**FOOD ALLERGY ACROSS THE GLOBE**

Vanitha Sampath1, PhD, Elissa M Abrams2, MD, MPH, Bahman Adlou, MS1, Cezmi Akdis3, MD, Mübeccel Akdis3, MD, PhD, Helen A Brough4, PhD, MBBS, FRCPCH, Susan Chan4, MBBS, MD, Pantipa Chatchatee5, MD, R. Sharon Chinthrajah, MD1, Renata Rodrigues Cocco6, MD, PhD, Antoine Deschildre7, MD, Philippe Eigenmann8, MD, Cesar Galvan9, MD, Ruchi Gupta10, MD, MPH, Elham Hossny11, MD, PhD, Jennifer J Koplin12, PhD, Gideon Lack4, MBBCH, FRCPCH, MD, Michael Levin13, MBBS, Lynette P Shek14, MBBS, FRCPCH, Mika Makela15, MD, PhD, David Mendoza-Hernandez16, MD, Antonella Muraro17, MD, PhD, Nikolos G. Papadooulos18, MD, PhD, FRCP, Ruby Pawankar19, MD, PhD, Kirsten P Perrett12, MBBS FRACP PhD, Graham Roberts20, DM, FRCPCH, Cansin Sackesen21, MD, Hugh Sampson22, MD, Mimi LK Tang12, MBBS, PhD, FRACP, FRCPA, Alkis Togias23, MD, Carina Venter24, PhD RD, Christopher Michael Warren10, PhD, Lisa M Wheatley23, MD, MPH, Gary WK Wong25, MD, FRCPC, Kirsten Beyer26, MD\*, Kari Nadeau1, MD, PhD\*, Harald Renz, MD, PhD\*27,28

\*: Co-senior authors

1Sean N. Parker Center for Allergy and Asthma Research at Stanford University and Division of Pulmonary and Critical Care Medicine, Department of Medicine, Stanford University, Stanford, CA, USA.

2Department of Paediatrics, Section of Allergy and Clinical Immunology, University of Manitoba, Winnipeg, MB R2A 5L9 Canada; Department of Paediatrics, Division of Allergy and Immunology, University of British Columbia, Vancouver, BC, Canada.

3Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.

4Department Women and Children's Health (Pediatric Allergy), School of Life Course Sciences, Faculty of Life Sciences and Medicine and Peter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, London, United Kingdom, and Children's Allergy Service and Evelina Children's Hospital, Guy's and St. Thomas's NHS Foundation Trust, Westminster Bridge Rd, London, United Kingdom.

5Pediatric Allergy and Clinical Immunology Research Unit, Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, Thailand.

6Albert Einstein Medical School, São Paulo, Brazil.

7CHU Lille, Univ Lille, Pediatric Pulmonology and Allergy Unit, Hôpital Jeanne de Flandre, 59000 Lille, France.

8University Hospitals of Geneva and University of Geneva, Switzerland.

9National Institute of Children Health, National Reference Center of Allergy, Asthma and Immunology, and International Clinic, B&D Health Clinic, Lima, Peru.

10Center for Food Allergy and Asthma Research, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA.

11Pediatric Allergy, Immunology and Rheumatology Unit, Children’s Hospital, Ain Shams University, Cairo, Egypt.

12Murdoch Children’s Research Institute and Department of Paediatrics, University of Melbourne, Melbourne, Australia.

13Division of Paediatric Allergy, Department of Paediatrics, University of Cape Town, Cape Town, South Africa; inVIVO Planetary Health Group of the Worldwide Universities Network (WUN).

14Department of Paediatrics, National University of Singapore, Singapore.

15Skin and Allergy Hospital, Helsinki University Hospital and University of Helsinki, Finland.

16Allergy Service, Instituto Nacional de Pediatria, Mexico City, Mexico

17Food Allergy Centre, Department of Woman and Child Health, Padua University hospital, Padua, Italy.

18Allergy Department, National and Kapodistrian University of Athens, Athens, Greece and Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, UK.

19Department of Pediatrics, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.

20Clinical and Experimental Sciences & Human Development in Health, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Hospital, Southampton, United Kingdom; and David Hide Asthma and Allergy Research Centre, St Mary’ Hospital, Isle of Wight, United Kingdom.

21Division of Pediatric Allergy, Department of Pediatrics, Koc University School of Medicine, Istanbul, Turkey.

22The Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Kravis Children's Hospital, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

23Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.

24Pediatric Allergy and Immunology, University of Colorado/Childrens Hospital Colorado

25Department of Pediatrics, Chinese University of Hong Kong, Hong Kong.

26Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charite Universitatsmedizin Berlin, Berlin, Germany.

27Institute of Laboratory Medicine, Philipps University Marburg, Member of the German Center for Lung Research (DZL), Member of Universities Giessen and Marburg Lung Center (UGMLC), Marburg, Germany.

28Department of Clinical Immunology and Allergology, Laboratory of Immunopathology, Sechenov University, Moscow, Russia.

Corresponding author: Kari C. Nadeau, MD, PhD, Director, Sean N. Parker Center for Allergy and Asthma Research at Stanford University, 240 Pasteur Dr. BMI Rm.1755, Palo Alto, CA 94304, USA. E-mail: [knadeau@stanford.edu](mailto:knadeau@stanford.edu).

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**ABSTRACT**

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 infants to between 1-3 years of age. 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 breastfeeding. Early introduction of allergenic foods is recommended by most guidelines for allergy prevention after a period of exclusive breastfeedng (6 months (WHO) or 4 months (EAACI)). 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 FDA and EMA 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.

ABBREVIATIONS  
AAAI: American Academy of Allergy, Asthma and Immunology

AAP: American Academy of Pediatrics

ACAAI: American College of Allergy, Asthma and Immunology

Alpha gal: Galactose-α-1,3-galactose

APT: Atopy patch test

ASCIA: Australasian Society of Clinical Immunology and Allergy

CSACI: Canadian Society for Allergy and Clinical Immunology

DBPCFC: Double-blind placebo-controlled food challenge

EAACI: European Academy of Allergy and Clinical Immunology

EAT: Enquiring About Tolerance

EFSA: European Food Safety Authority

EMA: European Medicines Agency

FA: Food allergy

FDA: Food and Drug Administration

FLG: Filaggrin

GIN: Guidelines International Network

IOM: Institute of Medicine

LEAP: Learning Early About Peanut Allergy

MALT1: Mucosal-associated lymphoid tissue lymphoma translocation

NIAID: National Institute of Allergy and Infectious Diseases

OFC: Oral food challenge

PPV: Positive predictive values

SAFFA: South African Food Allergy

sIGe: Allergen-specific IgE

SPT: Skin prick test

SERPINB7: Serine protease inhibitor

PASTURE: Protection Against Allergy Study in Rural Environments

QoL: Quality of life

TGA: Therapeutic Goods Administration

WAO: World Allergy Organization

GLAD-P: Guidelines for Allergic Disease Prevention

INTRODUCTION

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 co-existing 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 in order 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 labs and not readily available. In 2020, Palforzia®, an oral immunotherapy drug for peanut allergy obtained US FDA approval. This was an important milestone for FA therapy as it was the first-ever drug approved for treatment of FA. Palforzia®, a biological oral immunotherapy drug for FA , is comprised of peanut allergen powder for 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 new developments into diagnostics, prevention strategies, and treatments. The aim of this document is to provide an overview of the incidence of FA, causes, prevention strategies, diagnostic methods, and recommendations for therapies in FA and to report on global similarities and differences in FA guidelines.

**EPIDEMIOLOGY OF FOOD ALLERGY**

More than 160 foods are known to cause food allergies, 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 gold standard for 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 serum sIgE. sIgE tests are associated 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. 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 since 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 only be confirmed in 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 over 10% in infants16 and 4-5% in older children and young adolescents17, 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, two 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 children19 and 10.8% of adults had probable FA20. In children with FA, 40% were affected by more than one FA. The study has the potential of over diagnosing FA as 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 (FPIES), early onset Eosinophilic esophagitis (EoE) 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 over 12,000 participants revealed a mean incidence at 2 years of age of 1.23% for hen’s egg allergy with country specific incidence from 0.07% in Greece to 2.18% in the UK23 and 0.54% for cow’s milk allergy (ranging from <0.3% in Lithuania, Germany and Greece to 1% in the Netherlands and UK).24 The types of FAs differed substantially between countries. 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.25Among the children in the EuroPrevall studies, 23.6% had non-IgE mediated cow’s milk allergy with most children in the the UK 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 CMA was defined as CMA diagnosed by DBPCFC with sIgE to milk <0.35 kU/l and SPT <3 mm wheal diameter.24

In many Asian countries, South and Central America, and Africa26, 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 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 allergy26 or are performed in high-risk populations. The South African Food Allergy (SAFFA) 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 1-3 in Cape Town, but only 0.5% in the rural Eastern Cape.31 Unusual allergens may occur in various parts of Africa, including Mopane worms32, 33 and there are areas in Africa with high rates of both sensitization to galactose-α-1,3-galactose (alpha gal) and allergy to mammalian meat (alpha gal syndrome).34

The studies of prevalence in South and Central America mostly employ parent-proxy or self-reported allergic reaction symptoms with few studies measuring SPT. Prevalence rates reported in these studies range between 0.9% to 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 alpha gal allergy are also being reported in Mexico and Colombia, respectively.46, 47

It should be noted that the data relied upon to estimate global FA prevalence are subject to substantial limitations, most notably the non-specificity of proxy measures of allergic sensitization (e.g. SPT, 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 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. While high quality prevalence data for FA is lacking for many geographical regions and age groups, increases in FA prevalence is supported by hospitalization rates for FA. A nationwide survey in the United States of hospitalization due to pediatric food-induced anaphylaxis found a significant 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 to 2011/2012 (2.0 to 8.2 per 100,000).49 However, additional studies using standardized methodologies are necessary for accurate detection of FA in order to better understand the true extent of the problem and its impact on health services.

**CAUSES OF FOOD ALLERGY**

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 (FLG), and serine protease inhibitor ( SERPINB7 )), 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 (ILCs), which contribute to type 2 immune responses, have also been implicated in mediating FA. ILCs are localized at barrier surfaces of the airways, gut, and skin and form a link between the 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 4-6 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 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 tolerance60, the role of prebiotics, probiotics, or symbiotics in mediating these effects are 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 barrier61-72. According to the epithelial barrier hypothesis (Figure 1), exposure to many of these substances damage and initiate 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 TSLP play a major role in the development and exacerbation of allergic diseases74, 75.

The importance of a diverse microbiome in reducing the risk of FA is now recognized. A greater number of siblings and 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 multi-factorial and are likely to result from a complex interaction of genetic, dietary, and environmental factors. Arguably, at present, the two 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 food allergy 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, prior to 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**

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

The international gold standard for FA diagnosis is the double-blind placebo-controlled food challenge (DBPCFCs). However, as 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 was developed according to the Institute of Medicine/ Guidelines International Network (IOM /GIN) 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 based on the level of evidence available, with D indicating when experts’ opinion had to complement the existing data. The EAACI algorithm for FA diagnosis (Figure 3) includes five 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 (Grade A-C ) (3) elimination diet for diagnostic purposes, i.e. short term avoidance 2-4 weeks (Grade D), (4) an OFC to definitely confirm or exclude the diagnosis (Grade D) (5) evaluation for non-IgE mediated FA when the history is convincing and SPT 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.78 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 serum allergen-specific sIgE and/ or APT tests marginally improved positive and negative predictive values, but did not obviate the need for DBPCFC. The guideline, however, did not recommended 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, DBPCFC were cited as the gold 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 tests, whilst the diagnosis of IgE-mediated contact urticaria is supported by history, including the absence of symptoms while the causative food is avoided, positive sIgE tests or SPTs, and positive immediate epicutaneous skin tests (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 only be used in conjunction with the clinical history. In carefully selected patients to confirm or exclude FA, medically supervised OFCs are performed. Recently, due to the increased use of widely available online allergy testing services, ASCIA has written a position paper that strongly recommends against using online allergy tests,79 due to potential harm (even if evidenced-based tests are ordered since 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 healthcare system. In Australia, most paediatric allergy clinics use SPT in preference to sIgE testing because results are immediately available. Consistently SPT have been shown to have a high sensitivity, but low specificity 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 gold 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 80-83. Predictive threshold values for SPTs and food-specific IgE are lacking in Asian populations, and this is an important unmet need as it is unlikely that data accrued from other ethnicities can be used in Asia84. In fact, one of the challenges in diagnosis of FA in Asian countries is that many countries are resource-limited, both in the number of trained allergy specialists as well as in access to SPT reagents, laboratory facilities and food challenge set-ups 26, 85. Countries that do not currently have a national allergy specialty training and accreditation program should see this as a priority for their healthcare needs.

There are many diagnostics tests that are used to support diagnosis, although not recommended by current guidelines. However, some of these tests are only available in specialized centers and not available in many countries.83 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 3mm to 8mm or sIgE 0.35kUA/L to 15kUA/L)86. 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 thirds87. Other examples of component resolved diagnostics include Ana o 3 for cashew, Gal d 1, 2, 3 and 5 for egg88, and Cor a 9 and Cor a 14 for hazelnut allergy.89, 90 Other specialized and research based tests include allergen specific IgG4 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.83

While recent diagnostic advances (e.g. component-resolved diagnostics, basophil activation testing, allergenic epitope-specific IgE91) 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 (e.g. sensitivity, specificity, 95% PPV) are unavailable for many key allergens. Therefore, further work—much of which is ongoing—is still needed to refine these approaches prior to their more widespread utilization.

**PREVENTION OF FOOD ALLERGY**

Guidelines regarding timing of introduction of allergenic foods have undergone dramatic changes as new data have emerged in the last few years. Table 1 lists FA prevention guidelines from around the world. Table 2 highlights key recommendations from a few international guidelines. Although some earlier studies92-94 and guidelines recommended allergen avoidance during pregnancy and lactation, these were not supported by later studies.95 The 2019 American Academy of Pediatrics (AAP) Clinical Report specifically state 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.96 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 consumption of potentially allergenic foods during pregnancy or breastfeeding 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 upon allergen ingestion 97 However, a number of subsequent studies showed either no benefits of allergen avoidance or benefits of early allergen consumption.98 The 2015 LEAP99 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 five times more likely in children who avoided peanuts. The 2016 Enquiring About Tolerance (EAT)100 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 breastfeeding and showed the benefits with cooked egg. Subsequent to the publication of these two pivotal studies that early introduction of egg and peanut were 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 4-6 months;57, 96, 100 however some guidelines recommend not delaying introduction83 of allergen or introduction during the first year of life.101 A few guidelines recommend screening before allergen ingestion in high-risk infants.

In 2017, the NIAID-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.102 In 2019, the AAP issued a clinical report concluding that there is no evidence that delaying the introduction of allergenic foods, including peanuts, eggs, and fish, beyond 4 to 6 months prevents FA and indicated that there is now evidence that early introduction of peanuts may prevent peanut allergy96. In 2021, a consensus approach to the primary prevention of FA was published, endorsed by the American Academy of Allergy, Asthma and Immunology (AAAI); the American College of Allergy, Asthma and Immunology (ACAAI); and the Canadian Society for Allergy and Clinical Immunology (CSACI).6 Among all infants irrespective of risk, it recommends introduction of cooked egg and peanut at around 6, but not before 4 months of life, at home when the infant is developmentally ready. For other allergens, it recommends not deliberately delaying introduction as there are no data showing harm with introduction of other allergens in the first year of life (but also no data showing specific benefit). Prior to allergen introduction, such as peanut, pre-emptive screening is not required but the guidance notes 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 introduction of allergenic foods including cooked egg and peanut in the first year of life.103 Studies have shown high levels of adoption of this advice with over 80% of infants now introduced to peanut in the first year of life, with a median age of introduction of 6 months.104 Whether the successful adoption of earlier introduction of allergenic foods has had an impact on 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 2004105, 2008106, and 2014107. In 2019, the European Food Safety Authority (EFSA) 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.108 A systematic review was carried out using the GRADE approach56 and based on this, guidelines were written using the AGREE II framework. The key changes from the 2014 guidelines were for recommendation of introduction of peanut and well-cooked egg (between 4-6 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 breastfeeding is effective for the prevention of allergic disease. However, for optimal health of the infant the WHO57 and the EAACI109 recommend EBF for a minimum of 6 months and 4 months, respectively. Some guidelines recommend continuing breastfeeding alongside solid food introduction for up to 1110,57 or 2 years84 or as long as possible.101 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, 110 or having no recommendations83, or recommending their use (for high risk infants)111. The EAACI guidelines also recommends 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 WAO GLAD-P guideline panel determined that there is a likely net benefit from using probiotics resulting primarily from prevention of eczema, but not FA.112 Other guidelines that recommend their use include Singapore81, 113, and Hong Kong114, 115. Current EAACI and ASCIA guidelines do not recommend their use.57, 101

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.116 In 2014, the PASTURE study 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 6 and 12 months of age reduced by 10.8% and 33.2% respectively, the odds of developing FA over the first 10 years of life.117 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.118

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 vicious cycle. Research into skin emollient to protect the skin and prevent developing a proinflammatory atopic state, which could lead to the development of AD and subsequently, FA is an active area of research.119, 120

**TREATMENTS**

The most recent 2014 Practice Parameter from the Joint Task Force of the AAAAI and the ACAAI recommends absolute avoidance of the allergenic food(s) and preparedness for treatment with an intra muscular injection of epinephrine in case of reactions after inadvertent exposures in those with FA.121 Nevertheless, OIT using off the shelf food products and allowing ingestion of the allergenic food is widespread in private practices in the USA. 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 300mg 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 (CSACI) 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.122 Uncontrolled asthma is an absolute contraindication to OIT, as is pregnancy in the CSACI guidelines.

The EAACI guidelines on IgE-mediated FA management, published in 2014, differentiate acute management from long term strategies.109 Appropriate dietary avoidance remains the corner stone. 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.123, 124 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 EMA also approved Palforzia® for treating children between 4-17 years old with peanut allergy.125

The current ASCIA guidelines on treatment of FA is to adhere to strict allergen avoidance. At this time, there are no Therapeutic Goods Administration (TGA) 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.126, 127 The ASCIA Position Paper on OIT for FA128 currently recommends against the use of OIT for treatment of FAs, and highlights the need for additional studies to establish safety, tolerability, cost-effectiveness, quality of life and long-term outcomes. Several phase 2 studies are underway in Australia to evaluate whether use of an adjuvant alongside OIT can improve efficacy and/or safety of OIT for treatment of peanut, egg and milk allergies.129-132

Guidelines regarding the treatment of FA in Latin America are scarce, and all of them focused on the pediatric population.133-137 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.135-137 The common ground between most of these guidelines is the relevance attributed to the restriction of FAs both in the patient and the lactating mother, the strategies that practitioners might use to avoid malnutrition, and the importance of treating anaphylactic episodes with intramuscular epinephrine.133-137 The use of OIT and monoclonal antibodies is supported by the Colombian, Brazilian, and Argentinian guidelines,135-137 however, the latter also mentions the usefulness of some other types of immunotherapy, including sublingual and epicutaneous routes.135 Additionally, 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.136 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 management of FA recommended by all guidelines is the avoidance of causative foods.83, 113, 138-141 The more current guidelines mention OIT.83, 139, 140 The Japanese guideline advocate minimum avoidance of causative foods with recommendation for patients to take lower amounts of foods or hypoallergenic forms such as heated or cooked.83 In Malaysia and Hong Kong, cow’s milk allergy guidelines whilst recognizing the promise of OIT, do not recommend it in routine clinical practice.139, 140 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.83 Further, 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.142

While 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 towards 'real life' OIT studies where patients are enrolled without OFCs. In these patients, enrollment is based on history and positive serum sIgE or skin prick tests. To reduce risk of allergic reaction, the maintenance dose reached after stepwise incremental increases in allergen was lowered. A study by Vickery et al demonstrated that low dose peanut OIT (300 mg/day) achieved similar sustained desensitization to those achieved by high dose (3000 mg/day) treatment.143 For those with multiple FAs (about 45% of individuals with FA), OIT is even more burdensome, both in study duration and 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, allergens used in multiOIT were one or more of the the following allergens: cashew, walnut, hazelnut, almond, sesame, cow's milk, hen's egg, peanut, soy, or wheat. 144 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 are ongoing (NCT03881696). Research into combination of multiOIT 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 quality of life (QoL). A recent meta-analysis showed that in FA patients, OIT is associated with an improvement in health-related QoL.145 However, well-designed and long-term health-related QoL studies are necessary to ascertain sustained benefits of OIT.145 While tremendous strides in FA therapeutics have occurred in the past decade, much ground remains to be covered in order 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 FA patients and caregivers.146 Furthermore, concerns about the treatment burden of OIT have led to numerous innovations designed to reduce risk of anaphylaxis and more rapidly induce desensitization, including use of biologic, probiotic, and Chinese herbal adjunct therapies.147 However, despite their promise, the effectiveness of these novel approaches on improving patient outcomes remains largely unknown. Finally, despite the current lack of FDA/EMA-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.148 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 quality of life.

**FUTURE RESEARCH/CONCLUSION**

In conclusion, FA guidelines across the globe have differences, some of which reflect regional cultural and societal preferences while 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.

While clinical research in the field needs to reflect local needs, coordination with regards 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 be 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: (1) Efforts to replace OFC as the gold 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 foods. 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 (e.g. other forms of allergen exposure, 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 towards development of improved methods (including genetic tests) for determining infants at high risk, development of non-allergen 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.

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| **Summary:**  **What is known?**   * The incidence/prevalence of food allergy 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 breastfeeding for preventing sensitization is not recommended. * Early intervention with active food allergen introduction, increased diet diversity might prevent food allergy. * Early intervention with proper emollient care might prevent sensitization to foods.   **What is 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 needs 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 food allergy 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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**FIGURE LEGENDS**

Figure 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 S. aureus, moraxella, haemophilus and pnemoccocus. An immune response develops towards 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 allergens, but also commensals and opportunistic pathogens. For example, anti-S. aureus antibodies show a very high prevalence in asthma CRS 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.

Figure 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

Figure 3: EAACI Diagnostic guidelines in 2014. (\*:Figures adapted from Kanao Otsu, Peanut allergy: an evolving clinical challenge, Discovery medicine 2011 Oct 12:319-28 (IgE-mediated), Food Protein Induced Enterocolitis (FPIES) Ed., Terri Brown-Whitehorn and Antonella Cianferoni. Springer International Publishing (non-IgE mediated), Mulder D, Justinich C. Understanding eosinophilic esophagitis: the cellular and molecular mechanisms of an emerging disease. Mucosal Immunol. 2021 4,139–147 (Mixed)).

TABLES

Table 1: Global Food Allergy documents on Prevention of Food Allergy since 2000 2

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Year** | **North America** | **Australia and New Zealand** | **Europe** | **Asia** |
| 2004 |  |  | EAACI105 |  |
| 2005 |  | ASCIA149 |  |  |
| 2006 | ACAAI5 |  |  |  |
| 2007 |  |  | ESPGHAN150 |  |
| 2008 | AAP96 |  | EAACI106 |  |
| 2009 |  |  | DGAKI, DGKJ151 |  |
| 2010 | NIAID152 | ASCIA153 |  | AMS-MOH81, 113 |
| 2012 |  |  | Finnish Allergy Program 2008-2018154 |  |
| 2013 | CPS, CSACI155 |  |  |  |
| 2014 |  |  | DGAKI, DGKJ156, EAACI107 |  |
| 2015 | AAP157 |  |  | GLAD-P158 |
| 2016 |  |  | ISPAI, ISP159 | HKIA114, 115, GLAD-P112 |
| 2017 | NIAID102 |  | BSACI110, ESPGHAN160 | JSPACI161, PSAII, PSPGHN162 |
| 2018 |  |  | BSACI163, SACN, COT164 | APAPARI84 |
| 2019 | AAP96, CPS and CSACI165 | ASCIA101 |  | AMSMOH 111 |
| 2020 |  |  | EAACI57 | JSPACI83, Chinese Expert Consensus166, ISPGHAN 167 |
| 2021 | AAAAI, ACAAI, and CSACI6 |  |  | MAP168 |

AAAAI: American Academy of Asthma, Allergy and Immunology; AAP: American Association 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 ASCIA: Australasian Society of Allergy and Clinical 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; EAACI: European Society of Allergy and Clinical Immunology; ESPGHAN: European Society for Paediatric Gastroenterology Hepatology and Nutrition; HKIA: Hong Kong Institute of Allergy; ISPGHAN: Indian society of pediatric gastroenterology, hepatology and nutrition; ISPAI: Italian Society of Paediatric Allergy and Immunology; ISP: Italian Society of Pediatrics; JSPACI: Japanese Society of Pediatric Allergy and Clinical Immunology; MAP: Malaysia Allergy Prevention; NAIAD: 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; World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P)

Table 2: Comparison of international FA Prevention guidelines

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| International food allergy guidelines | | | | | | | | | |
|  | Australasian Society of Clinical Immunology and Allergy ASCIA 2017103 | National Institute of Allergy and Infectious Diseases 2017102 | Commission on Toxicity (COT) UK 2018164, 169 | Asian Pacific Association of Pediatric Allergy, Respirology and Immunology (APAPARI), 201884 | British Society of Allergy and Clinical Immunology (BSACI) 2018163 | American Academy of Pediatrics 201996 | Consensus statement: American Academy of Asthma, Allergy and Immunology, American College of Asthma, Allergy and Immunology, Canadian Society of Allergy and Clinical Immunology 20206 | European Academy of Allergy and Clinical Immunology (2004105, 2008106, 2014107, 202057 ) | Japanese Pediatric Guideline for Food Allergy (JPGFA) 202083 |
| Foods of relevance | All foods | Peanut | Peanut | All foods | Peanut and Egg | All foods | All foods | All foods | All foods |
| Breastfeeding | BF: at least 6 months and for as long as mother and infant wish to continue |  | EBF for around the first six months of life | Continue breastfeeding up to 2 years. | EBF for around the first six months of life and cont BF for 1st year | No conclusions can be made about the role of breastfeeding in either preventing or delaying the onset of specific food allergies | EBF: recommended for all mothers, no association between EBF and prevention of FA | EBF for around the first six months of life and cont BF for 1st year | No evidence that breastfeeding prevents food allergy. |
| High risk definition | Infants with severe eczema and/or egg allergy, | Infant with AD and/or HE FA | Infants with a history of early-onset AD or suspected FA | Infants with severe eczema | 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 one 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 peanut-allergic child is at increased risk of developing peanut allergy, though such infants may be at risk of developing peanut allergy secondary to delayed introduction of peanut. | (2004105, 2008106, 2014107, 202057 )Infants with one or two parents and /or older siblings with an history of atopic diseases  2020 Limited to PN Populations with high prevalence of PN allergy | Infants with eczema |
| Pregnant/Breast feeding mother | Healthy diet  Excluding any foods (incl. allergenic) not recommended  Up to 3 serves of oily fish p/w  No recommedation on probiotics |  |  |  | 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 (2004105, 2008106, 2014107, 202057 ) | Avoidance of allergens not recommended |
| Introduction of solid foods | All infants: When infant is ready: around 6 m, but not before 4 m |  | CF: introduce in an age- appropriate form from around 6m. | Healthy infants: complementary foods at 6 m | From 4 m on (HR)  From around 6 m when developmentally ready, not before 4 m (GR) |  |  | All infants: Some families choose to start complementary feeding between 4-6 m (2004105, 2008106, 2014107, 202057 ) | All infants: Around 5-6 months (for all) |
| Introduction of allergens | All infants should be given allergenic solid foods including PN, cooked HE, dairy and wheat in 1st year - includes HR  HR: Good evidence: regular PN intake < 12 m can reduce PN allergy. Mod evidence: cooked HE < 8 months (family history of allergy), reduce developing HE allergy | Different PN introduction schedules depending on risk: between 4-6 m in infants with severe AD and/or HE allergy; around 6m 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 m 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 peanut and egg may be required.  Introduction of allergenic foods should not be delayed. | GR: PN and HE as part of the family diet  HR:Introduce HE and PN when ready; from 4 m on; HE before PN. | All infants: No evidence that delaying the introduction of allergenic foods, including PN, HE, Fish, beyond 4 to 6 m prevents atopic disease. There is now evidence that early introduction of PN may prevent PNallergy (based on NIAID guidelines) | Introduce PN and cooked HE to all infants starting around 6 m, not before 4 m  Do not delay introduction of other allergenic CF (CM, soy, wheat, tree nuts, sesame, fish, shellfish) around 6 m, not before 4 m | All infants: Introduce PN and well-cooked HE as part of CF  from 4-6 months of life (202057) | All infants/high risk: Delayed introduction of FA not recommended. |
| Continued intake |  | Peanut protein to be regularly consumed per week should be approximately 6 to 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. |  | Once successfully introduced, continue to give the allergen food to baby regularly as part of their usual diet (e.g. at least once per week). |  |  |  |  |
| Formula | Hydrolysed (partially and extensively) infant formula are not recommended for prevention of allergic disease. If BF is not possible, use std cow's milk formula |  | Does not support the use of hydrolysed cow’s milk formulae, either eHF or pHF, to influence the risk of developing allergic or autoimmune disease |  | Soya based or hydrolysed infant formula are 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 hydrolysed infant formulas  Against: soy protein formula in the first six months of life | Insufficient evidence on the usefulness of hydrolyzed milk in preventing the onset of food allergies |
| Other |  |  |  |  |  |  | Infants should be fed a diverse diet, as this may prevent FA. No recommendation on pre and probiotics. | No recommendation for or against: vitamin supplements, fish oil, prebiotics, probiotics or synbiotics in pregnancy when breastfeeding or in infancy; altering the duration of exclusive breastfeeding; hydrolyzed infant formulas, | No recommendation on probiotics during pregnancy. |

COT UK: Committee on Toxicity United Kingdom; BSACI: British Society of Allergy and Clinical Immunology; ASCIA: Australasian Society of Allergy and Clinical Immunology; EAACI: European Society of Allergy and Clinical Immunology: NAIAD: National Institute of Allergy and Infectious Diseases; AAAAI: American Academy of Asthma, Allergy and Immunology; ACAAI: American College of Asthma Allergy and Clinical Immunology; CSACI: Canadian Society of Allergy and Clinical Immunology;; EBF: exclusive breast feeding; CF: complementary foods; PN: Peanut; HE: Hen’s egg; FA: Food Allergy; AD: Atopic dermatitis; HR: High risk; GR: general risk; F&V: fruit and vegetables