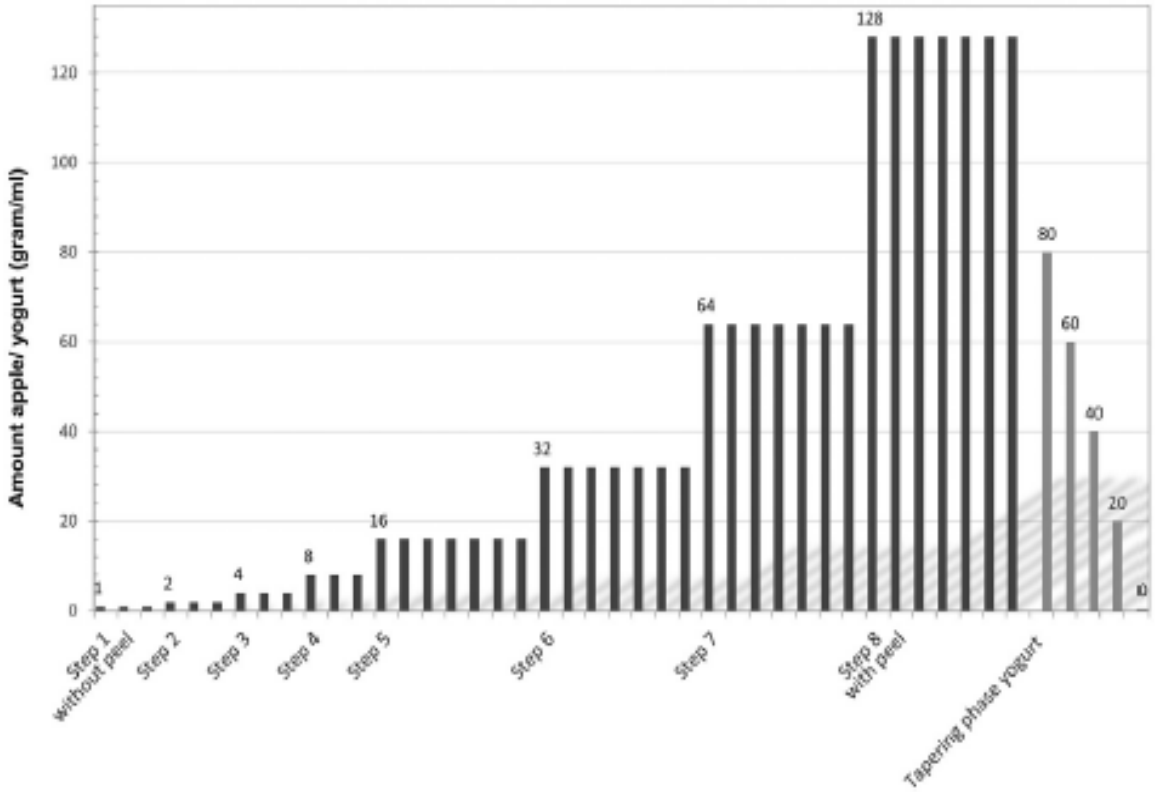


FIG 1. Stepwise protocol of OIT with apple. Each bar represents 1 instance of consumption on 1 day. In phase 1 (*black bars*), the amount of apple in yogurt is gradually increased until 128 g per day. In phase 2 (*gray bars*), the amount of yogurt is tapered from 100 to 0 mL.

- Peeled grated golden delicious apple/yogurt mixture (buildup from 1g to 128g apple) = 1 whole small apple
- 9 patients, mean 38yo
- Median max tolerated amount at baseline OFC = 4g
- **Home-based** OIT protocol completed average 39 days
- No severe reactions. 3 mild angioedema.
- 8 did follow-up survey:
  - 6 ate multiple types of apple regularly
    - 2 developed increased tolerance to other Rosaceae fruits (peach, pear, cherry, plum)
  - 2 unable to eat regularly and lost tolerance
- Shorter buildup than previous papers (doubling q 3-7 days instead of 2-3 weeks), & allowed to continue buildup despite tingling

Dijkema D et al. J Allergy Clin Immunol Glob. 2024 Ma

Case: home-based apple oral immunotherapy (OIT)

- 8 yo boy with peanut/tree nut allergy
  - Doing well on maintenance OIT to peanut, cashew, hazelnut, walnut, macadamia
- Apple PFAS
  - Sensitized to tree/grass pollen (no history of allergic rhinoconjunctivitis)
  - Past 1-2 years, throat itch and 7/10 ear itch if eats apple with skin (Ok with whole peeled apple), e.g.) Ambrosia
  - SPT: Ambrosia 4.5mm, Fuji 8mm, Honey crisp 9mm, Jazz 9mm, Pink Lady 4mm, Red Delicious 5mm
- Home-based apple OIT
  - Start daily maintenance dosing with whole peeled Ambrosia apple

PFAS take home messages

- PFAS is generally a low risk condition
- Clinical diagnosis
  - SPT with raw food +/- component testing can be considered
- Although uncommon, systemic reactions may occur
  - to stable allergens (LTP)
  - to labile allergens (PR-10 and profilins): due to co-factors
  - carry an epinephrine device
- Home-based OIT for labile allergens very feasible (safe and minimal impact on clinic). More research needed on efficacy.

*Take home message

Thank you

FAIT PROGRAM

Food Allergy Immunotherapy