Food allergy across the globe

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1. To recognize emerging guidelines regarding prevention of food allergy in children.
2. To understand important trends in food allergy management.
3. To identify challenges to implementing emerging therapies for food allergy.

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The prevalence of food allergy (FA) is increasing in some areas of the globe, highlighting the need for better strategies for prevention, diagnosis, and therapy. In the last few decades, we have made great strides in understanding the causes and mechanisms underlying FAs, prompting guideline updates. Earlier guidelines recommended avoidance of common food allergens during pregnancy and lactation and delaying the introduction of allergenic foods in children aged between 1 and 3 years. Recent guidelines for allergy prevention recommend consumption of a healthy and diverse diet without eliminating or increasing the consumption of allergenic foods during pregnancy or breast-feeding. Early introduction of allergenic foods is recommended by most guidelines for allergy prevention after a period of exclusive breast-feedng (6 months [World Health Organization] or 4 months [European Academy of Allergy and Clinical Immunology]). New diagnostics for FA have been developed with varied availability of these tests in different countries. Finally, the first oral immunotherapy drug for FA was approved by the US Food and Drug Administration and European Medicines Agency in 2020. In this review, we will address the global prevalence of FA, our current understanding of the causes of FA, and the latest guidelines for preventing, diagnosing, and treating FA. We will also discuss similarities and differences between FA guidelines. (J Allergy Clin Immunol 2021;148:1347-64.)

Key words: *Food allergy, guidelines, prevention, treatment, epidemiology*

Food allergy (FA) prevalence is increasing in some regions of the world.[1,2] However, geographical variability in the incidence, type, and clinical presentation of FA as well as variations in symptoms and clinical phenotypes due to race, ethnicity, age, and coexisting allergic diseases exist.[3,4]

The increasing incidence of FA in certain regions of the world has spurred efforts to understand the causes and mechanisms underlying FA and tolerance to optimize diagnostics and find ways to prevent or treat FA. Early guidelines recommended dietary avoidance or delayed introduction of allergenic foods in infants to prevent FAs.[5] However, later studies either did not see a benefit of delayed introduction or indicated that early introduction may potentially be beneficial in preventing FA. Findings from recent studies of early-life dietary interventions for FA prevention have led to revised guidelines, moving away from an avoidance approach of allergenic foods to actively recommending introduction of allergenic foods in the first 4 to 6 months of life.[6-8] A number of novel diagnostics have been developed, but these are still mainly performed in research laboratories and not readily available. In 2020, Palforzia, an oral immunotherapy drug for peanut allergy, obtained US Food and Drug Administration approval. This was an important milestone for FA therapy because it was the first-ever drug approved for the treatment of FA. Palforzia, a biological oral immunotherapy drug for FA, is composed of peanut allergen powder for the treatment of peanut allergy.[9]

We have gained valuable insights into FA over the last few years regarding the causes and the mechanisms of FA as well as new developments into diagnostics, prevention strategies, and treatments. The aim of this article was to provide an overview of the incidence of FA, causes, prevention strategies, diagnostic methods, and recommendations for therapies in FA, and report on global similarities and differences in FA guidelines.

EPIDEMIOLOGY OF FA

More than 160 foods are known to cause FAs, with varying prevalence rates by specific food and population affected.[10-12] Large population-based studies using double-blind placebo-controlled food challenges (DBPCFCs), the criterion standard for the diagnosis of FA, hold promise for accurate FA prevalence assessment; however, DBPCFCs and oral food challenges (OFCs) are resource-intensive and pose risk of severe allergic reactions, thereby raising concerns about low participation rates among participants and selection bias. Therefore, prevalence data using OFCs are very limited.[13] A 2013 survey of 89 countries found that only 10% of countries had prevalence data based on OFC.[14] Instead of OFCs, surrogate markers are often used for determination of FA. These include self-reported clinical history of FA, clinical or hospital visits for FA, or determination of allergen-specific IgE (sIgE) either by skin prick test (SPT) or by serum sIgE. sIgE tests are associated

Abbreviations used
AAAAI: American Academy of Allergy, Asthma & Immunology
APT: Atopy patch test
ASCIA: Australasian Society of Clinical Immunology and Allergy
DBPCFC: Double-blind placebo-controlled food challenge
EAACI: European Academy of Allergy and Clinical Immunology
FA: Food allergy
OFC: Oral food challenge
OIT: Oral immunotherapy
QOL: Quality of life
sIgE: Allergen-specific IgE
SPT: Skin prick test

with high rates of false positives, leading to overestimation. A false-positive diagnosis carries the risk of nutritional deficiency and significantly impacts quality of life (QOL). Misdiagnosis also leads to an increased economic burden on the health care system, with increased costs associated with specialist referral, additional testing, and unnecessary medication prescriptions. Self-reporting of FAs also leads to overestimation because these may also include food intolerances or toxicities. For example, a study found that 14% of families reported a milk allergy in their infant, but milk allergy could be confirmed in only 1.4%.[15]

The Melbourne HealthNuts and SchoolNuts studies are large population-based studies with challenge-confirmed FA. These studies provide the highest quality of prevalence data and show rates of more than 10% in infants[16] and 4% to 5% in older children and young adolescents.[17,18] However, a limitation of the HealthNuts study is that it clinically evaluated only a few of the food allergens—egg, peanut, sesame, cow's milk, and shrimp in infants. The SchoolNuts study evaluated only 15 food allergens.

In the United States, 2 large (N > 38,000) cross-sectional well-designed population-based surveys have been conducted. Reported FAs were considered as convincingly IgE-mediated if reported symptoms to specific allergens met well-defined criteria consistent with IgE-mediated reactions. The studies found that 7.6% of children[19] and 10.8% of adults had probable FA.[20] In children with FA, 40% were affected by more than 1 FA. The study has the potential of overdiagnosing FA because vomiting is one of the self-reporting symptoms, which is not exclusive for FA. It is also a symptom of food protein–induced enterocolitis syndrome, early-onset eosinophilic esophagitis, and other food intolerances.

Initial reports on the prevalence of FA in Europe did not consider the wide variety of eating habits of the various geographical areas and cultures. Data were available for specific countries or regions, with extrapolations for other areas. The EuroPrevall research project addressed this diversity by applying the same methodology in various centers across the continent.[21,22] In the study, children with suspected FA symptoms were diagnosed via OFCs and sIgE (SPT or serum measurements). Birth cohorts with more than 12,000 participants revealed a mean incidence at age 2 years of 1.23% for hen's egg allergy, with country-specific incidence from 0.07% in Greece to 2.18% in the United Kingdom[23] and 0.54% for cow's milk allergy (ranging from <0.3% in Lithuania, Germany, and Greece to 1% in the Netherlands and the United Kingdom).[24] The types of FAs differed substantially between countries, with fish and shrimp allergy being more prevalent in the Mediterranean area and in Iceland, and nuts, fruits, and vegetable allergies being more prevalent in Central Europe.[25] Among the children in the EuroPrevall studies, 23.6% had non–IgE-mediated cow's milk allergy, with most children in the United Kingdom reporting non–IgE-mediated cow's milk allergy, whereas the Netherlands reported no child with non–IgE-mediated cow's milk allergy. In this study, non–IgE-associated cow's milk allergy was defined as cow's milk allergy diagnosed by DBPCFC with sIgE to milk less than 0.35 kU/L and SPT wheal diameter less than 3 mm.[24]

In many Asian countries, South and Central America, and Africa,[26] FA is thought to be uncommon; however, reliable epidemiological data are limited.[27,28] An epidemiological investigation of FA in an urban area of Wenzhou, China, found FA prevalence to be at least 0.84% among children aged 3 to 6 years based on OFC and sIgE or SPT.[29] Using a definition of probable FA as reporting allergic symptoms within 2 hours of ingestion of a specific food plus the presence of allergic sensitization to the specific food (positive sIgE and/or positive SPT result), the EuroPrevall-INCO surveys found that the prevalence of FA was 1.50% (Hong Kong), 0.21% (Guangzhou, China), 0.69% (Shaoguan, China), and 0.14% (India).[27]

In Africa, most studies use sensitization as a surrogate marker for allergy[26] or are performed in high-risk populations. The South African Food Allergy study is the sole study using challenge-proven FA as an outcome in an unselected population.[30] The study showed marked urban-rural differences, with the prevalence of FA of 2.5% in children aged 1 to 3 years in Cape Town, but only 0.5% in the rural Eastern Cape.[31] Unusual allergens may occur in various parts of Africa, including Mopane worms,[32,33] and there are areas in Africa with high rates of both sensitization to galactose-α-1,3-galactose and allergy to mammalian meat (galactose-α-1,3-galactose syndrome).[34]

The studies of prevalence in South and Central America mostly use parent-proxy or self-reported allergic reaction symptoms, with few studies measuring SPT wheal diameter. Prevalence rates reported in these studies range between 0.9% and 52%.[35-43] Foods that trigger these reactions are similar to those in other parts of the world although in some countries such as Mexico, Costa Rica, and Colombia, sensitizations to tropical vegetables and fruits have been found.[40,42,44] In tropical regions of South America, oral mite syndrome (due to mite-contaminated wheat flour) has been described and in a case series study in Venezuela represented the third most reported cause of anaphylaxis.[45] Recently, more studies on oral allergy syndrome and galactose-α-1,3-galactose allergy are also being reported in Mexico and Colombia, respectively.[46,47]

It should be noted that the data relied on to estimate global FA prevalence are subject to substantial limitations, most notably the nonspecificity of proxy measures of allergic sensitization (eg, SPT and sIgE) and lack of concordance between survey-reported and food challenge–confirmed prevalence estimates. However, the overall consensus is that FA has significantly increased in developed countries, potentially due to changes in environmental exposures and lifestyle. The study by Botha et al[31] using OFCs to confirm a diagnosis of FA found a significant increase in the prevalence of FA between children born in urban and rural areas. This suggests that urbanization is leading to increases in FA.

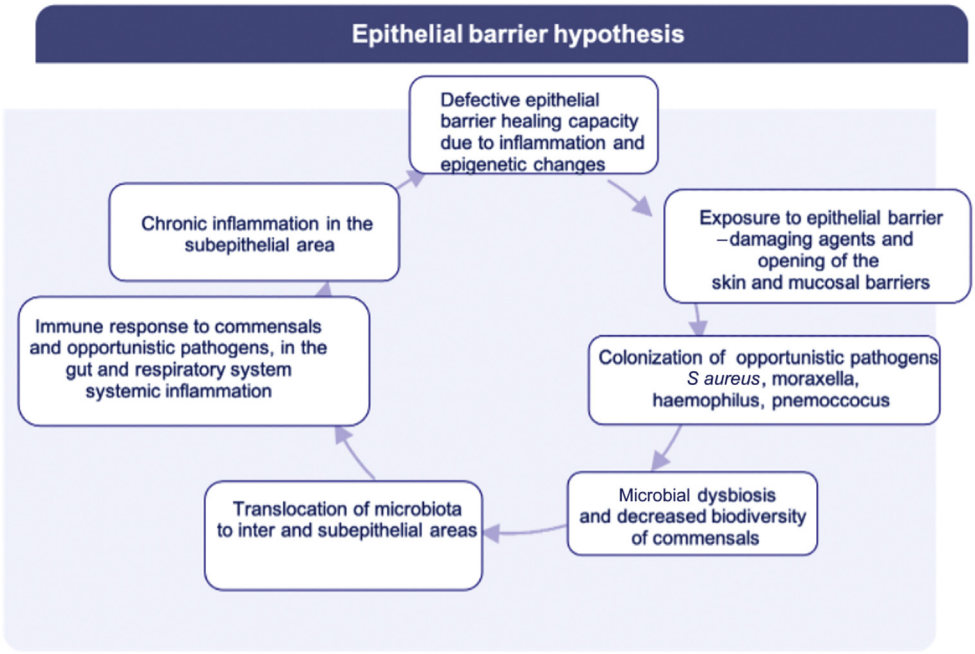


FIG 1. The physiopathology of epithelial barrier hypothesis: The facit circle of chronic epithelial barrier leakiness. Genetic defects in barrier-related molecules or exposure to epithelial barrier–damaging agents cause an opening of the skin and mucosal tight junction barriers. This is followed by translocation of microbiota to inter and subepithelial areas and colonization of opportunistic pathogens, such as *Staphylococcus aureus*, moraxella, haemophilus, and pnemoccocus. An immune response develops toward commensals and opportunistic pathogens in the gut and respiratory system and a systemic inflammation takes place. In most cases of allergic diseases, a systemic type 2 inflammation predominates, and is directed against not only allergens but also commensals and opportunistic pathogens. For example, anti–*S aureus* antibodies show a very high prevalence in asthma chronic rhinosinusitis and atopic dermatitis. This is associated with microbial dysbiosis and decreased biodiversity of commensals. Chronic inflammation in the subepithelial area prevails, as one of the main reasons for the development of chronic diseases in the affected tissues. Defective epithelial barrier healing capacity due to inflammation and epigenetic changes take place, instigating a vicious circle of leaky barriers, microbial dysbiosis, and chronic inflammation.

Although high-quality prevalence data for FA are lacking for many geographical regions and age groups, increases in FA prevalence are supported by hospitalization rates for FA. A nationwide survey in the United States of hospitalization due to pediatric food-induced anaphylaxis found a significantly increasing trend from 1.2 per 100,000 children in 2006 to 1.5 per 100,000 children in 2012. The leading causes of hospitalizations due to food-induced anaphylaxis were peanut, followed by tree nuts and seeds, and milk products.[48] In Australia, a 4-fold increase in hospitalizations for FA-related anaphylaxis was observed between 1998/1999 and 2011/2012 (2.0-8.2 per 100,000).[49] However, additional studies using standardized methodologies are necessary for accurate detection of FA to better understand the true extent of the problem and its impact on health services.

CAUSES OF FA

FA is a complex immune disorder caused by specific genetic variants in combination with environmental and nutritional exposures. Genome-wide association studies have found certain loci for FA including genes involving barrier integrity (filaggrin and serine protease inhibitor), immune function, and others.[50-53] However, the increase in FA is too rapid to be due to genetics alone, and migration studies show us that these increases can occur in a single generation.[54] Epigenetics provides a framework for understanding the mechanisms by which environmental and nutritional factors interact with genetic factors to mediate FA.

Innate lymphoid cells, which contribute to type 2 immune responses, have also been implicated in mediating FA. Innate lymphoid cells are localized at barrier surfaces of the airways, gut, and skin and form a link between innate and adaptive immunity.[55]

A number of studies have evaluated the role of nutrition and diet in the development of FA.[56] There is strong evidence that early introduction of allergens in infants, such as the introduction of peanut or egg beginning at age 4 to 6 months, prevents the development of FA.[57] For milk, the window of opportunity is probably much earlier—while infants fed cow's milk formula from birth rarely develop cow's milk allergy, allergy is seen in infants who are temporarily supplemented during the first week of life with avoidance thereafter.[56,58] Less is known about the development of FA in later life although anecdotally, novel FAs are seen in populations when new foods are introduced into the national diet.[59] Besides allergens, other dietary factors that have

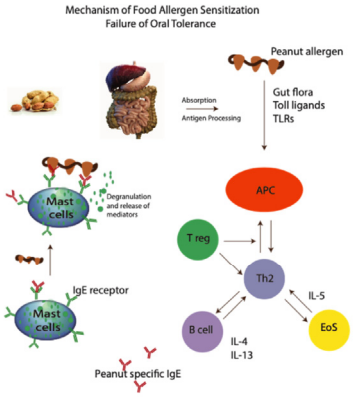
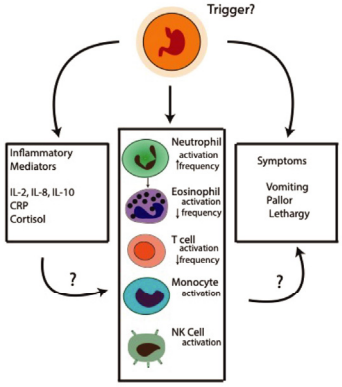
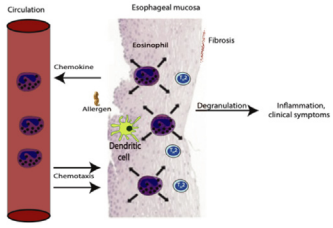
Types of FA	Representative patient	Mechanism	Risk Factor	Incidence Global variability
IgE-mediated,	Peanut anaphylaxisis		Atopy, acute reactions, infections, exercise, alcohol etc,	1%-10%, depending on age, large variability by allergens globallyipsum
Non–IgE-mediated,	Acute FPIES with milk allergy		Family history, short duration of breast-feeding, ethnicity?	0.15%-0.7%, by 2 years of age
Mixed (IgE non–IgE-mediated),	Eosinophilic esophagitis		Atopy, early-life antibiotic exposure, family history	10-57/100,000

FIG 2. Example of IgE-mediated, non–IgE-mediated, and mixed IgE- and cell-mediated FAs along with their prevalence, mechanisms, and examples of causal allergens. *FPIES*, Food protein–induced enterocolitis syndrome. Figures for IgE-mediated, non–IgE-mediated, and mixed adapted from Otsu and Dreskin,[78] Brown-Whitehorn and Cianferoni,[79] and Mulder and Justinich,[80] respectively.

been associated with FA are prebiotics, probiotics, vitamin D, and omega-3 polyunsaturated fatty acids. However, the evidence for these associations is weak. Although specific microbiome patterns are associated with FA or tolerance,[60] the role of prebiotics, probiotics, or symbiotics in mediating these effects is not well understood.

Allergens, certain bacteria, fungus, viruses, laundry and dishwasher detergents, household cleaners, surfactants, enzymes and emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, and microplastics all disrupt the epithelial barrier.[61-72] According to the epithelial barrier hypothesis (Fig 1), exposure to many of these substances damages and initiates inflammation around the epithelium that covers the surface of the skin, and respiratory, urogenital, and gastrointestinal tracts.[73] Epithelial cell activation and release of epithelial cell cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin, play a major role in the development and exacerbation of allergic diseases.[74,75]

The importance of a diverse microbiome in reducing the risk of FA is now recognized. A greater number of siblings and

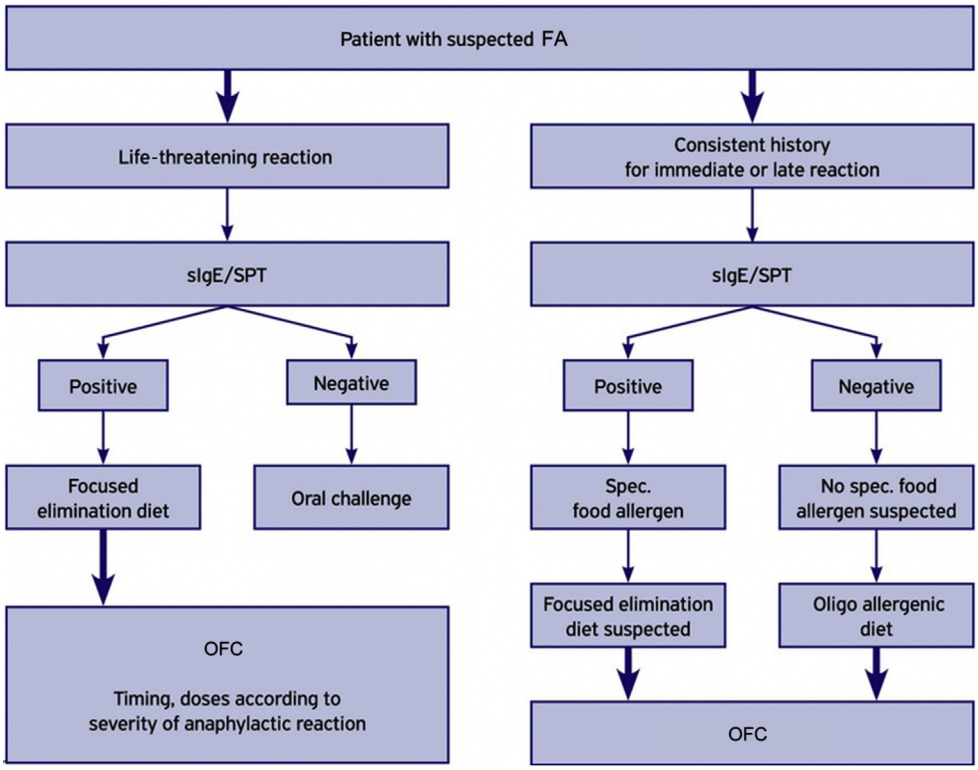


FIG 3. EAACI Diagnostic guidelines in 2014.

dog ownership, both of which can increase microbial diversity, have been associated with a reduced risk of developing FA.[76,77]

Clearly, the causes of FA are multifactorial and are likely to result from a complex interaction of genetic, dietary, and environmental factors. Arguably, at present, the 2 most important risk factors for FA development early in life are skin barrier dysfunction and delayed introduction of allergenic solids. However, remarkably little remains known about the determinants and mechanisms of adult-onset FA, wherein oral tolerance is lost among patients who previously tolerated the offending food without incident. In many cases of adult-onset FA to previously tolerated foods, there is a period of abstention to the food (either instructed by physician often due to atopic dermatitis or the initiation of a new exclusionary diet, before onset of adult-onset FA). Furthermore, many of the putative causal mechanisms outlined above have not been extensively tested in human subjects via well-designed randomized controlled trials and therefore are of limited utility, both clinically and for informing policies aiming to reduce the public health burden of FA.

DIAGNOSTICS

FAs are primarily IgE-mediated; however, mixed IgE- and cell-mediated, and non–IgE-mediated FAs also exist. Fig 2 list examples of IgE-mediated, non–IgE-mediated, and mixed IgE- and cell-mediated FAs along with their prevalence, and mechanisms.

The international criterion standard for FA diagnosis is the DBPCFCs. However, because these are time and resource-intensive and pose risk of severe allergic reactions, other surrogate diagnostic tests are often used.

In Europe, the 2014 European Academy of Allergy and Clinical Immunology (EAACI) Guidelines for FA Diagnosis were developed according to the Institute of Medicine/Guidelines International Network reference, involving all the relevant stakeholders and combining the level of evidence with the experts' opinion, when evidence was lacking. Grades A to D recommendations were created on the basis of level of evidence available, with D indicating when experts' opinion had to complement the existing data. The EAACI algorithm for FA diagnosis (Fig 3) includes 5 essential steps: (1) the patient's clinical history with the use of structured questions (Grade D), (2) determination of sensitization with standardized SPT and/or sIgE directed by case history as well as the use of molecular allergology with component-resolved diagnostics to better profile the patient (Grades A-C) (3) elimination diet for diagnostic purposes, that is, short-term avoidance 2 to 4 weeks (Grade D), (4) an OFC to definitely confirm or exclude the diagnosis (Grade D), and (5) evaluation for non–IgE-mediated FA when the history is convincing and SPT result and sIgE are negative (Grade D).

In the United States, the 2010 Guidelines for the Diagnosis and Management of Food Allergy recommends the use of SPT or sIgE to evaluate FA.[81] They do not recommend the use of intradermal testing, total serum IgE, or the atopy patch test (APT). The guidelines stated that a combination of 2 or more of SPT plus

TABLE I. Global FA documents on prevention of FA since 2002

Year	North America	Australia and New Zealand	Europe	Asia
2004			EAACI[95]	
2005		ASCIA[96]		
2006	ACAAI[5]			
2007			ESPGHAN[97]	
2008	AAP[98]		EAACI[99]	
2009			DGAKI and DGKJ[100]	
2010	NIAID[101]	ASCIA[102]		AMS-MOH[84,103]
2012			Finnish Allergy Program 2008-2018[104]	
2013	CPS and CSACI[105]			
2014			DGAKI, DGKJ,[106] and EAACI[107]	
2015	AAP[108]			GLAD-P[109]
2016			ISPAI and ISP[110]	HKIA[111,112] and GLAD-P[113]
2017	NIAID[114]		BSACI[115] and ESPGHAN[116]	JSPACI,[117] PSAII, and PSPGHN[118]
2018			BSACI,[119] SACN, and COT[120]	APAPARI[87]
2019	AAP,[98] CPS, and CSACI[121]	ASCIA[122]		AMSMOH[123]
2020			EAACI[57]	JSPACI,[86] Chinese Expert Consensus,[124] ISPGHAN[125]
2021	AAAAI, ACAAI, and CSACI[6]			MAP[126]

AAP, American Academy of Pediatrics; *ACAAI*, American College of Asthma, Allergy and Clinical Immunology; *AMSMOH*, Academy of Medicine, Singapore Ministry of Health; *APAPARI*, Asia Pacific Association of Pediatric Allergy, Respirology & Immunology; *BSACI*, British Society of Allergy and Clinical Immunology; *COT UK*, Committee on Toxicity United Kingdom; *CPS*, Canadian Pediatric Society; *CSACI*, Canadian Society of Allergy and Clinical Immunology; *DGAKI*, German Society for Allergology and Clinical Immunology; *DGKJ*, German Society for Pediatric and Adolescent Medicine; *ESPGHAN*, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; *GLAD-P*, World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention; *HKIA*, Hong Kong Institute of Allergy; *ISP*, Italian Society of Pediatrics; *ISPAI*, Italian Society of Paediatric Allergy and Immunology; *ISPGHAN*, Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition; *JSPACI*, Japanese Society of Pediatric Allergy and Clinical Immunology; *MAP*, Malaysia Allergy Prevention; *NIAID*, National Institute of Allergy and Infectious Diseases; *PSAII*, Philippine Society of Allergy, Asthma and Immunology; *PSPGHN*, Philippine Society for Paediatric Gastroenterology, Hepatology and Nutrition; *SACN*, Scientific Advisory Committee on Nutrition.

serum allergen-specific sIgE and/or APTs marginally improved positive and negative predictive values, but did not obviate the need for DBPCFC. The guideline, however, did not recommend the use of a combination of tests over the use of sIgE or SPT alone. Food elimination diets may be useful particularly in the diagnosis of non–IgE-mediated and mixed IgE/non–IgE-mediated FA, where no diagnostic test can otherwise identify the causative food. However, for definitive diagnosis, DBPCFCs were cited as the criterion standard for diagnosing FA, with allowance for single-blind and open challenges to be used in the clinical setting. The 2010 guideline states that further studies are necessary to determine the efficacy of food allergen epitope specificity and component protein–based assays. The diagnosis of eosinophilic gastrointestinal diseases is supported by dietary elimination, OFC, endoscopy, and esophageal biopsy. SPTs, sIgE tests, and APTs are not diagnostic but can be used to support the diagnosis. Food protein–induced enterocolitis syndrome, food protein–induced allergic proctocolitis, and food protein–induced enteropathy syndrome can be diagnosed by medical history in combination with an elimination diet, and an OFC. Allergic contact dermatitis and systemic contact dermatitis can be diagnosed by a combination of medical history, including resolution of symptoms when the causative food is avoided, and positive patch test results, whereas the diagnosis of IgE-mediated contact urticaria is supported by history, including the absence of symptoms while the causative food is avoided, positive sIgE test results or SPT results, and positive immediate epicutaneous skin test results (eg, positive immediate responses to APTs).

Similar to international approaches, a thorough clinical history that considers the symptoms indicative of IgE-mediated allergic reactions to food is the first-line approach in diagnosing FA in Australia. Second-line, evidence-based *in vivo* (SPT) and *in vitro* (sIgE) investigations of sensitization are essential adjunct tools, which the Australasian Society of Clinical Immunology and Allergy (ASCIA) specifically advises should be used only in conjunction with clinical history. In carefully selected patients to confirm or exclude FA, medically supervised OFCs are performed. Recently, because of the increased use of widely available online allergy testing services, ASCIA has written a position paper that strongly recommends against using online allergy tests,[82] due to potential harm (even if evidenced-based tests are ordered because advice is given in the absence of personal consultation), resulting in misdiagnosis, ineffective treatments, increased costs for the patient or caregiver, and a greater burden on the health care system. In Australia, most pediatric allergy clinics use SPT in preference to sIgE testing because results are immediately available. Consistently, SPTs have been shown to have a high sensitivity, but low specificity, and so more accurate diagnostic testing is being actively researched.

National guidelines of South and Central America are represented by a minority of the total of 36 countries. Clinical

history and physical examination are considered the most important step to proceed with further laboratory investigation; OFC is the criterion standard for diagnosis. Mexico and Chile local guidelines seem to follow the same general recommendations as Brazil.

The few Asian guidelines that discuss diagnosis of FA mention taking a good history, a careful physical examination, the use of food diaries, and elimination diets (where appropriate) as the first steps. This is followed by performing SPTs, measurement of specific IgE, and conducting OFC as needed.[83-86] Predictive threshold values for SPTs and food-specific IgE are lacking in Asian populations, and this is an important unmet need because it is unlikely that data accrued from other ethnicities can be used in Asia.[87] In fact, one of the challenges in the diagnosis of FA in Asian countries is that many countries are resource-limited, both in the number of trained allergy specialists and in access to SPT reagents, laboratory facilities, and food challenge set-ups.[26,88] Countries that do not currently have a national allergy specialty training and accreditation program should see this as a priority for their health care needs.

There are many diagnostics tests that are used to support diagnosis, although not recommended by current guidelines. However, some of these tests are available only in specialized centers and not available in many countries.[86] Component-resolved diagnostics (measuring IgE to specific food allergen components) is becoming increasingly used for confirming peanut allergy when tests of sensitization are in the middle range (SPT wheal diameter 3-8 mm or sIgE 0.35-15 kUA/L).[89] Ara h 2–specific antibody levels used following SPT or whole peanut sIgE in a 2-step algorithm were shown to successfully reduce the need for OFCs by almost two-thirds.[90] Other examples of component-resolved diagnostics include Ana o 3 for cashew, Gal d 1, 2, 3, and 5 for egg,[91] and Cor a 9 and Cor a 14 for hazelnut allergy.[92,93] Other specialized and research-based tests include allergen-specific IgG_4 determination and basophil activation tests. Specialized tests such as component-resolved testing, basophil activation measurements, and endoscopy for non–IgE-mediated FA are available only in select countries.[86]

Although recent diagnostic advances (eg, component-resolved diagnostics, basophil activation testing, and allergenic epitope-specific IgE[94]) hold considerable promise for improving accuracy and reliability of FA diagnosis in settings where OFC is impractical, their limited global availability and technical laboratory requirements render them of limited utility in many clinical and epidemiological contexts. Furthermore, the diagnostic validity of these emerging methods remains unknown within many subpopulations, and reference values (eg, sensitivity, specificity, and 95% positive predictive value) are unavailable for many key allergens. Therefore, further work—much of which is ongoing—is still needed to refine these approaches before their more widespread utilization.

PREVENTION OF FA

Guidelines regarding timing of introduction of allergenic foods have undergone dramatic changes as new data have emerged in the last few years. Table I lists FA prevention guidelines from around the world. Table II highlights key recommendations from a few international guidelines. Although some earlier studies[129-131] and guidelines recommended allergen avoidance during pregnancy and lactation, these were not supported by later studies.[132] The 2019 American Academy of Pediatrics Clinical Report specifically states that there is a lack of evidence to support deliberate maternal exclusion of high-risk allergens during pregnancy and while breast-feeding for the purposes of preventing allergic diseases, including FA.[98] There is now consensus among current guidelines, which predominantly recommend that women should consume a healthy diet in accordance with dietary recommendations for the general population and do not recommend eliminating or increasing the consumption of potentially allergenic foods during pregnancy or breast-feeding as a strategy for preventing the development or clinical course of FA.

Similarly, early guidelines recommended dietary avoidance or delayed introduction of allergenic foods in infants to prevent FAs. It was hypothesized that increased permeability of the immature infant gut would increase sensitization on allergen ingestion.[133] However, a number of subsequent studies showed either no benefits of allergen avoidance or benefits of early allergen consumption.[134] The 2015 Learning Early About Peanut Allergy[135] was a large trial in infants at high risk of allergy, and it demonstrated that early introduction of peanut was significantly associated with reduced risk of peanut allergy, and that peanut allergy was 5 times more likely in children who avoided peanuts. The 2016 Enquiring About Tolerance[136] study compared the effect of early introduction of the 6 most common childhood food allergens (cow's milk, hen's egg, peanut, sesame, cod fish, and wheat) after exclusive breast-feeding and showed the benefits with cooked egg. Subsequent to the publication of these 2 pivotal studies that reported that early introduction of egg and peanut was associated with reduced risk of egg and peanut allergy, FA prevention guidelines were reevaluated, which resulted in many guidelines reversing previous recommendations of allergen avoidance, and instead recommending early introduction of allergenic foods. A number of guidelines now recommend introduction of common food allergens between age 4 and 6 months[57,98,136]; however, some guidelines recommend not delaying the introduction[86] of allergen or introduction during the first year of life.[122] A few guidelines recommend screening before allergen ingestion in high-risk infants.

In 2017, the National Institute of Allergy and Infectious Diseases–sponsored expert panel reversed guidelines and recommended early introduction of peanut for infants who are deemed at risk of developing peanut allergy by virtue of their early-onset hen's egg allergy and/or eczema.[114] In 2019, the American Academy of Pediatrics issued a clinical report concluding that there is no evidence that delaying the introduction of allergenic foods, including peanuts, eggs, and fish, beyond age 4 to 6 months prevents FA and indicated that there is now evidence that early introduction of peanuts may prevent peanut allergy.[98] In 2021, a consensus approach to the primary prevention of FA was published, endorsed by the American Academy of Allergy, Asthma & Immunology (AAAI), the American College of Allergy, Asthma and Immunology, and the Canadian Society for Allergy and Clinical Immunology.[6] Among all infants irrespective of risk, it recommends introduction of cooked egg and peanut at around age 6 months, but not before 4 months of life, at home when the infant is developmentally ready. For other allergens, it recommends not deliberately delaying introduction because there are no data showing harm with introduction of other allergens in the first year of life (but also

TABLE II. Comparison of international FA prevention guidelines

	International FA guidelines			
Topic	**ASCIA 2017[127]**	**NIAID 2017[114]**	**Commission on Toxicity (COT) UK 2018[120,128]**	**APAPARI 2018[87]**
Foods of relevance	All foods	PN	PN	All foods
BF	BF: at least 6 mo and for as long as mother and infant wish to continue		EBF for around the first 6 mo of life	Continue BF up to 2 y
High-risk definition	Infants with severe eczema and/or egg allergy	Infant s with AD and/or HE FA	Infants with a history of early-onset AD or suspected FA	Infants with severe eczema
Pregnant/BF mother	Healthy diet Excluding any foods (including allergenic) not recommended Up to 3 serves of oily fish p/w No recommedation on probiotics			
Introduction of solid foods	All infants: when infant is ready: around 6 mo, but not before 4 mo		CF: introduce in an age-appropriate form from around 6 mo	Healthy infants: complementary foods at 6 mo
Introduction of allergens	All infants should be given allergenic solid foods including PN, cooked HE, dairy, and wheat in first year—includes HR HR: Good evidence: regular PN intake <12 mo can reduce PN allergy. Mod evidence: cooked HE <8 mo (family history of allergy), reduce developing HE allergy	Different PN introduction schedules depending on risk: between 4 and 6 mo in infants with severe AD and/or HE allergy; around 6 mo in infants with mild to moderate AD; family and cultural feeding practices should be followed in infants with no AD or FA	GR: PN and HE need NOT be differentiated from other CF Exclusion of PN and HE beyond 6-12 mo may increase risk of FA to these foods HR may wish to seek medical advice before introducing PN and HE	High-risk infants with family history of allergy: introduction of allergenic foods should not be delayed. High risk with severe eczema: SPT and/or OFC to PN and egg may be required. Introduction of allergenic foods should not be delayed
Continued intake		PN protein to be regularly consumed per week should be approximately 6-7 g over 3 or more feedings	Once introduced, PN and HE should be part of the infant's usual diet. If initial exposure is not continued, this may increase the risk of sensitization and FA	
Formula	Hydrolyzed (partially and extensively) infant formula is not recommended for prevention of allergic disease. If BF is not possible, use std cow's milk formula		Does not support the use of hydrolyzed cow's milk formulas, either exclusively or partially hydrolyzed, to influence the risk of developing allergic or autoimmune disease	
Other				

ACAAI, American College of Asthma, Allergy and Immunology; *AD*, atopic dermatitis; *APAPARI*, Asia Pacific Association of Pediatric Allergy, Respirology & Immunology; *BF*, breast-feeding; *BSACI*, British Society of Allergy and Clinical Immunology; *CF*, complementary foods; *COT UK*, Committee on Toxicity United Kingdom; *CSACI*, Canadian Society of Allergy and Clinical Immunology; *EBF*, exclusive breast-feeding; *F&V*, fruit and vegetables; *GR*, general risk; *HE*, hen's egg; *HR*, high risk; *JPGFA*, Japanese Pediatric Guideline for Food Allergy; *NIAID*, National Institute of Allergy and Infectious Diseases; *PN*, peanut.

International FA guidelines				
BSACI 2018[119]	American Academy of Pediatrics 2019[98]	Consensus statement: AAAAI, ACAAI, Canadian Society of Allergy and Clinical Immunology 2020[6]	European Academy of Allergy and Clinical Immunology (2004,[95] 2008,[99] 2014,[107] 2020[57])	JPGFA 2020[86]
PN and egg	All foods	All foods	All foods	All foods
EBF for around the first 6 mo of life and continue BF for first year	No conclusions can be made about the role of BF in either preventing or delaying the onset of specific FAs	EBF: recommended for all mothers, no association between EBF and prevention of FA	EBF for around the first 6 mo of life and continue BF for first year	No evidence that BF prevents FA
Infants with a history of early-onset AD or suspected FA		Consider infants: - infants with severe AD (highest risk) - mild to moderate AD, family history of atopy in either/both parents, or infants with 1 known FA potentially at some increased risk of developing FA (or an additional FA). FA often develops in infants who have no identifiable risk factors. No evidence to clearly support the younger sibling of a PN-allergic child is at increased risk of developing PN allergy, though such infants may be at risk of developing PN allergy secondary to delayed introduction of PN	(2004,[95] 2008,[99] 2014,[107] 2020[57]) Infants with 1 or 2 parents and/or older siblings with a history of atopic diseases 2020 Limited to PN Populations with high prevalence of PN allergy	Infants with eczema
Omega-3 fatty acids may help reduce the risk of atopic dermatitis in early life	Lack of evidence to support maternal dietary restrictions either during pregnancy or during lactation	Do not recommend maternal exclusion of common allergens We do support any food or supplement	Against: avoiding food allergens (2004,[95] 2008,[99]2014,[107] 2020[57])	Avoidance of allergens not recommended
From 4 mo on (HR) From around 6 mo when developmentally ready, not before 4 mo (GR)			All infants: some families choose to start complementary feeding between 4 and 6 mo (2004,[95] 2008,[99] 2014,[107] 2020[57])	All infants: around 5-6 mo (for all)
GR: PN and HE as part of the family diet HR: introduce HE and PN when ready; from 4 mo on; HE before PN	All infants: no evidence that delaying the introduction of allergenic foods, including PN, HE, and fish, beyond 4-6 mo prevents atopic disease. There is now evidence that early introduction of PN may prevent PN allergy (based on NIAID guidelines)	Introduce PN and cooked HE to all infants starting around 6 mo, not before 4 mo Do not delay introduction of other allergenic CF (cow's milk, soy, wheat, tree nuts, sesame, fish, shellfish) around 6 mo, not before 4 mo	All infants: introduce PN and well-cooked HE as part of CF from 4 to 6 mo of life (2020[57])	All infants/high risk: delayed introduction of FA not recommended
Once successfully introduced, continue to give the allergen food to baby regularly as part of their usual diet (eg, at least once per week)				
Soya-based or hydrolyzed infant formula is not recommended for prevention of allergic disease. If BF is not possible, use std cow's milk formula	Lack of evidence that partially or extensively hydrolyzed formula prevents atopic disease even HR	Do not use any HFs for prevention of FA or sensitization	There is no recommendation for or against hydrolyzed infant formulas Against: soy protein formula in the first 6 mo of life	Insufficient evidence on the usefulness of hydrolyzed milk in preventing the onset of FAs
		Infants should be fed a diverse diet, because this may prevent FA. No recommendation on prebiotics and probiotics	No recommendation for or against: vitamin supplements, fish oil, prebiotics, probiotics, or synbiotics in pregnancy when BF or in infancy; altering the duration of EBF; hydrolyzed infant formulas	No recommendation on probiotics during pregnancy

no data showing specific benefit). Before allergen introduction, such as peanut, preemptive screening is not required, but the guidance notes that the decision to screen is preference-sensitive. If screening is done, it is recommended that an OFC follows any positive result. Once allergens are introduced, ongoing regular ingestion for maintenance of tolerance is recommended (although noting insufficient evidence to support a precise dose and frequency of ingestion).

The Australian guidelines were updated in 2017 to actively recommend the introduction of allergenic foods including cooked egg and peanut in the first year of life.[127] Studies have shown high levels of adoption of this advice, with more than 80% of infants now introduced to peanut in the first year of life, with a median age of introduction of 6 months.[137] Whether the successful adoption of earlier introduction of allergenic foods has had an impact on the prevalence of FA and anaphylaxis is currently being investigated.

The EAACI updated its guidelines on the prevention of onset of development of FA in young children in 2020.[57] Previous guidelines were published in 2004,[95] 2008,[99] and 2014.[107] In 2019, the European Food Safety Authority Panel on Nutrition, Novel Foods and Food Allergens revised its Scientific Opinion of 2009 on the appropriate age for introduction of complementary feeding of infants.[138] A systematic review was carried out using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach[56] and based on this, guidelines were written using the Appraisal Guidelines for Research and Evaluation (AGREE II) framework. The key changes from the 2014 guidelines were for recommendation of introduction of peanut and well-cooked egg (between age 4 and 6 months) into the infant's diet as part of complementary feeding. The recommendations for egg and peanut were made for all infants regardless of risk status for the development of FAs, although it was noted that the high-risk infants would likely benefit more.

There is no consistent evidence that breast-feeding is effective for the prevention of allergic disease. However, for optimal health of the infant, the World Health Organization[57] and the EAACI[139] recommend exclusive breast-feeding for a minimum of 6 months and 4 months, respectively. Some guidelines recommend continuing breast-feeding alongside solid food introduction for up to 1[57,115] or 2 years[87] or as long as possible.[122] There is lack of strong evidence that partially or extensively hydrolyzed formula prevents atopic disease in infants and children, even in those at high risk for allergic disease, and discrepancy among guidelines exist, with major guidelines either not recommending their use,[57,115] or having no recommendations,[86] or recommending their use (for high-risk infants).[123] The EAACI guidelines also recommend against the use of regular cow's milk formula in the first week of life.[57]

Recommendations for the use of dietary supplements vary with guidelines. Currently available evidence does not indicate that probiotic supplementation reduces the risk of developing allergy in children. However, considering all critical outcomes in this context, the World Allergy Organization Guidelines for Allergic Disease Prevention guideline panel determined that there is a likely net benefit from using probiotics resulting primarily from prevention of eczema, but not FA.[113] Other guidelines that recommend their use include Singapore[84,103] and Hong Kong.[111,112] Current EAACI and ASCIA guidelines do not recommend their use.[57,122]

Diet diversity during infancy has been hypothesized to prevent FA, likely by exposing the gut microbiota to diverse foods, increased intake of fiber and nutrients, and promoting development of immune tolerance.[140] In 2014, the Protection Against Allergy Study in Rural Environments was the first to investigate the association between the introduction of several foods during the first year of life and the development of asthma, allergic rhinitis, FA, or atopic sensitization. Their hypothesis was that exposure in early life to diverse food antigens could increase maturation of the mucosal immune system and induce tolerance. The study evaluated diet diversity using 4 methods: minimum diet diversity (World Health Organization classification), food diversity, fruit and vegetable diversity, and food allergen diversity. Children were assessed for FA at 1, 2, 3, and 10 years. The study found that increased infant diet diversity, as measured by all 4 different methods, decreased the likelihood of developing FA. The study showed that the introduction of each additional food at age 6 and 12 months reduced by 10.8% and 33.2%, respectively, the odds of developing FA over the first 10 years of life.[141] A systematic review of diet diversity in infancy and childhood suggested that diet diversity in infancy may be associated with reduced allergy outcomes (including FA), but additional studies are required to define more clearly the role of diet diversity and diet patterns, while clearly adjusting for appropriate confounders.[142]

Current evidence suggests that allergic sensitization occurs through an impaired skin barrier, while consumption of these foods at an early age may result in tolerance (dual allergen exposure hypothesis). The loss of skin integrity is thought to enable penetration of allergens, pollutants, and microbes, leading to immune dysfunction and initiation of the allergic cascade and eventual formation of IgE. The immune dysfunction is thought to further exacerbate the impaired skin barrier, forming a vicious cycle. Research into skin emollient to protect the skin and prevent development of a proinflammatory atopic state, which could lead to the development of AD and subsequently, FA, is an active area of research.[143,144]

TREATMENTS

The most recent 2014 Practice Parameter from the Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology recommends absolute avoidance of the allergenic food(s) and preparedness for treatment with an intramuscular injection of epinephrine in case of reactions after inadvertent exposures in those with FA.[145] Nevertheless, oral immunotherapy (OIT) using off-the-shelf food products and allowing ingestion of the allergenic food is widespread in private practices in the United States. In January of 2020, the United States Food and Drug Administration approved Palforzia, which is the first drug ever approved for FA. Palforzia is an OIT drug for peanut allergy, in children aged 4 to 17 years, which mitigates the risk of allergic reactions, including anaphylaxis, due to accidental peanut ingestion. The drug consists of a characterized peanut powder. Treatment includes ingestion of the contents of a series of capsules with increasing doses of peanut protein, leading to a daily maintenance dose sachet of 300 mg of peanut protein. Patients on Palforzia must continue with strict peanut avoidance and continue daily dosing to maintain protection. The Canadian Society for Allergy and Clinical Immunology has taken a notably

different approach and recommends OIT with off-the-shelf foods as a treatment to achieve desensitization to allergenic foods in toddlers through adolescents, and possibly in adults.[146] Uncontrolled asthma is an absolute contraindication to OIT, as is pregnancy in the Canadian Society for Allergy and Clinical Immunology guidelines.

The EAACI guidelines on IgE-mediated FA management, published in 2014, differentiates acute management from long-term strategies.[139] Appropriate dietary avoidance remains the cornerstone. Education is highlighted as a key point, including diet and emergency kit/management plan utilizations. In 2018, following a systematic review on food immunotherapy, the EAACI concluded that the major benefit of OIT is to increase the threshold of reaction, particularly for cow's milk, hen's egg, and peanut in children.[147,148] Concerns about safety were addressed, and careful monitoring for local and systemic anaphylactic reactions was recommended. As a consequence, the European guidelines restrict immunotherapy to research centers or clinical centers with substantial experience. Up to now, they do not support biologicals, such as omalizumab, alone or in association with immunotherapy. In December 2020, the European Medicines Agency also approved Palforzia for treating children aged between 4 and 17 years with peanut allergy.[149]

The current ASCIA guidelines on the treatment of FA are to adhere to strict allergen avoidance. At this time, there are no Therapeutic Goods Administration–approved FA treatments in Australasia. Few allergists in Australasia currently perform OIT due to concerns regarding high rates of reaction including anaphylaxis. However, it has now been observed that over the long-term, rates decrease.[150,151] The ASCIA Position Paper on OIT for FA[152] currently recommends against the use of OIT for the treatment of FAs, and highlights the need for additional studies to establish safety, tolerability, cost-effectiveness, QOL, and long-term outcomes. Several phase 2 studies are underway in Australia to evaluate whether the use of an adjuvant alongside OIT can improve efficacy and/or safety of OIT for treatment of peanut, egg, and milk allergies.[153-156]

Guidelines regarding the treatment of FA in Latin America are scarce, and all of them focused on the pediatric population.[157-161] Mexico and Chile have developed government-issued recommendations, the former for all groups of food allergens, while the latter specifically for cow's milk protein allergy. Other groups of experts from Argentina, Brazil, Colombia, and Latin America in general have published consensuses regarding different allergens. Most of these documents are based on international guidelines and do not necessarily reflect the characteristics of the Latin American population.[159-161] The common ground between most of these guidelines is the relevance attributed to the restriction of FAs both in the patient and in the lactating mother, the strategies that practitioners might use to avoid malnutrition, and the importance of treating anaphylactic episodes with intramuscular epinephrine.[157-161] The use of OIT and mAbs is supported by the Colombian, Brazilian, and Argentinian guidelines[159-161]; however, the latter also mentions the usefulness of some other types of immunotherapy, including sublingual and epicutaneous routes.[159] In addition, the Brazilian consensus recommends the induction of oral tolerance through baked foods, due to the good response that most patients present to baked allergens, especially milk and egg.[160] Because of the lack of regional references, it is imperative for Latin American associations to develop local studies to deliver focused recommendations for this specific population.

In Asia, the standard approach for the management of FA recommended by all guidelines is the avoidance of causative foods.[86,103,162-165] The more current guidelines mention OIT.[86,163,164] The Japanese guideline advocates minimum avoidance of causative foods, with recommendation for patients to take lower amounts of foods or hypoallergenic forms such as heated or cooked.[86] In Malaysia and Hong Kong, cow's milk allergy guidelines while recognizing the promise of OIT do not recommend it in routine clinical practice.[163,164] In Japan, the FA guideline describes OIT as an investigational intervention in patients with immediate-type FA in whom natural early acquisition of tolerance is not expected.[86] Furthermore, OIT must be approved by the relevant ethics committee and administered only with informed consent. Protocols for OIT vary between institutes and countries including the practice of low-dose OIT.[166]

Although an OIT drug for peanut allergy has been approved and OIT for other allergens show promise in clinical trials, there are practical considerations that still need to be addressed. OIT generally requires multiple clinic visits and treatment over many months to years to reach desensitization. The fear of adverse reactions from OFCs during screening is an additional barrier to initiation of therapy. For these reasons, there is a push toward "real-life" OIT studies where patients are enrolled without OFCs. In these patients, enrollment is based on history and positive serum sIgE or SPT results. To reduce the risk of allergic reaction, the maintenance dose reached after stepwise incremental increases in allergen was lowered. A study by Vickery et al[167] demonstrated that low-dose peanut OIT (300 mg/d) achieved similar sustained desensitization to those achieved by high-dose (3000 mg/d) treatment. For those with multiple FAs (about 45% of individuals with FA), OIT is even more burdensome, both in study duration and in frequency of clinical visits. To address this, research into simultaneous introduction of multiple foods during OIT is being investigated. Some multi-OIT protocols used in clinical trials pretreat patients with a short course of anti-IgE antibody, omalizumab, before the start of OIT. In a randomized placebo-controlled study by Andorf et al,[168] allergens used in multi-OIT were 1 or more of the following: cashew, walnut, hazelnut, almond, sesame, cow's milk, hen's egg, peanut, soy, or wheat. Multifood OIT with adjunctive omalizumab has been found not only to be safe and effective but also has been shown to rapidly decrease time to desensitization to multiple foods. Further research on safety and efficacy as well as optimization of omalizumab and multifood OIT dose and frequency is ongoing (NCT03881696). Research into combination of multi-OIT with a novel biologic, dupilumab, approved for atopic dermatitis is also ongoing (NCT03679676).

A major gap is whether OIT provides real-world benefit in terms of reducing reactions and improving QOL. A recent meta-analysis showed that in patients with FA, OIT is associated with an improvement in health-related QOL.[169] However, well-designed and long-term health-related QOL studies are necessary to ascertain sustained benefits of OIT.[169] Although tremendous strides in FA therapeutics have been taken in the past decade, much ground remains to be covered to meaningfully reduce the population-level burden of FA. For example, awareness of and

access to OIT remains low among the affected patient population —at least in the United States where these data were recently obtained from a nationally representative sample of patients with FA and caregivers.[170] Furthermore, concerns about the treatment burden of OIT have led to numerous innovations designed to reduce the risk of anaphylaxis and more rapidly induce desensitization, including the use of biologic, probiotic, and Chinese herbal adjunct therapies.[171] However, despite their promise, the effectiveness of these novel approaches in improving patient outcomes remains largely unknown. Finally, despite the current lack of Food and Drug Administration/European Medicines Agency–approved therapeutic options for patients with allergies besides peanut, numerous other immunotherapeutic approaches are under investigation—including sublingual and epicutaneous immunotherapies, vaccines, and biologic monotherapies.[172] The ultimate goal of prevention and treatment strategies should be to create a personalized approach of shared decision making, taking into account not only the individual's FA characteristics (severity, number, and type of allergenic foods) but also their comorbidities and impact on QOL.

FUTURE RESEARCH/CONCLUSIONS

FA guidelines across the globe have differences, some of which reflect regional, cultural, and societal preferences, whereas others are associated with organizational aspects of local health delivery systems. However, a common theme behind guidelines is the lack of clear scientific evidence for some important matters and, consequently, reliance on expert opinion; this underlines the need for future clinical research, particularly in the diagnosis, management, and prevention of FA.

Although clinical research in the field needs to reflect local needs, coordination with regard to methodology and analytic approaches will help overcome some of the differences that currently exist. This can be achieved by the formation of a global consortium of FA researchers who can design common clinical research protocols that could then be applied in various parts of the globe with modifications based on local reality. Specific major research areas requiring intensive and coordinated efforts in the next few years include the following: (1) Efforts to replace OFC as the criterion standard for diagnosis using simple algorithms that combine standardized clinical tools (questionnaires and laboratory testing); these will most likely need to be specific for each of the major allergenic food. Such efforts will also contribute to improving our ability to conduct accurate, reliable epidemiologic studies and track the incidence and prevalence of FA around the world, (2) standardization of OIT or development of other allergen immunotherapy approaches (eg, other forms of allergen exposure and allergen plus an immunomodulator) aiming at improved safety and ease of use and conferring the ability to switch from immunotherapy to natural food consumption, and (3) better identification of risk factors for development of FA such that women who are pregnant, planning to become pregnant, or lactating can be provided clear information about their and their infants' diet, including optimal timing and quantities of specific food introduction before switching to *ad lib* food consumption. In the long run, efforts should be directed toward development of improved methods (including genetic tests) for determining infants at high risk, development of nonallergen treatments, and improvements in dietary and environmental approaches to improve barrier function and microbiome structure and function across all epithelial barriers (gut, skin, nose, ear, lung) to prevent FA.

What do we know?

- **The incidence/prevalence of FA is rising in certain regions of the world.**
- **The presentations are getting more complex, more severe, stretching across many different immune mechanisms, and development of tolerance is delayed.**
- **Food allergen identification is often based on surrogate markers of sensitization rather than food challenge.**
- **Eliminating allergenic food consumption during pregnancy or breast-feeding for preventing sensitization is not recommended.**
- **Early intervention with active food allergen introduction and increased diet diversity might prevent FA.**
- **Early intervention with proper emollient care might prevent sensitization to foods.**

What is still unknown?

- **The spectrum of food allergens is not identified in some geographic locations.**
- **The impact of immigration, ethnicity, and genetic variability on the clinical expression of FA needs to be evaluated.**
- **There are still many dietary and environmental factors and their specific role in epithelial integrity and microbiome structure and function that need further clarification.**
- **The level of specific IgE that positively predicts clinical reactivity is not identified for many food allergens.**
- **In addition to sIgE/SPT, new biomarkers predicting FA phenotype are needed.**
- **Evidence-based diagnostic criteria for non–IgE-mediated FA are needed.**
- **Global acceptability of OIT and multi-OIT needs to be further assessed.**
- **Long-term efficacy of OIT needs to be determined.**
- **New therapies to try to treat food allergies are under investigation.**
- **Early biomarkers of treatment response are needed.**
- **Molecular mechanisms of food allergen tolerance and desensitization to be efficiently used in the clinical setting.**

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