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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*

BACKGROUND: Pollen-food allergy syndrome (PFAS) is common among patients with allergic rhinitis. Treatment recommendations for patients with PFAS remain variable.

OBJECTIVE: To develop consensus recommendation statements for managing patients with PFAS.

METHODS: An international panel of allergists, researchers, and nutritionists with an interest in PFAS from 25 different institutions across 11 countries convened and a list of statements was written by 3 authors. The RAND/University of California Los Angeles methodology was adopted to establish consensus on the statements.

[a]Section of Allergy, Asthma & Immunology, Department of Medicine, Penn State College of Medicine, Hershey, Pa
[b]Department of Pediatrics, Division of Allergy and Immunology, Icahn School of Medicine at Mount Sinai, New York, NY
[c]Department of Pediatrics, Hassenfeld Children's Hospital, NYU R. Grossman School of Medicine, New York, NY
[d]Department of Pediatrics, Gastroenterology and Nutrition, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland
[e]Division of Allergy and Immunology, The Children's Hospital of Philadelphia, Philadelphia, Pa
[f]Immunology and Allergy Unit, Department of Medicine, Campbelltown Hospital and Western Sydney University, Sydney, New South Wales, Australia
[g]University of Antwerp, Faculty of Medicine and Health Sciences, Department of Immunology, Allergology, Rheumatology and the Infla-Med Centre of Excellence, Antwerp (Belgium) and Immunology, Allergology, Rheumatology, Antwerp University Hospital, Antwerp, Belgium
[h]Department of Immunology and Allergology, AZ Jan Palfijn Gent, Ghent, Belgium
[i]Department of Allergy and Clinical Immunology, 424 General Military Training Hospital, Thessaloniki, Greece
[j]Southdale Allergy and Asthma Clinic, Minneapolis, Minn
[k]Department of Pediatrics, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea
[l]Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Man, Canada
[m]Children's Hospital Research Institute of Manitoba, Winnipeg, Manitoba, Canada
[n]Basic and Clinical Immunology Unit and CINTESIS@RISE, Faculty of Medicine, University of Porto, Porto, Portugal
[o]Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Columbia University Irving Medical Center, New York, NY

Abbreviations used
AAAAI- American Academy of Allergy Asthma & Immunology
AIT- Allergen immunotherapy
BSACI- British Society of Allergy and Clinical Immunology
DBPCFC- Double-blind placebo-controlled food challenge
DI- Disagreement index
EAI- Epinephrine autoinjector
Ig- Immunoglobulin
NSAIDs- Nonsteroidal anti-inflammatory drugs
OIT- Oral immunotherapy
PFAS- Pollen-food allergy syndrome
PPI- Proton pump inhibitor
REDCap- Research Electronic Data Capture
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy

RESULTS: After 2 Delphi rounds, a consensus was reached on 14 statements. The panel agreed that patients with PFAS would benefit from counseling on the nature and basis of PFAS and the rare chance of more severe systemic reactions and their recognition. The panel agreed on avoiding the raw food responsible for the index reaction, but not potentially cross-reactive fruits/vegetables based on the responsible food of the index reaction. Epinephrine autoinjectors should be recommended for patients with PFAS who experienced severe symptoms (beyond the oropharynx) or for patients considered at risk for severe reactions. The panel agreed that the benefit of allergen immunotherapy remains unclear and that PFAS should not be considered the primary indication for such intervention.
CONCLUSIONS: We developed consensus statements regarding counselling patients about the nature and severity of PFAS, potential risk factors, dietary avoidance, epinephrine autoinjector prescription, and allergen immunotherapy consideration for patients with PFAS. © 2024 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2024;12:3242-9)

Key Words: *Pollen-food allergy syndrome; PFAS; Oral allergy syndrome; OAS; Delphi consensus; PFAS management*

INTRODUCTION

Pollen-food allergy syndrome (PFAS) or pollen-food syndrome, previously known as oral allergy syndrome (OAS), is a syndrome of type I hypersensitivity to plant-based foods secondary to pollen sensitization.[1] The PFAS is characterized by a constellation of symptoms often limited to the oropharynx, such as oropharyngeal pruritus, and angioedema and is frequently observed among patients with pollinosis.[1] The estimated prevalence of PFAS varies by geographic region, paralleling the prevalence of pollen sensitization ranging from 2% to 10.8%.[2-7] The PFAS occurs owing to the structural homology and consequent cross-reactivity between pollen proteins and heat-labile proteins, such as pathogenesis-related class 10 proteins and profilins, found in plant-based foods.[8] Owing to the nature of these cross-reactive panallergens, which are largely heat- and acid-labile, symptoms are generally limited to the oropharynx, and systemic type I hypersensitivity reactions, including anaphylaxis, are extremely rare.[9] Nonetheless, some patients can develop more severe and even systemic symptoms and certain risk factors or cofactors have been implicated as increasing the risk of such severe manifestations.[10]

The current management approach to patients with PFAS includes dietary avoidance, epinephrine autoinjector (EAI) prescription, and consideration of allergen immunotherapy (AIT); however, these practices and recommendations vary considerably and there are no conclusive studies to guide such treatment recommendations.[11-14] To address this unmet need, the American

[p]Section of Allergy and Clinical Immunology, Department of Medicine, Dartmouth Hitchcock Medical Center, Geisel School of Medicine, Lebanon, NH
[q]Department of Allergology and Pulmonology, National Research Institute of Tuberculosis and Lung Diseases, Rabka-Zdroj, Poland
[r]Department of Pathophysiology, Institute of Medical Sciences of Rzeszow University, Rzeszow, Poland
[s]Department of Respiratory Medicine, JSS Medical College, JSSAHER, Mysore, Karnataka, India
[t]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY
[u]Allergy Clinical Unit, Department of Medicine and Dermatology, Hospital Regional Universitario de Málaga-UMA-IBIMA, Málaga, Spain
[v]Allergy and Asthma Consultants, Indianapolis, Ind
[w]Department of Food Science and Technology, University of Nebraska-Lincoln, Lincoln, Neb
[x]Department of Pediatrics, Medical City Children's Hospital, Dallas, Texas
[y]Department of Pediatrics, University of Nebraska Medical Center, Omaha, Neb
[z]Clinical Research Center for Allergy and Rheumatology, NHO Sagamihara National Hospital, Kanagawa, Japan
[aa]Royal Brompton & Harefield Hospitals, part of Guys & St. Thomas National Health Services (NHS) Foundation Trust, London, UK

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Corresponding author: Taha Al-Shaikhly, MBChB, FACAAI, FAAAAI, Section of Allergy, Asthma & Immunology, Department of Medicine, Penn State College of Medicine; 500 University Dr., PO Box 850, Hershey, Pa 17033. E-mail: talshaikhly@pennstatehealth.psu.edu.

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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

Academy of Allergy, Asthma & Immunology (AAAAI) Plant Food Allergy Workgroup of the Adverse Reactions to Foods Committee set out to develop consensus management statements to guide practicing physicians caring for patients with PFAS. These statements are focused on patients with PFAS with sensitivity to the heat-labile pathogenesis-related class 10 or profilin antigens.

METHODS

Panel selection

An international panel of 25 experts with a particular interest in PFAS (allergists, scientists, and dietitians) from 25 different institutions across 11 countries convened and participated in a Delphi consensus process. This was conducted electronically using Research Electronic Data Capture (REDCap), an electronic data capture tool, hosted at Penn State Health Server.[15]

The Delphi consensus process

We followed the RAND/University of California Los Angeles methodology.[16] During the first round of the Delphi consensus process, participants were asked to rate the level of appropriateness/agreement of 22 statements pertinent to PFAS management using a scale of 1 (extremely inappropriate or strongly disagree) to 9 (extremely appropriate or strongly agree). These statements were generated based on a review of the literature and previously published practice management guidelines. These statements covered different domains such as education, dietary avoidance, treatment of acute reactions, need for EAI prescription, and AIT. Participants had the option of indicating "nonapplicable" if they did not have the expertise to rate a particular statement. Participants were also given the option to submit comments and suggest statement revision if they rated a particular statement less than 7.

For each statement, we calculated the median appropriateness level, and each statement was categorized as either inappropriate (median appropriateness level of 1−3.4), uncertain (median appropriateness level of 3.5−6.9), or appropriate (median appropriateness level of 7.0−9.0). We also calculated the disagreement index (DI) as previously described.[17] A DI of less than 1 was used to indicate agreement among the group. In the second Delphi round, experts ranked the level of appropriateness of new and revised statements. A consensus or acceptable statement for inclusion in our final management statements was defined as having a median appropriateness level of at least 8 and a DI of less than 1. We used these stringent criteria because our goal was to generate statements that are more likely to be adopted by practicing clinicians. A consensus was reached after the second round; therefore, a third round was not conducted. Authors T. Al-S., I. S., and A. N.-W. drafted the initial and revised statements. Further, we examined comments and incorporated these into the Discussion section.

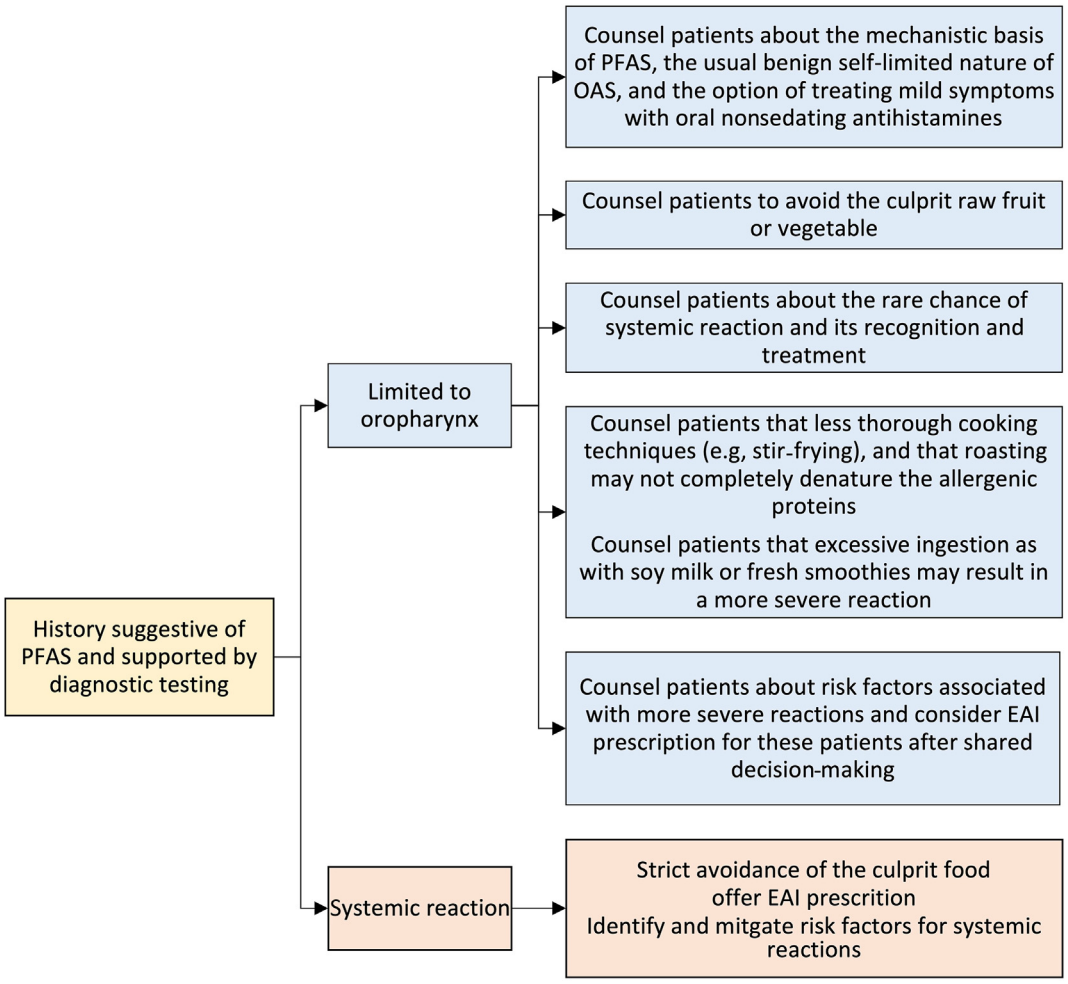

FIGURE 1. Approach for managing patients with PFAS. *OAS,* Oral allergy syndrome.

RESULTS AND DISCUSSION

In total, 22 statements were distributed electronically, and all 25 panel members responded to the first Delphi round. The level of appropriateness and DI of the original 22 statements are presented in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). Of the initial 22 statements, 14 revised/new statements were drafted considering the results and feedback received during the initial round. These 14 statements were then distributed for a second Delphi round and nearly all panel members (23 of 25; 92%) responded. Two members were not available during the second round. A consensus was reached on the revised 14 statements. These statements are presented here verbatim except for subtle modifications to ensure consistent language and terminology across the manuscript (Table I). In particular, the panel members favored the use of PFAS as a more proper terminology in lieu of the old designation OAS. Using these statements, we suggest an algorithm for the management of PFAS (Figure 1).

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.
- 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).

Understanding the mechanism of PFAS could reinforce for patients the benign nature of PFAS and the basis of dietary and treatment recommendations. Anaphylaxis as a manifestation of PFAS was first reported to only affect 1.7% of patients with PFAS,[3] although, subsequently, other studies have reported a much higher figure.[6,18] In a nationwide study on PFAS in Korea by Kim and colleagues,[18] 8.9% experienced anaphylaxis. In another study from Italy, 5% of patients with PFAS experienced systemic symptoms.[6] Considering this, the panel agreed that patients should be offered the opportunity to learn about the mechanistic basis of PFAS and be made aware that PFAS is

rarely severe and often limited to the oropharynx. Although experts considered that sharing information about more severe reactions with patients with PFAS may provoke undue anxiety among PFAS patients, the panel agreed that it was important for patients to be aware that there is a rare chance of systemic reaction including anaphylaxis. Patients with PFAS need to be aware that severe reactions are more likely during the corresponding peak pollen season.[19] Although there is a low risk of anaphylaxis among those with PFAS, these patients would nonetheless benefit from education about the signs and symptoms of severe reactions. Although not addressed in our Delphi consensus process, the panel notes that confirming PFAS with prick-to-prick testing with fresh food could be especially important in patients with more severe reactions and that, when feasible, consideration of component-resolved diagnostics to elucidate primary sensitization or sensitization to more stable components, such as the nonspecific lipid transfer protein, as identifying such sensitization could alter treatment recommendations.[11]

The panel agreed to counsel patients with PFAS that certain foods and factors may be associated with increased severity of PFAS reactions and to educate patients that avoiding these factors, when possible, might serve as an opportunity to mitigate their rare risk of more severe reactions. Several case reports and studies have attempted to explore factors associated with the rare risk of severe PFAS reactions, particularly drug risk factors.[10,20] In a multicenter, retrospective study aimed at identifying cofactors associated with systemic reactions to labile plant-food allergens, the authors identified that the use of PPIs was more prevalent among patients with PFAS who experienced systemic reactions.[10] The NSAID use was similarly more prevalent among patients with systemic reactions (3% vs 0%), but this was not statistically significant.[10] In another study evaluating adult patients with acute hypersensitivity reaction to NSAIDs, authors identified a subset of patients with history of PFAS limited to the oropharynx who experienced systemic reactions related to coexposure to NSAIDs and had no reaction upon drug challenge to the culprit NSAID without ingesting the food.[21] Ingestion of peanuts, tree nuts, fasting, and excessive ingestion such as with liquid forms (eg, soy beverages, and fresh smoothies) were also factors associated with systemic reactions.[10] Wolters and colleagues[20] described 9 patients with PFAS who had bariatric surgery and experienced systemic reactions to Rosaceae fruit, tree nuts, and peanuts that were either tolerated completely or caused only mild oropharyngeal symptoms before gastric bypass surgery. In another study, 2 of 18 patients with PFAS transitioned from experiencing only mild oropharyngeal symptoms to more generalized allergic reactions after gastric bypass surgery.[22] Lastly, although not specifically examined in the context of PFAS, alcohol consumption, exercise, and uncontrolled asthma are recognized cofactors for food-induced anaphylaxis and might, therefore, increase the severity of PFAS reactions.[21,23]

Dietary avoidance and food-processing recommend ations

- 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 stir-frying) may be insufficient to fully denature the allergens relevant to PFAS.
- 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.

Avoidance of the culprit food is a key consideration in the management of immunoglobulin E (IgE)—mediated food allergy.[12] However, the nature of cross-reactive proteins responsible for PFAS, being both heat- and acid-labile, and the consequent self-limited nature of the PFAS reaction, which is often confined to the oropharynx, requires special consideration.[3] There is considerable variability among U.S. allergists in their recommendations regarding dietary avoidance.[14] In 1 survey study of U.S. allergists, 53% recommended complete avoidance of responsible food, but approximately 40% indicated a case-by-case approach.[14] In a survey of health care professionals in the United Kingdom, 80% recommended avoidance of the triggering food.[24] In this Delphi exercise, the panel agreed that avoidance of the raw form of the culprit fruit/vegetable is advisable for most patients, particularly those with a history of systemic reaction, for whom strict avoidance of the culprit food is recommended. Although these foods are easily identifiable, the panel members pointed to the major risk of inadvertent ingestion in "juice bars" and commercial salads. Aside from avoiding the plant-derived food responsible for the index reaction, the panel disagreed that patients with PFAS should be provided with a list of fruits and vegetables that they may potentially react to on the basis of their index reaction history (Table E1). The panel cited the positive health impact of ingesting fruits and vegetables[25] and the concern of provoking undue anxiety.[26] The panel cautioned that such a practice might lead to unnecessary avoidance. On the contrary, 1 of the panel members suggested offering a graded challenge should the patient have a concern. Similarly, the avoidance of the cross-reactive fruit/vegetable based on the original food inciting the reaction did not meet our appropriateness cutoff of greater than 7 (Table E1).

Whereas a few panel members acknowledged that some patients with mild PFAS may tolerate the responsible raw fresh fruit or vegetable and only experience tolerable symptoms, a consensus was reached that patients should only consider ingesting the culprit fruit and vegetable when well-cooked, tinned, or as jams. Patients should be educated about the ineffectiveness of only removing the peels and of lighter cooking techniques such as steaming or stir-frying in completely denaturing the allergen responsible for PFAS and that roasting may similarly be inadequate in removing the culprit allergen responsible for nut-induced PFAS.[27] In a double-blind, placebo-controlled food challenge (DBPCFC) with roasted hazelnuts (140°C for 40 min) performed on 17 birch pollen—allergic patients, 5 of 17 experienced PFAS.[28] In another study, 17 of 20 patients developed PFAS after the DBPCFC with roasted hazelnut.[29] However, both of these studies indicated a higher threshold dose for eliciting a reaction.[30] Because the process of

nut roasting is not standardized, and there might be a high risk of cross-contamination in roasting facilities, in combination with the lack of studies demonstrating absolute tolerability of roasted nuts in patients with PFAS, patients would benefit from education on this fact to avoid false reassurance.[30]

Treatment of acute reactions and consideration of EAI prescription

- 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.

Because anaphylaxis has been reported secondary to PFAS, patients with PFAS might benefit from measures to mitigate the risk of severe reactions.[6,18] In addition to cofactors that have been specifically associated with the occurrence of systemic reactions in patients with PFAS such as the use of PPIs, NSAIDs, other generic factors commonly linked to severe food-induced anaphylaxis (eg, uncontrolled asthma), or factors linked to refractory anaphylaxis (e.g., the use of β-blockers or angiotensin-converting enzyme inhibitors) would need to be identified and, when possible, mitigated to lessen the risk of anaphylaxis from PFAS.[10,20,23] The panel acknowledged that these medications could be important to patients' overall health and, thus, a shared decision-making balancing the risks and benefits of continuation versus discontinuation of such medications along with the involvement of the respective specialty are advisable.

- Statement 11. Mild symptoms of PFAS limited to the oropharynx often resolve without treatment; a nonsedating antihistamine can be used for uncomfortable symptoms.

Symptoms of PFAS that are confined to the oropharynx are often self-limited to 30 minutes or less and do not require treatment with medication.[31] However, antihistamines are frequently advised by treating physicians with 18 out of 28 otolaryngologists indicating that they would recommend antihistamines as a treatment for PFAS in 1 survey study.[32] Further, the panel members considered that oropharyngeal symptoms might induce panic and apprehension that could further exacerbate throat symptoms with complaints that the throat is tightening or becoming restricted. Taken together, whereas the panel agreed that patients should be reassured of the self-limited nature of PFAS, nonsedating antihistamines may be used by patients who experience uncomfortable symptoms. This is in line with the British Society of Allergy and Clinical Immunology (BSACI) guidelines for the diagnosis and management of PFAS in the United Kingdom.[11] Although there is no supporting evidence, in theory, liquid or chewable nonsedating antihistamines may act more rapidly in relieving the oropharyngeal symptoms of PFAS.[33]

- Statement 12. The 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 should be offered.
- Statement 13. 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.

An EAI is a lifesaving intervention in patients with anaphylaxis due to food.[23] However, our panel members raised concerns about the cost and reluctance of some patients to carry an EAI.[34] Although anaphylaxis is considered a rare manifestation of PFAS,[18] 82 out of 122 U.S. allergists surveyed indicated that they would prescribe EAI for patients with PFAS on a case-by-case basis, with symptoms affecting the throat being the most common reason for prescribing EAI followed by facial edema and generalized urticaria.[14] A higher proportion of otolaryngologists consider EAI prescription. Of the 28 otolaryngologists who were familiar with PFAS, 14 prescribed EAI.[32] The tendency to prescribe EAI is less common among U.K. allergists (18% of the surveyed allergists).[24] In keeping with the 2014 practice parameter update on food allergy, which suggests prescribing EAI in patients with PFAS with a history of laryngeal swelling or respiratory compromise,[12,23] a consensus has been reached among panel members that patients with PFAS who have experienced a systemic reaction would benefit from EIA.

Because several studies and anecdotal reports suggested that certain factors could be associated with increased severity of PFAS reaction,[10,20,22,23] the panel agreed that for patients with PFAS who have nonmodifiable risk factors for systemic reactions (eg, gastric bypass surgery or asthma) a shared decision-making regarding the prescription of EAI should be adopted.[10] As the burden of carrying an EAI was cited by panel members as 1 reservation to prescribing EAI, the novel noninjectable epinephrine forms (intranasal, sublingual) under development may alter the threshold for prescribing rescue epinephrine for patients with PFAS.[35]

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.

Subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) are effective in alleviating symptoms of allergic rhinitis, allergic conjunctivitis, allergic asthma, and atopic dermatitis.[36,37] The benefit of AIT in alleviating symptoms of PFAS remains uncertain. Limited studies have explored the utility of SCIT for the treatment of PFAS.[38-48] Whereas several small-scale studies suggested benefit from SCIT in completely or partially alleviating symptoms of PFAS,[38,39,42,45,47] other studies failed to demonstrate such benefits or only a fraction of patients benefited from this intervention.[40,43,46,48] In a DBPCFC study, 1 year of AIT with the folding variant of recombinant Bet v 1 in 56 patients with birch-related soy allergy resulted in a higher threshold for eliciting objective signs of reaction; however, results were not statistically significant.[49] Further, resensitization to apple occurred after discontinuation of SCIT, although persistent tolerance has also been reported.[50] Taken together, the small sample size of studies exploring SCIT as a treatment for PFAS and the focus of these studies on apple-induced PFAS in birch-sensitive individuals limit the overall generalizability of these study findings.

Even more limited studies have explored the impact of aeroallergen SLIT on PFAS.[46,51-53] In 1 small study from Kinaciyan and colleagues,[52] 9 patients with apple-induced PFAS received SLIT with birch pollen extract (administered as drops; maintenance dose, 4.5 μg Bet v 1), which was successful in ameliorating their rhinoconjunctivitis symptoms, but symptoms of apple-

induced PFAS did not significantly decrease.[52] Authors noted that, although specific IgE and IgG4 to Bet v1 were increased, Mal d 1−specific IgE and IgG_4 levels were not altered, concluding that SLIT did not alter the immune response to the pollen-related food allergen.[52] However, subsequent studies were more promising. In an open-label observational study of 102 patients with pollen-induced rhinoconjunctivitis and PFAS, approximately 75% of patients responded to SLIT with a decrease in their symptom score of 50% or greater, and PFAS was rated as much or very much improved in approximately 73% of these patients.[51] In another placebo-controlled study, investigators randomized patients with PFAS to either a placebo or a sublingual tree pollen tablet and examined the impact of SLIT on PFAS through an open-label challenge to apple, noting improved tolerance suggesting a beneficial effect for SLIT.[53] *De novo* PFAS to apple, with progression to peaches, cherry, and carrot, has been reported in 1 40-year-old female patient a few months after starting birch-specific SLIT.[54] Considering the limited evidence for both SCIT and SLIT as a treatment for PFAS, consensus was reached that PFAS should not be considered an indication for AIT. In patients with allergic rhinoconjunctivitis, clinicians should counsel patients that there is insufficient evidence that pollen-specific AIT alleviates PFAS. Future larger studies with DBPCFC and assessment of such intervention on quality of life are needed to characterize the benefit of pollen AIT in PFAS, and as suggested by 1 panel member, whether AIT in early childhood would prevent the onset of PFAS.

Other treatment considerations

Other considerations that did not meet the consensus criteria included oral immunotherapy (OIT) and omalizumab use for PFAS. The OIT has transformed our approach to patients with peanut allergy.[55] The role of OIT in patients with PFAS has been explored. In 1 study, 40 birch-sensitive patients with allergic rhinitis and PFAS limited to the oropharynx were randomized to either daily consumption of incremental amounts of raw apple or no treatment (avoidance), and after 8 months, 17 out of the 27 patients randomized to active apple consumption were able to tolerate 128 g of apple as opposed to 0 patients in the placebo arm, suggesting a role for OIT in the management of PFAS.[56] Another phase II pilot study evaluated the effectiveness of incremental daily apple consumption in 16 patients with birch-pollen allergy. After 8 months, a provocative challenge demonstrated increased tolerance to apple and was accompanied by a decrease in skin reactivity to apple.[57] A SLIT with recombinant Mal d 1, but not with recombinant Bet v1 reduced clinical reactivity to apple.[58,59] Similarly, in a case series of 7 patients, sublingual drops with increasing concentrations of profilin resulted in decreased skin test wheal size in 5 patients and promoted tolerance to several foods that they could not tolerate before the induction phase in all 7 patients.[60] In our Delphi exercise, agreement among the panel members has been reached that OIT might be offered in a research capacity; however, the appropriateness level did not meet our cut off greater than 7 (Table E1).

Few cases have been reported of patients with PFAS who responded to omalizumab therapy, an anti-IgE monoclonal antibody. One described a birch-sensitive individual with apple-induced PFAS and another described an individual who experienced intractable lip edema and was sensitive to multiple fresh fruits including orange, apple, peach, and tomato.[36,61] Given the prohibitive cost of omalizumab, and limited evidence to support the use of omalizumab, the panel did not agree on using omalizumab for the sole purpose of treating PFAS (Table E1).

CONCLUSIONS

Through an international Delphi exercise, we established a consensus to guide treatment recommendations for patients with PFAS. Our panel members agreed on educating patients about the mechanistic basis of the disease, emphasizing the usual benign self-limited nature of the reaction, while providing the necessary education for prompt recognition of a worsening reaction and its treatment, recommending avoidance of the culprit raw plant-derived foods, discussing appropriate treatment options, and considering shared decision-making when prescribing EAI for patients who have experienced severe reactions or have risk factors for severe reactions. At present, there is insufficient evidence to recommend PFAS as an indication for AIT (Figure 1).

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ONLINE REPOSITORY

TABLE E1. Round 1 Delphi exercise*

Statement	Appropriateness, median	Disagreement index (DI)
Individuals with pollen-food allergy syndrome (PFAS) should be educated about the mechanistic basis of their PFAS.	9	0.132
Patients with PFAS should be reassured that reactions in PFAS are mostly benign, limited to the oropharynx (oral allergy syndrome OAS]), and self-limited.	9	0.132
Patients with PFAS should be cautioned about the possibility of rare severe reactions.	9	0
Patients with PFAS should be provided with a list of fruits and vegetables that they may potentially react to on the basis of their index reaction history.	7	0.379
Patients with PFAS should be educated about cofactors for severe reactions including medications (eg, PPIs, NSAIDs), bariatric surgery, and exercise.	9	0.257
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	0.146
Avoiding only the raw fruit/vegetable responsible for the index reaction should be recommended for individuals with PFAS	8	0.164
Avoiding the raw fruit/vegetable responsible for index reaction and its related fruits/vegetables should be recommended for individuals with PFAS.	6	1.613
Patients with PFAS irrespective of their index reaction severity (OAS or beyond) may continue to ingest the responsible fruit and vegetable if well-cooked or roasted.	6	2.103
Patients with PFAS limited to oral symptoms (OAS) may continue to ingest the responsible fruit and vegetable if well-cooked or roasted.	8	0.14
Patients should be advised that lighter cooking methods (eg, steaming or stir-frying) may be insufficient to denature the allergens.	8	0.132
Patients should be educated on the higher allergen contents in the peels and seeds of fruits but cautioned that peeling and removing the seeds is usually insufficient to prevent symptoms of PFAS.	8	0.132
Individuals with PFAS limited to oral symptoms (OAS) should be advised to self-treat with a nonsedating antihistamine.	8	0.313
Individuals with a history of systemic symptoms (defined as having symptoms that extend beyond the oropharynx) should be supplied and educated on how to use epinephrine autoinjector (EAI).	9	0.012
Individuals with PFAS and irrespective of the severity of their reported reaction and who have risk factors for systemic reactions (using gastric acid suppressive medications, gastric bypass surgery, narrow oropharyngeal anatomy) should be supplied and educated on how to use the EAI.	7	0.327
Individuals with PFAS should be educated to use EAI if they had accidental ingestion of the culprit fruit/vegetable and experience symptoms such as difficulty breathing, wheezing, lightheadedness, or hives in addition to oral pruritus.	9	0
Subcutaneous or sublingual pollen-specific immunotherapy might be discussed as an option for treating pollen-food syndrome in patients without allergic rhinitis, allergic conjunctivitis, or allergic asthma symptoms.	6	2.128
Patients seeking pollen-specific subcutaneous or sublingual immunotherapy for their allergic rhinitis or conjunctivitis should be counseled that pollen immunotherapy might also improve symptoms of an oral allergy syndrome.	7	0.561
Subcutaneous or sublingual pollen immunotherapy might be discussed as an option for treating pollen-food syndrome in patients with symptoms of allergic rhinitis or allergic conjunctivitis.	7.5	0.560
Individuals with PFAS may be offered oral immunotherapy only in a research capacity.	7	0.164
Omalizumab might be offered to patients with PFAS as a treatment strategy.	5	1.290
Patients receiving omalizumab for treating asthma, chronic urticaria, and chronic rhinosinusitis with nasal polyposis should be counseled that omalizumab might also lessen the severity of their oral allergy syndrome.	7	0.183

DI, Disagreement index; *EAI,* epinephrine autoinjector; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *OAS,* oral allergy syndrome; *PFAS,* pollen-food allergy syndrome; *PPIs,* proton pump inhibitors.

*Bolded statements did not meet criteria for inclusion (DI $>$ 1 or median appropriateness $<$ 8).