# Pediatric Food Allergy

## A Clinical Guide

Ruchi S. Gupta
*Editor*

Springer

# Pediatric Food Allergy

Ruchi S. Gupta
Editor

# Pediatric Food Allergy

## A Clinical Guide

Springer

*Editor*
Ruchi S. Gupta
Center for Food Allergy and Asthma Research
Northwestern University Feinberg School of Medicine
Chicago, IL
USA

*Associate Editor*
Waheeda Samady
Center for Food Allergy and Asthma Research
Northwestern University Feinberg School of Medicine
Chicago, IL
USA

ISBN 978-3-030-33291-4 ISBN 978-3-030-33292-1 (eBook)
https://doi.org/10.1007/978-3-030-33292-1



This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# Preface

Food allergies impact 1 in 13 kids and 1 in 10 adults in the USA. The rise in food allergies over a generation is epidemic. Due to both the rapid increase and life-threatening nature of food allergy, it is critical to improve awareness, diagnosis, management, and prevention practices. Clinicians need to be up-to-date on new guidelines and potential treatment options. Since we currently do not have a severity spectrum for food allergy and we do not know who may have a severe life-threatening allergic reaction, children and families live in constant vigilance everyday trying to make sure every meal and snack is safe. Food allergy management influences quality of life and social activities of children with food allergies.

I have been engaged in food allergy research for the past 15 years and personally impacted by my daughter's food allergies for the past 11 years. I am amazed and grateful for all the advances in research over this time, thanks to both public and private funding and incredible researchers across the world who are invested in improving our knowledge of the condition and how we can better manage, prevent, and treat food allergies.

This issue discusses the latest and greatest in food allergy to help clinicians better understand, manage, and advise their patients and families. These topics are divided into five major sections: (1) introduction to pediatric food allergy, (2) comorbid conditions in food allergy, (3) development of food allergies and current prevention recommendations, (4) food allergy management and prognosis, and (5) therapies for food allergy. Each section features authors/coauthors that are experts in their respective fields and provides a comprehensive summary of food allergy topics including epidemiology, diagnosis, atopic conditions related to food allergy, differential diagnoses of other food-related diseases, and the future of treatments. Additionally, this issue shares growing research on factors contributing to food allergy development such as the microbiome, early introduction, and breast-feeding.

As a pediatrician, researcher, and mother, food allergy has become my 24/7 passion as I see patients with it, educate future physicians about it, spend most of my time researching it, and learn to manage it daily at home. I am excited to share this issue with my fellow clinicians as it is a comprehensive story of what we currently know and understand about food allergy as well as

other food allergy-related conditions. I am incredibly grateful for all the authors and Springer. My hope is that this book will provide you with knowledge, improve care, and foster ideas for the future.

Chicago, IL, USA

Ruchi S. Gupta

# Acknowledgments

Special thanks to our Associate Editor, Dr. Waheeda Samady, as well as Jialing Jiang, Stephanie Frost, and our amazing and brilliant authors for making this issue possible.

# Contents

# Contributors

**Amanda Agyemang, MD** Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Kravis Children's Hospital, Icahn School of Medicine, New York, NY, USA

**Katrina J. Allen, MD, PhD** Murdoch Children's Research Institute, Melbourne, VIC, Australia

Federal Member of the Australian Parliament, Canberra, Australia

**Amal Assa'ad, MD** Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

**Lucy A. Bilaver, PhD** Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA

**Terri Brown-Whitehorn, MD** Division of Allergy & Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

**Mary M. Buschmann, PhD** Department of Pediatrics and Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, USA

**Emily M. Campbell, MD** Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

**Peter Capucilli, MD** Division of Allergy & Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

**Christina E. Ciaccio, MD, MSc** Department of Pediatrics and Medicine, The University of Chicago, Chicago, IL, USA

**Scott P. Commins, MD, PhD** University of North Carolina School of Medicine, Department of Medicine and Pediatrics, Chapel Hill, NC, USA

**Carla M. Davis, MD** Section of Immunology, Allergy and Retrovirology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

**Ashley A. Dyer, MPH** Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA

**Amy A. Eapen, MD** Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

**David M. Fleischer, MD** Department of Pediatrics, Section of Allergy and Immunology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

**Susan Fox, PA-C, MMS** Division of Allergy and Immunology, Department of Internal Medicine, Rush University Hospital, Chicago, IL, USA

**Jack A. Gilbert, PhD** Department of Pediatrics and Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, USA

**Ruchi S. Gupta, MD, MPH** Center for Food Allergy and Asthma Research, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

**Allison G. Hicks, MD** Department of Pediatrics, Section of Allergy and Immunology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

**Jialing Jiang, BA** Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA

**Madeleine K. Kanaley, BA** Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA

**Lauren M. Kao, MA** Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA

**Edwin H. Kim, MD, MS** University of North Carolina at Chapel Hill, Department of Medicine, Division of Rheumatology, Allergy and Immunology, Chapel Hill, NC, USA

**Jay A. Lieberman, MD** Department of Pediatrics, The University of Tennessee Health Science Center and LeBonheur Children's Hospital, Memphis, TN, USA

**Lisa Lombard, PhD** Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA

**Melanie M. Makhija, MD, MSC** Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

**Kari Christine Nadeau, MD, PhD** Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Department of Medicine and Pediatrics, Stanford, CA, USA

**Anna Nowak-Wegrzyn, MD, PhD** Allergy and Immunology, Department of Pediatrics, NYU Langone Health, New York, NY, USA

Department of Pediatrics, Gastroenterology and Nutrition, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland

**Anthony Olive, MD** Section of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

**Carla Perez, MD** Section of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

**Michael Pistiner, MD, MMSc** MassGeneral Hospital for Children, Food Allergy Center, Harvard Medical School, Boston, MA, USA

**Anne-Louise Ponsonby, PhD** Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia

School of Population & Global Health, University of Melbourne, Melbourne, VIC, Australia

**Efren Rael, MD** Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Stanford, CA, USA

**Waheeda Samady, MD, MSCI** Center for Food Allergy and Asthma Research, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

**Vanitha Sampath, PhD** Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Stanford, CA, USA

**Hemant P. Sharma, MD, MHS** Division of Allergy and Immunology, Children's National Health System, Washington, DC, USA

George Washington University School of Medicine and Health Sciences, Washington, DC, USA

**Victoria X. Soriano, BSc** Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia

Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia

**David R. Stukus, MD** Division of Allergy and Immunology, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, OH, USA

**Mary C. Tobin, MD** Division of Allergy and Immunology, Department of Internal Medicine, Department of Pediatrics, Rush University Hospital, Chicago, IL, USA

**Julie Wang, MD** Department of Pediatrics, Division of Allergy and Immunology, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

**Christopher M. Warren, PhD** Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA

**Alicia T. Widge, MD, MS** National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

**Luanna Yang, MD, PharmD** University of North Carolina at Chapel Hill, Department of Pediatrics, Division of Allergy, Immunology, and Rheumatology, Chapel Hill, NC, USA

**Alyson L. Yee, MD** Interdisciplinary Scientist Training Program, University of Chicago, Chicago, IL, USA

# Part I

# Introduction to Pediatric Food Allergy

# 1 Epidemiology and Racial/Ethnic Differences in Food Allergy

Jialing Jiang, Christopher M. Warren, and Ruchi S. Gupta

## Introduction

Food allergy is an adverse, immunologic reaction upon food consumption. Symptoms usually occur within minutes after eating and may involve symptoms from any body system including skin and/or oral mucosa, respiratory, gastrointestinal, and cardiovascular. Food-induced allergic disorders can be can be classified as immunoglobulin E (IgE) mediated or non-IgE mediated. Food allergies, specifically, are IgE mediated and may result in anaphylaxis, a life-threatening [1] and severe allergic reaction that is rapid in onset and often involves symptoms impacting two or more organ systems. Food allergy may also be associated with other atopic conditions (asthma, atopic dermatitis, and allergic rhinitis) [2], economic burden [3], and lower quality of life [4].

In the last few decades, food allergy has been described to be an increasingly prevalent public health concern across the globe [5–7]. However, previous research has indicated that the impact of food allergy may vary by country [8] and different racial/ethnic groups [9, 10]. Western countries such as the United States, the United Kingdom, and Australia have some of the highest observed rates of pediatric food allergy [11]. Among these Western populations, studies suggest Asians, Hispanic, and Black children may exhibit different rates of food allergy exacerbation compared to their White counterparts [12]. Therefore, to better understand the current state of food allergy, this chapter will summarize recent findings with respect to the epidemiology of this growing public health concern among the pediatric population, with a specific focus on possible racial differences in food allergy outcomes.

## Prevalence of Food Allergy

It is important to note that many of the studies discussed in this section cannot be directly compared due to differences in food allergy measurements (self-reported, physician diagnosed, confirmed through diagnostic testing, allergen sensitization), food allergy definitions (non-IgE-mediated and/or IgE-mediated food-induced allergic disorders), and methodology. Despite the differences, data from previous studies in other countries provide insight on general food allergy trends such as

The original version of this chapter was revised and updated. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-33292-1_20

J. Jiang · C. M. Warren
Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA
e-mail: jialing.jiang@northwestern.edu; christopher.warren@northwestern.edu

R. S. Gupta (✉)
Center for Food Allergy and Asthma Research, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: r-gupta@northwestern.edu



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_1

prevalence and common allergens, which warrant further research to better understand the true impact of food allergy that can be manifested through severity, tolerance, and racial/ethnic differences.

## The United States

In the United States, food allergy impacts nearly 11% of adults [13]. Pediatric food allergy, in particular, has become increasingly common as prevalence has increased in recent decades [14]. A systematic review of food allergy prevalence in the United States indicated an approximately 1% increase in self-reported food allergy per decade [15]. The National Health and Nutrition Examination Survey (NHANES) from 2007 to 2010 suggested that 6.5% of children are reported to have a food allergy [16]. In a 2015–2016 population-based study, 7.6% of children were estimated to have a food allergy [17]. This estimate utilized a combination of physician diagnosis and self-reported food allergy/symptoms to identify convincing cases of food allergy and exclude probable cases of non-IgE-mediated food allergy such as oral allergy syndrome/pollen food syndrome and food intolerances [17]. This same study also reported that 11.4% of children were reported to have a food allergy by their parent [17]. Among food-allergic children, an estimated 39.9% have multiple food allergies [17]. The most common food allergens among children in the United States are peanuts (2.2%), milk (1.9%), shellfish (1.3%), tree nut (1.2%), egg (0.9%), finfish (0.6%), wheat (0.5%), soy (0.5%), and sesame (0.2%) [17]. A previous nationwide, cross-sectional, random telephone survey assessing self-reported peanut, tree nut, and sesame allergy suggested that peanut allergy prevalence among children was 1.4% in 2008, a marked increase from 1997 (0.4%) and 2002 (0.8%) [18]. Tree nut allergy prevalence was estimated to be 1.1% in 2008 compared to 0.5% in 2002 and 0.2% in 1997 [18]. Overall, specific food allergens impact different age groups at varying rates (See Fig. 1.1).

## Australia

HealthNuts, a population-based, food allergy, cohort study in Australia observed a cohort of infants from enrollment at 11–15 months of age and has continued to examine these children at age 2, 4, 6, and 10 years old. In the initial analysis of $n$ = 2,848 infants, 10.4% of 1 year old, Australian infants were estimated to have a

| Age | Peanut | Tree nut | Milk | Shellfish | Egg | Fin fish | Wheat | Soy | Sesame |
|---|---|---|---|---|---|---|---|---|---|
| <1 years | 20.2% | 9.0% | 53.0% | 7.1% | 13.5% | 2.6% | 14.9% | 15.4% | 4.6% |
| 1 years | 24.6% | 8.0% | 37.8% | 5.1% | 22.8% | 6.4% | 6.0% | 16.6% | 4.9% |
| 2 years | 24.5% | 10.9% | 43.5% | 11.5% | 14.1% | 6.0% | 9.9% | 8.6% | 2.3% |
| 3–5 years | 25.1% | 15.9% | 33.6% | 13.0% | 15.0% | 6.2% | 6.6% | 6.9% | 2.7% |
| 6–10 years | 32.8% | 17.6% | 24.4% | 18.4% | 10.8% | 7.8% | 6.4% | 6.5% | 3.3% |
| 11–13 years | 30.5% | 21.3% | 14.9% | 20.2% | 12.8% | 7.1% | 6.2% | 3.6% | 1.8% |
| ≥14 years | 29.5% | 13.3% | 16.0% | 21.3% | 6.6% | 7.9% | 5.4% | 3.0% | 2.1% |

**Fig. 1.1** Specific food allergen prevalence by age among children with food allergy [17]

challenge-confirmed food allergy to peanut, raw egg, or sesame. Peanut allergy prevalence for 1-year-olds was 3.0%, raw egg was 8.9%, and sesame was 0.8% [19]. Following the same cohort, prevalence of food allergy among 4-year-old children was 3.8%. The prevalence of the aforementioned specific foods was 1.2% with egg allergy, 0.4% with sesame allergy, and 1.9% with peanut allergy [20].

## Europe

In a systematic review and meta-analysis of 42 European food allergy studies by Nwaru et al., the self-reported, pooled point prevalence of food allergy in Europe among children was estimated to be approximately 6.9% [21]. In general, Northern Europe had higher self-reported rates of food allergy [21]. In the United Kingdom, a randomized, control trial demonstrated that food allergy developed in 7.1% of children by the age of 3 years old. It is important to consider that estimates using skin prick tests, specific IgE, and oral food challenges are considerably lower compared to self-reported rates [22]. In Steinke et al.'s study of pediatric food allergy in 10 European countries, parent-reported prevalence rates varied from 1.7% reported in Austria to 11.7% reported in Finland [23]. Pyrhönen et al. has suggested that food allergy prevalence in Finland, as confirmed through oral food challenges, is 3.6% [24]. Additionally, Steinke et al. suggested that Italy has a parent-reported food allergy prevalence of 3.9% [23] while a cross-sectional study of children 5–14 years old in Italy estimated a lifetime food allergy prevalence of 10.5% [25].

In a birth cohort ($n$ = 12,049) recruited by the EuroPrevall group across nine countries, incidence of egg allergy for 2-year-olds was estimated to be 1.2% overall with the United Kingdom reporting the highest incidence rate of 2.2% [26]. In observing milk allergy, the highest rates were reported in the United Kingdom and the Netherlands (1%) [27].

## Asia

Efforts to estimate food allergy prevalence in Asian countries have been undertaken in recent years; however, few studies are population based and there is little data on the pediatric population specifically. However, of the current literature, it is postulated that the allergy profile of countries in Asia differs considerably from Western countries [28]. Seafood is one of the most common allergens reported in Asian countries, while prevalence of peanut allergy is lower in Asian countries compared to Western countries [28]. In India, adult food allergy prevalence was estimated to be 1.2%, while frequency of sensitization was estimated to be 26.5% [29]. The most common allergens reported were cow's milk and apple [29]. This trend may also translate to the pediatric population in India. In a cross-sectional prevalence study of children 2 years old and younger in China, food allergy prevalence was reported to be 2.5% in 1999 and 7.7% in 2009, while sensitization rates tested via SPT were reported to be 9.9% and 18%, respectively [30]. Japan, Korea, and Singapore have food allergy prevalence estimates around 5% [31–33].

## Africa

There are limited data on food allergy in African countries, particularly for the general population and children. Additionally, some estimates are over two decades old, including a South African study on asthmatic children from 1992 and a South Nigerian study on asthmatics in 1978 [34]. In a cross-sectional study of 512 children, 1–3 years old in Cape Town, South Africa, 9.6% were sensitized to a food allergen as assessed via SPT. The estimated prevalence of challenge-proven food allergy was 2.5% [35]. In Ghana, prevalence of food allergy (2006–2008) was estimated to be 2.9% while the sensitization rate via SPT is estimated to be 5% [36]. In a pilot study observing allergic conditions in a general practice in Kenya from 1983 to 1988, food allergy

prevalence is estimated to be 0.5% for children and adults [37]. While estimates are relatively low, self-reported, life prevalence of food allergy was reported to be 19.1% in a cross-sectional survey conducted with university students/staff in Mozambique [38]. Common allergens in this sample included seafood, meat, and fruit/vegetable [38].

## Central America/South America

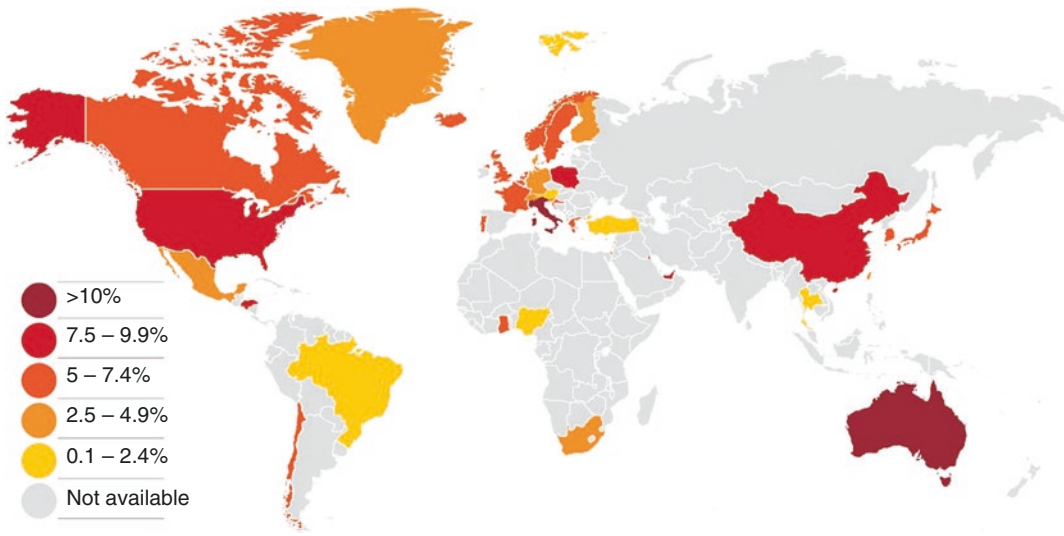
Many countries in Central/South America do not have published food allergy data focusing on the pediatric population. In a systematic review of overall food allergy in Latin America, rates of food allergy sensitization were studied by country, but there were limited studies on food allergy epidemiology and many were not population based [39]. A cross-sectional study based in Colombia observed a self-reported FA prevalence of 14.9% among children and adults [40]. In a study of food allergy among school children in El Salvador, parent-reported point prevalence was estimated to be 5.3% [41]. Interestingly, common allergens among this population included milk, shrimp, chili, chocolate, and nuts [41]. Observing infants and preschoolers in Brazil reveals that prevalence of food allergy among children age 4 months to roughly 5 years of age was 0.6%. Infants had a prevalence of 1.9% while preschoolers had a prevalence of 0.4% [42].

## Middle East

There is also limited food allergy research in the Middle East. A questionnaire administered in Lebanon estimated food allergy prevalence to be 4.1% among infants and children. Fruits, eggs, nuts, cow's milk, and spices were common allergens reported in this study [43]. In the United Arab Emirates, physician-diagnosed food allergy was estimated to be 8% for children and common allergens included egg, fruits, and fish [44]. Additionally, in Israel, food allergy is estimated to impact 3.6% of adolescents 13–14 years of age as indicated through self-report in a cross-sectional, population-based study [45]. Research on Jewish children in Israel and the United Kingdom has unveiled differences in peanut allergy manifestation in the two different countries. This may partly be attributed to cultural practices of timing of infant food introduction [46] but also possibly due to one's environment and genetics. Specifically, peanut allergy was less prevalent among Jewish infants in Israel who were exposed to peanut-containing products early in life compared to the Jewish children in London who generally delayed peanut introduction [46].

Food allergy appears to disproportionately impact individuals in industrialized/westernized regions [11]. A 2012 survey from the World Allergy Organization collected data from 89 countries on previously published food allergy prevalence and health care burden of food allergy. Within this study, food allergy was determined either through oral food challenge, symptoms and sensitization, or parental reporting. Over half of the countries did not have food allergy prevalence data. Only nine countries had prevalence estimates where food allergy cases were confirmed via oral food challenge [47]. Australia had the highest reported food allergy prevalence among children 5 years old or younger confirmed via oral food challenge (10%). In contrast, Thailand reported a prevalence of 1%. For children over 5 years old, Mozambique reported the highest rate of food allergy prevalence (nearly 20% as identified through parental report) compared to Kenya with a parent report of <1%. For children (0–18 years old), the United Kingdom reported the highest rate of food allergy prevalence of 16% compared to Austria's report of <2% [47]. Although these reports varied in methodology, these findings provide a snapshot of the current state of allergy worldwide.

Prevalence of food allergy for countries with published pediatric food allergy data are displayed in Fig. 1.2. Food allergy research has primarily been conducted in Australia, North America, and Europe. Some research on pediatric food allergy has been conducted in Asia, Africa, the Middle East, and Central/South America; however, as mentioned, there is a paucity of data on many countries in these regions. Evidently, food allergy




**NORTH AMERICA**

| | | |
|---|---|---|
| **USA** | 7.6% | Gupta 2018 |
| **Canada** | 7.1% | Soller 2012 |
| **Mexico** | 4.9% | Ontiveros 2016 |

**CENTRAL & SOUTH AMERICA**

| | | |
|---|---|---|
| **Honduras** | 9.3% | Gonzales-Gonzalez 2018 |
| **Chile** | 5.5% | Hoyos-Bachiloglu 2014 |
| **Brazil** | 0.6% | Goncalves 2016 |

**MIDDLE EAST**

| | | |
|---|---|---|
| **U.A.E.** | 8.0% | Al-Hammadi 2010 |
| **Kuwait** | 5.4% | Ali 2017 |
| **Lebanon** | 4.1% | Irani 2015 |
| **Israel** | 3.6% | Graif 2012 |
| **Turkey** | 0.8% | Orhan 2009 |

**EUROPE**

| | | |
|---|---|---|
| **Italy** | 10.5% | Caffarelli 2011 |
| **Poland** | 8.3% | Steinke 2007 |
| **U. Kingdom** | 7.1% | Perkin 2016 |
| **Sweden** | 6.8% | Protudjer 2016 |
| **Norway** | 6.8% | Kvenshagen 2009 |
| **France** | 6.7% | Rance 2005 |
| **Netherlands** | 6.2% | Saleh-Langenberg 2016 |
| **Portugal** | 5.7% | Gaspar-Marques 2014 |
| **Croatia** | 5.4% | Baricic 2015 |
| **Greece** | 5.2% | Papathoma 2016 |
| **Iceland** | 5.0% | Thrastardottir 2018 |
| **Belgium** | 4.9% | Steinke 2007 |
| **Slovenia** | 4.6% | Steinke 2007 |
| **Germany** | 4.2% | Roehr 2004 |
| **Greenland** | 4.1% | Krause 2002 |
| **Finland** | 3.6% | Pyrhonen 2011 |
| **Switzerland** | 3.1% | Steinke 2007 |
| **Denmark** | 2.5% | Steinke 2007 |
| **Austria** | 1.7% | Steinke 2007 |

**AFRICA**

| | | |
|---|---|---|
| **Ghana** | 5.0% | Obeng 2011 |
| **S. Africa** | 2.5% | Basera 2015 |
| **Nigeria** | O<R<2.5% | Kung 2014 |

**ASIA**

| | | |
|---|---|---|
| **China** | 7.7% | Hu 2010 |
| **Singapore** | 5.4% | Lee 2014 |
| **South Korea** | 5.3% | Kim 2011 |
| **Japan** | 5.1% | Noda 2010 |
| **Hong Kong** | 4.8% | Ho 2012 |
| **Taiwan** | 3.4% | Wu 2012 |
| **Thailand** | 1.1% | Lao - Araya 2011 |

**OCEANIA**

| | | |
|---|---|---|
| **Australia** | 10.4% | Osbourne 2011 |

*most studies with Children under 5yo

**Fig. 1.2** Available estimates of pediatric food allergy prevalence around the world varying in food allergy measurements and pediatric age groups

prevalence varies by country even within the same region/continent. Therefore, it is crucial to obtain country-specific estimates of food allergy in efforts to better understand the impact and burden of food allergy in different populations.

## Food Allergy Severity

In the United States, 42.3% of children with a food allergy have reported a severe food-allergic reaction while one in five have reported an emergency department visit for an allergic reaction in the past year [17]. Additionally, 42.0% of children with a food allergy have had at least one lifetime food allergy-related emergency department visit [17]. Severity of allergic reactions has been suggested to vary depending on a child's age and the specific food allergen among other individual-level factors [67]. Severe allergic reactions and emergency department visits are most commonly attributed to peanut and tree nuts/seeds [17, 68]. A recent population-based study also demonstrated that severe reactions were common among children with shellfish and finfish allergy [17]. Overall, rates of severe reactions among children varied by food allergen and ranged from 27% to 59% as indicated in Fig. 1.3 [17]. It is important

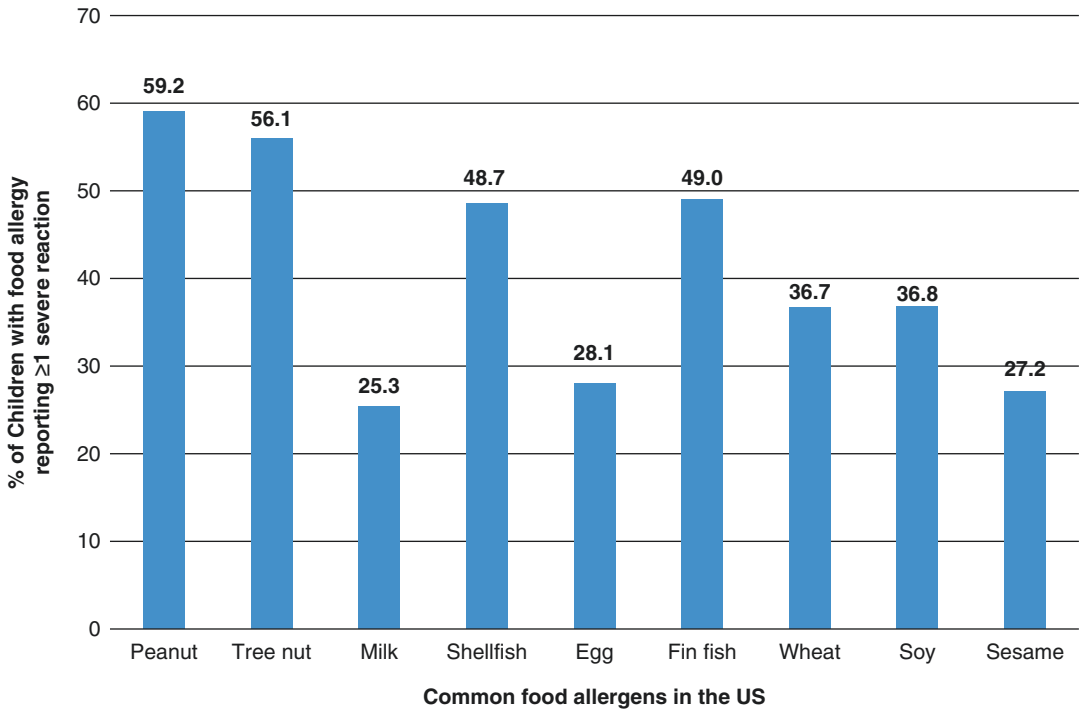



**Fig. 1.3** Severe reactions by allergen among children with specific food allergies [17]

to note that in this study, severe reactions were characterized as those involving multiple serious symptoms (e.g., hives, vomiting, wheeze) reported within multiple organ systems (i.e., skin, GI, respiratory, cardiovascular).

In a study observing emergency department visits and hospital admissions in Illinois due to anaphylaxis, there was 29.1% annual increase of ED and hospital admissions among children from 2008 to 2012 [69]. Incidence of anaphylaxis ranged from 10.5 per 100,000 person/year using specific ICD-9 codes for anaphylaxis vs. 68.4 per 100,000 person/year using nonspecific codes in a health maintenance organization [70].

## Food Allergy Tolerance

While food allergy is a worldwide phenomenon presenting with mild to severe reactions, food allergies can be outgrown. Currently, mechanisms for tolerance development are not well understood although possible explanations include active regulation by Tregs and clonal deletion and anergy of T cells [71]. It is estimated that over 26% of children with food allergy develop food allergy tolerance in the United States [72]. Severity of allergic reactions, type of food allergen, multiple vs. single food allergy, and other demographic factors (race and age) are related to the likelihood of outgrowing a food allergy [67]. Black children are less likely to report an outgrown allergy than White children [72]. Notably, research suggests that children with milk, egg, and soy allergies may be more likely to outgrow a food allergy [72]. In a prospective European study, 43% of children outgrew their milk allergy by age 10 [73]. In a retrospective study, 45% of children with soy allergy outgrew the allergy by age 6 [74] while a prospective study demonstrated that 50% of children with soy allergy outgrew the allergy by age 1 year old and 67% by age 2 years old [75, 76]. Peanut, tree nut, and seafood allergies often persist into adulthood [77–80]. Only approximately one in four children outgrows their peanut allergy by early adulthood [81].

## Racial/Ethnic Differences in Food Allergy

In the United States, studies on racial/ethnic differences in food allergy are limited. Race, as reported in the United States, includes White, Black or African American, Asian, American Indian and Alaska Native as well as Native Hawaiian and Other Pacific Islander. Ethnicity is separated by Hispanic or Latino and non-Hispanic or Latino [82]. Previous literature has suggested that Black children are more likely to have a food allergy compared to White children [17, 83–85]. Additionally, Asian children are more likely to have/develop a food allergy in Australia and the United States [84, 86]. A questionnaire in Australia demonstrated that Australian-born, Asian infants with parent(s) born in East Asia were three times more likely to develop a nut allergy compared to their non-Asian counterparts [87]. Previous literature also postulates that Hispanic children may be less likely to have a food allergy [84, 85]; however, there is a paucity of data on food allergy in this population. African American children and Hispanic children have been previously reported to be at high risk for severe atopic dermatitis [9, 88], which has been demonstrated to contribute to food allergy development. A systematic review by Greenhawt et al. noted a high risk of food allergy (sensitization, self-report, and clinic-based diagnosis) among Black children, but due to differences in food allergy measures/definitions and methodology as well as limited data, it is difficult to generalize trends [89]. This section will discuss previous research studying racial differences considering food allergy prevalence rates, adverse reactions/hospitalizations, and food allergy knowledge.

### Self-Reported Data: Food Allergy

In a 2004 study observing early infant vitamin supplements in relation to atopy risk, a longitudinal cohort data of 8,000 patients indicated that the odds of having food allergy at age 3 years old was lower among Black children compared to their White counterparts [90]. Alternatively, Sicherer et al. conducted a nationwide, cross-sectional, random survey via telephone obtaining information for 14,948 individuals with respect to reported seafood allergy and corresponding disease characteristics. Black respondents reported higher rates of seafood allergy than other racial/ethnic groups [91]. Similar differences were reported by Luccioli's study in 2008 which analyzed data from a longitudinal survey in which mothers self-reported food-related issues and any food allergy diagnoses. There were more Black children with reported, probable food allergy than White or Hispanic (12.5% vs. 5.6% vs. 5.1%, respectively) [92]. The 1997–2007 NHIS self-reported data suggested that there was a greater increase in parent-reported rates of food allergy among Black children relative to other races [93]. Similarly, findings from a systematic literature search indicated that there has been an increase in self-reported food allergy among African Americans than Caucasians or Hispanics over the past few decades [94]. In contrast, a study on the 2003 US National Survey of Children's Health data ($n$ = 102,353 children) noted that there were no significant differences in self-reported allergy prevalence based on race [95]. There were also no significant differences between different races for self-reported peanut/tree nut allergy in Sicherer et al.'s nationwide, cross-sectional, random telephone survey of peanut/tree nut allergy [18].

### Specific Immunoglobulin E: Allergen Sensitivity

In a study of a Detroit, Michigan area birth cohort ($n$ = 590 infants), a panel of allergists identified IgE-mediated food allergy cases to egg, milk, or peanut to explore racial differences in food allergy. African Americans had higher rates of sensitization compared to non-African American children but there were no statistical differences in IgE-mediated food allergy [96].

Sicherer et al. also obtained peanut-specific IgE levels on children across multiple allergy clinics ($n$ = 503). In observing differences in race, Black children were more likely to have a peanut-specific

IgE level of greater than 5 kUa/L than their White counterparts [97]. When studying other allergens (milk, egg, peanut, and shrimp) through the 2005–2006 nationally representative NHANES study, Black children were more likely to be sensitized over the diagnostic cutoff values (0.35) [83]. Reported food sensitization prevalence among Black individuals (regardless of age) was 27% compared to 13.8% for White and 21.2% for Hispanic individuals. The estimated clinical food allergy rates were 5.9%, 1.9%, and 2.7%, respectively [83]. Keet et al. also found that Black children born in the United States were more likely to be sensitized in a study on ImmunoCAP to milk, egg, and peanut [94]. Additionally, Kumar et al. studied 1,104 children in a birth cohort study. In the primarily Black and Hispanic cohort, 35.5% were sensitized to food. Black children (with African ancestry or self-reported race) had higher risk of food allergen sensitization [10]. Taylor-Black and Wang compared rates of food allergy and comorbidities by race and found that Black children were significantly more likely to report higher rates of food allergy [98]. It is unclear if there are disparities in allergy outcomes or between Black children and other racial groups, since it has yet to be systematically explored [99]. A cohort study of 817 children studying food allergy disease phenotypes among African American, Hispanic, and White children with food allergy indicated that food allergy phenotypes varied by racial/ethnic background [9]. African American children had higher odds of asthma compared to their White counterparts while African American and Hispanic children had higher odds of eczema than White children. It is suggested that African American and Hispanic children have higher rates of corn, shellfish, and fish allergy compared to White children. Wheat and soy are more common among African American children than White children while tree nut allergy was more common among White children [9].

## Adverse Reactions/Hospitalization

African American and Hispanic children are estimated to have higher rates of anaphylaxis related to food allergy and emergency department visits [9]. Various retrospective studies have examined racial/ethnic differences in food-induced anaphylaxis-related hospital admission rates using ICD-9 codes with mixed results. In Lin et al.'s study using the New York SPARCS database of anaphylaxis hospitalizations from 1990 to 2006, they conducted a longitudinal assessment of anaphylaxis and found no significant differences between races for anaphylaxis admission [100]. Rudders et al. concluded the same conjecture using ICD-9 codes for acute allergic reactions using NHAMCS database analysis (1993–2005). There were no differences in race for those presenting to the ED for anaphylaxis [101]. A 2011 study by Banerji et al. observed three Boston-area food allergy ED rates from 2001 to 2006 to study hospital admission for food-related allergic reaction. In this study, they used a combination of ICD-9 codes and chart reviews to study potential differences and also found no significant differences between races for hospitalization rates [102]. Harduar-Morano et al. conducted a population-based study of ED visits ($n$ = 2,751) and used ICD-9 codes to observe food-induced anaphylaxis. These findings reported that Black children had higher odds of food-induced anaphylaxis than White children [103]. In a retrospective review of electronic medical records from 2008 to 2010, 3.4% of children seen in a low-income, minority clinic had a food allergy documented by a physician. Black children were affected more than children of other races [98].

## Knowledge/Diagnosis

Food allergy knowledge and management is essential to ensure the safety of food-allergic children. It is particularly important in self-advocacy and among teenagers who are more often surrounded by peers and away from home. In a 2009 survey on food allergy knowledge among the general adult public, Black and Hispanic survey respondents were less likely to identify three food allergy triggers compared to their White counterparts [104]. Black, Hispanic,

and Asian adults were also less likely than White adults to identify two signs of a milk allergy [104]. However, Black and Hispanic survey respondents were more likely to note the importance of avoiding food allergens [104]. It is possible that differences in food allergy knowledge also exist by race among parents of food-allergic children.

Data from a nationally representative sample of U.S. children collected in 2009–2010 estimated that among children with parent-reported food allergy and a history of convincingly IgE-mediated reaction symptoms, Black and Asian children were significantly less likely to have a physician diagnosis compared to their White counterparts [105], even though they were significantly more likely to report a food allergy [84]. Appropriate physician diagnosis of food allergy is essential to ensure appropriate management and treatment.

## Other Disparities

In general, race, socioeconomic status, and health are closely related as race often influences these outcomes [106]. Economic disparities in food allergy expenditures have been exhibited in a cross-sectional survey administered to caregivers of children with food allergy in the United States. Children with a household income less than $50,000 had 2.5 times more emergency department and hospitalization costs compared to children with a household income of over $50,000 ($1,021 vs. $434, respectively) [107]. In observing expenditures on specialist visits and out-of-pocket medication costs, children with a household income over $100,000 incurred more costs compared to those with a household income of less than $50,000 [107]. Overall, the lowest amount of direct medical and out-of-pocket costs was observed among African American children [107]. It is possible that food allergy awareness, access to care, and food allergy reaction severity may contribute to reported costs [107]. Urban/rural differences may also exist in food allergy outcomes and are important to take into account when examining racial differences given the systematic differences in racial composition between urban and rural areas. In an observational study utilizing the Healthcare Cost and Utilization Project data for New York and Florida from 2009 to 2014, food-induced anaphylaxis cases among children were identified using an ICD-9 diagnostic code. Emergency department rates per 100,000 for anaphylaxis induced by food were 12.3 in an urban setting vs. 4.6 in rural settings. Urban children had higher rates of emergency department visits for anaphylaxis compared to rural children while Black children also exhibited higher ED visit rates compared to other races [108].

## Conclusion

Food allergy has been documented to impact different countries and populations at varying rates. Most food allergy research has been concentrated in Western countries, but available data in other countries exhibit food allergy profiles that vary from Western countries. Within regions and countries, food allergy affects children differently. Race/ethnicity may also impact food allergy outcomes in terms of allergy manifestation, sensitization, severity, and tolerance. It is important to capture any racial differences and potential disparities in order to better target educational and clinical efforts in treating and/or managing food allergy. Further research on food allergy prevalence in other countries and racial differences is necessary to elucidate food allergy trends.

## References

1. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001–2006. J Allergy Clin Immunol. 2007 Apr;119(4):1016–8.
2. Hill DA, Spergel JM. The atopic march: critical evidence and clinical relevance. Ann Allergy Asthma Immunol. 2018 Feb;120(2):131–7. https://doi.org/10.1016/j.anai.2017.10.037.
3. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013 Nov;167(11):1026–31. https://doi.org/10.1001/jamapediatrics.2013.2376.

4. Warren CM, Otto AK, Walkner MM, Gupta RS. Quality of life among food allergic patients and their caregivers. Curr Allergy Asthma Rep. 2016 May;16(5):38. https://doi.org/10.1007/s11882-016-0614-9.
5. Loh W, Tang MLK. The epidemiology of food allergy in the global context. Int J Environ Res Public Health. 2018 Sep 18;15(9):2043. https://doi.org/10.3390/ijerph15092043.
6. Tang ML, Mullins RJ. Food allergy: is prevalence increasing? Intern Med J. 2017 Mar;47(3):256–61. https://doi.org/10.1111/imj.13362.
7. Leung ASY, Wong GWK, Tang MLK. Food allergy in the developing world. J Allergy Clin Immunol. 2018 Jan;141(1):76–78.e1. https://doi.org/10.1016/j.jaci.2017.11.008.
8. Goossens NJ, Flokstra-de Blok BM, van der Meulen GN, Arnlind MH, Asero R, Barreales L, et al. Health-related quality of life in food-allergic adults from eight European countries. Ann Allergy Asthma Immunol. 2014 Jul;113(1):63–68.e1. https://doi.org/10.1016/j.anai.2014.04.004.
9. Mahdavinia M, Fox SR, Smith BM, James C, Palmisano EL, Mohammed A, et al. Racial differences in food allergy phenotype and health care utilization among US children. J Allergy Clin Immunol Pract. 2017 Mar–Apr;5(2):352–357.e1. https://doi.org/10.1016/j.jaip.2016.10.006.
10. Kumar R, Tsai HJ, Hong X, Liu X, Wang G, Pearson C, et al. Race, ancestry, and development of food-allergen sensitization in early childhood. Pediatrics. 2011 Oct;128(4):e821–9. https://doi.org/10.1542/peds.2011-0691.
11. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018 Jan;141(1):41–58. https://doi.org/10.1016/j.jaci.2017.11.003.
12. McGowan EC, Bloomberg GR, Gergen PJ, Visness CM, Jaffee KF, Sandel M, et al. Influence of early-life exposures on food sensitization and food allergy in an inner-city birth cohort. J Allergy Clin Immunol. 2015 Jan;135(1):171–8. https://doi.org/10.1016/j.jaci.2014.06.033.
13. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. JAMA Netw Open. 2019 Jan 4;2(1):e185630. https://doi.org/10.1001/jamanetworkopen.2018.5630.
14. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. NCHS Data Brief. 2013 May;121:1–8.
15. Keet CA, Savage JH, Seopaul S, Peng RD, Wood RA, Matsui EC. Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States. Ann Allergy Asthma Immunol. 2014 Mar;112(3):222–229.e3. https://doi.org/10.1016/j.anai.2013.12.007.
16. McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007–2010. J Allergy Clin Immunol. 2013 Nov;132(5):1216–1219.e5. https://doi.org/10.1016/j.jaci.2013.07.018.
17. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, Nadeau KC. The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States. Pediatrics. 2018 Dec;142(6):e20181235. https://doi.org/10.1542/peds.2018-1235.
18. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol. 2010 Jun;125(6):1322–6. https://doi.org/10.1016/j.jaci.2010.03.029.
19. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. HealthNuts Investigators. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011 Mar;127(3):668–76.e1–2. https://doi.org/10.1016/j.jaci.2011.01.039.
20. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. HealthNuts Study. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. J Allergy Clin Immunol. 2017 Jul;140(1):145–153.e8. https://doi.org/10.1016/j.jaci.2017.02.019.
21. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. EAACI Food Allergy and Anaphylaxis Guidelines Group. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014 Jan;69(1):62–75. https://doi.org/10.1111/all.12305.
22. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. EAT Study Team. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016 May 5;374(18):1733–43. https://doi.org/10.1056/NEJMoa1514210.
23. Steinke M, Fiocchi A, Kirchlechner V, Ballmer-Weber B, Brockow K, Hischenhuber C, et al. REDALL study consortium. Perceived food allergy in children in 10 European nations. A randomised telephone survey. Int Arch Allergy Immunol. 2007;143(4):290–5.
24. Pyrhönen K, Hiltunen L, Kaila M, Näyhä S, Läärä E. Heredity of food allergies in an unselected child population: an epidemiological survey from Finland. Pediatr Allergy Immunol. 2011 Feb;22(1 Pt 2):e124–32. https://doi.org/10.1111/j.1399-3038.2010.01095.x.
25. Caffarelli C, Coscia A, Ridolo E, Povesi Dascola C, Gelmett C, Raggi V, et al. Parents' estimate of food allergy prevalence and management in Italian school-aged children. Pediatr Int. 2011 Aug;53(4):505–10. https://doi.org/10.1111/j.1442-200X.2010.03294.x.
26. Xepapadaki P, Fiocchi A, Grabenhenrich L, Roberts G, Grimshaw KE, Fiandor A, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life-the EuroPrevall birth cohort study. Allergy.

2016 Mar;71(3):350–7. https://doi.org/10.1111/all.12801.
27. Schoemaker AA, Sprikkelman AB, Grimshaw KE, Roberts G, Roberts G, Grabenhenrich L, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children – EuroPrevall birth cohort. Allergy. 2015 Aug;70(8):963–72. https://doi.org/10.1111/all.12630.
28. Lee AJ, Thalayasingam M, Lee BW. Food allergy in Asia: how does it compare? Asia Pac Allergy. 2013 Jan;3(1):3–14. https://doi.org/10.5415/apallergy.2013.3.1.3.
29. Mahesh PA, Wong GW, Ogorodova L, Potts J, Leung TF, Fedorova O, et al. Prevalence of food sensitization and probable food allergy among adults in India: the EuroPrevall INCO study. Allergy. 2016 Jul;71(7):1010–9. https://doi.org/10.1111/all.12868.
30. Hu Y, Chen J, Li H. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. Pediatr Int. 2010 Oct;52(5):820–4. https://doi.org/10.1111/j.1442-200X.2010.03166.x.
31. Kim J, Chang E, Han Y, Ahn K, Lee SI. The incidence and risk factors of immediate type food allergy during the first year of life in Korean infants: a birth cohort study. Pediatr Allergy Immunol. 2011 Nov;22(7):715–9. https://doi.org/10.1111/j.1399-3038.2011.01163.x.
32. Noda R. Prevalence of food allergy in nursery school (nationwide survey). Jpn J Food Allergy. 2010;10:5–9.
33. Lee AJ, Shek LP. Food allergy in Singapore: opening a new chapter. Singapore Med J. 2014 May;55(5):244–7.
34. Kung SJ, Steenhoff AP, Gray C. Food allergy in Africa: myth or reality? Clin Rev Allergy Immunol. 2014 Jun;46(3):241–9. https://doi.org/10.1007/s12016-012-8341-z.
35. Basera W, Botha M, Gray CL, Lunjani N, Watkins AS, Venter C, et al. The South African food sensitisation and food allergy population-based study of IgE-mediated food allergy: validity, safety, and acceptability. Ann Allergy Asthma Immunol. 2015 Aug;115(2):113–9. https://doi.org/10.1016/j.anai.2015.06.003.
36. Obeng BB, Amoah AS, Larbi IA, Yazdanbakhsh M, van Ree R, Boakye DA, et al. Food allergy in Ghanaian schoolchildren: data on sensitization and reported food allergy. Int Arch Allergy Immunol. 2011;155(1):63–73. https://doi.org/10.1159/000318704.
37. De Souza M. Allergic conditions in a general practice in Nairobi: a pilot study. East Afr Med J. 1992 Dec;69(12):700–2.
38. Lunet N, Falcão H, Sousa M, Bay N, Barros H. Self-reported food and drug allergy in Maputo. Mozamb Public Health. 2005 Jul;119(7):587–9.
39. Sánchez J, Sánchez A. Epidemiology of food allergy in Latin America. Allergol Immunopathol (Madr). 2015 Mar-Apr;43(2):185–95. https://doi.org/10.1016/j.aller.2013.07.001.
40. Marrugo J, Hernández L, Villalba V. Prevalence of self-reported food allergy in Cartagena (Colombia) population. Allergol Immunopathol (Madr). 2008 Nov-Dec;36(6):320–4.
41. Cabrera-Chávez F, Rodríguez-Bellegarrigue CI, Figueroa-Salcido OG, Lopez-Gallardo JA, Arámburo-Gálvez JG, Vergara-Jiménez MJ, et al. Food Allergy Prevalence in Salvadoran Schoolchildren Estimated by Parent-Report. Int J Environ Res Public Health. 2018 Nov 2;15(11):E2446. https://doi.org/10.3390/ijerph15112446.
42. Gonçalves LC, Guimarães TC, Silva RM, Cheik MF, de Ramos Nápolis AC, Barbosa E, Silva G, et al. Prevalence of food allergy in infants and pre-schoolers in Brazil. Allergol Immunopathol (Madr). 2016 Nov–Dec;44(6):497–503. https://doi.org/10.1016/j.aller.2016.04.009.
43. Irani C, Maalouly G. Prevalence of self-reported food allergy in Lebanon: a middle-eastern taste. Int Sch Res Notices. 2015;2015:639796. https://doi.org/10.1155/2015/639796.
44. Al-Hammadi S, Al-Maskari F, Bernsen R. Prevalence of food allergy among children in Al-Ain city, United Arab Emirates. Int Arch Allergy Immunol. 2010;151(4):336–42. https://doi.org/10.1159/000250442.
45. Graif Y, German L, Livne I, Shohat T. Association of food allergy with asthma severity and atopic diseases in Jewish and Arab adolescents. Acta Paediatr. 2012 Oct;101(10):1083–8. https://doi.org/10.1111/j.1651-2227.2012.02776.x.
46. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008 Nov;122(5):984–91. https://doi.org/10.1016/j.jaci.2008.08.039.
47. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JK, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organ J. 2013 Dec 4;6(1):21. https://doi.org/10.1186/1939-4551-6-21.
48. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in canada. J Allergy Clin Immunol. 2012 Feb;129(2):AB234. https://doi.org/10.1016/j.jaci.2011.12.162.
49. Ontiveros N, Valdez-Meza EE, Vergara-Jiménez MJ, Canizalez-Román A, Borzutzky A, Cabrera-Chávez F. Parent-reported prevalence of food allergy in Mexican schoolchildren: a population-based study. Allergol Immunopathol (Madr). 2016 Nov–Dec;44(6):563–70. https://doi.org/10.1016/j.aller.2016.03.003.
50. Gonzales-González VA, Díaz AM, Fernández K, Rivera MF. Prevalence of food allergens sensitization and food allergies in a group of allergic

Honduran children. Allergy Asthma Clin Immunol. 2018 Jun 18;14:23. https://doi.org/10.1186/s13223-018-0245-x.
51. Hoyos-Bachiloglu R, Ivanovic-Zuvic D, Álvarez J, Linn K, Thöne N, de los Ángeles Paul M, et al. Prevalence of parent-reported immediate hypersensitivity food allergy in Chilean school-aged children. Allergol Immunopathol (Madr). 2014 Nov-Dec;42(6):527–32. https://doi.org/10.1016/j.aller.2013.09.006.
52. Ali F. A survey of self-reported food allergy and food-related anaphylaxis among young adult students at Kuwait University. Kuwait Med Princ Pract. 2017;26(3):229–34. https://doi.org/10.1159/000464361.
53. Orhan F, Karakas T, Cakir M, Aksoy A, Baki A, Gedik Y. Prevalence of immunoglobulin E-mediated food allergy in 6-9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. Clin Exp Allergy. 2009 Jul;39(7):1027–35. https://doi.org/10.1111/j.1365-2222.2009.03263.x.
54. Protudjer JL, Vetander M, Kull I, Hedlin G, van Hage M, Wickman M, et al. Food-related symptoms and food allergy in Swedish children from early life to adolescence. PLoS One. 2016 Nov 15;11(11):e0166347. https://doi.org/10.1371/journal.pone.0166347.
55. Kvenshagen B, Halvorsen R, Jacobsen M. Is there an increased frequency of food allergy in children delivered by caesarean section compared to those delivered vaginally? Acta Paediatr. 2009 Feb;98(2):324–7. https://doi.org/10.1111/j.1651-2227.2008.01074.x.
56. Rancé F, Grandmottet X, Grandjean H. Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. Clin Exp Allergy. 2005 Feb;35(2):167–72.
57. Saleh-Langenberg J, Bootsma GM, van Ginkel CD, Kollen BJ, Flokstra-de Blok BM, Dubois AE. The prevalence of food allergy and epinephrine autoinjectors in Dutch food-allergic adolescents. Pediatr Allergy Immunol. 2016 Nov;27(7):755–9. https://doi.org/10.1111/pai.12611.
58. Gaspar-Marques J, Carreiro-Martins P, Papoila AL, Caires I, Pedro C, Araújo-Martins J, et al. Food allergy and anaphylaxis in infants and preschool-age children. Clin Pediatr (Phila). 2014 Jun;53(7):652–7. https://doi.org/10.1177/0009922814527502.
59. Baricic TV, Catipovic M, Cetinic EL, Krmek V, Horvat I. Parental perception, prevalence and primary care Physicians' knowledge on childhood food allergy in Croatia. Children (Basel). 2015 Jul 17;2(3):305–16. https://doi.org/10.3390/children2030305.
60. Papathoma E, Triga M, Fouzas S, Dimitriou G. Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood. Pediatr Allergy Immunol. 2016 Jun;27(4):419–24. https://doi.org/10.1111/pai.12552.
61. Thrastardottir AR, Thordardottir FR, Torfadottir J. Protocols Related to Food Allergies and Intolerances in Preschools in Reykjavik, Iceland. Laeknabladid. 2018 Jan;104(1):11–7. https://doi.org/10.17992/lbl.2018.01.168.
62. Roehr CC, Edenharter G, Reimann S, Ehlers I, Worm M, Zuberbier T, et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. Clin Exp Allergy. 2004 Oct;34(10):1534–41.
63. Krause TG, Koch A, Poulsen LK, Kristensen B, Olsen OR, Melbye M. Atopic sensitization among children in an Arctic environment. Clin Exp Allergy. 2002 Mar;32(3):367–72.
64. Ho M, Lee SL, Wong WH, Ip P, Lau YL. Prevalence of self-reported food allergy in Hong Kong children and teens--a population survey. Asian Pac J Allergy Immunol. 2012 Dec;30(4):275–84.
65. Wu TC, Tsai TC, Huang CF, Chang FY, Lin CC, Huang IF, et al. Prevalence of food allergy in Taiwan: a questionnaire-based survey. Intern Med J. 2012 Dec;42(12):1310–5. https://doi.org/10.1111/j.1445-5994.2012.02820.x.
66. Lao-araya M, Trakultivakorn M. Prevalence of food allergy among preschool children in northern Thailand. Pediatr Int. 2012 Apr;54(2):238–43. https://doi.org/10.1111/j.1442-200X.2011.03544.x.
67. Dyer AA, Gupta R. Epidemiology of childhood food allergy. Pediatr Ann. 2013 Jun 1;42(6):91–5. https://doi.org/10.3928/00904481-20130522-08.
68. Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. National trends in emergency department visits and hospitalizations for food-induced anaphylaxis in US children. Pediatr Allergy Immunol. 2018 Aug;29(5):538–44. https://doi.org/10.1111/pai.12908.
69. Dyer AA, Lau CH, Smith TL, Smith BM, Gupta RS. Pediatric emergency department visits and hospitalizations due to food-induced anaphylaxis in Illinois. Ann Allergy Asthma Immunol. 2015 Jul;115(1):56–62. https://doi.org/10.1016/j.anai.2015.05.006.
70. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS, et al. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. J Allergy Clin Immunol. 2004 Mar;113(3):536–42.
71. Nowak-Wegrzyn A. What makes children outgrow food allergy? Clin Exp Allergy. 2015 Nov;45(11):1618–20. https://doi.org/10.1111/cea.12592.
72. Gupta RS, Lau CH, Sita EE, Smith B, Greenhawt MJ. Factors associated with reported food allergy tolerance among US children. Ann Allergy Asthma Immunol. 2013 Sep;111(3):194–198.e4. https://doi.org/10.1016/j.anai.2013.06.026.
73. Santos A, Dias A, Pinheiro JA. Predictive factors for the persistence of cow's milk allergy. Pediatr Allergy Immunol. 2010 Dec;21(8):1127–34. https://doi.org/10.1111/j.1399-3038.2010.01040.x.

74. Savage JH, Kaeding AJ, Matsui EC, Wood RA. The natural history of soy allergy. J Allergy Clin Immunol. 2010 Mar;125(3):683–6. https://doi.org/10.1016/j.jaci.2009.12.994.
75. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. J Pediatr. 1989 Jul;115(1):23–7.
76. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. J Pediatr. 1985 Nov;107(5):669–75.
77. Al-Muhsen S, Clarke AE, Kagan RS. Peanut allergy: an overview. CMAJ. 2003 May 13;168(10):1279–85.
78. Lee LA, Burks AW. Food allergies: prevalence, molecular characterization, and treatment/prevention strategies. Annu Rev Nutr. 2006;26:539–65.
79. Sampson HA. Update on food allergy. J Allergy Clin Immunol. 2004 May;113(5):805–19; quiz 820.
80. Sicherer SH, Bock SA. An expanding evidence base provides food for thought to avoid indigestion in managing difficult dilemmas in food allergy. J Allergy Clin Immunol. 2006 Jun;117(6):1419–22.
81. Bégin P, Paradis L, Paradis J, Picard M, Des RA. Natural resolution of peanut allergy: a 12-year longitudinal follow-up study. J Allergy Clin Immunol Pract. 2013 Sep-Oct;1(5):528–30.e1–4. https://doi.org/10.1016/j.jaip.2013.05.008.
82. Office of Budget and Management. Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity 1997. Federal Register (FR Doc No: 97–28653);62(210):58782. Available from: https://www.federalregister.gov/documents/1997/10/30/97-28653/revisions-to-the-standards-for-the-classification-of-federal-data-on-race-and-ethnicity
83. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. J Allergy Clin Immunol. 2010 Oct;126(4):798–806.e13. https://doi.org/10.1016/j.jaci.2010.07.026.
84. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011 Jul;128(1):e9–17. https://doi.org/10.1542/peds.2011-0204.
85. McGowan EC, Matsui EC, McCormack MC, Pollack CE, Peng R, Keet CA. Effect of poverty, urbanization, and race/ethnicity on perceived food allergy in the United States. Ann Allergy Asthma Immunol. 2015 Jul;115(1):85–6.e2. https://doi.org/10.1016/j.anai.2015.04.021.
86. Wang Y, Allen KJ, Suaini NHA, Peters RL, Ponsonby AL, Koplin JJ. Asian children living in Australia have a different profile of allergy and anaphylaxis than Australian-born children: a state-wide survey. Clin Exp Allergy. 2018 Oct;48(10):1317–24. https://doi.org/10.1111/cea.13235.
87. Koplin JJ, Peters RL, Ponsonby AL, Gurrin LC, Hill D, Tang ML, et al. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. Allergy. 2014 Dec;69(12):1639–47. https://doi.org/10.1111/all.12487.
88. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. J Allergy Clin Immunol. 1983 May;71(5):473–80.
89. Greenhawt M, Weiss C, Conte ML, Doucet M, Engler A, Camargo CA Jr. Racial and ethnic disparity in food allergy in the United States: a systematic review. J Allergy Clin Immunol Pract. 2013 Jul-Aug;1(4):378–86. https://doi.org/10.1016/j.jaip.2013.04.009.
90. Milner JD, Stein DM, McCarter R, Moon RY. Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. Pediatrics. 2004 Jul;114(1):27–32.
91. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. J Allergy Clin Immunol. 2004 Jul;114(1):159–65.
92. Luccioli S, Ross M, Labiner-Wolfe J, Fein SB. Maternally reported food allergies and other food-related health problems in infants: characteristics and associated factors. Pediatrics. 2008 Oct;122(Suppl 2):S105–12. https://doi.org/10.1542/peds.2008-1315n.
93. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009 Dec;124(6):1549–55. https://doi.org/10.1542/peds.2009-1210.
94. Keet CA, Wood RA, Matsui EC. Personal and parental nativity as risk factors for food sensitization. J Allergy Clin Immunol. 2012 Jan;129(1):169–75.e1–5. https://doi.org/10.1016/j.jaci.2011.10.002.
95. Victorino CC, Gauthier AH. The social determinants of child health: variations across health outcomes – a population-based cross-sectional analysis. BMC Pediatr. 2009 Aug 17;9:53. https://doi.org/10.1186/1471-2431-9-53.
96. Joseph CL, Zoratti EM, Ownby DR, Havstad S, Nicholas C, Nageotte C, et al. Exploring racial differences in IgE-mediated food allergy in the WHEALS birth cohort. Ann Allergy Asthma Immunol. 2016 Mar;116(3):219–224.e1. https://doi.org/10.1016/j.anai.2015.12.019.
97. Sicherer SH, Wood RA, Stablein D, Lindblad R, Burks AW, Liu AH, et al. Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. J Allergy Clin Immunol. 2010 Dec;126(6):1191–7. https://doi.org/10.1016/j.jaci.2010.08.036.
98. Taylor-Black S, Wang J. The prevalence and characteristics of food allergy in urban minority children. Ann Allergy Asthma Immunol. 2012 Dec;109(6):431–7. https://doi.org/10.1016/j.anai.2012.09.012.
99. Wegienka G, Johnson CC, Zoratti E, Havstad S. Racial differences in allergic sensitization: recent findings and future directions. Curr Allergy

Asthma Rep. 2013 Jun;13(3):255–61. https://doi.org/10.1007/s11882-013-0343-2.
100. Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990–2006. Ann Allergy Asthma Immunol. 2008 Oct;101(4):387–93. https://doi.org/10.1016/S1081-1206(10)60315-8.
101. Rudders SA, Espinola JA, Camargo CA Jr. North-south differences in US emergency department visits for acute allergic reactions. Ann Allergy Asthma Immunol. 2010 May;104(5):413–6. https://doi.org/10.1016/j.anai.2010.01.022.
102. Banerji A, Rudders SA, Corel B, Garth AP, Clark S, Camargo CA Jr. Predictors of hospital admission for food-related allergic reactions that present to the emergency department. Ann Allergy Asthma Immunol. 2011 Jan;106(1):42–8. https://doi.org/10.1016/j.anai.2010.10.011.
103. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. A population-based epidemiologic study of emergency department visits for anaphylaxis in Florida. J Allergy Clin Immunol. 2011 Sep;128(3):594–600.e1. https://doi.org/10.1016/j.jaci.2011.04.049.
104. Gupta RS, Kim JS, Springston EE, Smith B, Pongracic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs in the United States. Ann Allergy Asthma Immunol. 2009 Jul;103(1):43–50. https://doi.org/10.1016/S1081-1206(10)60142-1.
105. Gupta RS, Springston EE, Smith B, Pongracic J, Holl JL, Warrier MR. Parent report of physician diagnosis in pediatric food allergy. J Allergy Clin Immunol. 2013 Jan;131(1):150–6. https://doi.org/10.1016/j.jaci.2012.07.016.
106. Williams DR, Priest N, Anderson NB. Understanding associations among race, socioeconomic status, and health: patterns and prospects. Health Psychol. 2016 Apr;35(4):407–11. https://doi.org/10.1037/hea0000242.
107. Bilaver LA, Kester KM, Smith BM, Gupta RS. Socioeconomic disparities in the economic impact of childhood food allergy. Pediatrics. 2016 May;137(5):e20153678. https://doi.org/10.1542/peds.2015-3678.
108. Sakai-Bizmark R, Friedlander SMI, Oshima K, Webber EJ, Mena LA, Marr EH, et al. Urban/rural residence effect on emergency department visits arising from food-induced anaphylaxis. Allergol Int. 2019 Feb 5; https://doi.org/10.1016/j.alit.2018.12.007.

# 2 Pathophysiology and Symptoms of Food Allergy and Anaphylaxis

Alicia T. Widge and Hemant P. Sharma

## Abbreviations

| | |
|---|---|
| CD | Celiac disease |
| DCs | Dendritic cells |
| EG | Eosinophilic gastroenteritis |
| EOE | Eosinophilic esophagitis |
| FA | Food allergy |
| FPIAP | Food protein-induced allergic proctocolitis |
| FPIES | Food protein-induced enterocolitis syndrome |
| HLA | Human leukocyte antigen |
| MSG | Monosodium glutamate |
| OAS | Oral allergy syndrome |
| PFS | Pollen-food allergy syndrome |

## Introduction

About 40% of children in the United States with a food allergy will experience a severe reaction [1]. Food allergy is one of the most common causes of anaphylaxis and accounts for 30–50% of all anaphylaxis cases and up to 81% of anaphylaxis cases in children [2].

Given the increasing prevalence and life-threatening consequences of food allergy, accurate and timely diagnosis of food allergies is critical. Clinicians require the tools to distinguish food allergy versus intolerance and describe the pathophysiology that contributes to the development of food allergies. This review will describe and categorize food allergies by clinical presentations and their underlying immune mechanisms. History and exam findings that contribute to the diagnosis will be reviewed.

## Food Allergy Versus Intolerance

The 2010 Expert Panel Report sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) defined food allergy as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" and food intolerance as "foods or food components that elicit reproducible adverse reactions but do not have established or likely immunologic mechanisms" [3]. Food intolerances can result from metabolic,

A. T. Widge
National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
e-mail: Alicia.Widge@NIH.gov

H. P. Sharma (✉)
Division of Allergy and Immunology, Children's National Health System, Washington, DC, USA

George Washington University School of Medicine and Health Sciences, Washington, DC, USA
e-mail: HSharma@childrensnational.org


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_2

pharmacologic, toxins, and chemical reactions. Examples of each will now be discussed and are summarized in Table 2.1 [4].

Metabolic causes of food intolerance include lactose intolerance, galactosemia, and alcohol intolerance. Patients who are lactose intolerant are unable to digest lactose leading to excess fluid in the gut, resulting in abdominal pain, bloating, and diarrhea. This is important to differentiate from an allergy to cow's milk, which is an immunologic response to cow's milk protein that can result in anaphylaxis [3]. Galactosemia is a metabolic food intolerance due to a deficiency in the enzyme required to process galactose. This results in vomiting, diarrhea, failure to thrive, jaundice, and lethargy in infants but is commonly detected before the onset of clinical symptoms on newborn metabolic screening. Pharmacologic food intolerances result from chemically active compounds including caffeine and alcohol. Toxic effects of foods can result from scombroid poisoning due to elevated histaminic chemicals in decomposing dark-flesh fish like tuna, mackerel, mahi-mahi, and sardine. Symptoms of scombroid poisoning closely mimic a food allergy and can involve urticaria, angioedema, flushing, vomiting, diarrhea, dizziness, and hypotension after eating spoiled fish [5]. While the symptoms are histamine mediated and very closely mimic an allergy, scombroid poisoning is not a food allergy because it does not have an immunologic mechanism. Chemical reactions can occur due to vagally mediated gustatory rhinitis [6] or auriculotemporal syndrome, also called Frey Syndrome, which results in redness and sweating of the cheek following salivation [7]. Non-immunologic reactions can also occur due to sulfites, nitrites, and monosodium glutamate (MSG). Sulfites have been implicated in asthma reactions, and these patients generally have a history of asthma exacerbations triggered by sulfite-rich foods like dried fruit or wine [8]. Finally, some patients have food intolerances that are psychologically driven including food phobias or aversions.

**Table 2.1** Non-immunologic food reactions. These are adverse reactions which are not allergies [4]

| | |
|---|---|
| Metabolic | Lactose intolerance<br>Galactosemia (galactose-1-phosphate uridyl transferase deficiency)<br>Sucrose intolerance (sucrose-isomaltase deficiency)<br>Alcohol intolerance |
| Pharmacologic | Caffeine<br>Foods high in histamine (wine, aged cheese, sauerkraut)<br>Tyramine (fermented foods)<br>Dopamine (fava beans)<br>Phenylethylamine (aged cheese, red wine, chocolate)<br>Serotonin (banana, kiwi, pineapple, plum, tomato, walnut)<br>Theobromine (chocolate, tea)<br>Monosodium glutamate (MSG)<br>Nitrites<br>Sulfite |
| Toxic (food poisoning) | Scombroid poising (tuna, mackerel, mahi-mahi, and sardine)<br>Ciguatera poisoning (barracuda, grouper, snapper)<br>Shellfish (paralytic shellfish poising from saxitoxin)<br>Fungal toxins (aflatoxins, trichothecenes, ergot)<br>Food poising (botulism from *Clostridium botulinum*, *Staphylococcus aureus*, *Salmonella*) |
| Chemical | Gustatory rhinitis<br>Auriculotemporal syndrome (Frey syndrome) |
| Psychologic | Food phobias or aversions |

Adapted from Sharma et al. [4], with permission from Elsevier

Key questions in the patient's history, as reviewed later in this chapter, can help clinicians distinguish food allergy from non-immune adverse food reactions. When the diagnosis remains uncertain, referral to an allergist/immunologist should be considered.

## Immune Responses

Immune responses to foods can be grouped into three types: (1) immunoglobulin E (IgE)-mediated reactions, (2) non-IgE- or cell-mediated reactions, and (3) mixed reactions.

## IgE-Mediated Food Reactions

Patients with IgE-mediated FA present with a variety of symptoms most commonly involving the skin, gastrointestinal tract, respiratory tract, and cardio-

vascular systems. It is important to note that the timing, sequence, and severity of symptoms vary widely between reactions even in the same individual [9]. The highly unpredictable nature and potential for high morbidity and mortality make recognizing and treating reactions of utmost importance.

IgE-specific antibodies for food allergens develop during initial sensitization to a food. Once sensitization occurs, food antigen-specific IgE is present in the circulation and on the surface of tissue mast cells and circulating basophils bound to the high-affinity FcεRI receptor. After re-exposure to the food, cross-linking of the food protein-specific IgE bound to FcεRI results in degranulation of mast cells and basophils releasing preformed histamine and proteases along with synthesis of leukotrienes, prostaglandins, and cytokines [10].

Because IgE cross-linking releases preformed allergic mediators, signs and symptoms of IgE-mediated food allergies develop rapidly and should be considered in patients who develop signs and symptoms within minutes up to 2 hours after ingesting the suspected food allergen. The delayed release of mediators that are synthesized following IgE cross-linking may result in a delayed phase of symptoms hours after the initial reaction though the mechanisms behind delayed and biphasic reactions are not well understood.

The key features of reactions by organ system will now be described and are also noted in Table 2.2.

**Table 2.2** Signs and symptoms of IgE-mediated food allergies

| Immunopathology | Clinical features | Common causal foods | Pathophysiology |
|---|---|---|---|
| Immediate IgE hypersensitivity (Symptoms occur within minutes up to 2 hours after exposure) | Cutaneous:<br>urticaria, diffuse pruritis, flushing, angioedema | Any food, but most commonly peanuts, tree nuts, milk, soy, egg, fish, shellfish | Cross-linking of food antigen-specific IgE on the surface of tissue mast cells (FcεRI receptor) and circulating basophils results in degranulation releasing preformed histamine and proteases along with synthesis of leukotrienes, prostaglandins, and cytokines |
| | GI:<br>Mouth itching, nausea, vomiting, abdominal pain, diarrhea | | |
| | Respiratory:<br>Upper – sneezing, rhinorrhea, congestion, nasal and/or eye itching, conjunctival erythema, tearing<br>Lower – dyspnea, chest tightness, cough, wheezing | | |
| | CV:<br>Tachycardia, hypotension, dizziness, syncope, urinary incontinence | | |
| | Anaphylaxis:<br>Rapidly progressive, multi-system involvement. Can lead to shock and death secondary to respiratory or cardiovascular compromise | | |
| Alpha-Gal | Symptoms identical to those above but are delayed by 4–6 hours | Mammalian meat (beef, pork, lamb, venison, etc.). Some patients also react to mammalian milk and gelatin | Sensitization occurs to the carbohydrate antigen, galactose-alpha-1,3-galactose following lone star tick bites |
| Food-dependent, exercise-induced anaphylaxis | Symptoms identical to those above, but food only triggers anaphylaxis if patient exercises within 4 hours after ingestion | Wheat, shellfish, nuts, celery | Mast cell degranulation and release of mediators. Unclear why exercise precipitates anaphylaxis |
| Pollen-food allergy syndrome | Itching or mild swelling of oral cavity, 5% progress to a more systemic reaction | Raw fruits, vegetables, nuts, or certain spices. Cooked forms tolerated | Cross-reactivity to shared epitopes between the pollen and fresh fruit and vegetables. Antigen is degraded by heat |

### Skin Reactions

Symptoms involving the cutaneous and subcutaneous tissue are very common in IgE-mediated food reactions and include urticaria, diffuse pruritis, flushing, and angioedema. Urticarias are raised erythematous wheals that are pruritic, typically well circumscribed or coalescing, and evanescent. Angioedema is non-pitting edema that involves non-gravitationally dependent areas. It commonly affects the face (especially the lips and eyelids), extremities, and upper airway. IgE-mediated FA should be suspected in a patient who develops urticaria or angioedema within minutes to 2 hours after ingestion of a suspected food allergen. Both ingestion of food and direct contact can cause urticaria. For example, a child who is peanut allergic may develop contact urticaria after touching peanut butter to their skin without actually ingesting it. In this case, hives are typically limited to the area in contact with the allergenic food. Urticaria secondary to food reactions typically fade shortly after exposure, within several minutes to several hours, though this is highly variable depending on the trigger, severity of the reaction, ongoing exposure, and treatments. Urticarias that persist for greater than 6 weeks are chronic and FA is unlikely the cause [11].

Urticaria is the result of cross-linking of antigen-specific IgE on cutaneous mast cells in the superficial dermis. Angioedema, on the other hand, is due to cross-linking of IgE on mast cells in the deeper dermis and subcutaneous tissues. While urticaria can be the result of a wide variety of allergies including medications and insect bites, and non-allergic causes like infections, it is estimated that at least 20% of acute urticaria is due to food allergy [12, 13]. While the majority of anaphylactic reactions include skin symptoms, it is worth noting that up to 20% of cases of anaphylaxis do not, and the lack of skin symptoms may result in delayed diagnosis of an allergic reaction.

### Respiratory Tract Reactions

Reactions can be divided into those affecting the upper and lower respiratory tract. Upper respiratory tract symptoms include sneezing, rhinorrhea, congestion, nasal and/or eye itching, conjunctival erythema, and tearing. Rhinoconjunctivitis is more commonly seen during systemic reactions and is rarely the only presenting symptom [14].

Lower respiratory signs and symptoms are present in up to 70% of anaphylactic reactions and include dyspnea, chest tightness or pain, cough, wheezing, dysphonia, and stridor [15]. Respiratory manifestations such as edema of the glottis and wheezing are the primary cause of death in patients with food-induced anaphylaxis and need to be treated aggressively, especially in asthmatic patients [2]. Bronchospasm can be due to inhalation of food allergens, specifically vapors from cooking fish and shellfish [16, 17].

### Gastrointestinal Symptoms

GI symptoms occur in 45% of cases of anaphylaxis [15]. Many patients experience tingling or itching in their mouth. Young children may scratch at their mouth, tongue, throat, or ears. Nausea and vomiting may occur within minutes of ingestion, whereas abdominal pain, cramping, and diarrhea may occur either immediately or with a delay of up to several hours after ingestion [14]. These symptoms can result in dehydration and electrolyte disturbances in infants and young children, and volume loss from vomiting/diarrhea can cause hypovolemic shock.

### Cardiovascular Symptoms

Cardiovascular symptoms occur in 45% of cases of anaphylaxis and most commonly include tachycardia, hypotension with resulting dizziness and/or syncope, and urinary incontinence [15]. Up to 35% of the intravascular volume can shift to the extravascular space within 10 minutes of onset of a reaction due to increased vascular permeability from histamine and other vasodilatory mediators, which can result in hypotensive shock and cardiac arrest.

Cardiovascular symptoms may include syncope, a feeling of faintness, palpitations, and/or chest pain. Hypotension or shock may be the result of vascular collapse, cardiac arrhythmia, or asphyxia. Anaphylaxis may be complicated by myocardial ischemia [15].

## Anaphylaxis

Anaphylaxis is an IgE-mediated acute life-threatening systemic allergic reaction that affects up to 2% of the population [18]. FAs are the most common cause of anaphylaxis in infants and children [3, 19]. Peanuts are the most common food to cause anaphylaxis in children and shellfish is the most common in adults [20, 21]. Risk factors for fatal reaction from food-induced anaphylaxis are adolescent or young adult age, coexistent asthma, and reactions due to peanut or tree nut [14]. Anaphylaxis is caused by cross-linking of antigen-specific IgE on mast cells and basophils. This cross-linking causes the mast cells and basophils to release allergic mediators including histamine, tryptase, chymase, platelet-activating factor, prostaglandin D2, cysteinyl leukotrienes, IL-6, and TNF-α [22], resulting in multi-organ effects that can present with up to 40 potential signs and symptoms and result in death secondary to respiratory or cardiovascular compromise.

The National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network have developed diagnostic criteria for anaphylaxis (Table 2.3) [23]:

1. Acute onset (minutes to hours) of involvement of skin, mucosal tissue, or both (hives, flushing, pruritis, angioedema) and either respiratory or cardiovascular compromise
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient: involvement of the skin or mucosal tissue (generalized hives, itch, flushing, swelling), respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxia), cardiovascular compromise (hypotension, collapse), persistent gastrointestinal symptoms (crampy abdominal pain, vomiting)
3. Hypotension after exposure to known allergen for that patient

Fifteen percent of patients exhibit neurologic symptoms of impending doom, headache, or confusion. Young children and infants can exhibit sudden behavioral changes like cessation of play, irritability, and clinginess [15].

**Table 2.3** Diagnostic criteria for anaphylaxis [23]

| |
|---|
| *Anaphylaxis is a clinical diagnosis that is highly likely when any one of the following three criteria are met:* |
| 1. *Onset of symptoms within minutes to hours involving the skin, mucosal tissue, or both (i.e., generalized hives, pruritus, flushing, angioedema)* |
| AND at least one of the following: |
| A. Respiratory compromise (i.e., dyspnea, wheezing, stridor, reduced peak expiratory flow, hypoxemia) |
| B. Hypotension or symptoms of end-organ dysfunction (i.e., syncope, hypotonia, urinary incontinence) |
| 2. *Two or more of the following occurring within minutes to several hours after exposure to a likely allergen for that patient* |
| A. Skin/mucosal symptoms (i.e., generalized hives, pruritus, flushing, angioedema) |
| B. Respiratory compromise (i.e., dyspnea, wheezing, stridor, reduced peak expiratory flow, hypoxemia) |
| C. Hypotension or symptoms of end-organ dysfunction (i.e., syncope, incontinence) |
| D. Persistent gastrointestinal symptoms (i.e., abdominal pain, vomiting) |
| 3. *Hypotension within minutes to several hours after exposure to a known allergen for that patient* |
| Hypotension defined as: |
| Children: |
| 1 month–1 year: less than 70 mm hg |
| 1–10 years: less than 70 mm hg + 2× age |
| 11–17 years: less than 90 mm hg |
| All ages: greater than a 30% decrease in systolic BP from that person's baseline |
| Adults: systolic BP less than 90 mmHg or a greater than 30% decrease from that person's baseline |

Adapted from Sampson et al. [23], with permission from Elsevier

Biphasic reactions are estimated to occur in 1–20% of anaphylactic reactions and involve a recurrence of symptoms after the apparent resolution of the initial reaction. Biphasic reactions typically occur about 8 hours after the initial reaction but have been reported up to 72 hours later [3]. The pathophysiology of biphasic reactions is not well understood, but it is more likely to occur in cases of moderate to severe anaphylaxis or when treatment with epinephrine is delayed [24]. It has been hypothesized that due to the large variation in time intervals, biphasic reactions may be due to a multitude of factors with earlier onset indicating medication wear-off or inadequate initial treatment and later onset due to biphasic

release of mediators like histamine and platelet-activating factor or activation of secondary inflammatory pathways [25].

### Alpha-Gal Allergy

The only known IgE-mediated food allergy that characteristically has a delayed reaction is allergy to galactose-alpha-1,3-galactose (alpha-gal). This is an allergic reaction to a carbohydrate epitope on mammalian meats, for example, beef, pork, and lamb. This reaction typically occurs 4–6 hours after ingestion [26]. Symptoms are similar to other IgE-mediated food allergies with hives, pruritus, and gastrointestinal symptoms being most common. Patients can experience severe anaphylaxis with cardiovascular and respiratory compromise. In most patients, eliminating beef, pork, lamb, and all other sources of non-primate mammalian meat is sufficient to avoid further allergic reactions. However, some patients continue to have reactions and require additional elimination of dairy and gelatin to fully avoid reactions since alpha-gal is also found in mammalian milk and bovine gelatin [27, 28]. The reaction is related to sensitization to the carbohydrate antigen galactose-alpha-1,3-galactose, which occurs after the bite of the lone star tick (*Amblyomma americanum*) in the United States and *Ixodes* species in Europe and Australia. The lone star tick is common in the East, Southeast, and Midwest United States [29]. The pathophysiology underlying IgE sensitization to alpha-gal after tick bite and resulting mammalian meat allergy is not well understood. The delay in reaction time is likely related to the time it takes for antigen digestion and/or processing, and it is likely that the allergic form of the oligosaccharide does not enter the circulation until several hours after eating. Alpha-gal is the only known carbohydrate antigen to induce an IgE-mediated reaction as all the remainder are due to proteins [26, 27, 30]. Alpha-gal allergy should be considered in children who live in areas where the lone star tick is common and who have a history of delayed reactions to red meat or recurrent urticaria, angioedema, or idiopathic anaphylaxis [31].

### Food-Dependent Exercise-Induced Anaphylaxis

Food-dependent exercise-induced anaphylaxis results in typical symptoms of anaphylaxis only after patients physically exert themselves within a few hours after eating. The symptoms are the same as anaphylaxis due to other causes. Symptoms typically begin during vigorous exercise, but the level of exertion that precipitates symptoms is unpredictable [32]. Patients do not have reactions if they consume the foods to which they are sensitized without exercising afterwards. Most patients only experience symptoms to specific foods to which they are sensitized, but some patients experience anaphylaxis if they exercise after consuming any food or drink. The foods most commonly implicated are wheat, shellfish, and nuts; however, a wide variety of triggering foods have been identified including celery, oranges, apples, rice, tomatoes, and cow's milk with geographic variability in sensitization patterns [9, 33]. Patients typically have positive IgE on skin prick or serum testing. Pathogenesis of this type of anaphylaxis is believed to similarly be due to mast cell degranulation and release of mediators. Patients have demonstrated skin biopsies with mast cell degranulation and transient elevations in tryptase. The specific mechanism by which exercise precipitates anaphylaxis in these patients has yet to be elucidated, but a number of hypotheses exist suggesting changes in serum osmolality, pH, gut permeability, and blood flow redistribution [33–35].

### Pitfalls in Making the Diagnosis of Anaphylaxis

Identifying IgE-mediated food allergy and anaphylaxis is challenging due to the high variability between symptoms and timing of reactions. The same individual can have widely variable reactions to the same food, and there is no way to predict the type or severity of the reaction. Anaphylaxis is often underreported and underdiagnosed in part due to this variability. Especially if it is a patient's first reaction, it can be difficult to identify a trigger. Young children are often not able to describe their symptoms, and patients who have altered consciousness or impaired

judgment will also not be able to describe the reaction. Hypotension can be challenging to recognize in very young children or infants. Skin symptoms (hives, itching, angioedema) are very helpful in identifying reactions; however, these are absent in 10–20% of all anaphylactic reactions [15]. Diagnosis of anaphylaxis can be aided by the expert guidelines (Table 2.3), and is highly likely when any one of the criteria is fulfilled. The presence of one of the three criteria predicts diagnosis of anaphylaxis 95% of the time [36]. Food allergy anaphylaxis plans are also available to caregivers to aid in the diagnosis and treatment of anaphylactic reactions [37]. Additionally, there are scoring tools available to grade the severity of anaphylaxis ranging from mild including only skin and subcutaneous involvement, moderate including respiratory, cardiovascular, or gastrointestinal involvement, and severe with hypoxia, hypotension, or neurologic compromise [38].

### Pollen-Food Allergy Syndrome (PFS) or Oral Allergy Syndrome (OAS)

Patients sensitized to pollen aeroallergens can experience symptoms after eating raw fruits, vegetables, nuts, or certain spices. Symptoms are typically limited to the oropharynx, though systemic reactions have been rarely reported. The cause of PFS is cross-reactivity that develops due to shared epitopes between the structure of pollen and fresh fruit and vegetables. The cross-reactive antigen in food is degraded by digestive enzymes and heat; therefore, patients can typically tolerate the heated versions of these foods, and symptoms are most often limited to local reactions in the oral cavity without progression to systemic symptoms. Symptoms characteristically occur within minutes and are usually mild and transient. The most common symptom is oropharyngeal pruritus, typically described as itching or tingling of the mouth and palate. Some patients describe throat tightness, and there has been reported oral and perioral angioedema, mucosal vesicles, conjunctivitis, congestion, and coryza. Rare other symptoms are facial rash, and nasal and otic pruritus. Patients with atopic dermatitis sensitized to birch pollen can experience worsening of eczema after consumption of a cross-reactive food. Less than 5% of patients progress to a more generalized reaction with nausea, vomiting, abdominal pain, upper respiratory obstruction and rarely progress to anaphylaxis [39]. PFS is further discussed in Chap. 5.

## Pathophysiology of Food Allergy Sensitization

Mechanisms underlying allergic sensitization are currently the subject of widespread investigation and are likely a complex interaction of genetic and environmental factors [40]. Sensitization can occur through the GI tract, the skin, and the respiratory tract and is thought to be related to impaired or inflamed mucosal barrier [41]. Tolerance to food antigens requires food antigen-specific regulatory T cells (T-regs) and is mediated by antigen presentation by CD103+ dendritic cells (DCs) in the GI tract and CD11b + dermal DCs and Langerhans cells in the skin. These cells migrate to lymph nodes where they induce antigen-specific Treg cells [42]. CD103 + DCs in the gut produce TGF-β and retinoic acid which drive Treg differentiation [43], and T-regs in turn produce suppressor cytokines like TGF-β, IL-10, and IL-35 [41]. In patients with food allergies, instead of induction of Treg cells, they develop antigen-specific $T_H2$ cells that produce IL-4, 5, and 13 and induce IgE class switching [40].

The specific factors that lead to this breakdown in tolerance and allergic sensitization are not yet understood, but it is likely that multiple factors are involved. The microbiota has been shown to have a strong association with allergic disease; however, the exact mechanisms through which the microbiome influences the immune system have yet to be fully elucidated [44]. Route of allergen exposure also likely plays a role, with increased exposure through non-oral routes resulting in allergic sensitization. For example, children with atopic dermatitis have impaired skin barrier function, which is hypothesized to lead to allergen exposure through the skin before the GI tract. This may contribute to increased rates of food allergies in these patients [43].

Despite the clear role of IgE in mediating anaphylaxis, IgE levels do not always correlate with clinical symptoms. Patients with high levels of allergen-specific IgE do not always develop clinical symptoms with food exposure, and similarly patients can have low or undetectable serum levels of allergen-specific IgE and still develop anaphylaxis to a specific food, indicating the causes of anaphylaxis are more complex than is currently understood.

## Non-IgE-/Cell-Mediated Food Allergies

Non-IgE- or cell-mediated food allergies are mediated by T cells and commonly result in delayed or chronic reactions. These reactions include food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES), celiac disease, and food-induced pulmonary hemosiderosis (Heiner syndrome). Key clinical features of each are summarized in Table 2.4.

### Food Protein-Induced Allergic Proctocolitis (FPIAP)

FPIAP presents with blood, and sometimes mucous, in the stools of otherwise healthy appearing, normally growing, and developing infants. Symptoms typically develop in the first 2–8 weeks of life [45]. Infants can have increased gas, colic, and increased frequency of bowel movements but are otherwise well appearing

**Table 2.4** Non-IgE-mediated food allergy reactions

| Immunopathology | Clinical features | Common causal foods | Pathophysiology |
|---|---|---|---|
| Food protein-induced allergic proctocolitis (FPIAP) | Blood +/− mucous in stool, gas, colic, increased frequency of bowel movements in the first 2–8 weeks of life. Infants are otherwise healthy appearing with normal growth and development | Maternal ingestion or formula with cow's milk, soy, and/or egg | Unknown. Likely related to dietary proteins causing inflammation in the lower GI tract |
| Food protein-induced enterocolitis syndrome (FPIES) | Severe projective emesis 1–4 hours after ingestion resulting in hypovolemic shock, pallor, lethargy, hypothermia, acidemia, methemoglobinemia, anemia, and leukocytosis with left shift. Findings often mistaken for sepsis. Diarrhea often follows 5–10 hours after ingestion | <3 months: cow's milk, soy<br>4–7 months: rice, oat, poultry<br>Older children: seafood, egg<br>Chronic: cow's milk or soy-fed infants <6 months | Unknown. Possible mechanism of antigen-specific T-cell-mediated inflammation and causing increased intestinal permeability |
| Celiac disease | Chronic diarrhea, bloating, abdominal pain<br>Chronic consequences related to malabsorption include growth problems and vitamin deficiencies. Failure to thrive is seen in young children<br>Classic skin finding dermatitis herpetiformis | Gluten | Autoinflammatory destruction of villi in the small intestine due to gliadin-specific CD4+ $T_H1$ cells. Virtually all patients are HLA-DQ2 and HLA-DQ8 positive |
| Food-induced pulmonary hemosiderosis (Heiner syndrome) | Infants with chronic respiratory symptoms with pulmonary infiltrates and hemosiderosis with iron-laden macrophages in the bronchial fluid, eosinophilia, iron deficiency anemia, and failure to thrive | Cow's milk | Unknown |

*HLA* Human leukocyte antigen

with normal growth [46]. Cow's milk is the most common trigger followed by soy and egg [45]. FPIAP can occur in breast- or formula-fed infants [45, 47]. Symptom improvement results after maternal avoidance of the triggering food or starting a hypoallergenic formula typically within 72 hours, but it can take up to 2 weeks for symptoms to fully resolve [48]. FPIAP typically completely resolves within 1–3 years, with the majority resolving within the first year [45]. The pathophysiology is largely unknown but is thought to be due to dietary proteins in breast-milk or formula causing inflammation in the lower GI tract [49, 50].

### Food Protein-Induced Enterocolitis Syndrome (FPIES)

FPIES affects infants and young children and presents with gastrointestinal symptoms of repetitive severe projective emesis 1–4 hours after ingestion of trigger foods. Diarrhea can occur 5–10 hours after ingestion [51, 52]. Infants triggered by cow's milk and soy typically present in the first 3 months of life, while children triggered by solids like rice, oat, or poultry typically present between 4 and 7 months [52, 53]. FPIES in older children has been reported to seafood and egg but is highly uncommon [52]. Symptoms are often severe and can result in significant dehydration and hypovolemic shock with pallor, lethargy, and hypothermia with hypotension reported in 15% of cases [46]. Associated lab findings of acidemia, methemoglobinemia, anemia, and leukocytosis with left shift are common and contribute to the condition being commonly misdiagnosed as sepsis. FPIES is considered a medical emergency given the rapid progression and clinical consequences of shock. Symptoms generally resolve within 24 hours with supportive care with anti-emetics and intravenous fluid resuscitation. A more chronic form of FPIES can be seen in cow's milk or soy formula-fed infants under 6 months old and presents with chronic vomiting, diarrhea, and failure to thrive. Symptoms resolve within several days of removing the triggering formula. If re-exposed, patients can present with acute FPIES [51].

The pathophysiology of FPIES is currently unknown, but hypothesized mechanisms involve antigen-specific T-cell-mediated inflammation causing increased intestinal permeability. FPIES is not an IgE-mediated food allergy; however, it is associated with comorbid atopic disease including eczema and allergic rhinitis. In addition, some patients with FPIES have positive IgE to the trigger food, especially casein in patients with cow's-milk-induced symptoms. The relationship between IgE and non-IgE mechanisms in patients with FPIES is still under investigation, and recent research has also suggested the role of innate immunity in the pathogenesis as well [54]. Ondansetron, a serotonin 5-HT3 receptor antagonist, is highly effective in improving FPIES symptoms, suggesting possible involvement of neuroimmune mechanisms [46, 51, 52].

### Celiac Disease

Celiac disease (CD) is caused by chronic mucosal inflammation in the small bowel. Symptoms are commonly chronic diarrhea, bloating, abdominal pain, and malabsorption with resulting failure to thrive in young children. Older children and adolescents can present with similar symptoms along with short stature and delayed puberty. Other findings are variable and can include osteoporosis, dental enamel hypoplasia, oral aphthae, arthritis, neurologic problems (headaches, cerebellar ataxia, idiopathic epilepsy, peripheral neuropathy), unexplained elevation of transaminases, and as the disease progresses vitamin deficiencies like iron, vitamin D, and vitamin K [55]. Dermatitis herpetiformis, an intensely pruritic vesicular rash, is a classic dermatologic finding. Extra-intestinal manifestations tend to increase with age [56]. Symptoms and histologic abnormalities typically resolve after gluten is removed from the diet within weeks to months.

CD is caused by autoreactivity resulting in destruction of the villi in the small intestine [57]. The pathogenesis is determined by a combination of genetic factors, exposure to gluten, and environmental influences. There is a strong genetic predisposition, and virtually all patients with CD have Human Leukocyte Antigen (HLA)-DQ2 and HLA-DQ8. Gluten is digested into gliadin fragments that are taken up by B cells, macrophages, and dendritic cells expressing HLA class II DQ2

and/or DQ8 molecules on their surface. These cells then present the antigen to gliadin-specific CD4+ $T_H1$ cells. Inflammatory cytokines including IFN-gamma and IL-15 contribute to the differentiation of intraepithelial lymphocytes into cytotoxic CD8+ T cells resulting in the classic histologic findings of villous atrophy and crypt hyperplasia. While almost all patients with CD are HLA-DQ2 or DQ8 positive, these alleles are also prevalent in about 30% of the general population who do not develop CD, indicating there are environmental factors that are yet to be understood [58]. The infant microbiota and the timing and amount of initial gluten exposure are hypothesized mechanisms still under investigation [56].

### Heiner Syndrome

Heiner syndrome or food-induced pulmonary hemosiderosis is a rare condition that affects infants exposed to cow's milk who develop chronic respiratory symptoms that can progress to pulmonary infiltrates and hemosiderosis with iron-laden macrophages in the bronchial fluid. Patients also frequently have eosinophilia, iron deficiency anemia, and failure to thrive. It is associated with milk-specific IgG antibodies. Avoidance of milk protein results in resolution of symptoms and pulmonary infiltrates [59–61]. The pathophysiology is poorly understood. A high index of suspicion is required as the presentation is variable and symptoms and imaging findings can be mistaken for recurrent or persistent infections.

## Mixed IgE-Mediated and Non-IgE-Mediated Reactions

### Eosinophilic Esophagitis and Eosinophilic Gastroenteritis

Eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EG) are examples of mixed IgE and non-IgE (T-cell mediated) reactions. Patients with EoE have a diverse clinical presentation depending on their age. Young children commonly present with feeding difficulties, failure to thrive, vomiting, reflux, and abdominal pain, while older children present with dysphagia and food impaction. Patients have been found to cut food into small pieces or drink large amount of liquids during meals [62, 63]. EoE is a histologic diagnosis that requires biopsy to confirm the presence of greater than 15 eosinophils per high-powered field in the esophagus [8]. Patients with EoE commonly have other atopic conditions and up to 90% have either allergic rhinitis, asthma, or an IgE-mediated food allergy [64]. Many cases of EoE exhibit seasonal variability with symptoms and eosinophilic infiltration worsening during high aeroallergen counts to which the patient is sensitized. For example, some patients with tree pollen allergies have been shown to exhibit worsening of disease in the spring [63]. EG is diagnosed when eosinophils are found distal to the esophagus in the stomach or lower GI tract and symptoms are variable, in part dependent on the location of eosinophil inflammation.

The pathophysiology of EoE and EG remains largely unknown but is likely multifactorial with genetic and environmental factors contributing. Although EoE is not solely an IgE-driven food allergy, it is primarily $T_H2$-driven with increased levels of IL-5, IL-9, and IL-13, increased eosinophilia, mucosal mast cells, and $T_H2$ lymphocytes in the esophageal tissue [63, 65]. There is likely a contribution of impaired epithelial barrier. Males are disproportionately affected with a 3:1 male to female ratio, and evidence points to a strong genetic component with a sibling risk ratio of 80, which is 40 times higher than for asthma [64].

## Key Questions in the History of Patients with Possible Food Allergy

Overall, a detailed history is the key in approaching a suspected food allergy. When obtaining a reaction history, clinicians should obtain details about all potential food triggers, timing of the reaction, response to treatments, and categorize the type of food allergy to determine whether it is IgE-mediated or another mechanism [8]. Important aspects of the history are detailed in Table 2.5 [4].

**Table 2.5** Key questions in obtaining the history for a patient with a suspected food allergy [4]

| | |
|---|---|
| Reaction history | Detailed description of symptoms including typical allergic symptoms (urticaria/angioedema, rhinoconjunctivitis, respiratory, gastrointestinal, cardiovascular)<br>Inquire whether symptoms are acute or chronic<br>Obtain exact timing of reaction in relation to suspected exposure and the overall time course of the reaction<br>Was the exposure ingestion, topical, or inhaled? |
| Triggers | Detailed history of possible exposures leading up to the reaction including all foods, beverages, medications or supplements, topical exposures, concurrent illnesses (i.e., was the child sick with an upper respiratory or other illness?)<br>Amount of food ingested prior to reaction<br>Was the food raw or cooked?<br>Whether the patient tolerated this food in the past or subsequently<br>Whether the suspected food has consistently triggered reactions<br>If the child is breastfed, obtain a dietary history from the mother<br>Inquire about others who ingested the same food to rule out food poisoning or scombroid which can closely mimic an IgE-mediated food allergy<br>Did the patient exercise in close proximity to symptoms? |
| Treatment response | Have there been any additional reactions since the food has been avoided?<br>Were antihistamines, epinephrine, or any other medications given?<br>Was medical attention sought and what was the treatment?<br>Was treatment beneficial?<br>What was the time course of recovery? |

Adapted from Sharma et al. [4], with permission from Elsevier

## Conclusion

FAs are a common threat in the pediatric population that is increasing in prevalence. FAs can have life-threatening consequences when they progress to anaphylaxis, and as such the accurate diagnosis is critical for preventing morbidity and mortality. An understanding of the underlying pathophysiology is key to differentiating the different types of FAs and anticipating their clinical consequences and anticipated management.

## References


1. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.
2. Cianferoni A, Muraro A. Food-induced anaphylaxis. Immunol Allergy Clin North Am. 2012;32(1):165–95.
3. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6):S1–58.
4. Sharma HP, Bansil S, Uygungil B. Signs and symptoms of food allergy and food-induced anaphylaxis. Pediatr Clin North Am. 2015;62(6):1377–92.
5. Hungerford JM. Scombroid poisoning: a review. Toxicon. 2010;56(2):231–43.
6. Settipane RA. Other causes of rhinitis: mixed rhinitis, rhinitis medicamentosa, hormonal rhinitis, rhinitis of the elderly, and gustatory rhinitis. Immunol Allergy Clin North Am. 2011;31(3):457–67.
7. Motz KM, Kim YJ. Auriculotemporal syndrome (Frey syndrome). Otolaryngol Clin North Am. 2016;49(2):501–9.
8. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014;134(5):1016–25.e43.
9. Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111(3):1601–8.
10. Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. J Allergy Clin Immunol. 2017;140(2):335–48.
11. Kobza Black A, Greaves MW, Champion RH, Pye RJ. The urticarias 1990. Br J Dermatol. 1991;124(1):100–8.
12. Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angio-oedema: a review of 554 patients. Br J Dermatol. 1969;81(8):588–97.
13. Sehgal VN, Rege VL. An interrogative study of 158 urticaria patients. Ann Allergy. 1973;31(6):279–83.
14. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 1992;327(6):380–4.
15. Simons FE. Anaphylaxis. J Allergy Clin Immunol. 2010;125(2):S161–81.
16. Crespo JF, Pascual C, Dominguez C, Ojeda I, Muñoz FM, Esteban MM. Allergic reactions associated with airborne fish particles in IgE-mediated fish hypersensitive patients. Allergy. 1995;50(3):257–61.
17. Roberts G, Lack G. Relevance of inhalational exposure to food allergens. Curr Opin Allergy Clin Immunol. 2003;3(3):211–5.

18. Lieberman P. Epidemiology of anaphylaxis. Curr Opin Allergy Clin Immunol. 2008;8(4):316–20.
19. Yu JE, Lin RY. The epidemiology of anaphylaxis. Clin Rev Allergy Immunol. 2018;54(3):366–74.
20. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. J Allergy Clin Immunol. 2004;114(1):159–65.
21. Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. J Allergy Clin Immunol. 2007;120(3):491–503.
22. Ono E, Taniguchi M, Mita H, Fukutomi Y, Higashi N, Miyazaki E, et al. Increased production of cysteinyl leukotrienes and prostaglandin D2 during human anaphylaxis. Clin Exp Allergy. 2009;39(1):72–80.
23. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second national institute of allergy and infectious disease/food allergy and anaphylaxis network symposium. J Allergy Clin Immunol. 2006;117(2):391–7.
24. Waleed A, Ellis AK. Do corticosteroids prevent biphasic anaphylaxis? JACI. 2017;5(5):1194–205.
25. Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. Immunol Allergy Clin North Am. 2007;27(2):309–26.
26. Commins SP, Platts-Mills TAE. Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,3-galactose (alpha-gal). Curr Allergy Asthma Rep. 2013;13(1):72–7.
27. Tripathi A, Commins SP, Heymann PW, Platts-Mills TAE. Delayed anaphylaxis to red meat masquerading as idiopathic anaphylaxis. J Allergy Clin Immunol Pract. 2014;2(3):259–65.
28. Mullins RJ, James H, Platts-Mills TAE, Commins S. Relationship between red meat allergy and sensitization to gelatin and galactose-α-1,3-galactose. J Allergy Clin Immunol. 2012;129(5):1334–42.
29. Centers for Disease Control and Prevention. Approximate distribution of the Lone Star Tick. https://www.cdc.gov/ticks/maps/lone_star_tick.html (2011). Accessed 6 Dec 2018.
30. Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis BD, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2009;123(2):426–33.
31. Kennedy JL, Stallings AP, Platts-Mills TAE, Oliveira WM, Workman L, James HR, et al. Galactose-alpha-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children. Pediatrics. 2013;131(5):e1545–52.
32. Castells MC, Horan RF, Sheffer AL. Exercise-induced anaphylaxis (EIA). Clin Rev Allergy Imunol. 1999;17(4):413–24.
33. Wong GK, Krishna MT. Food-dependent exercise-induced anaphylaxis: is wheat unique? Curr Allergy Asthma Rep. 2013;13(6):639–44.
34. Feldweg AM. Exercise-induced anaphylaxis. Immunol Allergy Clin North Am. 2015;35(2):261–75.
35. Barg W, Medrala W, Wolanczyk-Medrala A. Exercise-induced anaphylaxis: an update on diagnosis and treatment. Curr Allergy Asthma Rep. 2011;11(1):45–51.
36. Kemp SF. Navigating the updated anaphylaxis parameters. Allergy Asthma Clin Immunol. 2007;3(2):40–9.
37. Food Allergy Research & Education (FARE). Food Allergy & Anaphylaxis Emergency Care Plan. https://www.foodallergy.org/sites/default/files/2018-06/emergency-care-plan.pdf (2018). Accessed 1 Dec 2018.
38. Brown SGA. Clinical features and severity grading of anaphylaxis. JACI. 2004;114(2):371–6.
39. Price A, Ramachandran S, Smith GP, Stevenson ML, Pomeranz MK, Cohen DE. Oral allergy syndrome (pollen-food allergy syndrome). Dermatitis. 2015;26(2):78–88.
40. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41–58.
41. Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA. Mechanisms of food allergy. J Allergy Clin Immunol. 2018;141(1):11–9.
42. Tordesillas L, Berin MC, Sampson HA. Immunology of food allergy. Immunity. 2017;47(1):32–50.
43. Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ, Nadeau KC. Molecular and cellular mechanisms of food allergy and food tolerance. J Allergy Clin Immunol. 2016;137(4):984–97.
44. Gensollen T, Blumberg RS. Correlation between early-life regulation of the immune system by microbiota and allergy development. J Allergy Clin Immunol. 2017;139(4):1084–91.
45. Leonard SA. Non-IgE-mediated adverse food reactions. Curr Allergy Asthma Rep. 2017;17(12):84.
46. Nowak-Wegrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. J Allergy Clin Immunol. 2015;135(5):1114–24.
47. Feuille E, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome, allergic proctocolitis, and enteropathy. Curr Allergy Asthma Rep. 2015;15(8):50.
48. Lake AM. Food-induced eosinophilic proctocolitis. J Pediatr Gastroenterol Nutr. 2000;30:S58–60.
49. Lake AM, Whitington PF, Hamilton SR. Dietary protein-induced colitis in breast-fed infants. J Pediatr. 1982;101(6):906–10.
50. Kaya A, Toyran M, Civelek E, Misirlioglu E, Kirsaclioglu C, Kocabas CN. Characteristics and prognosis of allergic proctocolitis in infants. J Pediatr Gastroenterol Nutr. 2015;61(1):69–73.
51. Cherian S, Varshney P. Food protein-induced enterocolitis syndrome (FPIES): review of recent guidelines. Curr Allergy Asthma Rep. 2018;18(4):28.

52. Nowak-Wegrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: executive summary – workgroup report of the adverse reactions to foods committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2017;139(4):1111–1126.e4.
53. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. Pediatrics. 2003;111(4):829–35.
54. Goswami R, Blazquez AB, Kosoy R, Rahman A, Nowak-Wegrzyn A, Berin MC. Systemic innate immune activation in food protein-induced enterocolitis syndrome. J Allergy Clin Immunol. 2017;139(6):1885–96.e9.
55. Barker JM, Liu E. Celiac disease: pathophysiology, clinical manifestations, and associated autoimmune conditions. Adv Pediatr Infect Dis. 2008;55:349–65.
56. Guandalini S, Assiri A. Celiac disease: a review. JAMA Pediatr. 2014;168(3):272–8.
57. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med. 1997;3(7):797–801.
58. Green PHR, Lebwohl B, Greywoode R. Celiac disease. J Allergy Clin Immunol. 2015;135(5):1099–106.
59. Heiner DC, Sears JW, Kniker WT. Multiple precipitins to cow's milk in chronic respiratory disease. A syndrome including poor growth, gastrointestinal symptoms, evidence of allergy, iron deficiency anemia, and pulmonary hemosiderosis. Am J Dis Child. 1962;103:634–54.
60. Moissidis I, Chaidaroon D, Vichyanond P, Bahna SL. Milk-induced pulmonary disease in infants (Heiner syndrome). Pediatr Allergy Immunol. 2005;16(6):545–52.
61. Lee SK, Kniker WT, Cook CD, Heiner DC. Cow's milk-induced pulmonary disease in children. Adv Pediatr Infect Dis. 1978;25:39–57.
62. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med. 2004;351(9):940–1.
63. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med. 2015;373(17):1640–8.
64. Cianferoni A, Spergel JM. Eosinophilic esophagitis and gastroenteritis. Curr Allergy Asthma Rep. 2015;15(9):58.
65. Caldwell JM, Paul M, Rothenberg ME. Novel immunologic mechanisms in eosinophilic esophagitis. Curr Opin Immunol. 2017;48:114–21.

# 3 Diagnosis and Differential Diagnosis of Food Allergy

Efren Rael, Vanitha Sampath, and Kari Christine Nadeau

## Introduction

Adverse reactions to foods are common and vary in clinical presentation, severity, and etiology [1]. Broadly, they are classified as immune mediated and non-immune mediated (Fig. 3.1). Non-immune-mediated adverse food reactions are the most common and are non-specific. Immune-mediated adverse reactions to foods include food allergy and celiac disease. Although celiac disease is an immune disorder, it is an autoimmune disease and not allergic in etiology. When people with celiac disease eat gluten, the immune system attacks and damages the villa of the small intestine.

Food allergy is defined as an adverse antigen-specific immune-mediated response, which occurs reproducibly on exposure to a given food [2, 3]. As prevalence has continued to rise over the past few decades, there has been increased focus on research into methods to prevent, diagnose, and treat food allergy. Worldwide, they now affect 6–11% of the population [4–11]. Food allergy is often confused with food intolerances, and a diagnosis of food allergy is challenging as it varies in type, severity, and clinical presentation and necessitates the exclusion of non-immune and environmental allergens as causative factors. Identifying food allergy correctly is important for preventing allergic reactions but also to prevent unnecessary dietary restriction of foods. A thorough clinical history and physical examination is a key first step in diagnosing those with adverse reactions to foods as it guides clinicians regarding further testing (skin and blood serum tests, elimination diets, biopsies, or oral food challenge (OFCs)) that can assist with food allergy diagnosis. In those with suspected food allergy, a clinical history should include age, dietary history, information on suspected food allergen such as quantity ingested, form of food allergen (cooked, raw), time between ingestion of suspected food allergen and symptoms, route of exposure (dermal, inhalation, oral), time to resolution of symptoms, nature of symptoms, reproducibility of symptoms on repeated ingestion, personal and family history of comorbid atopic diseases, medications, illnesses, and other lifestyle factors such as exercise. During the evaluation, a differential diagnosis to rule out toxic reactions to foods or other food intolerances is important [12]. Food allergy is broadly classified into IgE mediated, non-IgE mediated, and mixed (IgE- and non-IgE mediated). The main diseases associated with each of these three types of food allergies are illustrated in Table 3.1. This chapter

E. Rael · V. Sampath
Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Stanford, CA, USA
e-mail: erael@stanford.edu; vsampath@stanford.edu

K. C. Nadeau (✉)
Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Department of Medicine and Pediatrics, Stanford, CA, USA
e-mail: knadeau@stanford.edu



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_3

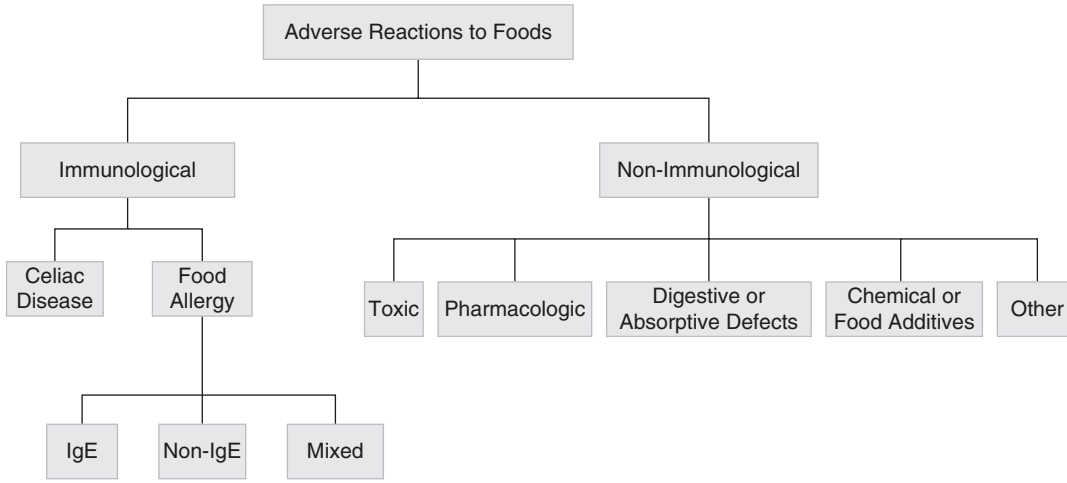



**Fig. 3.1** Classification of adverse reactions to foods

**Table 3.1** Types of food allergy

| Type of food allergy | Disease |
|---|---|
| IgE | Immediate GI hypersensitivity<br>Alpha-gal allergy<br>Oral allergy syndrome<br>Anaphylaxis<br>Food-dependent exercise-induced anaphylaxis |
| Non-IgE | Food protein-induced allergic proctitis (FPIAP)<br>Food protein-induced enteropathy (FPE)<br>Food protein-induced enterocolitis (FPIES) |
| Mixed (IgE and non-IgE) | Eosinophilic esophagitis<br>Eosinophilic gastroenteritis<br>Eosinophilic colitis |

focuses on the clinical presentation of the different types of food allergies and the tools available to assist a clinician with diagnosis and differential diagnosis of food allergy.

## Differential Diagnosis of Adverse Food Reactions

Differential diagnosis of food allergy is extensive. A variety of anatomical and digestive problems, including pancreatic insufficiency, Shwachman-Diamond syndrome, pyloric stenosis, Hirschsprung's disease, tracheoesophageal fistula, gall bladder disease, hiatus hernia, gastric reflux, gastric ulcers, cancer, irritable bowel syndrome, and others, can also produce symptoms that mimic food allergy such as nausea, flatulence, bloating, vomiting, diarrhea, and dyspepsia. Further, non-immune food intolerances are common with various etiologies including enzyme deficiencies, deficiencies of digestion and absorption, inborn errors of metabolism, pharmacologic, psychosomatic, sensitivity to food additives, or reactions to naturally occurring chemicals or toxins in foods [13, 14].

Examples of adverse reactions that are not classified as food allergy include reactions to food preservatives, flavoring agents, or sweeteners (e.g., butylated hydroxyanisole and butylated hydroxytoluene, sodium metabisulfite, benzoates, monosodium glutamate, nitrites, nitrates, tartrazine). Food additives should be suspected in patients with a history of reactions to a number of commercially prepared unrelated foods but not to similar homemade foods [15]. Adverse food reactions are also caused by foodborne toxins from bacteria (e.g., *Escherichia coli* O104:H4 –Shiga, *Clostridium botulinum* –botulinum neurotoxin) [16], fungi (e.g., *Aspergillus* species – Aflatoxin, *Fusarium* species – trichothecenes) [17], and fish (e.g., scombroid poisoning in tuna and mackerel, ciguatera toxin poisoning from mackerel, snapper and barracuda, saxitoxin from shellfish) [18, 19].

**Table 3.2** Common non-immune adverse food reactions

| Common non-immune adverse food reactions (differential diagnosis of food allergy) |
|---|
| Autoimmune: |
| Celiac disease |
| Digestive or absorptive disorders and inborn errors of metabolism |
| Lactose and fructose intolerance, gluten sensitivity, galactosemia, phenylketonuria |
| Pharmacological reactions: |
| Tyramine (aged cheese, pickled herring) |
| Glycosidal alkaloid solanine (potatoes) |
| Caffeine (coffee, tea) |
| Theobromine (chocolate, tea) |
| Chemicals and food additives: |
| Sulfites, nitrites, food colorants, sweeteners, flavor enhancers, and preservatives (e.g., monosodium glutamate, sodium metabisulfite, nitrites) |
| Toxins: |
| Excess histamine (scombroid fish toxin in tuna and mackerel) |
| Aflatoxins (*Aspergillus* species) |
| Shiga (foods contaminated by *Escherichia coli*) |
| Saxitoxin (shellfish) |
| Other: |
| Viral infections, spicy foods |
| Psychosomatic |

Adverse food reactions can occur with food-related agents. Vasoactive amines such as tyramine (e.g., in cheeses, pickled herring), serotonin (e.g., in banana and tomato), tryptamine (e.g., in tomato and plum), phenylethylamine (e.g., chocolate), histamine (e.g., in some fish and sauerkraut) caffeine (e.g., coffee, tea, and soft drinks), theobromine (in chocolate and tea), and glycoside alkaloid solanine (potatoes) are common ingredients in foods [20, 21]. Accidental contaminants from heavy metals such as mercury and copper, pesticides, antibiotics, and dust/storage mites have been reported to cause gastrointestinal symptoms.

Other conditions that can lead to adverse food reactions include psychological reactions from food aversions and food phobias. Examples of common non-immune-mediated adverse reactions to foods are listed in Table 3.2.

## IgE-Mediated Food Allergy

IgE-mediated allergies are the best understood and characterized. They include immediate gastrointestinal hypersensitivity, anaphylaxis, food-dependent exercise-induced anaphylaxis, oral allergy syndrome, and alpha-gal allergy [22]. A clinical history can assist the physician towards determining the type of IgE-mediated food allergy and guide them towards further testing to support the diagnosis. Common food allergens associated with immediate gastrointestinal hypersensitivity are cow's milk, egg, peanut, tree nuts, soy, shellfish, and finned fish. Symptoms are typically observed within minutes to about 2 hours after ingestion of the suspected allergen, generally proteins in foods. A physical exam during an acute reaction may indicate reactions involving one or many organs (cutaneous, ocular, gastrointestinal, respiratory, and cardiovascular) (Table 3.3) and may be mild, moderate, or severe. The most severe reaction is anaphylaxis, which is a rapid and systemic allergic reaction with involvement of the upper and lower airways, skin, conjunctiva, and gastrointestinal and cardiovascular systems. If untreated, anaphylaxis can be fatal. Death due to anaphylaxis usually occurs as a result of respiratory obstruction or cardiovascular collapse, or both. In anaphylaxis, biphasic reactions can also occur, with recurrence of symptoms 2–24 hours after the initial reaction [23]. Anaphylaxis can also be induced by exercise as in food-dependent exercise-induced anaphylaxis (FDEIAn). In individuals with this disorder, anaphylaxis is likely

**Table 3.3** Symptoms commonly associated with acute food allergy

| Organ system involved | Symptom |
|---|---|
| Cutaneous | Erythema, pruritus, urticaria, angioedema, rash (morbilliform or eczematous), burning sensation |
| Ocular | Pruritus, tearing, periorbital edema |
| Gastrointestinal | Nausea, abdominal pain, vomiting, diarrhea, oral pruritus and angioedema, pharyngeal pruritis, reflux |
| Respiratory | Nasal congestion, rhinorrhea, sneezing, cough, wheezing, laryngeal edema, chest tightness, dyspnea |
| Cardiovascular | Tachycardia, dizziness, headache, decreased blood pressure, arrhythmia, pallor |

if the food allergen is ingested within 2–4 hours before or after exercise [24]. The best characterized FDEIAn is to ω5-gliadin in wheat [25]. The World Allergy Organization; the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma, and Immunology; and the European Academy of Allergy and Clinical Immunology have issued guidelines on anaphylaxis. Laboratory tests are not helpful in diagnosing anaphylaxis at the time of patient presentation. Measurement of a biologic marker such as serum total tryptase is only elevated in about 60% of clinically confirmed anaphylaxis, takes hours, and test results are not available on an emergency basis [26–28].

Cross-reactivity between allergens from a number of sources (plant, fungal, invertebrate, mammalian, or avian origin) and food allergens or between food allergens has been described. However, these may indicate sensitivity rather than true clinical reactivity. Using data obtained from OFCs and other factors, the probability of cross-reactivity between some foods has been estimated. For example, the risk of cross-reactivity between cow's and goat's milk is estimated at 92% whereas between peanuts (a legume) to other legumes such as peas, lentils, and beans is estimated at about 5% [29]. Two IgE-mediated allergic diseases, Oral Allergy Syndrome and Alpha-Gal Allergy, are caused by cross-reacting allergens.

Oral allergy syndrome, also called pollen food allergy syndrome or pollen allergy syndrome, is generally triggered mainly on ingesting fruits and vegetables but also other plant-based foods [30]. Symptoms are generally mild and limited to pruritus of the lips, throat, and mouth although, rarely, oral angioedema may be observed. In simple food allergies, reactions are caused by direct sensitization to food proteins; in oral allergy syndrome, reactions occur due to cross-reactivity between food proteins and inhalant allergens. Pollen-sensitized individuals (generally with symptoms of rhinorrhea) mount an allergic reaction to structurally similar foods. For example, one of the most common tree pollen-fruit cross-reactivity is between Bet v 1 (birch pollen) and Mal d I (apple) [31]. Those with latex allergy have increased risk of allergy to fruits such as kiwi, tomato, bell pepper, and others. Some common pollinoses associated with oral food allergy include birch, ragweed, Timothy grass, Japanese cedar, and mugwort [32]. Common food triggers are kiwi, apple, and celery. Symptoms tend to vary with worsening symptoms during pollen season and improvement in symptoms out of pollen season. Many allergens are heat labile, and allergenicity of the foods is lost in cooking.

Alpha-gal allergy is an atypical IgE-mediated allergy. Most allergens are proteins; however, in alpha-gal allergy, the allergen is an oligosaccharide (galactose-alpha-1,3-galactose) rather than a protein. It is found in non-primate mammalian red meats such as a beef, pork, and lamb. On exposure to tick bites, α-gal immunoglobulin E is generated in susceptible individuals. An allergic reaction is then mounted when a person eats red meat due to cross-reactivity between the α-gal injected in the individual during a tick bite and those in red meat. Symptoms in alpha-gal allergy are not immediate but are delayed and appear 3–6 hours after ingestion of these meats and may include anaphylaxis, angioedema, or urticaria [33, 34].

## Diagnosing IgE-Mediated Food Allergy

Based on clinical history, if an IgE-mediated food allergy is suspected, in vivo skin prick tests (SPT) and in vitro blood serum tests, both of which measure IgE to specific food allergens (sIgE), can be considered as a secondary diagnostic step; however, both tests have high sensitivities and low specificities and are associated with a high number of false positives and indicates sensitization to the allergen (circulating IgE) that may or may not indicate clinically relevant food allergy (mast cell-bound IgE). Differentiating between allergy and sensitization is challenging but important for preventing unnecessary elimination of non-allergenic foods from the diet. History should guide the clinician on the choice of allergens tested. OFCs are the

definitive means of confirming a food allergy; however, these are time consuming and carry the risk of severe reaction. A stepped approach, starting with clinical history and physical examination, followed by SPTs and sIgE, can assist with reducing the number of OFC tests [35].

## In Vivo Skin Prick Tests

The advantages of SPTs are that they are simple, inexpensive, and the results can be obtained quickly (usually 15 minutes). However, as risk of anaphylaxis with SPTs is present, although rare, testing should be conducted by trained staff in a clinician's office. Clinical history should guide choice of allergens tested as the use of routine panels of allergens on every patient is wasteful and can be misleading with irrelevant positives. In general, the larger the WC, the more likely that the diagnosis of food allergy is clinically relevant; however, larger values do not correlate with severity of reactions.

SPTs involve a prick puncture of the skin with allergen, either placed on the forearms or the back. Intradermal testing is not recommended due to unacceptably high false-positive rate and potential to trigger a systemic reaction. The test depends on the release of histamine from sensitized mast cells and, therefore, this test is not useful for those patients who cannot discontinue use of antihistamines before testing. Other medications can also interfere with test results [36]. The test is also unsuitable for people with dermatographism or extensive skin disease. SPT is considered positive if there is a mean wheal diameter of 3 mm or greater than the saline negative control. Age, device, and potency, source and nature of allergen (commercial extracts or fresh foods), and technique (pressure, body location, timing of measurement) can influence results and, therefore, the test should be conducted by trained health care staff. Where no reliable commercial antigens are available, generally for fruit or vegetable antigens that are labile and degrade easily, direct prick-prick skin test with such foods may be desirable. In the prick-prick skin test, the food is first pricked and then the patient's skin is pricked. SPTs have high negative predictive values and are useful for excluding food allergy [37]; however, false negatives may occur if the extract used for testing lacks the allergen in sufficient quantities.

**Table 3.4** SPT positive predictive values (≥95%) for some common allergenic foods

| Food | Diagnostic cutoff points SPT (mm) ≥ 95% PPV or |
|---|---|
| Egg | ≥4 [38], ≥5 [39], ≥7 [37, 40, 41], ≥13 [42] |
| Cow's milk | ≥8 [37, 40, 41], ≥15 [43], 12.5 [42] |
| Peanut | ≥8 [37, 38, 40, 41], ≥16 [44] |
| Sesame | 8 [38] |

The positive predictive values of SPTs cited in the literature vary substantially, likely due to differences in the population studied, the test allergens used, and SPT and OFC protocols used. A positive predictive value of 95% or greater indicating a very high probability of an allergic reaction to the suspected allergen has been determined for certain allergens (Table 3.4) and can be useful for the diagnosis of food allergy but further testing in broader populations under standardized conditions are warranted.

## In Vitro Serum Tests for Detecting IgE

Conventional sIgE tests use crude whole-food extracts containing allergenic and non-allergenic components to measure IgE antibody levels to specific foods. Recently, component-resolved diagnostic (CRD) tests measuring IgE to specific proteins in foods rather than using whole-food extracts have been developed. These tests measure circulating sIgE using fluorescence enzyme immunoassay. Total IgE is not recommended, and studies evaluating any additional value of sIgE to total IgE ratio have been inconclusive [45–47].

### sIgE Using Whole Food Extracts

Current methodologies for quantitatively detecting sIgE to single whole-allergen extracts using ELISAs include ImmunoCAP (Thermo Fisher, Uppsala, Sweden), Immulite (Siemens, Los

Angeles, CA), HYTEC-288 [48], and others. Similar to SPT tests, clinical history should guide choice of allergens tested and the use of routine panels is not recommended. The test has a high sensitivity but low specificity. A positive value indicates sensitization to the allergen, but may or may not indicate clinically relevant allergy, although increasing levels correlate with increased likelihood of a diagnosis of clinical allergy. An undetectable IgE level (<0.35 kU/L) for peanut is still associated with about a 20% chance of reactivity [49], likely caused by underrepresentation of minor allergens or instability of allergens during allergen extract preparation. Probability curves, sensitivity, and specificity serve as useful references for interpretation of these tests to determine the need for OFC to confirm allergy. PPVs have been established for a few allergens and are indicated in kUA/L ($U_A$ = allergen-specific units; 1 unit ≈ 2.4 ng IgE); increasing PPVs indicating greater likelihood of allergy. However, these values may differ based on the assay method [50, 51] and age. Physicians should take this into account when extrapolating PPVs from published studies into clinical practice and in recommending a physician-supervised OFC to confirm or exclude food allergy. Table 3.5 lists 95% PPV values for common allergens.

## sIgE to Allergenic Components in Foods Using CRD

As whole-food allergen extracts are inherently complex, variable, and can include true allergens, cross-reactive, and non-allergenic components making interpretation difficult, there has been a push to develop well-characterized allergenic components. With increased knowledge of the molecular characteristics of allergens, specific protein allergens (purified or recombinant), or protein epitopes, rather than whole-food allergen extracts are being increasingly used to determine sIgE. Research on the identification and characterization of food allergen is an active ongoing process. A nomenclature standardization website approved by the World Health Organization and the International Union of Immunological Societies is available at http://www.allergen.org. A number of allergen families have been classified based on their structural and functional properties. Among plant allergens, the majority of allergens belong to the prolamin, Bet v1 homologs, the cupin, or the PR-10 family. Although all animal proteins have the potential to become allergens, the majority fall into the tropomyosin, EF-hand, and casein families [55, 56]. Some major components of food allergens and their clinical relevance are summarized in Table 3.6.

**Table 3.5** sIgE positive predictive values (≥95%PPV) for some common foods

| Food | sIgE kUA/L (95%PPV) |
|---|---|
| Egg | 1.7 [38], 12.6 [52], 6 [49] |
| Cow's milk | 42.7 [53], 32 [49] |
| Peanut | 34 [38], 13.0 [54], 15 [49] |
| Fish | 20 [49] |
| Walnut | 18.5 [54] |
| Wheat | 100 [49] |

**Table 3.6** Clinical correlation of common allergenic components in foods

| Food | Clinical correlation | Allergenic component |
|---|---|---|
| Peanut | Best predictors of severe peanut allergy [57] | Ara h 2 and Ara h 6 |
| | Best diagnostic accuracy [58] | Ara h 2 and Ara h 6 |
| | Best predictor of tolerance to peanuts [58] | Ara h8 |
| Cow's milk | Best predictor of milk allergy [59] | Bos d 12 |
| Hazelnut | Best predictor of hazelnut allergy [60] | Cor a 14 |
| | Best predictor of severe hazelnut allergy [61] | Cor a 9 and Cor a 14 |
| Egg | Good predictor of tolerance to cooked egg [62] | Gal d 1 (ovomucoid) |
| Wheat | Associated with exercise-induced anaphylaxis [63] | Omega-5 gliadin |
| Walnut | Cross-reactive with hazelnut, sesame, and pistachio [64] | Jug r 6 |
| Soy | Marker of severe reaction [65] | Gly m 4 |
| Meat | Predictive of delayed IgE allergy to non-primate mammalian meats [66] | Galactose-alpha-1,3-galactose |

CRDs using molecular components of food allergens are rapidly evolving and increase our possibility to treat food-allergic patients with a more individual approach. As a research tool, CRD provides us the ability to comprehensively piece together the molecular characteristics of allergenic proteins. Understanding structural similarities between allergens can also assist in understanding cross-sensitization. Overall, CRD is a promising technique for improved diagnosis, ability to distinguish sensitivity due to cross-sensitization from true tolerance, prognosis with treatment, resolution of food allergy, and prediction of reaction severity. For example, in a study of children with peanut allergy, Ara h 6 and Ara h 2 were found to be the best predictors of peanut allergy [67]. A limitation of CRD is that not all relevant allergenic components are available, and diagnostic cut off values still need to be validated in different populations.

CRD methods currently available can be used to determine allergenicity to a single allergen (ImmunoCAP) or multiple allergens (ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC)) simultaneously. Using only 30 μl of serum or plasma, ImmunoCAP ISAC microarray technology currently enables measurement of IgE antibodies to a fixed panel of over 100 components from around 50 allergen sources in a single step. The need for only a small volume of blood is important, particularly for infants and young children. While ImmunoCAP is a quantitative assay with results expressed in kUA/L, ImmunoCAP ISAC is a semi-quantitative assay with results expressed in ISAC standardized units. In recent years, a number of studies have demonstrated the utility of CRD to improve the specificity of current allergy testing or predict the severity of food allergy. However, validation of these tests with larger more diverse populations is required. Table 3.6 lists some clinically relevant allergenic components. Relevant sequential and conformational epitopes are also being identified and validated, and peptide microarray assays for IgE epitope mapping are being optimized and validated [68]. It has been suggested that IgE-recognizing sequential epitopes of ovalbumin have more persistent egg allergy than those binding conformational epitopes [69]. In another study, greater diversity of IgE epitopes and higher affinity, as determined using the peptide microarray, were associated with clinical phenotypes and severity of milk allergy [69]. Use of protein epitopes in allergy testing has been attempted only for a few foods and is still a research tool.

## Basophil Activation Test (BAT)

The BAT is a whole blood in vitro functional assay using flow cytometry. It measures the expression of activation markers (CD63 and CD203c) on basophils on allergen stimulation and can distinguish true allergy from sensitization and predict anaphylaxis. BAT results are reported as basophil reactivity or basophil sensitivity. Basophil reactivity is the maximum proportion of activated basophils at any concentration of the stimulating allergen. Basophil sensitization is the smallest allergen concentration causing 50% of maximum basophil activation. Studies indicate that BAT has comparable sensitivity and enhanced specificity over SPTs and sIgEs, respectively [70]. In peanut-allergic children, Santos et al. showed BAT to be superior to SPT, sIgE, and Arah2-sIgE with 100% specificity, 83.3% sensitivity, 100% PPV, and 93.4% accuracy, enabling a diagnosis of IgE-mediated food allergy with a high degree of certainty [71] and decreasing the need for an OFC. BAT reactivity and sensitivity has been shown to correlate with severity and threshold of allergic reactions during OFCs [72]. BAT has also shown promise in predicting the resolution of food allergies naturally [71] and with immunotherapy [73]. Although BAT appears promising, further standardization of the methodology and data analyses and validation of different allergens and patient populations would help to enable a wider clinical application of BAT.

## Oral Food Challenge

An OFC involves the administration of increasing amounts of the suspected food allergen to

diagnose food allergy. It can be either open, single blinded, or double blind, placebo controlled [74, 75]. It is important to take into consideration the importance of confirming the diagnosis, the risk of life-threatening anaphylaxis, the time and resources involved in conducting the OFC, the strength of clinical history, and the results of the physical exam, in vitro serum IgE, and SPTs to aid in the determination of whether to proceed with the OFC and whether to conduct the OFC at home or at the clinic. In case of a history of very severe reaction, the benefit of a challenge has to be carefully weighed against the risk.

The open OFC involves ingestion of the food in a commonly encountered form (such as peanut butter) with both the patient and the doctor aware of the challenge food. In a single-blinded OFC, the food is administered in a masked form (either in a capsule or mixed with another food to hide the flavor and texture) and the doctor (but not the patient) is aware of the food being challenged. The double-blind placebo-controlled food challenge, which is the gold standard for a definite confirmation of food allergy, involves administration of the food so that neither the doctor nor the patient is aware if the food they are being challenged with is a placebo or an allergen. In OFCs, the food must first be completely eliminated from the diet for at least 2 weeks prior to the challenge. Both the open and single-blinded OFCs carry the risk of bias although the single-blind OFC carries a lower risk of bias as subjective symptoms, such as itching, anxiety, and nausea, are hard to objectively quantify.

## Non-IgE-Mediated Food Allergy

Non-IgE-mediated food allergies primarily affect the gastrointestinal tract and almost always affect children. Non-IgE-mediated reactions are delayed and symptoms are generally observed after 1 hour to days after ingestion of the suspected allergen. By definition, they do not involve the production of IgE, and currently there are no validated tests to confirm non-IgE-mediated food allergy. The mechanisms underlying non-IgE food allergies are poorly characterized and are thought to be T-cell mediated. The absence and presence of symptoms on elimination and reintroduction of the suspected allergen can indicate food allergy. However, the lack of specific diagnostic tests and biomarkers can make the clinical diagnosis challenging [3]. Well-recognized non-IgE-mediated gastrointestinal food allergies include food protein-induced enterocolitis syndrome (FPIES), food protein-induced proctocolitis (FPIP), and food protein enteropathy (FPE) [76, 77]. Their main distinguishing clinical characteristics include delayed repetitive vomiting (FPIES), benign blood and mucus in stool (FPIAP), and chronic diarrhea (FPE).

### Food Protein-Induced Enterocolitis (FPIES)

FPIES typically presents in infancy with the most common triggers being cow's milk and soy milk but other foods such as grains (predominantly rice), meats, vegetables, and fruits have also been reported to cause the disease. Symptoms may be acute or chronic with acute FPIES being the most common form of the disease. FPIES usually develops in infants under 9 months of age. Symptoms occur 1–4 hours following food ingestion, and reactions are quite dramatic with repetitive bouts of protracted emesis, with or without diarrhea, and can lead to lethargy and pallor due to fluid loss. Shock can occur with progression and can lead to symptoms mimicking sepsis with hypotension, acidemia, hypothermia, and methemoglobinemia. Chronic FPIES occurs with continuing ingestion of the offending food and can be associated with failure to thrive and poor weight gain, but elimination of the offending foods from the diet is associated with resolution of symptoms and recovery of growth parameters and health status.

Diagnosis of FPIES is challenging and misdiagnosis is common. It remains a diagnosis of exclusion. The differential diagnosis for FPIES is extensive with symptoms often mimicking other diseases such as infectious gastroenteritis, anaphylaxis, or sepsis. The lack of diagnostic biomarkers contributes to the diagnostic challenge.

Symptoms typically do not involve the skin or the respiratory tract often distinguishing clinical presentation with IgE-mediated anaphylaxis [78]. Diagnosis of FPIES is commonly based on history alone, positive response after food elimination and, if necessary, a clinically supervised OFC. Recently, an international consensus guideline with diagnostic criteria for FPIES was published [78, 79]. Briefly, criteria for diagnosing FPIES are infants under 9 months of age, symptoms are solely gastrointestinal and reproducible (vomiting and/or diarrhea) and occur within 1–4 hours of ingestion of the causative food, elimination of the offending food resolves symptoms with 24 hours, and absence of other IgE-mediated allergies.

### Food Protein-Induced Allergic Proctocolitis (FPIAP)

FPIAP is a benign transient non-IgE-mediated food allergy and a common cause of rectal bleeding in infants. Prevalence is estimated at 0.16% in healthy infants and occurs in early infancy (weeks to months after birth) [80]. Inflammation in the distal colon and rectum and presence of blood and mucus in the stools are observed in infants with FPIAP. Cow's milk is the most common trigger, followed by egg, soy, and corn [81]. FPIES is seen in both breastfed and formula-fed infants. The diagnosis of FPIAP is based on clinical history and resolution of symptoms following elimination of the causative food. Rectal and colonic biopsies show significant eosinophilic infiltration of the lamina propria as its most prominent feature. Resolution usually occurs over a few weeks and often without the need for maternal dietary food elimination [82].

### Food Protein-Induced Enteropathy (FPE)

Clinical findings include prolonged diarrhea, emesis, failure to thrive, malabsorption, and anemia with or without protein loss in the first months of life. FPE involves the small bowel and is typically present in infants under 9 months of age. Cow's milk is most commonly implicated, but soy, egg, rice, wheat, fish, and chicken have been associated with this condition. Both osmotic and secretory diarrhea contribute to symptoms [77].

The diagnosis is based on the history, endoscopy, and biopsy. Small intestinal bowel biopsy shows mild to moderate villous atrophy, inflammation, crypt hyperplasia, lymphonodular hyperplasia, increased intraepithelial lymphocytes, and extracellular deposition of major basic protein (an eosinophilic granule protein) [83, 84]. With elimination of food triggers, villi typically recover by 6 months and symptoms usually improve within a few weeks. Resolution of this condition typically takes place by year 1–2 of life.

## Mixed Food Allergy

Mixed food allergy is characterized by both IgE-dependent and IgE-independent mechanisms and affect the skin (delayed food- allergy-associated atopic dermatitis) and gastrointestinal tract (eosinophilic gastrointestinal disorders (EGIDs)). EGIDs include eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC) and are characterized by chronic inflammation of the esophagus, stomach, small intestine, and colon, respectively, with increases in the number of eosinophils. Patients can present with abdominal pain, reflux, vomiting, dysphagia, cough, food impaction, and chest pain. Patients with EGIDs often have comorbid atopic diseases such as atopic dermatitis and asthma. Differential diagnosis should rule out other causes of gastrointestinal eosinophilic infiltration such as parasitic infections, inflammatory bowel disease, some cancers, or drug allergy [85]. The clinical symptoms vary depending on the area of the gastrointestinal tract affected and can be useful in distinguishing the different EGIDs. EoE is the best characterized of the EGIDs with consensus guidelines on diagnosis and management [86].

## Eosinophilic Esophagitis

EoE is a relatively new disease and was first described in 1993. EoE is defined as a chronic, local immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [87, 88]. The incidence of EoE has increased and currently varies widely from 1 to 20 new cases per 100,000 inhabitants per year [86]. EoE can manifest at any age and occurs more commonly in males than females. Dysphagia, food impaction, heartburn, and chest pain are the most commonly reported symptoms in older children and adults; reflux-like symptoms, vomiting, abdominal pain, food refusal, and failure to thrive are the most common symptoms in younger children and infants. EoE is the number one cause of dysphagia and food impaction in pediatric populations [89]. Untreated EoE is usually associated with persistent symptoms and inflammation, leading to esophageal remodeling and resulting in stricture formation and functional abnormalities. Endoscopy is of paramount importance and the accepted threshold for the diagnosis of EoE is 15 eosinophils per high power field. Patients with EoE have a history of atopic disease including asthma, allergic rhinitis, and food allergy. Both food allergens and airborne allergens appear to play a role in the pathogenesis of EoE [88]. The majority of EoE patients test positive for food allergy by total and sIgE measurements and by SPTs; however, these tests have yielded variable results and often do not provide meaningful data for identifying the causative allergen and generating a foundation for elimination diets [90]. Currently, the only way to determine causative allergens to assist with long-term dietary therapy is through elimination diets. The empirical 6-food elimination diet is commonly used as therapy and to identify the causative allergen. The foods eliminated are those commonly associated with EoE (cow's milk, soy, wheat, egg, peanut, and seafood). Serial reintroduction of these foods back into the diet with endoscopic evaluation after each reintroduction along with identification of the causative allergen can assist with long-term dietary therapy [91]. Recently, a 2-4-6 step-up approach has been found to be effective starting with the elimination of milk and gluten-containing grains (2-food elimination diet), followed by the elimination of eggs and legumes (4-food elimination diet) and finally with the elimination of nuts and fish/seafood (6-food elimination diet). Forty-three percent of patients had EoE remission on a 2-food elimination diet without the need to eliminate further foods in their diet. Compared to the standard 6-food elimination diet, the step-up methods decreased endoscopic procedures by 20% [92].

## Conclusion

Diagnosis of food allergy is complex. Clinical history is of primary importance and a key first step in diagnosing food allergy. Laboratory tests can assist with differential diagnosis, but cannot positively confirm food allergy. Using current available methods, researchers are working on algorithms using a combination of factors to predict food challenge outcomes [93] and severity of reactions during OFC [94]. However, there is still an unmet need for a safe, simple, inexpensive, and reliable in vitro test for accurately diagnosing food allergy. There is much progress in the field, and the major food allergens have been identified for many common foods. A number of new assays, such as BAT and CRD, are currently being used primarily in research settings and are likely to gain more widespread use in near future.

## References

1. Nowak-Wegrzyn A, Sampson HA. Adverse reactions to foods. Med Clin North Am. 2006;90(1):97–127.
2. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 0):S1.
3. Bierme P, Nowak-Wegrzyn A, Caubet JC. Non-IgE-mediated gastrointestinal food allergies. Curr Opin Pediatr. 2017;29(6):697–703.
4. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.

5. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. NCHS Data Brief. 2013;(121):1–8. PubMed PMID: 23742874
6. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69(8):992–1007.
7. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011;127(3):668–76.e1–2.
8. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. J Allergy Clin Immunol. 2017;140(1):145–53 e8.
9. Rinaldi M, Harnack L, Oberg C, Schreiner P, St Sauver J, Travis LL. Peanut allergy diagnoses among children residing in Olmsted County, Minnesota. J Allergy Clin Immunol. 2012;130(4):945–50.
10. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol. 2010;125(6):1322–6.
11. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol. 2012;130(4):986–8.
12. Zopf Y, Baenkler HW, Silbermann A, Hahn EG, Raithel M. The differential diagnosis of food intolerance. Dtsch Arztebl Int. 2009;106(21):359–69; quiz 69–70; 4 p following 70.
13. Leung J, Crowe SE. Food allergy and food intolerance. World Rev Nutr Diet. 2015;111:76–81.
14. Turnbull JL, Adams HN, Gorard DA. Review article: the diagnosis and management of food allergy and food intolerances. Aliment Pharmacol Ther. 2015;41(1):3–25.
15. Wilson BG, Bahna SL. Adverse reactions to food additives. Ann Allergy Asthma Immunol. 2005;95(6):499–507; quiz, 70.
16. Miwa N, Kawamura A, Masuda T, Akiyama M. An outbreak of food poisoning due to egg yolk reaction-negative *Staphylococcus aureus*. Int J Food Microbiol. 2001;64(3):361–6.
17. Alshannaq A, Occurrence YJH. Toxicity, and analysis of major mycotoxins in food. Int J Environ Res Public Health. 2017;14(6):pii: E632.
18. Coleman RM, Ojeda-Torres G, Bragg W, Fearey D, McKinney P, Castrodale L, et al. Saxitoxin exposure confirmed by human urine and food analysis. J Anal Toxicol. 2018 May 25;42:e61. https://doi.org/10.1093/jat/bky031; [Epub ahead of print].
19. Pennotti R, Scallan E, Backer L, Thomas J, Angulo FJ. Ciguatera and scombroid fish poisoning in the United States. Foodborne Pathog Dis. 2013;10(12):1059–66.
20. David TJ. Adverse reactions and intolerance to foods. Br Med Bull. 2000;56(1):34–50.
21. Skypala IJ, Williams M, Reeves L, Meyer R, Venter C. Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. Clin Translat Allergy. 2015;5:34.
22. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol. 2016;16(12):751–65.
23. Lee J, Garrett JP, Brown-Whitehorn T, Spergel JM. Biphasic reactions in children undergoing oral food challenges. Allergy Asthma Proc. 2013;34(3):220–6.
24. Pravettoni V, Incorvaia C. Diagnosis of exercise-induced anaphylaxis: current insights. J Asthma Allergy. 2016;9:191–8.
25. Feldweg AM. Exercise-induced anaphylaxis. Immunol Allergy Clin N Am. 2015;35(2):261–75.
26. Simons FE, Ardusso LR, Bilo MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J. 2014;7(1):9.
27. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010;126(3):477–80 e1–42.
28. Simons FE, Ardusso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol. 2011;127(3):587–93 e1–22.
29. Sicherer SH. Clinical implications of cross-reactive food allergens. J Allergy Clin Immunol. 2001;108(6):881–90.
30. Price A, Ramachandran S, Smith GP, Stevenson ML, Pomeranz MK, Cohen DE. Oral allergy syndrome (pollen-food allergy syndrome). Dermatitis. 2015;26(2):78–88.
31. Popescu FD. Cross-reactivity between aeroallergens and food allergens. World J Methodol. 2015;5(2):31–50.
32. Katelaris CH. Food allergy and oral allergy or pollen-food syndrome. Curr Opin Allergy Clin Immunol. 2010;10(3):246–51.
33. Wilson JM, Schuyler AJ, Schroeder N, Platts-Mills TA. Galactose-alpha-1,3-galactose: atypical food allergen or model IgE hypersensitivity? Curr Allergy Asthma Rep. 2017;17(1):8.
34. Flaherty MG, Kaplan SJ, Jerath MR. Diagnosis of life-threatening alpha-gal food allergy appears to be patient driven. J Prim Care Community Health. 2017;8(4):345–8.
35. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41–58.
36. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test – European standards. Clin Translat Allergy. 2013;3(1):3.

37. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014;134(5):1016–25 e43.
38. Peters RL, Allen KJ, Dharmage SC, Tang ML, Koplin JJ, Ponsonby AL, et al. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. J Allergy Clin Immunol. 2013;132(4):874–80.
39. Nacaroglu HT, Erdem SB, Karaman S, Dogan D, CS UK, E TK, et al. Diagnostic values for egg white specific IgE levels with the skin prick test in Turkish children with egg white allergy. Allergol Immunopathol (Madr). 2017;45(5):445–51.
40. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clin Exp Allergy. 2000;30(11):1540–6.
41. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. Pediatr Allergy Immunol. 2004;15(5):435–41.
42. Verstege A, Mehl A, Rolinck-Werninghaus C, Staden U, Nocon M, Beyer K, et al. The predictive value of the skin prick test weal size for the outcome of oral food challenges. Clin Exp Allergy. 2005;35(9):1220–6.
43. Calvani M, Alessandri C, Frediani T, Lucarelli S, Miceli Sopo S, Panetta V, et al. Correlation between skin prick test using commercial extract of cow's milk protein and fresh milk and food challenges. Pediatr Allergy Immunol. 2007;18(7):583–8.
44. Rance F, Abbal M, Lauwers-Cances V. Improved screening for peanut allergy by the combined use of skin prick tests and specific IgE assays. J Allergy Clin Immunol. 2002;109(6):1027–33.
45. Gupta RS, Lau CH, Hamilton RG, Donnell A, Newhall KK. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. J Allergy Clin Immunol Pract. 2014;2(3):300–5.
46. Mehl A, Verstege A, Staden U, Kulig M, Nocon M, Beyer K, et al. Utility of the ratio of food-specific IgE/total IgE in predicting symptomatic food allergy in children. Allergy. 2005;60(8):1034–9.
47. Federly TJ, Jones BL, Dai H, Dinakar C. Interpretation of food specific immunoglobulin E levels in the context of total IgE. Ann Allergy Asthma Immunol. 2013;111(1):20–4.
48. Goikoetxea MJ, Sanz ML, Garcia BE, Mayorga C, Longo N, Gamboa PM, et al. Recommendations for the use of *in vitro* methods to detect specific immunoglobulin E: are they comparable? J Investig Allergol Clin Immunol. 2013;23(7):448–54; quiz 2 p preceding 55.
49. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol. 2001;107(5):891–6.
50. Sato S, Yanagida N, Ebisawa M. How to diagnose food allergy. Curr Opin Allergy Clin Immunol. 2018;18(3):214–21.
51. Park KH, Lee J, Sim DW, Lee SC. Comparison of Singleplex specific IgE detection immunoassays: ImmunoCAP Phadia 250 and Immulite 2000 3gAllergy. Ann Lab Med. 2018;38(1):23–31.
52. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. Clin Exp Allergy. 2005;35(3):268–73.
53. Sato S, Ogura K, Takahashi K, Sato Y, Yanagida N, Ebisawa M. Usefulness of antigen-specific IgE probability curves derived from the 3gAllergy assay in diagnosing egg, cow's milk, and wheat allergies. Allergol Int. 2017;66(2):296–301.
54. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008;122(1):145–51.
55. Van Gasse AL, Mangodt EA, Faber M, Sabato V, Bridts CH, Ebo DG. Molecular allergy diagnosis: status anno 2015. Clin Chim Acta. 2015;444:54–61.
56. Masilamani M, Commins S, Shreffler W. Determinants of food allergy. Immunol Allergy Clin N Am. 2012;32(1):11–33.
57. Kukkonen AK, Pelkonen AS, Makinen-Kiljunen S, Voutilainen H, Makela MJ. Ara h 2 and Ara 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled study. Allergy. 2015;70(10):1239–45.
58. Asarnoj A, Nilsson C, Lidholm J, Glaumann S, Ostblom E, Hedlin G, et al. Peanut component Ara h 8 sensitization and tolerance to peanut. J Allergy Clin Immunol. 2012;130(2):468–72.
59. Grimshaw KE, Bryant T, Oliver EM, Martin J, Maskell J, Kemp T, et al. Incidence and risk factors for food hypersensitivity in UK infants: results from a birth cohort study. Clin Translat Allergy. 2015;6(1):1.
60. Eller E, Mortz CG, Bindslev-Jensen C. Cor a 14 is the superior serological marker for hazelnut allergy in children, independent of concomitant peanut allergy. Allergy. 2016;71(4):556–62.
61. Datema MR, van Ree R, Asero R, Barreales L, Belohlavkova S, de Blay F, et al. Component-resolved diagnosis and beyond: multivariable regression models to predict severity of hazelnut allergy. Allergy. 2018;73(3):549–59.
62. Bartnikas LM, Sheehan WJ, Tuttle KL, Petty CR, Schneider LC, Phipatanakul W. Ovomucoid specific immunoglobulin E as a predictor of tolerance to cooked egg. Allergy Rhinol (Providence). 2015;6(3):198–204.
63. Kennard L, Thomas I, Rutkowski K, Azzu V, Yong PFK, Kasternow B, et al. A multicenter evaluation of diagnosis and management of omega-5 gliadin allergy (also known as wheat-dependent exercise-induced anaphylaxis) in 132 adults. J Allergy Clin Immunol Pract. 2018 Mar 1. pii: S2213–2198(18)30105–3. https://doi.org/10.1016/j.jaip.2018.02.013. [Epub ahead of print].

64. Dubiela P, Kabasser S, Smargiasso N, Geiselhart S, Bublin M, Hafner C, et al. Jug r 6 is the allergenic vicilin present in walnut responsible for IgE cross-reactivities to other tree nuts and seeds. Sci Rep. 2018;8(1):11366.
65. Berneder M, Bublin M, Hoffmann-Sommergruber K, Hawranek T, Lang R. Allergen chip diagnosis for soy-allergic patients: Gly m 4 as a marker for severe food-allergic reactions to soy. Int Arch Allergy Immunol. 2013;161(3):229–33.
66. Fischer J, Biedermann T. Delayed immediate-type hypersensitivity to red meat and innards: current insights into a novel disease entity. J Dtsch Dermatol Ges. 2016;14(1):38–44.
67. Agabriel C, Ghazouani O, Birnbaum J, Liabeuf V, Porri F, Gouitaa M, et al. Ara h 2 and Ara h 6 sensitization predicts peanut allergy in Mediterranean pediatric patients. Pediatr Allergy Immunol. 2014;25(7):662–7.
68. Lin J, Sampson HA. IgE epitope mapping using peptide microarray immunoassay. Methods Mol Biol. 2017;1592:177–87.
69. Wang J, Lin J, Bardina L, Goldis M, Nowak-Wegrzyn A, Shreffler WG, et al. Correlation of IgE/IgG4 milk epitopes and affinity of milk-specific IgE antibodies with different phenotypes of clinical milk allergy. J Allergy Clin Immunol. 2010;125(3):695–702, e1-e6.
70. Santos AF, Shreffler WG. Road map for the clinical application of the basophil activation test in food allergy. Clin Exp Allergy. 2017;47(9):1115–24.
71. Santos AF, Douiri A, Becares N, Wu SY, Stephens A, Radulovic S, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. J Allergy Clin Immunol. 2014;134(3):645–52.
72. Santos AF, Du Toit G, Douiri A, Radulovic S, Stephens A, Turcanu V, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. J Allergy Clin Immunol. 2015;135(1):179–86.
73. Vila L, Moreno A, Gamboa PM, Martinez-Aranguren R, Sanz ML. Decrease in antigen-specific CD63 basophil expression is associated with the development of tolerance to egg by SOTI in children. Pediatr Allergy Immunol. 2013;24(5):463–8.
74. Ballmer-Weber BK, Beyer K. Food challenges. J Allergy Clin Immunol. 2018;141(1):69–71 e2.
75. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, et al. Work group report: oral food challenge testing. J Allergy Clin Immunol. 2009;123(6 Suppl):S365–83.
76. Leonard SA. Non-IgE-mediated adverse food reactions. Curr Allergy Asthma Rep. 2017;17(12):84.
77. Nowak-Wegrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. J Allergy Clin Immunol. 2015;135(5):1114–24.
78. Nowak-Wegrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2017;139(4):1111–26 e4.
79. Leonard SA, Pecora V, Fiocchi AG, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome: a review of the new guidelines. World Allergy Organ J. 2018;11(1):4.
80. Elizur A, Cohen M, Goldberg MR, Rajuan N, Cohen A, Leshno M, et al. Cow's milk associated rectal bleeding: a population based prospective study. Pediatr Allergy Immunol. 2012;23(8):766–70.
81. Lake AM. Food-induced eosinophilic proctocolitis. J Pediatr Gastroenterol Nutr. 2000;30(Suppl):S58–60.
82. Feuille E, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome, allergic Proctocolitis, and Enteropathy. Curr Allergy Asthma Rep. 2015;15(8):50.
83. Walker-Smith JA. Cow milk-sensitive enteropathy: predisposing factors and treatment. J Pediatr. 1992;121(5 Pt 2):S111–5.
84. Iyngkaran N, Robinson MJ, Prathap K, Sumithran E, Yadav M. Cows' milk protein-sensitive enteropathy. Combined clinical and histological criteria for diagnosis. Arch Dis Child. 1978;53(1):20–6.
85. Kovalszki A, Weller PF. Eosinophilia. Prim Care. 2016;43(4):607–17.
86. Lucendo AJ, Molina-Infante J, Arias A, von Arnim U, Bredenoord AJ, Bussmann C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017;5(3):335–58.
87. Schoepfer A, Blanchard C, Dawson H, Lucendo A, Mauro A, Ribi C, et al. Eosinophilic esophagitis: latest insights from diagnosis to therapy. Ann N Y Acad Sci. 2018 May 15. https://doi.org/10.1111/nyas.13731; [Epub ahead of print].
88. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128(1):3–20 e6; quiz 1–2.
89. Kavitt RT, Hirano I, Vaezi MF. Diagnosis and treatment of eosinophilic esophagitis in adults. Am J Med. 2016;129(9):924–34.
90. Sugnanam KK, Collins JT, Smith PK, Connor F, Lewindon P, Cleghorn G, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. Allergy. 2007;62(11):1257–60.
91. Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. J Allergy Clin Immunol. 2013;131(3):797–804.

92. Molina-Infante J, Arias A, Alcedo J, Garcia-Romero R, Casabona-Frances S, Prieto-Garcia A, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 study. J Allergy Clin Immunol. 2018;141(4):1365–72.
93. DunnGalvin A, Daly D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajeunesse M, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. J Allergy Clin Immunol. 2011;127(3):633–9 e1–3.
94. Chinthrajah RS, Purington N, Andorf S, Rosa JS, Mukai K, Hamilton R, et al. Development of a tool predicting severity of allergic reaction during peanut challenge. Ann Allergy Asthma Immunol. 2018;121(1):69–76 e2.

# Quality of Life in Children with Food Allergy

4

Ashley A. Dyer, Madeleine K. Kanaley, Lisa Lombard, Christopher M. Warren, and Ruchi S. Gupta

## Introduction

Food allergy affects approximately 8% of the pediatric population in the United States and has been shown to adversely impact quality of life (QoL) of food allergy patients and their families. Of those living with food allergy, roughly one in five children and adolescents has experienced a severe reaction requiring an emergency department visit within the last year and two in five have experienced a severe reaction requiring an emergency room visit over the course of their life [1]. While severe reactions are not uncommon, food allergy is a unique condition insofar as it largely allows for good physical health in the absence of allergen exposure [2].

To date, researchers have tried to better understand how food allergy impairs health-related QoL through the rigorous dissemination of surveys that collect experiences from children, adolescents, and caregivers themselves [2–7]. Factors well known to impair QoL include the stress and anxiety associated with the heightened awareness required for constant allergen avoidance, lack of widely available prevention or treatment strategies, the inability of children and adolescents to fully participate in social life, and the potential to further isolate affected individuals due to the lack of inclusive food allergy policies within schools and the larger community [2]. While much work is needed to better understand the lived experiences of affected individuals, improving understanding of how food allergy impacts QoL throughout a child's life as they transition into young adulthood now challenges the food allergy community to explore strategies that balance the need for safety with practices that enhance well-being.

Striking a balance between establishing safe environments with the need to empower children and adolescents to fully participate in their lives requires constant negotiation of relationships – from notifying peers of their food allergy to meaningfully engaging physicians in proactive management strategies. As with any chronic health condition, managing relationships remains crucial for successfully supporting food-allergic individuals throughout their physical, psychological, and social development. To better understand how to manage relationships throughout the life course of a child and adolescent, this chapter will explore the current discourse regarding food allergy-related QoL and provide a clear overview

A. A. Dyer · M. K. Kanaley · L. Lombard
C. M. Warren
Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA
e-mail: ashley.dyer@northwestern.edu; madeleine.kanaley@northwestern.edu; christopher.warren@northwestern.edu

R. S. Gupta (✉)
Center for Food Allergy and Asthma Research, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: r-gupta@northwestern.edu


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_4

of the factors well known to impact QoL. While living with a food allergy can be challenging, we also want to shed light on the emerging ideas, interventions, and policies that may improve QoL and enhance well-being for children, adolescents, and caregivers.

## Food Allergy-Related Quality of Life

Quality of life is a dynamic, multi-dimensional construct that characterizes individuals' estimation of their own well-being [2]. The World Health Organization (WHO) defines QoL as:

> An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. [Quality of Life] is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment [8].

In relationship to health, QoL focuses on subjectively measuring the experience of individuals or caregivers managing a chronic condition or disability through patient-reported questionnaires. Several general pediatric health-related QoL scales are available for use [9, 10]. However, due to the unique context of children and adolescents living with food allergy experiencing few, if any, symptoms outside of an accidental ingestion, it is often preferable to use QoL scales that were developed and validated to specifically assess food allergy-related QoL [11–16]. While this review focuses on food allergy-related QoL outcomes and other measures of patient and caregiver well-being, Table 4.1 summarizes a variety of food allergy-specific QoL measures [2].

## Clinical Considerations: Food Allergy Management, Provider Role, and Patient Engagement

### Guideline-Informed Food Allergy Diagnosis and Management

Current guideline-based care for diagnosing and managing childhood food allergy includes the following: (1) Documenting a clinical history whereby the patient experiences a reproducible immune-mediated reaction after ingesting an offending food; (2) Performing specific-IgE (or skin prick) tests to suspected food allergens, followed by confirmatory oral food challenge when greater specificity is needed; (3) Completing an anaphylaxis action plan to ensure the patient, caregivers, and support networks know how to adequately respond in a food allergy emergency; (4) Prescribing an appropriate number of epinephrine auto-injectors to store at home, school, and with the child or adolescent (if age-appropriate); and (5) Providing clinical counseling to the patient and their caregivers [17]. While much of the counseling and education emphasizes equipping patients and caregivers with the skills required to appropriately respond in a food allergy emergency, researchers are also beginning to appraise how diagnosis, management, and emerging treatments affect food allergy-related QoL.

### Gold Standard Diagnosis: Oral Food Challenges and Quality of Life

The gold standard for diagnosing food allergy is a double-blinded, placebo-controlled, food challenge (DBPCFC), which helps the clinician to determine whether or not a child has an IgE-mediated food allergy. In short, the challenge requires the patient to ingest small amounts of the suspected allergen while the patient is observed oftentimes within an allergist's office. Although it is often more pragmatic to conduct a single-blinded (where the ingested allergen is known only to the clinician) or open challenge (where the ingested allergen is known to both the patient and the clinician), a DBPCFC (where the ingested allergen is known to neither the patient nor the clinician) is preferred as it allows for minimal bias to be introduced into the diagnosis process [2]. Anxiety from the clinician or the patient themselves as it relates to ingesting a potential allergen can affect diagnosis outcomes as many symptoms related to heightened anxiety (e.g., increased heart rate, dizziness, agitation) are also symptoms consistent with anaphylaxis – a severe, potentially life-threatening food allergy reaction [17].

**Table 4.1** Food Allergy-specific Quality of Life Instruments

| Questionnaire name | Abbreviation | Number of items | Response scale overview | Sample survey items |
|---|---|---|---|---|
| *Patient Self-Report* | | | | |
| *Food Allergy Quality of Life Questionnaires* [3] | | | | |
| Child Form (ages 8–12) | FAQLQ – CF | 24 | Responses are on a seven-point scale from "Not at all" to "extremely" | *How troublesome do you find it, because of your food allergy, that you:*<br>*Sometimes frustrate people when they are making an effort to accommodate your food allergy?*<br>*That people underestimate your problems caused by food allergy?* |
| Teenager Form (ages 13–17) | FAQLQ – TF | 28 | | |
| Adult Form (ages 18+) | FAQLQ – AF | 29 | | |
| *Food Allergy Independent Measure* [3] | | | | |
| Child Form (ages 8–12) | FAIM – CF | 6 | Responses are on a seven-point scale from "0% chance" to "100% chance" | *How great do you think the chance is that you:*<br>*Will die if he/she accidentally eats something to which he/she is allergic?*<br>*Cannot effectively deal with an allergic reaction should you accidentally eat something to which you are allergic?* |
| Teenager Form (ages 13–17) | FAIM – TF | 5 | | |
| Adult Form (ages 18+) | FAIM – AF | 6 | | |
| *Caregiver Proxy Report* | | | | |
| Food Allergy Independent Measure – Parent Form | FAIM-PF | 6 | Responses are on a seven-point scale from "0% chance" to "100% chance" | How great do you think the chance is that your child:<br>*Will accidentally eat something to which you are allergic?*<br>*Will have a severe reaction if you accidentally eat something to which you are allergic?* |
| Food Allergy Quality of Life Questionnaire – Parent Form | FAQLQ – PF | | Responses are on a seven-point scale from "not at all" to "extremely" | *Because of food allergy, my child feels different from other children.*<br>*Because of food allergy, my child has a lack of variety in his/her diet.* |
| Ages 0–3 version | FAQLQ – PF | 14 | | |
| Ages 4–6 version | FAQLQ – PF | 26 | | |
| Ages 7–12 version | FAQLQ – PF | 30 | | |
| *Caregiver Self-Report* | | | | |
| Food Allergy Quality of Life – Parental Burden | FAQoL – PB | 17 | Responses are on an eight-point scale from "not troubled" to "extremely troubled" | *How troubled have you been by sadness regarding the burden your child carries because of their food allergy?*<br>*If you and your family were planning a holiday/vacation, how much would your choice of holiday/vacation be limited by your child's food allergy?* |

While undergoing a food challenge may elicit some initial anxiety, previous studies have demonstrated that undergoing a DBPCFC may improve QoL for patients and caregivers. For example, one study of caregivers of children ($N$ = 77) and adolescents ($N$ = 71) with physician-diagnosed food allergy found that caregivers whose children underwent DBPCFC to confirm their allergy reported better food allergy-related QoL than a comparable group of caregivers whose food-

allergic child did not receive a food challenge. Interestingly, the improvements in caregiver QoL associated with their child receiving a DBPCFC were similar between caregivers of children whose allergy was confirmed by the food challenge (i.e., who reacted to the test) and the caregivers of children who were deemed non-allergic after passing the food challenge [18]. Moreover, research indicates that food allergy-related QoL can improve post-challenge among the patients themselves, regardless of whether their allergy is confirmed or ruled out by the test results [19]. Nevertheless, such initial improvements to food allergy-related QoL post-challenge may not be sustained over time. In a 2014 study by Soller et al., the researchers found that regardless of positive or negative food challenge results, food allergy-related QoL improved at 2 months. However, among the children diagnosed with food allergy, improvements in food allergy-related QoL were not sustained past 6 months [20].

## Food Allergy Clinical Intervention: Immunotherapy

Although the benefits of immunotherapy (e.g., desensitization to allergens) can be profoundly positive in a child and family's life, treatment burdens including the potential for experiencing an adverse reaction, heightened anxiety, and developing food aversions may also occur. Previous research on how immunotherapy impacts psychosocial functioning is mixed. For example, in a study by LeBovidge et al. (2014) patients report experiencing adverse psychological reactions during the treatment; yet, these same patients exhibit improved QoL following the completion of the immunotherapy despite confronting challenges during the treatment itself [21, 22]. Arasi et al. (2014) also found that caregiver QoL significantly improved over the course of a 2-year immunotherapy treatment period. In addition to known improvements in caregiver QoL, participants who achieved desensitization to greater than four allergens and/or participants over 10 years of age also experienced enhanced QoL [23].

When considering immunotherapy interventions, treatments can pose a unique psychological and emotional opportunity for children and adolescents with food allergies as they are required to confront and consume a known food allergen that has previously contributed to distress and QoL impairment. While the idea of consuming a known allergen may increase anxiety, researchers are beginning to elucidate strategies to combat further impairing patient and caregiver QoL. For example, Howe et al. (2019) demonstrated that mindset and language influence the psychological experience of oral immunotherapy [24]. In this randomized study of 50 children and adolescents who completed 6-month oral immunotherapy protocol for peanut allergies, the two groups were provided different information about non-life-threatening symptoms. The first group was told that the side effects were an unfortunate consequence of treatment, and the second group was informed that non-life-threatening symptoms could signal desensitization. Families participated in a variety of reinforcing activities consistent with these two symptom mindsets and resulted in the families who were counseled that the symptoms were thought to signal desensitization experiencing better psychosocial outcomes. This research signals that how we counsel patients – including the framing of the treatment process itself – can be used to help families undergo therapy and potentially improve QoL outcomes. Shifting how providers inform patients about non-life-threatening symptoms is a promising avenue for improving overall food allergy counseling. The association between mindset and outcome suggests that it may be valuable to further include and explore practices utilizing positive language, mindfulness, and stress management training (e.g., progressive muscle relaxation, guided imagery, and diaphragmatic breathing) to help patients and families create a positive framework that aims to reframe the immunotherapy experience. Better structuring counseling through more precise language coupled with a positive framework has the potential to both meaningfully invite patients and families to engage in their care and reduce the overall burden of treatment [24].

### Food Allergy Management Intervention: Food Allergy Hotline

Timely support, particularly, when confronting a health emergency such as food-induced anaphylaxis remains of particular importance; yet, very few real-time interventions have been developed to support children, adolescents, and caregivers experiencing a food allergy emergency. In a study by Kelleher et al. (2013), the research team assessed the effectiveness of families being able to access expert management advice from a 24-hour helpline when confronting food-induced anaphylaxis [25]. When compared to the families that were receiving usual care (i.e., no access to the hotline), children in the intervention group showed a significant improvement in QoL that was sustained 6 months post-intervention [25]. Wide-scale access to services like a 24-hour anaphylaxis helpline has the potential to enhance food allergy emergency response training and systematically accompanying children, adolescents, and families confronting anaphylaxis.

## Provider Role

Within the domain of food allergy, physicians are encountering a growing population of affected patients and are being challenged to provide comprehensive, developmentally appropriate care [5]. However, many primary care physicians report a lack of confidence in their ability to effectively diagnose and treat food allergies, possibly stemming from the relatively recent onset of the current allergy epidemic and the corresponding lack of food allergy-specific training during their medical education. Furthermore, with limited treatment options to offer, clinicians have found themselves frustrated with the lack of guidance available to them beyond guideline-informed strategies that take an "*all or nothing*" approach, focusing on strict allergen avoidance and a swift response to accidental ingestions with the prompt use of epinephrine [26].

At the very least, physicians want to adhere to the age-old sentiment of first "doing no harm." Increasingly, providers are being asked to reflect on how their limited treatment approach for food allergies could have an unintentional iatrogenic effect of contributing to QoL impairment rather than ameliorating it [5]. Larger drivers influencing the role that physicians play within the clinician-patient relationship continue to evolve and shift as the healthcare paradigm trends towards a more evidence-informed, patient-centered model of care. Historically, physicians have been trained to provide care according to one or more of the following four approaches: (1) Paternalistic Care – "Doctor as Guardian"; (2) Informative Care – "Doctor as Technical Expert"; (3) Interpretive Care – "Doctor as Counselor/Advisor"; and (4) Deliberative Care "Doctor as Friend/Teacher" [27]. Physicians treating food allergy have largely provided "Informative Care – Doctor as Expert," recommending food challenges, avoidance strategies, and prescribing epinephrine auto-injectors. However, this approach seems to fall short of patient and family expectations as much of the morbidity and QoL impairment remains outside the scope of best available clinical practices.

Improving a provider's ability to partner with patients and families remains integral to improving food allergy-related QoL while the number of treatment options available to clinicians and patients slowly starts to expand. Research remains promising regarding effective immunotherapy treatment options (e.g., peanut immunotherapy) [28, 29] and even prevention strategies (e.g., early introduction) [17, 30], yet communicating these treatment options will still need to be balanced with counseling tailored to meet the needs of individual patients and families. As such, physicians will need to potentially take a more interpretive approach to care by including more targeted counseling and advising. While the current specialization of healthcare has historically limited providers in developing and widely implementing interpretive capacities that often require much time and a high level of patient engagement, another approach to consider is expanding the network of providers that patients can readily access beyond allergists and pediatricians [27]. Instead of the physician shouldering all of the responsibility for management, expanding the network of support to include highly trained

nurses, nutritionists, mental health providers, integrative health providers, child life specialists, and community health practitioners – particularly when patients are first diagnosed – may help patients to both safeguard against accidental ingestions and support the development of positive coping mechanisms to better mitigate food allergy-related QoL impairment.

## Promising Patient Engagement

### Caregiver Intervention to Improve Food Allergy-Related Quality of Life

Developing evidence-informed protocols that tailor counseling to best meet the needs of at-risk patients and families remains an important step in meeting the overall management needs of families. As we begin to better understand how anxiety can manifest within a family – with evidence of transference of anxiety from maternal caregivers to children – it remains critical to explore strategies that take an ecological approach to better understand family dynamics and potentially include the whole family in food allergy-related QoL interventions.

Previous research by Baptist et al. (2012) uses an intervention grounded in self-regulation theory, which remains a promising model for mitigating the development of maladaptive coping strategies [31]. Using self-regulation theory to guide interventions in chronic disease management underscores the importance of engaging the patient in their own care while developing positive management strategies. Overall, behavioral management is broken down into more digestible, sequential steps that allows for the patient and caregiver to meaningfully consider the food allergy-related challenge. Self-regulation theory allows for caregivers to (1) acknowledge their concern; (2) discuss the likelihood the concern might occur; (3) critically appraise potential barriers; and (4) contemplate a coping mechanism [31].

In a blinded randomized control study, Baptiste et al. (2012) evaluated a food allergy management intervention informed by self-regulation theory [31]. Fifty-eight families with a food allergy diagnosis were randomized into control or intervention groups. All families received a general education packet. The intervention group also received three 25-minute telephone calls from a trained nurse to discuss concerns, goals, and barriers the caregiver associated with their child's food allergy. During the first call, the nurse discussed potential strategies to help support the caregiver and patient. The second call was used to check in with the caregiver and family regarding the identified challenges, how they were being addressed, and to assess any additional issues that were not previously discussed. The third and final call focused on reviewing coping strategies and how to implement these strategies as problems arose moving forward.

After three months, the groups were compared and several specific domains had improved among the intervention group, including frustration, helplessness, and confidence. This research remains promising and more trials are needed to assess how to best accompany patients and families. Evidence from this trial suggests that incorporating more pragmatic and targeted approaches grounded in self-regulation theory have the potential to improve positive coping mechanism development while lessening food allergy-related QoL impairment [31].

### Group Intervention to Improve Food Allergy-Related Quality of Life

In a 2008 study by LeBovidge et al., the study team sought to assess the utility of a group intervention designed for children with food allergies ages 5–7 years old and their caregivers ($N = 61$) [32]. Caregivers completed two food allergy-specific questionnaires, the *Food Allergy Quality of Life – Parental Burden Questionnaire* and the *Family Coping with Food Allergy Questionnaire*, which assessed perceived competence and caregiver perceived burden, respectively. Caregivers completed questionnaires before the food allergy workshop, directly after the workshop, and then 4–8 weeks after the workshop.

The half-day workshop included multiple facilitators, including pediatric psychologists, pediatric allergists, pediatric nurse practitioners, and child life specialists. The workshop was designed to hold separate caregiver and child discussions. The child life specialist ensured that the children felt comfortable expressing their feelings and discussed

building confidence in the children's food allergy management skills. Overall, the group intervention yielded positive results: 74% exhibited improved competence scores post-workshop and 63% of caregivers perceived a significant decrease in child burden at the follow-up evaluation. These pilot data suggest that food allergy-related group interventions may be useful in supporting the development of caregiver and child adaptive coping skills [32]. Future studies should consider developing age-specific workshops to better assess school-age children, adolescents, and young adults. In addition, having the children, adolescents, and young adults complete food allergy-related QoL assessments in addition to caregiver assessments remains critical to further inform developmentally appropriate interventions.

## Community Considerations: Schools, Student Engagement, and Participatory Research

Building strong communities and positive school culture through the development of inclusive school policies remains critical for children and adolescents to thrive. Progressive food allergy-specific policies include training school personnel on strategies to ensure an inclusive classroom and food allergy emergency response readiness; making stock epinephrine widely available; and systematically implementing federal policies, including the development of food allergy-specific 504 plans to help outline individual-level accommodations [2, 11–16]. In addition, the advent of social-emotional learning standards paired with growing awareness of the stress confronting today's students has challenged the educational and medical communities to take pause. The current challenge requires balancing the individual needs of students while simultaneously challenging them to grow academically, socially, and emotionally alongside their non-allergic peers.

### Food Allergy and Bullying

Accompaniment – partnering with individuals – remains the cornerstone of supporting children and adolescents with progressively taking on age-appropriate levels of food allergy self-management. As caregivers, knowing when and how to support children remains an evolving process and can become particularly challenging if your child is confronting problems within the school environment. In 2018, Shemesh et al. assessed how a food allergy diagnosis may predispose a child or adolescent to unique social vulnerability, which may include increased incidents of harassment and bullying. Of the 251 families included in the study, harassment and bullying impacted a considerable proportion. Over 36% of children and 24% of caregivers indicated they had experienced, or they thought their child had experienced, food allergy-related harassment or bullying [33].

In a study by Lieberman et al. (2010), food allergy-related harassment and bullying was estimated to affect one in four food-allergic children and adolescents. Of the affected population, a large proportion (86%) reported experiencing multiple episodes. The majority of events occurred within the school environment, and 80% reported that the perpetrators were fellow classmates. Alarmingly, 57% reported bullying that included physical events of taunting the child with their known allergen, including throwing of the allergen at the allergic child or intentional contamination of the allergic child's food. Moreover, while classmates comprised the majority of bullying and harassment, 21% reported that school staff and teachers were the perpetrators [34].

Previous research has indicated that bullying is a known risk factor that impairs food allergy-related QoL, causing distress to families [35]. Moreover, a child or adolescent's QoL is further impaired when they do not notify their caregivers of the harassment or bullying [33]. However, most children and adolescents do notify a member of their social network, including caregivers (71%), teachers (35%), friends (32%), siblings (20%), and even principals (13%) [33]. Creating open communication about these experiences remains integral for addressing the problem with appropriate school personnel. While ensuring the immediate safety of the child remains of paramount importance, previous research indicates that larger, school-based interventions may hold promise in

addressing the issue of food allergy-related harassment and bullying [35]. Shifting the victimization paradigm to one that more holistically addresses the need to change the school culture to be one less tolerant of bullying and harassment may prove to be the long-term strategy in cultivating sustainable change within the school environment [35–37].

### Positive Aspects of Living with Food Allergy

Leveraging the positive aspects of students living with a food allergy also has the potential for both individual-level empowerment and to further support a shift in school culture. For example, among a population of adolescents and young adults living with food allergy, over 70% indicated that their lived experience strengthened their resolve to become better advocates for members of their community and themselves [38]. In addition, adolescents and young adults also reported that the unique experience of living with a food allergy helped them to recognize and respond to others with special needs [38]. Helping affected individuals to recognize the strengths that accompany living with a food allergy – such as improved interpersonal relationships and enhanced advocacy skills – may help to further support a recent paradigm shift in leveraging aspects of resiliency and grit among the adolescent and young adult population who manage chronic conditions. Future work should consider exploring how both the medical and educational systems can better balance the development of emotional and social resilience with helping affected individuals to reduce food allergy associated risks [38, 39].

## Leaving for College

### Developmental Transitions and Opportunities for Engagement

Whether a child is leveling up from preschool to elementary school or matriculating from high school to college, such transitions mark a time where chronic disease management shifts for the child, adolescent, and caregivers. Roles and needs need to be assessed and aligned with the child progressively assuming more age-appropriate management responsibilities. Transitioning to college, in particular, can heighten stress and anxiety for families – particularly if the young adult is living outside the family home for the first time.

Few studies to date have focused on the transition to college; yet some pilot research assessing the unmet needs of college students with food allergies indicates there is a need for support across three domains: (1) Improving notification systems regarding how a student's food allergy is communicated to his or her campus network; (2) Establishing clearly defined roles and responsibilities of how peers and others in the student's college network can specifically help to prevent accidental exposures to a food allergen; and (3) Heightening awareness through increased public education across college campuses – from dining halls to campus housing – regarding how to recognize the signs and symptoms of a food allergy emergency and how to appropriately respond [40]. Overall, students with food allergies, caregivers, and college stakeholders indicated a need for designing coordinated systems that provide comprehensive support to college students throughout their transition process. With this information, a suite of five interventions, collectively called *Spotlight*, was developed that focuses on accompanying young adults and their caregivers throughout their transition to college with five coordinated programs: (1) Spotlight Cares: Preparing for Orientation; (2) Orientation; (3) Campus Clubs: Joining a Club Sports Team; (4) External Food Vendors: Increasing the Use of Best Practices on Campus; and (5) Emergency Response: Addressing Emergencies Involving Anaphylaxis [40]. Future work with this population should explore how these interventions impact caregiver and young adult food allergy-related QoL.

## Staying In or Dining Out: Nutrition, Meal Preparation, and Food in Society

### Nutrition

Ensuring that safe and nutritional foods are readily available within the home remains essential for families impacted by food allergy. Previous research has shown that depending on the food allergy type, avoidance and elimination of certain

foods may place children at higher risk for impaired growth and nutritional deficits when compared to their peers without food allergy [7, 41, 42]. Overall, restricted diets impair QoL among children and their caregivers [42]. For example, children with multiple food allergies tend to experience lower QoL as they avoid more foods throughout their diet when compared to their peers with fewer allergies [2, 43–45]. In addition, children who are allergic to foods that are more difficult to avoid in American culture – egg, milk, wheat – report worse QoL when compared to children allergic to foods that are less ubiquitous, more clearly labeled, and/or otherwise easier to identify and avoid (e.g., peanuts) [2, 46, 47]. Moreover, QoL impairment remains variable by allergen type and is largely dependent on how much the specific food allergen is embedded within the family's culture [6].

Previous research conducted by Pollini et al. (2013) investigated the impact of food allergy on nutritional behavior and found that 62% of respondents reported the following food allergy-related issues: (1) Having a "monotonous diet" for reasons such as strict avoidance; (2) Confronting a limited choice of food industry safe products; and (3) Experiencing difficulties preparing traditional recipes [48]. The concern families disclose about trying to ensure their child is equipped with nutritional meals can be daunting. While there is much stress involved in trying to meet the nutritional needs of individual children, some families acknowledge the unexpected health benefits of living with food allergy. For example, caregivers' report that they are more likely to avoid processed and packaged foods due to the threat of mislabeled packages and the potential for accidental ingestions. Moreover, respondents shared that avoiding packaged foods not only increased the nutritional quality of foods they purchased but also decreased feelings of stress when shopping [41].

## Meal Preparation

Meal preparation while living with food allergy can be challenging as the necessary avoidance of certain foods requires families to adequately plan meals ahead of time, adapt certain recipes with appropriate substitutions, and strive to meet the nutritional needs of the entire family. The time spent trying to interpret labels can become cumbersome and result in distress for many caregivers. For example, in a study conducted by Bollinger et al. (2006), 75% of caregivers reported that their child's food allergies significantly impacted their grocery shopping behaviors and 66% reported that this impacted their meal preparation [49]. Moreover, additional research by Springston et al. (2010) found that when evaluating daily living with a child or adolescent with food allergy, 66% of caregivers reported feeling "moderately or extremely troubled" due to the extra time required for preparing meals and grocery shopping [41].

Currently, food allergen labeling laws in the United States require mandatory disclosure of peanut, tree nut, cow's milk, shellfish, egg, finfish, soy, and wheat in packaged foods. However many manufacturers also choose to include additional precautionary allergen labeling (e.g., may contain, manufactured on shared equipment with), which is entirely voluntary [50]. Since use of precautionary allergen labeling is unregulated and unstandardized, it can leave families confused when trying to make informed, safe decisions about the risk of allergen exposure present in a given food product. Interestingly, a recent study of children with peanut and tree nut allergies found that children who consumed foods with the label "may contain" reported higher food allergy-related QoL compared to children who avoided these foods, despite the potential greater risk of allergen exposure. Mothers of the children who ate foods labeled "may contain" also had better food allergy-related QoL, perhaps due to decreased vigilance and having to enforce fewer restrictions on their child's diet [4].

In Springston's 2010 study, the risk of being extremely troubled by everyday factors such as meal preparation was significantly higher among caregivers with high knowledge of food allergy; however, a number of these respondents also mentioned that they have learned to appreciate the positive aspects of managing food allergy over time, including the development of a routine. Moreover, caregivers shared that stress related to meal planning decreased after the first 1–2 years of managing a food allergy diagnosis

[41]. This finding may indicate that providing more supportive services with a particular emphasis on nutritional counseling during the first year after diagnosis may be warranted. Moreover, understanding that managing food allergy is a dynamic process that shifts over time challenges researchers to extend their methods beyond cross-sectional surveys to include more longitudinal study designs. Promising data collection strategies include ecological momentary assessment, which aims to repeatedly assess behavior and other constructs of interest via brief, repeated assessments, which are often administered via phone and can be linked to mobile phone sensors and other environmental data. Such methods can permit respondents to better disclose real-time challenges and factors that impair QoL and in turn may be useful to inform the development of real-time supports [2, 51].

## Food in Society

Aside from meal preparation and maintaining safety in the home, families with food allergy must also practice vigilance when preparing for social occasions. Sporting events, birthday parties, and restaurant dining often revolve around food, which sometimes leaves families feeling withdrawn and fearful of an unexpected allergic reaction [52]. For example, Polloni et al. found that after surveying 124 mother-child dyads about their behavior and attitudes in social settings with food allergy, 44% noted that they always attended social gatherings, but that they were very likely to bring their own food or only eat their well-known "safe" foods as a precautionary measure [48].

When it comes to dining out habits, many families reported that they frequently attend the same restaurant due to the security they feel. This repetitive dining behavior is understandable as research conducted to explore the perceived risk and risk communication-related behaviors in the United States found that most servers lack knowledge about food allergies and believe that initiating communication and preventing allergic reactions was the customer's responsibility [53].

# Individual and Family Mental Health Considerations: Anxiety, Coping Behaviors, and Integrative Interventions

## Anxiety and Coping Behaviors

Children and adolescents living with food allergy often exhibit symptoms consistent with generalized anxiety and emotional distress [54–58]. Yet, very little clinical training in allergy is structured to consider the whole patient from physical, psychoemotional, and spiritual perspectives. In particular, there is a deficit regarding how to holistically partner with children, adolescents, and families confronting comorbid conditions – particularly when considering food allergy and anxiety [59].

### Striking a Balance: Food Allergen Avoidance and Anxiety Management

Previous research suggests that the relationship between food allergy and anxiety is not an all-or-nothing phenomenon; rather, the food allergy community needs to recognize the utility of anxiety that is potentially protective all while recognizing that balancing healthy levels of anxiety may require a nuanced approach to management [60]. Tipping into heightened anxiety over time can result in impaired physical and mental health outcomes related to chronic stress, which has been previously shown to negatively mediate related atopic pediatric conditions (e.g., asthma) [61–64]. Previous work has employed the so-called "Goldilocks principle" to conceptualize the level of anxiety that might be "just right" for affected individuals [2]. In this view, an optimal level of anxiety is purported to lie somewhere between inadequate allergen avoidance (as evidenced by frequent, avoidable reactions) and hypervigilance (which is associated with substantially impaired QoL) [65]. Ideally, an appropriate level of anxiety can help a child or adolescent minimize both their risk of food-allergic reactions and the level of psychosocial impairment associated with daily food allergy management [66, 67].

Klinnert et al. (2015) further conceptualizes how caregiver-level factors (e.g., anxiety), child-level factors (e.g., developmental level), and ill-

ness parameters (e.g., number of food allergies) contribute to food allergy management practices. The combination of factors may mediate adaptive or maladaptive coping behaviors, which influence how anxiety manifests at individual and family levels [67]. Understanding the multiple factors that contribute to the daily experience of living with a food allergy remains integral to identifying useful psychological resources and management supports that may be missing from a family's overall management approach. Identifying and linking families to resources may contribute to families being able to achieve a more balanced integration of food allergy management and psychosocial adjustment.

### Cognitive-Behavioral Theory and Anxiety

In a 2006 review of the literature focused on the intersection of food allergy and anxiety, Friedman and Morris provide two cognitive-behavioral theories to explain the relationship between these conditions [58]. The first understanding of these common comorbid conditions includes the psychological theory of classical conditioning. Within the context of food allergy, when a person has an allergic reaction (i.e., an unconditioned stimulus), they fear the recurrence of these symptoms. The child then experiences feelings of anxiety and fear (i.e., a conditioned response) related to the symptoms associated with an allergic reaction.

The second cognitive-behavioral understanding is largely based on learning and parental modeling of behaviors. For example, caregivers have the opportunity to model adaptive or maladaptive coping skills in response to anxiety-provoking allergic events. If maladaptive, this response over time can result in the caregivers becoming overprotective as a means to overcome feelings of fear. As such, the child models the caregiver's behavior and learns to practice maladaptive coping skills, thus subsequently developing anxious responses to these stimuli [58].

### Parental/Caregiver Anxiety

On the family level, previous research has confirmed some aspects of these aforementioned cognitive-behavioral theories. The more heightened anxiety of the caregiver all too often results in heightened levels of anxiety among children and adolescents [68]. Moreover, caregivers who perceive their children to be medically vulnerable have been shown to engage in hypervigilant, intrusive, and restrictive parenting behaviors that limit the development of age-appropriate autonomy. Within the food allergy community, studies have illustrated that high levels of maternal anxiety can play a role in increasing child anxiety, largely due to mothers shouldering the majority of work required in caring for children with food allergies, which often includes executing day-to-day nutrition and meal planning, managing medical care and communication of food allergy action plans with school personnel, and ensuring that their larger community is aware of their child's allergies throughout daily living – from sporting events to holiday celebrations [69].

Manassis [71] published a review of 24 studies focused on better understanding the intersection of anxiety and anaphylaxis within the pediatric population [71]. The paper distills down four key aspects to understanding how anxiety manifests in relationship to anaphylaxis as follows: (1) Physiological (e.g., flushing, asthma attacks), (2) Cognitive (e.g., managing one's own anaphylaxis risk), (3) Behavioral (e.g., unnecessary avoidance, clinging), and (4) Parental (e.g., parental anxiety) [71]. Overall, better understanding how anxiety manifests among a population at risk of experiencing anaphylaxis could help to inform the development of pragmatic interventions designed to both reduce anxiety and improve overall food allergy-related QoL for patients and families.

## Integrative Interventions

Over the past two decades, research has demonstrated the utility of integrating approaches derived from the field of positive psychology and integrative systems of health (e.g., Chinese medicine, Ayurvedic medicine) to confront anxiety among the general population [70]. For example, to address the physiological expression of anxiety,

teaching children mind-body coping strategies like mindfulness, guided imagery, and utilizing progressive muscle relaxation approaches has been useful [72–75]. Additional integrative methods like yoga, medical hypnosis, and acupuncture are also well known to reduce generalized anxiety and should be further explored by the food allergy community as potential integrative care methods that may lessen anxiety while simultaneously improving food allergy-related QoL [76–91]. Future work should consider how to best align these approaches according to patient and family needs as well as train clinicians in feasible interventions that could be implemented within short appointment times (e.g., auricular acupuncture, yoga breathing) [67].

## Conclusion

The overall goal in translating current scientific knowledge into accessible daily food allergy management practices is to ensure that living with a food allergy does not unnecessarily limit a child or adolescent's ability to fully engage in their lives at home, in school, and throughout their community. Building stronger communities requires strengthening relationships of affected individuals with their families, peer groups, clinical care providers, and school communities. As evolving treatment and prevention strategies become more widely available to the general food allergy community, physicians and other members of the clinical care team will need to accompany affected families by providing well-timed counseling and access to interventions that seek to meet the physical, psycho-emotional, and nutritional needs of affected families. Meeting families where they are to better address identified food allergy-related challenges – be it support with meal planning or help with navigating school policies to ensure a supportive academic environment – remains critical to improving food allergy-related QoL for children, adolescents, and caregivers. Moreover, research focused on better understanding what factors continue to impair QoL balanced with better investigating and articulating the positive outcomes associated with living with a food allergy remains critical. We must continue to provide the necessary resources to prevent and adequately respond in a food allergy emergency and build upon the strengths and capacities of those affected to influence change that ultimately enhances well-being.

## References

1. Gupta RS, Warren CM, Smith BM et al. The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States. Pediatrics 2018;142.
2. Warren CM, Otto AK, Walkner MM, Gupta RS. Quality of life among food allergic patients and their caregivers. Curr Allergy Asthma Rep. 2016;16(5):38.
3. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy. 2010;65(8):933–45.
4. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. Pediatr Allergy Immunol. 2010;21(4 Pt 1):586–94.
5. Greenhawt M. Food allergy quality of life. Ann Allergy Asthma Immunol. 2014;113(5):506–12.
6. Lieberman JA, Sicherer SH. Quality of life in food allergy. Curr Opin Allergy Clin Immunol. 2011;11(3):236–42.
7. Walkner M, Warren C, Gupta RS. Quality of life in food allergy patients and their families. Pediatr Clin N Am. 2015;62(6):1453–61.
8. The World Health Organization quality of life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403–9.
9. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr. 2003;3(6):329–41.
10. Skevington SM, Lotfy M, O'Connell KA, Group W. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res. 2004;13(2):299–310.
11. Knibb RC, Stalker C. Validation of the food allergy quality of life-parental burden questionnaire in the UK. Qual Life Res. 2013;22(7):1841–9.
12. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy. 2010;65(5):630–5.
13. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL ques-

tionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clin Exp Allergy. 2008;38(6):977–86.
14. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, et al. Development and validation of the food allergy quality of life questionnaire – adult form. Allergy. 2009;64(8):1209–17.
15. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of a self-administered food allergy quality of life questionnaire for children. Clin Exp Allergy. 2009;39(1):127–37.
16. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of the self-administered food allergy quality of life questionnaire for adolescents. J Allergy Clin Immunol. 2008;122(1):139–44, 144 e131–132.
17. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. J Allergy Clin Immunol. 2010;126(6):1105–18.
18. van der Velde JL, Flokstra-de Blok BM, de Groot H, et al. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. J Allergy Clin Immunol. 2012;130(5):1136–1143.e1132.
19. Franxman TJ, Howe L, Teich E, Greenhawt MJ. Oral food challenge and food allergy quality of life in caregivers of children with food allergy. J Allergy Clin Immunol Pract. 2015;3(1):50–6.
20. Soller L, Hourihane J, DunnGalvin A. The impact of oral food challenge tests on food allergy health-related quality of life. Allergy. 2014;69(9):1255–7.
21. LeBovidge JHS, Olney E, Hoyte L, Rachid R, Nadeau K, et al. The psychological impact of oral immunotherapy for children with food allergy: perceived benefits and treatment burden. Clin Pract Pediatr Psychol. 2014;2:13–26.
22. Carraro S, Frigo AC, Perin M, et al. Impact of oral immunotherapy on quality of life in children with cow milk allergy: a pilot study. Int J Immunopathol Pharmacol. 2012;25(3):793–8.
23. Arasi S, Otani IM, Klingbeil E, et al. Two year effects of food allergen immunotherapy on quality of life in caregivers of children with food allergies. Allergy Asthma Clin Immunol. 2014;10(1):57.
24. Howe LC, Leibowitz KA, Perry MA, et al. Changing patient mindsets about non-life-threatening symptoms during oral immunotherapy: a randomized clinical trial. J Allergy Clin Immunol Pract. 2019; https://doi.org/10.1016/j.jaip.2019.01.022. pii: S2213–2198(19)30075–3. [Epub ahead of print].
25. Kelleher MM, DunnGalvin A, Sheikh A, Cullinane C, Fitzsimons J, Hourihane JO. Twenty four-hour helpline access to expert management advice for food-allergy-triggered anaphylaxis in infants, children and young people: a pragmatic, randomized controlled trial. Allergy. 2013;68(12):1598–604. https://doi.org/10.1111/all.12310.
26. Gupta RS, Springston EE, Kim JS, et al. Food allergy knowledge, attitudes, and beliefs of primary care physicians. Pediatrics. 2010;125(1):126–32.
27. Emanuel EJ, Emanuel LL. Four models of the physician-patient relationship. JAMA. 1992;267(16):2221–6.
28. AR101 Oral immunotherapy for peanut allergy. N Engl J Med. 2018;379(21):1991–2001.
29. Sampson HA, Shreffler WG, Yang WH, et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with Peanut sensitivity: a randomized clinical trial. JAMA. 2017;318(18):1798–809.
30. Du Toit G, Roberts G, Sayre PH, et al. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. J Allergy Clin Immunol. 2013;131(1):135–143.e131–112.
31. Baptist AP, Dever SI, Greenhawt MJ, Polmear-Swendris N, McMorris MS, Clark NM. A self-regulation intervention can improve quality of life for families with food allergy. J Allergy Clin Immunol. 2012;130(1):263–265.e266.
32. LeBovidge JS, Timmons K, Rich C, et al. Evaluation of a group intervention for children with food allergy and their parents. Ann Allergy Asthma Immunol. 2008;101(2):160–5.
33. Shemesh E, Annunziato RA, Ambrose MA, et al. Child and parental reports of bullying in a consecutive sample of children with food allergy. Pediatrics. 2013;131(1):e10–7.
34. Lieberman JA, Weiss C, Furlong TJ, Sicherer M, Sicherer SH. Bullying among pediatric patients with food allergy. Ann Allergy Asthma Immunol. 2010;105(4):282–6.
35. Annunziato RA, Rubes M, Ambrose MA, Mullarkey C, Shemesh E, Sicherer SH. Longitudinal evaluation of food allergy–related bullying. J Allergy Clin Immunol Pract. 2014;2(5):639–41.
36. Rigby K, Slee P. Interventions to reduce bullying. Int J Adolesc Med Health. 2008;20(2):165–83.
37. Vreeman RC, Carroll AE. A systematic review of school-based interventions to prevent bullying. Arch Pediatr Adolesc Med. 2007;161(1):78–88.
38. Warren CM, Dyer AA, Otto AK, et al. Food allergy-related risk-taking and management behaviors among adolescents and young adults. J Allergy Clin Immunol Pract. 2017;5(2):381–390.e313.
39. Sawyer SM, Drew S, Yeo MS, Britto MT. Adolescents with a chronic condition: challenges living, challenges treating. Lancet (London, England). 2007;369(9571):1481–9.
40. Dyer AA, O'Keefe A, Kanaley MK, Kao LM, Gupta RS. Leaving the nest: improving food allergy management on college campuses. Ann Allergy Asthma Immunol. 2018;121(1):82–89.e85.
41. Springston EE, Smith B, Shulruff J, Pongracic J, Holl J, Gupta RS. Variations in quality of life among caregivers of food allergic children. Ann Allergy Asthma Immunol. 2010;105(4):287–294.e283.

42. Hobbs CB, Skinner AC, Burks AW, Vickery BP. Food allergies affect growth in children. J Allergy Clin Immunol Pract. 2015;3(1):133–134.e131.
43. Howe L, Franxman T, Teich E, Greenhawt M. What affects quality of life among caregivers of food-allergic children? Ann Allergy Asthma Immunol. 2014;113(1):69–74.e62.
44. Wassenberg J, Cochard MM, Dunngalvin A, et al. Parent perceived quality of life is age-dependent in children with food allergy. Pediatr Allergy Immunol. 2012;23(5):412–9.
45. Allen CW, Bidarkar MS, vanNunen SA, Campbell DE. Factors impacting parental burden in food-allergic children. J Paediatr Child Health. 2015;51(7):696–8.
46. Ward CE, Greenhawt MJ. Treatment of allergic reactions and quality of life among caregivers of food-allergic children. Ann Allergy Asthma Immunol. 2015;114(4):312–318.e312.
47. Warren CM, Gupta RS, Sohn MW, et al. Differences in empowerment and quality of life among parents of children with food allergy. Ann Allergy Asthma Immunol. 2015;114(2):117–25.
48. Polloni L, Toniolo A, Lazzarotto F, et al. Nutritional behavior and attitudes in food allergic children and their mothers. Clin Transl Allergy. 2013;3(1):41. Published 2013 Dec 10. https://doi.org/10.1186/2045-7022-3-41.
49. Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol. 2006;96(3):415–21.
50. Marchisotto MJ, Harada L, Kamdar O, et al. Food allergen labeling and purchasing habits in the United States and Canada. J Allergy Clin Immunol Pract. 2017;5(2):345–351.e342.
51. Peniamina RL, Mirosa M, Bremer P, Conner TS. The stress of food allergy issues in daily life. Psychol Health. 2016;31(6):750–67.
52. National Academies of Sciences E, Medicine. Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy. Washington, DC: The National Academies Press; 2017.
53. Wen H, Kwon J. Restaurant servers' risk perceptions and risk communication-related behaviors when serving customers with food allergies in the U.S. Int J Hosp Manag. 2017;64:11–20.
54. Goodwin RD, Rodgin S, Goldman R, et al. Food allergy and anxiety and depression among ethnic minority children and their caregivers. J Pediatr. 2017;187:258–264.e251.
55. Lebovidge JS, Stone KD, Twarog FJ, et al. Development of a preliminary questionnaire to assess parental response to children's food allergies. Ann Allergy Asthma Immunol. 2006;96(3):472–7.
56. Shanahan L, Zucker N, Copeland WE, Costello EJ, Angold A. Are children and adolescents with food allergies at increased risk for psychopathology? J Psychosom Res. 2014;77(6):468–73.
57. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. Ann Allergy Asthma Immunol. 2001;87(6):461–4.
58. Friedman AH, Morris TL. Allergies and anxiety in children and adolescents: a review of the literature. J Clin Psychol Med Settings. 2006;13(3):318–31.
59. Greenhawt M. Food allergy quality of life and living with food allergy. Curr Opin Allergy Clin Immunol. 2016;16(3):284–90.
60. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol. 2003;14(5):378–82.
61. Dave ND, Xiang L, Rehm KE, Marshall GD Jr. Stress and allergic diseases. Immunol Allergy Clin N Am. 2011;31(1):55–68.
62. Compas BE, Jaser SS, Dunn MJ, Rodriguez EM. Coping with chronic illness in childhood and adolescence. Ann Rev Clin Psychol. 2012;8:455–80.
63. Cohen MH. The unknown and the unknowable – managing sustained uncertainty. West J Nurs Res. 1993;15(1):77–96.
64. Cousino MK, Hazen RA. Parenting stress among caregivers of children with chronic illness: a systematic review. J Pediatr Psychol. 2013;38(8):809–28.
65. Mandell D, Curtis R, Gold M, Hardie S. Anaphylaxis: how do you live with it? Health Soc Work. 2005;30(4):325–35.
66. Stjerna M-L, Vetander M, Wickman M, Olin Lauritzen S. The management of situated risk: a parental perspective on child food allergy. Health. 2013;18(2):130–45.
67. Klinnert MD, McQuaid EL, Fedele DA, et al. Children's food allergies: development of the food allergy management and adaptation scale. J Pediatr Psychol. 2015;40(6):572–80.
68. Fedele DA, McQuaid EL, Faino A, et al. Patterns of adaptation to children's food allergies. Allergy. 2016;71(4):505–13.
69. Chow C, Pincus DB, Comer JS. Pediatric food allergies and psychosocial functioning: examining the potential moderating roles of maternal distress and overprotection. J Pediatr Psychol. 2015;40(10):1065–74.
70. McClafferty H. Complementary, holistic, and integrative medicine: mind-body medicine. Pediatr Rev. 2011;32(5):201–3.
71. Manassis K. Managing anxiety related to anaphylaxis in childhood: a systematic review. J Allergy (Cairo). 2012;2012:316296.
72. Yapko MD. Mindfulness and hypnosis: the power of suggestion to transform experience. New York: W W Norton & Co; 2011.
73. Uman LS, Chambers CT, McGrath PJ, Kisely S. A systematic review of randomized controlled trials examining psychological interventions for needle-related procedural pain and distress in children and adolescents: an abbreviated cochrane review. J Pediatr Psychol. 2008;33(8):842–54.

74. Kuttner L, Friedrichsdorf S. Hypnosis and palliative care for children and their families. In: Sugarman LI, Wester WC, editors. Therapeutic hypnosis with children and adolescents. Bancyfelin: Crown House Publishing; 2014.
75. Uman LS, Birnie KA, Noel M, Parker JA, Chambers CT, McGrath PJ, Kisely SR. Psychological interventions for needle-related procedural pain and distress in children and adolescents. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD005179. https://doi.org/10.1002/14651858.CD005179.pub3.
76. Wang SM, Kain ZN. Auricular acupuncture: a potential treatment for anxiety. Anesth Analg. 2001;92(2):548–53.
77. Michalek-Sauberer A, Gusenleitner E, Gleiss A, Tepper G, Deusch E. Auricular acupuncture effectively reduces state anxiety before dental treatment – a randomised controlled trial. Clin Oral Investig. 2012;16(6):1517–22.
78. Kober A, Scheck T, Schubert B, et al. Auricular acupressure as a treatment for anxiety in prehospital transport settings. Anesthesiology. 2003;98(6):1328–32.
79. Kirkwood G, Rampes H, Tuffrey V, Richardson J, Pilkington K. Yoga for anxiety: a systematic review of the research evidence. Br J Sports Med. 2005;39(12):884–91.
80. Kaiser P. Childhood anxiety, worry, and fear: individualizing hypnosis goals and suggestions for self-regulation. Am J Clin Hypn. 2011;54(1):16–31.
81. Kaiser P. Childhood anxiety and psychophysiological reactivity: hypnosis to build discrimination and self-regulation skills. Am Clin Hypnosis. 2014;56(4):343–67.
82. Kohen DP, Wynne E. Applying hypnosis in a preschool family asthma education program: uses of storytelling, imagery, and relaxation. Am J Clin Hypn. 1997;39:2–14.
83. Kohen DPO, K.N. Hypnosis and Hypnotherapy with Children. 4th ed. New York, NY, USA: Routledge Publications, Taylor & Francis; 2011.
84. Kohen DPW, E. Interview and demonstration of relaxation and mental imagery for an 11 y.o. boy (John H.) with Asthma and Anxiety. Minneapolis. 1996.
85. Kohen D. Relaxation/mental imagery: self-hypnosis for childhood asthma: behavioral outcomes in a prospective, controlled study. Aust J Clin Exp Hypn. 1996;24:12–28.
86. Anbar RD. Self-hypnosis for anxiety associated with severe asthma: a case report. BMC Pediatr. 2003;3:7–7.
87. Cyr LR, Culbert T, Kaiser P. Helping children with stress and anxiety: an integrative medicine approach. Biofeedback. 2003;31:12–7.
88. Sugarman LI. Therapeutic hypnosis with children and adolescents. 2nd ed. Wales/Bancyfelin: Crown House Publishing; 2014.
89. Zeltzer L, LeBaron S. Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. J Pediatr. 1982;101(6):1032–5.
90. Golden WL. Cognitive hypnotherapy for anxiety disorders. Am J Clin Hypnosis. 2012;54(4):263–74.
91. Kuttner L. Pain – an integrative approach. In: Oxford textbook of palliative care for children. 2nd ed. New York: Oxford University Press; 2012. p. 332–41.

# Part II

# Comorbid Conditions in Food Allergy

# 5 Environmental Allergies and Pollen Food Syndrome (PFS)

Susan Fox and Mary C. Tobin

## Introduction

Pollen allergy has increased in the last 20 years both in the United States and worldwide leading to an associated rise in reports of pollen food syndrome (PFS) [1]. The initial descriptive term for PFS was oral allergy syndrome (OAS) [2, 3]. The term OAS is ambiguous because it has been used indiscriminately in the literature without regard to the antigens or mechanisms causing the oral symptoms. The diagnosis and treatment of PFS require an understanding of the antigens implicated, path of antigen sensitization, the associated plant foods and the potential clinical syndromes involved. Many authors are now advocating the use of the term "pollen food syndrome" (PFS) or "pollen food allergy syndrome" (PFAS) to describe specifically the cross-reactivity to shared cross-reactive antibodies among the pollens, fresh fruits, raw vegetables, nuts, and spices. This is because the term OAS is used to describe the oropharyngeal symptoms resulting from eating any food, not just plant food [4–7]. PFS is used precisely to mean class 2 food allergy resulting from plant food allergens cross-reacting with pollen allergens and causing oral symptoms in pollen allergic patients [8, 9].

S. Fox
Division of Allergy and Immunology, Department of Internal Medicine, Rush University Hospital, Chicago, IL, USA
e-mail: susan_fox@rush.edu

M. C. Tobin (✉)
Division of Allergy and Immunology, Department of Internal Medicine, Department of Pediatrics, Rush University Hospital, Chicago, IL, USA
e-mail: mary_tobin@rush.edu

## Definition

PFS is the most common food allergy in adolescents and adults and the incidence is rising in young children [6, 10]. PFS is an allergic reaction to fresh fruits, raw vegetables, nuts, or spices which can cause swelling and pruritus of the lips, oral mucosa, tongue, and throat. The symptoms occur within seconds to minutes as the food contacts the oral mucosa. It is usually isolated to the oral mucosa and infrequently associated with systemic signs of anaphylaxis [6, 11].

## Epidemiology of PFS

Tuft and Blumstein first described the phenomena of OAS in 1942 [2]. They observed a reaction to foods, particularly raw fruits and vegetables, among their patients. Patients described localized itching of the inner cheeks, roof of the mouth, with itching often extending to the throat, plus swelling of the lips with occasionally an urticarial rash around the mouth. Patients noted, however, that cooked or canned produce did not cause the same reaction and their reactions were worse during pollen season. The authors demonstrated that the antigens causing the reaction could be detected



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_5

by skin testing with the suspected fresh fruit. In the 1940s, the idea of using fresh foods to skin test was novel, but the description of the oral allergy syndrome and its clinical significance were not fully appreciated until the late 1980s.

Amlot used the term OAS in 1987 when evaluating 80 highly atopic patients who either had atopic eczema or were skin test positive for food allergy [3]. He used this term because patients described the immediate onset of symptoms of oral irritation and throat tightness upon the ingestion of their food allergen. It reflected a precise time frame in the patient's experience of food allergies – the oral symptoms occurred first with small amounts of food, with progression to a systemic reaction with larger quantities of food. He also noted that in a subgroup of patients, urticaria, asthma, or anaphylaxis developed following the oral symptoms.

In 1988, Ortolani et al. studied 262 patients and used the term OAS to apply specifically to subjects with hay fever who developed oral allergy syndrome after fruit and vegetable ingestion. The patients had local reactions, and a few had systemic reactions [11]. There was a close connection between age of onset of hay fever and the occurrence of their oral allergy symptoms. In addition, the authors described an association between allergy to some pollens and certain fruits. For example, apple, carrot, pear, and cherry correlated with birch pollen allergy, and while tomato, melon, and watermelon correlated with grass pollen allergy. The presence of pollen and plant cross-reacting antibodies had not been demonstrated; therefore, the term OAS was connected with the spectrum of reactions associated with food allergy based on the presence of oral symptoms but not the type or source of the antigen.

In 1999, Kazemi-Shirazi et al. demonstrated convincingly that as distinguished from OAS, PFS is the result of cross-reacting antibodies between pollen and plant food [12]. Pre-incubation of sera from patients with PFS in the presence of natural pollen allergens led to an almost complete inhibition of IgE binding to plant food allergens in Western blots as well as in RAST inhibition experiments. When incubating the patients' serum with the plant food, there was poor inhibition of IgE binding. The key antigens were the pollen antigens causing the reactions. Sensitization was occurring through the respiratory tract because of pollen antigens, which shared epitopes with plant-based food. Patients were the bystanders in the reactions and were responding to the plant food as if they were eating the pollen directly due to the cross-reactive antibodies.

Researchers proposed that food allergy reactions could be classified according to the type of antigen and the path to sensitization; and categorized the food reactions into class 1 food allergy or class 2 food allergy [9]. In class 1 food allergy, IgE antibodies develop against food proteins, which were "complete," meaning not affected by proteolytic digestion or affected by heat, and were the result of direct sensitization occurring primarily in the gut. Class 1 food allergies cause the allergic reactions most common in early childhood to milk, egg, soy, fish, shellfish, peanut, and tree nuts [9, 13]. Alternatively, class 2 food allergy sensitization takes place through the respiratory tract when pollen antigens share epitopes with plant-based food. The allergens are often heat labile and known as "incomplete allergens" [8].

## Cross-Reactive Pan-Allergens

Pollen and food are not botanically related but do contain homologous proteins [8]. The shared epitopes between the pollen and the plant food involve both primary and tertiary structures [4, 8]. These shared proteins are highly conserved across the plant kingdom and widely distributed and are known as pan-allergens. Depending on the pan-allergen inducing the reaction, symptoms can range from PFS to anaphylaxis [6, 14].

## Pathogenesis-Related Proteins (PRPs)

The most common pan-allergens are pathogenesis-related proteins (PRPs), including lipid transfer proteins (LTPS) and profilins. PR proteins are

defense proteins that plants express to protect themselves in response to fungi, bacterial or viral infections, and injury or exposure to chemicals which mimic both infections and stress [9]. PR proteins were first discovered as proteins present in tobacco plants infected with tobacco mosaic virus [15]. They did not occur in non-infected plants but were evident after viral infection. The PRs are composed of 17 families with very similar biochemical functions and sequences [16]. The PR protein families constitute a repertoire of protective responses for the plant kingdom. In particular, the PR-10 protein family, represented by the Bet v 1 homologous proteins, is linked to an ancient primordial gene and is responsible for the majority of cross-reacting epitopes causing PFS [17]. The Bet v 1 antigen is the major birch pollen allergen. The homologous proteins in birch pollen-related fruits are apple (Mal d 1), cherry (Pru av. 1), apricot (Pru ar 1), and pear (Pyr c 1). The vegetables that are cross-reactive are carrot (Dau c 1), celery (Api g 1), parsley (pcPR), and potato (pSTH). Hazelnut allergy is related to another: Bet v 1 homolog and Cor a 1. Other important PRs allergens include PR-2, 3, 4, 5, and 14. The PR-2 family is known as B-1, 3 glucanases and can degrade fungal cell walls of actively growing hyphae. Most are extracellular but the basic glucanases are located intracellularly in vacuoles. The most important is *Hevea brasiliensis* (Hev b 2) from the latex of the tropical rubber tree and one the epitopes that causes latex allergy. It provokes an antibody responsible for the latex-fruit syndrome, causing hypersensitivity to avocado, banana, chestnut, fig, and kiwi [9, 18, 19].

The chitinases, PR-3, are found in seed-producing plants and digest the chitin that is in the skeleton of most insects and fungal cell walls. The latex prohevein, Hevein (Hev b 6.02), belongs to the chitin-binding proteins and also contributes to the epitopes present in the fruit associated with the latex-fruit syndrome [9, 19, 20] (Table 5.1).

PR-4 represents another family of chitinases occurring in potatoes in response to trauma. The PR-5 family constitutes thaumatin-like proteins with diverse antifungal functions. The foods that contain these proteins are cherry, apple (Mal d 2), paprika, and bell pepper (P23), and these cross-react with the pollen of mountain cedar (Jun a 3) [9].

## Lipid Transfer Proteins (nsLTP)

Another significant group is the non-specific lipid transfer proteins (PR-14) that transfer phospholipids from liposomes to mitochondria, which are located in the outer cell layer of the plant and form part of the plant defense system against fungus and bacteria. They are highly resistant to heat and changes in pH. They are the most important allergens in the Rosaceae family, which contains three significant subfamilies: Prunoideae (peach, apricot, plum, almond cherry), the Pomoideae subfamily (apple, pear); and the Rosoideae subfamily (blackberry, strawberry) [21]. The oral reactions that these proteins cause are different from the other defense proteins because pollen allergy is not a prerequisite. Sensitization can occur via class 2 sensitization and is limited to the oral mucosa; however, if sensitization occurs via class 1 sensitization the reactions can be systemic [22].

## Profilins

Profilins are monomeric, actin-binding proteins that regulate the actin filaments to form the cytoskeleton and are present in trees, grasses, and weeds. It is estimated that 20% of pollen allergic subjects are reactive to profilins which are shared by a wide variety of inhalant and food allergens [23]. Bet v 2, also another birch pollen allergen, is an example of a profilin that will cause birch pollen allergic patients to react to apple, celery, carrot, and pear. It is a complete antigen and often is not degraded by heating. It is associated with anaphylaxis in the celery-mugwort syndrome. (Table 5.1).

**Table 5.1** Food-pollen and latex-fruit syndromes

| Syndrome | Allergen | Fruit | Vegetable | Spice | Nut |
|---|---|---|---|---|---|
| *Birch fruit* [9, 22, 46]. Image from iStock.com/otme  | PR-10 | Apple, apricot, cherry, kiwi, peach, pear | Carrot, celery, fennel, parsley, potato | Chicory | Almond, hazelnut, peanut, walnut |
| *Ragweed-melon-banana* [8]. Image from iStock.com/vvzann  | Profilins/ LTPs | Cantaloupe, cucumber, melon, watermelon, zucchini | | | |

**Table 5.1** (continued)

| Syndrome | Allergen | Fruit | Vegetable | Spice | Nut |
|---|---|---|---|---|---|
| *Celery-mugwort-spice* [8]. Image from iStock.com/jopelka  | Profilins | Mango | Celery, carrot, garlic, leek, onion | Aniseed, caraway, coriander, fennel, paprika, parsley | |
| *Mugwort-peach* [8] | Profilins/ LTPs | Peach | | | |
| *Mugwort-mustard* [8] | Profilins/ LTPs | | Broccoli, cabbage, cauliflower, mustard | | |

(continued)

**Table 5.1** (continued)

| Syndrome | Allergen | Fruit | Vegetable | Spice | Nut |
|---|---|---|---|---|---|
| *Grass* [22, 47]. Image from iStock.com/bokasin  | Profilins | Kiwi, melon, tomato, watermelon | | | |
| *Latex-fruit* [9]. Image from iStock.com/elenathewise  | PR-2 (β-1-3 glucanases) | Avocado, banana, fig, kiwi | | | |
| | PR-3 (chitinases) | Avocado, banana | | | Chestnut |

## Pollen Food Syndrome Worldwide

The increase in PFS is related to multiple factors. Environmental changes worldwide and the agricultural practices of developing more resilient plants seem to have increased the expression of homologous proteins possibly leading to plant food becoming more allergenic [4]. Other factors include specific geography, climate, local diet, and food preparation [1, 9, 24].

Investigators in England, Italy, Australia, and Mexico recently examined their pediatric patients with allergic rhinitis for signs of PFS and found some surprising results. Studies from these countries have demonstrated a PFS prevalence of 10–24%. The effects of predominant plant foods varied among countries, possibly in relation to geography, climate, local dietary habits, and pollen exposures [7, 22, 25, 26].

The Australian investigators studied atopic children in southwest Sydney to assess the

occurrence of PFS in that pediatric population. They considered OAS to include PFS, food allergy, and latex-fruit syndrome. They found that the prevalence of PFS alone in patients with allergic rhinitis and pollen sensitization was 12.1%. The fruits causing PFS symptoms were all tropical fruits, and watermelon was the most common. In the broader definition of OAS, where reactions begin with oral symptoms but progress to systemic symptoms, OAS was compatible with typical reactions characteristic of food allergy, class 1, most frequently caused by peanut (13.6%) [26].

In Mexico, researchers evaluated children 6–14 years seen for the first time in their allergy clinic. They were given questionnaires to assess for PFS and skin testing for pollens and foods. In 267 patients PFS occurred in 10–12% of patients with allergic rhinitis to pollen. Pineapple was the most common food cited, related to the pollen of the *Quercus* species [25].

In Italy, Mastororilli et al. tested for pan-allergens to estimate the prevalence of PFS and then to identify endotypes of PFS in children with seasonal allergic rhinoconjunctivitis (SAR). They examined 1271 children from 4–18 years of age. They skin tested with both commercial pollen extracts and the pan-allergens. Foods eliciting symptoms were determined by questionnaire. The pan-allergens Phl p 12 (profilin), Bet v 1(PR-10), and Pru p 3 (nsLTP) were tested by immunoCAP FEIA. They found PFS in 24% of patients. They identified five PFS endotypes associated with pan-allergen IgE sensitization. There was a multi-pan-allergen group (sensitization equal to two or more pan-allergens) who had more severe allergic disease comorbidities and multiple foods causing symptoms; mono pan-allergen group (only reacting to one of the three pan-allergens tested) or no pan-allergen sensitization. The sensitization patterns were informative. The group who were sensitized to two or more pan-allergens (PR-10, profilin, nsLTP) lived in Northern Italy (84%). This region has a continental climate with more birch and alder pollen than in Southern Italy. They had more asthma, atopic dermatitis, urticaria, and anaphylaxis, as well as higher total IgE levels and more foods that triggered symptoms. The mono-sensitized patients who were reactive to profilin were more frequently from Central Italy, had a high IgE level and a defined group of foods that caused symptoms from the Cucurbitaceae family (watermelon, melon, and cucumber) as well as peach, banana, and kiwifruit. This pattern is characteristic of sensitization to grass, plantain, plane, and olive trees seen in Central Italy. The LTP endotype was more common in Southern Italy where birch is rare but Rosaceae fruits (apple, peach, and pear), bananas, and nuts cause symptoms. Both class 1 and class 2 food allergy sensitizations can be present in this LTP endotype and if the sensitization is via class 1 "complete antigens" the reactions are more likely to be systemic. PR-10 endotype was more common in Central Italy. Interestingly, it was not related to the birch pollen but to other Fagales (Quercus spp.) or beech tree pollen. The related plant foods which caused symptoms were apple, peach, and kiwifruit. Finally, children with no pan-allergen sensitivity detected usually had mild allergic disease and comorbidities. Forty percent of these children reacted to kiwifruit. Further prospective studies are needed to assess the value of the endotype classification and how it might provide strategies for prevention and therapy [22].

In London, Ludman et al. set out to discern the patterns of PFS and their relationship to three age groups: 0–5, 6–10, and 11–15 years of age. Overall, PFS was present in 48% of all the children recruited from their specialty allergy clinic. Starting from youngest to the oldest group the occurrence was 17%, 50%, and 78% of PFS, respectively. From microarray data, pan-allergen sensitization was demonstrated at 2.8 years of age and symptoms started at 4.5 years much earlier than expected [7].

## PFS and Associated Atopic Conditions

### Atopic Dermatitis

The study of birch pollen allergy (Bet v1) and its cross-reactive allergens in plant food has provided insights into the immunologic connections between pollen sensitization via upper respira-

tory allergy and other atopic manifestations. Reekers et al. demonstrated that birch pollen-related foods trigger atopic dermatitis in a subgroup of patients that were highly allergic to birch pollen. They evaluated 37 patients without immediate reactions to birch pollen-related food. After an elimination diet avoiding the cross-reactive foods for 4 weeks, the patients underwent an oral challenge of carrots, celery, hazelnuts, and apple mashed together and masked with carob and an orange flavor. Seventeen out of 37 patients responded with worsening of their eczema within 48 hours. The blood lymphocytes of the food responsive patients with atopic dermatitis expressed CLA+, a homing antigen that facilitated the appearance of these lymphocytes in patients' lesional skin from the punch biopsies when these patients were exposed to the birch pollen. None of them realized that they were sensitive to birch pollen-related foods and were unaware of its relationship to worsening of their eczema [27].

Bohle et al. extended the observations of Reekers in another study looking at patients with birch pollen allergy and eczema. Allergists usually counsel their patients to cook the foods cross-reacting with birch pollen because heat will denature the tertiary structure. In many cases, this allows the patient to consume the food without any oral allergy symptoms. The authors, however, demonstrated that heating does not destroy the expression of birch pollen (Bet v 1) T cell epitopes and can cause an increase in the patient's eczema. Eating birch pollen-related foods supports the pollen-specific $T_H^2$ inflammation and ongoing synthesis of IL-4. The continuing stimulation, even with small concentrations of Ig E binding allergens, through mucosal surfaces might foster perennial IgE synthesis in B cells [28].

## Eosinophilic Esophagitis

The insight that aeroallergens could contribute to eosinophilic esophagitis (EoE) was articulated first by Mishra et al. [29]. In their mouse model, after respiratory exposure to *Aspergillus fumigatus* they noted esophageal eosinophilia. To explain this finding they postulated that aeroallergens could be topically spread to the esophageal mucosa and contribute to ongoing inflammation in EoE. This theory was supported by Fogg et al. who reported a case study involving a 21-year-old woman who recounted worse symptoms, proven by esophageal biopsy of her EoE in pollen season with no change in diet or medication [30]. In another study in children with EoE, Ram et al. demonstrated that seasonal allergic rhinitis is associated with seasonal flares of esophageal eosinophilia. This was seen in 14% of patients with EoE; 84% were male and all had allergic rhinitis. They hypothesize that the allergic rhinitis may contribute to exacerbations of EoE in pollen season and by intensifying anti-inflammatory therapy during pollen season, the disease could be better controlled [31]. The impact of pollen allergy was also seen in another study by van Rhijn, whose patients with eosinophilic esophagitis (EoE) had a higher prevalence of sensitization to pan-allergens including profilins and PR-10. Thirty-nine percent of their patients with EoE were sensitized to birch pollen (rBet v 1) and corresponding food allergen components supporting a link with PFS [32]. Mahdavinia et al. surveyed a group of adults with EoE and found that greater than 50% of patients with EoE had PFS with pollen sensitization. They postulated that uncontrolled nasal inflammation due to pollen exposure along with the ingestion of pan-allergens in fruits and vegetables, prior to denaturation by stomach enzymes, could contribute to esophageal eosinophilia and subsequently the esophageal inflammation [33].

## Seasonal Intestinal Inflammation and Irritable Bowel Syndrome

Seasonal intestinal inflammation also correlates with aeroallergen sensitization in patients. Magnusson et al. evaluated nine patients with documented birch pollen allergy and PFS [34]. The patients had two duodenal biopsies: one at the end of birch pollen season and one 6 months later (out of season). They found during birch pollen season there was an increase in activated eosinophils (MBP+) and IgE+ mast cells present in the mucosa, villi, and basal lamina propria compared with off-season biopsies. They noted that five of nine patients satisfied the criteria for

irritable bowel syndrome (IBS) during the pollen season. Another study of patients with irritable bowel syndrome (IBS) by Tobin et al. found that in patients identified with diarrhea-predominant IBS, 80% had seasonal allergic rhinitis (SAR) and 51% reported atopic eczema (AE). The patients were specifically asked about symptoms of itching or swelling of the mouth, tongue, and throat, and fruits were cited most often as the cause [35]. It is thought provoking that respiratory sensitization to pollen allergens might be related and contributes to seasonal immunologic inflammatory changes in the small intestine as well as in the esophagus and skin.

### Pollen Food Syndromes (Table 5.1)

*Birch fruit syndrome* is the most common of all the pollen food syndromes. It is rarely associated with anaphylaxis. There is a risk of reaction to at least one food of 55% [1].

*Ragweed-melon-banana* syndrome in North America is related to weed pollen and usually associated with at least one other food approximately 90% of the time, i.e., avocado, banana, kiwi, and peach [1]. In Spain, melon allergy is associated with several pollens, especially grass. In Australia, watermelon is seen in patients reporting grass, tree, and weed pollen allergies [26].

*Celery-mugwort-spice* syndrome is seen with severe reactions especially in patients who are allergic to both the birch and mugwort pollen [8]. Spice allergy is usually related to shared epitopes of profilins and Bet v 1.

*Mugwort-peach* syndrome is related to sensitization to extensive cross-reactivity toward the LTPs, Bet v1, and profilins. In Spain, the allergen is the LTP, Pru p 3, the cause of the peach allergy [36]. If there is no pollen sensitization, systemic reactions are more common. Cross-reactivity with the Rosaceae fruits is 55% [1].

*Mugwort-mustard syndrome* in patients with mustard allergy 97% were sensitized to mugwort. Ten percent reported anaphylaxis and 40% reported reactions to cauliflower, cabbage, and broccoli [37].

*Grass pollen syndrome* is associated with reactions to kiwi, melon, tomato, and watermelon [38].

*Latex-fruit syndrome* can cause patients to experience reactions to plant foods. Almost 50% of patients allergic to natural rubber latex (NRL) will respond to avocado, banana, kiwi, chestnut, peach, tomato, white potato, and bell pepper [1, 20].

## Quality of Life

In the study of children in the United Kingdom, a quality of life questionnaire was administered to families with children having PFS. The questions encompassed family and social activities, such as school and camp, social activities involving food, vacation, restaurant meals, leaving children in the care of others, and children being near others who are eating. The questionnaire discussed the time needed for meal preparation and diet precautions observed when leaving the home. Parents' concerns about nutrition and feeling empowered to manage a reaction were addressed. In addition, the questionnaire assessed emotional issues including anxiety about reactions, frustration in dealing with others, and worries about the lack of a "normal childhood" [39]. All of the parameters measured showed moderate disruption with the most notable being the caregiver's anxiety regarding the need to read labels and spend extra time to preparing foods [7]. Ludman's results were in line with a similar caregiver survey by Springston et al. [40].

## Clinical History

In atopic patients, seasonal allergic rhinitis develops first and then PFS. The more symptomatic the patient is with itchy eyes and nose as well as rhinorrhea the more likely they are to develop PFS, which can occur in the first 5 years of life [7]. Documenting the months when the patient has allergic rhinitis symptoms will help to isolate potential foods if unrecognized by the patient. Fresh fruits, nuts, and raw vegetables are most frequently implicated. Inquiring whether cooked food causes symptoms is important. It is essential to inquire about the associated symptoms that the food causes. The questions should

focus on the presence of mucosal itching, tingling, burning, or swelling of the checks, tongue, lip swelling, change in voice or problems swallowing, gastrointestinal symptoms, urticarial lesions or anaphylaxis. The time course is informative because symptoms are apparent almost as soon as or within minutes of the food being in the mouth. It is usually relieved by swallowing or drinking water. Occasionally antihistamines are needed. Some patients will complain of gastrointestinal symptoms. Less than 8% suffer from systemic symptoms such as urticaria, angioedema, profuse diarrhea, coughing, wheezing, and hypotension [6].

Certain foods like those in the Rosaceae family can cause anaphylaxis without pollen allergy. They are considered class 1 food allergy and not PFS. Peach is the most common of these fruits to cause systemic symptoms due to LTP. There is a higher rate of clinical cross-reactivity in this family of foods and so questioning regarding reactions to related foods is important (Table 5.1). Also any history of allergic reactions to peanut or tree nut allergy should be treated as a class 1 allergy. Both peanut and hazelnut can cause PFS but it is difficult to distinguish at times from class 1 food allergy. If anaphylaxis is a concern, an epinephrine auto injector should be prescribed. If other than mild symptoms are present, an allergy consultation should be obtained.

## Testing

An allergist will do testing for inhalants and suspected foods for children with allergic rhinitis and/or asthma. The season when the symptoms occur, the plant food involved and the history of the reaction will usually suggest an accurate diagnosis. Skin testing with inhalant allergens will confirm sensitization to pollen. For foods, skin testing using fresh or frozen fruit and raw vegetables usually gives better results via the prick method than skin testing with commercial extracts [26]. The commercial extracts contain more stable allergens and may not contain sufficient cross-reacting antigens to elicit a positive skin test [41, 42]. If the patient had anaphylaxis, dermographism, severe dermatitis, or cannot stop antihistamines, the initial step is to draw blood for specific IgE immunoassays. They can be informative especially if the cross-reactive antibody is heat stable. If there are questions regarding safe ingestion of a particular plant food and the testing is equivocal or negative then an oral food challenge should be done with the appropriate part of the fruit, peel, and or pulp. This is especially true if the patient had a systemic reaction to peach because there is a high clinical cross-reactivity with other food in the Rosaceae family, and the patient may want to include it in their diet. Many believe that future testing will involve utilizing component-resolved diagnostics (CRD) with a microarray of specific antigens, like the recombinant PRs, LTPs, and profilins, which will greatly enhance our diagnostic abilities. Using CRD that are available for peanut or hazelnut is helpful. In testing for peanut, the Ara h 2 is elevated in patients with more severe reactions. Not all the molecular components, like Bet v 1, PR-10, or Bet v 2, are routinely available but hopefully will provide a better picture of the natural history and severity of the PFS.

## Therapy

There is no cure for food allergy, class 1 or class 2. Avoidance is currently advised for management of these food allergies. As noted, earlier allergists have advised patients to cook the cross-reacting foods to destroy the tertiary structure and render the food safe for consumption. In the presence of associated atopic conditions, when the T cell epitopes are conserved even when the food is cooked, ingesting the food might promote ongoing inflammation as seen in AD and perhaps EoE or even IBS. In the last 20 years, investigators have suggested that pollen immunotherapy could modify the symptoms of PFS. The success rate of remission with subcutaneous immunotherapy with birch pollen has reportedly ranged from 84% success to concerns that birch immunotherapy might have triggered the onset of PFS [43, 44]. There has been no success with sublingual therapy with birch pollen with regard

to tolerance for apple [45]. The studies cited are not robust. The hope of future immunotherapy lies in the ability to define and administer immunotherapy with the significant clinical epitopes. Molecularly directed immunotherapy will lead to significant reduction in the oral symptoms induced and is a potential cure for both pollen and related plant food allergy.

## Summary

Pollen food syndrome is increasing in the pediatric population. Studies from abroad suggest that it may occur in as high as 24% of the pediatric population and that it will increase in late childhood and adolescence depending on the severity and number of pollen allergens causing the rhinitis [10]. The foods most frequently identified as allergens are related to birch pollen and most often do not involve systemic reactions but only local reactions of the oral mucosa. A good clinical history will elicit the extent of the symptoms and whether further allergy consultation and testing is necessary. If there is any question of a systemic reaction, an epinephrine auto injector should be provided and allergy consultation should be obtained. Depending on associated atopic diseases, cooking the fruits and vegetables may be an acceptable alternative to allow the food to be ingested. Current research with recombinant allergens is hoped to bring about more accurate diagnosis and potential immunotherapy.

## Case Studies

### Case Study 5.1

A 5-year-old boy comes to the allergy clinic with itchy eyes, runny nose, and sneezing which started during the spring. He has had atopic eczema since he was 6 months old. His eczema is also worse. His mom notes complaints that his favorite fruit, apples, make his mouth and throat feel funny. It starts as soon as the apple is in his mouth and goes away quickly. His skin test shows a significant reaction to birch pollen, grass, and ragweed. The skin test with commercial apple extract is negative. A skin-prick test with the apple, touching the applicator through the peel, and applying pulp to the patient's forearm is positive.

*Case 5.1* illustrates a typical birch pollen-related reaction to apple. The reaction is usually worse in the pollen season and may be ameliorated with cooking of the fruit. What is interesting is the cooking of the fruit denatures the tertiary structure so the mediator release from mast cells is inhibited but does not alter the primary structure which has cross-reacting T cell epitopes that can cause worsening of eczema within 24 hours of ingestion. A small percentage, less than 8%, of patients with throat symptoms may progress to a systemic reaction. A prescription for an epinephrine auto injector would be indicated if this is a concern as well as an allergy consultation. In addition, the child is allergic to three pollens which is a risk factor of PFS. As he gets older, he might experience PFS with an increasing number of foods related to each of the pollens.

### Case Study 5.2

A 12-year-old girl has a history of seasonal allergic rhinitis, atopic eczema, and moderate persistent asthma. She noted that after she ate peanut, her throat felt like it was closing after just a few bites and she developed urticaria. She has a similar reaction with cantaloupe and tomato.

*Case 5.2* illustrates pan-allergen sensitization which is seen in older children with more allergic comorbidities. She may have reactions to Bet v 1, PR-14, and profilin. Her eczema might worsen within 24 hours of ingestion due to the T cell epitopes for birch pollen. Due to her symptoms and severity of atopic comorbidities, strict avoidance of the foods is advised and a prescription for an epinephrine auto injector is indicated. Consultation with an allergist is advised. If her asthma was stable she could be skin tested for the inhalants to confirm pollen sensitivity. Because of her reaction to the foods, specific IgE immunoassay to each food would be ordered. If the results

were negative or very low titer, then skin testing would be done. In addition, CRD for peanut would be helpful. A high titer against Ara h 2 is consistent with more serious reactions, whereas Ara h 8 is related to the birch pollen allergens and not likely to be proceed to anaphylaxis.

## References


1. Sicherer SH. Clinical implications of cross-reactive food allergens. J Allergy Clin Immunol. 2001;108(6):881–90.
2. Tuft L, Blumstein G. Studies in food allergy-sensitization to fresh fruits: clinical and experimental observations. J Allergy. 1942;13:574–8.
3. Amlot PL, Kemeny DM, Zachary C, Parkes P, Lessof MH. Oral allergy syndrome (OAS): symptoms of IgE-mediated hypersensitivity to foods. Clin Allergy. 1987;17(1):33.
4. Hofmann A, Burks A. Pollen food syndrome: update on the allergens. Curr Allergy Asthma Rep. 2008;8(5):413–7.
5. Kelso JM. Pollen food allergy syndrome. Clin Exp Allergy. 2000;30:905–7.
6. Ma S, Sicherer SH, Nowak-Wegrzyn A. A survey on the management of pollen-food allergy syndrome in allergy practices. J Allergy Clin Immunol. 2003;112(4):784–8.
7. Ludman S, Jafari-Mamaghani M, Ebling R, Fox AT, Lack G, Du Toit G. Pollen food syndrome amongst children with seasonal allergic rhinitis attending allergy clinic. Pediatr Allergy Immunol. 2016;27(2):134–40.
8. Egger M, Mutschlechner S, Wopfner N, Gadermaier G, Briza P, Ferreira F. Pollen-food syndromes associated with weed pollinosis: an update from the molecular point of view. Allergy. 2006;61(4):461–76.
9. Breiteneder H, Ebner C. Molecular and biochemical classification of plant-derived food allergens. J Allergy Clin Immunol. 2000;106(1):27–36.
10. Dondi A, Tripodi S, Panetta V, Asero R, Businco ADR, Bianchi A, et al. Pollen-induced allergic rhinitis in 1360 Italian children: comorbidities and determinants of severity. Pediatr Allergy Immunol. 2013;24(8):742–51.
11. Ortolani C, Ispano M, Pastorello E, Bigi A, Ansaloni R. The oral allergy syndrome. Ann Allergy. 1988;61(6 Pt 2):47–52.
12. Kazemi-Shirazi L, Pauli G, Purohit A, Spitzauer S, Hoffmann-Sommergruber K, Breiteneder H, et al. Quantitative IgE inhibition experiments with purified recombinant allergens indicate pollen-derived allergens as the sensitizing agents responsible for many forms of plant food allergy. J Allergy Clin Immunol. 2000;105(1):116–25.
13. Aalberse RC. Structural biology of allergens. J Allergy Clin Immunol. 2000;106(2):228–38.
14. Asero R, Pravettoni V. Anaphylaxis to plant-foods and pollen allergens in patients with lipid transfer protein syndrome. Curr Opin Allergy Clin Immunol. 2013;13(4):379–85.
15. Kauffmann S, Legrand M, Fritig B. Isolation and characterization of six pathogenesis-related (PR) proteins of Samsun NN tobacco. Plant Mol Biol. 1990;14:381–90.
16. Tellis M, Mathur M, Gurjar G, Kadoo N, Gupta V. Identification and functionality prediction of pathogenesis-related protein 1 from legume family. Proteins. 2017;85(11):2066–80.
17. Radauer C, Lackner P, Breiteneder H. The Bet v 1 fold: an ancient, versatile scaffold for binding of large, hydrophobic ligands. BMC Evol Biol. 2008;8(1):286.
18. Barre A, Culerrier R, Granier C, Selman L, Peumans WJ, Van Damme EJ, et al. Mapping of IgE-binding epitopes on the major latex allergen Hev b 2and the cross-reacting 1, 3 Beta-glucanase fruit allergens as a molecular for the latex-fruit syndrome. Mol Immunol. 2009;46(8–9):1595–604.
19. Midoro-Horiuti T, Brooks EG, Goldblum RM. Pathogenesis-related proteins of plants as allergens. Ann Allergy Asthma Immunol. 2001;87(4):261–71.
20. Blanco C, Diaz-Perales A, Collada C, Sánchez-Monge R, Aragoncillo C, Castillo R, et al. Class I chitinases as potential panallergens involved in the latex-fruit syndrome. J Allergy Clin Immunol. 1999;103(3):507–13.
21. Rodriguez J, Crespo JF, Lopez-Rubio A, de la Cruz-Bertolo J, Ferrando-Vivas P, Vives R, et al. Clinical cross-reactivity among foods of the Rosaceae family. J Allergy Clin Immunol. 2000;106(1):183–9.
22. Mastrorilli C, Tripodi S, Caffarelli C, Perna S, Di Rienzo-Businco A, Sfika I, et al. Endotypes of pollen-food syndrome in children with seasonal allergic rhinoconjunctivitis: a molecular classification. Allergy. 2016;71(8):1181–91.
23. Valenta R, Duchene M, Ebner C, Valent P, Sillaber C, Deviller P, et al. Profilins constitute a novel family of functional plant pan-allergens. J Exp Med. 1992;175(2):377–85.
24. Yagami T, Sato M, Nakamura A, Komiyama T, Kitagawa K, Akasawa A, et al. Plant defense–related enzymes as latex antigens. J Allergy Clin Immunol. 1998;101(3):379–85.
25. Bedolla-Barajas M, Kestler-Gramajo A, Alcalá-Padilla G, Morales-Romero J. Prevalence of oral allergy syndrome in children with allergic diseases. Allergol Immunopathol (Madr). 2017;45(2):127–33.
26. Brown CE, Katelaris CH. The prevalence of the oral allergy syndrome and pollen-food syndrome in an atopic paediatric population in south-west Sydney. J Paediatr Child Health. 2014;50(10):795–800.
27. Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen–related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses

to birch pollen antigens. J Allergy Clin Immunol. 1999;104(2):466–72.
28. Bohle B, Zwölfer B, Heratizadeh A, Jahn-Schmid B, Antonia YD, Alter M, et al. Cooking birch pollen–related food: divergent consequences for IgE- and T cell–mediated reactivity in vitro and in vivo. J Allergy Clin Immunol. 2006;118(1):242–9.
29. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. J Clin Invest. 2001;107(1):83–90.
30. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. J Allergy Clin Immunol. 2003;112(4):796–7.
31. Ram G, Lee J, Ott M, Brown-Whitehorn TF, Cianferoni A, Shuker M, et al. Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis. Ann Allergy Asthma Immunol. 2015;115(3):224–228.e1.
32. van Rhijn BD, van Ree R, Versteeg SA, Vlieg-Boerstra BJ, Sprikkelman AB, Terreehorst I, et al. Birch pollen sensitization with cross-reactivity to food allergens predominates in adults with eosinophilic esophagitis. Allergy. 2013;68(11):1475–81.
33. Mahdavinia M, Bishehsari F, Hayat W, Elhassan A, Tobin MC, Ditto AM. Association of eosinophilic esophagitis and food pollen allergy syndrome. Ann Allergy Asthma Immunol. 2016;118(1):116–7.
34. Magnusson J, Magnusson O, Lin XP, Dahlman-Höglund A, Hanson LÅ, Telemo E, et al. Seasonal intestinal inflammation in patients with birch pollen allergy. J Allergy Clin Immunol. 2003;112(1):45–51.
35. Tobin MC, Moparty B, Farhadi A, DeMeo MT, Bansal PJ, Keshavarzian A. Atopic irritable bowel syndrome: a novel subgroup of irritable bowel syndrome with allergic manifestations. Ann Allergy Asthma Immunol. 2008;100(1):49–53.
36. Pascal M, Muñoz-Cano R, Reina Z, Palacín A, Vilella R, Picado C, et al. Lipid transfer protein syndrome: clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. Clin Exp Allergy. 2012;42(10):1529–39.
37. Figueroa J, Blanco C, Dumpierrez AG, et al. Mustard allergy confirmed by double-blind placebo-controlled food challenges: clinical features and cross-reactivity with mugwort pollen and plant-derived foods. Allergy. 2005;60(1):48–55.
38. Ricci G, Righetti F, Menna G, Bellini F, Miniaci A, Masi M. Relationship between Bet v 1 and Bet v 2 specific IgE and food allergy in children with grass pollen respiratory allergy. Mol Immunol. 2005;42(10):1251–7.
39. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol. 2004;114(5):1159–63.
40. Springston EE, Smith B, Shulruff J, Pongracic J, Holl J, Gupta RS. Variations in quality of life among caregivers of food allergic children. Ann Allergy Asthma Immunol. 2010;105(4):287–94.
41. Webber CM, England RW. Oral allergy syndrome: a clinical, diagnostic, and therapeutic challenge. Ann Allergy Asthma Immunol. 2010;104(2):101–8.
42. Ortolani C, Ispano M, et al. Comparison of results of skin prick test (with fresh foods and commercial extracts) and RAST in 100 patients with oral allergy syndrome. J Allergy Clin Immunol. 1989;83(3):683–90.
43. Asero. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. Clin Exp Allergy. 1998;28(11):1368–73.
44. Modrzyński M, Zawisza E. Possible induction of oral allergy syndrome during specific immunotherapy in patients sensitive to tree pollen. Med Sci Monit. 2005;11(7):CR351–5.
45. Kinaciyan T, Jahn-Schmid B, Radakovics A, Zwölfer B, Schreiber C, Francis JN, et al. Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. J Allergy Clin Immunol. 2007;119(4):937–43.
46. Hoffmann HJ, Santos AF, Mayorga C, Nopp A, Eberlein B, Ferrer M, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. Allergy. 2015;70(11):1393–405.
47. Price A, Ramachandran S, Smith GP, Stevenson ML, Pomeranz MK, Cohen DE. Oral allergy syndrome (pollen-food allergy syndrome). Dermatitis. 2015;26(2):78–88.

# Asthma

6

Amy A. Eapen and Amal Assa'ad

## Abbreviations

| | |
|---|---|
| ACT | Asthma control test |
| EAACI | European Academy of Allergy and Clinical Immunology |
| ED | Emergency department |
| FAAP | Food Action Allergy Plan |
| FARE | Food Allergy Research and Education |
| FEV1 | Forced expiratory volume in 1 second |
| FVC | Forced vital capacity |
| ICU | Intensive care unit |
| NCHS | National Center for Health Statistics |
| NHANES | National Health and Nutrition Examination Survey |
| NHIS | National Health Interview Survey |
| OFC | Oral food challenge |
| OIT | Oral immunotherapy |

AE is supported by the National Research Service Award for Fellowship in Immunology and Allergy, National Institute of Allergy and Infectious Diseases T32 AI60515-01

A. A. Eapen (✉) · A. Assa'ad
Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: amy.eapen@cchmc.org; amal.assa'ad@cchmc.org

## Food Allergy Overview

The prevalence of food allergy has increased significantly in the last several years, affecting approximately 8% of children and presenting a large economic burden as a public health concern in the United States [1, 2]. Among those with food allergy, the prevalence of severe reaction to foods is estimated to be at 42.3%, with 40% of children with food allergy having multiple food allergies [3]. In a recent population-based survey by Gupta et al., the most common childhood food allergies reported have been to peanut (2.2%) and milk (1.9%) [3]. Racial/ethnicity data followed trends reported by previous analysis of the National Health and Nutrition Examination Survey (NHANES), and the population-based 2009–2011 National Health Interview Survey (NHIS) conducted by the Center for Disease Control reported that non-Hispanic African American children were more likely to have a food allergy than non-Hispanic white children [4] (Table 6.1).

Several studies have addressed the increase in food allergy seen globally. Keet et al. reported an overall increase of more than 1% per decade in the childhood prevalence of food allergy based on US-based surveys conducted by the CDC [5]. There are also noted racial disparities in the presence of food allergy among ethnic groups. In a multicenter retrospective cohort study of children 0–17 years of age with food allergy seen at Cincinnati Children's Hospital Medical Center and



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_6

**Table 6.1** Age-adjusted percentage demographics on prevalence of food allergy and respiratory allergy (2016) [4]

| | Food allergy | Respiratory allergy |
|---|---|---|
| *Gender* | | |
| Male | 6 | 11.4 |
| Female | 6.3 | 9.2 |
| *Race* | | |
| White | 5.9 | 9.8 |
| Black | 5.9 | 11.5 |
| Hispanic | 4.7 | 8.0 |
| Asian | 6.2 | 7.2 |

Data from Black and Benson [4]

Rush University Medical Center, African American children and Hispanic children were noted to have increased rates of food allergy–associated anaphylaxis and emergency department (ED) visits compared to Caucasians [6]. They were also noted to have a different food allergen profile with African American children and Hispanic children having increased rates of corn, shellfish, and fish allergies compared to Caucasian children.

Family history of atopy is also a known risk factor for food allergy risk. In a population-based study of 1-year-old infants diagnosed with food allergy by an oral food challenge (OFC), the risk of food allergy was increased by 40% in patients with one immediate family member with any allergic disease and by 80% in patients with two immediate family members with any allergic disease, compared with children without a family history of allergy [7]. Although family history increases the risk of food allergy in a child, routine testing is not recommended for children with a family history of food allergy prior to introduction of highly allergenic foods such as milk, peanut, or egg [8].

## Asthma Overview

The prevalence of asthma is also increasing and a large contributor to national healthcare costs. It is the most common chronic disease in children [9]. The estimated cost of caring for children with asthma between 2005 and 2009 was $10.7 billion [10]. In recent years, its prevalence has increased globally in children and adolescents, particularly in lower socioeconomic status children [11]. Its prevalence is higher in males than females, which is thought to be due to the smaller airways of male children relative to lung size when compared to the airways of female children [12]. There is a switch in prevalence of asthma during puberty from being more common in females to males, which is thought to be due to a reversal in the pattern of airway size [12]. Overall for both girls and boys, asthma can cause a burden on patients, families, as well as life at school. There are several indirect and intangible costs of asthma including impairment in quality of life, limitation of physical activities and study performance, and its psychological effects [11]. There is a noted racial disparity in the presence of asthma as well, with more African American children having asthma compared to Caucasians [13]. This burden is further exacerbated by the addition of food allergy as a comorbidity.

## Pathophysiology of Asthma and Food Allergies

### Asthma

Asthma, as an inflammatory disease, has been noted to have several different phenotypes. These phenotypes can be classified by the type of inflammatory process involved. Immunologically, there are several cell types involved with asthma's pathophysiology. CD4+ T cells are an important cell type that drives this inflammation. The inflammatory response can be further divided into different subsets, including T helper 2 cells (Th2) and non-Th2 cells. Th2-driven disease involves recruitment and action of eosinophils, mast cells, and basophils, while non-Th2 disease can involve neutrophils. These produce two different pediatric phenotypes, including allergic asthma representing eosinophilic inflammation and obese asthma involving non-Th2-mediated inflammation [14]. This distinction is important due to different treatment modalities being treatments of choice for the different phenotypes. Ross, et al. reported that based on a multivariable analysis, the risk factors associated with obese-related asthma phenotype were largely the same as some of the risk factors for pediatric obesity. These include parental obesity, greater than

8 hours of television per week, more weight gain in the first year of life, heavier birth weight, less sleep, lower socioeconomic status, being male, African American or Hispanic race/ethnicity, and increased sedentary time [14]. In managing asthma, it thus becomes important to manage comorbidities that are present and worsen the disease such as obesity. With allergic asthma, both food and aeroallergen sensitization are involved in control and management of asthma. Finally, another presentation is a mixed phenotype of allergic and obesity type, which is associated with more severe asthma. Mast cells are thought to be involved in the pathophysiology of this mixed subtype of asthma [15].

## Food Allergy

Food allergy can be due to IgE-mediated reactions, non-IgE-mediated reactions, and mixed IgE-mediated reactions [16]. IgE-mediated food allergy occurs due to the release of preformed mediators as well as the presence of IgE specific to the food the child is allergic to. Specific IgE present on mast cells are implicated in this process. Upon ingestion of a specific food allergen, IgE present on mast cells cross-links, resulting in the release of preformed mediators that cause the signs and symptoms we see in anaphylaxis. It often occurs within minutes to 2 hours of ingestion of the culprit food. Many children with IgE-mediated food allergies are at risk of asthma. Non-IgE-mediated food allergy includes eosinophilic esophagitis, where exposure to food over time causes disease, often up to 6 weeks [16]. IgE-mediated food reactions are often distinguished from non-IgE-mediated food reactions with skin prick tests and serum specific IgE levels.

## Clinical Presentation of Asthma

Clinically, wheezing is commonly one of the most important symptoms in the identification of asthma. Wheezing can occur in the setting of asthma as well as in the setting of a viral illness. It is known that children who have lower respiratory tract illnesses in early life are at increased risk of wheezing and asthma [17, 18]. However, there does not seem to be a correlation with children who are early transient wheezers and the risk of having asthma as older children [19, 20]. There also seems to be a distinction in onset of symptoms when looking at the different severities of asthma. Severe asthma is often characterized by persistence of symptoms despite being on high doses of inhaled or oral corticosteroids. Those children with severe asthma present at school age, around 6–11 years of age, but have reported chronic symptoms earlier on in life within the first 3 years of life when compared to children with moderate persistent asthma [21].

## Clinical Presentation of Food Allergy

Symptoms of food allergy often present as multisystem. Anaphylaxis is defined as being a severe, potentially life-threatening systemic hypersensitivity reaction [22]. It is characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems as defined in the European Academy of Allergy and Clinical Immunology (EAACI) anaphylaxis guidelines [22]. The National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network defines anaphylaxis as "a serious allergic reaction that is rapid in onset and may cause death" [23]. Symptoms can include rash/urticaria, wheezing, shortness of breath, emesis, and/or lethargy. Adolescents and young adults have the highest rate of life-threatening and fatal food-allergy-related reactions [24]. Therefore, after diagnosis of a food allergy, thorough and comprehensive counseling must be given to this age group to ensure they recognize symptoms promptly and seek medical attention appropriately.

## Clinical Presentation of Food Allergy and Asthma

Food allergy and asthma present as a manifestation of the atopic march. Figure 6.1 depicts the atopic march, described as the overall progres-

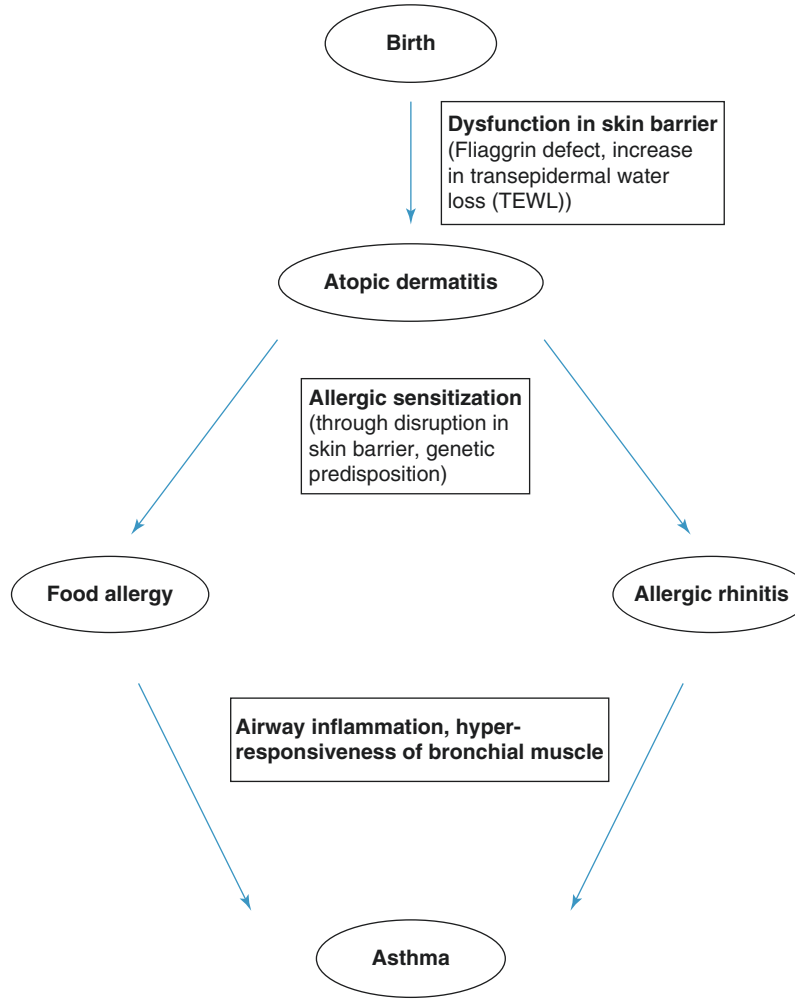



**Fig. 6.1** Atopic march

sion among allergic diseases. The atopic march often starts with atopic dermatitis early in childhood, which affects about 10–20% of children. It is then followed by the development of other allergic diseases such as asthma, and allergic rhinitis. Food allergy is implicated in one third of those with atopic dermatitis although asymptomatic food sensitization can also be seen [25]. Evidence suggests that this dysfunction in the skin barrier is an important factor in the development of allergic sensitization [26, 27]. This sensitization can lead to both food allergy and allergic rhinitis, then leading to allergic asthma. There is debate as to whether the atopic march represents a causal relationship versus atopic dermatitis and asthma having shared genetic and environmental risk factors [27]. Nonetheless, having one allergic disease does predispose a child to having another allergic disease.

Food allergy is thus in general associated with an increased risk of asthma [28]. The NIAID-Sponsored Expert Panel Guidelines for the Diagnosis and Management of Food Allergy in the United States summarized the risks associated with food allergy and asthma. They report that children with asthma who are sensitized to foods have a higher rate of hospitalization and increased utilization of oral corticosteroids [29]. In an analysis of a family-based food allergy cohort in Chicago, IL, Schroeder et al. demonstrated that symptomatic food allergy was associated with asthma in children, and the association

was stronger with multiple or severe food allergies [30]. Thirty-six percent of children younger than 6 years of age and 2 or more food allergies had a diagnosis of asthma ($p = 0.0033$) [30]. Children with food allergies have increased asthma morbidity and health care utilization [31], and this is also increased with multiple food allergies [32]. A multicenter prospective study of 163 children with anaphylaxis reported that a clinical history of asthma doubled the risk of respiratory arrest by seven-fold [33]. Gupta et al. reported an estimated annual economic impact of $24.8 billion or $4184 per year per child [1]. These patients are at increased risk of asthma-related hospitalizations and have significantly decreased lung function (FEV1 and FEV1/FVC ratios) [32]. The presence of self-reported food allergy is also more likely in patients with asthma admitted to the intensive-care unit (ICU) compared with patients with asthma who seek ambulatory care or are admitted to the hospital but not to the ICU [29].

Additionally, there is a risk of more severe reactions to accidental exposure to foods in children with asthma. In a previous registry established by the American Academy of Allergy, Asthma, and Immunology and with the assistance of the Food Allergy and Anaphylaxis Network, Bock, et al. reviewed the 32 fatal cases of anaphylaxis noted in the registry. In those subjects, all but one was noted to have asthma [8]. This increased association was also seen in previous studies where almost all fatal food allergy reactions were associated with a comorbidity of asthma [34]. Patients with food allergy and asthma have been found to have lower forced expiratory volume in 1 second (FEV1) scores as compared to asthmatic patients without food allergy [32]. Patients with multiple food allergies have been found to have three times the risk of daytime asthma symptoms and five times the risk of hospitalization [32]. This risk was maintained even when adjusting for other atopic diseases including atopic dermatitis [32]. It is thus important that pediatricians managing a patient's asthma with a history of food allergy take extra care to enforce adherence to controller medications and work to prevent exacerbations. It is also important to monitor for early signs of asthma in children with known food allergy due to this increased risk of severe allergic food reaction.

With poorly controlled asthma, anaphylaxis becomes more life threatening. There are reports of epinephrine being less effective in treatment of anaphylaxis in the presence of an asthma diagnosis [35]. The presentation of anaphylaxis can also be more severe with the presence of asthma. With the baseline obstruction, the increased hyperresponsiveness that occurs with anaphylaxis can make airflow even more difficult. It thus becomes of vital importance to recognize the symptoms of asthma in a child, especially in the presence of food allergy, and to initiate epinephrine sooner rather than later on a suspected anaphylaxis episode.

Food allergy can be fluid as tolerance may occur as children become older. Milk and egg allergy are often outgrown in the first 4–6 years of life, but peanut and tree nut food allergy persist more often into adulthood and natural tolerance is less often achieved [24]. The persistence of sensitization to food allergens in school-age children is associated with more severe asthma [36]. This is important to consider in the management of a child's asthma and food allergy. It gives foresight that these children are more likely to develop more severe asthma, and thus care must be taken in management of symptoms and asthma control.

## Tools for Management of Asthma and Food Allergy

We summarize the management of food allergy and asthma in Fig. 6.2. Table 6.2 presents important references for medical caregivers of children with food allergy and asthma.

It is important for a child's caregiver to know the importance of the increased severity of a food reaction on accidental exposure when the child has uncontrolled asthma. There are several tools to manage these two comorbidities. In allergy clinic, care is taken to assess the patient's asthma on each visit. Patients are often asked to complete

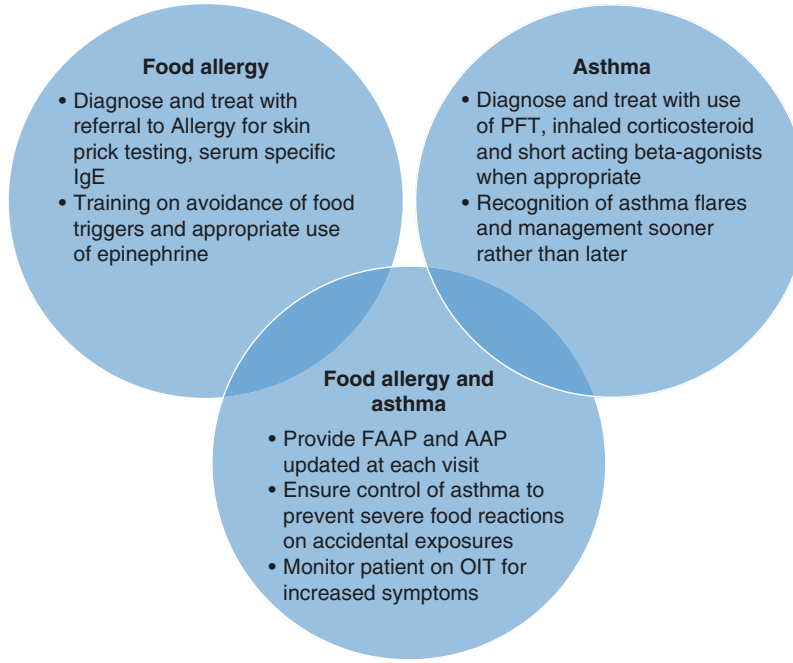



**Fig. 6.2** Management of food allergy and asthma

**Table 6.2** Important references for key points on asthma and food allergy

| Reference | Year | Key finding |
|---|---|---|
| Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents [34] | 1992, 2001 | Increased fatalities of food-induced anaphylaxis in asthmatic patients |
| Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods [8] | | |
| Mahdavinia M, Fox SR, Smith BM, James C, Palmisano EL, Mohammed A, et al. Racial Differences in Food Allergy Phenotype and Health Care Utilization among US Children [6] | 2017 | Increased rates of food allergy anaphylaxis occur among African Americans and Hispanics than Caucasians |
| Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang JL, Davis MM, et al. The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States [3] | 2018 | Approximately 42% of children with food allergies have severe reactions, and 40% of children with food allergies have multiple food allergies |
| Savage J, Johns CB. Food allergy: epidemiology and natural history [37] | 2015 | Most common food allergies among children are milk, peanut, and shellfish |
| Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet [12] | 2018 | Asthma prevalence switches from being more in males to females at puberty |
| Friedlander JL, Sheehan WJ, Baxi SN, Kopel LS, Gaffin JM, Ozonoff A, et al. Food allergy and increased asthma morbidity in a School-based Inner-City Asthma Study [32] | 2013 | Children with food allergy are at an increased risk of asthma-related hospitalizations and have decreased lung function compared to children without food allergy |
| Jat KR. Spirometry in children. Prim Care Respir J [38] | 2013 | Pulmonary function tests should be utilized in children with asthma and food allergy, including preschool children |
| Krogulska A, Dynowski J, Jedrzejczyk M, Sardecka I, Malachowska B, Wasowska-Krolikowska K. The impact of food allergens on airway responsiveness in schoolchildren with asthma: A DBPCFC study. Pediatr Pulmonol [39] | 2016 | Increased bronchial hyper-responsiveness in children undergoing oral food challenges with a history of asthma |
| Vazquez-Ortiz M, Alvaro M, Piquer M, Giner MT, Dominguez O, Lozano J, et al. Life-threatening anaphylaxis to egg and milk oral immunotherapy in asthmatic teenagers. Ann Allergy Asthma Immunol [40] | 2014 | Adolescents with asthma on OIT are at increased risk for adverse reactions |

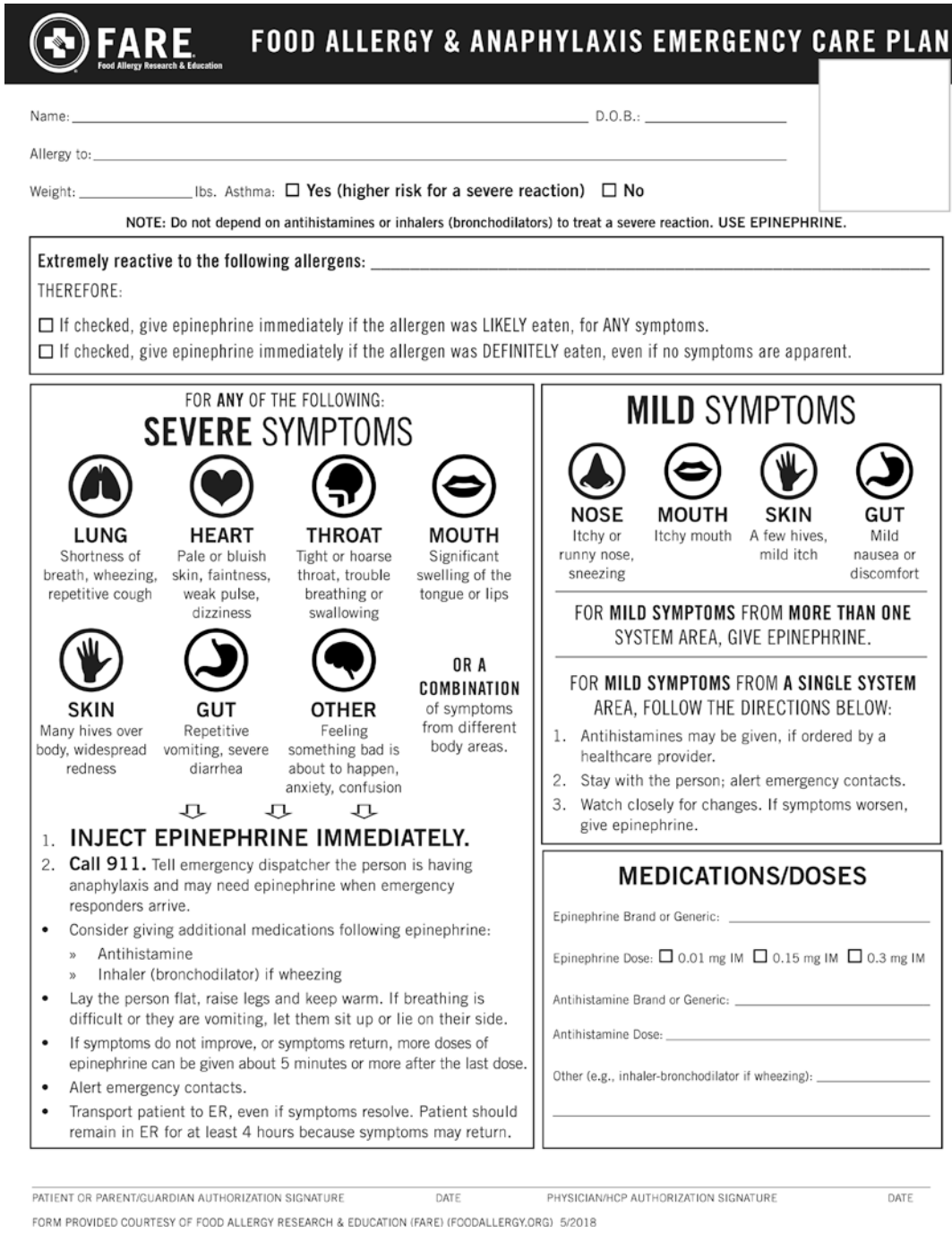
the asthma control test (ACT) to assess the symptomatic score for control of asthma. The ACT assesses subjectively the control of a patient's asthma in the preceding 4 weeks. Patients are asked to report how much time was kept from school, how often they have felt short of breath, are wheezing, are coughing, and how often they have used their rescue inhaler. When assessing use in the primary care setting, it has been shown to be beneficial in assessing asthma control [41]. Banasiak et al. conducted a pre- and post-implementation study comparing two different groups of patients with asthma seen in clinic over a 5-week period. After the implementation of the ACT, increased awareness of poor asthma control that was not previously noted was identified and adjustments made in their medication therapy. It is thus a simple, self-administered validated questionnaire that can be incorporated into the primary care setting to assist in screening patients on a regular basis for asthma control that may not be seen in a history and physical.

The increased risk of food allergy in the presence of asthma is highlighted in the Food Allergy Research and Education (FARE) Food Action Allergy Plan (FAAP) (Fig. 6.3). An updated FAAP is routinely provided to patients with food allergy so that other caregivers, schools, and daycares will know what specific foods should be avoided and what medications to be utilized if an accidental exposure with reaction occurs. The FAAP as noted below has an area to check if the patient has asthma and denotes that it indicates a higher risk of severe reaction. This further highlights the extra vigilance should be present for asthmatic patients with food allergy who have an accidental exposure.

Managing food allergy and asthma can be especially anxiety provoking for school-aged children. Food allergy alone can cause children to perceive themselves as different at school. It may also make them more vulnerable to bullying or being singled-out among their peers [43]. Evidence also shows that a variety of school systems may not have the appropriate readiness to manage a child with food allergy [44]. This makes it of utmost importance that clinicians equip patients and families with thorough counseling and guidance in managing food allergy and asthma. Although a child's school may not require the possession of a FAAP or AAP, it is our duty to provide families with these to give to schools to help prevent inappropriate treatment and delayed recognition of an accidental ingestion.

Objectively, pulmonary function tests (PFT) are a useful tool in assessing a patient's asthma with a history of food allergy. It is most useful to track the changes that occur on FEV1 and FEV1/FVC ratio (forced expiratory volume in 1 second/forced vital capacity) in the patient as a measure of asthma control. FEV1 is a good measure of the degree of obstruction. It is often underused in the outpatient setting and can be utilized as a progressive monitoring of asthma. There can be variability in the accuracy of pulmonary function tests in children due to the ability to perform the test, especially in preschool children age 3–5 years [45]. However, with recent improvements in available spirometry equipment, preschool children can effectively perform the test with the assistance of a trained personnel [38]. It is thus an effective method of monitoring the control of asthma from an objective standpoint.

Pulmonary function tests are especially important when determining whether a patient would be a good candidate for an oral food challenge (OFC) to the food allergy. OFCs are the current gold standard in diagnosing clinical reactivity and presence of a food allergy [46]. However, the risks and benefits of performing the challenge must not be taken lightly. An OFC consists of increasing doses of the food in question to a total goal dose, and is performed in an allergist's office. The patient at the time should be well with control of comorbid conditions such as asthma. Often allergists will not perform an OFC to a food when a patient's asthma is not under control due to the increased risk of a severe reaction that may not be responsive to acute therapy management. Data has demonstrated the increased airway hyper-responsiveness seen in food allergy patients with asthma. After performance of double-blind placebo controlled challenges in asthmatic patients with food allergy and those without, the patients with food allergy were noted



FARE Food Allergy Research & Education

# FOOD ALLERGY & ANAPHYLAXIS EMERGENCY CARE PLAN

Name: _____ D.O.B.: _____

Allergy to: _____

Weight: _____ lbs. Asthma: ☐ Yes (higher risk for a severe reaction) ☐ No

**NOTE: Do not depend on antihistamines or inhalers (bronchodilators) to treat a severe reaction. USE EPINEPHRINE.**

**Extremely reactive to the following allergens:** _____

THEREFORE:

☐ If checked, give epinephrine immediately if the allergen was LIKELY eaten, for ANY symptoms.

☐ If checked, give epinephrine immediately if the allergen was DEFINITELY eaten, even if no symptoms are apparent.

FOR **ANY** OF THE FOLLOWING:

## **SEVERE** SYMPTOMS

**LUNG** — Shortness of breath, wheezing, repetitive cough

**HEART** — Pale or bluish skin, faintness, weak pulse, dizziness

**THROAT** — Tight or hoarse throat, trouble breathing or swallowing

**MOUTH** — Significant swelling of the tongue or lips

**SKIN** — Many hives over body, widespread redness

**GUT** — Repetitive vomiting, severe diarrhea

**OTHER** — Feeling something bad is about to happen, anxiety, confusion

**OR A COMBINATION** of symptoms from different body areas.

1. **INJECT EPINEPHRINE IMMEDIATELY.**
2. **Call 911.** Tell emergency dispatcher the person is having anaphylaxis and may need epinephrine when emergency responders arrive.

- Consider giving additional medications following epinephrine:
  - » Antihistamine
  - » Inhaler (bronchodilator) if wheezing
- Lay the person flat, raise legs and keep warm. If breathing is difficult or they are vomiting, let them sit up or lie on their side.
- If symptoms do not improve, or symptoms return, more doses of epinephrine can be given about 5 minutes or more after the last dose.
- Alert emergency contacts.
- Transport patient to ER, even if symptoms resolve. Patient should remain in ER for at least 4 hours because symptoms may return.

## **MILD** SYMPTOMS

**NOSE** — Itchy or runny nose, sneezing

**MOUTH** — Itchy mouth

**SKIN** — A few hives, mild itch

**GUT** — Mild nausea or discomfort

FOR **MILD SYMPTOMS** FROM **MORE THAN ONE** SYSTEM AREA, GIVE EPINEPHRINE.

FOR **MILD SYMPTOMS** FROM **A SINGLE SYSTEM** AREA, FOLLOW THE DIRECTIONS BELOW:

1. Antihistamines may be given, if ordered by a healthcare provider.
2. Stay with the person; alert emergency contacts.
3. Watch closely for changes. If symptoms worsen, give epinephrine.

## MEDICATIONS/DOSES

Epinephrine Brand or Generic: _____

Epinephrine Dose: ☐ 0.01 mg IM ☐ 0.15 mg IM ☐ 0.3 mg IM

Antihistamine Brand or Generic: _____

Antihistamine Dose: _____

Other (e.g., inhaler-bronchodilator if wheezing): _____

_____

PATIENT OR PARENT/GUARDIAN AUTHORIZATION SIGNATURE DATE PHYSICIAN/HCP AUTHORIZATION SIGNATURE DATE

FORM PROVIDED COURTESY OF FOOD ALLERGY RESEARCH & EDUCATION (FARE) (FOODALLERGY.ORG) 5/2018

**Fig. 6.3** Food allergy action plan [42]. (Reprinted from FARE. © 2018, Food Allergy Research & Education. Used with permission)

to have increased bronchial hyper-responsiveness with changes noted on methacholine challenge compared to those without [39].

## Oral Immunotherapy and Asthma

Oral immunotherapy (OIT) to specific food allergens is a promising future therapy for IgE-mediated food allergies. OIT involves consuming small amount of the specific food allergen on a daily basis with increases in dose incrementally under the supervision of an allergist. It has consistently been shown to significantly change the threshold of reactivity [47]. Currently, the most common foods that oral immunotherapy is being performed with are peanut, milk, and egg. However, it does come with some risks and adverse reactions, especially in the presence of asthma. Previous studies have found increased chest symptoms in patients receiving peanut OIT with a history of asthma [48]. In an open-label treatment program performed with patients with milk allergy and treatment with milk OIT, patients with asthma were found to not reach as high of a starting dose compared to non-asthmatics [49]. This was not related to asthma exacerbations at the time of the updosing. Asthmatic patients were also noted to have more reactions when compared to those without asthma. When looking at the high-risk group of adolescents with asthma, more adverse events were seen with adolescents on milk or egg oral immunotherapy and high milk or egg-specific IgE levels [40]. This was attributed to their risk-taking behaviors and poor compliance. It is thus critical that patients considering OIT who have a history of asthma have well-controlled asthma before initiation and care taken through the treatment in making sure their asthma is under control.

Severe allergic asthma patients are often placed on biologic treatments including omalizumab and mepolizumab. Patients on omalizumab, an anti-IgE therapy, who are undergoing OIT have tolerated it with fewer adverse events than those not on omalizumab [50]. Several studies have found that the addition of omalizumab to OIT can decrease both the time required to reach maintenance dosing as well as adverse events [51]. However, omalizumab does not currently carry an indication for adjunctive therapy with food OIT.

## Conclusion

Food allergy and asthma are a common occurrence in the pediatric population. Asthma predisposes a child with food allergy to more risk of a severe or fatal reaction. Thus, we must take extra care to ensure a child's asthma is under control with continued monitoring, ensuring compliance to medications, and appropriate counseling on the recognition of food allergy reactions and the management of these reactions. Specifically, the adolescent age group is more vulnerable to severe reactions and may have less insight into when symptoms of asthma are poorly controlled. Appropriate clinic visits to monitor progression can help prevent these adverse events and better equip patients and families to manage the comorbidities of asthma and food allergy.

## References

1. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013;167(11):1026–31.
2. Allen KJ, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. Immunol Allergy Clin N Am. 2012;32(1):35–50.
3. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang JL, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.

4. Black LI, Benson V. Tables of Summary Health Statistics for U.S. Children: 2016 National Health Interview Survey, C-2a, 2018. Available from: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2016_SHS_Table_C-2.pdf
5. Keet CA, Savage JH, Seopaul S, Peng RD, Wood RA, Matsui EC. Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States. Ann Allergy Asthma Immunol. 2014;112(3):222–9.e3.
6. Mahdavinia M, Fox SR, Smith BM, James C, Palmisano EL, Mohammed A, et al. Racial differences in food allergy phenotype and health care utilization among US children. J Allergy Clin Immunol Pract. 2017;5(2):352–7.e1.
7. Koplin JJ, Allen KJ, Gurrin LC, Peters RL, Lowe AJ, Tang ML, et al. The impact of family history of allergy on risk of food allergy: a population-based study of infants. Int J Environ Res Public Health. 2013;10(11):5364–77.
8. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 2001;107(1):191–3.
9. Collaborators GBDM. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1084–150.
10. Jang J, Gary Chan KC, Huang H, Sullivan SD. Trends in cost and outcomes among adult and pediatric patients with asthma: 2000-2009. Ann Allergy Asthma Immunol. 2013;111(6):516–22.
11. Ferrante G, La Grutta S. The burden of pediatric asthma. Front Pediatr. 2018;6:186.
12. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018;391(10122):783–800.
13. Akinbami LJ, Moorman JE, Simon AE, Schoendorf KC. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001–2010. J Allergy Clin Immunol. 2014;134(3):547–53.e5.
14. Ross MK, Romero T, Sim MS, Szilagyi PG. Obese- and allergic-related asthma phenotypes among children across the United States. J Asthma. 2018;56:1–10.
15. Sismanopoulos N, Delivanis DA, Mavrommati D, Hatziagelaki E, Conti P, Theoharides TC. Do mast cells link obesity and asthma? Allergy. 2013;68(1):8–15.
16. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008–25.
17. Jackson DJ. Early-life viral infections and the development of asthma: a target for asthma prevention? Curr Opin Allergy Clin Immunol. 2014;14(2):131–6.
18. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995;332(3):133–8.
19. Hovland V, Riiser A, Mowinckel P, Carlsen KH, Lodrup Carlsen KC. The significance of early recurrent wheeze for asthma outcomes in late childhood. Eur Respir J. 2013;41(4):838–45.
20. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005;172(10):1253–8.
21. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. Lancet. 2008;372(9643):1058–64.
22. Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014;69(8):1026–45.
23. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47(4):373–80.
24. Longo G, Berti I, Burks AW, Krauss B, Barbi E. IgE-mediated food allergy in children. Lancet. 2013;382(9905):1656–64.
25. Shaker M. New insights into the allergic march. Curr Opin Pediatr. 2014;26(4):516–20.
26. Flohr C, Perkin M, Logan K, Marrs T, Radulovic S, Campbell LE, et al. Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. J Invest Dermatol. 2014;134(2):345–50.
27. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. Allergy. 2014;69(1):17–27.
28. Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. J Clin Cell Immunol. 2014;5(2):67–73.
29. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. J Allergy Clin Immunol. 2010;126(6):1105–18.
30. Schroeder A, Kumar R, Pongracic JA, Sullivan CL, Caruso DM, Costello J, et al. Food allergy is associated with an increased risk of asthma. Clin Exp Allergy. 2009;39(2):261–70.
31. Anagnostou A. Anaphylaxis in children: epidemiology risk factors and management. Curr Pediatr Rev. 2018;14(3):180–6.
32. Friedlander JL, Sheehan WJ, Baxi SN, Kopel LS, Gaffin JM, Ozonoff A, et al. Food allergy and increased asthma morbidity in a School-based inner-city Asthma Study. J Allergy Clin Immunol Pract. 2013;1(5):479–84.
33. Calvani M, Cardinale F, Martelli A, Muraro A, Pucci N, Savino F, et al. Risk factors for severe pediatric

food anaphylaxis in Italy. Pediatr Allergy Immunol. 2011;22(8):813–9.
34. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 1992;327(6):380–4.
35. Simons FE. First-aid treatment of anaphylaxis to food: focus on epinephrine. J Allergy Clin Immunol. 2004;113(5):837–44.
36. Zicari AM, Indinnimeo L, De Castro G, Zappala D, Tancredi G, Bonci E, et al. Food allergy and the development of asthma symptoms. Int J Immunopathol Pharmacol. 2012;25(3):731–40.
37. Savage J, Johns CB. Food allergy: epidemiology and natural history. Immunol Allergy Clin North Am. 2015;35(1):45–59.
38. Jat KR. Spirometry in children. Prim Care Respir J. 2013;22(2):221–9.
39. Krogulska A, Dynowski J, Jedrzejczyk M, Sardecka I, Malachowska B, Wasowska-Krolikowska K. The impact of food allergens on airway responsiveness in schoolchildren with asthma: a DBPCFC study. Pediatr Pulmonol. 2016;51(8):787–95.
40. Vazquez-Ortiz M, Alvaro M, Piquer M, Giner MT, Dominguez O, Lozano J, et al. Life-threatening anaphylaxis to egg and milk oral immunotherapy in asthmatic teenagers. Ann Allergy Asthma Immunol. 2014;113(4):482–4.
41. Banasiak NC. Implementation of the asthma control test in primary care to improve patient outcomes. J Pediatr Health Care. 2018;32(6):591–9.
42. Food Allergy & Anaphylaxis Emergency Care Plan. Food Allergy Research and Education (FARE). https://www.foodallergy.org/life-with-food-allergies/food-allergy-anaphylaxis-emergency-care-plan. Accessed May 2019.
43. Walkner M, Warren C, Gupta RS. Quality of life in food Allergy patients and their families. Pediatr Clin N Am. 2015;62(6):1453–61.
44. Eldredge C, Patterson L, White B, Schellhase K. Assessing the readiness of a school system to adopt food allergy management guidelines. Wis Med J. 2014;113(4):155–61.
45. Crenesse D, Berlioz M, Bourrier T, Albertini M. Spirometry in children aged 3 to 5 years: reliability of forced expiratory maneuvers. Pediatr Pulmonol. 2001;32(1):56–61.
46. Santos AF, Gomes-Belo J, Hannachi F, Swan K. Advances in food allergy diagnosis. Curr Pediatr Rev. 2018;14(3):139–49.
47. Parrish CP, Har D, Andrew Bird J. Current status of potential therapies for IgE-mediated food allergy. Curr Allergy Asthma Rep. 2018;18(3):18.
48. Varshney P, Steele PH, Vickery BP, Bird JA, Thyagarajan A, Scurlock AM, et al. Adverse reactions during peanut oral immunotherapy home dosing. J Allergy Clin Immunol. 2009;124(6):1351–2.
49. Elizur A, Goldberg MR, Levy MB, Nachshon L, Katz Y. Oral immunotherapy in cow's milk allergic patients: course and long-term outcome according to asthma status. Ann Allergy Asthma Immunol. 2015;114(3):240–4.e1.
50. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol. 2013;132(6):1368–74.
51. Dantzer JA, Wood RA. The use of omalizumab in allergen immunotherapy. Clin Exp Allergy. 2018;48(3):232–40.

# Eczema

7

Peter Capucilli and Terri Brown-Whitehorn

## A Case of Eczema and Food Allergy (Fig. 7.1)

**Case 7.1**
A 3-month-old boy was brought to the pediatric allergy clinic by his family with concern for eczema and food allergy (FA). The patient was born full term with no significant neonatal history. Family history was notable for seasonal allergies in mother, mild asthma in father and an older sibling who had eczema as an infant, which had resolved in childhood. In addition to eczema, our patient had a history of ongoing reflux and two staphylococcal skin infections requiring antibiotic treatment. Breast feeding was stopped and several different formulas were trialed with concern for food allergy. He showed no improvement on cows' milk-based or soy formulas, and despite transition to a partially hydrolyzed formula continued to experience eczema symptoms and progressively worsening reflux. Upon presentation to our clinic, he was using 2.5% hydrocortisone ointment twice daily without much improvement, though parents noted that his rash would worsen if topical steroids were removed. Parents also noted that in the past he had even received an oral steroid course when his eczema was at its worst.

**Fig. 7.1** Our patient

P. Capucilli (✉) · T. Brown-Whitehorn
Division of Allergy & Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
e-mail: capucillip@email.chop.edu; brownte@email.chop.edu

## Introduction to Eczema and Atopic Dermatitis

Eczema, often synonymous with atopic dermatitis (AD), is the most common chronic inflammatory disorder of the skin in children, affecting


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_7

roughly 10–20% of pediatric patients, of which up to 80% have evidence of allergy or other atopic phenotypes [1, 2]. The etiology of AD is complex, involving an interaction between genetic and environmental factors associated with dysfunction and dysregulation of the body's epidermal barrier, the immune system, interaction with infectious agents and response to inflammation. The role of diet and dietary manipulation in the treatment of AD has long been explored and debated. Current robust evidence supports an association between AD and food allergy (FA), though this relationship is likely not fully understood. With rates of FA on the rise, and the significant burden of FA in the pediatric population, understanding the implication of comorbid AD is paramount for both the practicing allergist as well as for other pediatric clinicians.

The term "eczema" is used to describe a broad set of inflammatory skin (dermatitis) conditions with the shared feature of an associated skin barrier defect [3]. AD is a subset of eczema that typically begins in early infancy or in childhood, with the underlying inflammatory process being primary driven by a helper T lymphocyte and the immunoglobulin E (IgE)-antibody-mediated immune response. This suggests an important role for allergen triggers and the intervention of allergen avoidance in management of symptoms. Age is an important factor in the consideration of AD diagnosis. In 85% of affected individuals, the onset of AD occurs before 5 years of age, with 60% of children impacted within the first year of life and 45% within the first 6 months of life [4]. Of these, 80% have elevated total IgE and evidence of allergic sensitization [5]. However, as will be discussed ahead, with development of very early AD (within the first months of life) or very severe early AD, physicians should consider intrinsic etiologies, such as immunodeficiency.

AD is phenotypically characterized by extreme pruritus, xerosis, and rash that occur in a chronic relapsing and remitting pattern, often leading to significant disability, including profound impacts on the quality of life of children and caregivers [6]. The rash is typically erythematous and papular but may also involve vesicular lesions, weeping, excoriations, and crusting with thickened and lichenified papules characteristic of chronicity over time [7]. Lesion distribution also tends to vary by age. In infants, AD presents on the scalp, face (cheeks and chin) and extensor surfaces of the extremities, with involvement of the flexor extremity surfaces (especially the antecubital and popliteal fossa) in children and progression to the hands, wrists, and feet in older children and young adults [8] (Fig. 7.2). Cracked and fissured xerotic skin, importantly, increases patients' susceptibility to infection, commonly involving staphylococcal and streptococcal bacteria, as well as herpes simplex virus (HSV) [9].

Treatment is focused on maintenance and rehabilitation of the skin barrier with prevention targeted towards avoidance of xerosis, infection, and inflammation, with long-term maintenance and adherence to an appropriate skin care regimen. In the case of AD-associated with specific triggers, including food, additional evaluation is often necessary.

## History of AD and FA

The question of food protein hypersensitivity triggering eczematous skin rashes has been of long-standing historical interest. Case reports in the early 1900s describe patients who experienced improvement in their dermatitis with avoidance of specific foods in the diet and recurrence with food reintroduction [10–12]. Other reports over the twentieth century questioned these initial theories, leading to long-standing debate and controversy regarding the relationship between FA and AD [13]. Nevertheless, current cumulative research strongly supports a clinical role for FA in a percentage of children affected by AD, with reports of food elimination leading to improvement in skin symptoms [14–16], reintroduction leading to symptom exacerbation [17–19], and food avoidance associated with AD prevention [20–22].

## Prevalence of FA in AD

There is a common misconception that all (or most) children with eczema or AD have comorbid food allergies, and if identified, avoidance of

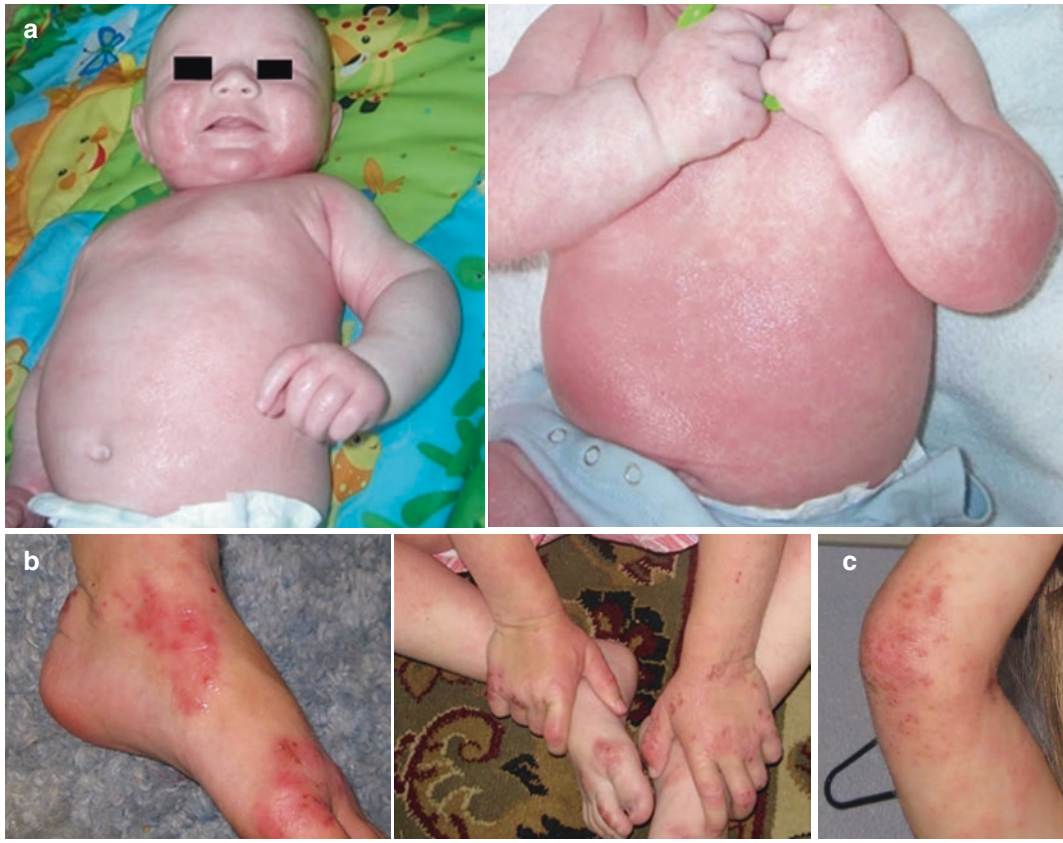



**Fig. 7.2** (**a**) Infantile eczema vs. (**b**) and (**c**) childhood eczema

the specific food allergen will cure AD. As compared to the large number of children affected with eczema, the prevalence of FA in the United States is only 8% [23]. While this percentage is not insignificant, AD triggered specifically by a food allergen is relatively rare. Careful assessment of baseline skin care practices to ensure appropriate treatment should also be integral to the initial evaluation. Often, AD is severe or uncontrolled due to inadequate treatment/prevention routine, either due to poor adherence to regular moisturizing or lack of appropriate topical steroid use. In general, the presentation of a younger patient and/or patient with more severe AD should prompt clinicians to consider food as a possible contributing factor while also maintaining a broad differential diagnosis for other potential triggers. Older children or adults presenting with new onset AD are, in contrast, are less likely to have a food-related trigger [24].

Although differentiating the exact prevalence of FA in AD is difficult given various triggers of atopic disease, several studied have sought to determine these rates with controlled research methods (Table 7.1). It is generally well accepted that roughly one-third to 40% of children with moderate-severe AD have FA (potentially as a contributing factor to AD) [29, 34, 35] with only a small percent of mild eczema associated with FA [36]. Interpretation of these rates must take into consideration the limitations of prevalence comparison between studies with different intrinsic study design and definitions used to identify severity in AD. Additionally, studies performed in children seen for evaluation at large referral centers may report higher prevalence rates compared to the true rate in the general population. Importantly, however, in a previous assessment of children who had not been referred to an allergist for management as well as in the evaluation

**Table 7.1** Prevalence of FA in children with AD studies[a] [24, 25]

| Study | Number of patients | Years | Positive SPT or positive IgE (%) |
|---|---|---|---|
| Breuer et al. [26] | 64 | 2004 | 46 |
| Burks et al. [27] | 46 | 1988 | 33 |
| Burks et al. [28] | 165 | 1998 | 39 |
| Eigenmann et al. [29] | 63 | 1998 | 37 |
| Eigenmann et al. [30] | 74 | 2000 | 34 |
| Garcia et al. [31] | 44 | 2007 | 27 |
| Niggemann et al. [32] | 107 | 1999 | 51 |
| Sampson et al. [18] | 113 | 1985 | 56 |
| Sampson et al. [33] | 320 | 1992 | 63 |

[a]Data from Forbes et al. [24] and from Rance et al. [25] Adapted from Rance et al. [25] with permission from John Wiley and Sons

of children outside of the United States, similar FA prevalence rates associated with AD have been described [29, 30].

## Foods Triggering AD and Patterns of Clinical Reactivity

Over 90% of FA in children with AD can be attributed to the following foods: cow's milk, hen's egg, wheat, soy, peanuts, tree nuts, and fish [35], though variations in susceptibility exist based on age. In infants, cow's milk, hen's egg, wheat, and soy are most commonly implicated, with peanut, tree nuts, and fish triggers beginning more commonly in childhood and through adolescence [37]. It is important to note that these trends may change with changes in food introduction recommendations as will be discussed ahead. With this in mind, differentiating which patients might be more likely to have FA as a factor contributing to uncontrolled or difficult-to-treat AD relies initially on a thorough clinical history and physical examination along with targeted allergy testing when clinically indicated.

Before pursuing allergy referral or specific allergy testing, it is important to ensure that optimal skin care practices have been performed and with appropriate adherence. Especially with increasing awareness of FA and various community and school interventions to raise awareness about accidental FA exposures, parents may be heightened to the potential that food could be contributing to uncontrolled AD. However, in a double-blind placebo-controlled OFC challenge study, only 35–40% of parent-reported suspicions to FA could be clinically verified [34]. Further research demonstrated that parental concern regarding FA contributing to AD exacerbations decreased significantly with initiation of adequate skin care treatment [38]. In the subgroup of infants and children with unimproved or recurrent AD, despite adequate skin care regimens, consideration of a possible culprit food is warranted.

According to the International Collaboration in Asthma, Allergy and Immunology, an allergy work-up should be pursued in children who meet the following criteria: (1) children who demonstrate an immediate reaction to a specific food or (2) children with moderate-to-severe AD despite optimal skin care [39]. In the first case, concern for FA, arguably, may be more readily apparent given the time-course pattern of food ingestion leading to an immediate AD flare. Symptom onset is typically within 2 hours of food ingestion and may be observed with presence of other classic IgE-mediated symptoms along the anaphylaxis spectrum, including development of hives (urticaria), angioedema, flushing, pruritus, and gastrointestinal and respiratory symptoms.

Identifying a specific food trigger in children with moderate-to severe AD despite optimal skin care can be more challenging, and thus allergy testing can be a useful tool to support clinical evaluation in this instance. With the burden of persistent eczematous inflammation, identifying a cause and effect relationship between food ingestion and a flare in AD may not be readily perceived. Further, difficult-to-treat AD or other types of dermatitis may be worsened both with exposure to a specific food trigger and by other non-food triggers simultaneously (Table 7.2),

**Table 7.2** Triggers associated with dermatitis in childhood

| |
|---|
| Environmental triggers |
| Inhalant allergens (pollens, dust mite) |
| Pet allergens (cats > dogs) |
| Contact allergens |
| Cosmetics |
| Medication |
| Adhesives |
| Blue dye ("blue jean diaper dermatitis) |
| Nickel, gold |
| Soaps, shampoo, detergents, fragrances, perfumed, colognes, diffusers, air fresheners, nail polish |
| Lanolin |
| Poison ivy |
| Latex |
| Irritants |
| Soaps, creams |
| Wool |
| Saliva (saliva dermatitis) |
| Sweat |
| Diaper dermatitis |
| Juices (fresh fruit, vegetables) |
| Bacterial/viral |
| Staphylococcus |
| Streptococcus |
| Coxsackievirus and others |
| Physical |
| Dry skin |
| Heat, cold |
| Psychological |
| Anxiety, stress |
| Food specific triggers |
| Cow's milk[a], egg[a], wheat[a], soy[a], peanut, tree nut, fish, shellfish, sesame, pollen-associated foods |

[a]Most common in early infancy

which can confound the clinical timeline [40]. Often, patients experience continued AD symptoms, despite elimination of a suspected food, given the involvement of other non-food-related triggers. Finally, it is important to consider that children with moderate-to-severe AD have higher rates of FA overall given increased atopic propensity, and, thus, identification of a positive food allergen by testing may indicate presence of an IgE-mediated FA, which may be independent and noncontributory to the patient's current dermatitis [41].

Non-IgE eczematous reactions related to food must also be considered. While fewer studies have identified these types of reactions, isolated late AD exacerbations have been described [26, 42], with one study showing that 10% of children who reacted during OFC developed isolated dermatitis 16 hours following a challenge [26]. Finally, isolated pruritus in the immediate setting following food ingestion may also be suspicious of an IgE-mediated reaction, with subsequent exacerbation of AD precipitated by scratching [43].

## Diagnosis and Management of FA in AD

In the previous section, we discussed when to be concerned for a potential FA trigger in the setting of AD. To make an accurate diagnosis of a specific FA contributing to AD symptoms, one must combine the clinical history with targeted testing and closely document changes in symptoms with trials of elimination diets and eventual OFC. FA testing can be performed either in vivo using skin prick tests (SPTs) or in vitro with specific IgE measurements in the serum, though both tests have significant limitations that must be considered. While both tests are designed to detect presence of a food-specific IgE as a marker of food sensitization, presence does not entirely indicate that a child will experience a reaction with food ingestion.

SPTs are usually performed as first-line screening by allergists, given rapid interpretation and minimal invasiveness of the procedure. In general, the negative predictive value for food testing is quite good (over >95%) and so a negative test is helpful to rule out FA whereas positive tests have low positive predictive values of less than 40% [18, 44–46]. Thus, a positive skin test alone cannot be considered as evidence that a patient will display a clinical reaction to a specific food. Intradermal skin testing, often utilized routinely for more specific aeroallergen testing, should not be performed for food due to risk of anaphylaxis and high false-positive rates [46]. To complicate the matter further, dermatitis of the skin itself can impact SPT results. It is well described that children with AD show positive reactions at especially high rates with prick testing, one study suggesting a false-positive rate in children with AD of over 80% [47]. Serum IgE (RAST) testing can also be helpful in excluding

FA, but positive values, like prick tests, have limited predictive value and results are often difficult to interpret [34]. Use of serum IgE testing can be attractive as testing can be performed in patients without the need for prick testing materials, can be performed in patients currently taking antihistamines (unlike SPTs), and offer easy accessibility to broad FA testing with widely available "food panels." Unfortunately, given the high false-positive rates that inevitably occur with comprehensive testing to various foods, children are often unnecessarily subjected to extensive avoidance diets, often limiting important nutritional components. Unfortunately, cases of failure to thrive due to extensive dietary restriction based solely on allergy testing have been described [48, 49]. For this reason, clinicians are strongly discouraged against sending wide-ranging food panels to various food allergens, especially in infants and children who have not yet ingested and demonstrated clinical reactivity to a food. In any case, where a potentially severe food allergy is suspected, an epinephrine autoinjector is recommended. We would also recommend referral to an allergist in any child with positive allergy testing for continued evaluation.

In combination with the above testing and clinical history, use of a limited, closely supervised and targeted food elimination diet can be a helpful tool in the diagnosis of a suspected food trigger in AD. In practice, clinicians should work with families to carefully record changes in skin symptoms with elimination of a suspected food over a 2–3-week trial period. Given the substantial concern for nutritional deficiencies, a team approach between primary clinician and a knowledgeable nutritionist or dietician is often warranted. With no prior concern for anaphylaxis symptoms, foods can be individually added back into the diet with close observation. Evidence of immediate worsening AD with addition of the food back into the diet at that point would be suggestive of a food trigger and the food should then be eliminated completely, potentially inclusive of the food from the maternal diet in infants receiving breast milk. In circumstances where mothers are eliminating foods from the diet, involvement of a nutritionist is also important to ensure that maternal nutrition is otherwise intact. If there remains a question of the role of FA in AD, an oral food challenge can be performed [34]. As mentioned above, given that AD can be multifactorial in etiology, one must be mindful that elimination of a suspected food allergen from the diet may not lead to improvement of AD if other triggers and inadequate skin care practices are not also addressed. Every effort by clinicians to safely re-introduce non-contributory foods into the diet, to avoid unnecessary dietary restrictions, should be made.

There are other diagnostic tests to be aware of related to diagnosis of FA in AD. Epicutaneous testing or atopy patch testing has been utilized individually and in combination with SPT and IgE tests, most often outside of the United States, however, is not yet standardized for clinical practice [50–52]. Food-specific IgG and $IgG_4$ tests have notably not been shown to have any clinical validity in the diagnosis of FA, as positive values reflect normal immune responses to foods tolerated in the diet and as such should not be measured [53]. Finally, the basophil activation test has been assessed for FA diagnosis but only currently on a research basis [54].

## Prognosis and Natural History of FA in AD

AD in early infancy and childhood may be the initial manifestation of progressive allergy over time known as the atopic march, and so primary care clinicians should monitor for potential onset of other FA with new food exposures as well as concomitant allergic rhinitis, allergic conjunctivitis, cough, or wheeze (asthma) through childhood. While not all patients need to be seen by an allergist, those with moderate-to-severe atopic disease would likely benefit from specialist evaluation.

In regards to FA and AD, it is classically accepted that approximately one third of children with AD and FA will outgrow their food sensitivity over the first 3 years of life, depending on the causal food [55]. Some children may also outgrow their AD, though rates vary. In most

patients, allergy to cow's milk, hen's egg, wheat, and soy has a positive prognosis, whereas peanut, tree nuts, fish, and shellfish are more difficult to outgrow [55–59]. More recent data, however, suggest that the rate of resolution of FA may be slower than previously reported [60], and therefore follow ups with an allergist at regular intervals for potential repeat testing is recommended.

It should also be noted that food elimination in the diet can impact allergic sensitivity and reactivity to a specific food [61]. For example, in a child who only initially experienced an eczema flare with exposure to a specific food, and subsequently eliminated the food from their diet, re-exposure to the food after a period of elimination could precipitate a severe anaphylactic reaction if the child remains allergic. Further, children may develop intolerance to specific foods that had been tolerated in the past if the food is eliminated from the diet for too long. This is a particular concern in children who undergo allergy testing for AD to foods regularly consumed in the diet without reaction. We see this in our allergy clinic, unfortunately, not infrequently. Thus, a properly observed and structured OFC prior to reintroduction of a food allergen that has been avoided is most prudent to assess for the possibility that a FA has been outgrown.

As mentioned previously, food introduction practices regarding "highly allergenic foods" have changed over time. In 2015, the landmark Learning Early about Peanut Allergy (LEAP) showed that early introduction to peanut in infants as young as 4 months of age was associated with lower rates of IgE-mediated peanut allergy, though allergen screening in infants with severe eczema and/or egg allergy was recommended [62, 63]. This and other studies regarding optimizing food introduction timing as well as early skin care efforts will likely impact trends in infantile eczema in the future.

## Other Considerations

Children and adults with birch pollen sensitization may demonstrate AD exacerbation with ingestion of cross-reacting foods [64]. This clinical entity, known as "oral allergy syndrome" or "pollen allergy syndrome," is due to IgE cross-reactivity between pollen proteins and food epitopes, most commonly associated with fresh fruits or nuts such as cherries, apples, peaches, carrots, celery, and hazelnut. While the reaction is typically benign and localized to pruritus in the mouth, AD flares can occur. This clinical entity may be particularly notable in adults especially in those with seasonal allergy onset at an older age or those without prior history of classic IgE-mediated FA as a child.

Eczematous lesions and AD can also be associated with primary immunodeficiencies. Infants and children with primary immunodeficiencies may have history of failure to thrive, frequent or recurrent infections, including otitis media, pneumonias, sinus infections, recurrent or chronic diarrhea as well as cutaneous manifestation such as abscesses or deep tissue infections. Certainly, patients with AD as well as any severe, life-threatening illness, early autoimmune or atypical infection should be considered for immunologic evaluation.

Specifically, patients with Wiskott-Aldrich syndrome demonstrate eczema associated with thrombocytopenia (both low platelet count and decreased mean platelet volume) and a combined immunodeficiency. In these patients, dermatitis is often complicated by bacterial or viral pathogens including HSV or molluscum [65]. Hyper IgE syndrome, another combined immunodeficiency, is also characterized by severe AD and recurrent infections (pneumonias and *Staph. aureus* skin abscesses). Further, these children often display comorbid FA, particularly relevant to this chapter [66]. Finally, Omenn syndrome, a form of severe combined immunodeficiency (SCID), may present with AD at a young age associated with lymphadenopathy and hepatosplenomegaly due to oligoclonal expansion of autoreactive T-cells [67]. Thus, in a child with any of the above concerns, the primary care clinicians should maintain a low threshold for referral to a pediatric allergy/immunologist for comprehensive evaluation.

## Take-Home Points (Table 7.3)

**Case 7.1 Discussion**

Our patient presented to the allergy clinic with refractory AD despite regular use of an appropriate topical steroid for age. He also showed intolerance to several types of formulas, both cow's milk and soy-based, including partially hydrolyzed cow's milk formula. No other solid foods had been introduced. In this setting, we worked with the family to perform a trial 2-week elimination diet, with initiation of a fully hydrolyzed amino acid-based formula. We know that some infants with IgE-mediated milk allergy will still react to only partially broken-down formula. Within 2 weeks, parents noticed a significant improvement in rash severity. Reductions in episodes of reflux were noted. Parents also reported the patient seemed more playful and brighter. Given the severity of AD, early onset, and associated skin infections, a screening workup of the patient's immune system was performed and was found to be normal. Zinc deficiency was also ruled out. Given the clear time course improvement with elimination of milk including both improvement of skin and GI symptoms, skin prick testing to milk and soy was performed and was found to be positive.

Over the ensuing 7 months, and with adherence to the amino acid-based formula, the patient experienced almost full resolution of AD, with areas of flare responsive to short courses of hydrocortisone ointment. At 6 months of age, solid foods were able to be introduced into the diet, including cereals, fruits and vegetables (though allergenic foods were not initially introduced due to food introduction guidelines at that time). Over time, he was also able to add eggs and peanuts. With the help of a nutritionist and his primary care clinician, he was able to transition from elemental formula to almond milk. At 3 years of age, following gradually decreasing skin prick test measurements, the patient underwent food challenge to milk and soy and these were able to be reintroduced into the diet. Despite having a dog in the house and developing allergic rhinitis symptoms over time, the patient's eczema remained manageable, suggesting the dog was an unlikely trigger for eczema.

At 9 years of age, the patient did experience an anaphylactic reaction to cashew, a food not previously introduced. Symptoms included immediate vomiting and hives necessitating an emergency room visit. Confirmed by positive allergy testing, he has continued to maintain strict avoidance with an epinephrine autoinjector readily available at all times.

This case reflects a significant example of infantile AD directly secondary to a FA trigger that resolved over time. Further, our patient's severe eczema might have been considered a risk factor for development of other food allergies in the future as was eventually determined.

**Table 7.3** Take-home points

| |
|---|
| Eczema or atopic dermatitis (AD) is the most common chronic inflammatory disorder of the skin in children, affecting roughly 10–20% of pediatric patients. |
| Food allergy as the underlying cause for AD is rare, though children with moderate-severe AD have higher rates of food allergy. |
| In general, food allergy should be suspected in patients with AD who are younger, have more severe AD or are refractory to treatment. |
| AD management relies on optimal skin care management to promote skin barrier and appropriate pharmacologic therapies when needed. |
| Food allergy should be suspected in children with AD who develop an immediate flare following food ingestion. |
| Food allergy testing, such as SPTs can be useful in ruling out food allergy in patients with moderate-severe AD, however, has low positive predictive rates. |
| Use of broad food allergy testing, such as "food panels," is not recommended given high risk for false positives and unnecessary dietary eliminations that can lead to dramatic nutritional deficiencies. |
| Patients may reasonably undergo limited food elimination trials, though close monitoring by an allergist and nutritionist is recommended. |
| AD may also be an important presenting feature for non-allergic diseases including several rare primary immunodeficiencies. |

**Conflicts of Interest** The authors declare that they have no relevant conflicts of interest.

**Consent** Parental consent was obtained for reproduction of clinical history and patient photos presented.

## References


1. ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet. 1998;351:1225–32.
2. Roduit C, Frei R, Loss G, Buchele G, Weber J, Depner M, et al. Development of atopic dermatitis according to age of onset and association with early-life exposures. J Allergy Clin Immunol. 2012;130(1):130–6.e5.
3. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832–6.
4. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. J Am Acad Dermatol. 1994;30(1):35–9.
5. Leung DY. Atopic dermatitis: the skin as a window into the pathogenesis of chronic allergic diseases. J Allery Clin Immunol. 1995;96:302–18.
6. Chamlin SL, Chren MM. Quality-of-life outcomes and measurement in childhood atopic dermatitis. Immunol Allergy Clin N Am. 2010;30(3):281–8.
7. Blaylock WK. Atopic dermatitis: diagnosis and pathobiology. J Allergy Clin Immun. 1976;57:62–79.
8. Lookingbill D, Marks JG. Eczematous rashes. In: Principles of dermatology. 2nd ed. Philadelphia: Saunders; 1993. p. 127–30.
9. Correale CE, Walker C, Murphy L, Craig TJ. Atopic dermatitis: a review of diagnosis and treatment. Am Fam Physician. 1999;60(4):1191–8.
10. Schloss OM. Allergy to common foods. Trans Am Pediatr Soc. 1915;27:62–8.
11. Talbot FB. Eczema in childhood. Med Clin N Am. 1918;1:985–96.
12. Blackfan KD. A consideration of certain aspects of protein hypersensitiveness in children. Am J Med Sci. 1920;160:341–50.
13. Hanifin JM. Critical evaluation of food and mite allergy in the management of atopic dermatitis. J Dermatol. 1997;24(8):495–503.
14. Atherton DJ, Sewell M, Soothill JF, et al. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. Lancet. 1978;1(8061):401–3.
15. Juto P, Engberg S, Winberg J. Treatment of infantile atopic dermatitis with a strict elimination diet. Clin Allergy. 1978;8(5):493–500.
16. Lever R, MacDonald C, Waugh P, et al. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. Pediatr Allergy Immunol. 1998;9(1):13–9.
17. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. J Allergy Clin Immunol. 1983;71(5):473–80.
18. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. J Pediatr. 1985;107(5):669–75.
19. Sampson HA. Atopic dermatitis. Ann Allergy. 1992;69(6):469–79.
20. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy and/or lactation for preventing or treating atopic disease in the child. Cochrane Database Syst Rev. 2003;4:CD000133.
21. Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study. Pediatrics. 1990;86(4):541–6.
22. Kajosaari M. Atopy prophylaxis in high-risk infants. Prospective 5-year follow-up study of children with six months exclusive breastfeeding and solid food elimination. Adv Exp Med Biol. 1991;310:453–8.
23. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.
24. Forbes LR, Saltzman RW, Spergel JM. Food allergies and atopic dermatitis: differentiating myth from reality. Pediatr Ann. 2008;38(2):84–90.
25. Rance F, Boguniewicz M, Lau S. New visions for atopic eczema: an iPAC summary and future trends. Pediatr Allergy Immunol. 2008;19:17–25.
26. Breuer K, Heratizadeh A, Wulf A, et al. Late eczematous reactions to food in children with atopic dermatitis. Clin Exp Allergy. 2004;34:817–24.
27. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. J Pediatr. 1988;113:447–51.
28. Burks AW, James JM, Hiegel A, et al. Atopic dermatitis and food hypersensitivity reactions. J Pediatr. 1998;132:132–6.
29. Eigenmann PA, Sicherer SH, Borkoski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics. 1998;101:E8.
30. Eigenmann PA, Calza AM. Diagnosis of IgE mediated food allergy among Swiss children with atopic dermatitis. Pediatr Allergy Immunol. 2000;11:95–100.
31. García C, El-Qutob D, Martorell A, et al. Sensitization in early age to food allergens in children with atopic dermatitis. Allergol Immunopathol (Madr). 2007;35(1):15–20.
32. Niggemann B, Sielaff B, Beyer K, et al. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. Clin Exp Allergy. 1999;29:91–6.
33. Sampson HA. The immunopathogenic role of food hypersensitivity in atopic dermatitis. Acta Derm Venereol. 1992;176:34–7.

34. Sampson HA. The evaluation and management of food allergy in atopic dermatitis. Clin Dermatol. 2003;21(3):183–92.
35. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. J Allergy Clin Immunol. 1999;104(3 Pt 2):S114–22.
36. Spergel JM, Boguniewicz M, Schneider L, Hanifin JM, Paller AS, Eichenfield LF. Food allergy in infants with atopic dermatitis: limitations of food-specific IgE measurements. Pediatrics. 2015;136(6):e1–9.
37. Sampson HA. Update on food allergy. J Allergy Clin Immunol. 2004;113:805–19.
38. Thompson MM, Hanifin JM. Effective therapy of childhood atopic dermatitis allays good allergy concerns. J Am Acad Dermatol. 2005;53:S214–9.
39. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. J Allergy Clin Immunol. 2012;129:906–20.
40. Bergmann MM, Caubet JC, Boguniewicz M, Eigenmann PA. Evaluation of food allergy in patients with atopic dermatitis. J Allergy Clin Immunol Pract. 2013;1(1):22–8.
41. Du Toit G, Roberts G, Sayre PH, Plaut M, Bahnson HT, Mitchell H, et al. Identifying infants at high risk of Peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. J Allergy Clin Immunol. 2013;131:135–43.
42. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, Niggemann B. The predictive value of specific immunoglobulin E levels in seru, for the outcome of oral food challenges. Clin Exp Allergy. 2005;35(3):268–73.
43. Caubet JC, Eigenmann PA. Allergic triggers in atopic dermatitis. Immunol Allergy Clin N Am. 2010;30:289–307.
44. Bock SA, Lee WY, Remigio L, Holst A, May CD. Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. Clin Allergy. 1978;8:559–64.
45. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. J Allergy Clin Immunol. 1984;74:26–33.
46. Bock S, Buckley J, Holst A, May C. Proper use of skin tests with food extracts in diagnosis of food hypersensitivity. Clin Allergy. 1977;7(4):375–83.
47. Fleischer DM, Bock SA, Spears GC, Wilson CG, Mitazawa NK, Gleason MC, et al. Oral food challenges in children with a diagnosis of food allergy. J Pediatr. 2011;158(4):578–583.e1.
48. Noimark L, Cox HE. Nutritional problems related to food allergy in childhood. Pediatr Allergy Immunol. 2008;18:188–95.
49. David TJ, Waddington E, Stanton RH. Nutritional hazards of elimination diets in children with atopic eczema. Arch Dis Child. 1984;59:323–5.
50. Kekki OM, Turjanmaa K, Isolauri E. Differences in skin-prick and patch-test reactivity are related to the heterogeneity of atopic eczema in infants. Allergy. 1997;52:755–9.
51. Niggemann B, Reibel S, Wahn U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. Allergy. 2000;55:281–5.
52. Turjanmaa K, Darsow U, Niggemann B, Rance F, Vanto T, Werfel T. EAACI/GA2LEN position paper: present status of the atopy patch test. Allergy. 2006;61:1377–84.
53. Stapel SO, Asero R, Ballmer-Weber BK, Knol EF, Strobel S, Vieths S, et al. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. Allergy. 2008;63:793–6.
54. Ocmant A, Mulier S, Hanssens L, Goldman M, Casimir G, Mascart F, et al. Basophil activation tests for the diagnosis of food allergy in children. Clin Exp Allergy. 2009;39:1234–45.
55. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. J Pediatr. 1989;115:23–7.
56. Bock SA. The natural history of food sensitivity. J Allergy Clin Immunol. 1982;69:173–7.
57. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: resolution and the possibility of recurrence. J Allergy Clin Immunol. 2003;112:183–9.
58. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. J Allergy Clin Immunol. 2005;116:1087–93.
59. Savage JH, Limb SL, Brereton NH, Wood RA. The natural history of peanut allergy: extending out knowledge beyond childhood. J Allergy Clin Immunol. 2007;120:717–9.
60. Savage JH, Matsui EC, Skripak JM, et al. The natural history of egg allergy. J Allergy Clin Immunol. 2007;120(6):1413–7.
61. Flinterman AE, Knulst AC, Meijer Y, Bruijnzeel-Koomen CA, Pasmans SG. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. Allergy. 2006;61:370–4.
62. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803–13.
63. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR, Beck LA, et al. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious

Diseases-sponsored expert panel. World Allergy Organ J. 2017;10(1):1.
64. Breuer K, Wulf A, Constien A, Tetau D, Kapp A, Werfel T. Birth pollen-related food as a provocation factor of allergic symptoms in children with atopic eczema/dermatitis syndrome. Allergy. 2004; 59(9):988–94.
65. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr. 1994;125(6):876–85.
66. Su HC. DOCK 8 (dedicator of cytokinesis 8) deficiency. Curr Opin Allergy Clin Immunol. 2010;10(6):515–20.
67. Villa A, Notaragelo LD, Roifman CM. Omenn syndrome: inflammation in leaky severe combined immunodeficiency. J Allergy Clin Immunol. 2008;122(6):1082–6.

# Eosinophilic Esophagitis

8

Carla Perez, Anthony Olive, and Carla M. Davis

Eosinophilic esophagitis (EoE) is the second most common cause of chronic esophagitis after gastroesophageal reflux disease (GERD) and the leading cause of dysphagia and food impaction in children [1]. Its incidence and prevalence have been on the rise over the last two decades [2, 3]. EoE is defined as a chronic immune-mediated condition characterized by an eosinophilic predominant inflammation of the esophagus and symptoms associated with esophageal dysfunction [1, 4]. Genetic and environmental factors have been demonstrated to have a role in the development of EoE; however, the pathogenesis still remains unknown [5]. If not recognized or treated, EoE can progress to esophageal stricture and functional abnormalities that can impair the quality of life of children.

C. Perez (✉) · A. Olive
Section of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA
e-mail: carla.perez@bcm.edu; apolive@texaschildrens.org

C. M. Davis
Section of Immunology, Allergy and Retrovirology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA
e-mail: carlad@bcm.edu

## Etiology

EoE was initially described as a distinct clinicopathologic condition in pediatrics. In 1995, Kelly et al. first reported improvement of esophageal eosinophilia and symptoms when children were placed on an exclusive amino acid–based formula with subsequent recurrence of esophageal symptoms with re-exposure to a regular diet [6]. The role of dietary antigens in the pathogenesis of EoE was further suggested by the resolution of symptoms and esophageal inflammation with treatment using elimination diet [7–10]. This concept of a food antigen disorder has been applied in the widespread use of elimination diets for the treatment of EoE [8, 11, 12].

Delayed hypersensitivity was considered a possible immune mechanism for EoE with the observations made during exposures to food antigens. The slow resolution of clinical symptoms despite elimination of food triggers and, conversely, the slow development of symptoms after reintroduction suggested a role for delayed hypersensitivity [13]. This delayed response paralleled that observed in other atopic disorders such as asthma and eczema and led to investigation of similar mechanistic pathways. In EoE, esophageal damage is provoked by antigens or acid leading to a Th2 immune response with production of thymic stromal lymphopoietin (TSLP) and eotaxin-3 [14–16]. These lead to an influx of eosinophils, mast cells, basophils, innate lymphoid cells (ILCs) and adaptive B & T lymphocytes [17, 18].



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_8

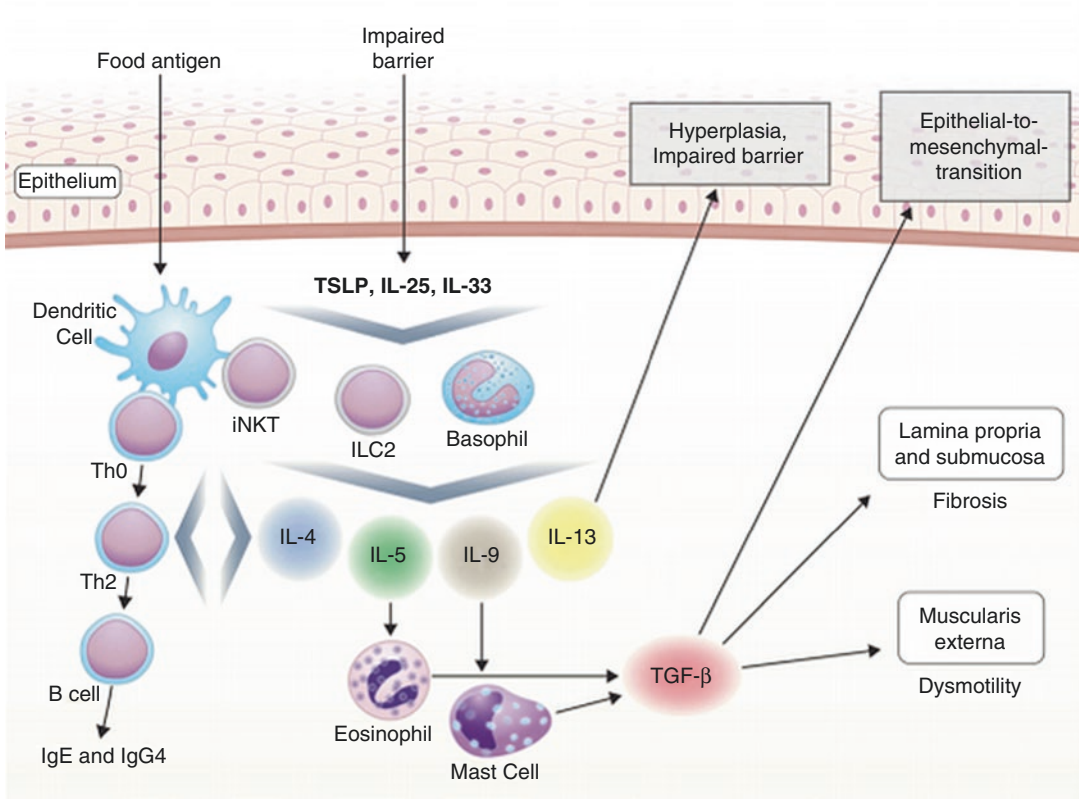



**Fig. 8.1** Pathophysiologic mechanisms involved in EoE. Mechanistic model of eosinophilic esophagitis (EoE). Impaired barrier function appears to be central to the pathophysiology of EoE. This impaired barrier likely leads to alarmin (TSLP, IL-15, IL-33) release. Alarmins then initiate, via ILC2s and basophils, a coordinated immune response orchestrated by the cytokine milieu (IL-4, IL-5, IL-9, IL-3). In parallel to this process is antigen sensitization, occurring through dendritic cell processing and presentation leading to activated Th2 and iNKT cells, which further contribute to the cytokine milieu and skew B cell and antibody development. The downstream effects of cytokines effect the epithelium, lamina propria, submucosa, and smooth muscle remodeling and dysfunction (hyperplasia, impaired barrier, EMT in the epithelium; fibrosis in the lamina propria and submucosa; and smooth muscle dysmotility within the muscularis interna and externa). EMT epithelial-to-mesenchymal transition, IgE immunoglobulin E, IgG4 immunoglobulin G4, IL interleukin, ILC innate lymphoid cells, iNKT invariant natural killer T cells, TGF-β tissue growth factor beta, Th T helper cells, TSLP thymic stromal lymphoprotein [5]. (Reprinted from Davis [5], with permission from Springer Nature)

In the presence of prolonged inflammation, the esophagus develops remodeling, loss of barrier function, development of fibrosis, angiogenesis, and smooth muscle hypertrophy, which manifests clinically with vomiting, dysphagia, food impactions, and strictures [19] (See Fig. 8.1).

Further support for delayed immune response is derived from evidence against immediate hypersensitivity, for example, the poor effectiveness of anti-IgE therapy, namely omalizumab, in EoE patients [20]. Additionally, serum-specific IgE and skin prick tests (SPTs) measure sensitization in IgE-mediated hypersensitivity and are not consistently reliable in identifying food triggers in EoE [5, 6]. Intriguingly, atopy patch tests (APTs), which measure delayed hypersensitivity, have demonstrated limited utility in EoE, identifying the food trigger 50% of the time with a significant negative predictive value (90%) [10, 21]. The lack of reliability of APTs is speculated to be the lack of direct testing of antigens on esophageal tissue.

Despite the abundance of evidence for a delayed hypersensitivity, the role of IgE-mediated hypersensitivity has not been completely excluded. A subset of EoE patients (15%) have a history of food anaphylaxis, a classic IgE-mediated response

[13, 21–23]. Pediatric patients with IgE-mediated allergy to foods are 100 times more likely to have EoE compared with the general public [24]. Additionally, the development of EoE in the setting of oral immunotherapy (OIT) for treatment of food allergies also poses questions to the underlying mechanism of EoE [24]. OIT induces allergen tolerance or desensitization partially through the IgE receptor blocking antibody immunoglobulin 4 ($IgG_4$), which recently has been described to be elevated in the serum of children and adults with EoE, and esophageal $IgG_4$ levels correlate with EoE histopathology and transcriptomic features [25–27]. Interestingly, $IgG_4$ is involved in other fibroinflammatory conditions like autoimmune pancreatitis and pemphigus, but its role in the pathogenesis of EoE requires further investigation [26, 28].

While the majority of EoE patients respond to elimination of dietary antigens (72% respond to a six food elimination diet), in those that do not respond, there is the suggestion of a role for other antigens [29]. In vivo murine studies and human reports reveal that inhalation of Aspergillus and pollen, respectively, lead to increased esophageal eosinophils [30]. This experimental EoE phenotype, demonstrating a role for aeroallergens, can also be induced by delivering cytokines produced by Th2 lymphocytes or by epicutaneous antigen introduction followed by airway challenge to same substance [31]. Atopy is highly prevalent (50–60%) in EoE patients, which has raised the question of the applicability of the hygiene hypothesis and dysbiosis in EoE [30, 32]. Several early life exposures including antibiotics, acid suppressant therapy, and cesarean section delivery have been associated with an increased risk for EoE, suggesting a role for dysbiosis and the microbiome; however, mechanistic studies are needed [32–34]. Additionally, the lack of concordance between dizygotic twins (22%) and siblings (2.4%) of patients with EoE, suggest that 81% of phenotypic differences are due to environmental factors [35, 36].

In addition to the environment, including dietary and aeroallergen exposures, genetics is also involved in the development of EoE. Candidate and genome-wide approaches have identified several genetic loci that increase the risk of EoE, most notably TSLP/WDR36 (5q22), CAPN14 (2p23), STAT6 (12q13), and ANKRD2y (19q13) [37, 38]. While some of these loci are shared with allergic disease, logistic regression analysis of 5q22, llq13.5 and 12q13 have indicated a specific role in EoE [38, 39]. These loci contain genes involved in the immune response and pathogenesis of EoE including eosinophilic recruitment, disrupted esophageal epithelial barrier, and disorganized esophageal epithelium. Additionally, the recognition of EoE in inherited connective tissue disorders (Loetyz-Dietz syndrome, Marfan syndrome type II, and Ehlers Danlos syndrome) has led to the understanding of the dysregulation of transforming factor-beta (TGF-β) and collagen in the pathogenesis of EoE [40]. Whole-exome sequencing has also recently identified abnormal variants in DHTKD1 and OGDHL among EoE patients (compared to non-affected family members) involved in mitochondrial function, suggesting an additional mechanism for EoE [41].

Five hundred and seventy-four genes make up the EoE transcriptome according to an analysis of the gene expression profile of patients with EoE compared to healthy controls and those with GERD [14]. These findings along with more sensitive approaches using RNA-seq profiling clarified the important distinction between EoE and GERD and exposed potential mediators in the immune mechanisms involved in EoE, such as IL-13 [42]. Over the last 5 years, numerous studies have described that EoE results from impaired barrier function provoking an antigen sensitization and immunologic response that can lead to esophageal fibrosis or dysmotility (see Fig. 8.1) [16]. Several of these intermediate mediators are being assessed as therapeutic targets or biomarkers for EoE. Many questions still remain regarding the triggers and underlying mechanisms of EoE.

## Clinical Presentation

EoE can present at any age and occurs worldwide. Its incidence of 0.7 to 10 per 100,000 children per year is increasing, only partially due to improved recognition [3]. It is more commonly

observed in Caucasians compared to other ethnic groups and three times more common in males than females [2, 3, 13, 43]. Patients may present with various symptoms that differ by age. Young children often present with regurgitation, food refusal, vomiting, or failure to thrive [13]. Older children and adolescents more commonly present with nausea, epigastric pain, chest pain, decreased appetite, water brash, globus, or vomiting. In adolescents and adults, the initial presentation of EoE can sometimes be more abrupt with solid food dysphagia or food impaction, necessitating endoscopy. Retrospective studies have suggested that approximately half of endoscopies for food impaction are secondary to EoE [44].

Many of presenting symptoms overlap with GERD and other gastrointestinal disorders, highlighting the necessity of endoscopy with biopsy for the diagnosis. Other clinical clues that may support the diagnosis of EoE include atopic comorbidities. As mentioned previously, 50% of EoE patients have other allergic disease [1, 45, 46]. Additionally, a family history of allergies, in particular on the paternal side, has been implicated to be more common in pediatric EoE [47].

## Evaluation and Diagnosis

The diagnosis of EoE is established based on clinical symptoms of esophageal dysfunction and pathologic findings of eosinophil-rich inflammation in esophageal biopsies (≥ 15 eos/hpf). Patients with symptoms consistent with esophageal dysfunction and personal or family history of atopy should raise the suspicion for EoE and require an endoscopy with a biopsy to confirm the presence of esophageal inflammation. The diagnosis can be challenging as many symptoms overlap with GERD. Moreover, the traditional strategy of differentiating GERD and EoE with a proton pump inhibitor (PPI) trial is no longer valid as a subset (35%) of EoE patients respond to PPIs [42]. This cohort of patients are referred to as having PPI-responsive esophageal eosinophilia (PPI-REE), which is now considered part of the EoE continuum due to significant overlap in the esophageal transcriptome pattern for EoE and PPI-REE patients in contrast to that in GERD patients [42]. A recent guideline document recommends a PPI trial as a treatment for EoE rather than a requirement for diagnosis [48].

As discussed previously, endoscopy remains a necessary procedure for the diagnosis of EoE. The endoscopic features suggestive of EoE include a concentric ring formation referred to as "trachealization" or "felinization" of the esophagus, longitudinal linear furrows, patches of small, white papules on the esophageal surface, loss of mucosal vascularity, and narrowing or stricture (See Fig. 8.2) [49]. An endoscopic classification and grading system called the EoE Endoscopic Reference Score (EREFS), using five findings of edema, rings, exudates, furrows, and strictures, has been validated in both children and adults [49]. Given EoE's patchy nature, a total of at least six biopsies, from at least two levels of the esophagus, are useful to maximize diagnostic yield [50, 51]. The current gold standard for the histopathologic diagnosis of EoE requires a peak eosinophil count ≥15 intraepithelial eosinophils in at least one high power field (eos/hpf) in an esophageal biopsy [52]. Other histologic features observed in EoE include basal zone hyperplasia, eosinophilic abscess, eosinophilic surface layering, thickened lamina propria fibers, dyskeratotic epithelial cells, and dilated intercellular spaces on hematoxylin-eosin staining (See Fig. 8.3) [53, 54]. The scoring of these histologic features as a whole, referred to as the EoE Histologic Scoring System, has been studied as a superior assessment to peak eosinophil count in detecting eosinophilic esophagitis with initial success [54].

In addition to endoscopy, other serologic, radiologic, and diagnostic studies can aid in distinguishing EoE from other disorders. The presence of eosinophils in the esophagus is never normal. The differential diagnosis for esophageal eosinophilia includes celiac disease, eosinophilic gastroenteritis, Crohn's disease, hypereosinophilic syndrome, infection, achalasia, and graft-versus-host disease. However, by far the most common cause is GERD, typically with less than 10 eos/hpf [55]. Previously a 24-hour pH probe

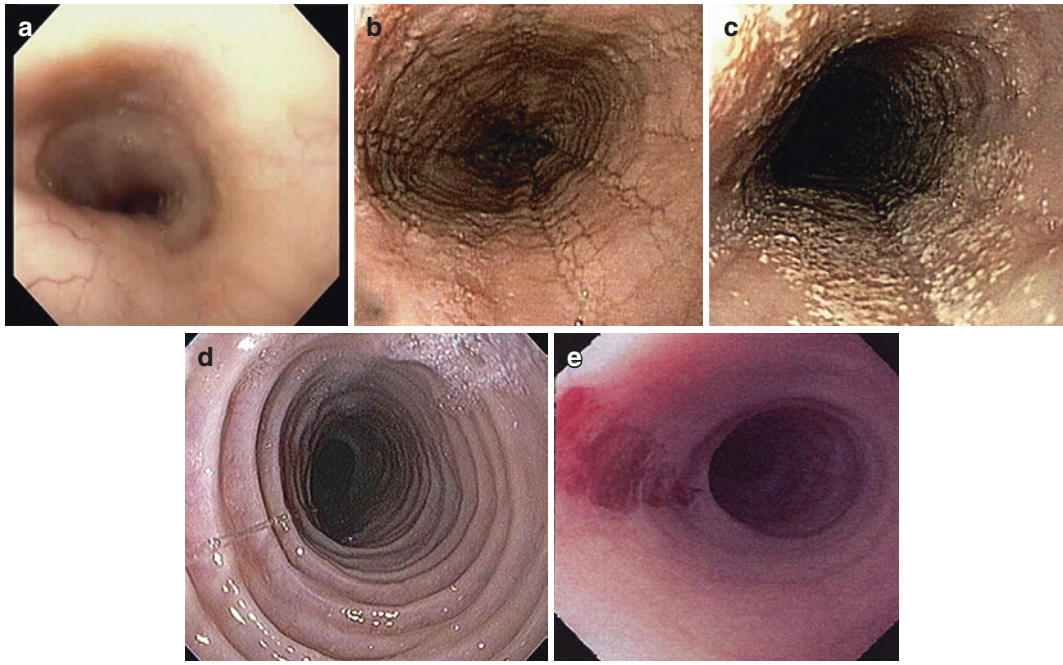



**Fig. 8.2** EoE endoscopic images. EoE endoscopic esophageal images. (**a**) Esophageal stricture. (**b**) Furrowing. (**c**) White papules. (**d**) Trachelinization. (**e**) Ulceration [4]. (Reprinted from Liacouras et al. [4], with permission from Elsevier)

was required in the diagnostic algorithm of EoE; however, GERD and EoE can both occur in the same patient, estimated in 25–50% of patients with EoE [4]. Other laboratory findings that are associated with atopy and raise the suspicion for EoE include peripheral eosinophilia and elevated specific serum IgE levels. Upper gastrointestinal series may identify long-term sequelae of EoE such as a stricture and esophageal manometry may reveal dysmotility; however, none of these studies can substitute endoscopy for the diagnosis of EoE.

Alternative EoE diagnostic modalities are under active investigation in adult patients, including the esophageal string test (a capsule filled with 90 cm of string) and cytosponge (an ingestible gelatin capsule comprising compressed mesh attached to a string). These noninvasive diagnostic modalities measure eosinophilic-derived inflammatory proteins in secretions and sample the esophageal epithelium, respectively, and have demonstrated good correlation with esophageal eosinophilia [56, 57]. In pediatrics, a trans-nasal endoscopy has been reported as a more cost-effective alternative to a sedated endoscopy; however, this is not an option for young and uncooperative children, limiting its utility [58].

Another important area of investigation in EoE is developing methods to measure esophageal fibrosis and remodeling with the hope of preventing strictures. Endoscopic ultrasonography has been used to detect expansion of esophageal wall and tissue layers in children with EoE compared to healthy children, but further research is required [59]. The EndoFLIP is an endoluminal functional lumen imaging probe using impedance to determine the distensibility of hollow organs, like the esophagus [60]. Decreased distensibility has been linked with increased risk of food impaction and disease severity [60] in adult EoE patients [60].

In addition to the well-described association of EoE with atopy, some reports show an

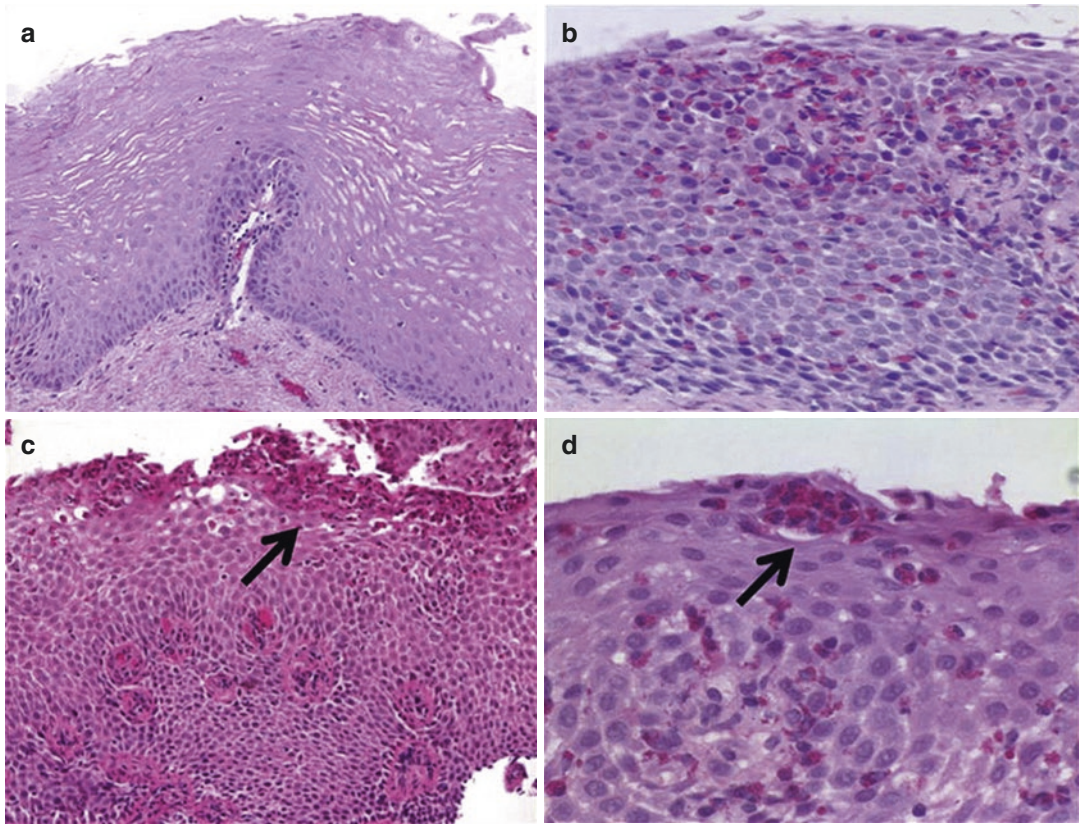



**Fig. 8.3** Histology of EoE. EoE histologic images. (**a**) Normal esophageal mucosa. (**b**) Eosinophilic predominant infiltrate. (**c**) Superficial layering of eosinophils. (**d**) Microabscess [4]. (Reprinted from Liacouras et al. [4], with permission from Elsevier)

association of EoE with celiac disease, Crohn's disease, and other hypereosinophilic syndromes; however, no causal or temporal relation has been firmly established [1, 34, 61, 62]. EoE remains a distinct disorder limited to the esophageal mucosa with infrequent cases with progression to the remaining gastrointestinal tract [1]. In the pediatric population, some case series have linked EoE with esophageal atresia as both diagnoses are associated with a male predominance, sensitization to food and/or aeroallergens, and peripheral eosinophilia [63, 64]. The link with esophageal atresia has also been suggested by mice models demonstrating FOXF1 protein involvement in the development of esophageal atresia and as a promoter region for inflammatory genes like eotaxin [42]. The relationship of EoE with other diseases is not well established.

## Management

Once the diagnosis of EoE is established, the therapeutic goals include resolving the esophageal symptoms, improving esophageal inflammation (achieve mucosal remission), preventing esophageal dysfunction and stricture, restoring normal esophageal caliber in the setting of stenotic disease, avoiding iatrogenic drug effects, preventing nutritional deficiencies, and improving quality of life [65]. The natural history of EoE involves chronic inflammation which can progress to fibrous remodeling of the esophageal wall with collagen deposition, lamina propria fibrosis, and development of strictures [66]. The treatment goals of EoE are best achieved with the input from many disciplines including allergists, gastroenterologists, dietitians, psychologists and pathologists.

Monitoring illness to achieve EoE treatment goals remains a challenge for providers, particularly in pediatrics. To assess symptom resolution, various questionnaires have been created. In pediatrics, the validated Pediatric EoE Symptom Score only weakly correlates with histopathologic and molecular features of the disease [67]. The discrepancy between symptoms and histology necessitate repeated endoscopic evaluation for proper assessment [68, 69]. At this time, endoscopy remains the mainstay of histologic assessment. There is a need for less invasive procedures or methods to monitor the disease, particularly in the pediatric population, given the risks on neurocognitive development associated with prolonged or repeated anesthesia exposure in children less than 4 years of age [70]. Repeated assessments are required to ensure the eosinophilic inflammation is improving, which is commonly utilized as an endpoint in clinical trials [50, 51, 71]. On average, EoE symptoms resolve in approximately 2 to 4 weeks, and histological improvement is observed after 8 weeks. An additional challenge arises from the lack of consensus for criteria defining mucosal remission in EoE; studies report range of peak eosinophil count from <15 to <5 eos/hpf or even a 90% improvement from baseline [1].

The three main treatment approaches for EoE patients, including children, are PPI therapy, dietary restriction, and steroid therapy. The initial treatment course is best made in discussion with patient and family to assure compliance, taking into consideration disease severity, family's lifestyle, and preference. PPI, if not already attempted, has demonstrated a 50–70% histologic remission in children with EoE by reducing the expression of eotaxin-3 in esophagus and reversing the inflammatory transcriptome [72, 73]. Additionally, a trend towards higher rates of histologic remission on PPI twice daily dosing compared with once daily is promising but requires further investigation. A standard dose of 1 mg/kg daily maintained histologic remission for 78.6% of the pediatric population at least 1 year after initiation of therapy [74]. While long-term use of PPIs has been demonstrated to be safe in adults at standard doses, no long-term PPI safety research in children is available [75].

Dietary therapy in EoE is effective when food triggers are eliminated and result in an improvement of eosinophilic inflammation. Over the years, varied approaches towards achieving this goal have been developed to provide the patient with practical options. The first efficacious treatment identified for EoE was the use of an amino acid–based formula described in the seminal paper by Kelley et al. The effectiveness of elemental formulas was confirmed repeatedly in children and adults with EoE [4, 9, 76]. Elemental formulas have yielded a 90% efficacy in meta-analyses including both children and adults [9, 76]. Despite its effectiveness, the poor palatability of the elemental formula and frequent need for nasogastric tube placement in children make it a less attractive option. It is also limited by its cost and potential for speech delay in young children if they are unable to develop their facial muscles appropriately in the absence of chewing [7]. The elemental diet approach is most useful in treating small children who have not been introduced to solids.

To avoid the demanding exclusion of all table foods with an elemental diet, an elimination diet based on testing has had limited success. Skin prick testing and serum specific IgE are useful for IgE-based allergic disorders while APTs are helpful in delayed hypersensitivity. In a study using both SPTs and APTs, histologic remission was induced in only 49% of pediatric patients, however, this study had a very wide heterogeneity ($I^2$ 75%), suggesting poor reproducibility [21]. With the current allergy testing available, test-based elimination therapy has limited effectiveness and is not first-line practice in the implantation of EoE dietary therapy [1, 4, 29].

An alternative to test-based elimination is empiric removal of the six most common food antigens. One approach is the elimination of milk protein, soy, egg, wheat, peanuts/tree nuts, and fish/seafood. This "six-food elimination diet" (SFED) strategy was first proposed and evaluated by Dr. Kagalwalla, a pediatric gastroenterologist [8]. Several studies have evaluated the SFED in

children and adults with an overall effectiveness of approximately 72% [29]. The caveat of this approach is the necessity for endoscopy not only to document remission with diet, but also after reintroduction of every food group to assess recurrence [8]. This is necessary given the lack of predictability of histologic remission with symptom resolution [8, 29].

Another approach is the elimination of milk, wheat, egg, and soy/legumes known as the four-food elimination diet (FFED). This strategy limits the dietary restriction and subsequent endoscopies required upon food reintroduction. After initial success of the FFED in adults, a multicenter study in pediatrics demonstrated a 64% remission rate, defined by <15 eos/hpf [11]. Analysis of sequential food reintroduction identified the most common triggers in children were milk (85%), egg (35%), wheat (33%), and soy (19%) [11]. To minimize restriction, a step-up approach coined "2-4-6" study was appraised, initiating restriction with milk and gluten in both adults and children. The two-food elimination diet achieved clinicohistologic remission in 43% of patients [12]. While less effective compared to FFED and SFED, the "2-4-6" strategy reduced endoscopic procedures by 20% [12].

Due to the immune nature of EoE, systemic steroid therapy (oral prednisone and intravenous methylprednisolone) was attempted early on and was found to induce clinical and histologic remission. However, the extensive side effect profile of oral (prednisone) and intravenous steroids (methylprednisolone), including impaired growth and adrenal insufficiency, among others, prompted the consideration of alternatives. Swallowed topical steroids, such as fluticasone proprionate and beclomethasone, proved effective in treating EoE in adults and children [77]. Swallowed topical steroids are administered followed by a time period where the patient does not eat or drink, so the medication stays on the esophageal epithelium [77]. A double-blinded, placebo-controlled study of swallowed fluticasone demonstrated its effectiveness and limited side effect profile including esophageal candidiasis (5%) [78]. Another study demonstrated that 4.7% of EoE pediatric patients developed adrenal insufficiency on swallowed fluticasone, but all were receiving additional steroids including inhaled or nasal for comorbidities [79]. Swallowed fluticasone has also been reported to induce long-term remission in 60% of pediatric patients at 2-year follow-up [80]. Dellon et al., in a seminal paper, reported a viscous preparation of budesonide led to significantly higher remission than the nebulized formulation (65% vs. 27%) at equivalent doses [81]. This finding revolutionized delivery of swallowed topical steroids. This also promoted the discovery of new formulations like effervescent tablets, which remain under investigation, with the goals of optimizing drug application and maximizing contact with the esophageal surface. In treatment failures, a combination of swallowed steroid and dietary restriction has showed some promise and could be considered in refractory cases [82]. Swallowed steroid therapies provide a safe and effective option for many patients.

Other immunosuppressants have been investigated for the treatment of EoE with mixed success, including immunomodulators and biologic medications. In adults, several case series demonstrated remission in patients on azathioprine or 6-mercaptopurine (immunomodulators); this effect was not observed with infliximab (anti-TNFα) [83]. Mepolizumab and resiluzumab are monoclonal antibodies (mAb) directed towards IL-5, involved in the recruitment of eosinophils to the esophagus. These medications show improved esophageal eosinophilia, but showed little improvement in symptoms [84]. Lucendo et al. recently described that human mAb against alpha subunit of IL-4 and IL13, dupilumab, has been effective in reducing symptoms and esophageal eosinophils in adults [85]. As the field advances and the molecular mechanisms of EoE are further elucidated, the expectation is that more therapeutic and diagnostic targets will develop.

A delay in EoE diagnosis and treatment of disease is associated with the development of esophageal fibrotic strictures [66]. Children are unfortunately not spared with narrow-caliber esophagi being reported in series using barium swallows [86, 87]. For those with strictures from prolonged inflammation, esophageal dilation with hydropneumatic balloons may be a necessary

treatment to aid in the dysphagia symptoms. Dilation therapy, although not addressing underlying inflammation, demonstrated a significant improvement in dysphagia symptoms in both children and adults [88]. For these patients with strictures, it is imperative to assure they are on medical or dietary therapy to avoid recurrence.

The management of EoE is a complex and multidisciplinary endeavor. EoE is optimally managed by a team consisting of gastroenterologists, allergists, pathologists, dietitians, and psychologists [74]. This multidisciplinary team brings unique expertise to address the many needs of an EoE patient. Together, this team determines the most effective initial treatment in discussion with family and patient. They are able to evaluate the medical, nutritional, and psychosocial impact of any dietary or pharmacologic therapy [65].

In addition to achieving clinical and histologic remission, another outcome measure of successful treatment includes improvement in the quality of life (QOL) of EoE patients. Franciosi et al. demonstrated that EoE has a psychosocial impact on children and their families, demonstrating that those with poorly controlled disease and dietary restrictions scored worse on QOL indicators [89]. Additionally, the number of foods restricted in EoE dietary therapy is inversely correlated with QOL indicators [89]. When clinical symptoms were evaluated predicting poor physical and psychosocial quality of life, persistent epigastric pain stood out [90, 91]. Targeting interventions to improve epigastric pain, minimize patient suffering, and dietary restrictions may improve the quality of life of pediatric EoE patients.

## Conclusions

Despite having been recognized as a distinct clinical entity only recently, the advancements in recognizing and managing EoE are very promising. This chronic immune-mediated disease which plagues both children and adults requires further investigation. There are varied strategies including dietary and pharmacologic approaches for treating this disease and preventing long-term sequelae. Potential areas for research include elucidating the pathophysiology of the development of EoE, identifying biochemical markers to identify and monitor EoE using a non-invasive approach, and expanding and optimizing therapeutic options.

## References

1. Lucendo AJ, Molina-Infante J, Arias A, von Arnim U, Bredenoord AJ, Bussmann C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017;5(3):335–58.
2. Arias A, Perez-Martinez I, Tenias JM, Lucendo AJ. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther. 2016;43(1):3–15.
3. Soon IS, Butzner JD, Kaplan GG, deBruyn JC. Incidence and prevalence of eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr. 2013;57(1):72–80.
4. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128(1):3–20 e6; quiz 1–2
5. Davis BP. Pathophysiology of eosinophilic esophagitis. Clin Rev Allergy Immunol. 2018 Aug;55(1):19–42.
6. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995;109(5):1503–12.
7. Arias A, Lucendo AJ. Dietary therapies for eosinophilic esophagitis. Expert Rev Clin Immunol. 2014;10(1):133–42.
8. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2006;4(9):1097–102.
9. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol. 2003;98(4):777–82.
10. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol. 2012;130(2):461–7 e5.
11. Kagalwalla AF, Wechsler JB, Amsden K, Schwartz S, Makhija M, Olive A, et al. Efficacy of a 4-food elimination diet for children with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2017;15(11):1698–707 e7.

12. Molina-Infante J, Arias A, Alcedo J, Garcia-Romero R, Casabona-Frances S, Prieto-Garcia A, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 study. J Allergy Clin Immunol. 2018;141(4):1365–72.
13. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. J Pediatr Gastroenterol Nutr. 2009;48(1):30–6.
14. Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest. 2006;116(2):536–47.
15. Bullock JZ, Villanueva JM, Blanchard C, Filipovich AH, Putnam PE, Collins MH, et al. Interplay of adaptive th2 immunity with eotaxin-3/c-C chemokine receptor 3 in eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2007;45(1):22–31.
16. Rothenberg ME, Spergel JM, Sherrill JD, Annaiah K, Martin LJ, Cianferoni A, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. Nat Genet. 2010;42(4):289–91.
17. Ahrens R, Waddell A, Seidu L, Blanchard C, Carey R, Forbes E, et al. Intestinal macrophage/epithelial cell-derived CCL11/eotaxin-1 mediates eosinophil recruitment and function in pediatric ulcerative colitis. J Immunol. 2008;181(10):7390–9.
18. Konikoff MR, Blanchard C, Kirby C, Buckmeier BK, Cohen MB, Heubi JE, et al. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2006;4(11):1328–36.
19. Schoepfer A, Safroneeva E, Straumann A. Eosinophilic esophagitis: impact of latest insights into pathophysiology on therapeutic strategies. Dig Dis. 2016;34(5):462–8.
20. Rocha R, Vitor AB, Trindade E, Lima R, Tavares M, Lopes J, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. Eur J Pediatr. 2011;170(11):1471–4.
21. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. Ann Allergy Asthma Immunol. 2005;95(4):336–43.
22. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med. 2004;351(9):940–1.
23. Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. J Allergy Clin Immunol. 2007;119(3):731–8.
24. Maggadottir SM, Hill DA, Ruymann K, Brown-Whitehorn TF, Cianferoni A, Shuker M, et al. Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food. J Allergy Clin Immunol. 2014;133(5):1487–9, 9 e1.
25. Schuyler AJ, Wilson JM, Tripathi A, Commins SP, Ogbogu PU, Kruzsewski PG, et al. Specific IgG4 antibodies to cow's milk proteins in pediatric patients with eosinophilic esophagitis. J Allergy Clin Immunol. 2018;142(1):139–48 e12.
26. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology. 2014;147(3):602–9.
27. Rosenberg CE, Mingler MK, Caldwell JM, Collins MH, Fulkerson PC, Morris DW, et al. Esophageal IgG4 levels correlate with histopathologic and transcriptomic features in eosinophilic esophagitis. Allergy. 2018;73(9):1892–901. https://doi.org/10.1111/all.13486.
28. Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. Clin Exp Allergy. 2009;39(4):469–77.
29. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology. 2014;146(7):1639–48.
30. Egan M, Atkins D. What is the Relationship Between Eosinophilic Esophagitis (EoE) and aeroallergens? Implications for allergen immunotherapy. Curr Allergy Asthma Rep. 2018;18(8):43.
31. Herrick CA, MacLeod H, Glusac E, Tigelaar RE, Bottomly K. Th2 responses induced by epicutaneous or inhalational protein exposure are differentially dependent on IL-4. J Clin Invest. 2000;105(6):765–75.
32. Jensen ET, Dellon ES. Environmental factors and eosinophilic esophagitis. J Allergy Clin Immunol. 2018;142(1):32–40.
33. Jensen ET, Kuhl JT, Martin LJ, Rothenberg ME, Dellon ES. Prenatal, intrapartum, and postnatal factors are associated with pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2018;141(1):214–22.
34. Lucendo AJ, Hervias D, Roncero O, Lorente R, Bouhmidi A, Angueira T, et al. Epidemiology and temporal trends (2000–2012) of inflammatory bowel disease in adult patients in a central region of Spain. Eur J Gastroenterol Hepatol. 2014;26(12):1399–407.
35. Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. J Allergy Clin Immunol. 2014;134(5):1084–92 e1.
36. Kottyan LC, Rothenberg ME. Genetics of eosinophilic esophagitis. Mucosal Immunol. 2017;10(3):580–8.
37. Litosh VA, Rochman M, Rymer JK, Porollo A, Kottyan LC, Rothenberg ME. Calpain-14 and its association with eosinophilic esophagitis. J Allergy Clin Immunol. 2017;139(6):1762–71 e7.
38. Sleiman PM, Wang ML, Cianferoni A, Aceves S, Gonsalves N, Nadeau K, et al. GWAS identifies four novel eosinophilic esophagitis loci. Nat Commun. 2014;5:5593.
39. Sorimachi H, Hata S, Ono Y. Impact of genetic insights into calpain biology. J Biochem. 2011;150(1):23–37.

40. Abonia JP, Wen T, Stucke EM, Grotjan T, Griffith MS, Kemme KA, et al. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. J Allergy Clin Immunol. 2013;132(2):378–86.
41. Sherrill JD, Kc K, Wang X, Wen T, Chamberlin A, Stucke EM, et al. Whole-exome sequencing uncovers oxidoreductases DHTKD1 and OGDHL as linkers between mitochondrial dysfunction and eosinophilic esophagitis. JCI Insight. 2018;3(8) https://doi.org/10.1172/jci.insight.99922.
42. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. J Allergy Clin Immunol. 2015;135(1):187–97.
43. Sperry SL, Woosley JT, Shaheen NJ, Dellon ES. Influence of race and gender on the presentation of eosinophilic esophagitis. Am J Gastroenterol. 2012;107(2):215–21.
44. Sperry SL, Crockett SD, Miller CB, Shaheen NJ, Dellon ES. Esophageal foreign-body impactions: epidemiology, time trends, and the impact of the increasing prevalence of eosinophilic esophagitis. Gastrointest Endosc. 2011;74(5):985–91.
45. Almansa C, Krishna M, Buchner AM, Ghabril MS, Talley N, DeVault KR, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. Am J Gastroenterol. 2009;104(4):828–33.
46. Chehade M. IgE and non-IgE-mediated food allergy: treatment in 2007. Curr Opin Allergy Clin Immunol. 2007;7(3):264–8.
47. Hiremath G, Byramji D, Pacheco A, Constantine G, Davis C, Shulman R, et al. Eosinophilic esophagitis in children and its relationship with parental allergies: Texas Children's Hospital experience. Dig Dis Sci. 2016;61(2):501–6.
48. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology. 2018;155(4):1022–1033.e10. https://doi.org/10.1053/j.gastro.2018.07.009.
49. Wechsler JB, Bolton SM, Amsden K, Wershil BK, Hirano I, Kagalwalla AF. Eosinophilic esophagitis reference score accurately identifies disease activity and treatment effects in children. Clin Gastroenterol Hepatol. 2018;16(7):1056–63.
50. Nielsen JA, Lager DJ, Lewin M, Rendon G, Roberts CA. The optimal number of biopsy fragments to establish a morphologic diagnosis of eosinophilic esophagitis. Am J Gastroenterol. 2014;109(4):515–20.
51. Gonsalves N, Policarpio-Nicolas M, Zhang Q, Rao MS, Hirano I. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. Gastrointest Endosc. 2006;64(3):313–9.
52. Sperry SL, Shaheen NJ, Dellon ES. Toward uniformity in the diagnosis of eosinophilic esophagitis (EoE): the effect of guidelines on variability of diagnostic criteria for EoE. Am J Gastroenterol. 2011;106(5):824–32; quiz 33
53. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterol Clin North Am. 2014;43(2):257–68.
54. Collins MH, Martin LJ, Alexander ES, Boyd JT, Sheridan R, He H, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus. 2017;30(3):1–8.
55. Kia L, Hirano I. Distinguishing GERD from eosinophilic oesophagitis: concepts and controversies. Nat Rev Gastroenterol Hepatol. 2015;12(7):379–86.
56. Furuta GT, Kagalwalla AF, Lee JJ, Alumkal P, Maybruck BT, Fillon S, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. Gut. 2013;62(10):1395–405.
57. Katzka DA, Geno DM, Ravi A, Smyrk TC, Lao-Sirieix P, Miremadi A, et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2015;13(1):77–83 e2.
58. Friedlander JA, DeBoer EM, Soden JS, Furuta GT, Menard-Katcher CD, Atkins D, et al. Unsedated transnasal esophagoscopy for monitoring therapy in pediatric eosinophilic esophagitis. Gastrointest Endosc. 2016;83(2):299–306 e1.
59. Fox VL, Nurko S, Teitelbaum JE, Badizadegan K, Furuta GT. High-resolution EUS in children with eosinophilic "allergic" esophagitis. Gastrointest Endosc. 2003;57(1):30–6.
60. Nicodeme F, Hirano I, Chen J, Robinson K, Lin Z, Xiao Y, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2013;11(9):1101–7 e1.
61. Mulder DJ, Hookey LC, Hurlbut DJ, Justinich CJ. Impact of Crohn disease on eosinophilic esophagitis: evidence for an altered T(H)1-T(H)2 immune response. J Pediatr Gastroenterol Nutr. 2011;53(2):213–5.
62. Ludvigsson JF, Aro P, Walker MM, Vieth M, Agreus L, Talley NJ, et al. Celiac disease, eosinophilic esophagitis and gastroesophageal reflux disease, an adult population-based study. Scand J Gastroenterol. 2013;48(7):808–14.
63. Chan LJ, Tan L, Dhaliwal J, Briglia F, Clarkson C, Krishnan U. Treatment outcomes for eosinophilic esophagitis in children with esophageal atresia. Dis Esophagus. 2016;29(6):563–71.
64. Kassabian S, Baez-Socorro V, Sferra T, Garcia R. Eosinophilic esophagitis in patients with esophageal atresia and chronic dysphagia. World J Gastroenterol. 2014;20(47):18038–43.
65. Munoz-Persy M, Lucendo AJ. Treatment of eosinophilic esophagitis in the pediatric patient: an evidence-based approach. Eur J Pediatr. 2018;177(5):649–63.

66. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc. 2014;79(4):577–85 e4.
67. Franciosi JP, Hommel KA, DeBrosse CW, Greenberg AB, Greenler AJ, Abonia JP, et al. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. BMC Gastroenterol. 2011;11:126.
68. Safroneeva E, Straumann A, Coslovsky M, Zwahlen M, Kuehni CE, Panczak R, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. Gastroenterology. 2016;150(3):581–90 e4.
69. Martin LJ, Franciosi JP, Collins MH, Abonia JP, Lee JJ, Hommel KA, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. J Allergy Clin Immunol. 2015;135(6):1519–28 e8.
70. Schneuer FJ, Bentley JP, Davidson AJ, Holland AJ, Badawi N, Martin AJ, et al. The impact of general anesthesia on child development and school performance: a population-based study. Paediatr Anaesth. 2018;28(6):528–36.
71. Shah A, Kagalwalla AF, Gonsalves N, Melin-Aldana H, Li BU, Hirano I. Histopathologic variability in children with eosinophilic esophagitis. Am J Gastroenterol. 2009;104(3):716–21.
72. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14(1):13–22 e1.
73. Gutierrez-Junquera C, Fernandez-Fernandez S, Cilleruelo ML, Rayo A, Echeverria L, Borrell B, et al. Long-term treatment with proton pump inhibitors is effective in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2018 Aug;67(2):210–6.
74. Molina-Infante J, Bredenoord AJ, Cheng E, Dellon ES, Furuta GT, Gupta SK, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. Gut. 2016;65(3):524–31.
75. Tjon JA, Pe M, Soscia J, Mahant S. Efficacy and safety of proton pump inhibitors in the management of pediatric gastroesophageal reflux disease. Pharmacotherapy. 2013;33(9):956–71.
76. Peterson KA, Byrne KR, Vinson LA, Ying J, Boynton KK, Fang JC, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. Am J Gastroenterol. 2013;108(5):759–66.
77. Schaefer ET, Fitzgerald JF, Molleston JP, Croffie JM, Pfefferkorn MD, Corkins MR, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol. 2008;6(2):165–73.
78. Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology. 2006;131(5):1381–91.
79. Hsu S, Wood C, Pan Z, Rahat H, Zeitler P, Fleischer D, et al. Adrenal insufficiency in pediatric eosinophilic esophagitis patients treated with swallowed topical steroids. Pediatr Allergy Immunol Pulmonol. 2017;30(3):135–40.
80. Andreae DA, Hanna MG, Magid MS, Malerba S, Andreae MH, Bagiella E, et al. Swallowed fluticasone propionate is an effective long-term maintenance therapy for children with eosinophilic esophagitis. Am J Gastroenterol. 2016;111(8):1187–97.
81. Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology. 2012;143(2):321–4 e1.
82. Constantine G, Seth N, Chokshi N, Minard CG, Guffey D, Olive AP, et al. Combination steroid and test-based food elimination for eosinophilic esophagitis: a retrospective analysis. J Pediatr Gastroenterol Nutr. 2017;64(6):933–8.
83. Netzer P, Gschossmann JM, Straumann A, Sendensky A, Weimann R, Schoepfer AM. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. Eur J Gastroenterol Hepatol. 2007;19(10):865–9.
84. Assa'ad AH, Gupta SK, Collins MH, Thomson M, Heath AT, Smith DA, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology. 2011;141(5):1593–604.
85. Lucendo AJ, Molina-Infante J. Emerging therapeutic strategies for eosinophilic esophagitis. Curr Treat Options Gastroenterol. 2014;12(1):1–17.
86. Lipka S, Kumar A, Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. J Clin Gastroenterol. 2016;50(2):134–40.
87. van Rhijn BD, Oors JM, Smout AJ, Bredenoord AJ. Prevalence of esophageal motility abnormalities increases with longer disease duration in adult patients with eosinophilic esophagitis. Neurogastroenterol Motil. 2014;26(9):1349–55.
88. Moawad FJ, Molina-Infante J, Lucendo AJ, Cantrell SE, Tmanova L, Douglas KM. Systematic review with meta-analysis: endoscopic dilation is highly effective and safe in children and adults with eosinophilic oesophagitis. Aliment Pharmacol Ther. 2017;46(2):96–105.
89. Franciosi JP, Hommel KA, Bendo CB, King EC, Collins MH, Eby MD, et al. PedsQL eosinophilic esophagitis module: feasibility, reliability, and validity. J Pediatr Gastroenterol Nutr. 2013;57(1):57–66.
90. Klinnert MD, Silveira L, Harris R, Moore W, Atkins D, Fleischer DM, et al. Health-related quality of life

over time in children with eosinophilic esophagitis and their families. J Pediatr Gastroenterol Nutr. 2014;59(3):308–16.
91. Lynch MK, Barnes MJ, Dimmitt RA, Martin L, Rothenberg ME, Goodin BR. Disease-related predictors of health-related quality of life in youth with eosinophilic esophagitis. J Pediatr Psychol. 2018;43(4):464–71.

# 9 Food-Protein-Induced Enterocolitis Syndrome: A Pediatric Gastrointestinal Food Allergy

Amanda Agyemang and Anna Nowak-Wegrzyn

## Abbreviations

| | |
|---|---|
| APT | Atopy patch testing |
| CM | Cow's milk |
| FPIES | Food-protein-induced enterocolitis syndrome |
| IQR | Interquartile range |
| IV | Intravenous |
| OFC | Oral food challenge |
| ssIgE | Serum-specific IgE |

## Introduction

Non –IgE-mediated food allergies are considered to be rare food allergy disorders that are less understood compared to their IgE-mediated counterparts and characterized by the production of mild to severe gastrointestinal symptoms in the presence of reaction-inducing foods. Food-protein-induced enterocolitis syndrome (FPIES) is the best studied of these disorders and, although rare, it is increasingly becoming recognized in the medical community as a disorder with significant impact on patient morbidity [1]. FPIES mostly presents in young infants and children although adult cases have been reported. It is defined by a clear pattern of delayed onset of mild to severe vomiting accompanied by pallor and lethargy 1–4 hours after ingestion of an FPIES-inducing food that may then be followed by diarrhea within 6–8 hours. Varying levels of agreement exist in the allergy community regarding pathogenesis, prevalence, diagnosis, and management of FPIES. Overall, there is still much to be uncovered about this disorder. In this chapter, we will provide a comprehensive summary on the current literature of FPIES and discuss future directions to move our understanding forward.

## History of FPIES

In the 1970s, the recurrent clinical presentation of infants under 6 weeks of age who developed enterocolitis after exposure to milk or soy-based formula was initially observed and reported by Powell [2]. Specifically, reproducible symptoms of severe vomiting within 4 hours of ingesting cow's milk (CM) or soy milk and/or diarrhea lead to the suspicion of food-induced gastrointestinal symptoms in infants. Additionally, the infants developed hematologic abnormalities including neutrophilia without other indications of infection. Management of these food-induced symptoms included intravenous hydration, avoiding

A. Agyemang
Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Kravis Children's Hospital, Icahn School of Medicine, New York, NY, USA
e-mail: amanda.agyemang@mountsinai.org

A. Nowak-Wegrzyn (✉)
Allergy and Immunology, Department of Pediatrics, NYU Langone Health, New York, NY, USA

Department of Pediatrics, Gastroenterology and Nutrition, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland
e-mail: anna.nowak-wegrzyn@nyulangone.org



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_9

CM and soy formulas, and replacing CM nutrition with a hypoallergenic hydrolyzed cow's milk formula. Powell further characterized this disorder, which would come to be known as FPIES, by describing criteria for diagnosis and introduced oral food challenge (OFC) protocols as a practice to confirm the diagnosis [3].

Infants developing these delayed gastrointestinal symptoms with CM and/ or soy exposure continued to appear in the literature, with additional observations that removing the milk protein source resulted in resolution of symptoms within 24 hours [4]. Since these initial characterizations of FPIES, we have developed a better understanding of symptom manifestation, epidemiology, triggers, and management of patients with FPIES.

## Classifications of FPIES

### Acute FPIES

FPIES is categorized into two major phenotypes: acute FPIES and chronic FPIES. Acute FPIES, the most common phenotype, is defined by delayed recurrent vomiting approximately 1–4 hours (typically 2 hours) after exposure to a triggering food (Table 9.1) [5]. The vomiting is described by parents as severe and projectile and can occur on average 5–10 times within an episode. Watery diarrhea, when present, usually develops 5–10 hours after the onset of vomiting or at some point within 24 hours of food exposure. In severe cases, patients can become hypothermic, pale, and lethargic. Laboratory findings can include neutrophilia, methemoglobinemia, thrombocytosis, and metabolic acidosis [5].

When vital sign instability and hypotension are also present in FPIES patients, this constellation of symptoms is suggestive of a sepsis/shock. These patients are often evaluated for sepsis with negative findings [6, 7]. Fortunately, symptoms usually resolve 24 hours after their onset as long as the offending agent is removed from the diet. The children return to their baseline, tolerate oral foods, and have unaffected growth and development [1].

**Table 9.1** Phenotypes of FPIES [1]

| | Clinical symptoms | Laboratory values |
|---|---|---|
| *Acute FPIES*[a] | Recurrent vomiting 1–4 h after food ingestion<br>Diarrhea within 24 h<br>Lethargy<br>Pallor<br>Dehydration<br>Hypovolemia<br>+/−shock<br>Hypothermia<br>Normal growth | Leukocytosis with neutrophilia<br>Thrombocytosis<br>Metabolic acidosis<br>Methemoglobinemia<br>Stool leukocytes, eosinophils<br>Increased stool carbohydrate content<br>Stool occult or frank blood<br>CSF neutrophilia |
| *Chronic FPIES*[a] | Symptoms develop over days-weeks with frequent (e.g., daily) feedings with the offending foods<br>Intermittent emesis<br>Progressive diarrhea<br>Dehydration<br>Hypovolemia<br>+/− shock<br>Failure to thrive/ poor growth<br>Abdominal distension | Hypoalbuminemia<br>Leukocytosis with neutrophilia<br>Anemia<br>Thrombocytosis<br>Metabolic acidosis<br>Methemoglobinemia<br>Stool reducing substances |
| *Classic FPIES* | Acute or chronic FPIES symptoms | Negative IgE to trigger food |
| *Atypical FPIES* | More protracted FPIES course<br>IgE-mediated allergy to food | Positive IgE to trigger food |

[a]Acute and chronic FPIES may occur in the same patient, e.g., an infant with chronic FPIES to cow's milk at the age 6 weeks whose symptoms resolve with elimination of cow's milk may develop acute FPIES when reintroduced to cow's milk, e.g., in the form of yogurt, at an older age of several months

Adapted from Nowak-Wegrzyn et al. [1], with permission from Elsevier

### Chronic FPIES

Infants with chronic daily exposure to milk or soy protein who develop intermittent vomiting and watery diarrhea over several days to weeks are suspected to have chronic FPIES. Commonly, these infants present under 4 months of age and have prominent watery or mucus-streaked diarrhea. Over time, vomiting and diarrhea progressively worsen and may lead to dehydration, metabolic acidosis, lethargy, and neutrophilia (Table 9.1) [8]. Poor growth and hypoalbumin-

emia distinguish chronic FPIES from acute FPIES. Resolution of symptoms is noted within days to several weeks of eliminating of CM or soy protein. If the trigger food protein is reintroduced after a period of avoidance, an acute FPIES reaction will develop [1, 9]. Similarly presenting non-IgE-mediated allergic syndromes triggered by CM in infancy include food-protein-induced allergic proctocollitis (FPIAP) and food protein enteropathy (FPE) [10]. In FPIAP, commonly referred to as milk protein intolerance, patients present with bloody or mucus streaked stools which differ from diarrhea noted in patients with chronic FPIES. Additionally, the infant with FPIAP is well appearing and thriving in growth and development. FPE is rare and characterized predominantly by chronic diarrhea and malabsorption that can produce steatorrhea. Additionally, there can be vomiting and abdominal distension, which together frequently result in failure to thrive. The progression of FPE symptoms is slower (over the period of several months) than with chronic FPIES, in which watery diarrhea and vomiting progressively worsen over a period of days to weeks and culminate in dehydration, metabolic acidosis, methemoglobinemia, and/or hypovolemic shock.

### Atypical FPIES

Though not an IgE-mediated disorder, up to 20% of patients with FPIES demonstrate ssIgE sensitization to their trigger food [11, 12]. These individuals have atypical FPIES and typically exhibit a more prolonged course of FPIES with decreased likelihood of developing tolerance (Table 9.1). Children with atypical CM FPIES were less likely to note resolution of their symptoms by the age of 3 than individuals with typical FPIES as noted by Caubet et al. [11]. Atypical FPIES patients otherwise present similarly to acute FPIES with delayed gastrointestinal symptoms after exposure to triggering foods; however over time a subset may transition to more immediate symptoms of IgE-mediated food allergy unlike typical FPIES patients [11, 13].

Rarely, patients with IgE-mediated food allergies to cow's milk develop non-IgE-mediated food allergy and vice versa [14–17]. A recent case report described the conversion of an egg IgE-mediated allergy to the FPIES phenotype [18]. A child who had been avoiding egg for a year due to immediate hives on ingestion, was challenged to baked egg and tolerated it during the immediate (2 hour) observation period, but then developed reproducible delayed profuse vomiting and diarrhea [18]. The mechanisms of the development of ssIgE against foods triggering non-IgE-mediated food allergy and the interaction between IgE- and non-IgE-mediated allergies are dynamic and still require further study for better understanding.

## Pathophysiology

FPIES is a non-IgE, cell-mediated food allergy for which the pathophysiology has not yet been fully elucidated. Research indicates that there is likely a cellular-driven process of gut inflammation that occurs after the introduction of triggering foods. Specifically T-cells are implicated in driving the inflammatory process as evidenced by the following: increased TNF alpha expression and increased CD4+ cell proliferation upon stimulation, and CM challenges in FPIES patients demonstrate increased Th2 as opposed to Th1 cytokines expression [19–21].

A more recent investigation of FPIES inflammatory processes did not demonstrate an increase in T cell proliferation or a significant difference in Th2 inflammatory cytokine expression in CM FPIES subjects challenged with casein [22]. Therefore, the exact role of T cells in FPIES has yet to be revealed. Other arms of the immune systems that might be involved include innate immune cells. In food challenges with trigger foods to FPIES, patients demonstrate increased activation of monocytes, neutrophils, NK cells, and eosinophils [22–24]. Additionally, an increase in serum IL-8 and tryptase has been described in acute FPIES reactions, thereby supporting the presence of neutrophils and mast cells [25].

Serum cortisol levels have also been implicated in the mechanism of FPIES and were recently measured before and after (6 h and 24 h) the positive OFCs of six Japanese children with CM FPIES [26]. Significant increases were noted in serum cortisol level at 6 hours, and serum cortisol increases were significantly correlated with the increase of absolute neutrophil count and the presence of vomiting [26]. This suggests a role for cortisol in the inflammatory mechanisms of FPIES that additional studies will examine in the future.

The ramifications of increased inflammation specifically target the gut in FPIES, and how the localization occurs is unclear. The colon and the ileum are the main sites of inflammation as evidenced by endoscopy and colonoscopy studies in these patients. The increased inflammation produces increased permeability of the intestines and fluid shifts that result in the prominent vomiting and diarrhea that characterize the disease [1, 27]. Ondansetron improves the repetitive vomiting and cramping in patients with an acute FPIES reaction, suggesting a relationship between serotonin signaling and FPIES. Ondansetron is a serotonin 5-HT3 receptor antagonist, thus its effectiveness suggests a neurological component is involved in FPIES that should be studied further to illuminate the mechanism [28, 29].

## Trigger Foods

Multiple studies have examined the breadth of different foods that trigger FPIES. Sixty-five percent of FPIES cases are induced by liquid CM proteins consumed by infants. CM (44%–70%), soy (36–40%), or both (44%) most commonly trigger acute FPIES in infants in the United States [6, 7, 11]. Interestingly infants in the United States who are breastfed appear to be protected from developing FPIES with less than 5% of breastfed infants actually developing the syndrome [1, 30, 31]. Conversely in Japan, 20% of infants with CM FPIES develop symptoms during exclusive breastfeeding [32].

Rice is the most common solid food FPIES trigger in the United States closely followed by oats, barley, and other grains [6, 11]. Other common solid foods include vegetables (peas, sweet potato), banana, poultry, fish, shellfish, nuts, and legumes. Overall, solid foods account for 35% of cases of FPIES [6, 11, 33]. FPIES reactions to fruits and vegetables are unlikely; however, when it does occur it is most frequently observed in infants [31]. The country of origin also appears to play a significant role in the specific foods that trigger FPIES reactions in patients. For instance, in Mediterranean countries like Italy and Spain, fish is the most common solid food inducing an FPIES reaction [34, 35].

Most patients with FPIES are triggered by one food (65%); however, it is not uncommon for patients to be reactive to multiple foods (35%) as noted in Table 9.2 [11]. For instance, patients reactive to one type of grain have a 40% likelihood of having an FPIES to multiple grains [6]. Exhibiting symptoms within the first month of life actually increases the likelihood of co-allergy developing to other foods. The frequency of exposure to food also appears to directly affect FPIES reactivity. In 2014, Katz et al. reported individuals with FPIES to rice, chicken, cod, and wheat developed lower thresholds to reaction after repeat exposures to the food. In other words,

**Table 9.2** Co-allergies prevalent in FPIES [1]

| FPIES induced by | Co-allergy[a] | Rate of occurrence |
|---|---|---|
| *Cow's milk* | Soy | <30–40% |
| | Solid foods | <16% |
| *Soy* | Cow's milk | <30–40% |
| | Solid foods | <16% |
| *Legumes* | Soy | <80% |
| *Grains* | Grains such as rice, wheat, barley, oat, etc. | Approximately 50% |
| *Poultry* | Alternate poultry | <40% |
| *Solid food* | Alternate solid food | <44% |
| | Cow's milk and or soy | <25% |

[a]Co-allergy is most common in the first 12 months, especially under 6 months of age

Adapted from Nowak-Wegrzyn et al. [1], with permission from Elsevier

individuals have FPIES reactions to smaller amounts of the inciting food with every subsequent ingestion [36].

## Epidemiology

Data on the global prevalence of FPIES is limited. In the first prospective population study characterizing its prevalence, Katz et al. (2011) noted an incidence of 0.34% CM FPIES among 10,000 infants born at a single hospital over 2 years in Israel compared to a 0.5% prevalence of IgE-mediated CM allergy [37]. In 2017, Mehr performed an assessment of national FPIES prevalence in Australian infants under 24 months from 2012 to 2014 and described an incidence of 15.4/100,000 cases per year [31]. This increase in documented cases over time may reflect either the increased awareness of the disorder among clinicians or a true increase of FPIES incidence [31]. The most recent FPIES prevalence data come from Spain and report an incidence of 0.7% in the first year of life based on a birth cohort of 1142 children from a single medical center (Prevale study) [38]. FPIES was diagnosed according to the strict diagnostic criteria, and an OFC was performed in the majority of the patients to confirm the diagnosis. The most common food trigger was CM, followed by fish and egg yolk; one of the eight infants presented with symptoms of chronic FPIES to cow's milk.

A personal history of atopy is one of the largest contributing risk factors to developing FPIES. As one study demonstrated, FPIES is highly associated with the diagnosis of asthma (25%), allergic rhinitis (38%), atopic dermatitis (57%), and IgE-mediated food allergy to other foods (39%) [11]. Family history of atopy is also significantly correlated with FPIES with evidence of atopic disease found in >70% of patient families [7, 11]. Immutable factors such as cesarean birth and male gender also increase the likelihood of an FPIES diagnosis [5, 11, 37]. Siblings of a patient with FPIES develop FPIES themselves in about 7% of cases [31]. No significant findings of parent to child transmission of FPIES have been reported.

## Natural Course

The age of presentation of FPIES is variable; however, it is usually observed in patients less than 9 months old and at a median of 5.5 months in the US [1, 7, 37]. Regarding liquid foods specifically, the US studies report the onset of FPIES to cow's milk is usually before 6 months of age [4, 36]. However, presentation of symptoms occurring anywhere from a few days of life to 12 months of age has also been reported. Symptom onset typically occurs with the first or second ingestion of the food [4, 36]. The time to resolution of CM FPIES is difficult to predict and appears to vary geographically. Katz et al. followed Israeli infants with CM FPIES and noted a 50% resolution rate by the age of 1, and 88.9% resolution rate by the age of 2 [36]. Contrary to this finding, only 35% of US infants with CM FPIES experienced resolution of symptoms by 2 years of age [6]. In fact, the majority of these patients (85%) did not note a resolution of symptoms until age 5 [6].

Solid food FPIES diagnosis is typically established at median 12 months of age although FPIES usually develops within days and rarely within a few weeks following new solid food introduction into the diet of an infant [6]. Grain FPIES resolves in the fourth year of life with studies demonstrating a median age of resolution of 4 years for oats and 4.7 years for rice [6, 11]. The other solid food triggers, i.e., fish and egg, resolve after a median of 60 months [39]. Some researchers hypothesize that the later onset of symptoms and resolution of solid food FPIES reflect the later introduction of these foods into the diet. However, Ruffner et al. did not demonstrate a significant difference in the resolution of symptoms in children triggered by liquid versus solid foods [6]. There have been no reports of long-term complications in children with FPIES and it is largely a self-limiting, generally benign disorder of infancy and childhood.

### FPIES in Adults

Adult-onset FPIES is a rare phenomenon, first characterized by Fernandes et al. in 2012 in an adult developing a reaction to mollusks [40]. Unlike children, adults have life-long tolerance to their culprit food prior to their initial reaction. Common foods inducing FPIES reactions in adults include crustaceans (shrimp), mollusks, fish, dairy, wheat, and egg (Table 9.3) [41–43]. In the first US report, 8 of 38 (21%) adults with suspected shrimp allergy reported delayed gastrointestinal symptoms consistent with FPIES. The majority were females (7/8) and reported 2–6 prior reactions to shrimp. All of them have tolerated shrimp in the past [44]. Abdominal pain appears to be the predominant symptom found in the majority of adults with FPIES (70–100%), and diarrhea was the least common presenting symptom (50–64%) according to studies [43, 45, 46]. There are no conclusive findings on the natural course and resolutions of symptoms in adults; however, the available literature suggests these symptoms tend to persist throughout the duration of their adult life [45].

## Diagnosis

FPIES is a clinical diagnosis of exclusion and requires a detailed history and careful consideration of the differential diagnosis to be successfully identified (Table 9.4). There are no laboratory findings or imaging tests that establish diagnosis of FPIES with specificity. FPIES is often missed on initial clinician assessment, and the median length of delay to diagnosis is reportedly four to 7 months [11, 47]. Obtaining a thorough history includes eliciting reaction symptoms, the timing of symptoms in relation to food intake, the suspected causative foods, and the attempted interventions [1]. Diagnostic criteria were recently revised according to an international consensus group and are included in Tables 9.5a and 9.5b.

### Oral Food Challenges (OFC)

The gold standard for diagnosing FPIES is the OFC, and this approach is typically utilized if the history is equivocal (e.g., mild symptoms, unusual timing, isolated reaction) and not supportive of the diagnosis alone. OFCs are specifically indicated when chronic FPIES is suspected, and a trial of elimination of foods has not yielded a cause of symptoms. International consensus guidelines recommend refraining from OFCs if there is a history of severe reactions, especially in infants with a compelling history [1].

Proper setting and personnel must be available before an OFC is pursued, and OFCs should be performed under experienced physician supervision. Access to intravenous (IV) hydration should be readily available, considering that up to 50% of patients who undergo diagnostic challenges have severe symptoms requiring IV hydration [13]. It is also suitable per guidelines to opt to obtain IV access prior to the start of the challenge [1, 9].

Protocols for OFC can vary; however, in 2009 the American Academy of Allergy, Asthma, and Immunology work group published a standardized FPIES OFC protocol used commonly in the United States [48]. Per the guidelines, 0.3 g (0.06–0.6 g) per kilogram of body weight of food should be offered to the patient in either a single dose or divided into 3 doses over 30 minutes. Lower doses are typically selected for patients with a history of severe reactions requiring hospitalization. The initial dose should not contain more than 3 grams of food protein or 10 g of total food. Since reactions are delayed, patients should be observed for 4–6 hours after ingestion of the total dose for signs of reaction [48].

If the calculated dose of the challenge food is less than 30% of the age-appropriate serving size, the second feeding with a regular serving size of the food may be considered. In children with atypical FPIES, the OFC protocol is modified to include incremental dosing (to account for immediate symptoms) and 4–6 hours of observation time (to account for FPIES symptoms).

**Table 9.3** Adult FPIES review of presentations in the literature

| | Food(s) | Age at onset/age at evaluation/diagnosis | Number of prior reactions | Reported symptoms | OFC outcome |
|---|---|---|---|---|---|
| Fernandes et al. [40] Case report, UK | Scallop and clams | One male patient diagnosed at 53 years old with FPIES | Two prior episodes | Vomiting and diarrhea 2–4 hours post-ingestion | Vomiting, hematochezia, and hypotension 1.5 hours post-ingestion +neutrophilia |
| Gleich et al. [44] Case series, USA | Shrimp, scallops, crab, lobster, clam, abalone | 8 of 38 patients with shrimp sensitivity presenting with GI symptoms consistent with FPIES Range of age at diagnosis: 23–69 yrs Range of symptom onset: 12–62 yrs | Range of 2 to >100 episodes | Nausea, vomiting, abdominal pain, and diarrhea 1–5 hours post-ingestion | Not done |
| Tan JA et al. [43] Case series, Australia | Crustaceans, mollusks, fish, egg | 31 patients with exclusively GI symptoms on repeat exposure to specific food Median age of diagnosis 47 yrs. (IQR 30.5–57.5) Median age of symptom onset 29 yrs. (IQR 22–45.8) | Median of two prior episodes | Abdominal pain, vomiting, and diarrhea median time to symptom onset 60 min (IQR 52.5–120) | Not done |
| Du YJ et al. [46] Retrospective case series, North America | Shellfish, dairy, wheat, eggs | 20 patients with exclusively GI symptoms on repeat exposure to specific food Median age 38.5 yrs. (range 16–67) | Median of three prior episodes (range 2–7) | Severe abdominal pain, vomiting, diarrhea Median time to symptom onset 3 hours (range 1–11) | Not done |
| Gonzalez-Delgado P et al. [45] Prospective case series, Spain | Crustaceans, fish, mollusks | 25 patients with strictly GI symptoms after eating seafood Median age of onset of symptoms: 28 yrs. (IQR, 20.5–38) | Median of eight prior reactions (IQR 5.5–10) | Abdominal pain, vomiting, diarrhea, hypothermia/ lethargy Range of time to symptom onset (1–4 hours) | OFC performed in eight patients to confirm diagnosis +neutrophilia |

Ultimately, the manner in which a challenge is performed is determined by the clinical judgment of the physician. Food challenges are deemed positive per previously published criteria in Table 9.6 [1]. A CBC should be obtained for research purposes pre- and post-challenge and monitored for increased neutrophils (above 1500 cells/ml), which typically peak at 6 hours after food consumption [1–3, 11].

## Laboratory Testing

Additional clinical tests that are suggestive of FPIES are occasionally utilized to confirm a high suspicion; however, they are not diagnostic and therefore not routinely recommended [1]. In peripheral blood studies of patients with acute FPIES, the neutrophil count is elevated at the onset of the reaction, peaks 6 hours after inges-

**Table 9.4** FPIES differential diagnosis [1]

| Diagnosis | Similarities with FPIES | Differentiating features from FPIES |
|---|---|---|
| *Allergic disorders* | | |
| Food-protein-induced proctocolitis | Stool with blood or mucus, associated with cow's milk formula intake | No failure to thrive, no vomiting, resolution sooner (~1 year of age), patients not sick appearing |
| Food-protein-induced enteropathy | Failure to thrive, intermittent vomiting or diarrhea with ingestion of specific food (e.g., cow's milk, egg, etc.) | Small bowel injury and malabsorption. No lethargy, pallor, or dehydration. No methemoglobinemia or acidemia. Confirm diagnosis with endoscopy and biopsy |
| Anaphylaxis | Vomiting, diarrhea with ingestion of specific food, reproducible | Immediate symptoms with ingestion of food (minutes to 1 hr), positive SPT and food ssIgE, other systemic symptoms (i.e., urticaria, angioedema, etc.) |
| Eosinophilic esophagitis | Triggered by specific food, vomiting, failure to thrive | Vomiting less profuse, non-projectile, early satiety, older children–dysphagia/ food impaction sensation, chronic |
| *Gastrointestinal disorders* | | |
| Celiac disease | Failure to thrive, chronic diarrhea, vomiting, anemia | Celiac serology positive and confirmed with biopsy, malabsorption |
| Gastrointestinal reflux | Intermittent vomiting | No diarrhea, no dehydration, vomiting usually minimal |
| Lactose intolerance | Diarrhea with ingestion of specific food (lactose) | Symptoms with liquid cow's milk / large amounts of cheese or cream/ lactose; bloating, flatulence, low prevalence under 5–6 years of age; frequently positive family history of lactose intolerance |
| Cyclic vomiting | Repetitive recurrent vomiting, lethargy | Not associated with food, stereotypical vomiting typically early in the day, associated with prodrome (can be associated with headache, photophobia) |
| *Anatomical GI obstruction* | | |
| Malrotation/volvulus | Vomiting in an infant, bloody stool (bowel ischemia), dehydration and shock, failure to thrive, distended loops of bowel on X-ray | Bilious vomiting, abdominal distension, sepsis from necrotic bowel, fluid resuscitation alone does not improve symptoms |
| Intussusception | Intermittent, vomiting, bloody diarrhea, lethargy, and pallor | Severe cramping abdominal pain, intermittent, not associated with specific food, abdominal mass on exam, detectable on ultrasound |
| Hirschsprung's disease | Vomiting, failure to thrive in infant/young child | Abdominal distension, constipation, delayed passage of meconium, bilious emesis |
| Pyloric stenosis | Recurrent projectile vomiting leading to dehydration | No diarrhea, diagnosis with ultrasound |
| Necrotizing enterocolitis | Lethargy, vomiting, bloody diarrhea, neutrophilia | Higher risk in premature low birth weight infants, formula-fed infants; requires parental nutrition, IV antibiotics, pneumatosis intestinalis on X-ray |
| Very early onset inflammatory bowel disease | Failure to thrive, diarrhea, blood or mucus in stool, vomiting | Symptoms are not often linked to specific food; family history may be positive for IBD |
| *Infections* | | |
| Sepsis | Sudden lethargy, vomiting, hypotension, hypothermia, neutrophilia | Fever present, treatment with fluid resuscitation alone does not improve |

**Table 9.4** (continued)

| Diagnosis | Similarities with FPIES | Differentiating features from FPIES |
|---|---|---|
| Acute viral gastroenteritis | Vomiting, watery diarrhea | Fever present, slower course over days, no specific food trigger |
| Bacterial gastroenteritis (*Shigella*, *Salmonella*, *Campylobacter*, *E.coli*) | Vomiting, abdominal pain | Watery or bloody diarrhea, fever, positive stool culture, responds to antibiotics |
| Inborn errors of metabolism: galactosemia, fructose intolerance, methylmalonic acidemia, ornithine transcarbamylase deficiency | Intermittent vomiting/lethargy | Inability to process sugars, amino acids, and organic acids; many patients may self- avoid food that cannot be metabolized (avoidance of fruit in fructose intolerance and dairy in galactosemia) |
| Inadequate energy production Mitochondrial, fatty acid oxidation disorders, glycogen storage disorder | Intermittent vomiting/lethargy | Failure to thrive, heart and muscle involvement, splenomegaly, hypoglycemia No diarrhea or food avoidance |
| *Disorders of complex molecules* | | |
| Lysosomal storage disorders Congenital disorder of glycosylation | Poor growth, feeding swallowing difficulties Vomiting, diarrhea | Hepatosplenomagaly, developmental delay, short stature, chronic pain Low tone, seizures, dysmorphic features |
| Congenital methemoglobinemia (type I) | Methemoglobinemia | Mostly asymptomatic, no vomiting or diarrhea, general fatigue, dyspnea |
| Primary immunodeficiency | Chronic diarrhea (due to frequent or persistent GI infections, e.g., enterovirus) | Not specific to food, abnormality in lymphocyte counts, immunoglobulins, etc. |
| Immune enteropathy | Chronic diarrhea | Diarrhea frequently with blood or mucus, severe diarrhea with no food association, rare in infants and toddlers |
| Mast cell activation syndrome | Chronic/intermittent watery diarrhea | Symptoms from other organ systems, e.g., skin, respiratory, cardiovascular, not specific to food; elevated serum tryptase and or urinary histamine metabolites or PGD2 or 11-b-PGF2-alpha during at least two acute episodes |

Adapted from Nowak-Wegrzyn et al. [1], with permission from Elsevier

tion, and is back to baseline within 18–24 hours [1, 3]. Hypereosinophilia and elevated platelets are also characteristic of FPIES along with methemoglobinema and metabolic acidosis [49]. Occult blood, mucus, carbohydrates, and leucocytes are noted in stool studies of acute FPIES patients [3]. Interestingly, neutrophilia in cerebral spinal fluid has also been demonstrated in acute FPIES; however, lumbar puncture is not a common practice used to diagnose FPIES [7].

Chronic FPIES shares similarities with acute FPIES in also demonstrating metabolic acidosis, methemoglobinemia, eosinophilia, and leukocytosis in serum studies. Hypoalbuminemia and anemia are characteristic features of chronic FPIES presentations that distinguish itself from acute FPIES [50]. Similarly, stool studies also demonstrate red blood cells and neutrophils and are differentiated from acute FPIES stool samples by the presence of reducing substances and Charcot-Leyden crystals [50].

## Gastric Aspirate Testing

Considering the time and costs needed to perform food challenges, non-conventional study methods have been explored to facilitate the diagnosis of FPIES and have resulted in varying levels of success. In 2008 Hwang et al., performed gastric aspirations in patients suspected of FPIES and discovered that patients with >10 leukocytes /hpf in their aspirate were much more likely to have food challenge confirmed FPIES [51]. There

**Table 9.5a** Acute FPIES diagnostic criteria [1]

| Acute FPIES | |
|---|---|
| Major criterion | Minor criteria |
| Vomiting 1–4 hours after ingestion without IgE-mediated allergic skin or respiratory symptoms | Two or more episodes of repetitive vomiting after ingesting the same trigger food<br>Repetitive vomiting episode 1–4 h after ingesting a different food<br>Significant lethargy with a suspected reaction<br>Significant pallor with a suspected reaction<br>Necessary visit to the emergency room with a suspected reaction<br>Diarrhea within 24 hours of onset of symptoms (typically 5–10 hours)<br>Hypothermia<br>Hypotension |
| A positive diagnosis must meet the major criterion and ≥ 3 minor criteria. A positive FPIES OFC confirms the diagnosis, particularly if only one FPIES episode has occurred. | |

Adapted from Nowak-Wegrzyn et al. [1], with permission from Elsevier

**Table 9.5b** Chronic FPIES diagnostic criteria [1]

| Chronic FPIES | |
|---|---|
| *Major criterion*:<br>Resolution of the symptoms within days after elimination of the trigger food and occurrence of acute FPIES reaction when food is reintroduced (vomiting 1–4 hours after ingestion and diarrhea within 24 h).<br>Diagnosis only confirmed with positive OFC. | |
| *Mild presentation*: low or infrequent doses of the suspected food induce the following:<br>Intermittent vomiting and/or diarrhea<br>Poor weight gain/failure to thrive<br>No dehydration or metabolic acidosis | *Severe presentation*: regular ingestion of suspected food induces the following:<br>Intermittent, worsening vomiting and/or diarrhea (can be bloody)<br>Dehydration and metabolic acidosis |

Adapted from Nowak-Wegrzyn et al. [1], with permission from Elsevier

**Table 9.6** Diagnostic criteria for positive FPIES oral food challenge [1]

| |
|---|
| *Major criterion*<br>Vomiting 1–4 hours after ingestion of culprit food without IgE-mediated allergic skin or respiratory symptoms |
| *Minor criteria*<br>Lethargy<br>Pallor<br>Diarrhea 5–10 hours after food ingestion<br>Hypotension<br>Hypothermia<br>Increased neutrophil count >1500 neutrophils above baseline |
| Diagnostic of FPIES requires 1 major and ≥ 2 minor criteria. Limitations include use of ondansetron, which can hinder the development of minor criteria such as pallor, lethargy, and repetitive vomiting. Obtaining a neutrophil account also may not be possible within the necessary timeframe. In these two situations, a challenge may be considered positive from the major criterion alone. |

Adapted from Nowak-Wegrzyn et al. [1], with permission from Elsevier

were no patients with negative FPIES challenges that produced >10 leukocytes /hpf [51]. While informative, the invasive nature of the study limits its practical use in clinical settings with pediatric patients.

## Allergy Testing

Clinical studies effective in other allergic disorders have not been successfully used to diagnose FPIES patients. Skin prick tests (SPT) are categorically used to identify IgE-mediated allergy and are typically negative in patients with FPIES [11]. Similarly patients with acute and chronic FPIES have undetectable ssIgE levels to their trigger food except in the rare cases of atypical FPIES. Therefore, SPT and ssIgE are not recommended in diagnosis [1]. Food ssIgE can be useful in follow-up of patients with FPIES diagnosis to identify atypical individuals at risk for a protracted course as discussed previously [11]. It is also useful in potentially predicting a future IgE-mediated allergy as in CM FPIES patients who are at increased risk of conversion to IgE-mediated food allergic symptoms with exposure to CM [1].

Atopy patch skin testing (APT) testing is also not recommended for identifying FPIES trigger per guidelines [1]. APT demonstrated only 12% sensitivity, 40% positive predictive value, and 55% negative predictive value when attempting to identify milk, soy, oat, and rice sensitization in patients with FPIES reactions to these foods [52]. More recent APT studies further corroborate these findings [6, 25, 53].

Imaging studies are also not recommended in the diagnosis of FPIES on the basis of non-specific clinical findings [1]. Classic findings from past studies include air fluid levels in the bowel, a ribbon like ileum, and thickened and inflamed plicae circularis in X-rays and barium studies of the small bowel. The large bowel has demonstrated evidence of narrowing and intermittent spasms in plain film imaging [27]. Additional techniques such as endoscopy range in findings from normal mucosa to friability and ulceration along the gut to the rectum [27, 54]. These notable findings are unfortunately not helpful in discriminating FPIES from other gastrointestinal pathologies.

## Management

The most important aspect of management in patients with acute or chronic FPIES is avoidance of trigger foods. Parents and families must be educated on reading labels and avoiding accidental ingestions at home and in public spaces such as school, restaurants, etc. Food avoidance management also includes providing alternative nutrition sources for patients who significantly rely on the culprit food for nourishment. Infants with FPIES to CM are recommended to avoid CM-based formula for the first year of life. Thirty to sixty-five percent of patients with CM FPIES are also reactive to soy-based formula in the United States [6, 7]. Thus, soy introduction is usually delayed until after 1 year of age as well [1, 11]. Instead, extensively hydrolyzed casein formula is initially recommended for the first year of life in the United States until an OFC can be performed. If hydrolyzed formula is not tolerated, an amino acid–based formula may be needed in up to 20% of cases [1, 11].

The simultaneous presence of CM and soy FPIES is much lower internationally as in Australia and Israel [5, 37, 39]. Soy is recommended as an acceptable substitute for CM in FPIES if an OFC has ruled out soy reactivity and vice versa for soy FPIES [1]. Sheep and goats milk are not acceptable animal milk substitutes due to their high protein homology with CM [1, 55]. Camel and donkey milk are available in select geographical areas and have decreased homology and likelihood of cross-reactivity with CM. Therefore, they can also be used for animal milk in patients with CM FPIES when readily available and preferably under the guidance of a nutritionist [1, 56–58].

Exclusive breastfeeding can be continued in patients with FPIES. Mothers can maintain an unrestricted diet while breastfeeding unless there is a history of FPIES reaction in the infant after maternal ingestion of the culprit food. Maternal transmission of the culprit food through breastmilk is a rare phenomenon in the United States; however, cases have been documented more frequently in Japan and Australia [31, 32]. In these cases, or if the infant fails to thrive, the suspected food should be excluded from the maternal diet. Hydrolyzed and/or amino acid–based formulas are indicated if the maternal elimination diet does not yield a resolution of symptoms in the infant with FPIES [1].

Variability exists in the volume of trigger foods that can be tolerated in FPIES patients before reaction, which is similarly observed in patients who exhibit IgE-mediated food allergy [37]. Conventionally, patients do not avoid foods with precautionary allergen labeling warning of "trace amounts" of the allergenic food, unless there has been a history of severe reactions to minute amounts [1].

## New Food Introduction

The FPIES diagnosis creates a lot of concern and anxiety regarding food introduction in both families and clinicians alike. Guidance for families in terms of introduction of new foods and re-introduction of the allergenic food(s) is warranted.

Our goals as clinicians are to support nutritional diversity while minimizing the risks of FPIES reactions as much as possible. Thus, recommendations permit introduction of solid foods at home when developmentally appropriate and not to delay introduction beyond 6 months of age [1, 59]. Infants with CM- or soy FPIES are at higher risk for FPIES to solid foods, especially oat and rice [1, 6, 11]. Therefore, lower risk foods that are recommended in the initial solids introductory phases include fruits and vegetables, meats, and lastly grains (Table 9.7).

Food is introduced in a gradual manner with slowly increasing doses over several days until an appropriate serving size per age is reached. Once the food is tolerated it should be continued in the diet at regular intervals (per experience). A food tolerated from one food group (i.e., chicken from poultry) increases the likelihood that all foods will be tolerated within that group [1, 13]. Prior history of severe reactions may lead the clinician to challenge new foods in the clinic setting before home introduction.

## Reintroduction of the Food That Caused FPIES in the Past

Reintroduction of foods that have caused FPIES reactions should be performed with supervised OFCs [1]. The best timing of reintroduction has not firmly been established by studies. In the United States and Europe, challenges are usually performed 12–18 months after the child's last

**Table 9.7** Guidelines for introduction of foods [1]

| Ages of introduction | Low-risk foods | Moderate-risk foods | High-risk foods |
|---|---|---|---|
| *4–6 months* | *Vegetables* | | |
| If developmentally appropriate should start with:<br>Smooth, thin purees and progress to thicker textures<br>Select foods with high iron levels | Broccoli, cauliflower, parsnip, turnip, pumpkin | Carrot, squash, green bean, white potato | Sweet potato, green pea |
| *6 months* | *Fruits* | | |
| Complementary feeding should begin <6 months:<br>Expand diversity of fruits, vegetables, legumes, grains, meats, as tolerated<br>In BF infants, add high iron foods or supplement iron (1 mg/kg/d) by 6 months | Berries (strawberry, blueberries), peach, plum, avocado, watermelon | Pear, apple, oranges | Banana |
| *8 months or if developmentally appropriate* | *High-iron foods* | | |
| Introduce soft-cooked and easily dissolved texture foods | Lamb, fortified quinoa, cereal, millet | Fortified grits and corn cereal, beef, whole wheat and fortified wheat, fortified barley cereal | Fortified infant rice, oat cereal, other higher-iron-fortified foods |
| *12 months or if developmentally appropriate* | *Other* | | |
| Offer table foods modified for developmental appropriateness: chopped meats, soft cooked vegetables, grains, and fruits | Tree nut and seed butters (sesame, sunflower, almond)<br>Prepare by thinning with water or infant puree to reduce choking risk | Peanut, other legumes | Milk, soy, poultry, egg, fish |
| Exclusive breast feeding until 4–6 months is recommended per the AAP.<br>There is increased likelihood of tolerating multiple foods within the same group after one food is tolerated.<br>Additionally, when more foods are tolerated overall, a more liberal approach can be taken. | | | |

Adapted from Nowak-Wegrzyn et al. [1], with permission from Elsevier

reaction [13, 60]. Alternatively, Korean infants diagnosed with CM- or soy FPIES at a median of 36 days demonstrated tolerance to CM and soy, respectively, at 6 months of age (27% and 75%), 8 months of age (42% and 91%), and 10 months of age (66% and 92%) [61]. This study supports an earlier attempt at OFC (within 1 year of age) for liquid food reintroduction and highlights the importance of additional large cohort studies examining the natural course of early tolerance of foods. Similar to new food introduction, when the OFC is passed the food should be added gradually at home and remain in the diet [62].

Unlike IgE-mediated CM or egg allergy, the introduction of extensively heated food products in patients with FPIES is not a widely performed practice. In 2013, a small study of seven subjects with CM or egg FPIES demonstrated tolerance to baked egg and baked milk in some patients during OFCs [14]. However, larger, more conclusive studies must be performed to provide evidence on the safety of OFCs and home introduction to extensively heated CM or egg in FPIES patients. For now, the recommendation is to avoid baked egg or milk products in patients, unless the patient is already tolerating it in the diet. If baked product introduction is considered, for example, due to poor growth and nutrition in the child, the initial ingestion should be performed under the supervision of a physician [1]. The risks and benefits of such a challenge should be discussed between the clinician and family.

Adults do not have guidelines on food reintroduction given the lack of studies addressing the resolution of FPIES in this population. Current recommendations are to attempt OFCs at various intervals to reassess if FPIES has resolved [63]. Further studies evaluating the natural history of FPIES in older children and adults are needed.

Finally, a multidisciplinary approach appears to work well in optimizing nutrition and management of patients with FPIES. Aside from the physician, the dietician's input is key to educating families on nutritional requirements and alternate options of food available during the time of avoidance [1]. Guidelines recommend varying the preparations of the foods tolerated (i.e. pureed vs baked, vs raw fruits) to diversify early encounters with food. Dieticians work with families to help ensure this occurs.

Introduction of new and solid foods at an appropriate time of development is essential for the child's oral motor skills and willingness to try different foods. When eating is hindered by familial anxiety or multifood reactivity, the child can develop aversion to food textures and flavors or oral motor dysfunction, disrupting the mechanical actions of eating. Feeding and speech language therapy should be utilized if solid introduction proves to be difficult due to these reasons [1]. Caregivers of infants with FPIES may need and benefit from the support of the lay patient organization, e.g., International FPIES Association, fpies.org, etc.

## Management of Acute Reactions

In an acute reaction, the initial course of action is to cease eating the food causing the reaction. Typically, an acute reaction will resolve within 4–12 hours after discontinuing the food whereas chronic FPIES reactions resolve about 3–10 days later [2, 3]. Sequels of FPIES reactions includes mild to severe dehydration. In mild to moderate cases of dehydration, oral rehydration with breast milk or clear fluids can be administered at home with close observation [37]. When dehydration is severe, hemodynamic instability and even shock can ensue, requiring aggressive rehydration and supportive care. Patients should receive intravenous boluses (10–20 ml/kg of normal saline) and dextrose maintenance fluids, and in certain severe cases, bowel rest [1–3].

Ondansetron has been used in an attempt to reduce vomiting in acute FPIES reactions; however, there are no blinded randomized control trials to evaluate its effectiveness. Evidence for the use of ondansetron is noted in a small case study of young children with positive FPIES OFC whose symptoms ceased after receiving intravenous or intramuscular ondansetron within 15 minutes of reacting [28, 29]. A larger retrospective case control study evaluated ondasentron in an acute FPIES reactions and reported a 0.2 relative risk reduction in the onset of vomit-

ing [29]. Almost 20% of patients did not respond to ondansetron; however, those who did respond were less likely to be hospitalized [29].

Given reports of some improvement noted in studies, the guidelines suggest in infants over 6 months of age, an IM or IV ondansetron dose of 0.15 mg/kg (max dose of 16 mg) may be attempted to reduce the severity of an FPIES reaction in a challenge [1]. In our experience, clinicians should not rely on ondansetron in patients with a severe reaction history and should remain prepared to administer appropriate supportive care. At home, oral ondansetron can be administered for accidental ingestions; however, it is imperative that patients are instructed to still seek medical advice [64].

Intravenous corticosteroids are thought to reduce gut inflammation during an acute reaction. Methylprednisolone (1 mg/kg with maximum dose of 60–80 mg) is administered as a single dose at the hospital when severe symptoms initiate [1]. If reaction severity persists despite the aforementioned interventions, transfer to the intensive care unit (ICU) is appropriate particularly when protracted dehydration is unresponsive to boluses and vasopressors are required. The ICU can also provide supplemental oxygen and if needed positive pressure support via mechanical ventilation. Metabolic acidemia or methemoglobinemia may require bicarbonate supplementation or methylene blue, respectively.

Arguably, the most important instruction clinicians can offer families is how to recognize symptoms early and quickly perform the necessary steps of initial management during an acute reaction. All FPIES-diagnosed patients should have an emergency action plan readily available and an allergist written letter informing other emergency health care providers of the diagnosis and best medical management in the event of a reaction [1, 9]. Parents should be advised to take their child for medical evaluation if he/she develops repetitive (>3) episodes of projectile vomiting, lethargy, unresponsiveness, and/or pallor [9]. Epinephrine and antihistamines are not useful in the midst of classic FPIES reactions [1, 9]. However, they are prescribed to patients in case of other IgE-mediated food allergic reactions or as a precaution in patients with atypical FPIES.

## Conclusions

Once a rare disease with limited investigation into its features, our knowledge of FPIES has grown tremendously over the last 2–3 decades. We understand the clinical presentation, established diagnostic criteria, well-characterized food triggers, and have a general understanding of its natural course in children. Advancements in diagnosis with OFC protocols, acute treatment options, and food reintroduction have culminated in publication of the first consensus guidelines on the diagnosis and management of FPIES in 2017. There is increased awareness of the disorder among the greater pediatric clinical community, which improves the morbidity and quality of life for patients.

There are still several deficits in our knowledge that require additional investigation. The pathologic mechanism of this disorder and genetic and/or environmental influences remain largely unknown. Geographic discrepancies in prevalence and natural course also persist without much understanding of the reasoning. Future studies will likely prioritize clinical management and food introduction such as examining the tolerance of baked allergen products and developing diagnostic testing/biomarkers to confirm diagnosis and/or indicate the resolution of symptoms and safe reintroduction of foods.

## References

1. Nowak-Wegrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2017;139(4):1111–26.e4.
2. Powell GK. Enterocolitis in low-birth-weight infants associated with milk and soy protein intolerance. J Pediatr. 1976;88(5):840–4.

3. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. J Pediatr. 1978;93(4):553–60.
4. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. J Pediatr. 1998;133(2):214–9.
5. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. Pediatrics. 2009;123(3):e459–64.
6. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. J Allergy Clin Immunol Pract. 2013;1(4):343–9.
7. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. Pediatrics. 2003;111(4 Pt 1):829–35.
8. Weinberger T, Feuille E, Thompson C, Nowak-Wegrzyn A. Chronic food protein-induced enterocolitis syndrome: characterization of clinical phenotype and literature review. Ann Allergy Asthma Immunol. 2016;117(3):227–33.
9. Nowak-Wegrzyn A, Jarocka-Cyrta E, Moschione Castro A. Food protein-induced enterocolitis syndrome. J Investig Allergol Clin Immunol. 2017;27(1):1–18.
10. Feuille E, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome, allergic proctocolitis, and enteropathy. Curr Allergy Asthma Rep. 2015;15(8):50.
11. Caubet JC, Ford LS, Sickles L, Jarvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol. 2014;134(2):382–9.
12. Nomura I, Morita H, Ohya Y, Saito H, Matsumoto K. Non-IgE-mediated gastrointestinal food allergies: distinct differences in clinical phenotype between Western countries and Japan. Curr Allergy Asthma Rep. 2012;12(4):297–303.
13. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J Allergy Clin Immunol. 2005;115(1):149–56.
14. Miceli Sopo S, Buonsenso D, Monaco S, Crocco S, Longo G, Calvani M. Food protein-induced enterocolitis syndrome (FPIES) and well cooked foods: a working hypothesis. Allergol Immunopathol (Madr). 2013;41(5):346–8.
15. Banzato C, Piacentini GL, Comberiati P, Mazzei F, Boner AL, Peroni DG. Unusual shift from IgE-mediated milk allergy to food protein-induced enterocolitis syndrome. Eur Ann Allergy Clin Immunol. 2013;45(6):209–11.
16. Kessel A, Dalal I. The pendulum between food protein-induced enterocolitis syndrome and IgE-mediated milk allergy. Acta Paediatr. 2011;100(10):e183–5.
17. Onesimo R, Dello Iacono I, Giorgio V, Limongelli MG, Miceli Sopo S. Can food protein induced enterocolitis syndrome shift to immediate gastrointestinal hypersensitivity? A report of two cases. Eur Ann Allergy Clin Immunol. 2011;43(2):61–3.
18. Duffey H, Egan M. Development of food protein-induced enterocolitis syndrome (FPIES) to egg following immunoglobulin E (IgE)-mediated egg allergy. Ann Allergy Asthma Immunol. 2018 Sep;121(3):379–80. https://doi.org/10.1016/j.anai.2018.05.028.
19. Caubet JC, Nowak-Wegrzyn A. Current understanding of the immune mechanisms of food protein-induced enterocolitis syndrome. Expert Rev Clin Immunol. 2011;7(3):317–27.
20. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor beta1, transforming growth factor type I and II receptors, and TNF-alpha in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol. 2002;109(1):150–4.
21. Morita H, Nomura I, Orihara K, Yoshida K, Akasawa A, Tachimoto H, et al. Antigen-specific T-cell responses in patients with non-IgE-mediated gastrointestinal food allergy are predominantly skewed to T(H)2. J Allergy Clin Immunol. 2013;131(2):590–2 e1-6.
22. Caubet JC, Bencharitiwong R, Ross A, Sampson HA, Berin MC, Nowak-Wegrzyn A. Humoral and cellular responses to casein in patients with food protein-induced enterocolitis to cow's milk. J Allergy Clin Immunol. 2017 Feb;139(2):572–83. https://doi.org/10.1016/j.jaci.2016.02.047.
23. Goswami R, Blazquez AB, Kosoy R, Rahman A, Nowak-Wegrzyn A, Berin MC. Systemic innate immune activation in food protein-induced enterocolitis syndrome (FPIES). J Allergy Clin Immunol. 2017 Jun;139(6):1885–1896.e9. https://doi.org/10.1016/j.jaci.2016.12.971.
24. Bencharitiwong R, Giavi S, Vereda A, Ibanez MD, Jarvinen KM, Papadopoulos NG, et al. Heating does not decrease immunogenicity of goat's and ewe's milk. J Allergy Clin Immunol Pract. 2013;1(4):418–21.
25. Gonzalez-Delgado P, Caparros E, Moreno MV, Clemente F, Flores E, Velasquez L, et al. Clinical and immunological characteristics of a pediatric population with food protein-induced enterocolitis syndrome (FPIES) to fish. Pediatr Allergy Immunol. 2016;27(3):269–75.
26. Shimomura MIY, Tanaka H, Meguro T, Kimura M. Increased serum cortisol on oral food challenge in infants with food protein-induced enterocolitis syndrome. Pediatr Int. 2017;60(1):13–8.
27. Richards DG, Somers S, Issenman RM, Stevenson GW. Cow's milk protein/soy protein allergy: gastrointestinal imaging. Radiology. 1988;167(3):721–3.
28. Holbrook T, Keet CA, Frischmeyer-Guerrerio PA, Wood RA. Use of ondansetron for food protein-induced enterocolitis syndrome. J Allergy Clin Immunol. 2013;132(5):1219–20.
29. Miceli Sopo S, Battista A, Greco M, Monaco S. Ondansetron for food protein-induced enterocolitis syndrome. Int Arch Allergy Immunol. 2014;164(2):137–9.

30. Monti G, Castagno E, Liguori SA, Lupica MM, Tarasco V, Viola S, et al. Food protein-induced enterocolitis syndrome by cow's milk proteins passed through breast milk. J Allergy Clin Immunol. 2011;127(3):679–80.
31. Mehr S, Frith K, Barnes EH, Campbell DE, Group FS. Food protein-induced enterocolitis syndrome in Australia: a population-based study, 2012–2014. J Allergy Clin Immunol. 2017;140(5):1323–30.
32. Nomura I, Morita H, Hosokawa S, Hoshina H, Fukuie T, Watanabe M, et al. Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms. J Allergy Clin Immunol. 2011;127(3):685-8.e1-8.
33. Miceli Sopo S, Dello Iacono I, Greco M, Monti G. Clinical management of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2014;14(3):240–5.
34. Miceli Sopo S, Monaco S, Badina L, Barni S, Longo G, Novembre E, et al. Food protein-induced enterocolitis syndrome caused by fish and/or shellfish in Italy. Pediatr Allergy Immunol. 2015;26(8):731–6.
35. Vila L, Garcia V, Rial MJ, Novoa E, Cacharron T. Fish is a major trigger of solid food protein-induced enterocolitis syndrome in Spanish children. J Allergy Clin Immunol Pract. 2015;3(4):621–3.
36. Katz Y, Goldberg MR. Natural history of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2014;14(3):229–39.
37. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. J Allergy Clin Immunol. 2011;127(3):647-53.e1-3.
38. Alonso SB, Ezquiaga JG, Berzal PT, Tardon SD, San Jose MM, Lopez PA, et al. Food protein-induced enterocolitis syndrome: increased prevalence of this great unknown-results of the PREVALE study. J Allergy Clin Immunol. 2019;143(1):430–3.
39. Sopo SM, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. Clin Exp Allergy. 2012;42(8):1257–65.
40. Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. J Allergy Clin Immunol. 2012;130(5):1199–200.
41. Gleich GJ, Sebastian K, Firszt R, Wagner LA. Shrimp allergy: gastrointestinal symptoms commonly occur in the absence of IgE sensitization. J Allergy Clin Immunol Pract. 2016 Mar-Apr;4(2):316–8. https://doi.org/10.1016/j.jaip.2015.09.020.
42. Du YJ, Nowak-Wegrzyn A, Vadas P. FPIES in adults. Ann Allergy Asthma Immunol. 2018 Dec;121(6):736–8. https://doi.org/10.1016/j.anai.2018.08.003.
43. Tan JA, Smith WB. Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults. J Allergy Clin Immunol Pract. 2014;2(3):355–7.e1.
44. Gleich GJ, Sebastian K, Firszt R, Wagner LA. Shrimp allergy: gastrointestinal symptoms commonly occur in the absence of IgE sensitization. J Allergy Clin Immunol Pract. 2016;4(2):316–8.
45. Gonzalez-Delgado P, Caparros E, Moreno MV, Cueva B, Fernandez J. Food protein-induced enterocolitis-like syndrome in a population of adolescents and adults caused by seafood. J Allergy Clin Immunol Pract. 2019 Feb;7(2):670–2. https://doi.org/10.1016/j.jaip.2018.07.028.
46. Du YJ, Nowak-Wegrzyn A, Vadas P. FPIES in adults. Ann Allergy Asthma Immunol. 2018;121(6):736–8.
47. Ludman S, Harmon M, Whiting D, du Toit G. Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom. Ann Allergy Asthma Immunol. 2014;113(3):290–4.
48. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, et al. Work Group report: oral food challenge testing. J Allergy Clin Immunol. 2009;123(6 Suppl):S365–83.
49. Murray KF, Christie DL. Dietary protein intolerance in infants with transient methemoglobinemia and diarrhea. J Pediatr. 1993;122(1):90–2.
50. Hwang JB, Park MH, Kang YN, Kim SP, Suh SI, Kam S. Advanced criteria for clinicopathological diagnosis of food protein-induced proctocolitis. J Korean Med Sci. 2007;22(2):213–7.
51. Hwang JB, Song JY, Kang YN, Kim SP, Suh SI, Kam S, et al. The significance of gastric juice analysis for a positive challenge by a standard oral challenge test in typical cow's milk protein-induced enterocolitis. J Korean Med Sci. 2008;23(2):251–5.
52. Jarvinen KM, Caubet JC, Sickles L, Ford LS, Sampson HA, Nowak-Wegrzyn A. Poor utility of atopy patch test in predicting tolerance development in food protein-induced enterocolitis syndrome. Ann Allergy Asthma Immunol. 2012;109(3):221–2.
53. Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol. 2006;17(5):351–5.
54. Gryboski JD. Gastrointestinal milk allergy in infants. Pediatrics. 1967;40(3):354–62.
55. Sopo SM, Iacono ID, Greco M, Monti G. Clinical management of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2014 Jun;14(3):240–5.
56. Businco L, Giampietro PG, Lucenti P, Lucaroni F, Pini C, Di Felice G, et al. Allergenicity of mare's milk in children with cow's milk allergy. J Allergy Clin Immunol. 2000;105(5):1031–4.
57. Bellioni-Businco B, Paganelli R, Lucenti P, Giampietro PG, Perborn H, Businco L. Allergenicity of goat's milk in children with cow's milk allergy 1. J Allergy Clin Immunol. 1999;103(6):1191–4.
58. Jarvinen KM, Chatchatee P. Mammalian milk allergy: clinical suspicion, cross-reactivities and diagnosis. Curr Opin Allergy Clin Immunol. 2009;9(3):251–8.

59. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol Pract. 2013;1(1):29–36.
60. Jarvinen KM, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome (FPIES): current management strategies and review of the literature. J Allergy Clin Immunol Pract. 2013;1(4):317–22.
61. Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. Arch Dis Child. 2009;94(6):425–8.
62. Groetch M, Nowak-Wegrzyn A. Practical approach to nutrition and dietary intervention in pediatric food allergy. Pediatr Allergy Immunol. 2013;24(3):212–21.
63. Michelet M, Schluckebier D, Petit LM, Caubet JC. Food protein-induced enterocolitis syndrome: a review of the literature with focus on clinical management. J Asthma Allergy. 2017;10:197–207.
64. Leonard SA, Nowak-Wegrzyn A. Food Protein-Induced Enterocolitis Syndrome. Pediatr Clin North Am. 2015;62(6):1463–77.

# Part III

# Development of Food Allergies and Current Prevention Recommendations

# Potential Factors Related to Food Allergy Development

10

Victoria X. Soriano, Anne-Louise Ponsonby, and Katrina J. Allen

## Introduction

An increasing number of studies have been investigating rising trends in food allergy and its associated factors. Food allergies, defined as an adverse reaction that occurs reproducibly on exposure to a specific food [1], can be either IgE mediated or non-IgE mediated – here we focus on the former. Food allergy prevalence appears to be on the rise, concerning both the medical community and the general population. Food allergy cases now account for an overwhelming number of allergy clinic appointments, which costs more than $24 billion dollars in the United States [2] and reduces quality of life. There is increasing evidence showing a rapid increase in developed countries, and prevalence rates also seem to be increasing in developed countries as they adopt more Westernized lifestyles [3]. Current hypotheses attempt to explain how environmental factors may be involved in this differential rise in prevalence across this socioeconomic divide. One theory postulates that widespread urbanization and industrialization in the developed world underpin this rapid increase. Other rapidly changing ecological factors of the modern lifestyle that may explain the rise in food allergy include lower microbial exposure, increased hygiene, and reduced sun exposure.

Multiple genetic and environmental factors have been shown to be associated with food allergy. Evolutionary changes in our genome would take several generations to manifest and thus are unlikely to explain a phenomenon that has occurred so rapidly. Nevertheless, allergies run in families suggesting some genes are more likely to predispose to food allergy in the context of the emerging food allergy epidemic. Migration provides an interesting natural history experiment to provide some insights into genetic predisposition and changing environments and may help explain the rise of food allergy.

## How Common Is Food Allergy?

Food allergy prevalence varies by geographic location, age, ethnicity, and dietary history, as do triggers for food allergy and anaphylaxis (the most

V. X. Soriano
Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia

Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia
e-mail: victoria.soriano@mcri.edu.au

A.-L. Ponsonby
Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia

School of Population & Global Health, University of Melbourne, Melbourne, VIC, Australia
e-mail: annelouise.ponsonby@florey.edu.au

K. J. Allen (✉)
Murdoch Children's Research Institute, Melbourne, VIC, Australia

Federal Member of the Australian Parliament, Canberra, Australia


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_10

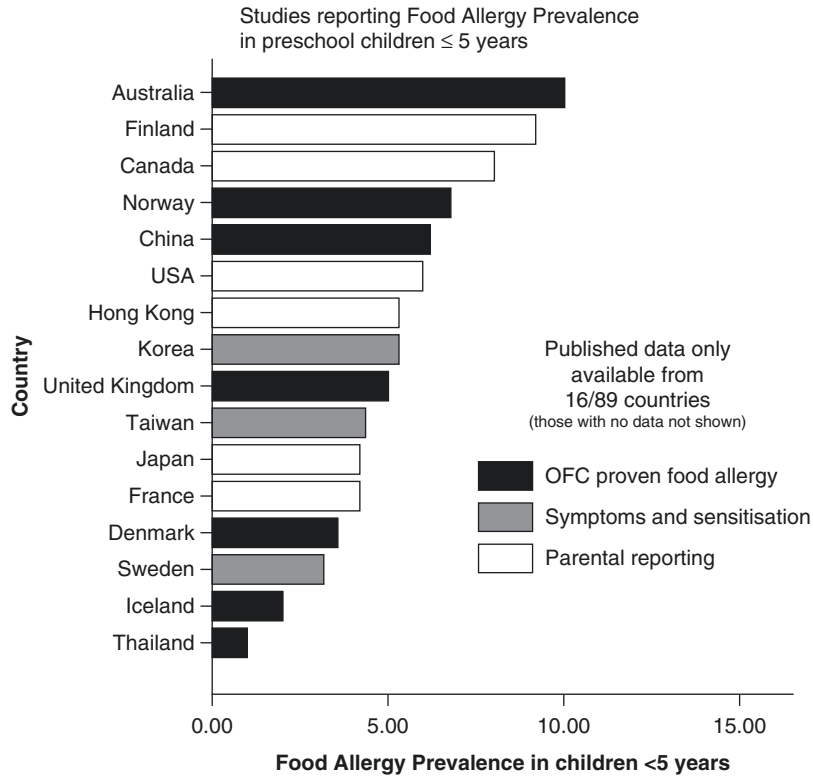



**Fig. 10.1** Summary of food allergy prevalence for children under 5 years of age. Studies were categorized by OFC-proven food allergy (black bars), based on symptoms and sensitization (grey bars) or questionnaires/parental reporting (white bars) [3]. (Reprinted and adapted from Prescott et al. [3])

serious expression of the condition). High-quality population data are sparse because large studies are expensive to undertake. The gold standard for the diagnosis of IgE-mediated food allergy is the Oral Food Challenge (OFC) , although an acceptable surrogate is "doctor-diagnosed food allergy" – especially if the history includes objective acute allergic signs or symptoms of reaction paired with evidence of IgE antibody production through skin prick test or blood test. This includes estimates for incidence of anaphylaxis (an allergic reaction that can be life threatening) since even the definition for this event varies widely internationally. Another common measure of food allergy prevalence is parent or patient reported, usually through questionnaires.

## Prevalence

High levels of heterogeneity in studies included in systematic reviews result in difficulty drawing conclusions on the overall prevalence of food allergy worldwide. Nevertheless, a 2012 World Allergy Organization survey of 89 countries was completed by pediatric allergists [3]. Challenge-proven food allergy prevalence in children under 5 years of age ranged from 1% in Thailand to 10% in Australia (Fig. 10.1), although the prevalence in children over 5 years of age is lower [3].

In 2010, the NIAID/NIH published guidelines which reported on food allergy prevalence based on a range of systematic reviews and meta-analyses where self-reported prevalence was between 12% in children and 13% in adults, but only 3% when confirmed by sensitization or by double-blind, placebo-controlled OFC [4]. A population-based study estimated that food allergy impacts 7.6% of children in the United States [5]. HealthNuts, a population-based study conducted in Melbourne, Australia, between 2007 and 2010, demonstrated that the prevalence of challenge-proven peanut and egg allergy was 3.0% and 8.9%, respectively, with an overall prevalence of 10% for all foods tested [6].

Notable reviews published more recently include systematic reviews of fish, seafood [7], and

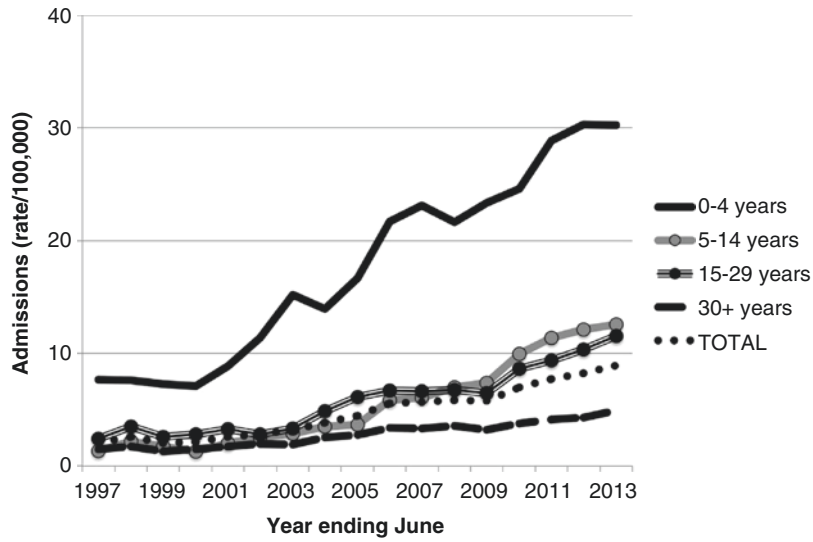



**Fig. 10.2** Food anaphylaxis admission rates from 1997 to 2013 by age group in Australia. Calculated according to Australian National Hospital Morbidity Database data and population estimates derived from the Australian Bureau of Statistics [10]. (Reprinted from Mullins et al. [10], with permission from John Wiley and Sons)

tree nut allergy [8]. Fish allergy prevalence ranged from 0% to 0.3%, seafood allergy ranged from 0% to 0.9%, and tree nut allergy was less than 2% in studies where food challenges were performed.

## Trends

Most countries report an increase in the prevalence of food allergy and allergic events over the last 10–15 years, with published evidence in developed and rapidly developing countries alike, including Australia, the United States, and China [3]. The CDC has reported in the United States that food allergy, based on self-reporting, has increased 18% from 1997 to 2007 in children under 18 years old, with 3.9% reporting a food allergy in 2007, as well as a significant increase in hospital discharges related to food allergy in 2007 compared to 1997 [9]. Mullins et al. used data from the Australian Bureau of Statistics and the Australian National Coronial Information System to describe changes in food allergy-related anaphylaxis in Australia from 1997 to 2013. Rates of anaphylaxis fatalities have increased in Australia between 1997 and 2013 by 6.2% per year, with fatal food anaphylaxis increasing by 9.7% per year (95% CI, 0.3–20%; $P = 0.04$) [10]. Hospital admissions due to food anaphylaxis also increased by 10.2% from year to year (95% CI, 9.9–10.6%; $P < 0.0001$), reaching up to a 16.1% yearly increase in children 5–14 years old (Fig. 10.2) [10].

Overall, studies since the 1990s have consistently shown evidence that food allergy has been increasing, especially in developed and rapidly developing countries [3, 11–13]. In the upcoming sections, we will outline some factors that may be involved in this allergy epidemic.

## Why Is Food Allergy on the Rise?

The cause of the global rise in food allergy prevalence is not known; however, the increase has occurred too rapidly for genetic factors alone to explain as changes to the genome occur at an evolutionary pace. Environmental factors associated with food allergy must, therefore, be central to the increase in prevalence. Some environmental factors may also exert their influence through microbiome alternations or epigenetic modifications in genes.

### Heritability and Predisposition to Food Allergy

Like many complex diseases, there is evidence to suggest genetic factors influence food allergy.

The influence of genetic factors is measured by heritability, which is defined as "the proportion of observed variation in a particular trait that can be attributed to inherited genetic factors in contrast to environmental ones," where 0 indicates no genetic contribution and 1 indicates complete genetic influence [14]. Sicherer et al. published a twin study showing a strong possible genetic influence of peanut allergy with heritability ranging from 0.82 to 0.87 [15]. A more recent twin study on 826 twin pairs estimated the heritability of food sensitization in a 12- to 28-year old Chinese population to be between 0.51 and 0.68, suggesting both genetic and environmental factors influence food allergy [16]. A family-based study including 581 nuclear families from the United States, with food allergy diagnosed through clinical symptoms and food-specific IgE, found heritability ranging from 0.15 to 0.35 for the nine food allergens tested [17]. The authors also found familial aggregation patterns of food allergy between mother and child and the child with other siblings. Currently, food allergy is assumed to be a complex polygenic disease with a significant environmental contribution.

A recently published systematic review assessed 32 candidate-gene and genome-wide association studies (GWAS) associated with food allergy, following the PRISMA protocol. Findings suggested that the genes for filaggrin (FLG), HLA, and IL13 have reproducible associations with food allergy, though others, such as IL10, SPINK5, SERPINB, and C110rf30, have also been found to be associated with food allergy [18].

The FLG gene has been shown to be associated to eczema and food allergy, although some authors argue that the association is with food sensitization rather than food allergy itself. A case–control study replicated in three distinct populations (English, Dutch, and Canadian) found a strong and significant association between peanut allergy and FLG mutations, even after controlling for coexistent atopic dermatitis [19]. In addition, our population-based study in 1-year-old infants found that the FLG mutation was significantly associated with both food sensitization and food allergy in infants irrespective of their eczema [20]. FLG appears to increase the risk of food sensitization (adjusted odds ratio [aOR], 3.0; 95% CI, 1.0–8.7; $P = 0.043$), but it may not increase the risk of food allergy per se.

Males have also been found to be more likely to be food sensitized and have a higher mortality rate due to food allergy-related anaphylaxis [10, 21]. A systematic review published in the United States found disparity in food allergy according to race and ethnicity [22]. The authors reviewed 20 papers, none of which used OFC to define food allergy, and reported that African Americans were found to have an increased risk of food sensitization and food allergy. While genes may explain some variability in food allergy prevalence among specific ethnicities, environmental factors contribute to these findings as well.

## Is the Rapidly Changing Environment Causing the Rise of Food Allergy?

Environmental exposures have changed dramatically in the last decades of the twentieth century, particularly in developed countries. The urbanization and industrialization of cities have led to improved hygiene in the population including cleaner water supplies and cleaner food supplies. Even so, there has been an increase in pollutants in the last century, especially in urban areas, and though there has been a decrease in smoking, people are leading more sedentary lifestyles and there has been a significant increase in obesity. Awareness of the dangers of sun exposure and an increased electronic-based lifestyle have led to widespread use of sun protection and sun avoidance, which have been associated with a higher prevalence of vitamin D deficiency over time. Infants are born more commonly by cesarean sections and immunization uptakes have increased significantly, while infant feeding patterns are changing and diets are becoming more Westernized [23].

There has also been growing use of antibiotics in humans and livestock and a declining prevalence of *Helicobacter pylori* infection. Although population evidence for the association of *H. pylori* and food allergy is inconclusive [24], a

longitudinal study of children up to 7 years of age showed that children prescribed antibiotics three or more times by that age or 60 days before diagnoses (whichever occurred earlier) had greater odds of having cow's milk or other food allergies than children with no antibiotic use, and this varied by antibiotic classes, penicillin having the highest association with food allergy [25]. The latter may be explained by co-association of food allergy and eczema and the fact that children with eczema have higher rates of skin infection requiring penicillin-based antibiotics [26].

One theory that incorporates several key epidemiological associations that have been hypothesized to play a role in increased risk of food allergy is referred to as the 5 Ds – **D**ry skin, **D**iet, **D**ogs (external microbial exposure), **D**ribble (internal microbial exposure), and Vitamin **D** [27].

## Dry Skin and the Function of a Healthy Skin Barrier

Multiple studies have documented an association between eczema and food allergy [28–30]. Our population-based HealthNuts cohort found that half of infants with severe, early-onset eczema developed challenge-proven food allergy by 1 year of age. Infants with eczema were five times more likely to develop IgE-mediated food allergy than infants without eczema (odds ratio [OR], 6.2; 95% CI, 4.9–7.9; $P < 0.001$) [31]. As certain gene variants have been shown to be associated with eczema and food sensitization, but not food allergy per se, we hypothesize that a second step may be required to convert food sensitization to food allergy [20], as reflected in the Dual Allergen Exposure Hypothesis.

The Dual Allergen Exposure Hypothesis (or "Lack" Hypothesis after Professor Gideon Lack who proposed this theory) proposes that sensitization is caused by exposure to allergens through the skin barrier, but can be prevented through oral exposure [32]. An in vitro study performed on mice suggests that exposing skin to environmental allergens would reduce oral tolerance of neonates heterozygous for skin barrier mutations in FLG and mattrin genes, but was prevented if oral allergen exposure preceded skin exposure [29]. This same study also reported that the application of sodium dodecyl sulfate, a soap component found in cleaning wipes, along with the allergen could sensitize the food allergen response in neonatal mice with skin barrier mutations, suggesting possible sensitization in human infants, particularly those with skin barrier mutations through skin exposure to soap and food allergens. The importance of the skin barrier is reinforced by an observational study which described increased peanut sensitization in 3- to 15-month-old children with moderate-to-severe atopic dermatitis when environmental peanut protein levels in household dust increased (1.7-fold; 95% CI, 1.1- to 2.6-fold; $P = 0.01$) [33].

## Diet and Early Allergen Exposure

The Dual Allergen Exposure Hypothesis also proposes that the development of food allergy is abrogated by oral exposure to allergenic foods in early infancy. The sentinel randomized trial LEAP (Learning Early About Peanut Allergy) formally assessed whether early peanut introduction reduced peanut allergy at age 5. LEAP showed a reduction of peanut allergy in a group of high-risk infants by feeding them regular, high doses of peanut from infancy until 5 years of age [34]. Another randomized, double-blind, placebo-controlled trial in Japan (PETIT) in 4- to 5-month infants with eczema found early introduction of heated egg powder (lower allergenicity than the raw egg powder usually used in trials) in a stepwise manner significantly reduced the risk of egg allergy at 12 months (95% CI, 0.08–0.6; $P = 0.0012$) [35], though these results should be interpreted with some caution as the trial was terminated early. Evidence from a number of trials collected in a meta-analysis, including LEAP, reported similar data for reduced egg allergy in infants who consume egg from 4 to 6 months (risk ratio, 0.56; 95% CI, 0.4–0.9; $P = 0.009$) [36, 37]. A recently published review on the efficacy of oral tolerance induction in randomized controlled trials (RCT) found that dosage was important with 2 g of food protein per week protecting against peanut and egg white allergy by approximately 90%; thus, early introduction of allergenic foods such as peanut and hen's egg could protect from food allergy [38].

Population changes in diet diversity may also be a factor that coincides with the rise in food allergy. A prospective birth cohort study of 856 children from rural areas of five European countries reported an association between increased diversity of complementary foods in the first year of life and a reduction in the risk of food allergy [39]. In another prospective longitudinal study of infants, a higher intake of fresh fruit and vegetables and home-prepared meals in a child's first year of life were also associated with lower risk of food allergy at 2 years of age [40].

Studies investigating the role of breastfeeding in potential protection from food allergy have shown conflicting results, with limitations in their methodologies as it would be unethical to conduct a RCT to breastfeed or not to breastfeed. A systematic review and meta-analysis of 89 articles demonstrated breastfeeding for longer time periods provides no protective effect against food allergy [41]. Nonetheless, these results must be interpreted with caution due to many of these studies being low quality and high possibility of recall bias in many cases. Although one study has shown a protective effect of breastfeeding for at least 4 months on the development of cow's milk allergy in high-risk infants for the first 18 months of age [42], another has previously suggested that extended and exclusive breastfeeding in high-risk infants may increase the likelihood of food sensitization or allergy [43]. The latter may be related to delayed introduction to allergenic and complementary foods rather than the effect of breast milk per se or to reverse causation where mothers decide to keep breastfeeding if they suspect food allergy or have a family history of food allergy.

Infant diet and feeding patterns vary around the world by region and even country. In the majority of both developed and developing countries around the world, complimentary infant feeding starts between 4 and 6 months. Some exceptions exist, including some Middle Eastern countries, such as Egypt, Jordan, and Kuwait, where parents tend to introduce solid foods earlier around 3–4 months, and in Austria and Uruguay where parents commonly introduce foods after 6 months [3]. Australian infant feeding guidelines have recently changed from recommending delayed introduction of allergenic foods and now recommend introducing allergenic foods in the first year of life after solids have been introduced around 6 months, but not before 4 months [44]. Our HealthNuts study found changes [45] in infant introduction to allergenic foods based on community awareness of emerging data [34, 46]. We have recently mounted a new population-based study called Early Nuts, which aims to assess the impact of changed guidelines on infant feeding practices and also the impact of these changes on the prevalence of food allergy at age 1 year, with findings estimated by the end of 2019.

### Microbial Exposure (Dogs and Dribble)

There is evidence that microbial exposure and a diverse gut microbiome are critical for the development of the immune system. The hygiene hypothesis, first proposed by Strachan in 1989, describes the protective effects of siblings through unhygienic contact and increased microbial exposure by prompting the maturation of the mucosal immune system [47]. Building on the basis of the hygiene hypothesis, Rook et al. developed the "Old Friends" hypothesis, describing how harmless microorganisms and commensals, such as helminths and saprophytic mycobacteria, activate IgE antibodies for protection and may have a beneficial role in the maturation of the immune system, more specifically the activation of regulatory T cells which are fundamental for the suppression of allergy [48, 49]. The protective effect of siblings and pets, indicative of higher external microbial exposure, was confirmed more recently through challenge-proven food allergy in the HealthNuts infant cohort study [6]. There is also evidence to suggest differences in the prevalence of food allergy in rural and urban environments, as shown in rising food allergy rates in Chinese cities that are undergoing rapid urbanization rates [13].

Alterations to the internal gut microbiome diversity have been associated to allergic disease. A review by the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology in 2017 suggests that gut microbial richness in

early infancy is important for the development of the immune system and, thus, alters the risk of developing food allergy [50]. It has also been suggested that maternal gut microbiota during pregnancy is associated with food allergy outcomes in their infants [51].

Several studies have investigated the association between taking probiotics as a way to increase microbial exposure for allergy prevention; however, results from systematic reviews and meta-analysis are inconclusive [52, 53]. One such review of 17 trials indicated that prenatal and postnatal administration of probiotics could reduce food sensitization; however, they are missing results on confirmed food allergy as the few studies available report nonsignificant and conflicting effects of probiotics on food allergy [52]. Microbial load is one hypothesis to explain the increased incidence of food sensitization, as there has been a reduction in early childhood infection, as well as changing patterns in the type of infections from parasitic and bacterial to viral, particularly in developed countries.

### Vitamin D

There is evidence of a latitude gradient of food allergy from Australia, United States, and Chile, with people living further from the equator, and therefore experiencing lower ambient ultraviolet radiation [54–56], having higher rates of food allergy. Multiple authors have also found increased pediatric admissions for food allergy-related events, more prescriptions of hypoallergenic formulas for the treatment of cow's milk allergy and adrenaline injectors for the treatment of anaphylaxis in children further from the equator [10, 27, 55]. In Australia, children further from the equator in the southernmost part of the country were more likely to have food allergy and eczema than those in the north at ages 4–5 [54]. These findings seem to be independent of longitude, socioeconomic status, or physician density, though season of birth may also play a role.

Children with vitamin D deficiency have been found to be three times more likely to have peanut or egg allergy, and food-sensitized children with vitamin D deficiency were six times more likely to have food allergy [57]. Interestingly, this effect was only observed among children of Australian-born parents, but not children of non-Australian-born parents (reflecting a gene–environment interaction, as outlined below). Even so, recent World Allergy Organization guidelines in 2016 did not find enough evidence to support clinicians or parents using vitamin D to prevent food allergy [58]. Because of this, results from our ongoing RCT (Vitality) assessing the role of vitamin D in the protection against food allergy in infants will be important to inform the evidence base about vitamin D guidelines in infants [59].

## Migration and Gene–Environment Interaction

### Migration

By following families who have recently migrated, it is possible to observe environmental changes for migrating populations and compare them to populations who are genetically dissimilar in the same environment or populations who are genetically similar in different environments. Regarding the latter, when populations of Jewish children were compared in Israel and the United Kingdom, children in the United Kingdom were found to have significantly higher prevalence of peanut allergy, with authors establishing an association between delayed introduction to and reduced consumption of peanut in the United Kingdom and increased prevalence of peanut allergy [60]. There is further evidence from the HealthNuts study of an association between parents' country of birth and infant peanut allergy [61]. We reported that challenge-proven peanut allergy is three times more common in Australian-born infants with parents born in East Asia compared with infants with parents born in Australia (OR, 3.4; 95% CI, 2.2–5.1), but not in infants with parents born in the United Kingdom or Europe, suggesting an important interaction between genes and environment may be at play [61]. Importantly, this increase in food allergy occurred in a single generation, as Asian-born parents have lower prevalence of allergy compared to Australian-born parents.

The rapid increase in food allergy from one generation to the next generation suggests that the Asian early-life environment could protect against food allergy. Koplin et al. suggest changes in humidity could impact the skin barrier function, as infants of Asian-born parents had a significantly higher prevalence of eczema which, as we have previously mentioned, could be a risk factor for food sensitization and allergy [61]. Other environmental changes for populations migrating from East Asia could include lower levels of microbial exposure related to the hygiene hypothesis, different latitude compared to the parents' country of birth and therefore reduced sun exposure, and dietary differences in Western culture including increased sterilization and alternative methods of cooking food, also leading to altered microbiome. Notably, it has been reported that children of Asian-born parents who were born in Asia and subsequently migrate to Australia later in life are protected against food allergy just as their parents are [61], which strongly suggests that there is an early-life effect. Similar results have been observed in the United Kingdom and the United States, as there is an overrepresentation of non-Caucasian children in pediatric allergy clinics [62, 63].

### Genetic and Environmental Interactions

The interaction between genetic predisposition and response to environment risk factors, "gene–environment interaction," is critical to examine to attempt to understand the complex factors that might drive a predisposition to food allergy [64]. Our group has demonstrated that vitamin D deficiency increased the risk of food allergy in infants of Australian-born parents (aOR, 3.1; 95% CI, 1.1–8.6; $P$ = 0.032), but infants of Asian-born parents did not demonstrate this (aOR, 0.39; 95% CI, 0.1–1.8; $P$ = 0.22, 57). It was suggested that this observation could be attributed to genetic difference as almost 80% of the variation in vitamin D levels can be explained by genetic polymorphisms, which contribute to vitamin D-binding protein (DBP) levels [65]. Binding protein levels alter the biological availability of serum vitamin D (25OHD3) as lower levels of the protein increase the availability of serum vitamin D. The association between vitamin D deficiency and food allergy has been found to be dependent on the polymorphism an infant carries. The GG genotype results in higher levels of DBP, whereas the GT/TT genotypes, more common in Asian-born parents, result in lower levels of DBP. Low serum vitamin D (≤50 nM/L) in 1-year-old infants was associated with food allergy, principally among infants with the polymorphism resulting in higher levels of DBP (OR, 6.0; 95% CI, 0.9–38.9), but not in those with polymorphisms resulting in lower levels of DBP (OR, 0.7; 95% CI, 0.2–2.0; difference in effect, $P$ = 0.014) [66].

The interaction between genes and environment can express itself through epigenetic modifications in DNA and other immune system alterations [67, 68]. Some reviews have addressed how the environment may be altering phenotypes through epigenetic differences, such as DNA methylation and acetylation, though there are few food allergy–specific studies [69–71]. The immune system has been shown to be under epigenetic regulation and studies on animal models have described how environmental factors modify gene expression, unbalancing immune response and, therefore, altering the risk of allergic disease [72]. One of our recent studies has established how epigenetic dysregulation disrupts the activation of CD4+ T cells, a critical step for the healthy development of the immune system, thus increasing the risk of food allergy [73]. More epigenetic findings are expected over the next 5 years.

## Future Directions

There is now emerging evidence that the rise of food allergy may be primarily due to the changing environment in developed countries and that increase is now reflected in rapidly developing countries as they adopt a more Westernized lifestyle. The next step would be to focus on the mechanisms by which environmental candidates act through the microbiome, epigenetic, and other mechanisms. Multiple allergy prevention trials have been undertaken with varied results, but

LEAP provides the most compelling evidence that early introduction of allergenic foods can protect from food allergy. As a result, recent guidelines and consensus on food allergy, anaphylaxis, and early introduction to allergenic foods in Europe, pacific Asia, and Australia agree that there is no longer any need to delay introduction to allergenic foods [44, 74, 75]. We are interested to see whether the increase in food allergy continues at the same rate or if the changes implemented around the world are enough to slow down this epidemic. Eight RCTs are investigating other factors that may be important in the prevention of food allergy (Box 10.1) [76]. Daily vitamin D supplementation in infants is being evaluated in VITALITY, with the primary aim of reducing the risk of food allergy at age 12 months [59]. MIS BAIR aims to evaluate whether the BCG vaccine could promote the development of the immune system in infants, therefore reducing allergy and infection in children. Future studies will also need to focus on the interaction between genetics and environment to elucidate the mechanisms behind this complex disease. Finally, current food allergy research has provided a platform, with several risk factors described and RCTs in progress, likely to accelerate the understanding of gene–environment interactions and molecular mechanisms in allergy.

**Box 10.1 Active RCTs Focusing on Food Allergy Prevention (*ClinicalTrials.gov NCT Number Identifier*) [76]. Accessed August 22, 2018**

- Can Vitamin D Supplementation in Infants Prevent Food Allergy in the First Year of Life? The VITALITY Trial (VITALITY) – Recruiting in Australia *(NCT02112734)*
- Melbourne Infant Study – Bacille Calmette Guérin (BCG) for Allergy & Infection Reduction (MIS BAIR) – Not recruiting (*NCT01906853)*
- Effect of Mediterranean Diet During Pregnancy on Gut Microbiota and on the Epigenetics (PREMEDI) – Recruiting in Italy *(NCT03337802)*
- Probiotic Supplementation in Breastfed Newborn Infants – Recruiting in the United States *(NCT02286999)*
- The EAT-On Study: Sensitisation, Allergy and Child Health – Enrolling by invitation in Australia (*NCT03495583*)
- Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) – Not recruiting (*NCT02449850*)
- Follow-up of LEAP Participants and Their Families – Recruiting in the United Kingdom (*NCT03546413*)
- Canadian Peanut Thresholds Study – Not recruiting (*NCT01812798*)

∗SEARCH: (96 studies found for Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | "Food Hypersensitivity" and "Food Allergy"), last updated August 22, 2018.

## References


1. National Academies of Sciences E, Medicine. In: Stallings VA, Oria MP, editors. Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy. Washington, DC: The National Academies Press; 2016. p. 574.
2. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013;167(11):1026–31. https://doi.org/10.1001/jamapediatrics.2013.2376.
3. Prescott SL, Pawankar R, Allen KJ, Campbell DC, Sinn JKH, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organ J. 2013;6(21):1–12. https://doi.org/10.1186/1939-4551-6-21.
4. Panel N-SE, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1–58. https://doi.org/10.1016/j.jaci.2010.10.007.
5. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235. https://doi.org/10.1542/peds.2018-1235.

6. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011;127(3):668–76 e1-2. https://doi.org/10.1016/j.jaci.2011.01.039.
7. Moonesinghe H, Mackenzie H, Venter C, Kilburn S, Turner P, Weir K, et al. Prevalence of fish and shellfish allergy: A systematic review. Ann Allergy Asthma Immunol. 2016;117(3):264–72.e4. https://doi.org/10.1016/j.anai.2016.07.015.
8. McWilliam V, Koplin J, Lodge C, Tang M, Dharmage S, Allen K. The prevalence of tree nut allergy: a systematic review. Curr Allergy Asthma Rep. 2015;15(9):54. https://doi.org/10.1007/s11882-015-0555-8.
9. Branum A, Lukacs SL. Food allergy among U.S. Children: Trends in prevalence and hospitalizations. NCHS Data Brief. 10. Hyattsville: National Center for Health Statistics; 2008. p. 1–8.
10. Mullins RJ, Wainstein BK, Barnes EH, Liew WK, Campbell DE. Increases in anaphylaxis fatalities in Australia from 1997 to 2013. Clin Exp Allergy. 2016;46(8):1099–110. https://doi.org/10.1111/cea.12748.
11. Peters RL, Koplin JJ, Allen KJ, Lowe AJ, Lodge CJ, Tang MLK, et al. The prevalence of food sensitization appears not to have changed between 2 Melbourne Cohorts of high-risk infants recruited 15 Years apart. J Allergy Clin Immunol Pract. 2018;6(2):440–8.e2. https://doi.org/10.1016/j.jaip.2017.11.018.
12. Arakali SR, Green TD, Dinakar C. Prevalence of food allergies in South Asia. Ann Allergy Asthma Immunol. 2017;118(1):16–20. https://doi.org/10.1016/j.anai.2016.09.441.
13. Hu Y, Chen J, Li H. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. Pediatr Int. 2010;52(5):820–4. https://doi.org/10.1111/j.1442-200X.2010.03166.x.
14. Merriam-Webster. 2019. Heritability. Available from: https://www.merriam-webster.com/dictionary/heritability. Accessed 14 Jan 2019.
15. Sicherer SH, Furlong TJ, Maes HH, Desnick RJ, Sampson HA, Gelb BD. Genetics of peanut allergy: a twin study. J Allergy Clin Immunol. 2000;106(1 Pt 1):53–6. https://doi.org/10.1067/mai.2000.108105.
16. Liu X, Zhang S, Tsai H-J, Hong X, Wang B, Fang Y, et al. Genetic and environmental contributions to allergen sensitization in a Chinese twin study. Clin Exp Allergy. 2009;39(7):991–8. https://doi.org/10.1111/j.1365-2222.2009.03228.x.
17. Tsai H-J, Kumar R, Pongracic J, Liu X, Story R, Yu Y, et al. Familial aggregation of food allergy and sensitization to food allergens: a family-based study. Clin Exp Allergy. 2009;39(1):101–9. https://doi.org/10.1111/j.1365-2222.2008.03111.x.
18. Suaini NHA, Wang Y, Soriano VX, Martino DJ, Allen KJ, Ellis JA, et al. Genetic determinants of paediatric food allergy: a systematic review. Allergy. 2019;74:1631. https://doi.org/10.1111/all.13767.
19. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. J Allergy Clin Immunol. 2011;127(3):661–7. https://doi.org/10.1016/j.jaci.2011.01.031.
20. Tan HT, Ellis JA, Koplin JJ, Matheson MC, Gurrin LC, Lowe AJ, et al. Filaggrin loss-of-function mutations do not predict food allergy over and above the risk of food sensitization among infants. J Allergy Clin Immunol. 2012;130(5):1211–3 e3. https://doi.org/10.1016/j.jaci.2012.07.022.
21. Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang ML, Gurrin LC, et al. Cohort profile: the HealthNuts study: population prevalence and environmental/genetic predictors of food allergy. Int J Epidemiol. 2015;44(4):1161–71. https://doi.org/10.1093/ije/dyu261.
22. Greenhawt M, Weiss C, Conte ML, Doucet M, Engler A, Camargo CA Jr. Racial and ethnic disparity in food allergy in the United States: a systematic review. J Allergy Clin Immunol Pract. 2013;1(4):378–86. https://doi.org/10.1016/j.jaip.2013.04.009.
23. Allen KJ, Koplin JJ. Why does Australia appear to have the highest rates of food allergy? Pediatr Clin N Am. 2015;62(6):1441–51. https://doi.org/10.1016/j.pcl.2015.07.005.
24. Ma ZF, Majid NA, Yamaoka Y, Lee YY. Food allergy and helicobacter pylori infection: a systematic review. Front Microbiol. 2016;7:368. https://doi.org/10.3389/fmicb.2016.00368.
25. Hirsch AG, Pollak J, Glass TA, Poulsen MN, Bailey-Davis L, Mowery J, et al. Early-life antibiotic use and subsequent diagnosis of food allergy and allergic diseases. Clin Exp Allergy. 2017;47(2):236–44. https://doi.org/10.1111/cea.12807.
26. Tsakok T, McKeever TM, Yeo L, Flohr C. Does early life exposure to antibiotics increase the risk of eczema? A systematic review. Br J Dermatol. 2013;169(5):983–91. https://doi.org/10.1111/bjd.12476.
27. Allen KJ, Koplin JJ. Prospects for prevention of food allergy. J Allergy Clin Immunol Pract. 2016;4(2):215–20. https://doi.org/10.1016/j.jaip.2015.10.010.
28. Lowe AJ, Leung DYM, Tang MLK, Su JC, Allen KJ. The skin as a target for prevention of the atopic march. Ann Allergy Asthma Immunol. 2018;120(2):145–51. https://doi.org/10.1016/j.anai.2017.11.023.
29. Walker MT, Green JE, Ferrie RP, Queener AM, Kaplan MH, Cook-Mills JM. Mechanism for initiation of food allergy: dependence on skin barrier mutations and environmental allergen costimulation. J Allergy Clin Immunol. 2018;141(5):1711–25. e9. https://doi.org/10.1016/j.jaci.2018.02.003.
30. Foong RX, Brough H. The role of environmental exposure to peanut in the development of clinical allergy to peanut. Clin Exp Allergy. 2017;47(10):1232–8. https://doi.org/10.1111/cea.12992.
31. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. Clin Exp Allergy. 2015;45(1):255–64. https://doi.org/10.1111/cea.12406.

32. Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol. 2012;129(5):1187–97. https://doi.org/10.1016/j.jaci.2012.02.036.
33. Brough HA, Liu AH, Sicherer S, Makinson K, Douiri A, Brown SJ, et al. Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. J Allergy Clin Immunol. 2015;135(1):164–70. https://doi.org/10.1016/j.jaci.2014.10.007.
34. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372(9):803–13. https://doi.org/10.1056/NEJMoa1414850.
35. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10066):276–86. https://doi.org/10.1016/s0140-6736(16)31418-0.
36. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. JAMA. 2016;316(11):1181–92. https://doi.org/10.1001/jama.2016.12623.
37. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016;374(18):1733–43. https://doi.org/10.1056/NEJMoa1514210.
38. Du Toit G, Sampson HA, Plaut M, Burks AW, Akdis CA, Lack G. Food allergy: update on prevention and tolerance. J Allergy Clin Immunol. 2018;141(1):30–40. https://doi.org/10.1016/j.jaci.2017.11.010.
39. Roduit C, Frei R, Depner M, Schaub B, Loss G, Genuneit J, et al. Increased food diversity in the first year of life is inversely associated with allergic diseases. J Allergy Clin Immunol. 2014;133(4):1056–64. e7. https://doi.org/10.1016/j.jaci.2013.12.1044.
40. Grimshaw KE, Maskell J, Oliver EM, Morris RC, Foote KD, Mills EN, et al. Diet and food allergy development during infancy: birth cohort study findings using prospective food diary data. J Allergy Clin Immunol. 2014;133(2):511–9. https://doi.org/10.1016/j.jaci.2013.05.035.
41. Lodge CJ, Tan DJ, Lau MX, Dai X, Tham R, Lowe AJ, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatr. 2015;104(467):38–53. https://doi.org/10.1111/apa.13132.
42. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part III: critical review of published peer-reviewed observational and interventional studies and final recommendations. Pediatr Allergy Immunol. 2004;15(4):291–307. https://doi.org/10.1111/j.1399-3038.2004.00127.x.
43. Saarinen KM, Juntunen-Backman K, Jarvenpaa AL, Kuitunen P, Lope L, Renlund M, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. J Allergy Clin Immunol. 1999;104(2 Pt 1):457–61.
44. Netting MJ, Campbell DE, Koplin JJ, Beck KM, McWilliam V, Dharmage SC, et al. An Australian consensus on infant feeding guidelines to prevent food allergy: outcomes from the Australian infant feeding summit. J Allergy Clin Immunol Pract. 2017;5(6):1617–24. https://doi.org/10.1016/j.jaip.2017.03.013.
45. Tey D, Allen KJ, Peters RL, Koplin JJ, Tang ML, Gurrin LC, et al. Population response to change in infant feeding guidelines for allergy prevention. J Allergy Clin Immunol. 2014;133(2):476–84. https://doi.org/10.1016/j.jaci.2013.11.019.
46. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al. Can early introduction of egg prevent egg allergy in infants? J Allergy Clin Immunol. 2010;126(4):807–13. https://doi.org/10.1016/j.jaci.2010.07.028.
47. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259–60.
48. Rook GA, Martinelli R, Brunet LR. Innate immune responses to mycobacteria and the downregulation of atopic responses. Curr Opin Allergy Clin Immunol. 2003;3(5):337–42. https://doi.org/10.1097/01.all.0000092602.76804.ad.
49. Mukai K, Tsai M, Starkl P, Marichal T, Galli SJ. IgE and mast cells in host defense against parasites and venoms. Semin Immunopathol. 2016;38(5):581–603. https://doi.org/10.1007/s00281-016-0565-1.
50. Huang YJ, Marsland BJ, Bunyavanich S, O'Mahony L, Leung DYM, Muraro A, et al. The microbiome in allergic disease: current understanding and future opportunities—2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European academy of allergy and clinical immunology. J Allergy Clin Immunol. 2017;139(4):1099–110. https://doi.org/10.1016/j.jaci.2017.02.007.
51. Vuillermin PJ, Macia L, Nanan R, Tang ML, Collier F, Brix S. The maternal microbiome during pregnancy and allergic disease in the offspring. Semin Immunopathol. 2017;39(6):669–75. https://doi.org/10.1007/s00281-017-0652-y.
52. Zhang G-Q, Hu H-J, Liu C-Y, Zhang Q, Shakya S, Li Z-Y. Probiotics for prevention of atopy and food hypersensitivity in early childhood: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. Medicine. 2016;95(8):e2562. https://doi.org/10.1097/MD.0000000000002562.
53. Cuello-Garcia C, Fiocchi A, Pawankar R, Yepes-Nunez JJ, Morgano GP, Zhang Y, et al. Prebiotics for the prevention of allergies: a systematic review and meta-analysis of randomized controlled trials. Clin Exp Allergy. 2017;47(11):1468–77. https://doi.org/10.1111/cea.13042.
54. Osborne NJ, Ukoumunne OC, Wake M, Allen KJ. Prevalence of eczema and food allergy is associ-

ated with latitude in Australia. J Allergy Clin Immunol. 2012;129(3):865–7. https://doi.org/10.1016/j.jaci.2012.01.037.
55. Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. J Allergy Clin Immunol. 2007;120(1):131–6. https://doi.org/10.1016/j.jaci.2007.03.049.
56. Hoyos-Bachiloglu R, Morales PS, Cerda J, Talesnik E, González G, Camargo CA, et al. Higher latitude and lower solar radiation influence on anaphylaxis in Chilean children. Pediatr Allergy Immunol. 2014;25(4):338–43. https://doi.org/10.1111/pai.12211.
57. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. J Allergy Clin Immunol. 2013;131(4):1109–16,. 16 e1-6. https://doi.org/10.1016/j.jaci.2013.01.017.
58. Yepes-Nunez JJ, Fiocchi A, Pawankar R, Cuello-Garcia CA, Zhang Y, Morgano GP, et al. World allergy organization-McMaster University guidelines for allergic disease prevention (GLAD-P): vitamin D. World Allergy Organ J. 2016;9:17. https://doi.org/10.1186/s40413-016-0108-1.
59. Allen KJ, Panjari M, Koplin JJ, Ponsonby AL, Vuillermin P, Gurrin LC, et al. VITALITY trial: protocol for a randomised controlled trial to establish the role of postnatal vitamin D supplementation in infant immune health. BMJ Open. 2015;5(12):e009377. https://doi.org/10.1136/bmjopen-2015-009377.
60. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008;122(5):984–91. https://doi.org/10.1016/j.jaci.2008.08.039.
61. Koplin JJ, Peters RL, Ponsonby AL, Gurrin LC, Hill D, Tang ML, et al. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. Allergy. 2014;69(12):1639–47. https://doi.org/10.1111/all.12487.
62. Dias RP, Summerfield A, Khakoo GA. Food hypersensitivity among Caucasian and non-Caucasian children. Pediatr Allergy Immunol. 2008;19(1):86–9. https://doi.org/10.1111/j.1399-3038.2007.00582.x.
63. Keet CA, Wood RA, Matsui EC. Personal and parental nativity as risk factors for food sensitization. J Allergy Clin Immunol. 2012;129(1):169–75 e1-5. https://doi.org/10.1016/j.jaci.2011.10.002.
64. Ellis JA, Kemp AS, Ponsonby AL. Gene-environment interaction in autoimmune disease. Expert Rev Mol Med. 2014;16:e4. https://doi.org/10.1017/erm.2014.5.
65. Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med. 2013;369(21):1991–2000. https://doi.org/10.1056/NEJMoa1306357.
66. Koplin JJ, Suaini NH, Vuillermin P, Ellis JA, Panjari M, Ponsonby AL, et al. Polymorphisms affecting vitamin D-binding protein modify the relationship between serum vitamin D (25[OH]D3) and food allergy. J Allergy Clin Immunol. 2016;137(2):500–6. e4. https://doi.org/10.1016/j.jaci.2015.05.051.
67. Allen KJ, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. Immunol Allergy Clin N Am. 2012;32(1):35–50. https://doi.org/10.1016/j.iac.2011.11.008.
68. Lambrecht BN, Hammad H. The immunology of the allergy epidemic and the hygiene hypothesis. Nat Immunol. 2017;18(10):1076–83. https://doi.org/10.1038/ni.3829.
69. Tan TH, Ellis JA, Saffery R, Allen KJ. The role of genetics and environment in the rise of childhood food allergy. Clin Exp Allergy. 2012;42(1):20–9. https://doi.org/10.1111/j.1365-2222.2011.03823.x.
70. Ponsonby AL, Symeonides C, Vuillermin P, Mueller J, Sly PD, Saffery R. Epigenetic regulation of neurodevelopmental genes in response to in utero exposure to phthalate plastic chemicals: how can we delineate causal effects? Neurotoxicology. 2016;55:92–101. https://doi.org/10.1016/j.neuro.2016.05.011.
71. Potaczek DP, Harb H, Michel S, Alhamwe BA, Renz H, Tost J. Epigenetics and allergy: from basic mechanisms to clinical applications. Epigenomics. 2017;9(4):539–71. https://doi.org/10.2217/epi-2016-0162.
72. Martino DJ, Prescott SL. Silent mysteries: epigenetic paradigms could hold the key to conquering the epidemic of allergy and immune disease. Allergy. 2010;65(1):7–15. https://doi.org/10.1111/j.1398-9995.2009.02186.x.
73. Martino D, Neeland M, Dang T, Cobb J, Ellis J, Barnett A, et al. Epigenetic dysregulation of naive CD4+ T-cell activation genes in childhood food allergy. Nat Commun. 2018;9(1):3308. https://doi.org/10.1038/s41467-018-05608-4.
74. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. Allergy. 2014;69(5):590–601. https://doi.org/10.1111/all.12398.
75. Tham EH, Shek LPC, Bever HPV, Vichyanond P, Ebisawa M, Wong GW, et al. Early introduction of allergenic foods for the prevention of food allergy from an Asian perspective—an Asia Pacific Association of Pediatric Allergy, Respirology & Immunology (APAPARI) consensus statement. Pediatr Allergy Immunol. 2018;29(1):18–27. https://doi.org/10.1111/pai.12820.
76. U.S. National Library of Medicine. ClinicalTrials.gov. 2018. Available from: www.clinicaltrials.gov. Accessed 22 Aug 2018.

# The Microbiome in Food Allergy and Eosinophilic Esophagitis

11

Alyson L. Yee, Mary M. Buschmann, Christina E. Ciaccio, and Jack A. Gilbert

## Introduction

The incidence of food allergies has risen dramatically in just one generation. In fact, food allergy was estimated to have increased by 50% between 1997 and 2011 while the prevalence of peanut or tree nut allergy may have tripled in the United States during the same time period [1–3]. In addition, allergy severity has increased with increased hospital admissions and longer stays following anaphylaxis [4, 5]. The rapid rise in food allergy suggests the increased incidence is unlikely to be explained by genetics alone; rather, the rate hints that environmental and epigenetic factors are driving the development of this disease.

Changes in microbial exposures (the so-called hygiene hypothesis) may help explain the recent increase in food allergy incidence [6]. In 1989, David Strachan, an epidemiologist at the London School of Hygiene and Tropical Medicine, observed that children born into a household with many siblings were less susceptible to hay fever later in life [7]. He proposed that early childhood infections protect against allergic disease [8]. More recently, Graham Rook proposed the "old friends" hypothesis, suggesting that early and regular exposure to harmless microorganisms train the immune system [9]. This updated understanding of the hygiene hypothesis implied that exposure to microbes that co-evolved with humans, rather than infectious pathogens, keeps the immune system in balance and prevents overreaction to allergens. Exposure to diverse microorganisms during infancy, when immunoregulatory systems are developing, increases the repertoire of organisms that can be tolerated and may pattern memory immune mechanisms to recognize pathogens [9].

Since Strachan's original hypothesis, the key role of commensal microorganisms in human health has become increasingly clear. Numerous changes in the Western lifestyle have led to a decrease in crucial immunostimulatory microorganisms. These include dietary changes (high intake of processed food: high in fat, sugar, food emulsifiers, and artificial sweeteners and low in fiber), increased use of antibiotics, increased rates of Caesarean section delivery, and increased use of formula feeding. The resulting relative absence of immune-regulating signals may have led to the expression of chronic non-infectious inflammatory diseases, including but not limited to food allergy. In this chapter, we will review what is known about the early life influences on

A. L. Yee (✉)
Interdisciplinary Scientist Training Program, University of Chicago, Chicago, IL, USA

M. M. Buschmann · J. A. Gilbert
Department of Pediatrics and Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, USA
e-mail: jagilbert@ucsd.edu

C. E. Ciaccio
Department of Pediatrics and Medicine, The University of Chicago, Chicago, IL, USA
e-mail: cciaccio@peds.bsd.uchicago.edu



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_11

the development of food allergy, early life microbial colonization of the human gut, intestinal dysbiosis and gut barrier function, and the potential for the development of therapeutics to modulate the microbiome and/or mimic its effects on the immune system.

## Microbiome-Immune System Interactions

The normal physiological response to food antigens is oral tolerance, but in the absence of tolerance, T cells differentiate into food antigen–specific Th2 cells and drive B cells to produce antigen-specific IgE [10]. Compared to conventionally raised mice, germ-free mice show aberrant immune cell populations and altered size and structure of lymphoid tissues [11]. Furthermore, germ-free mice show elevated serum IgE concentrations, increased circulating basophil populations, and allergic inflammation, underscoring the role of the commensal microbiota in promoting tolerance [12, 13].

The microbiota interacts with both the innate and adaptive immune systems in the intestinal mucosa and can promote tolerance via many mechanisms. Commensal microbes produce metabolites that induce inflammasome activation in epithelial cells, triggering strengthening of the epithelial barrier [14]. Microbes can also act on macrophages, which stimulate innate lymphoid cells to produce IL-22 to promote the epithelial barrier. Alternatively, macrophage-derived IL-1β stimulates innate lymphoid cells to act on dendritic cells (DCs) to secrete IL-10 and retinoic acid, which are key to the differentiation of regulatory B and T cell subsets [14]. Microbes contain ligands and can also produce metabolites, such as short-chain fatty acids (SCFAs) and histamine, which act on mucosal dendritic cells via G-protein-coupled receptors. Metabolites produced both by microbes and by the host's innate signaling cells can act directly on Bregs and Tregs [14]. Therefore, the commensal microbiota can induce cytokine production by multiple cell types, which have downstream effects on adaptive immune cells and epithelial barrier function, or directly stimulate Bregs and Tregs to promote tolerance.

### Cytokine Production

Microbial cellular components and metabolic products are responsible for inducing cytokine production. More specifically, lipopolysaccharide (LPS) from the outer membrane of Gram-negative bacteria has long been known to restore tolerance in germ-free mice [15]. TLR4 is an important receptor for microbial products, including LPS. Mice lacking TLR4 signaling show increased allergen-specific IgE levels compared to TLR4-sufficient mice [10, 16]. In the same study, broad-spectrum antibiotics evoked allergic sensitization in mice with TLR4 signaling, supporting the hypothesis that the intestinal bacteria were the source of TLR4 ligand [16]. Therefore, LPS is immunostimulatory, and the level of immune stimulation can depend on its source. Metagenomic analysis of fecal samples from genetically related, but geographically separated children, revealed differences in LPS synthesis. Children with low risk for allergy had higher proportions of *Bifidobacterium* and the LPS in their samples derived primarily from *E. coli*, while children with higher risk for allergy had increased abundance of *Bacteroides*, which accounted for the majority of their LPS [17]. Exposure to *E. coli* LPS can elicit high levels of cytokine production [17]. TLR4 expression is significantly increased just before birth but is rapidly attenuated within hours of exposure to the microbiota [18]. This is evidence of priming of the fetal epithelium for an early immune response and desensitization to inflammatory signals when adapting to an increased bacterial load [19]. This suggests that LPS is a key microbial ligand involved in priming the immune system and plays a protective role in mitigating allergic responses [10]. (See Fig. 11.1).

### Microbial Stimulation of Treg and Breg Cells

Regulatory T (Treg) cells are crucial for maintaining homeostasis and preventing inflammation at mucosal interfaces. In the colon, a class of Treg cells is peripherally educated: starting from

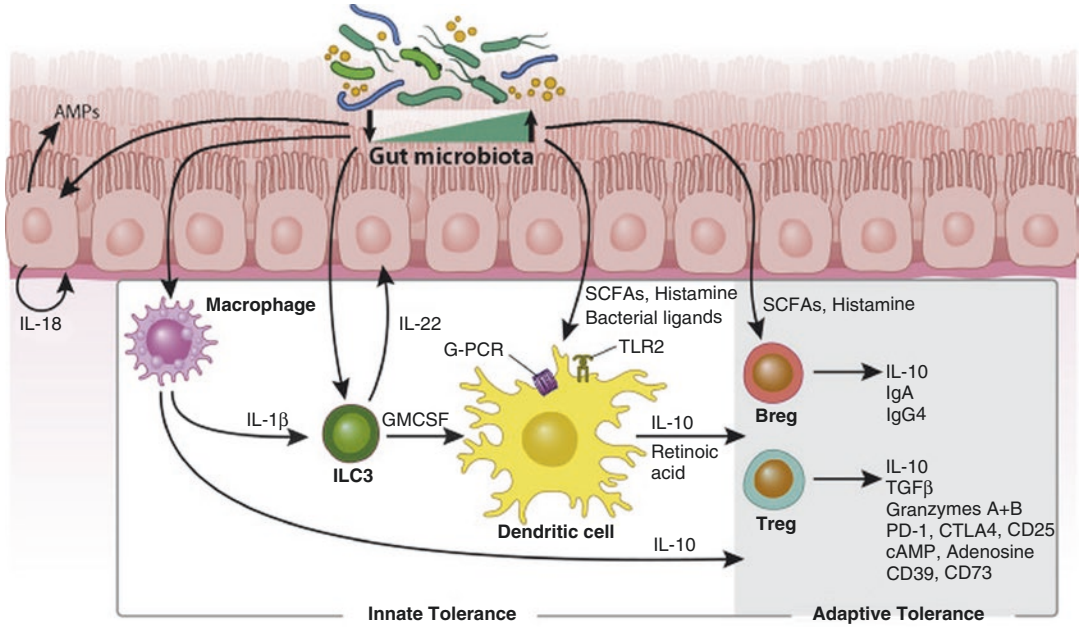



**Fig. 11.1** Interactions between the microbiota and innate and adaptive immune systems in tolerance induction within the mucosa. The gut microbiota has been shown to interact with the mucosal immune system at many levels to support the induction of tolerance. Microbially derived metabolites induce inflammasome activation in ECs, leading to release of IL-18 and antimicrobial peptide (*AMP*) secretion, thereby strengthening the epithelial barrier. ILC3-derived IL-22 also promotes the epithelial barrier. Macrophage-derived IL-1β promotes GM-CSF release from ILC3s, further promoting IL-10 and retinoic acid secretion by DCs, which are essential for induction of Breg and Treg cells. Mucosal DCs can be influenced directly by microbially associated metabolites, such as short-chain fatty acids (*SCFAs*) and histamine, which polarize cytokine production through G protein–coupled receptor (*G-PCR*) signaling. Bacterially derived ligands can directly activate DC pattern recognition receptors, in particular Toll-like receptor 2 (*TLR2*), also promoting IL-10 and retinoic acid secretion. Mucosal macrophages secrete large amounts of IL-10, thereby contributing to the tolerance state. In addition to the influence of immunoregulatory factors released by microbiota-exposed innate immune cells, on Breg and Treg polarization, the microbiota can also have direct effects on both Breg and Treg cells. Metabolites, such as SCFAs and histamine, promote polarization of these regulatory cells, and activation of Toll-like receptor 9 supports expansion of IL-10$^{+}$ Breg cells. *cAMP*, Cyclic AMP; *CTLA4*, cytotoxic T lymphocyte–associated protein 4; *PD-1*, programmed cell death 1 [14] (Reprinted from Sampson et al. [14], with permission from Elsevier)

naïve CD4+ T cells, they efficiently differentiate into Foxp3+ Tregs upon encountering bacterially derived antigens [20]. The endogenous microbiota can promote Treg induction directly or via cytokine production. Colonizing germ-free mice with a standardized reference microbiota, known as Altered Schaedler Flora, resulted in the expansion of the CD4+ CD25+ Foxp3+ Treg population in the colonic lamina propria [21]. In particular, *Clostridia* species, especially from clusters IV and XIVa, have been shown to drive expansion of colonic Treg cells [22]. By a different mechanism, both *Bacteroides fragilis* and *Bifidobacterium bifidum* can also induce Foxp3+ Tregs, which underscores the functional redundancy of the microbiota [23]. Cell surface polysaccharides in these two species have been reported to activate TLR2 and act via dendritic cells to induce Tregs [24, 25]. When the antigen-presenting cells in the gut promote T helper cell differentiation into Th2 cells, B cells switch and mature into IgE-producing cells, which drives allergy [26]. Tolerance is the result of antigen presentation in the gut-associated lymphoid tissue (GALT), leading to Treg development and driving B cells to produce primarily IgG antibodies to foods. Regulatory B cells also secrete IL-10 and drive IgG4 responses [26].

## Microbial Metabolites

The gut microbiota produces metabolites that interface with the immune system. Some examples include short-chain fatty acids (SCFAs; including propionate, butyrate, and acetate), long-chain fatty acids (LCFAs; especially ω3), D-type amino acids, and vitamins.

SCFAs act as an energy source for colonocytes and can regulate tight junction organization, promoting barrier function [27]. Furthermore, SCFAs can protect against allergic disease via induction of Treg cells in the colon [28–30]. In a germ-free mouse model, adding SCFAs to drinking water increased the abundance of colonic Tregs and was protective against inflammation [29]. Another murine study demonstrated that high fiber diet increased the release of SCFAs, enhanced retinal dehydrogenase activity in CD103+ dendritic cells, and improved oral tolerance [28]. Mice lacking receptors for SCFAs had exacerbated food allergy and lower levels of CD103+ dendritic cells [28]. SCFAs can bind 'metabolite-sensing' G-protein-coupled receptors, which influence Treg biology, epithelial integrity, gut homeostasis, DC biology, and IgA antibody responses [31]. $CD103^+$ DCs metabolize vitamin A to retinoic acid, which promotes Treg cell differentiation and homing to the gut [31]. Western diets are predominantly low in fiber and possibly vitamin A, which lowers the tolerogenic capacity of $CD103^+$ DCs and may increase allergic sensitization [31]. SCFAs also inhibit histone deacetylase, which affects gene transcription in many cells and tissues, and can lead to epigenetic modification of host DNA [31].

In addition to SCFAs, the microbiota can secrete a range of other metabolites that influence mucosal immune responses, such as long chain fatty acids, histamine, and vitamins. Long-chain fatty acids (LCFAs) are generally derived from dietary components and act both as energy sources and in the regulation of immune responses [32]. Germ-free animals exhibit alterations in the composition in their lipid metabolites, and commensal microbes play a role in LCFA metabolism [33, 34]. The ω3 and ω6 FAs are essential FAs that mammals cannot produce, and ω3 FAs have been shown to have anti-inflammatory and anti-allergic effects [35–37].

Histamine is a biogenic amine that induces smooth muscle and vasodepressor activity during anaphylaxis [27]. Cells of both the innate and adaptive immune systems harbor histamine receptors. Histamine can be produced by a number of different bacterial strains, and these bacteria are more abundant in patients with asthma – a related atopic disease – compared to controls [27].

Vitamins act as antioxidants, transcription factors, and cofactors for metabolism, so they are indispensable for many biological processes. They are obtained from dietary sources and also are produced by the commensal microbiota. In addition to directly affecting metabolism, microbial metabolites of some vitamins act as ligands for immune cell signaling.

## The Importance of Microbe-Host Immune Interactions in Early Life

It appears that immune cell populations are regulated by the microbiota in a time-restricted manner [38]. There may be a critical window during early life when microbial perturbations can have persistent effects on the immune system in later life. While humans were canonically considered sterile in utero, colonization may occur prior to birth. Some groups have reported isolating bacteria from the umbilical cord, placenta, and meconium of healthy deliveries, while other studies and the ability to rear germ-free animals argue against these findings [39–44]. Regardless of whether live bacteria can cross the placenta, it seems clear that microbial products, or their influence on the maternal immune system, might affect fetal development. A significant source of the neonatal microbiota is vertical transmission from the mother peripartum [40]. Germ-free mice develop with an abnormal immune system, including smaller lymphoid structures, and decreased activation of T and B cells [38]. Seeding a germ-free mouse with a microbiota

as an adult results in gene transcriptional differences compared with germ-free mice that get a microbiota at birth, suggesting that some of these immune cell abnormalities are regulated by the microbiota during the early life time window [45].

Neonates are exposed to maternal microbes during birth. Many studies have examined the effects of delivery mode (Caesarean versus vaginal delivery), gestational age (term versus preterm birth), and feeding source (breastfeeding versus formula) on the initial microbiome. Infants born via Caesarean section harbor a microbiota that resembles their mother's skin microbiota, while the microbiota of infants born by vaginal birth is similar to that of their mother's vagina and gut [46, 47]. Caesarean-delivered infants show lower diversity of microbes. These differences by mode of delivery persist, with microbes associated with Caesarean delivery detectable up to 2 years following birth [48]. Furthermore, Caesarean delivery has been linked to increased risk for allergy and atopic disease [49, 50]. Breastfeeding versus formula feeding has been shown to influence the child's gut microbiome and provide another route of vertical transmission of maternal microbes [51, 52]. Formula feeding has been inconsistently linked to allergy risk, implying that breast milk is complex and its bioactive properties are not fully understood [53–55].

In the context of vertical transmission, the decreased microbial exposure associated with Westernized diet and hygiene likely compounds over generations. That is, each subsequent generation loses key members of the microbiota, so decreased microbial diversity and its potential immune consequences accumulate in highly developed societies [9]. In a murine model, humanized mice fed a diet low in microbially accessible carbohydrates showed alterations to the microbiota that were reversible within the same generation. However, over several generations, the low carbohydrate diet caused a progressive loss of diversity that was not reversed with the reintroduction of the dietary carbohydrates [56]. Indeed, a high-fiber maternal diet was demonstrated to be protective against offspring developing allergic airway disease in mice, implying that diet is strongly linked to microbiome function and can have intergenerational effects [57]. Notably, the timeframe during pregnancy when maternal diet affects the offspring's immune phenotype remains to be clarified [58]. The effects of maternal diet may be transient, via the gut microbiome and inflammation, or longer lasting, such as by epigenetic programming.

Other sources of early-life exposure, such as environmental influences and sharing a home with other children and/or pets, also appear to be important [9, 59]. Bacterial communities in residences with dogs or cats present are significantly richer and more diverse compared to those without pets, and having pets correlates with lower incidence of food sensitivity [59–61]. Pre- and postnatal exposure to furry pets increased the abundance of two bacteria, *Ruminococcus* and *Oscillospira*, which have been negatively associated with childhood atopy [62]. The presence of older siblings in the home has been shown to be protective against asthma and food allergy [63, 64]. In fact, Strachan's original hygiene hypothesis stemmed from his observation of the reduced rate of hay fever among children with more siblings [7]. The mechanisms by which exposure to other children and/or pets alters microbiome composition remain unclear, but it is generally thought that these would increase a child's contact with environmental microbes, promoting a diverse and healthy gut microbiota [59]. Parents who "cleaned" an infant's pacifier by sucking on it imparted their own salivary microbiota, and this practice was protective against asthma development in a small cohort [65].

Antibiotic exposure has been shown to perturb the microbiome. Early life courses of antibiotics correlate with allergic sensitization in humans and mouse models [54, 66, 67]. Taken together, these studies have identified sources of environmental exposure that contribute to differences in microbial composition in early life and may affect the immune system.

## Microbes Associated with Food Allergy

In studies of gut microbial composition, both overall diversity and specific microbial taxa have been correlated with food sensitization. Reduced bacterial diversity in the infant's intestinal microbiome has been correlated with increased risk of allergic sensitization at school age [67, 68]. However, other studies have demonstrated that children with cow's milk allergy have, overall, a significantly greater bacterial diversity than healthy controls [69]. Interestingly, no specific bacterial taxa have been consistently associated with the onset of food allergy; rather, a broad range of microbes have been linked to tolerogenic mechanisms [4].

Observational studies in humans yield variable findings, probably due to microbial heterogeneity in study populations, study design, and lack of a standardized definition of food sensitivity [70]. However, several large cohort studies have correlated the relative abundance of specific organisms with allergic sensitization – characterizing the microbiota by 16S rRNA gene amplicon sequencing. The 16S rRNA gene encodes a ribosomal subunit and contains both highly conserved sites (ideal for primer binding) and hypervariable regions (which can provide taxon-specific identification) [71, 72]. Many studies have identified specific taxa within the microbiota that are more abundant in healthy controls than in individuals with allergy. Relatively few studies have examined food allergy as opposed to asthma or other atopic manifestations. The major patterns of bacterial abundance identified in large cohort studies of food allergy are summarized in Table 11.1.

**Table 11.1** Major patterns of bacterial abundance identified in large cohort studies of food allergy

| Cohort | Taxa implicated | Findings |
|---|---|---|
| 216 US children, ages 3–6 months, with parental history of allergy or asthma [6] | *Haemophilus, Dialister, Dorea, Clostridium, Citrobacter, Oscillospira, Lactococcus* | Lower levels of *Haemophilus, Dialister, Dorea,* and *Clostridium* in children with sensitization (sIgE ≥0.10 $kU_A/L$) to at least one food allergen among milk, egg, peanut, soy, and wheat. Lower relative abundances of *Citrobacter, Oscillospira, Lactococcus,* and *Dorea* in stool collected at ages 3 to 6 months in children who had food allergy by age 3 years |
| 166 Canadian children, ages 3–12 months [73] | Enterobacteriaceae, Bacteroidaceae | Lower gut microbial richness at age 3 months was associated with increased likelihood of food sensitization (SPT wheal ≥2 mm than negative control) by age 12 months. Enterobacteriaceae were overrepresented and Bacteroidaceae were underrepresented in food-sensitized infants at 3 months and 1 year |
| 226 milk-allergic children in the United States [74] | Firmicutes, Clostridia | Firmicutes including Clostridia enriched in the gut microbiome of infants ages 3 to 6 months whose milk allergy resolved by age 8 years |
| 141 US children with egg allergy or non-food-allergic controls [75] | Lachnospiraceae, Streptococcaceae, and Leuconostocaceae | Genera from Lachnospiraceae, Streptococcaceae, and Leuconostocaceae were differentially abundant in the gut microbiome of U.S. children with egg allergy versus non-food-allergic controls |
| 1879 American gut participants (primarily adult, mean age 45 years), 2.5% self-reported allergy to peanuts, 3.2% to tree nuts, 2.6% to shellfish, and 9.1% to other foods [76] | *Bacteroides fragilis,* Clostridiales, *Prevotella*, and *Ruminococcaceae* | Marked reduction in microbial richness and alpha diversity in those adults self-reporting peanut or tree nut allergy compared to those without peanut or tree nut allergy. Positive correlation of peanut/tree nut allergy with *Bacteroides fragilis* abundance; negative correlation with Clostridiales, *Prevotella*, and *Ruminococcaceae* abundance |
| 2737 UK adults (89% female, age = 60 ± 12), 532 of whom had self-reported allergy to nuts, penicillin, fish, shellfish, alcohol, or fruits [77] | Prevotellaceae | Negative association between Prevotellaceae and food allergy |

## Notable Humanized Mice Studies

While these observational human studies have identified correlations between microbial abundance and disease states, recent studies take advantage of humanized mouse models to identify causative relationships underlying tolerogenic mechanisms in the gut microbiota.

Using a food-allergy prone transgenic mouse model, Noval Rivas and colleagues demonstrated that allergic disease correlated with numerous taxa annotated to the Bacteroidetes and the family Lachnospiraceae [78]. They transferred this microbiota into wild-type mice, which led to the development of the food allergy phenotype in the recipients [78]. Round and colleagues monocolonized mice with *Bacteroides fragilis* and found that polysaccharide A mediated the suppressive capacity of Tregs and induced anti-inflammatory cytokine production [79].

Atarashi and colleagues used germ-free mice to examine the effect of *Clostridium* species on IgE responses in egg allergy models [80]. They determined that among the indigenous commensal bacteria, *Clostridium* spp. belonging to clusters IV and XIVa were outstanding inducers of Tregs in the colon. They then rationally selected a mixture of 17 strains that attenuated pathology in models of colitis and allergy [22]. Butyrate production is widely distributed among anaerobic bacteria and, in particular, has been identified as a key metabolic function in the *Clostridial* clusters XIVa and IV [81, 82]. By selectively colonizing germ-free mice, Stefka and colleagues also demonstrated that food allergy protective capacity is conferred by a *Clostridia*-containing microbiota. They showed that *Clostridia* colonization induced intestinal IL-22 production, which resulted in reduced intestinal barrier permeability to peanut allergens [83]. Subsequently, Feehley and colleagues colonized germ-free mice with stool from healthy or cow's milk allergic infants and found that the mice receiving the healthy stool were protected against anaphylaxis to a cow's milk allergen [84]. Using 16S rRNA gene abundance, they identified *Anaerostipes caccae*, a clostridial species that correlated with differentially expressed ileal epithelium genes in healthy-colonized mice. They then mono-colonized germ-free mice with *A. caccae* and confirmed that it was protective against cow's milk allergy [84].

## Microbiome-Based Therapies

Fecal microbiota transplantation (FMT) has been shown to be effective in restoring diversity lost with recurrent *Clostridium difficile* infection. The high (>80%) success of this microbiota replacement tactic provides evidence for the efficacy of microbiota-based therapies [23]. However, the components of the 'ideal' donor feces remain unknown. In some studies, cell-free supernatant achieved a similar success rate to that of whole feces, implying that small molecules and phages may be more clinically relevant than the microbes themselves [85]. Small molecules produced by gut commensals can be synthesized or metabolized from dietary compounds. These metabolites are involved in signaling, both with other microbial cells and with host cells. They can enter the circulation and are, therefore, less circumscribed than the microbiota itself [23]. Therefore, identifying small molecules produced by the microbiota represent promising drug development targets.

Microbiota-based therapies currently under study for food allergy fall into three main categories:

1. Dietary supplementation with prebiotics
2. Probiotics (administered with or without immunotherapy)
3. Small molecules

### Prebiotics

Human milk oligosaccharides (HMOs) found in breast milk are associated with an increased proportion of *Bifidobacterium* and *Lactobacillus* taxa in the infant gut microbiome [86–88]. The composition of HMOs in breast milk varies based on maternal factors such as diet and genetics,

but HMOs pass undigested through the infant's gastrointestinal tract and lead to an increase in taxa that can use these complex structures as a carbon substrate [88]. Bifidobacteria are widely considered probiotic, and allergic mothers have been shown to have lower relative abundance of bifidobacteria in their milk [86, 89].

The relationship between the gut microbiome and diet is undeniable. Various studies have shown that maternal diet during pregnancy and the child's diet through 24 months of age may influence the risk of food allergy [4, 90, 91]. Indeed, a higher intake of fruits, vegetables, and home-prepared foods in the first 2 years of life was associated with reduced food allergy incidence [92]. Several of these studies have shown that the dietary differences may be tied to nutrients, including short-chain fatty acids, which are produced by colonic microbiota metabolizing dietary fibers. SCFAs can bind to metabolite-sensing G-protein-coupled receptors. These receptors and their downstream metabolites have immunomodulatory effects on Tregs, epithelial integrity, gut homeostasis, dendritic cell biology, and IgA antibody responses [28]. SCFAs can also inhibit histone deacetylase, which affects gene transcription in many cells and tissues, and leads to epigenetic modification of DNA [31].

Because the Westernized diet is dominated by simple carbohydrates from ultra-processed food, fiber supplementation has been proposed as a dietary intervention. Indeed, potato starch has been shown to be a particularly impactful form of fiber with regard to butyrate synthesis by key SCFA-anabolic microbiota [93], and therefore represents a potential avenue to improve gut-health, tight-junction integrity, and allergic desensitization. The Western diet also lacks sufficient omega-3 rich fatty acids and interestingly is often elevated in pro-inflammatory omega-6 fatty acids. A retrospective analysis of three randomized controlled trials of omega-3 supplementation during pregnancy and lactation showed that omega-3 supplementation prevented food allergy [94]. The mechanism may be microbiome mediated: circulating omega-3 fatty acids correlate with microbiome diversity [95], and in a randomized trial, omega-3 supplementation increased of the proportion short-chain fatty acid producing bacteria in the gut microbiome [96].

## Probiotics

Probiotics are defined as nonpathogenic live microorganisms that, when consumed in adequate amounts, have a positive effect on the health of the host [97]. However, studies on probiotics are limited due to the fact that in vivo effects of a strain may be different than in vitro effects, and the effects can be strain specific even within the same species [97].

In allergy, probiotics are believed to act on the immune system on multiple levels. For example, they could modulate the commensal gut microbiota structure and function through nutrient competition or cross-feeding. In cow's milk allergic infants given formula supplemented with *Lactobacillus rhamnosus GG*, there was an expansion in butyrate-producing taxa in the gut microbiota [69]. Another possible route of action of probiotics is inducing a low degree of mucosal inflammation, stimulating the innate immune system and downregulating allergic responses. By maintaining a homeostatic gut environment, probiotics may play a role in preventing epithelial barrier leakage and antigen absorption. Probiotic strains can interact with host enterocytes and lead to changes in mucus thickness and gut permeability [98–100]. Finally, probiotics can modulate tolerogenic mechanisms, for example, by stimulating secretory IgA production or altering the cytokine response of immune cells [29, 80, 83, 101].

A recent randomized double-blind placebo-controlled trial of peanut oral immune therapy +/− probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 (PPOIT) demonstrated that the probiotic induced high rates of desensitization and reduced peanut skin test reactivity, decreased peanut-specific IgE, and increased peanut-specific IgG4 [102]. Subjects received a fixed dose of probiotic along with peanut OIT daily for 18 months. PPOIT was well tolerated compared to OIT with no participants withdrawing from adverse reac-

tions. A follow-up at 4 years post-study showed that 67% of PPOIT group still consumed peanuts safely. However, there was no probiotic-only arm of the study, so the effect of the probiotic alone versus OIT alone versus synergistic effects remain unclear [103].

While further work is required to determine the timing and efficacy of probiotics, the current evidence suggests that probiotics are more effective in the prevention, rather than treatment, of food allergies. This again underscores the key immune training window during early life. Furthermore, the effects of probiotics seem likely to be strain specific, which underscores the importance of accounting for functional, rather than taxonomic, nuances [70].

## The Microbiota in Eosinophilic Esophagitis

### An Example of Severe Food Allergic Disease

Eosinophilic esophagitis (EoE) is a chronic allergic disease in which food or environmental allergens trigger a Th2-mediated response leading to eosinophilic esophageal infiltration [104]. As is the case with food allergy more broadly, the incidence of EoE has dramatically increased in industrialized countries over the past few decades, suggesting that environmental and microbial factors might contribute to its etiology [105]. EoE risk appears to correlate with early life exposures, including Caesarean delivery and antibiotic use [106, 107]. Although the exact allergic event that incites EoE has remained elusive, dietary elimination therapies and allergen-free formulas are highly effective in treating EoE, underscoring the role of dietary antigens as triggers [108]. As such, it can be considered as a special case of severe food allergy with particular considerations for the microbiome.

While studies on EoE pathogenesis have identified risk factors and human genes that may contribute, the interplay with the microbiome is less well studied. The microbiota could induce inflammation, or EoE could cause perturbations to the microbiota, or the relationship may be bidirectional. For example, esophageal eosinophils are reservoirs of anti-microbial products that can act on the commensal microbial population when released [109]. EoE inflammation can alter esophageal motility, which can affect the normal dynamics within the gastrointestinal tract and potentiate blooms of certain taxa [109]. Patients with EoE have restricted diets to avoid food allergens, representing a different nutritional substrate from healthy controls.

The intestinal microbiome has been extensively studied, particularly via fecal samples; however, the rest of the gastrointestinal tract is less well characterized [110]. A small number of studies have examined the esophageal microbiome in the context of EoE. A prospective study using esophageal string test samples from children and adults undergoing upper endoscopy showed an increase in overall bacterial load, but not diversity, in EoE and GERD patients by quantitative PCR [109]. Patients with active EoE harbored increased levels of *Haemophilus* compared to normal controls, while the microbial pattern returned to that of a normal esophagus following standard of care EoE treatment [109]. An esophageal biopsy study comparing children with and without EoE revealed a distinct difference in their microbiota, with an elevated abundance of Proteobacteria (especially taxa belonging to *Neisseria* and *Corynebacterium*) in patients with active EoE [104]. Other studies have examined other esophageal diseases and found similar increases in Proteobacteria and *Haemophilus* with reflux esophagitis, so it may be the case that patterned shifts in the esophageal microbiome may be common to multiple forms of inflammation [110].

### Considerations for EoE Treatment

One of the potential drivers of changes in the EoE-associated microbiome is the use of proton pump inhibitors (PPI). PPI administration increases gastric pH, which may have downstream effects on the microbiome. PPIs are frequently used in evidence-based care to treat

EoE but may also play a role in its pathogenesis. For example, pepsin proteinases responsible for digesting food proteins into small peptides operate at pH between 1.8 and 3.2; if the gastric pH is increased enough to inactivate the pepsins, undigested proteins may be absorbed intact and provoke an immune response [111]. Furthermore, PPIs have been demonstrated to increase mucosal permeability, which would facilitate the absorption of undigested food allergens [111]. Thus, PPIs can act directly on the microbiome to alter the populations of acid-sensitive bacteria or potentially alter the host response to food via changes in digestion and absorption of allergens. Indeed, the infant immune system might be most susceptible to PPI exposure: the early life factor identified as the strongest risk factor for EoE development was acid suppressant usage during the first year of life [106, 111]. Overall, further investigation into the consequence of PPI therapy is warranted due to its widespread application in cases of EoE [110].

In some cases of EoE, patients cannot meet their nutritional or caloric needs through oral diet alone and, therefore, may require enteral nutrition through a feeding tube in the short or long term until the esophageal inflammation has subsided. However, the use of a tube bypasses host defenses and acts as a direct conduit for microbial migration, a drastic change in how food travels in the gastrointestinal tract, which can lead to increases in microbial biomass in the stomach and duodenum. This microbial overgrowth in the upper gastrointestinal tract may result in impaired barrier function and cause complications like diarrhea, sepsis, or malabsorption [112]. Diarrhea is a common side effect of enteral nutrition, and while causality remains to be established, diarrhea can be caused by alterations in the microbiome and can also result in reduced diversity of strains present and increase in potentially pathogenic microorganisms [113]. A few studies have specifically examined microbiome composition and associated metabolites in the context of enteral feeding though none have been performed in EoE patients specifically. In patients with Crohn's disease as well as in healthy controls, enteral feeding altered the microbial metabolites found in stool and breath [114]. A clinical trial is ongoing to examine the fecal microbiome pre- and post- tube feeding with standard formula versus blenderized nutrition [114]. Due to the potential of tube feeding to affect the microbiome, it warrants further consideration for EoE patients.

## Conclusions

There is considerable evidence correlating changes in the microbiome with alterations in allergic sensitivity. The human microbiome maintains an equilibrium with the host immune and physiological states. Indeed, the host immune system evolved to manage and control the microbiota that interacts with the human body. Therefore, it is axiomatic that disruption of the microbiome could result in changes in host physiology and immune activity that could precipitate or exacerbate food allergy. The use of animal studies, especially gnotobiotic investigations, has shown that a food allergy phenotype can be transferred from one animal to another purely by transferring the gut microbial contents. Similarly, desensitization to an allergen can be achieved by altering gut microbial contents. While the evidence to support the extrapolation of these findings to human populations is limited, the numerous studies demonstrating that probiotics, prebiotics, or changes in lifestyle (diet, furry pets, outdoor activity) can influence sensitization rates and even reverse allergy in some cases suggest that microbial manipulation presents real potential as a mechanism for treating food allergy. Future work must target mechanistic understanding of the mechanism by which host-microbe interactions alter allergy onset and identify more defined strategies, including probiotic formulations and small molecule therapeutics, to enhance the efficacy of existing desensitization efforts as well as reducing onset in vulnerable populations.

## References


1. Sicherer SH, Allen K, Lack G, Taylor SL, Donovan SM, Oria M. Critical issues in food allergy: a national academies consensus report. Pediatrics. 2017;140:e20170194.
2. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. NCHS Data Brief. 2013;121:1–8.
3. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.
4. Berni Canani R, Paparo L, Nocerino R, Di Scala C, Della Gatta G, Maddalena Y, et al. Gut microbiome as target for innovative strategies against food allergy. Front Immunol. 2019;10:191. https://doi.org/10.3389/fimmu.2019.00191.
5. Leung ASY, Wong GWK, Tang MLK. Food allergy in the developing world. J Allergy Clin Immunol. 2018;141:76–78.e1.
6. Savage JH, Lee-Sarwar KA, Sordillo J, Bunyavanich S, Zhou Y, O'Connor G, Set a. A prospective microbiome-wide association study of food sensitization and food allergy in early childhood. Allergy. 2018;73:145–52.
7. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299:1259–60.
8. Scudellari M. News feature: cleaning up the hygiene hypothesis. Proc Natl Acad Sci. 2017;114:1433–6.
9. Bloomfield SF, Rook GA, Scott EA, Shanahan F, Stanwell-Smith R, Turner P. Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. Perspect Public Health. 2016;136:213–24.
10. Plunkett CH, Nagler CR. 2017. The influence of the microbiome on allergic sensitization to food. J Immunol Baltim Md. 1950;198:581–9.
11. Hansen CHF, Nielsen DS, Kverka M, Zakostelska Z, Klimesova K, Hudcovic T, Tlaskalova-Hogenova H, Hansen AK. Patterns of early gut colonization shape future immune responses of the host. PLoS One. 2012;7:e34043.
12. Hill DA, Siracusa MC, Abt MC, Kim BS, Kobuley D, Kubo M, et al. Commensal bacteria–derived signals regulate basophil hematopoiesis and allergic inflammation. Nat Med. 2012;18:538–46.
13. Rodriguez B, Prioult G, Bibiloni R, Nicolis I, Mercenier A, Butel M-J, Waligora-Dupriet A-J. Germ-free status and altered caecal subdominant microbiota are associated with a high susceptibility to cow's milk allergy in mice. FEMS Microbiol Ecol. 2011;76:133–44.
14. Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA. Mechanisms of food allergy. J Allergy Clin Immunol. 2018;141:11–9.
15. Wannemuehler MJ, Kiyono H, Babb JL, Michalek SM, McGhee JR. Lipopolysaccharide (LPS) regulation of the immune response: LPS converts germ-free mice to sensitivity to oral tolerance induction. J Immunol. 1982;129:959–65.
16. Bashir MEH, Louie S, Shi HN, Nagler-Anderson C. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. J Immunol. 2004;172:6978–87.
17. Vatanen T, Kostic AD, d'Hennezel E, Siljander H, Franzosa EA, Yassour M, et al. Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. Cell. 2016;165:842–53.
18. Lotz M, Gütle D, Walther S, Ménard S, Bogdan C, Hornef MW. Postnatal acquisition of endotoxin tolerance in intestinal epithelial cells. J Exp Med. 2006;203:973–84.
19. Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. Nature. 2012;489(7415):231–41. https://doi.org/10.1038/nature11551.
20. Kraj P, Ignatowicz L. The mechanisms shaping the repertoire of CD4+ Foxp3+ regulatory T cells. Immunology. 2018;153:290–6.
21. Geuking MB, Cahenzli J, Lawson MAE, Ng DCK, Slack E, Hapfelmeier S, et al. Intestinal bacterial colonization induces mutualistic regulatory T cell responses. Immunity. 2011;34:794–806.
22. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature. 2013;500:232–6.
23. Skelly AN, Sato Y, Kearney S, Honda K. Mining the microbiota for microbial and metabolite-based immunotherapies. Nat Rev Immunol. 2019;19:305–23.
24. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian SK. The Toll-like receptor pathway establishes commensal gut colonization. Science. 2011;332:974–7.
25. Verma R, Lee C, Jeun E-J, Yi J, Kim KS, Ghosh A, et al. Cell surface polysaccharides of *Bifidobacterium bifidum* induce the generation of Foxp3+ regulatory T cells. Sci Immunol. 2018;3(28):pii: eaat6975. https://doi.org/10.1126/sciimmunol.aat6975.
26. Turcanu V, Brough HA, Toit GD, Foong R-X, Marrs T, Santos AF, Lack G. Immune mechanisms of food allergy and its prevention by early intervention. Curr Opin Immunol. 2017;48:92–8.
27. Barcik W, Wawrzyniak M, Akdis CA, O'Mahony L. Immune regulation by histamine and histamine-secreting bacteria. Curr Opin Immunol. 2017;48:108–13.
28. Tan J, McKenzie C, Vuillermin PJ, Goverse G, Vinuesa CG, Mebius RE, et al. Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. Cell Rep. 2016;15:2809–24.
29. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013;341:569–73.

30. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013;504:446–50.
31. McKenzie C, Tan J, Macia L, Mackay CR. The nutrition-gut microbiome-physiology axis and allergic diseases. Immunol Rev. 2017;278:277–95.
32. Hirata S-I, Kunisawa J. Gut microbiome, metabolome, and allergic diseases. Allergol Int Off J Jpn Soc Allergol. 2017;66:523–8.
33. Shibata N, Kunisawa J, Kiyono H. Dietary and microbial metabolites in the regulation of host immunity. Front Microbiol. 2017;8:2171. https://doi.org/10.3389/fmicb.2017.02171.
34. Kishino S, Takeuchi M, Park S-B, Hirata A, Kitamura N, Kunisawa J, et al. Polyunsaturated fatty acid saturation by gut lactic acid bacteria affecting host lipid composition. Proc Natl Acad Sci. 2013;110:17808–13.
35. Kunisawa J, Arita M, Hayasaka T, Harada T, Iwamoto R, Nagasawa R, et al. Dietary ω3 fatty acid exerts anti-allergic effect through the conversion to 17,18-epoxyeicosatetraenoic acid in the gut. Sci Rep. 2015;5:9750.
36. Yates CM, Calder PC, Ed Rainger G. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. Pharmacol Ther. 2014;141:272–82.
37. Kremmyda L-S, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. Clin Rev Allergy Immunol. 2011;41:36–66.
38. Gensollen T, Blumberg RS. Correlation between early-life regulation of the immune system by microbiota and allergy development. J Allergy Clin Immunol. 2017;139:1084–91.
39. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome development: mom matters. Trends Mol Med. 2015;21:109–17.
40. Blaser MJ, Dominguez-Bello MG. The human microbiome before birth. Cell Host Microbe. 2016;20:558–60.
41. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Sci Transl Med. 2014;6(237):237ra65. https://doi.org/10.1126/scitranslmed.3008599.
42. Lauder AP, Roche AM, Sherrill-Mix S, Bailey A, Laughlin AL, Bittinger K, et al. Comparison of placenta samples with contamination controls does not provide evidence for a distinct placenta microbiota. Microbiome. 2016;4:29.
43. Leiby JS, McCormick K, Sherrill-Mix S, Clarke EL, Kessler LR, Taylor LJ, et al. Lack of detection of a human placenta microbiome in samples from preterm and term deliveries. Microbiome. 2018;6:196.
44. Moles L, Gomez M, Heilig H, Bustos G, Fuentes S, de Vos W, et al. Bacterial diversity in meconium of preterm neonates and evolution of their fecal microbiota during the first month of life. PLoS One. 2013;8:e66986.
45. Aidy SE, Hooiveld G, Tremaroli V, Bäckhed F, Kleerebezem M. The gut microbiota and mucosal homeostasis. Gut Microbes. 2013;4:118–24.
46. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe. 2015;17:852.
47. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci. 2010;107:11971–5.
48. Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, Jernberg C, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. Gut. 2014;63:559–66.
49. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between caesarean section and childhood asthma. Clin Exp Allergy. 2008;38:629–33.
50. Lieberman JA, Greenhawt M, Nowak-Wegrzyn A. The environment and food allergy. Ann Allergy Asthma Immunol. 2018;120:455–7.
51. Jost T, Lacroix C, Braegger CP, Rochat F, Chassard C. Vertical mother-neonate transfer of maternal gut bacteria via breastfeeding. Environ Microbiol. 2014;16:2891–904.
52. Penders J, Vink C, Driessen C, London N, Thijs C, Stobberingh EE. Quantification of *Bifidobacterium* spp., *Escherichia coli* and *Clostridium difficile* in faecal samples of breast-fed and formula-fed infants by real-time PCR. FEMS Microbiol Lett. 2005;243(1):141–7.
53. Azad MB, Becker AB, Guttman DS, Sears MR, Scott JA, Kozyrskyj AL. Gut microbiota diversity and atopic disease: does breast-feeding play a role? J Allergy Clin Immunol. 2013;131:247–8.
54. Yasmin F, Tun HM, Konya TB, Guttman DS, Chari RS, Field CJ, et al. Cesarean section, formula feeding, and infant antibiotic exposure: separate and combined impacts on gut microbial changes in later infancy. Front Pediatr. 2017;5:200. https://doi.org/10.3389/fped.2017.00200. eCollection 2017.
55. Lodge CJ, Tan DJ, Lau MXZ, Dai X, Tham R, Lowe AJ, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatr. 2015;104:38–53.
56. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. Nature. 2016;529:212–5.
57. Thorburn AN, McKenzie CI, Shen S, Stanley D, Macia L, Mason LJ, et al. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. Nat Commun. 2015;6:7320.
58. Chu DM, Meyer KM, Prince AL, Aagaard KM. Impact of maternal nutrition in pregnancy and lactation on

offspring gut microbial composition and function. Gut Microbes. 2016;7:459–70.
59. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Sears MR, et al. Infant gut microbiota and the hygiene hypothesis of allergic disease: impact of household pets and siblings on microbiota composition and diversity. Allergy Asthma Clin Immunol Off J Can Soc Allergy Clin Immunol. 2013;9:15.
60. Bufford JD, Reardon CL, Li Z, Roberg KA, DaSilva D, Eggleston PA, et al. Effects of dog ownership in early childhood on immune development and atopic diseases. Clin Exp Allergy. 2008;38(10):1635–43. https://doi.org/10.1111/j.1365-2222.2008.03018.
61. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA. 2002;288:963–72.
62. Tun HM, Konya T, Takaro TK, Brook JR, Chari R, Field CJ, et al. CHILD study investigators. Exposure to household furry pets influences the gut microbiota of infant at 3–4 months following various birth scenarios. Microbiome. 2017;5:40.
63. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med. 2000;343:538–43.
64. Koplin JJ, Dharmage SC, Ponsonby A-L, Tang MLK, Lowe AJ, et al. HealthNuts investigators. Environmental and demographic risk factors for egg allergy in a population-based study of infants. Allergy. 2012;67:1415–22.
65. Hesselmar B, Sjoberg F, Saalman R, Aberg N, Adlerberth I, Wold AE. Pacifier cleaning practices and risk of allergy development. Pediatrics. 2013;131:e1829–37.
66. Hirsch AG, Pollak J, Glass TA, Poulsen MN, Bailey-Davis L, Mowery J, Schwartz BS. Early-life antibiotic use and subsequent diagnosis of food allergy and allergic diseases. Clin Exp Allergy J. 2017;47:236–44.
67. Love BL, Mann JR, Hardin JW, Lu ZK, Cox C, Amrol DJ. Antibiotic prescription and food allergy in young children. Allergy Asthma Clin Immunol. 2016;12:41.
68. Bisgaard H, Li N, Bonnelykke K, Chawes BLK, Skov T, Paludan-Muller G, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol. 2011;128:646–652.e1–5.
69. Berni Canani R, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, et al. *Lactobacillus rhamnosus* GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. ISME J. 2016;10:742–50.
70. Zhao W, Ho H-E, Bunyavanich S. The gut microbiome in food allergy. Ann Allergy Asthma Immunol. 2019;122(3):276–82. https://doi.org/10.1016/j.anai.2018.12.012.
71. Yarza P, Yilmaz P, Pruesse E, Glöckner FO, Ludwig W, Schleifer K-H, et al. Uniting the classification of cultured and uncultured bacteria and archaea using 16S rRNA gene sequences. Nat Rev Microbiol. 2014;12:635–45.
72. Weinstock GM. Genomic approaches to studying the human microbiota. Nature. 2012;489:250–6.
73. Azad MB, Konya T, Guttman DS, Field CJ, Sears MR, HayGlass KT, et al. CHILD study investigators. Infant gut microbiota and food sensitization: associations in the first year of life. Clin Exp Allergy J. 2015;45:632–43.
74. Bunyavanich S, Shen N, Grishin A, Wood R, Burks W, Dawson P, Jet a. Early-life gut microbiome composition and milk allergy resolution. J Allergy Clin Immunol. 2016;138:1122–30.
75. Fazlollahi M, Chun Y, Grishin A, Wood RA, Burks AW, Dawson P, et al. Early-life gut microbiome and egg allergy. Allergy. 2018;73:1515–24.
76. Hua X, Goedert JJ, Pu A, Yu G, Shi J. Allergy associations with the adult fecal microbiota: analysis of the American gut project. EBioMedicine. 2016;3:172–9.
77. Jackson MA, Verdi S, Maxan M-E, Shin CM, Zierer J, Bowyer RCE, et al. Gut microbiota associations with common diseases and prescription medications in a population-based cohort. Nat Commun. 2018;9:2655.
78. Noval Rivas M, Burton OT, Wise P, Zhang Y, Hobson SA, Garcia Lloret M, et al. A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. J Allergy Clin Immunol. 2013;131:201–12.
79. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci. 2010;107:12204–9.
80. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, et al. Induction of colonic regulatory T cells by indigenous Clostridium species. Science. 2011;331:337–41.
81. Lopetuso LR, Scaldaferri F, Petito V, Gasbarrini A. Commensal Clostridia: leading players in the maintenance of gut homeostasis. Gut Pathog. 2013;5:23.
82. Chen C-C, Chen K-J, Kong M-S, Chang H-J, Huang J-L. Alterations in the gut microbiotas of children with food sensitization in early life. Pediatr Allergy Immunol. 2016;27:254–62.
83. Stefka AT, Feehley T, Tripathi P, Qiu J, McCoy K, Mazmanian SK, et al. Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci USA. 2014;111:13145–50.
84. Feehley T, Plunkett CH, Bao R, Choi Hong SM, Culleen E, Belda-Ferre P, et al. Healthy infants harbor intestinal bacteria that protect against food allergy. Nat Med. 2019;25:448–53.
85. Bojanova DP, Bordenstein SR. Fecal transplants: what is being transferred? PLoS Biol. 2016;14:e1002503.
86. Grönlund M-M, Gueimonde M, Laitinen K, Kociubinski G, Grönroos T, Salminen S, Isolauri E. Maternal breast-milk and intestinal bifidobacteria guide the compositional development of the Bifidobacterium microbiota in infants at risk of allergic disease. Clin Exp Allergy J. 2007;37:1764–72.

87. Garrido D, Dallas DC, Mills D. Consumption of human milk glycoconjugates by infant-associated bifidobacteria: mechanisms and implications. Microbiology. 2013;159(Pt 4):649–64. https://doi.org/10.1099/mic.0.064113-0. Epub 2013 Mar 4
88. Lewis ZT, Mills DA. Differential establishment of bifidobacteria in the breastfed infant gut. Nestle Nutr Inst Workshop Ser. 2017;88:149–59.
89. Gigante G, Tortora A, Ianiro G, Ojetti V, Purchiaroni F, Campanale M, et al. Role of gut microbiota in food tolerance and allergies. Dig Dis Basel Switz. 2011;29:540–9.
90. Garcia-Larsen V, Ierodiakonou D, Jarrold K, Cunha S, Chivinge J, Robinson Z, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: a systematic review and meta-analysis. PLoS Med. 2018;15:e1002507.
91. Wopereis H, Oozeer R, Knipping K, Belzer C, Knol J. The first thousand days – intestinal microbiology of early life: establishing a symbiosis. Pediatr Allergy Immunol. 2014;25:428–38.
92. Grimshaw KEC, Maskell J, Oliver EM, Morris RCG, Foote KD, Mills ENC, et al. Diet and food allergy development during infancy: birth cohort study findings using prospective food diary data. J Allergy Clin Immunol. 2014;133:511–9.
93. Venkataraman A, Sieber JR, Schmidt AW, Waldron C, Theis KR, Schmidt TM. Variable responses of human microbiomes to dietary supplementation with resistant starch. Microbiome. 2016;4:33.
94. Ciaccio CE, Girdhar M. Effect of maternal ω3 fatty acid supplementation on infant allergy. Ann Allergy Asthma Immunol. 2014;112:191–4.
95. Menni C, Zierer J, Pallister T, Jackson MA, Long T, Mohney RP, et al. Omega-3 fatty acids correlate with gut microbiome diversity and production of N-carbamylglutamate in middle aged and elderly women. Sci Rep. 2017;7:11079.
96. Watson H, Mitra S, Croden FC, Taylor M, Wood HM, Perry SL, et al. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. Gut. 2018;67:1974–83.
97. Vandenplas Y, De Greef E, Devreker T, Veereman-Wauters G, Hauser B. Probiotics and prebiotics in infants and children. Curr Infect Dis Rep. 2013;15:251–62.
98. Bron PA, Kleerebezem M, Brummer R-J, Cani PD, Mercenier A, MacDonald TT, et al. Can probiotics modulate human disease by impacting intestinal barrier function? Br J Nutr. 2017;117:93–107.
99. La Fata G, Weber P, Mohajeri MH. Probiotics and the gut immune system: indirect regulation. Probiotics Antimicrob Proteins. 2018;10:11–21.
100. Ma N, Guo P, Zhang J, He T, Kim SW, Zhang G, Ma X. Nutrients mediate intestinal bacteria–mucosal immune crosstalk. Front Immunol. 2018;9:5. https://doi.org/10.3389/fimmu.2018.00005.
101. Niers LEM, Timmerman HM, Rijkers GT, van Bleek GM, van Uden NOP, Knol EF, et al. Identification of strong interleukin-10 inducing lactic acid bacteria which down-regulate T helper type 2 cytokines. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2005;35:1481–9.
102. Tang MLK, Ponsonby A-L, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol. 2015;135:737–744.e8.
103. Tang R-B, Chang J-K, Chen H-L. Can probiotics be used to treat allergic diseases? J Chin Med Assoc JCMA. 2015;78:154–7.
104. Benitez AJ, Hoffmann C, Muir AB, Dods KK, Spergel JM, Bushman FD, Wang M-L. Inflammation-associated microbiota in pediatric eosinophilic esophagitis. Microbiome. 2015;3:23.
105. Noti M, EDT W, Kim BS, Siracusa MC, Giacomin PR, Nair MG, et al. Thymic stromal lymphopoietin–elicited basophil responses promote eosinophilic esophagitis. Nat Med. 2013;19:1005–13.
106. Jensen ET, Kuhl JT, Martin LJ, Rothenberg ME, Dellon ES. Prenatal, intrapartum, and postnatal factors are associated with pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2018;141:214–22.
107. Radano MC, Yuan Q, Katz A, Fleming JT, Kubala S, Shreffler W, Keet CA. Cesarean section and antibiotic use found to be associated with eosinophilic esophagitis. J Allergy Clin Immunol Pract. 2014;2:475–477.e1.
108. Green DJ, Cotton CC, Dellon ES. The role of environmental exposures in the etiology of eosinophilic esophagitis: a systematic review. Mayo Clin Proc. 2015;90:1400–10.
109. Harris JK, Fang R, Wagner BD, Choe HN, Kelly CJ, Schroeder S, et al. Esophageal microbiome in eosinophilic esophagitis. PLoS One. 2015;10:e0128346.
110. Corning B, Copland AP, Frye JW. The esophageal microbiome in health and disease. Curr Gastroenterol Rep. 2018;20:39.
111. Spechler SJ. Speculation as to why the frequency of eosinophilic esophagitis is increasing. Curr Gastroenterol Rep. 2018;20:26.
112. Smith AR, Macfarlane S, Furrie E, Ahmed S, Bahrami B, Reynolds N, Macfarlane GT. Microbiological and immunological effects of enteral feeding on the upper gastrointestinal tract. J Med Microbiol. 2011;60:359–65.
113. Schneider S-M. Microbiota and enteral nutrition. Gastroentérologie Clin Biol. 2010;34:S57–61.
114. Walton C, Montoya MPB, Fowler DP, Turner C, Jia W, Whitehead RN, et al. Enteral feeding reduces metabolic activity of the intestinal microbiome in Crohn's disease: an observational study. Eur J Clin Nutr. 2016;70:1052–6.

# Breastfeeding and Food Allergy

12

Scott P. Commins

**Key Points**

- Breast milk has important effects on the developing newborn and infant immune and gastrointestinal systems.
- The role of breast milk in the development of an infant's IgE response is uncertain but appears to be protective.
- Maternal dietary antigens can be found in breast milk, and the role of these antigens is the subject of ongoing research.

## Introduction

Breast milk is the most natural source of nutrition for babies. It is recommended by the American Academy of Pediatrics (AAP), who in 2012 reaffirmed its recommendation of *exclusive breastfeeding for about 6 months, followed by continued breastfeeding as complementary foods are introduced, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant* [1]. Breastfeeding rates are on the rise in the United States. In 2011, 79% of newborn infants started to breastfeed, 49% were breastfeeding at 6 months, and 27% at 12 months [2]. The incidence of food allergies is also on the rise: between 1997 and 2007, the incidence of food allergy increased by 18% in children under the age of 18 [3]. In 2018, approximately 8% of children had food allergies [4]. Moreover, 29% of patients with food allergies also reported other atopic conditions such as asthma and eczema compared to only 12% of children without food allergies [3]. The driving force – or forces – behind the increase in allergies is unknown and the subject of wide discussions and research.

The objective of this article is to review the composition of human breast milk and its role in food allergy. To do this, we will explore the nutrition and immunology of breast milk including the effects of a mother's diet and contemporary means of storage of breast milk. We will also review the current literature on breast milk and food allergy.

## The Physiology of Breast Milk

Human breast milk is synthesized to match the developmentally appropriate nutritional needs of the baby. The processes and structures needed to create human milk begin when the woman herself is in her mother's womb. As reviewed by Creasy and Resnik [5], the milk streak is present at the fourth week of gestation, and the mammary gland is formed at the sixth week of gestation. Proliferation of milk ducts continues throughout embryogenesis, and breast buds are present at

S. P. Commins (✉)
University of North Carolina School of Medicine, Department of Medicine and Pediatrics, Chapel Hill, NC, USA
e-mail: scommins@email.unc.edu



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_12

birth but, as maternal hormones diminish in the baby's circulation, the buds regress, growing proportionally to body growth until puberty.

Prepubertal changes in hormonal circulation induce the first phase of mammogenesis. Ductal growth is stimulated by estrogen production, which is generally unopposed in the first 1–2 years of menstrual cycles, creating type I lobules, which are alveolar buds clustered around a duct; upon cyclical changes in hormones, the types of lobules differentiate into type II lobules, which are more complex lobules that contain more alveoli [6]. This continues throughout puberty, completing mature breast development.

The second phase of mammogenesis occurs when a woman becomes pregnant so that breast milk may be produced by lactocytes, which utilize five transport mechanisms to create breast milk (see Table 12.1).

During the first half of pregnancy, lobules further differentiate into types III and IV, which have increased numbers of alveoli per lobule, thus establishing the milk-producing and milk-secreting framework [6]. During the second half of pregnancy, protein synthetic structures, such as the rough endoplasmic reticulum, mitochondria, and Golgi apparatus, begin to increase within the alveoli, and complex protein, milk fat, and lactose synthetic pathways are activated [6]. Regarding hormonal regulation, the initiation of human lactation involves (1) secretory differentiation in which mammary epithelial cells differentiate into lactocytes in the presence of progesterone, estrogen, and prolactin and (2) secretory activation, in which lactocytes secrete copious amounts of milk in the presence of prolactin, insulin, and cortisol when progesterone levels drop [8]. This ability to synthesize and secrete milk is termed lactogenesis. Lactogenesis I occurs about 12 weeks before parturition as acini produce colostrum while progesterone inhibits the production of milk. Lactogenesis II occurs around 2–3 days post delivery when the sudden drop in progesterone causes changes in the mammary epithelium, resulting in the beginning of mature-milk production. Lactogenesis III is the establishment of mature milk production occurring about 10 days after delivery and was formerly called galactopoiesis [9].

**Table 12.1** Transport of milk components by the mammary gland [7]

| Method of transport | Comments and components |
|---|---|
| Membrane route | Substances may traverse the apical cell membrane (and for those directly derived from blood, the basolateral membrane). Examples include<br>Water<br>Urea<br>Glucose<br>Sodium, potassium, and chloride ions |
| Golgi route | Secretory products are transported to, or sequestered by, the Golgi apparatus and secreted into the milk space by exocytosis. Examples include<br>Casein<br>Whey proteins<br>Lactose<br>Citrate<br>Calcium |
| Milk fat route | Milk fat globules are extruded from the apex of the secretory cell surrounded by membrane (milk-fat-globule membrane). Examples are<br>Milk fat<br>Lipid-soluble hormones and drugs<br>Growth factors (in milk-fat-globule membrane)<br>Leptin |
| Transcytosis | Vesicular transport involves various organelles and, in some cases, also involving extrusion by Golgi route. Examples include<br>Immunoglobulins (during colostrum formation)<br>Transferrin<br>Prolactin |
| Paracellular route | Direct passage from interstitial fluid to milk and this route reappears at the cessation of lactation |

Adapted from Shennan and Peaker [7]

## Nutrition of Expressed Breast Milk (EBM)

Regarded by the World Health Organization (WHO) and AAP as the optimum first food for infants, human milk is sufficient to meet the nutrition needs of the developing infant exclusively through the first 6 months of life and is the standard to which infant formulas are designed. The AAP recommends breastfeeding duration of 1 year minimum or as long as preferred by mother

and child, and WHO recommends breastfeeding continue through age two so that breast milk may continue to provide a substantial proportion of toddlers' nutrition needs [10, 11].

Though human milk is the standard for infant nutrition, its exact profile of nutritive substances is quite dynamic. On average, a deciliter of mature human milk provides 65–70 kilocalories, 0.9–1.2 grams of protein, 3.2–3.6 grams of lipid, and 6.7–7.8 grams of lactose [12]. In reality, the composition of human milk varies diurnally, within feedings, and individually from mother to mother; furthermore, compared to mature milk, the nutrient profiles of breast milk differ greatly among colostrum, transitional milk, and preterm milk (the milk of mothers who give birth prematurely) [11, 12].

## Macronutrients

### Protein

The total protein concentration of human milk is relatively lower compared to other mammalian milks, but the makeup is uniquely suited to provide both nutritive and non-nutritive benefits related to tolerance, development, and immune function. The relatively high proportion of whey compared to casein – the two main protein fractions – allows for greater solubility in gastric acid and faster gastric emptying compared to bovine proteins. Whey proteins of human milk include serum proteins (e.g., alpha-lactalbumin, lactoferrin), enzymes (e.g., lysozyme), and immunoglobulins (e.g., secretory IgA). Lactoferrin, lysozyme, and secretory IgA are resistant to proteolysis and impart initial immune defense in the gastrointestinal tract. Casein phosphopeptides, intermediates of casein digestion, maintain solubility of calcium, thereby aiding in absorption. Additionally, free amino acids taurine and glutamine may stimulate intestinal growth, and non-protein nitrogen from urea and nucleotides is used for the synthesis of nonessential amino acids, hormones, growth factors, and nucleic acids [11–13].

### Lipid

Human milk is lipid rich. Half of the total energy in human milk is provided by its lipid fraction, and its globule structure, which contains bile salt–stimulating lipase, promotes efficient digestion. Lipid concentrations are lower at the start of feed (foremilk) and rich toward the end of a feed (hindmilk). Breast milk is high in cholesterol as well, which contributes to cell membrane construction of the rapidly growing infant [11–13].

Unlike its protein and carbohydrate constituents, the fatty acid profile of human milk is impacted directly by maternal diet, making it the most variable macronutrient. Despite this element of variability, breast milk remains higher in the polyunsaturated fatty acids arachidonic acid and docohexaenoic acid (DHA) compared to bovine milk. DHA is integral to visual and neurological function [11].

### Carbohydrate

Lactose is the major carbohydrate source in breast milk, followed by oligosaccharides. Lactose facilitates calcium absorption and may contribute to the soft stools generally observed in breastfed infants. Oligosaccharides serve as prebiotics, aiding in the proliferation of beneficial *Bifidobacteria* and *Lactobaccilli* in the gut. Because they structurally resemble bacterial antigen receptors, they also impede bacteria from attaching to the gut mucosa [11–15].

## Micronutrients

### Vitamins

The vitamin content of breast milk is partly reflective of maternal diet and, in the case of fat-soluble vitamins, the overall fat content of the milk. An appropriately growing, healthy infant of a mother with a nutritionally adequate diet generally will meet his micronutrient requirements with the exceptions of vitamins K and D. Due to the low production of vitamin K by infant intestinal flora, infants are provided a single dose of vitamin K

at birth to prevent deficiency-associated hemorrhagic disease of the newborn. The vitamin D content of breast milk can be improved by maternal diet and sun exposure, but average levels are generally insufficient to meet the infant recommended daily allowances, necessitating routine supplementation [11–13].

### Minerals

Mineral content of breast milk decreases gradually over the first 4 months of infant life, but this decline does not impact infant growth and may be kidney-protective [11]. Human milk is notable for having lower amounts of calcium and phosphorus than bovine milk, but these are more bioavailable as are magnesium, iron, and zinc. Nearly half the iron content of breast milk is absorbed compared to 10% in bovine milk and bovine milk-based infant formulas [11, 12]. Maternal diet does not greatly impact mineral content of breast milk [16].

## Immunology of Breast Milk

### Neonatal Immune System

To better understand incorrect immune development, such as in food allergy development, and how breast milk is immunologically beneficial, a basic comprehension of a baby's immune system is beneficial. The ultimate goal of a newborn baby's immune system is to possess both innate and adaptive systems of protection with complement bridging these two arms of immunity. The innate immune system identifies and combats immediate defense concerns while also signaling the development and recruitment of the adaptive immune system. Because both the innate and the adaptive immune systems take time to develop, babies benefit from exogenous sources of immune protection, specifically in the form of breast milk.

Although immunologically immature in neonates, the innate immune system – composed primarily of complement, NK cells, polymorphonucelar cells, monocytes, and macrophages – provides more immune-protection than does the less developed adaptive immune system, which is composed of T lymphocytes, B lymphocytes, and immunoglobulins [17]. The four major categories of immunity are impaired in babies: phagocytosis, cell-mediated immunity, humoral immunity, and complement activity (see Table 12.2) [18]. Collectively, the diffuse immaturity in these individual areas of immunity results in great susceptibility to infection, and the immunologic foundation developed during infancy in the presence of breast milk may contribute to tolerance more than currently recognized.

**Table 12.2** Major categories of immunity in babies

| Major mechanism of immune activity | Explanation of process in the neonate |
|---|---|
| *Innate immunity*<br>(A) Phagocytosis: Ingestion and killing microbes [19] | Neutrophil chemotaxis is limited as is the presence of signaling molecules that participate in phagocytosis, such as immunoglobulins and complement [20] |
| (B) Cell-mediated immunity: Protection against intracellular pathogens provided by dendritic cells, NK T cells, and macrophages [21] | Neutrophils, monocytes, and antigen-presenting cells all hold both quantitative and qualitative defects [22] |
| (C) Complement activity<br>(i) Activates the inflammatory response<br>(ii) Opsonizes pathogens for phagocytosis and killing<br>(ii) Lyses susceptible organisms [23] | Complement proteins are found in limited amounts in neonates and, thus, also convey less protection [24, 25] |
| *Adaptive immunity*<br>(A) Humoral: Antibody-mediated protection against extracellular microbes and microbial toxins [26] | Neutrophils, monocytes, and antigen-presenting cells all hold both quantitative and qualitative defects [22] |
| (B) T cell-mediated<br>(i) Tolerogeneic reactivity<br>(ii) Reduced allo-antigen recognition<br>(iii) Poor responses to foreign antigens | Peripheral Treg population is high initially to promote self-tolerance; however, foreign antigen activation of neonatal T cells results in a response skewed towards Th2 immunity [27] |

## Breast Milk Immunology

Breast milk is composed not only of macro- and micro-nutrients but also of living cells, antibodies, and other immunologically active agents, some of which fill immunological gaps of the immature immune system. Breast milk composition is dynamic, changing as the baby develops and even altering with clinical changes, such as in the face of infection [28]. While breast milk generally contains a repertoire of components, mothers produce milk with different defense functionality profiles [29].

Antimicrobial, anti-inflammatory, and immunomodulatory factors that are under-developed in the neonatal immune system are found in human breast milk, playing a substitute role for those immune agents until the baby has developed them [30]. Secretory IgA, lactoferrin, complement C3, and lysozyme are just a few of the antimicrobial factors found in EBM. Secretory IgA provides antimicrobial protection not by activating complement but by immune exclusion, which is the prevention of bacteria traversing the gut epithelium, and possibly immune inclusion, which is the maintenance of protective gut biofilms [31, 32].

Lactoferrin is an iron-binding glycoprotein secreted in breast milk. Highest total amounts are found in colostrum [33]. The amount decreases as milk matures; however, the percentage of total protein that is lactoferrin starts at 27% in colostrum, dips to 19% by day 28, then increases to 30% by day 84 [34], the timing of which correlates with the iron-deficiency anemia found in some exclusively breast-fed babies. High levels of lactoferrin, such as those found in colostrum, stimulate intestinal proliferation, whereas low levels of lactoferrin stimulate intestinal differentiation, both of which elucidate lactoferrin's critical role as a first line of defense against pathogens invading the GI tract [35, 36]. Lactoferrin also takes up iron, preventing it from being used by bacteria and fungi, which thereby diminishes pathogen proliferation [30].

Components of the complement system, such as complement C3, are present in human milk. Although small concentrations are present, such opsonins supplement the neonate's slowly developing complement system and aids in pathogen protection [20, 37].

Secretory IgA, lactoferrin, and complement C3 (as well as secretory component – IgA's chaperone from mammary gland into the gut) vary greatly amongst lactating mothers; however, the proteins decrease between weeks 2 and 5, seemingly decreasing as the baby's immune system is expanding [29]. Lysozyme is another important immunologic protein in breast milk. This enzyme disrupts glycosidic linkages of some bacteria, a process that is aided by lactoferrin's damaging of bacterial outer membranes, creating a synergistic bacterial killing process [38]. From 6 weeks to 6 months, levels of secretory IgA, lactoferrin, lysozyme, and total protein vary greatly while playing important roles in neonatal immunity [39]. Of note, lactoferrin and lysozyme play roles against inflammation as do PAF-acetylhydrolase and IL-10 [30].

Immunomodulatory factors are underdeveloped in the neonatal immune system, and the complete roster of factors present in breast milk continues to grow: humoral immunity is enhanced by IL-4 and IL-10; cellular immunity is enhanced by IL-12, TNF-alpha, and interferon-gamma; growth is enhanced by G-CSF; and chemokine activity is enhanced by RANTES [30], which plays a role in macrophage recruitment [40].

Cells found in EBM (expressed breast milk) include immune cells – leukocytes, such as granulocytes and mononuclear leukocytes (including lymphocytes, monocytes, and macrophages) – as well as mammary epithelial cells and stem cells [41]. While the roles of mammary epithelial cells and breast milk stem cells in the neonatal immune system are not fully understood, immune cells play a vital role in neonatal protection, increasing in maternal and in infant infections [42].

Bacteria are also present in human breast milk. While the sources of some of these microorganisms are thought to include maternal skin, infant mouth and skin, and the environment, maternal dendritic macrophages can transport bacteria from the maternal gut through the lymphatic system and into the mammary gland where the bacteria are

transferred into the breast milk [43]. This has been further shown when breastfeeding mothers consumed the probiotic *Lactobacillus* then the same strain of *Lactobacillus* was found in her feces and in her baby's feces [44]. This is similar to the development of secretory IgA, which is produced by the mother when her enteric mucosa recognizes antigen and stimulates B cell production of IgA; those B cells travel to the mammary glands where the IgA is glycosylated and secreted into the breast milk [45]. In addition, oligosaccharides are present in breast milk and serve an important role in the development of an infant's gut microbiota (discussed below) [46].

## Effects of Storage on Breast Milk

Cultural trends affecting infant feeding and the recognition of breast milk's importance in the care of hospitalized infants have made feeding human milk apart from the breast increasingly a reality [47]. The AAP and the Academy of Breastfeeding Medicine have published guidelines for the storage of breast milk to ensure not only safe infant feeding but also that the integrity of breast milk's bactericidal and nutritional properties are preserved. Among these guidelines are parameters related to refrigeration, freezing and thawing, and storage containers.

### Refrigeration

Fresh breast milk that is not used within 4–6 hours should be refrigerated for up to 5 days. During this time, nutrients may degrade at variable rates with vitamin C noted to degrade rapidly [12, 47]. The cream component of breast milk will separate during refrigeration but will blend easily with agitation upon thawing. This does not affect the fat composition.

### Freezing and Thawing

Breast milk that will not be used within 72–120 hours of expression should be frozen. Freezing preserves its nutritional and immunologic properties for up to 3–4 months in a refrigerator freezer compartment or up to 6 months in a deep freezer. It is recommended that thawed milk should be used within 24 hours and not be refrozen. Heating breast milk will reduce the content and bioactivity of heat-labile vitamins and proteins [12, 47].

### Containers

Glass and hard plastic containers with airtight seals are the ideal storage containers for breast milk. For short-term (<72 hours) storage, plastic bags designed for human milk storage are appropriate. Longer storage increases adherence of milk components to the plastic, thus impacting the nutritional quality of the milk [47].

## Mom and Her Diet

The nutrient composition of breast milk remains relatively stable despite day-to-day fluctuations in maternal dietary intake and even during limited periods of dietary inadequacy. Chronic nutrient deprivation, however, can diminish the quality of human milk. Nutrients that are most vulnerable to maternal intake levels can vary [12].

### Macronutrients

The macronutrient concentrations in breast milk are largely unaffected by maternal diet, though the types of fatty acids present mimic maternal intake. Protein levels are impacted more by infant age than maternal protein intake with colostrum and preterm milk being highest in protein compared to transitional and mature milk; however, women who consume high protein diets have been found to have higher concentrations of total nitrogen in their milk due to higher levels of urea and free amino acids. Carbohydrate concentration and type is not impacted by maternal diet [11, 12].

### Micronutrients

Mature milk may be impacted by maternal diet depending on the nutrient. Vitamin concentrations decline when mothers are in deficiency states, and these concentrations respond to therapeutic supplementation. Upper thresholds for vitamin levels, particularly water-soluble vitamins, are regulated. In contrast to vitamins, minerals are not as susceptible to maternal intake. The exceptions are selenium and iodine, which correlate with maternal plasma levels [12].

## Food Allergy and Breast Milk

### Epidemiology and Developmental Pathophysiology of Food Allergies

Although the exact incidence of FA has yet to be established [48], a recent prospective, observational study found 9.9% of children developed food allergies by the age of 5 years old [49]. This finding in an inner-city, American cohort is similar to the >10% of 1-year-old children found to have food allergies in Melbourne, Australia [50]. What does appear certain is that the incidence of food allergy is increasing in westernized countries as well as countries in which food allergy was not previously considered to be a major issue, such as South Africa [51].

The pathophysiology of childhood food allergy is not understood and is likely a complex interaction of prenatal, neonatal, early childhood, and maternal immunity, specifically interacting with the environment. Sicherer and Sampson recently reviewed the possible mechanisms of the pathogenesis of food allergy, which include (1) gene-environment interaction, (2) the microbiome, (3) the route of sensitization (gut, skin, inhalation), (4) alteration of food preparation, such as heating/roasting, and (5) innate properties of the foods [52]. In fact, interactions of breastfeeding, genes, and the environment were highlighted in the study by Hong et al. in *JACI* in 2011 [53]. This study followed 970 children since birth and found that children who were ever breastfed were at higher risk of food sensitization. This risk was further increased in children with variations in IL-12 receptor, toll-like receptor 9, and thymic stromal lymphopoeitin genes.

Breast milk may also have a role in preventing certain infections, an additional factor that might influence development of food allergy. As proposed by Strachan in 1989, the hygiene hypothesis proposed that allergic disease is the result of increased cleanliness [54]. This has been further studied and currently includes that early-life exposure of microbial components induce Th1-type responses as opposed to Th2-type responses [55]. Such exposure involves immune mediators like toll-like receptors (TLRs). CD14 is a soluble component of TLR-4, which binds lipopolysaccharides of Gram-negative bacteria, thereby causing an immune response. While newborns initially have low levels of CD14, breast milk contains CD14 and is likely one of many breast milk constituents that influence allergy [56].

The gut microbiome, specifically the maternal gut microbiome, is an area of active research in food allergy and may have modifiable effects on breast milk that could be enhanced by probiotics and prebiotics. *Lactobacillus reuteri* was supplemented in breastfeeding mothers then found in the feces of 82% of those babies but only in 20% of the non-supplemented mothers' children's feces. *L. reuteri* was detected in more breast milk samples from the supplemented mothers compared to the non-supplemented mothers [44]. Human breast milk contains prebiotics in the form of oligosaccharides. These oligosaccharides are non-digestible to babies but are secreted in milk and feed the microbiota of the baby's gut, characteristics shared with prebiotics [46]. The oligosaccharides also serve to prevent pathogen invasion of the gut mucosa [44]. Taken together, these results demonstrate that bacteria in breast milk are modifiable and such changes do impact the constituents and relative populations of the infant microbiome. As additional data emerge, it will be important to understand whether such changes are as critical for regulating allergic responses to dietary antigens as some early data appear to suggest.

## Breastfeeding's History with Food Allergy

Recently, breastfeeding has been added to the list of theories behind the increase is food allergies, a change from its previously protective reputation. The protective role was observed in a 1995 study published in *Lancet*, in which breastfeeding was associated with a decrease in food allergy [57]. In 2004, Muraro et al. completed a thorough review of literature and concluded the following: *In prospective observational studies, breastfeeding for at least 3–6 months and late introduction of solid foods (after 4–6 months) is associated with a decreased risk of cow's milk protein allergy/FA and atopic eczema up to 3 year and recurrent wheeze/asthma up to 6–17 year. As such, exclusively breastfeeding for the first 6 months of life as recommended by World Health Organization should be attempted in all infants and also recommended as an allergy-preventive measure* [58]. It was noted, however, that components of breast milk can both enhance and suppress the immune response and participate in antigen exclusion depending on the balance of such components [59]. Recent mouse models have supported the theory that breast milk reduces allergies. A 2011 study showed that the transfer of antigen and antibody in breast milk led to tolerance [60], the results of which were similar to a 2010 study in which oral tolerance was shown in pups of aerosol-sensitized mothers exposed to allergen [61]. Finally, a 2012 review in *Journal of Pediatric Gastroenterology and Nutrition* further supported breast milk as being protective against allergy [56].

In contrast to studies that suggest breast milk protects against atopy, some work does suggest that breast milk is not protective against food allergy and may actually play a role in both food sensitization and in allergy. A 2005 rostrum by Drs. Friedman and Zeiger indicated that it could not be definitively determined that breast milk prevented sensitization to allergens [62]. In keeping with the lack of a protective role, a follow-up study in *Lancet* showed that breastfeeding did not protect against atopy and may have increased the risk of atopy [63]. More recently, a study of inner-city children of atopic parents showed breastfeeding of any duration was significantly associated with food allergies [49].

## Review of the Literature of Food Allergies and EBM

Understanding the relationship of food allergy and breast milk may create a new paradigm in allergy prevention research [64]. This area of allergy is already the focus of multiple studies including the content of allergen in breast milk and the immune factors in breast milk. Bernard et al. identified peanut antigen that had been transferred through breast milk of two non-atopic mothers and showed that IgE-mediated mast cell degranulation occurred in the presence of such antigen in mice, further arguing that such antigen can cause sensitization [65]. Macchiaverni et al. identified Der p 1 (a major allergen from house dust mite) in human breast milk and argued that it strongly promotes sensitization [66]. Palmer et al. found that the presence of egg ovalbumin in human milk was related to maternal egg intake but that excretion into breast milk varied amongst women and that some women did not secrete ovalbumin into their milk [67].

A mother's atopic status may impact her breast milk immunology. IL-4 has been shown to be higher in the breast milk of allergic mothers with similar trends in IL-5 and IL-13 compared to non-allergic mothers [68]. Atopic mothers have been found to have decreased levels of IgA in breast milk, but this was not associated with whether or not her child developed allergies [69]. Low levels of breast milk TGF-beta-2 have been associated with maternal allergy. In fact, TGF-beta in breast milk may play an important role in immune tolerance [70]. TGF-beta and IL-10 are tolerogenic cytokines found in breast milk [56]. In 2008, TGF-beta was shown to play a significant role in breast milk–induced tolerance, mediating CD4+ lymphocytes [71]. TGF-beta-1, along with IL-1beta, IL-6, and IL-10, was recently associated with tolerance to cow's milk [72]. Conversely, TGF-beta-1 has been shown not to be associated with atopy [73]. As previously

mentioned, low levels have been found in the milk of atopic mothers [74]; however, immune factors in breast milk that are related to milk allergy have been found to be independent of maternal atopy [72].

IgA is the major antibody found in breast milk and is inversely related to atopic dermatitis [73]. Atopic mothers have lower levels of IgA than non-atopic mothers, but these levels were not associated with food allergy in children [69]. Higher levels of IgA in breast milk were associated with positive skin prick testing at 6 months but not at 2 or 5 years of age [39]. Interestingly, and suggestive that some protein in breast milk may be associated with atopy in the first 2 years of life, the total protein in breast milk was higher in mothers with atopic babies compared to mothers with non-atopic babies [39].

While proteins are generally considered the immunologic compounds of breast milk, fatty acids may also play a role in food allergy. The rise in food allergy in westernized societies has been accompanied by increased consumption of saturated and omega-6 fats along with a concomitant decrease in omega-3 consumption, each of which may play a role in the development of allergy [75]. Thijs et al. recently explored this hypothesis in the context of fat content of human breast milk and found the sensitization at 1 year was inversely associated with breast milk concentrations of omega-3 fatty acids and rumenic fatty acids, which also had an impact on total IgE [76]. No differences in breast milk fatty acids or ratios were found between atopic and non-atopic mothers [76].

## Current Recommendations on Breastfeeding and Food Allergy

In 2014, the AAP included in its 2014 *Pediatrics Supplement: Best Articles Relevant to Pediatric Allergy and Immunology* McGowan's systematic review of the literature regarding primary prevention of food allergy, which concluded *the only intervention for which there is evidence of preventing the development of food allergy is to avoid cow's milk during the first 4 months of life in children at high risk* [77]. Some commonly agreed upon recommendations are found in the 2010-published NIAID guidelines in food allergy by Boyce et al., which included (1) the recommendation against maternal diet restriction during pregnancy and lactation, (2) the recommendation supporting exclusive breast feeding until 4 to 6 months of age, and (3) the suggestion that high-risk infants consume hydrolyzed formula when exclusive breast feeding is unavailable (and "high-risk" was defined as babies with biological parents or siblings with existing or a history of food allergy, atopic dermatitis, allergic rhinitis, or asthma) [78]. A 2012 update of risk factors published in *JACI* further explores this topic [79]. A Cochrane review in 2014 also recommended against maternal dietary avoidance of antigens during pregnancy or lactation regarding decreasing atopy [80]. In 2014, the AAAAI published "Food allergy: A practice parameter update—2014" that included recommendations regarding the prevention of food allergy (see Table 12.3).

Indeed, recent studies have found that maternal exposure to food allergens decreases allergy in offspring in humans and in mice [82–85]. In fact, a prospective US study showed no benefit of maternal and early childhood avoidance of milk, egg, or peanut in preventing food allergies [86]. These

**Table 12.3** AAAAI recommendations from food allergies practice parameter update 2014 [81]

| AAAAI 2014 recommendations to prevent food allergies |
|---|
| 1. Encourage *exclusive breastfeeding* for the first 4–6 months. |
| 2. For infants with a *family history of atopy*, consider a partially or extensively hydrolyzed infant formula for possible prevention of atopic dermatitis and infant cow's milk allergy *if exclusive breastfeeding is not possible*. |
| 3. Do not recommend allergen avoidance or avoidance of specific complementary foods at weaning because these approaches *have not proved effective* for primary prevention of atopic disease. |
| 4. Do not routinely recommend supplementation of the maternal or infant diet with probiotics or prebiotics as a means to prevent food allergy because there is *insufficient evidence* to support a beneficial effect. |

Reprinted from Sampson et al. [81], © 2014, with permission from Elsevier

studies and others provided experimental support for recent decisions to withdraw recommendations of allergen avoidance during pregnancy and breastfeeding and support potential beneficial effects of maternal allergen exposure to protect offspring from food allergy. Prior human studies examining the effect of maternal diets during pregnancy on peanut allergy have shown inconsistent results. However, a more recent study suggesting that early food introduction might decrease the risk of food allergy development underscored the potential benefit of food allergen transfer through breast milk as this may be the first food exposure for the infant [87]. Data from murine studies indicated a critical role of maternal immunoglobulin immune complexes in tolerance induction in offspring regardless of the sensitization status of mothers [27]. Interestingly, those findings could suggest a potential for immunoglobulin immune complexes as an immunotherapy to improve oral tolerance and possibly prevent food allergy in children [27].

## Conclusion

Breast milk is a complex immunologic liquid. In addition to the nutritional growth it provides, it plays a dynamic role in the neonatal immune system, contributing to defense as well as apparent hyper-defense in the form of allergy. The literature continues to grow regarding breast milk and food allergy, and research to date indicates that this is just the beginning of understanding how breast milk impacts the development of food allergy.

**Disclosures** Scott Commins: NIH grant support; UpToDate author; Genentech speaker's bureau.

## References


1. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827–41.
2. Breastfeeding Report Card. Centers for Disease Control and Prevention; 2014. p. 8. https://www.cdc.gov/breastfeeding/pdf/2018breastfeedingreportcard.pdf
3. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. NCHS Data Brief. 2013;121:1–8. https://www.cdc.gov/nchs/data/databriefs/db121.pdf
4. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.
5. Creasy R. Creasy and Resnik's maternal-fetal medicine: principles and practice. 7th ed., Philadelphia: Saunders; 2014.
6. Bland K. Breast: comprehensive management of benign and malignant diseases. 4th ed, Philadelphia: Saunders; 2009.
7. Shennan DB, Peaker M. Transport of milk constituents by the mammary gland. Rockville: Physiological Reviews; 2000;80(3):925–51.
8. Pang WW, Hartmann PE. Initiation of human lactation: secretory differentiation and secretory activation. J Mammary Gland Biol Neoplasia. 2007;12(4):211–21.
9. Lawrence R. Breastfeeding. 7th ed., Philadelphia: Mosby; 2011.
10. Breastfeeding: World Health Organization; 2014. Available from: http://www.who.int/maternal_child_adolescent/topics/child/nutrition/breastfeeding/en/
11. Kleinman R. Pediatric nutrition handbook. 6th ed. Elk Grove Village: American Academy of Pediatrics; 2009.
12. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin N Am. 2013;60(1):49–74.
13. Rodriguez-Palmero M, Koletzko B, Kunz C, Jensen R. Nutritional and biochemical properties of human milk: II. Lipids, micronutrients, and bioactive factors. Clin Perinatol. 1999;26(2):335–59.
14. Boehm G, Lidestri M, Casetta P, Jelinek J, Negretti F, Stahl B, et al. Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2002;86(3):F178–81.
15. Kunz C, Rudloff S. Biological functions of oligosaccharides in human milk. Acta Paediatr. 1993;82(11):903–12.
16. Prentice A. Calcium supplementation during breastfeeding. N Engl J Med. 1997;337(8):558–9.
17. Krishnan S, Craven M, Welliver RC, Ahmad N, Halonen M. Differences in participation of innate and adaptive immunity to respiratory syncytial virus in adults and neonates. J Infect Dis. 2003;188(3):433–9.
18. Lawrence RM, Pane CA. Human breast milk: current concepts of immunology and infectious diseases. Curr Probl Pediatr Adolesc Health Care. 2007;37(1):7–36.
19. Abbas A, Lichtman A, Basic Immunology PS. Functions and disorders of the immune system. 4th ed., Philadelphia: Saunders; 2014.
20. Henneke P, Berner R. Interaction of neonatal phagocytes with group B streptococcus: recognition and response. Infect Immun. 2006;74(6):3085–95.
21. Nairn R, Helbert M. Immunology for medical students. 2nd ed., Philadelphia: Mosby; 2007.

22. Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. Nat Rev Immunol. 2007;7(5):379–90.
23. Rich R, Fleisher T, Shearer W, Schroeder H, Frew A, Weyand C. Clinical immunology. 4th ed., Philadelphia: Elsevier Limited; 2013.
24. Pettengill MA, van Haren SD, Levy O. Soluble mediators regulating immunity in early life. Front Immunol. 2014;5:457.
25. McGreal EP, Hearne K, Spiller OB. Off to a slow start: under-development of the complement system in term newborns is more substantial following premature birth. Immunobiology. 2012;217(2):176–86.
26. Abbas A, Lichtman A, Pillai S. Cellular and molecular immunology. 8th ed., Philadelphia: Saunders; 2015.
27. Ohsaki A, Venturelli N, Buccigrosso TM, Osganian SK, Lee J, Blumberg RS, et al. Maternal IgG immune complexes induce food allergen-specific tolerance in offspring. J Exp Med. 2018;215(1):91–113.
28. Riskin A, Almog M, Peri R, Halasz K, Srugo I, Kessel A. Changes in immunomodulatory constituents of human milk in response to active infection in the nursing infant. Pediatr Res. 2012;71(2):220–5.
29. Broadhurst M, Beddis K, Black J, Henderson H, Nair A, Wheeler T. Effect of gestation length on the levels of five innate defense proteins in human milk. Early Hum Dev. 2014;91(1):7–11.
30. Goldman A, Chheda S, Keeney S, Schmalstieg F. Immunology of human milk and host immunity. In: Polin RL. Abman S. Benitz W., Rowitch D. (Eds.). Fetal and neonatal physiology. 4th ed., Philadelphia: Elsevier; 2008.
31. Mantis NJ, Rol N, Corthésy B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. Mucosal Immunol. 2011;4(6):603–11.
32. Everett ML, Palestrant D, Miller S, Bollinger RR, Parker W. Immune exclusion and immune inclusion: a new model of host-bacterial interactions in the gut. Clin Appl Immunol Rev. 2004;4:321–32.
33. Rai D, Adelman AS, Zhuang W, Rai GP, Boettcher J, Lönnerdal B. Longitudinal changes in lactoferrin concentrations in human milk: a global systematic review. Crit Rev Food Sci Nutr. 2014;54(12):1539–47.
34. Montagne P, Cuillière ML, Molé C, Béné MC, Faure G. Changes in lactoferrin and lysozyme levels in human milk during the first twelve weeks of lactation. Adv Exp Med Biol. 2001;501:241–7.
35. Jiang R, Du X, Lönnerdal B. Comparison of bioactivities of talactoferrin and lactoferrins from human and bovine milk. J Pediatr Gastroenterol Nutr. 2014;59(5):642–52.
36. Buccigrossi V, de Marco G, Bruzzese E, Ombrato L, Bracale I, Polito G, et al. Lactoferrin induces concentration-dependent functional modulation of intestinal proliferation and differentiation. Pediatr Res. 2007;61(4):410–4.
37. Ogundele MO. Activation and deposition of human breast-milk complement C3 opsonins on serum sensitive Escherichia coli 0111. J Reprod Immunol. 2000;48(2):99–105.
38. Ellison RT, Giehl TJ. Killing of gram-negative bacteria by lactoferrin and lysozyme. J Clin Invest. 1991;88(4):1080–91.
39. Zhang G, Lai CT, Hartmann P, Oddy WH, Kusel MM, Sly PD, et al. Anti-infective proteins in breast milk and asthma-associated phenotypes during early childhood. Pediatr Allergy Immunol. 2014;25(6):544–51.
40. Chatterton DE, Nguyen DN, Bering SB, Sangild PT. Anti-inflammatory mechanisms of bioactive milk proteins in the intestine of newborns. Int J Biochem Cell Biol. 2013;45(8):1730–47.
41. Hassiotou F, Geddes DT, Hartmann PE. Cells in human milk: state of the science. J Hum Lact. 2013;29(2):171–82.
42. Bode L, McGuire M, Rodriguez JM, Geddes DT, Hassiotou F, Hartmann PE, et al. It's alive: microbes and cells in human milk and their potential benefits to mother and infant. Adv Nutr. 2014;5(5):571–3.
43. Rodríguez JM. The origin of human milk bacteria: is there a bacterial entero-mammary pathway during late pregnancy and lactation? Adv Nutr. 2014;5(6):779–84.
44. Abrahamsson TR, Sinkiewicz G, Jakobsson T, Fredrikson M, Björkstén B. Probiotic lactobacilli in breast milk and infant stool in relation to oral intake during the first year of life. J Pediatr Gastroenterol Nutr. 2009;49(3):349–54.
45. Newburg DS. Innate immunity and human milk. J Nutr. 2005;135(5):1308–12.
46. Coppa GV, Bruni S, Morelli L, Soldi S, Gabrielli O. The first prebiotics in humans: human milk oligosaccharides. J Clin Gastroenterol. 2004;38(6 Suppl):S80–3.
47. Eglash A, Committee AoBMP. ABM clinical protocol #8: human milk storage information for home use for full-term infants (original protocol march 2004; revision #1 march 2010). Breastfeed Med. 2010;5(3):127–30.
48. Longo G, Berti I, Burks AW, Krauss B, Barbi E. IgE-mediated food allergy in children. Lancet. 2013;382(9905):1656–64.
49. McGowan EC, Bloomberg GR, Gergen PJ, Visness CM, Jaffee KF, Sandel M, et al. Influence of early-life exposures on food sensitization and food allergy in an inner-city birth cohort. J Allergy Clin Immunol. 2014;135(1):171–8.
50. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011;127(3):668–76.e1-2.
51. Botha M, Levin M. Prevalence of IgE-mediated food sensitisation and food allergy in unselected 12–36 month old south African children. J Allergy Clin Immunol. 2014;133:AB201.
52. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291–307. quiz 8.
53. Hong X, Wang G, Liu X, Kumar R, Tsai HJ, Arguelles L, et al. Gene polymorphisms, breast-feeding, and

development of food sensitization in early childhood. J Allergy Clin Immunol. 2011;128(2):374–81.e2.
54. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax. 2000;55(Suppl 1):S2–10.
55. Bvt L, Boehm G, Garssen J. Breast milk: components with immune modulating potential and their possible role in immune mediated disease resistance. In: Watson R. Zibadi S. Preedy V. (Eds.). Dietary Components and Immune Function. Nutrition and Health. Humana Press: Springer Science+Business Media; 2010.
56. Iyengar SR, Walker WA. Immune factors in breast milk and the development of atopic disease. J Pediatr Gastroenterol Nutr. 2012;55(6):641–7.
57. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. Lancet. 1995;346(8982):1065–9.
58. Muraro A, Dreborg S, Halken S, Høst A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part III: critical review of published peer-reviewed observational and interventional studies and final recommendations. Pediatr Allergy Immunol. 2004;15(4):291–307.
59. Muraro A, Dreborg S, Halken S, Høst A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part I: immunologic background and criteria for hypoallergenicity. Pediatr Allergy Immunol. 2004;15(2):103–11.
60. Yamamoto T, Tsubota Y, Kodama T, Kageyama-Yahara N, Kadowaki M. Oral tolerance induced by transfer of food antigens via Breast Milk of allergic mothers prevents offspring from developing allergic symptoms in a mouse food allergy model. Clin Dev Immunol. 2012;2012:721085. https://doi.org/10.1155/2012/721085.
61. Mosconi E, Rekima A, Seitz-Polski B, Kanda A, Fleury S, Tissandie E, et al. Breast milk immune complexes are potent inducers of oral tolerance in neonates and prevent asthma development. Mucosal Immunol. 2010;3(5):461–74.
62. Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. J Allergy Clin Immunol. 2005;115(6):1238–48.
63. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet. 2002;360(9337):901–7.
64. Munblit D, Boyle RJ. Modulating breast milk composition – the key to allergy prevention? Int Arch Allergy Immunol. 2012;159(2):107–8.
65. Bernard H, Ah-Leung S, Drumare MF, Feraudet-Tarisse C, Verhasselt V, Wal JM, et al. Peanut allergens are rapidly transferred in human breast milk and can prevent sensitization in mice. Allergy. 2014;69(7):888–97.
66. Macchiaverni P, Rekima A, Turfkruyer M, Mascarell L, Airouche S, Moingeon P, et al. Respiratory allergen from house dust mite is present in human milk and primes for allergic sensitization in a mouse model of asthma. Allergy. 2014;69(3):395–8.
67. Palmer DJ, Gold MS, Makrides M. Effect of maternal egg consumption on breast milk ovalbumin concentration. Clin Exp Allergy. 2008;38(7):1186–91.
68. Böttcher MF, Jenmalm MC, Garofalo RP, Björkstén B. Cytokines in breast milk from allergic and nonallergic mothers. Pediatr Res. 2000;47(1):157–62.
69. Hogendorf A, Stańczyk-Przyłuska A, Sieniwicz-Luzeńczyk K, Wiszniewska M, Arendarczyk J, Banasik M, et al. Is there any association between secretory IgA and lactoferrin concentration in mature human milk and food allergy in breastfed children. Med Wieku Rozwoj. 2013;17(1):47–52.
70. Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance relevant to food allergy. J Allergy Clin Immunol. 2011;127(3):576–84. quiz 85-6.
71. Verhasselt V, Milcent V, Cazareth J, Kanda A, Fleury S, Dombrowicz D, et al. Breast milk-mediated transfer of an antigen induces tolerance and protection from allergic asthma. Nat Med. 2008;14(2):170–5.
72. Järvinen KM, Suárez-Fariñas M, Savilahti E, Sampson HA, Berin MC. Immune factors in breast milk related to infant milk allergy are independent of maternal atopy. J Allergy Clin Immunol. 2015;135(5):1390–3.e1-6. https://doi.org/10.1016/j.jaci.2014.10.051.
73. Orivuori L, Loss G, Roduit C, Dalphin JC, Depner M, Genuneit J, et al. Soluble immunoglobulin a in breast milk is inversely associated with atopic dermatitis at early age: the PASTURE cohort study. Clin Exp Allergy. 2014;44(1):102–12.
74. Kuitunen M, Kukkonen AK, Savilahti E. Impact of maternal allergy and use of probiotics during pregnancy on breast milk cytokines and food antibodies and development of allergy in children until 5 years. Int Arch Allergy Immunol. 2012;159(2):162–70.
75. Black PN, Sharpe S. Dietary fat and asthma: is there a connection? Eur Respir J. 1997;10(1):6–12.
76. Thijs C, Müller A, Rist L, Kummeling I, Snijders BE, Huber M, et al. Fatty acids in breast milk and development of atopic eczema and allergic sensitisation in infancy. Allergy. 2011;66(1):58–67.
77. McGowan EC, Keet CA. Primary prevention of food allergy in children and adults: systematic review. Pediatrics. 2014;134(Suppl 3):S138.
78. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1–58.
79. Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol. 2012;129(5):1187–97.
80. Kramer MS, Kakuma R. Cochrane in context: maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Evid Based Child Health. 2014;9(2):484–5.
81. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: A practice

parameter update-2014. J Allergy Clin Immunol. 2014;134(5):1016–25.e43.
82. Fusaro AE, Brito CA, Victor JR, Rigato PO, Goldoni AL, Duarte AJ, et al. Maternal-fetal interaction: preconception immunization in mice prevents neonatal sensitization induced by allergen exposure during pregnancy and breastfeeding. Immunology. 2007;122(1):107–15.
83. Lopez-Exposito I, Song Y, Jarvinen KM, Srivastava K, Li XM. Maternal peanut exposure during pregnancy and lactation reduces peanut allergy risk in offspring. J Allergy Clin Immunol. 2009;124(5):1039–46.
84. Verhasselt V. Neonatal tolerance under breastfeeding influence: the presence of allergen and transforming growth factor-beta in breast milk protects the progeny from allergic asthma. J Pediatr. 2010;156(2 Suppl):S16–20.
85. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo CA Jr, et al. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. J Allergy Clin Immunol. 2014;133(5):1373–82.
86. Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. J Allergy Clin Immunol. 1989;84(1):72–89.
87. Perkin MR, Logan K, Marrs T, Radulovic S, Craven J, Flohr C, et al. Enquiring About Tolerance (EAT) study: feasibility of an early allergenic food introduction regimen. J Allergy Clin Immunol. 2016;137(5):1477–86 e8.

# 13 Prevention of Food Allergy: Early Introduction of Allergenic Foods

Waheeda Samady, Lauren M. Kao, Jialing Jiang, Emily M. Campbell, Ruchi S. Gupta, and Lucy A. Bilaver

## Introduction

Food allergy (FA) has increased sharply in prevalence over recent decades [1] and is now a major public health concern. A population-based study estimated that food allergy affects 8% of US children [2] and is costly – resulting in $24.8 billion dollars per year in expenditures by the healthcare system and US families [3]. Of all known food allergens, peanut has been found to be the most common, affecting 2% of US children [2]. It is also one of the least frequently outgrown, with prospective cohort studies in the United States and Australia observing that less than 20% of peanut-allergic infants outgrew their allergy [4, 5]. Furthermore, peanut allergy (PA) has been associated with substantially impaired quality of life among both peanut-allergic children and their families [6]. As there are no approved therapies for food allergies, there is a heightened need for effective food allergy prevention strategies.

Infant feeding recommendations from national expert committees such as the Committee on Nutrition of America Academy of Pediatrics (AAP) have evolved as researchers are shedding more light on the immune mechanisms of food allergy development and the role of infant feeding in potentially preventing the food allergy cascade. The objective of this chapter is to review what is currently known regarding the immune pathways to allergy development and explain how this is connected to solid food introduction and food allergy prevention. In doing so, we will review the current AAP and National Institute of Allergy and Infectious Disease (NIAID) guidelines for the prevention of peanut allergy as well as review the evidence for early introduction of other top food allergens.

W. Samady · R. S. Gupta
Center for Food Allergy and Asthma Research, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: wsamady@luriechildrens.org; r-gupta@northwestern.edu

L. M. Kao · J. Jiang · L. A. Bilaver (✉)
Northwestern University Feinberg School of Medicine, Center for Food Allergy and Asthma Research, Chicago, IL, USA
e-mail: lauren.kao@northwestern.edu; jialing.jiang@northwestern.edu; l-bilaver@northwestern.edu

E. M. Campbell
Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_13

## Immune Mechanisms of Food Allergy Development

Understanding the immune cascade that precedes allergy development as well as prominent theories regarding the route of antigen exposure is key to furthering our understanding of food allergy prevention.

### Th1 and Th2 Pathways

Food allergy is an immune-driven IgE antibody reaction to a food allergen while tolerance is the absence of an immune response to a food allergen. Two immunologic responses can occur, one leading to the development of food allergy and the other leading to the development of food tolerance. Sensitization is the first step in the immune process that produces antibodies in response to an innocuous, foreign protein. Two subsets of helper T cells, Th1 and Th2 cells, play a role in driving the body's response to an antigen. Th1 cells, or regulatory T cells, secrete interferon-ɣ and trigger the body's cell-mediated immune response. Th2 cells secrete IL-4, IL-5, IL-10, and IL-13 and promote the production of IgE by B cells as well as eosinophilic responses. A predominately Th2 response is responsible for the development of atopic diseases including food allergy [7]. A cascade that leads to food allergy is induced when antigen-presenting cells (APCs), such as dendritic cells in the gut, promote T helper cell differentiation into Th2 cells. Th2 cells then go on to induce B cells to develop into IgE producing cells, which in turn increases IgE levels to that specific allergen. However, if an APC instead promotes the development of regulatory T cells (Th1), this induces B cells to produce IgG antibodies, and this pathway is thought to promote food tolerance. The mechanisms that drive differentiation into Th1 vs. Th2 cells are not fully understood at this time [7]. For example, animal studies have shown that an allergy to ovalbumin (egg protein) can be transferred to naive mice by injecting Th2 cells from allergic mice into the naive mouse [8]. Conversely, mice that had been made tolerant to ovalbumin via oral administration did not mount an allergic response when injected with Th2 cells from allergic mice [9].

It is possible that the interplay between Th1 and Th2 cells leading to food tolerance vs. allergy may be an oversimplification of the mechanisms driving the immune system's response. In a recent study, the cytokines TSLP, IL25, and IL33 were each found to be necessary for the development of food allergy in a mouse egg white allergy model. During the sensitization phase, inhibition of any one of the three cytokines was sufficient to prevent the development of an allergy to ovalbumin. However, once an egg white allergy was established, inhibition of all three cytokines was required to suppress an allergic response [10]. In addition, the gut microbiome has been shown in multiple studies to contribute to the development of food allergy vs. tolerance. When mice with a normal gut microbiome were given oral ovalbumin, interferon-ɣ, and IgG2a, molecules associated with tolerance, were produced in response. However, sensitized germ-free mice are unable to produce interferon-ɣ and IgG2 and instead produce IgE and IL-4 when given oral ovalbumin [11]. Germ-free mice whose microbiome had been reconstituted with *Bifidobacterium infantis* prior to the sensitization were protected from their predisposition towards allergy, indicating that the gut microbiome may help promote food tolerance. This concept has also been demonstrated in humans. Children with less diversity in the gut microbiome have been shown to have greater allergen sensitization when compared to age matched controls [12]. A study published in the *Journal of Allergy and Clinical Immunology* compared the microbiome of 20 infants with eczema to a control group of infants without eczema and found that children with eczema had reduced microbial diversity [13]. Other studies have also found that changes in the human microbiome early in life were associated with food sensitization [14].

## The Dual-Allergen Exposure Hypothesis

The dual-allergen exposure hypothesis proposes that the route of allergen exposure also plays a

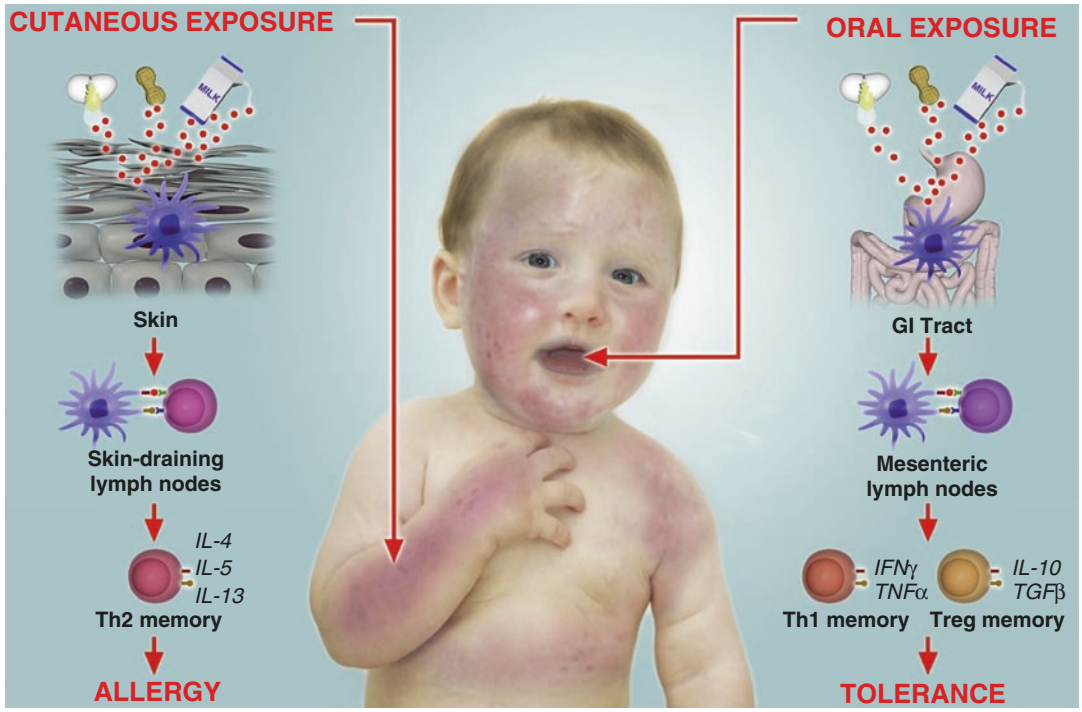



**Fig. 13.1** The pathogenesis of food allergy as described through the dual-allergen exposure hypothesis [19]. (Reprinted from Lack [19], with permission from Elsevier)

role in determining the development of allergy vs. tolerance. Studies have found that individuals with peanut allergy frequently report their first allergic reaction to peanut occurring upon their first known ingestion, implying prior sensitization through a non-oral route [15]. Studies have also found that up to 50% of children with severe, early-onset eczema go on to develop allergy to peanut, egg, or sesame [16]. These observations, coupled with eczema as an established risk factor for food allergy, led researchers to investigate the route of initial antigen exposure (skin vs. gut) as a factor in the development of allergy vs. tolerance [17]. Cutaneous application of 100 μg of peanut protein or ovalbumin to mice whose skin had been damaged via tape stripping induced a Th2 response and high levels of peanut- or ovalbumin-specific IgE. Subsequent oral exposure to peanut or ovalbumin triggered anaphylaxis, suggesting a skin sensitization pathway leading to anaphylaxis upon oral exposure. Further studies have demonstrated that exposure of a disrupted skin barrier, specifically, to an antigen is what may lead to a Th2 response (Fig. 13.1). This was demonstrated by Mondoulet et al., where epicutanous immunotherapy either reduced or reinforced a Th2 response in mice depending on whether the skin barrier was intact or disrupted, respectively [18].

## History of Infant Food Introduction Guidelines

The optimal timing of solid food introduction to infants and its relationship to the development of allergic disease has been a topic of debate over the past several decades. Introduction of solid foods by 3 months of age was common practice in the 1960s both in the United Kingdom [20, 21] and in the United States [22]. The AAP Committee on Nutrition was formed in 1954 and in its first report, emphasized that while age should not be a rigid standard for the introduction of foods, there were no known benefits attributed to introducing solid foods before the first 3 or 4 months of life.

Furthermore, it stressed that developmental maturity of the gut and neuromuscular system, growth rate, and activity level were better indicators for determining when to introduce solid foods to infants [23].

It was not until 1974 that guidelines specifically tied food introduction to disease prevention. At that time, the United Kingdom released guidelines to delay the introduction of cereals until 4 months of age based on a presumed link between the early introduction of gluten into the diet and the development of celiac disease [21]. The idea that delaying the introduction of solid foods could help prevent allergic disease continued to gain traction in subsequent years. In 1983, an allergy prevention strategy was published in the United States that aimed to prevent sensitization during infancy by avoiding exposing the infant to allergenic proteins in utero and during the early postnatal period [24]. It recommended exclusive breastfeeding or the use of extensively hydrolyzed formula for the first 6 months of life followed by introduction of foods of low allergenicity. This approach also recommended delayed introduction of highly allergenic foods between 1 and 3 years depending on the food allergen. In 1985, a study by Zeiger and Heller examined the effect of maternal and infant dietary allergen avoidance on atopic outcomes in high-risk infants. They found that maternal allergen avoidance, use of extensively hydrolyzed formulas, and delayed introduction of highly allergenic solid foods reduced rates of food sensitization at 24 months (16.5% versus 29.4%; $p = 0.019$) and atopic dermatitis at 12 months (5.1% versus 16.4%; $p = 0.007$) in their intervention group compared to controls [25]. However, the follow-up study published in 1995 showed no benefits in regard to having any atopic condition at 4 or 7 years of age [26].

Although the theory that sensitization to food allergens could be reduced through maternal allergen avoidance and/or delayed exposure to allergenic proteins gained support, there were a few additional studies with suggestive but inconclusive results [27–29] and a meta-analysis of all prospective controlled trials of partially hydrolyzed formula that reported a significant prophylactic effect in reducing subsequent allergy development. Additionally, there were new theories being introduced to support allergen avoidance in infants such as a "leaky gut" (gut permeability) and mucosal immaturity in infants [30]. Thus, with recommendations released by the expert bodies in the United Kingdom [31] in 1998 and Europe [32] in 1999 both encouraging allergen avoidance in infants and toddlers, the American Academy of Pediatrics (AAP) released guidelines in 2000 directing pediatricians to counsel parents to delay introduction of certain allergenic foods for infants at high risk (defined as those with family history of food allergy) [33]. Specifically, the guidelines recommended that solid foods not to be introduced before 6 months of age, dairy products be delayed until 12 months, eggs until 24 months, and peanuts, tree nuts, and fish until 36 years of age. These guidelines additionally recommended that lactating women avoid consuming peanuts and other highly allergenic foods. A report released by the World Health Organization (WHO) in 2002 further supported this strategy, recommending exclusive breastfeeding until 6 months of age [34]. It is important to emphasize that this report acknowledged that there was no evidence that these recommendations specifically prevented food allergy development. At the time, however, there was also no evidence that prolonging the period of exclusive breastfeeding and avoiding food allergens was linked to the development of atopic disease and food allergy. In 2006, the American College of Allergy, Asthma and Immunology released a consensus document reiterating the AAP recommendations, stating that "available information suggests that early introduction can increase the risk of food allergy, that avoidance of solids can prevent the development of specific food allergies" [35].

However, as food allergy prevalence continued to rise in the years following the 2000 guidelines and no further studies reinforced these initial recommendations, the AAP substantially

revised its guidelines in 2008 [36] to reflect the paucity of evidence that delaying introduction of allergenic foods prevented the development of food allergy. The new guidelines removed the recommendation to delay introduction of any foods, stating that there was "no current convincing evidence that delaying the introduction of foods, including highly allergenic foods, beyond 4–6 months [had] a significant protective effect on the development of atopic disease." The recommendation that pregnant and lactating women avoid consumption of any foods was also removed stating that the current evidence did not support maternal dietary restriction. Other expert committees in Europe issued similarly revised recommendations that same year [37]. However, insufficient evidence was available at the time to make recommendations about when solid foods or highly allergenic foods *should* be introduced into the infant's diet [38].

## Learning Early About Peanut (LEAP) Trial

In the same year that the revised 2008 AAP guidelines were released, DuToit et al. published an observational study which revealed striking differences in both the prevalence of peanut allergy and the timing of peanut introduction in infants of Jewish ancestry in the United Kingdom compared to those in Israel [39]. While 69% of Israeli infants consumed peanut products by 9 months of age, only 10% of infants in the United Kingdom consumed peanut by this time ($P < 0.0001$). When researchers looked at peanut allergy prevalence in the two communities, they found a tenfold higher prevalence in Jewish children in the United Kingdom compared to those in Israel. These observations led researchers to hypothesize that the early introduction of peanut products may be protective for the development of peanut allergy.

Based on the results of this study, Du Toit et al. conducted a double-blinded randomized controlled trial to evaluate the hypothesis that the introduction of peanut products into the diet during infancy could promote the development of oral tolerance and reduce the incidence of peanut allergy [40]. In the Learning Early About Peanut Allergy (LEAP) study, 640 children between the ages of 4 and 10 months with severe eczema, egg allergy, or both (risk factors for the development of peanut allergy [41] were randomly assigned to regularly consume peanut protein (at least 6 grams/week over 3 or more meals) or avoid peanut products until 60 months of age. All children had a peanut skin prick test (SPT) at study entry and those with either no wheal or a wheal ≤4 mm wheal diameter were randomized for participation. Those with wheal >5 mm were excluded. Of the 530 infants with a negative SPT at study entry, the prevalence of peanut allergy at 60 months of age was 1.9% in the peanut consumption group compared to 13.7% in the peanut avoidant group. Thus, early introduction of peanut was associated with an 86% relative risk reduction in peanut allergy development in this cohort. Among the 98 children with an initial positive SPT to peanut, the prevalence of peanut allergy in the consumption group was 10.6% compared to 35.3% in the peanut avoidant group, which translates into a 70% relative risk reduction. The LEAP trial was the first to demonstrate that a diet recommendation could decrease peanut allergy development and serve as a successful model for primary food allergy prevention.

LEAP researchers also measured serum levels of peanut-specific immunoglobulins IgE, IgG, and IgG4. IgE is a marker of allergic responses while IgG is considered a marker of antigen exposure. IgG4 is thought to be a marker of potential immune modulation. At the end of the trial, SPT wheal diameters and elevated IgE titers were higher in the peanut avoidant group while the children in the peanut consumption group showed a larger and earlier increase in the levels of peanut-specific IgG and IgG4, the same immunological effects seen in successful allergen immunotherapy.

While the LEAP trial showed that early and consistent introduction of peanuts to high-risk

infants prevented the development of a peanut allergy, researchers wanted to determine what would happen to peanut tolerance if peanuts were removed from the diet. To address this question, they conducted the Persistence of Oral Tolerance to Peanut study (LEAP-On). Researchers enrolled 556 children from the LEAP study to avoid peanut-containing products for the next 12 months in order to evaluate if peanut tolerance would be altered by diet changes after the first 5 years of life. This study demonstrated even after 12 months of avoiding peanuts, the reduction in the prevalence of peanut allergy persisted at 72 months of age. Children from the original peanut consumption group had 74% lower prevalence of peanut allergy than children in the original peanut avoidant group. New allergy to peanut developed in three children in the original peanut consumption group (1.1%) and three in the peanut avoidant group. Among children who were not allergic in the original peanut consumption group, levels of IgE remained low and ratios of IgG:IgE remained high during the 12 months with no peanut consumption, indicating their non-allergic status remained stable. Children in the peanut consumption group had elevated IgG4 levels as early as 12 months of age; they also found a decrease in the average IgE levels by 60 months which continued to 72 months of age. When compared to children in the peanut avoidant group, fewer children in the peanut consumption group had a high IgE level. Together, the LEAP and LEAP-On studies demonstrated that early introduction of peanut was able to induce tolerance to peanuts that persisted through at least 12 months of peanut avoidance.

## 2017 Addendum Guidelines for Peanut Allergy Prevention

The results of the landmark LEAP trial informed a dramatic reversal of national guidelines [42]. An expert panel convened by the National Institute of Allergy and Infectious Disease released the 2017 Addendum Guidelines for the Prevention of Peanut Allergy in the United States (Addendum Guidelines), endorsed by the AAP, which recommended the dietary introduction of peanut products during infancy based on stratification into three risk categories. Consistent with infants in the LEAP trial, the first category represents those at highest risk including infants with an egg allergy (defined as a history of reaction to egg and a positive skin prick test) and/or severe eczema (persistent or frequent eczema that has been diagnosed as severe and requires prescription medications). The guidelines recommend these infants be evaluated for peanut sensitization by a healthcare provider using peanut-specific IgE (sIgE) and/or skin prick testing and, according to the results, either be referred to a specialist for further management or introduced to peanut-containing foods as early as 4–6 months of age (Addendum Guideline 1). This requires that the introduction of solid foods begins at 4–6 months of age, starting with solid food other than peanut. However, if the 4- to 6-month time window is missed for any reason, evidence from the LEAP trial, which included infants up to 11 months of age, suggests that infants may still benefit from the introduction of peanut after the recommended window. After infants are introduced to peanut-containing foods, the guidelines further recommend that infants continue eating 6–7 grams of peanut-containing foods split into three or more servings per week.

In order to maximize the opportunity to introduce peanuts as early as possible, the guidelines state that testing for peanut-specific IgE may be the preferred initial approach in certain health care settings, particularly those that do not offer SPT services. For infants who test negative, the recommendation for peanut introduction can be made without referrals to other settings. However, the guidelines caution that food allergen panel testing or the addition of specific IgE testing for foods other than peanuts is not recommended due to poor positive predictive value.

The second guideline suggests that infants with mild to moderate eczema be introduced to peanut products at home at or around 6 months of age

(Addendum Guideline 2). While the LEAP trial did not include children with mild or moderate eczema, the expert panel concluded that the individual and societal benefits of introducing peanut in this population would be significant as there is no reason to believe that the mechanisms of protection of early dietary peanut differ in infants with mild-to-moderate eczema versus severe eczema. Similar to the first guideline, other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready. Unlike high-risk children, the guidelines recommend that these infants have dietary peanut introduced at home without an in-office evaluation. However, the guidelines acknowledged that some caregivers and healthcare providers may desire an in-office supervised feeding, evaluation, or both for these infants as well.

The third guideline recommends that infants with no eczema or any food allergy can be introduced to peanut products in accordance with family preferences and cultural practices whenever it is age appropriate (Addendum Guideline 3) (Table 13.1).

Following the release of the Addendum Guidelines, other countries also endorsed early introduction of peanut-containing foods [44, 45]. Notably, while introduction of solids at 4–6 months (but not before 4 months) departs from WHO guidelines that call for exclusive breastfeeding for about 6 months, infants who either consumed or avoided peanut in the LEAP cohorts did not differ in the duration or frequency of breastfeeding [46] and were indistinguishable in nutritional and metabolic parameters at 12, 30, and 60 months of age. Finally, while past recommendations also defined high-risk children as those with first-degree relatives with documented food allergy, the 2017 guidelines do not utilize history of familial food allergy to define high-risk infants (Fig. 13.2).

## Potential Barriers to Guideline Implementation

Concerns regarding assessment of risk factors have been expressed. As Hildebrand et al. suggest, severe eczema may be over-diagnosed by parents and medical providers. For example, a 2014 study estimated the prevalence of severe eczema in US infants to be 0.9% [47], suggesting that the majority of infants can be introduced to peanut products at home without further assessment. However, severe eczema, as defined by the HealthNuts team, reported estimates of 12% [48] and may be over-diagnosed by parents and medical providers [49]. Therefore, one concern is that the variable classification of eczema severity and the potential improper application of the guidelines could potentially lead to over-testing and over-referral to specialists. This runs the risk of false positives and/or delays in peanut introduction while waiting

**Table 13.1** Summary of Addendum Guidelines 1–3 [43]

| Addendum Guideline | Infant criteria | Recommendations | Earliest age of peanut introduction |
|---|---|---|---|
| 1 | Severe eczema, egg allergy, or both | Strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods | 4–6 months |
| 2 | Mild-to-moderate eczema | Introduce peanut-containing foods | Around 6 months |
| 3 | No eczema or any food allergy | Introduce peanut-containing foods | Age appropriate and in accordance with family preferences and cultural practices |

Reprinted from Togias et al. [43]

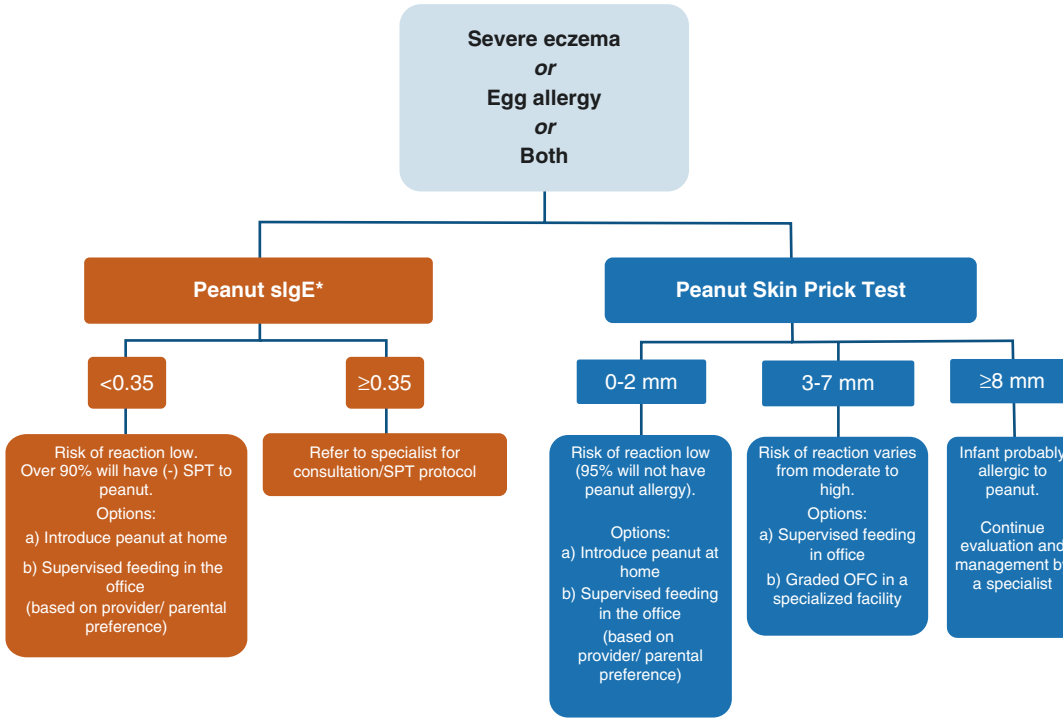



**Fig. 13.2** Recommended approach to infants with severe eczema or egg allergy [43]. (Reprinted from Togias et al. [43])

for appointments with specialists and test results. Similarly, although the use of panel testing is discouraged [50] in the Addendum Guidelines [43], physicians and/or families may be tempted to request testing for other foods during testing for peanut, which has been termed "screening creep" [51]. False positives during testing may lead to unnecessary food avoidance which may increase the risk for development of a true allergy. Importantly, individuals with atopy are more likely to have elevated IgE levels and false-positive test results [52].

A related concern is that patients who receive positive peanut sIgE results at their primary care physician's office may choose to avoid peanuts instead of following up with an allergy specialist for further assessment and management. Similarly, although the Addendum Guidelines include recommendations for in-office peanut introduction or oral food challenge (OFC), the availability of such appointments with allergists is often limited, which may cause peanut introduction to be delayed. The suggestion has been made to conduct in-office challenges as soon as possible [53].

There are also concerns about application of the screening and testing recommendations at the population level. Population modeling studies [48, 54] suggest that implementation of the Addendum Guidelines may pose substantial cost and logistical challenges [55]. For example, using data from the HealthNuts cohort, Koplin et al. found that applying the Guidelines would lead to testing 16% of the population but would still miss 23% of those with peanut allergy. Turner et al. state, "It is insufficient for population-based interventions to be based on the highest level of evidence; they also need to be generalizable, simple, cheap, doable, and have the ability to be evaluated after implementation" [56]. Others have expressed concerns about the use of egg allergy as a screening factor for peanut allergy risk given that egg is not commonly introduced to infants before 4–6 months of age and due to a lack of evidence that egg allergy is more strongly associated with peanut allergy than other top allergens, such as milk [55].

Finally, despite evidence that infants do not have severe reactions, many parents remain hesitant to introduce peanut products prior to or at 6 months of age [57]. This may be a consequence of prior recommendations to delay peanut introduction or fears of a reaction [48, 58]. During the LEAP study, only 7 of 319 infants randomized to consumption reacted at their initial supervised feeding and the reactions were generally mild, successfully treated with antihistamines, and did not require epinephrine. Other studies focused on anaphylaxis report that when infants have multiple symptoms, they are largely gastrointestinal and skin symptoms [59]. In this regard, guideline authors request full engagement of general pediatricians and allergists to educate families and encourage adoption of the guidelines to prevent a serious and potentially chronic and costly disease [46].

## Early Introduction of Other Foods

The early introduction of peanut-containing products has received global recognition and prompted research on early introduction of other allergenic foods as a means to prevent food allergy development. The Enquiring About Tolerance (EAT) study, in particular, is one of the first studies examining the role of timing of food introduction for infants in the general population in the United Kingdom This randomized control trial of 1303 three-month-old infants assessed the effect of early introduction of several allergenic foods: cow's milk, peanut, cooked egg, sesame, fish, and wheat. Infants in the intervention group started introduction of these foods at 3 months of age (early introduction) with continued breastfeeding if they have not yet developed a food allergy. Prior to beginning the regimen for early introduction, food allergy status was assessed through SPT and a subsequent open-label incremental oral food challenge for infants with a positive wheal size. If infants reacted to the food and failed the challenge during the assessment, caregivers were instructed to avoid feeding that food but continue introduction of the other observed allergenic foods. The standard introduction control group exclusively consumed breastmilk until 6 months of age and then commenced introduction of the aforementioned foods after 6 months of age upon caregiver discretion. Development of food allergy was assessed between 1 and 3 years of age [60].

In an intention-to-treat analysis, there was no significant difference between the two groups, with 5.6% of children in the early introduction group and 7.1% of children in the standard introduction group developing an allergy to any of the study foods by age 3. On the other hand, in a per-protocol analysis of those adherent to the assigned treatment, the prevalence of food allergy was significantly lower among children who received early introduction of allergenic foods compared to those that received standard introduction (2.4% vs. 7.3%, $p = 0.01$). The prevalence of specific food allergies (peanut and egg) were also significantly lower with early introduction than standard introduction in the per-protocol analysis. While the intention-to-treat analysis did not confirm an effect of early introduction, it suggests that dosage and adherence to regimen during introduction are important factors in food allergy prevention [61]. Appropriate age windows for food introduction could also affect the effectiveness of food allergy prevention in infants [62]. The narrow window of exposure in this study (3 months vs. 6 months) could have impacted findings. Overall, previous literature has suggested that early introduction of common food allergens may prevent food allergy development; therefore, the implications of the EAT study are crucial in considering future food allergy prevention research.

## Early Introduction of Egg

Egg allergy affects 2% of 12-month-old infants in the United States [2] and 9% in Australia [63]. This has prompted research on early introduction of egg into an infant's diet to prevent egg allergy. To date, the impact of early egg introduction is still not well understood as these studies report conflicting results. This section discusses five randomized controlled trials as well as a large population-based study

regarding early egg introduction. Despite these differences, the following studies provide insight on the potential of introducing egg early to infants.

HealthNuts, a population-based, cross-sectional study observing 11–15-month-old infants ($n$ = 2589) in Australia demonstrated lower rates of egg allergy among infants with early egg introduction at 4–6 months (5.6%) compared to delayed introduction at 7–9 months, 10–12 months, and >12 months (7.8%, 10.1%, and 27.6%, respectively) [64]. The two-step egg introduction for the prevention of egg allergy in high-risk infants with eczema (PETIT) study, a randomized, double-blind, placebo-controlled trial based in Japan studied infants 4–5 months old with atopic dermatitis and no history of egg consumption or any food ($n$ = 147). In the primary analysis population, egg allergy was confirmed via OFC for 8% of the intervention group (powder mixture of squash and heated egg powder, similar to a portion of a whole boiled egg) vs. 38% of the placebo group (squash powder) at 12 months of age, $p$ = 0.0001 [65]. The Beating Egg Allergy Trial (BEAT), conducted in Australia, is a randomized, double-blind, single-site, parallel-arm, controlled trial. Infants 4 months old with a first-degree relative with a history of atopy and SPT wheal size <2 mm to commercial egg white were observed ($n$ = 319). Overall, the proportion of 1-year-old infants sensitized to egg white in the intervention group (egg protein daily) was 10.7% vs. 20.5% in the control group (rice powder daily) [66].

Additionally, the Solids Timing for Allergy Research (STAR) study in Australia, a double-blind, randomized, controlled trial, observed infants at high-risk for food allergy with moderate-to-severe eczema ($n$ = 86). In the intervention group (pasteurized raw whole egg powder, comparable to the allergenic properties of raw egg), rates of diagnosed egg allergy and sensitization to egg were lower than the control group (placebo rice powder) at 12 months of age (egg allergy: 33% vs. 51%; sensitization: 45% vs. 63%). Neither difference was statistically significant, possibly due to the early termination of the study, impacting the sample size and statistical power. However, data suggest that early and regular oral exposure to egg may contribute to immune tolerance and reduction in egg allergy incidence [67].

In contrast, the Starting Time of Egg Protein (STEP) trial and the Hen's Egg Allergy Prevention (HEAP) studies present different findings. The STEP trial is a randomized, placebo-controlled trial in Australia that explored early introduction of egg to the infant diet to reduce egg allergy. Infants age 4–6 months were randomly assigned to the intervention group, instructed to mix egg-containing powder into their solid foods ($n$ = 407), or the control group, instructed to use a rice-based, egg-free powder ($n$ = 413). Overall, using the egg powder did not seem to impact egg allergy in the first year of life and did not affect sensitization to peanuts or other allergens (egg allergy: 7.0% vs. 10.3%; sensitization: 10.8% vs. 15.1% [68]. The HEAP study, a double-blind, randomized, placebo-controlled trial in Germany observed infants 4–6 months of age ($n$ = 383). At 12 months of age, 5.6% of children in the intervention group (pasteurized egg white powder with comparable allergenicity to raw hen's egg) were sensitized to hen's egg vs. 2.6% in the placebo group (rice) while 2.1% were confirmed to have a hen's egg allergy vs. 0.6%, respectively. However, these findings were not significant; therefore, the authors could not conclude that the early introduction of pasteurized hen's egg increased sensitization to hen's egg or allergy development [69].

It is unclear if early introduction of egg during infancy definitively plays a role in preventing egg allergy development. The aforementioned studies varied in methodology, infant egg allergy risk level, form of egg protein introduced, as well as egg dosage and, therefore, do not allow for a direct comparison of studies. However, there are general similarities in study implications, ultimately supporting further research on the early introduction of egg. Mechanisms of tolerance remain unclear and it is suggested that the windows of allergen exposure, the effective time for oral tolerance induction to food allergens, may impact allergy development [62].

## Early Introduction of Milk

Cow's milk is another common allergen among infants that has been studied in the context of early introduction to prevent food allergy. Similar to egg, the consideration of the form (baked vs. unbaked milk) has yet to be extensively studied and methodology varies. While many of the studies regarding cow's milk are observational, findings suggest that early exposure may decrease the rate of cow's milk allergy. However, further research is necessary to elucidate the relationship between early introduction of milk and the incidence of milk allergy.

In a prospective study, the feeding history of infants was obtained via phone or questionnaire. Infants that had a probable adverse reaction to milk received a skin prick test and OFC. Essentially, 0.05% of infants that had cow's milk protein formula early had an IgE-mediated cow's milk allergy compared to 1.75% of infants that were introduced to it roughly 3–6 months later. These findings suggest that early exposure to cow's milk protein may prompt tolerance to the protein [70]. Additionally, a case-control study retrospectively compared questionnaire responses on feeding patterns and family history of atopy between a group that had cow's milk allergy and a control group that was similar in age and sex. This study suggested that early introduction of cow's milk is associated with a lower cow's milk allergy incidence [71]. Additionally, a prospective birth cohort study observed the association between age of cow's milk/other solid food product introduction and atopy manifestation (eczema/atopic dermatitis, wheezing, and environmental/food allergen sensitization). These findings suggested that the delay of introducing cow's milk was related to a higher risk for eczema and the delay was associated with a lower risk of cow's milk sensitization although not statistically significant [72].

## Other Foods

There is a paucity of data on early introduction of other foods aside from peanut, milk, and egg. In a systematic review and meta-analysis of early introduction and risk of allergic or autoimmune disease, egg and peanut introduction were associated with lower risk of egg or peanut allergy development. However, evidence for early fish introduction relative to allergic sensitization was not conclusive while research on timing of gluten introduction was not associated with celiac disease risk [73]. In another systematic review of early infant feeding and wheat allergy risk, the relationship was also uncertain. Early gluten introduction was related to a reduced risk of wheat sensitization up to 5 years of age, but a randomized control trial did not find the same result [74]. Ultimately, further studies are necessary to determine whether the early introduction of other allergenic foods can produce a preventive effect similar to that found with peanut and egg.

## Conclusion

Food allergy prevention strategies are of utmost importance considering their increasing global prevalence, the low likelihood of spontaneous resolution, and the major impacts on quality of life. Increased understanding of the immune pathways and prominent theories such as the dual-allergen hypothesis have provided some insight into how infants develop food allergies. Furthermore, the landmark LEAP trial has effectively demonstrated that early peanut feeding (age 4–6 months) can reduce peanut allergy development in high-risk infants and has informed the current peanut prevention guidelines. While there is increasing evidence to support the early introduction of other foods such as egg, more evidence is needed regarding other allergenic foods.

## References

1. Keet CA, Savage JH, Seopaul S, Peng RD, Wood RA, Matsui EC. Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States. Ann Allergy Asthma Immunol. 2014 Mar;112(3):222–229.e3. https://doi.org/10.1016/j.anai.2013.12.007.

2. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, Nadeau KC. The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States. Pediatrics. 2018 Dec;142(6):pii: e20181235. https://doi.org/10.1542/peds.2018-1235.
3. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013 Nov;167(11):1026–31. https://doi.org/10.1001/jamapediatrics.2013.2376.
4. Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. J Allergy Clin Immunol. 1999 Apr;103(4):559–62.
5. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. J Allergy Clin Immunol. 2003 Dec;112(6):1203–7.
6. Warren CM, Otto AK, Walkner MM, Gupta RS. Quality of life among food allergic patients and their caregivers. Curr Allergy Asthma Rep. 2016 May;16(5):38. https://doi.org/10.1007/s11882-016-0614-9.
7. Berger A. Th1 and Th2 responses: what are they? BMJ. 2000;321(7258):424.
8. Turcanu V, Brough HA, Du Toit G, Foong RX, Marrs T, Santos AF, Lack G. Immune mechanisms of food allergy and its prevention by early intervention. Curr Opin Immunol. 2017 Oct;48:92–8. https://doi.org/10.1016/j.coi.2017.08.009.
9. Knight AK, Blázquez AB, Zhang S, Mayer L, Sampson HA, Berin MC. CD4 T cells activated in the mesenteric lymph node mediate gastrointestinal food allergy in mice. Am J Physiol Gastrointest Liver Physiol. 2007 Dec;293(6):G1234–43.
10. Perrier C, Thierry AC, Mercenier A, Corthésy B. Allergen-specific antibody and cytokine responses, mast cell reactivity and intestinal permeability upon oral challenge of sensitized and tolerized mice. Clin Exp Allergy. 2010 Jan;40(1):153–62. https://doi.org/10.1111/j.1365-2222.2009.03329.x.
11. Khodoun MV, Tomar S, Tocker JE, Wang YH, Finkelman FD. Prevention of food allergy development and suppression of established food allergy by neutralization of thymic stromal lymphopoietin, IL-25, and IL-33. J Allergy Clin Immunol. 2018 Jan;141(1):171–179.e1. https://doi.org/10.1016/j.jaci.2017.02.046.
12. Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. J Immunol. 1997 Aug 15;159(4):1739–45.
13. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol. 2012 Feb;129(2):434–440.e1–2. https://doi.org/10.1016/j.jaci.2011.10.025.
14. Chen CC, Chen KJ, Kong MS, Chang HJ, Huang JL. Alterations in the gut microbiotas of children with food sensitization in early life. Pediatr Allergy Immunol. 2016 May;27(3):254–62. https://doi.org/10.1111/pai.12522.
15. van Asperen PP, Kemp AS, Mellis CM. Immediate food hypersensitivity reactions on the first known exposure to the food. Arch Dis Child. 1983 Apr;58(4):253–6.
16. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. Allergy. 2014 Jan;69(1):17–27. https://doi.org/10.1111/all.12268.
17. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic Th2 response. Eur J Immunol. 2004 Aug;34(8):2100–9.
18. Mondoulet L, Dioszeghy V, Ligouis M, Dhelft V, Puteaux E, Dupont C, Benhamou PH. Epicutaneous immunotherapy compared with sublingual immunotherapy in mice sensitized to pollen (*Phleum pratense*). ISRN Allergy. 2012 Feb 2;2012:375735. https://doi.org/10.5402/2012/375735.
19. Lack G. Epidemiologic risks for food allergy. J Allergy Clin Immunol. 2008 Jun;121(6):1331–6. https://doi.org/10.1016/j.jaci.2008.04.032.
20. Challacombe DN. The incidence of coeliac disease and early weaning. Arch Dis Childhood. 1983;58(5):326.
21. Panel on Child Nutrition Working Party on Infant Feeding. Present-day practice in infant feeding report on health and social subjects No. 9, London: HSMO; 1974. p. 24–6.
22. Kleinman RE, Coletta FA. Historical overview of transitional feeding recommendations and vegetable feeding practices for infants and young children. Nutr Today. 2016 Jan;51(1):7–13.
23. American Academy of Pediatrics Committee on Nutrition. On the feeding of solid foods to infants. Pediatrics. 1958;21(4):685–92.
24. Middleton E Jr, Reed CE, Ellis EF, Schatz M, Zeiger RS, Mellon M, et al. The course and management of asthma and allergic disease during pregnancy. In: Middleton Jr E, Reed CE, Ellis EF, editors. Allergy: principles and practice. St. Louis: CV Mosby Co; 1983.
25. Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN, Schatz M. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. J Allergy Clin Immunol. 1989 Jul;84(1):72–89.
26. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. J Allergy Clin Immunol. 1995 Jun;95(6):1179–90.
27. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective fol-

low-up study until 17 years old. Lancet. 1995 Oct 21;346(8982):1065–9.
28. Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomised prospective study. BMJ. 1990 Mar 31;300(6728):837–40.
29. Oldaeus G, Anjou K, Björkstén B, Moran JR, Kjellman NI. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. Arch Dis Child. 1997 Jul;77(1):4–10.
30. Prescott SL, Smith P, Tang M, Palmer DJ, Sinn J, Huntley SJ, et al. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. Pediatr Allergy Immunol. 2008 Aug;19(5):375–80. https://doi.org/10.1111/j.1399-3038.2008.00718.x.
31. Committee on Toxicity of Chemicals in Food, Consumer Product and the Environment. COT Report on Peanut Allergy; 1998.
32. Høst A, Koletzko B, Dreborg S, Muraro A, Wahn U, Aggett P, et al. Dietary products used in infants for treatment and prevention of food allergy. Joint statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) committee on hypoallergenic formulas and the European Society for Paediatric Gastroenterology, Hepatology and nutrition (ESPGHAN) committee on nutrition. Arch Dis Child. 1999 Jul;81(1):80–4.
33. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. Pediatrics. 2000 Aug;106(2 Pt 1):346–9.
34. World Health Organization, Department of Nutrition for Health and Development. The optimal duration of exclusive breastfeeding: report of an expert consultation. Geneva; 2001 Mar 28–30.
35. Fiocchi A, Assa'ad A, Bahna S, Adverse Reactions to Foods Committee; American College of Allergy, Asthma and Immunology. Food allergy and the introduction of solid foods to infants: a consensus document. Ann Allergy Asthma Immunol. 2006 Jul;97(1):10–20; quiz 21, 77.
36. Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics. 2008 Jan;121(1):183–91. https://doi.org/10.1542/peds.2007-3022.
37. Grimshaw KE, Allen K, Edwards CA, Beyer K, Boulay A, van der Aa LB, Sprikkelman A, Belohlavkova S, et al. Infant feeding and allergy prevention: a review of current knowledge and recommendations. A EuroPrevall state of the art paper. Allergy. 2009 Oct;64(10):1407–16. https://doi.org/10.1111/j.1398-9995.2009.02172.x.
38. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1–58. https://doi.org/10.1016/j.jaci.2010.10.007.
39. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008 Nov;122(5):984–91. https://doi.org/10.1016/j.jaci.2008.08.039.
40. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803–13. https://doi.org/10.1056/NEJMoa1414850.
41. Du Toit G, Roberts G, Sayre PH, Plaut M, Bahnson HT, Mitchell H, et al. Learning Early About Peanut Allergy (LEAP) Study Team. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. J Allergy Clin Immunol. 2013 Jan;131(1):135–43.e1–12. https://doi.org/10.1016/j.jaci.2012.09.015.
42. Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. J Allergy Clin Immunol. 2015;136(2):258–61.
43. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. Allergy Asthma Clin Immunol. 2017;13(1):1.
44. Joshi PA, Smith J, Vale S, Campbell DE. The Australasian Society of Clinical Immunology and Allergy infant feeding for allergy prevention guidelines. Med J Aust. 2019 Feb;210(2):89–93. https://doi.org/10.5694/mja2.12102.
45. The British Society for Allergy & Clinical Immunology. Preventing food allergy in higher risk infants: guidance for healthcare professionals. Available from: https://www.bsaci.org/about/early-feeding-guidance (2019).
46. Sicherer SH, Sampson HA, Eichenfield LF, Rotrosen D. The benefits of new guidelines to prevent peanut allergy. Pediatrics. 2017 Jun;139(6):pii: e20164293. https://doi.org/10.1542/peds.2016-4293.
47. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. Dermatitis. 2014 May-Jun;25(3):107–14. https://doi.org/10.1097/DER.0000000000000034.
48. Koplin JJ, Peters RL, Dharmage SC, Gurrin L, MLK T, Ponsonby AL, et al. HealthNuts study investigators. Understanding the feasibility and implications of implementing early peanut introduction for prevention of peanut allergy. J Allergy Clin Immunol. 2016 Oct;138(4):1131–1141.e2. https://doi.org/10.1016/j.jaci.2016.04.011.

49. Hildebrand KJ, Abrams EM, Vander Leek TK, Upton JEM, Mack DP, Kirste L, et al. Primum non nocere-first do no harm. And then feed peanut. Allergy Asthma Clin Immunol. 2017 Feb 8;13:7. https://doi.org/10.1186/s13223-017-0180-2.
50. Bird JA, Crain M, Varshney P. Food allergen panel testing often results in misdiagnosis of food allergy. J Pediatr. 2015 Jan;166(1):97–100. https://doi.org/10.1016/j.jpeds.2014.07.062.
51. Turner PJ, Campbell DE. Implementing primary prevention for Peanut allergy at a population level. JAMA. 2017 Mar 21;317(11):1111–2. https://doi.org/10.1001/jama.2017.0922.
52. Fleischer DM, Burks AW. Pitfalls in food allergy diagnosis: serum IgE testing. J Pediatr. 2015;166(1):8–10.
53. Stukus DR, Prince BT, Mikhail I. Implementation of guidelines for early peanut introduction at a pediatric academic center. J Allergy Clin Immunol Pract. 2018 Sep–Oct;6(5):1784–6. https://doi.org/10.1016/j.jaip.2018.01.036.
54. O'Connor C, Kelleher M, JOB H. Calculating the effect of population-level implementation of the Learning Early About Peanut Allergy (LEAP) protocol to prevent peanut allergy. J Allergy Clin Immunol. 2016 Apr;137(4):1263–1264.e2. https://doi.org/10.1016/j.jaci.2015.11.029.
55. Wood RA, Burks AW. LEAPing forward with the new guidelines. J Allergy Clin Immunol. 2017 Jan;139(1):52–3. https://doi.org/10.1016/j.jaci.2016.11.005.
56. Turner PJ, Campbell DE, Boyle RJ, Levin ME. Primary prevention of food allergy: translating evidence from clinical trials to population-based recommendations. J Allergy Clin Immunol Pract. 2018 Mar–Apr;6(2):367–75. https://doi.org/10.1016/j.jaip.2017.12.015.
57. Greenhawt M, Chan ES, Fleischer DM, Hicks A, Wilson R, Shaker M, et al. Caregiver and expecting caregiver support for early peanut introduction guidelines. Ann Allergy Asthma Immunol. 2018 Jun;120(6):620–5. https://doi.org/10.1016/j.anai.2018.03.001.
58. Turner PJ, Campbell DE. Epidemiology of severe anaphylaxis: can we use population-based data to understand anaphylaxis? Curr Opin Allergy Clin Immunol. 2016 Oct;16(5):441–50. https://doi.org/10.1097/ACI.0000000000000305.
59. Samady W, Trainor J, Smith B, Gupta R. Food-induced anaphylaxis in infants and children. Ann Allergy Asthma Immunol. 2018 Sep;121(3):360–5. https://doi.org/10.1016/j.anai.2018.05.025.
60. Perkin MR, Logan K, Marrs T, Radulovic S, Craven J, Flohr C, et al. EAT Study Team. Enquiring About Tolerance (EAT) study: feasibility of an early allergenic food introduction regimen. J Allergy Clin Immunol. 2016 May;137(5):1477–1486.e8. https://doi.org/10.1016/j.jaci.2015.12.1322.
61. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. EAT Study Team. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016 May 5;374(18):1733–43. https://doi.org/10.1056/NEJMoa1514210.
62. Du Toit G, Sampson HA, Plaut M, Burks AW, Akdis CA, Lack G. Food allergy: update on prevention and tolerance. J Allergy Clin Immunol. 2018 Jan;141(1):30–40. https://doi.org/10.1016/j.jaci.2017.11.010.
63. Peters RL, Allen KJ, Dharmage SC, Lodge CJ, Koplin JJ, Ponsonby AL, et al. HealthNuts study. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. Clin Exp Allergy. 2015 May;45(5):953–63. https://doi.org/10.1111/cea.12478.
64. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. J Allergy Clin Immunol. 2010 Oct;126(4):807–13. https://doi.org/10.1016/j.jaci.2010.07.028.
65. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M, et al. PETIT Study Team. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. Lancet. 2017 Jan 21;389(10066):276–86. https://doi.org/10.1016/S0140-6736(16)31418-0.
66. Wei-Liang Tan J, Valerio C, Barnes EH, Turner PJ, Van Asperen PA, Kakakios AM, et al. Beating Egg Allergy Trial (BEAT) Study Group. A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy. J Allergy Clin Immunol. 2017 May;139(5):1621–1628.e8. https://doi.org/10.1016/j.jaci.2016.08.035.
67. Palmer DJ, Metcalfe J, Makrides M, Gold MS, Quinn P, West CE, et al. Early regular egg exposure in infants with eczema: a randomized controlled trial. J Allergy Clin Immunol. 2013 Aug;132(2):387–92.e1. https://doi.org/10.1016/j.jaci.2013.05.002.
68. Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized controlled trial of early regular egg intake to prevent egg allergy. J Allergy Clin Immunol. 2017 May;139(5):1600–1607.e2. https://doi.org/10.1016/j.jaci.2016.06.052.
69. Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Aksünger Ö, Kalb B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. J Allergy Clin Immunol. 2017 May;139(5):1591–1599.e2. https://doi.org/10.1016/j.jaci.2016.06.045.
70. Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, Leshno M. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. J Allergy Clin Immunol. 2010 Jul;126(1):77–82.e1. https://doi.org/10.1016/j.jaci.2010.04.020.
71. Onizawa Y, Noguchi E, Okada M, Sumazaki R, Hayashi D. The association of the delayed introduction of cow's milk with IgE-mediated cow's milk allergies. J Allergy Clin Immunol Pract. 2016 May–Jun;4(3):481–488.e2. https://doi.org/10.1016/j.jaip.2016.01.012.

72. Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow Milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA birth cohort study. P Pediatrics. 2008 Jul;122(1):e115–22. https://doi.org/10.1542/peds.2007-1651.
73. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis infant allergenic food introduction and risk of allergic/autoimmune disease infant allergenic food introduction and risk of allergic/autoimmune disease. JAMA. 2016 Sep 20;316(11):1181–92. https://doi.org/10.1001/jama.2016.12623.
74. Chmielewska A, Pieścik-Lech M, Shamir R, Szajewska H. Systematic review: early infant feeding practices and the risk of wheat allergy. J Paediatr Child Health. 2017 Sep;53(9):889–96. https://doi.org/10.1111/jpc.13562.

# Part IV

# Food Allergy Management and Prognosis

# 14 Clinical Management of Food Allergy

Melanie M. Makhija

Food allergies are common [1] and increasing in prevalence [2]. To date, there is no approved treatment for food allergy. If a food allergy is suspected or likely, the patient should be referred to an allergist for further diagnosis, monitoring for development of tolerance, as well as for guidance on food avoidance.

## Diagnostic Testing

Diagnostic testing for food allergy is discussed in detail in a previous chapter. In brief, IgE-mediated allergic reactions are diagnosed based on history and physical examination. A food allergy history should focus on trying to identify the culprit food allergen(s) by reviewing foods that consistently elicit symptoms and foods that may be hidden. Most reactions occur within minutes to hours of ingestion of the culprit food. Reactions often involve cutaneous symptoms including erythema, urticarial rash, worsening eczema, and/or angioedema. Reactions can also include GI symptoms such as vomiting and abdominal pain, laryngeal and respiratory symptoms, and cardiac symptoms. Testing for food allergy includes epicutaneous skin prick testing (SPT), serum food-specific IgE testing (sIgE), and oral food challenges. A positive test (either SPT or food-specific sIgE) indicates that a patient is sensitized to the food in question.

Epicutaneous skin prick testing (SPT) is the preferred method of testing for the detection of allergen-specific IgE antibody to foods, as it is standardized and inexpensive. Skin prick testing to foods has a low specificity and low positive predictive value. Unless there is a corroborative clinical history, a definitive diagnosis of food allergy cannot be made based on skin testing alone [3]. The sensitivity and negative predictive value of SPT are high (>90%) for most food allergens with the exception of foods with thermo-labile molecules; therefore, negative testing is generally predictive of tolerance [4].

Allergen-specific IgE antibody testing is the most common blood test used to diagnose immediate or IgE-mediated reactions to foods. It can be used as an alternative to SPT in patients with contraindications to SPT such as dermatographism or those who cannot be taken off antihistamines. It is also used as an adjunct test to SPT for food allergy as specific IgE levels to foods can be trended and followed over time. This may be useful if a patient is expected to outgrow their food allergy such as in the case of cow's milk or egg allergy [5]. Panel testing of food allergens is not recommended given a low positive predictive value in the absence of clear reaction to the culprit food with a high rate of false-positive tests.

M. M. Makhija (✉)
Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: mmakhija@luriechildrens.org


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_14

The FDA has approved allergen component resolved diagnostic (CRD) testing using the Immunocap system (Phadia Immunology Reference Library PiRL, Phadia US Inc). This testing is used primarily for food protein components. Knowledge of allergen component sensitizations may help differentiate between severe/anaphylactic allergy and other allergic diseases such as oral allergy syndrome/pollen food syndrome [6, 7]. This testing has been primarily used for peanut and individual tree nuts but is increasingly being used for other major food allergy protein components, as well as fruits, vegetables, and several environmental allergens (aeroallergens).

An oral food challenge (OFC) is the gold standard test to determine whether a patient has a food allergy. This includes understanding whether a patient has outgrown or developed tolerance to a culprit allergen. A food challenge may also be performed for patients who are sensitized to a food allergen with no clear history of reaction or conversely for patients who have had a reaction but are not sensitized. OFCs can be open, single blind, or double blind. In an open food challenge (the most commonly performed OFC in clinical practice), the patient is given up to a typical serving of the culprit food to determine tolerance. In research studies and clinical trials, single- and double-blind food challenges are performed, often with a placebo component. In a single-blind food challenge, the participant/patient does not know whether he or she is consuming an allergen or placebo. In a double-blind challenge, neither the participant nor the clinician knows whether the participant is consuming an allergen or placebo. Consent should be obtained and risks and benefits of the OFC, including the risk of a severe anaphylactic reaction, should be explained to the family prior to beginning the challenge [8]. All questions should be answered. A trained medical provider should supervise all OFCs. Emergency treatments for anaphylaxis should be readily available in case they are needed [9].

Oral food challenge protocols can be found in a working group report and the PRACTALL consensus report [10, 11]. A working group report outlines how to conduct an OFC to peanut in an infant [12]. In a typical food challenge, the patient ingests the potential allergen in a graded fashion beginning with 0.1–1% of the total dose, with increasing doses every 15 minutes. OFCs are performed in a graded fashion in order to minimize the risk of severe reaction and to understand the lowest provoking dose [8]. Patients should be observed for signs of reaction, and vital signs should be monitored in between doses [11]. Dose intervals may be increased for higher risk patients [13]. If a clinician is confident that the patient does not have an allergy to a particular food, based on lack of history of reaction and negative skin/blood testing results, an oral food challenge is likely not necessary. In this situation, home introduction or an in-office supervised feeding may be appropriate. A multicenter study of centers around the United States found that the rate of anaphylaxis for low risk in clinic challenges was 2% with a rate of allergic reactions of 14% [14]. Multiple studies have found that both patient and parent quality of life improves after a negative food challenge [15–19] and in some studies a positive OFC [16, 17, 19]. This may be due to reduced uncertainty around the allergy.

Currently, there are no approved treatments for IgE-mediated food allergy. The current standard of care for management of food allergies includes avoidance of trigger allergens and treatment of reactions caused by accidental exposures.

## Dietary Management

The goal of dietary management of food allergy is to prevent exposure to the allergen, which may result in a reaction. Avoiding relevant trigger foods from an individual's diet is crucial. The degree of avoidance needed depends on the individual and the allergen. For example, some patients with IgE-mediated milk and/or egg allergy are able to tolerate extensively heated forms of these foods despite reacting to less cooked forms. Difficulties may arise with complete avoidance of allergen, which includes avoiding traces of the allergen. Complete avoidance can lead to decreased quality of life [20–22] and can be challenging. In a study of children with peanut allergy, it was found that 50% had a reaction within 2 years

and 75% had a reaction within a 10-year period [23]. Adults with food allergy and parents of food allergic children spend 39% more time shopping for food than those without a food allergic family member [24]. If complete avoidance is necessary, the patient's family must be educated on label reading and avoiding possible cross-contamination. Cross-contamination occurs when a food ingested by the allergic individual has come into contact with the culprit food allergen. One study in Canada found that 17% of accidental exposures were caused by foods that had no advisory label but contained allergen due to cross-contamination during manufacturing or processing [25]. Although preventing cross-contamination is difficult, there are strategies that can be implemented to make things easier. Examples include washing hands and cooking utensils as well as chopping boards and work surfaces well when preparing food [26] and cooking different foods in clean oil and well-washed pans and using separate serving spoons for each dish [20].

Eating outside of the home may be difficult for patients with food allergies especially in places where accidental exposures due to cross-contamination commonly occur including buffets, salad bars, ice cream parlors, ethnic restaurants, and bakeries [27]. Patients eating in restaurants should speak to the server and the cook/chef to let them know about the allergy and to ask questions about ingredients in foods and possible cross-contamination. In ice cream parlors, scoops should not be shared between different ice cream tubs. One may consider carrying a chef card, which outlines foods that require special consideration. An example of an interactive food allergy card can be completed and downloaded from the Food Allergy Research and Education Website. This is available at https://www.foodallergy.org/life-food-allergies/managing-lifes-milestones/dining-out/food-allergy-chef-cards [28]. This chef card is available in English, Chinese, Dutch, French, German, Italian, Japanese, Portuguese, Spanish, and Swedish. Social gatherings can also be difficult for individuals with food allergies. Advice for school and social outings including birthday parties should be given to patients. Bringing the child their own snack for school or a dessert alternative for a birthday party can be helpful.

Although avoiding any food can be problematic, tree nut avoidance in particular is complex as a patient may be only allergic to some rather than all tree nuts. Avoiding all nuts instead of just the culprit allergenic nut decreases the risk of accidental reactions due to cross-contamination and is easier than avoiding just one or a few specific nuts. Conversely, avoiding all nuts may decrease quality of life and may possibly increase risk of becoming allergic to nuts that were previously tolerated. Oral food challenges to each specific nut that is positive on SPT/sIgE may be needed to understand which are true allergies rather than just sensitization. Patients should be given clear guidance for management of their nut allergy. Options of target avoidance or general avoidance of all nuts should be discussed with the family with an explanation of risks and benefits of both options [29].

## Travel

Travel can be daunting for the family of a child with food allergy, especially if traveling to countries where cultural and language differences may pose challenges.

When traveling on airplanes it is advisable to call the airline beforehand and let them know about the allergies. Some airlines may allow individuals to pre-board and wipe down the seating area and table. This is helpful especially if the allergic individual is a young child. It is also reasonable to carry your own food for the flight and carry all prescription medications on board including auto-injectable epinephrine, antihistamines, and asthma inhalers. Wearing medical-alert jewelry may be helpful especially if traveling alone. A survey of peanut and tree nut allergic participants found that 349 of 3273 participants had a reaction in flight and 13.3% received epinephrine as treatment. This study suggested that requesting accommodations for flight travel might lower the odds of having a reaction. These accommodations included (1) making any request of the airline, (2) requesting

a buffer zone, (3) requesting an announcement that passengers not eat peanut/tree nut–containing goods, (4) requesting a peanut/tree nut–free meal, (5) wiping their tray table, (6) bringing their own food from home, (7) avoiding use of an airline-provided pillow, and (8) avoiding use of an airline-provided blanket [30].

Previous surveys of individuals with food allergy suggest that reactions are more common if the flight crew was not informed of the allergy [31].

Learning the words for your food allergen in the language of the country of travel can be helpful. It is recommended to have a written statement (such as a chef card as outlined previously) to show to hotel and restaurant staff stating what the allergen is and that consumption can cause a severe reaction [8].

## Food Labeling

In the United States, the Food Allergy Labeling and Consumer Protection Act (FALCPA) was enacted in 2004 to help consumers with food allergies understand food labels [32]. This law requires that all packaged foods sold in the United States list the names of the top eight culprit allergens in English including milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish on the ingredient labels. The law applies to all food items manufactured in the United States or food imported for sale in the United States. The ingredients are to be listed by common name in the ingredient list or in a "contains" statement. Manufacturers are subject to penalties if the allergens do not appear on the labels. The law does not apply to meat, poultry or alcohol. There is little regulation on advisory statements such as "may contain" or "made in a facility with." These labels are voluntary. Additionally, it is difficult for families to navigate different precautionary allergen labels. One study demonstrated that families purchased food with "manufactured in a facility that also processes" labeling more often than foods with "may contain" labeling (40% vs. 11%) [33]. Existing misconceptions surrounding food allergen labeling may influence purchasing practices [33]. In Europe, the current food labeling law was updated in 2007 and requires all prepackaged food including alcoholic drinks sold in the EU to list all ingredients including all major allergens even if present in small amounts. The law again does not apply to advisory labels (i.e., "may contain" or "made in a facility with) [20, 34]. Although advisory labels are helpful, the widespread use of "allergen traces" labeling on pre-packaged foods can be difficult for families and can lead to anxiety and stress around shopping for packaged foods that are staples in many children's diets. Widespread use of this labeling may also lead to devaluation of the warning. In one study, up to 40% of individuals report that they ignore "may contain" statements [35] (Table 14.1).

**Table 14.1** Foods containing major allergens and alternative names for major food allergens

| Major allergen | Food allergens/foods containing allergen | Alternative names for allergen or allergen component |
|---|---|---|
| Milk | Butter, buttermilk, cheese, condensed milk, cottage cheese, cream, curds, custard, ghee, half and half, ice cream, milk (all forms of cow's, sheep, and goat's milk), sherbet, and yogurt<br>May contain milk:<br>Baked goods, chocolate, Deli meat, and some medications | Casein, casein hydrolate, caseinates, curd, diacetyl, lactalbumin, lactoferrin, lactoglobulin, lactose, lactulose, recaldent, rennet casein, tagatose, whey, and whey protein hydrolysate |
| Egg | Eggs (including turkey, quail, duck, and goose as they are cross-reactive with chicken eggs), eggnog, mayonnaise, meringue, surimi, and tamago<br>May contain egg:<br>Baked goods, pasta, nougat, marshmallows, and candy | Albumin, lysozyme, ovalbumin, ovomucin, ovovitellin, lecithin, and vitellin |

**Table 14.1** (continued)

| Major allergen | Food allergens/foods containing allergen | Alternative names for allergen or allergen component |
|---|---|---|
| Peanut | Peanut butter, beer nuts, cold-pressed peanut oil, goobers, ground nuts, mixed nuts, monkey nuts, nutmeat, nut pieces, and peanut flour<br>May contain peanut:<br>African, Asian, and some Mexican foods, candy, mole and enchilada sauce, nougat, and trail mix | Arachis and peanut protein hydrolysate |
| Tree nuts | Almonds, beechnut, Brazil nut, butternut, cashew chestnut, chinquapin, hazelnut/filbert, ginkgo nut, lychee nut, macadamia nut, marzipan, pecan/hickory nut, pesto, pine nut, pistachio, praline, walnut, nut oils, nut extracts, and alcoholic extracts (i.e., Amaretto). Nut butters, nut meal, nutmeat, nut paste, and nut pieces | |
| Wheat | Bread crumbs, baked goods, bulgur, couscous, cracker meal, cereals, flour (all purpose, bread, cake, durum, enriched, graham, gravies, pastry, self-rising, soft wheat, stone ground, whole wheat etc.), hydrolyzed wheat protein, kamut, matzo, matzo meal, pasta, seitan, semolina, spelt, whole wheat berries, soy sauce, starch, and surimi | Durum, einkorn, emmer, farina, triticale, sprouted wheat, vital wheat gluten, wheat, wheat bran hydrolysate, wheat germ oil, wheat grass, and wheat protein isolate |
| Fish | Anchovies, bass, catfish, caviar, cod, flounder, grouper, haddock, hake, herring, mahi mahi, monkfish, orange roughy, perch, pike, pollack, salmon, sardines, scrod, sole, snapper, smelt, swordfish, tilapia, trout, tuna, whitefish, and whiting fish<br>May contain fish:<br>Worcestershire sauce, Caesar salad dressing, surimi, fish sauce, kosher gelatin, gumbo, bonito broth, and fish oil supplements | |
| Shellfish | Crustaceans: barnacle, crab, crawfish, krill, lobster (langouste, langoustine) scampi, prawns, and shrimp<br>Mollusks: abalone, clams, cockle, cuttlefish, mussels, octopus, oyster, oyster sauce, and scallops<br>May contain shellfish: Bouillabaisse, fish stock, seafood flavoring cucumber, sea urchin, snails (escargot), and squid (calamari) | |
| Soy | Edamame, miso, natto, shoyu, soy (soy cheese, soy flour, soy ice cream, soy milk, soy nuts, soy sprouts, soy noodles, soy yogurt), soya, soybean, soy protein, soy sauce, tamari, tempeh, textured vegetable protein (TVP), and tofu<br>May contain soy:<br>Veggie burgers and sausages, and vegetable broth | |
| Sesame | Gomasio (sesame salt), sesame seed oil, tahini, and tahina<br>May contain sesame: Asian food, baked goods, bread crumbs, cereals, chips, crackers, dressing and dips, falafel, hummus, halvah, sushi, pasteli, middle eastern foods, and desserts, snacks, and soups | Benne seed, gingelly seed, sesamolina, *Sesamum indicum*, sim sim, tehina, and til |

Adapted from Food Allergy Research and Education (FARE) websites on food avoidance [36]

## Dietary Supplementation

Food-allergic children may suffer from nutritional deficiencies due to lack of intake of calories and micronutrients. Optimal nutrition is important for growth and development [37]. Eliminating one food that is not commonly consumed in the child's diet will be of little nutritional consequence [20]. However, avoidance of multiple foods or a food group that is staple (i.e., dairy or wheat) may cause significant nutritional consequences. Referral to a registered dietician or nutritionist can be extremely useful for families of children with food allergies for guidance on adequate caloric and micronutrient (i.e., vitamin D) intake.

## Treatment of Reactions

Despite avoidance of the culprit allergen, accidental ingestions can happen. As life-threatening anaphylactic reactions may occur to the culprit allergen, all patients with an IgE-mediated allergy should have emergency medications to treat reactions on hand at all times. All patients with IgE-mediated food allergy should be prescribed auto-injectable epinephrine. Intramuscular epinephrine is the first-line treatment for all cases of anaphylaxis. Epinephrine should be given to patients experiencing systemic symptoms, including respiratory or cardiovascular, or symptoms of laryngeal edema. Symptoms involving two organ systems such as skin and gastrointestinal should also be treated with epinephrine. If symptoms are progressing despite a single dose of 0.1 mg/kg (max 0.5 mg) of epinephrine, repeated doses may be given [7, 38]. Patients must be instructed on the correct use of epinephrine auto-injectors and should have them available at all times. Having at least two auto-injectors on hand is recommended in case a repeat dose is needed. Adjunctive treatments include antihistamines (H1 blockers) for skin symptoms. Short-acting bronchodilators such as albuterol should be prescribed to patients with asthma. If respiratory symptoms are occurring, epinephrine should be given prior to inhaler use. Additional medications that may be given in the emergency room include oxygen, corticosteroids, H2 blockers, pressers, and intravenous fluids [9].

## Emergency Action Plans and Medical-Alert Jewelry

All patients with IgE-mediated food allergy should have a written emergency action plan [9]. Template emergency action plans are available in both English and Spanish. The plan should be easy to read and follow and should be aimed at treating symptoms of a reaction. Doses of medications should be listed on the emergency action plan. There are commonly used action plans that have been created by the Academy of Allergy, Asthma and Immunology (AAAAI) as well as by Food Allergy Research and Education (FARE) (https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Anaphylaxis-Emergency-Action-Plan.pdf and https://www.foodallergy.org/sites/default/files/2018-06/emergency-care-plan.pdf) [39, 40].

Some schools, local school boards, and states may have their own emergency action plans.

Medical-alert jewelry including bracelets or necklace tags can be extremely helpful for first responders if a patient is found unconscious. They can also be helpful for young children or others who may not be able to articulate that they are having a reaction [8].

## Extensively Heated Milk and Egg

As discussed previously, many children who are allergic to milk and egg tolerate extensively heated forms of these foods. The proteins in milk and egg change conformation with extensive heating. Heating destroys many conformational epitopes and may reduce allergenicity of these foods [41]. Additionally, adding a matrix by baking food proteins with wheat may decrease allergenicity by altering the sequential IgE-binding epitopes that are unaffected by heat alone [42]. Studies suggest that between 69% and 83% of cow's milk allergic children tolerate baked cow's milk and between 63% and 83% of egg-allergic chil-

dren can tolerated baked egg ("baked milk and baked egg") [43]. Foods that contain "baked milk and baked egg" include muffins, cakes, and muffins. It is thought that tolerance of the extensively heated forms of these foods may also help speed up tolerance to the less cooked forms [44]. In addition, allowing these foods into a child's diet can improve their quality of life and ease in social situations (i.e., birthday party cake). Introduction of baked milk and egg should be performed in the physician's office as reactions, including anaphylaxis, can occur. In children who pass an oral food challenge to baked milk or egg, 1–3 servings of baked egg per day should be consumed by the child at least three times per week [45].

## Prevention of Food Allergy

There are multiple measures that have been tried in order to prevent allergy including avoiding foods in the mother's diet during pregnancy and lactation, exclusive breastfeeding in infancy, and avoiding allergens in the first year to 3 years of life. The American Academy of Pediatrics clinical practice guidelines in the year 2000 recommended avoidance of allergenic foods including cow's milk and egg for the first year of life and first peanut for the 3 years of life [46–48]. Looking back, these avoidance measures are felt to have had no protective effect overall as the prevalence of food allergy continued to rise in subsequent decades.

In recent years, research has emerged suggesting that early introduction of high-risk foods may be beneficial especially in children with personal or family history of atopy.

The Learning Early About Peanut trial (LEAP trial), a study of 640 high-risk infants in the United Kingdom, found that early introduction of peanut into the diet between 4 and 11 months of age with continued consumption led to an 81% reduction in peanut allergy at age 5 compared with children who were avoiding peanut-containing foods for the same time period [49]. Studies of early egg intake including the Australian BEAT study and Japanese Petit trial suggest that there may be some benefit to early egg introduction [50, 51]. A subsequent trial by the LEAP group entitled EAT (Enquiring about Tolerance) compared early introduction of multiple foods to exclusive breastfeeding until 6 months of age in the general population. This trial showed a reduced risk of any food allergy in the general population using a per protocol analysis but not the intention to treat analysis [52]. The clinical practice guidelines in the United States now recommend early introduction of peanut into an infant's diet for high- and standard-risk children [53], and the recommendations for avoidance of other allergic foods in infants' diets have been removed. There are currently no specific recommendations for maternal dietary changes while pregnant or breastfeeding as the research around this is mixed and controversial.

Patients with food allergies should be referred to an allergist for diagnosis, testing and monitoring for the development of tolerance. Follow up visits (often annual) will include assessment for accidental exposures, prescriptions refills and re-education on the use of auto-injectable epinephrine, update of emergency action plans, and monitoring of other co-existing atopic disease.

In conclusion, the management of food allergy to date centers around avoidance of the culprit allergen. Accurate diagnosis, counseling on dietary avoidance, and management of acute accidental exposures as well as monitoring for the development of tolerance are the foundations of food allergy management. New therapies currently in development will likely have significant clinical applications in the near future.

## References

1. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, Nadeau KC. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018 Dec;142(6):e20181235.
2. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. NCHS Data Brief. 2013;(121):1–8.
3. Bernstein IL, Storms WW. Practice parameters for allergy diagnostic testing. Joint task force on practice parameters for the diagnosis and treatment of asthma. The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol. 1995;75:543.

4. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test-European standards. Clin Translat Allergy. 2013 Feb 1;3(1):3.
5. Makhija M. In vivo and in vitro testing in allergy and immunology. In: Grammer LC, Greenberger PA, editors. Patterson's Allergic Diseases. 8th ed. Philadelphia: Wolters Kruger; 2018.
6. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update – 2014. J Allergy Clin Immunol. 2014;134(5):1016–24 e43.
7. Macchia D, Melioli G, Pravettoni V, et al. Guidelines for the use and interpretation of diagnostic methods in adult food allergy. Clin Mol Allergy. 2015;3:27.
8. Bird JA, Lack G, Perry TT. Clinical management of food allergy. J Allergy Clin Immunol Pract. 2015;3:1–11.
9. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. J Allergy Clin Immunol. 2010;126:1105–18.
10. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma and Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130:1260–74.
11. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work group report: oral food challenge testing. J Allergy Clin Immunol. 2009;123:S365–83.
12. Bird JA, Groetch M, Allen KJ, Bock SA, Leonard S, Nowak-Wegrzyn AH, et al. Conducting an oral food challenge to peanut in an infant. J Allergy Clin Immunol Pract. 2017;5(2):301–11.
13. MacGinnitie AJ, Young MC. The role of food challenges in clinical practice. J Allergy Clin Immunol Pract. 2018;6:353–60.
14. Akuete K, Guffey D, Israelsen RB, Broyles JM, Higgins LJ, Green TD, et al. Multicenter prevalence of anaphylaxis in clinic-based oral food challenges. Ann Allergy Asthma Immunol. 2017 Oct;119(4):339–348.e1.
15. Van der Velde JL, Flokstra-de Blok BM, de Groot H, et al. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents and children. J Allergy Clin Immunol. 2012;130:1136–1143;e2.
16. Kemp A, Allen CW, Campbell DE. Parental perceptions in egg allergy: does egg challenge make a difference? Pediatr Allergy Immunol. 2009;20:648–53.
17. Franxman TJ, Howe L, Teich E, Greenhawt MJ. Oral food challenge and food allergy quality of life in caregivers of children with food allergy. J Allergy Clin Immunol Pract. 2015;3:50–6.
18. Soller L, Hourihane J, DunnGalvin A. The impact of oral food challenge test on food allergy health-related quality of life. Allergy. 2014;69:1255–7.
19. Knibb RC, Ibrahim NF, Steifel G, et al. The psychological impact of diagnostic food challenges to confirm the resolution of peanut or tree nut allergy. Clin Exp Allergy. 2012;42:451–9.
20. Venter C, Meyer R. The challenges of managing food hypersensitivity. Proc Nutr Soc. 2010;69:11–24.
21. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. Ann Allergy Asthma Immunol. 2001;87:461–4.
22. Avery NJ, Kin RM, Knight S, et al. Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol. 2003;14:378–82.
23. Bock SA, Atkins FM. The natural history of peanut allergy. J Allergy Clin Immunol. 1989;83:900–4.
24. Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut allergic children. Clin Exp Allergy. 2003;30:1135–43.
25. Sheth SS, Wasserman S, Kagan R, et al. Role of food labels in accidental exposures in food-allergic individuals in Canada. Ann Allergy Asthma Immunol. 2010;104:60–5.
26. Simonte SJ, Ma S, Mofidi S, et al. Relevance of casual contact with peanut butter in children with peanut allergy. J Allergy Clin Immunol. 2003;112:180–2.
27. Furlong TJ, DeSimone J, Sicherer SH. Peanut and tree nut allergic reactions in restaurants and other food establishments. J Allergy Clin Immunol. 2001;108:867–70.
28. Food Allergy Research and Education Website. https://www.foodallergy.org/life-food-allergies/managing-lifes-milestones/dining-out/food-allergy-chef-cards
29. Eigenmann PA, Lack G, Mazon A, et al. Managing nut allergy: a remaining clinical challenge. J Allergy Clin Immunol Pract. 2017;5(2):296–300.
30. Greenhawt M, MacGillivray F, Batty G, et al. International study of risk-mitigating factors and in-flight allergic reactions to Peanut and tree nut. J Allergy Clin Immunol Pract. 2013;1(2):186–94.
31. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. Self-reported allergic reactions to peanut on commercial airliners. J. Allergy Clin Immunol. 1999;104(1):186–9.
32. Food Allergen Labeling and Consumer Protection Act (FALCPA). Available at: http://www.fda.gove/downloads/Food/GuidanceREgulation/UCM179394.pdf (2004).
33. Marchisotto MJ, Harada L, Kamdar O, et al. Food allergen labeling and purchasing habits in the United States and Canada. J Allergy Clin Immunol Pract. 2017;5(2):345–351 e342.
34. European Commission. Commission Directive 2007/68/EC of 27 November 2007 amending Annex IIIa to Directive 2000/13/EC of the European Parliament and of the council as regards certain food ingredients. Off J Eur Union. 2007;310:11–4.
35. Hefle SL, Furlong TJ, Niemann L, et al. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. J Allergy Clin Immunol. 2007;120:171–6.

36. Food Allergy Research and Education (FARE). Tips for avoiding your allergen. https://www.foodallergy.org/sites/default/files/migrated-files/file/tips-avoid-allergen.pdf
37. Vlieg-Boerstra BJ, van der Heide S, Bijleveld CM, et al. Dietary assessment in children adhering to a food allergen avoidance diet for allergy prevention. Eur J Clin Nutr. 2006;60:1384–90.
38. Simons FE, Ardusso LR, Dimov V, et al. World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol. 2013;162:193–204.
39. Academy of Allergy, Asthma and Immunology (AAAAI). https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Anaphylaxis-Emergency-Action-Plan.pdf
40. Food Allergy Research and Education (FARE). https://www.foodallergy.org/sites/default/files/2018-06/emergency-care-plan.pdf
41. Vila L, Beyer K, Jarvinen KM, et al. Role of conformational and linear epitopes in the achievement of tolerance in cow's milk allergy. Clin Exp Allergy. 2001;31:1599–606.
42. Nowak-Wegrzyn A, Fiocchi A. Rare, medium or well done? The effect of heating and food matrix on food protein allergenicity. Curr Opin Allergy Clin Immunol. 2009;9:234–7.
43. Leanord SA, Nowak-Wegrzyn A. Baked Milk and Egg Diets for Milk and Egg Allergy Management. Immunol Allergy Clin North Am. 2016;36:147–59.
44. Huang F, Nowak-Wegrzyn A. Extensively heated milk and egg as oral immunotherapy. Curr Opin Allergy Clin Immunol. 2012;12:283–92.
45. Leonard SA, Caubet JC, Kim JS, et al. Baked milk- and egg-containing diet in the management of milk and egg allergy. J Allergy Clin Immunol Pract. 2015;3:13–23.
46. American Academy of Pediatrics. Committee on nutrition. Hypoallerg Infant Formula Pediatrics. 2000;106:346–9.
47. Arshad SH. Food allergen avoidance in primary prevention of food allergy. Allergy. 2001;56:113–6.
48. Fiocchi A, Assa'ad A, Bahna S. Food allergy and the introduction of solid foods to infants: a consensus document. Ann Allergy Asthma Immunol. 2006;97:10–21.
49. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803–13.
50. Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized controlled trial of early regular egg intake to prevent egg allergy. J Allergy Clin Immunol. 2017;139:1600–7.
51. Natsume O, Kabashima S, Nakazato J, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. Lancet. 2017;389:276–86.
52. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016;374:1733–43.
53. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. J Allergy Clin Immunol. 2017;139:29–44.

# 15 Management of Food Allergy in the School Setting: The Clinician's Role

Michael Pistiner and Julie Wang

## Introduction

Food allergies are a significant national concern affecting an estimated 7.6% of US children [1]. With a growing number of school-age children carrying the diagnosis of food allergy, schools are tasked with providing safe learning environments while these children are under the school's oversight. It is critical that clinicians are proactively involved in preparing patients and their families as well as participating in the creation of safe school environments for food-allergic children because allergic reactions are not predictable. Potentially life threatening reactions can occur anytime and anywhere at school [2, 3].

## Clinician Roles

A number of clinicians participate in managing school-aged children with food allergies, including pediatricians, family physicians, pediatric specialists, nurse practitioners, and physician assistants. The pillars of food allergy management are prevention of and emergency preparedness to manage allergic reactions. These must be maintained at all times and in all circumstances. The school environment is no exception and necessitates thoughtful planning and support of students with food allergy. Clinicians play an important role whether directly or indirectly in the management of food allergies in school [4].

The clinician's role can be approached as (1) patient/student specific and (2) school wide/policy driven. Clinicians play an important role in their specific patient's care by providing patient/family medical education and management that is specific to their particular food allergies, comorbidities, and developmental capabilities. Some of these responsibilities include providing medical orders such as allergy and anaphylaxis emergency plans [5], prescriptions for epinephrine auto-injectors [6], and participation in the establishment of individual health care plans or 504s. In addition, many clinicians participate in school wide/policy-driven activities and not only take responsibility for their own patients in school, but also work and volunteer directly with schools and government agencies where they play key roles in creating and guiding food allergy policies. They prescribe stock epinephrine, provide school community education, and can work on the creation and implementation of school policy and or legislation pertaining to school policy [4, 7].

All clinicians, whether involved in the care of the individual student or general school health-related

M. Pistiner (✉)
MassGeneral Hospital for Children, Food Allergy Center, Harvard Medical School, Boston, MA, USA
e-mail: mpistiner@mgh.harvard.edu

J. Wang
Department of Pediatrics, Division of Allergy and Immunology, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: julie.wang@mssm.edu


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_15

issues, will need a solid understanding of practical food allergy management. Clinicians set and establish expectations that patients and their schools will count on. Their teachings and guidance will affect and shape future relationships with their school community [4, 7].

## Food Allergy Management in School

### Facilitate Communication Between the Family and the School

Effective food allergy management in school requires clear communication related to allergen avoidance and preparation in case of allergic reactions. The clinician's first and most important role is to provide patients and families with accurate diagnoses of food allergy. It is the clinician's role to provide up to date information for individualized allergy and anaphylaxis emergency plans (see below for further detail) [5], prescriptions for epinephrine auto-injectors, and assistance in creating school plans to address managing in case an allergic reaction occurs. Older students should be encouraged to take responsibility for self-care that is developmentally appropriate (for example, self-carry, self-administer). Open discussion with patients and their families that is on-going with the school is important, and adjustments to management plans should be considered at least yearly based on medical and/or developmental changes and realistic requests for the school environment [8]. All staff that interact with students with food allergies should be aware of their students' diagnoses and know their role in students' management plans and the school's policy regarding food allergy management [9].

An important tool that facilitates communication is the Allergy and Anaphylaxis Emergency Plan. Be aware that there are several ways to name such a plan including but not limited to anaphylaxis emergency care plan, anaphylaxis action plan, food allergy action plan, etc. [5]. This document is written and presented in a way that non-licensed staff can read and understand and often can serve as a medical order [10]. The form provides space for clinicians to clearly indicate which allergens need to be avoided by the child and guidance on which symptoms would require treatment with the epinephrine auto-injector. Clinicians should ensure that families understand the importance of these documents and encourage that they are submitted to the school in a timely manner. Select staff will have direct access to the individualized allergy and anaphylaxis emergency care plan per discretion of school health/administration [9]. These plans should be updated at least yearly and whenever there is a change to the medical status [5].

### Collaborate with School Nurses, School Nutrition Services, and Allergists

#### School Nurses

School nurses are key partners/collaborators as they have the necessary skills and leadership to create and implement food allergy policies, train and educate school staff, bring awareness to the school community, and respond to allergic emergencies. Also, they are aware of the resources and culture of their schools in addition to the school staff that they work with. They are instrumental in the management of anaphylaxis in both those with known allergies and those whose allergies are unknown to the school. School nurses create individual health care plans and play important roles in the implementation of 504s if needed. Additionally, they can facilitate positive interactions between the parents of children with food allergies and the rest of the school community [4, 7].

#### School Nutrition Services

School nutrition services are also integral members of the school community who should be informed of the student's allergy. Students with food allergy that is documented with a written and signed statement from a state-licensed healthcare professional are eligible for dietary substitutions [7, 11–13]. Health care professionals must specify the food allergen in addition to alternate foods to be given [11, 13]. As for all medical information provided to schools, updates in food allergy status and needed meal accommodations should be provided to the school at least yearly [7, 11].

### Board-Certified Allergists

Utilize allergists for confirmation of allergy diagnosis, further management, appropriate reassessment, and reevaluation to offer the least restrictive diet possible. Establish open communication and seek support when there are unreasonable expectations on the part of the family or school, or when school allergy management strategies are either not effectively keeping the student safe or are overly restrictive and impacting quality of life, the ability to learn, or the other students [7].

## Support Education/Training: Staff and School Community Education/ Training

Even in schools with full-time registered school nurses, building layout and distance make it challenging for them to always be immediately accessible. Unfortunately, full-time school nurses are not available in all US schools. Regardless of the presence of a full-time school nurse, staff training is needed; but in schools without a school nurse, staff training becomes even more critical. In cases when a school nurse is unavailable, staff will need to be trained to implement student-specific and school-wide food allergy management strategies. There should be staff who have been trained appropriately in managing children with food allergies. Therefore, school staff food allergy education and training is necessary. It is important for staff responsible for the care of food-allergic children to follow necessary avoidance strategies and school policies, have familiarity with and access to the emergency plans, and for some, have access and training to administer the epinephrine auto-injector. All school staff should be trained to recognize allergic reactions and anaphylaxis and know their role in their schools' food allergy emergency protocol. All members of the school community (including but not limited to staff, parents, and students) should to be aware of school food allergy–related policies [9]. Additionally, all members of the school community should have food allergy education and awareness as recommended by CDC, state, or local guidelines, and tailored to their specific role. In most states, select staff (with appropriate training) may be trained to administer epinephrine to those without a known history of allergic reactions when the school nurse is not immediately available. Staff play important roles in the care of students with food allergy, making their education and understanding absolutely critical [7].

### Understand Allergen Avoidance (See Table 15.1)

Allergen avoidance can be challenging in the school setting and requires an understanding of the potential for hidden ingredients, comfort and skill in interpreting ingredient labels, and prevention of cross-contact during food preparation. Allergen avoidance measures are necessary to minimize the chance of allergic reactions, with the focus on preventing oral allergen exposure, which is the primary route by which severe reactions are triggered. In contrast, exposure by skin contact or inhalation is unlikely to trigger severe reactions [14–17]. Label reading, implementing effective cleaning strategies, avoiding outside food, no sharing policies, in addition to effective hand cleaning are approaches that have been successfully implemented to reduce the chances of allergen exposure [8]. Also, hidden ingredients in school supplies or use of food in other activities (science experiments, art) may be sources of allergen exposure (Table 15.1). State and Federal Guidelines have been developed to help guide schools and discuss strategies to approach allergen avoidance.

Allergen restriction is an approach that has been part of many school policies and a potential cause of controversy. Allergen avoidance has typically focused on peanuts and tree nuts [18]. Peanut-free policies can lead to decreased peanut in schools but does not eliminate all peanut from being brought into the school [19]. "Nut-free" policies are, at times controversial, and effectiveness of such approaches has not been proven [20]. When considering specific allergen restriction policies, the developmental capabilities of affected students should be considered. For example, young children have increased mouthing behaviors. Tulve et al. [21] reported that children ages 1–2 years old put hands or objects in their mouth 80 times an hour and for

children ages 2–5 years old, 40 times an hour. As children get older they can start participating in more self-management responsibilities, and many health care providers expect some level of self-management by the high school years [22].

Clinicians have the opportunity to provide education and address misconceptions in addition to offering resources from evidence-based recommendations that take into account the student's age, developmental level, and school-specific situations [8]. Clinicians should direct families and schools to resources such as The Voluntary Guidelines for Managing Food Allergies in Schools and Early Care and Education Programs (CDC Food Allergy Guidelines) [9] in addition to state guidelines and other guidance documents, which are excellent resources to guide implementation of food allergy management in school [4].

**Table 15.1** Types of routes of exposure to food allergens in the school setting

| Type of exposure | Relevant concepts/facts/studies | Practical challenges | Practical interventions (see CDC, NSBA, and/or state guidelines) |
|---|---|---|---|
| Oral exposure | Unable to visualize allergens; they can be "hidden ingredients"<br>Labels and ingredients can change without warning [24]<br>Items with advisory labels can contain allergens [25]<br>Trace amounts can cause severe allergic reactions<br>Allergens can be detectable in saliva [26]<br>*Cross-contact of food allergen can occur from one surface to another, food to food, and with transfer of saliva. If a person is then exposed to these allergens, especially by mouth, it may be enough of an exposure to cause a serious allergic reaction.* | Without labels, it is impossible to know avoidance practices of those responsible for preparation of foods brought in to school<br>Classroom celebrations are common source of outside food and high risk for cross-contact<br>In schools, the majority of allergic reactions that occur start in classroom [27]<br>Resources and manpower in schools to read labels will vary among schools | If food is not from home then all labels must be accurately read by an assigned reader<br>Classrooms should have safe non-perishable snack or celebration items available if needed<br>Cafeterias should pre-publish menus and offer meal options without known allergens<br>Food-allergic children who are eating from the cafeteria should be assisted in selection of safe food<br>No sharing of food, drinks, utensils, etc., anywhere<br>No unlabeled food in classroom or cafeteria<br>Non-food celebrations and rewards are optimal/safest |
| | | *Additional consideration for pre-school/early elementary* | |
| | | Young children can pass saliva to each other via developmentally appropriate exploration<br>Some schools children eat in their classrooms/learning environments<br>Supervision during meal/snack time dependent on resources and staff | If meal/snack will be in the learning environment then effective strategies must be in place to clean and prevent accidental exposure/cross-contact<br>In some cases, food-free classrooms or selective allergen restriction (lower age groups) may be appropriate and practical if label reading is not possible |
| | | *Additional consideration for adolescent/teenage students* | |
| | | Older students under less supervision and more reliant on self-management<br>Increased risk taking, peer pressure, bullying, etc. [5, 6], kissing with salivary exchange | Periodic check ins to ensure continued self-management and safety from bullying<br>Discussion of intimate kissing and allergen exposure, and evidence-based preventive measures |

**Table 15.1** (continued)

| Type of exposure | Relevant concepts/facts/studies | Practical challenges | Practical interventions (see CDC, NSBA, and/or state guidelines) |
|---|---|---|---|
| Skin exposure | Anaphylaxis can occur without skin reactions<br>Isolated skin contact on intact skin did not cause severe or systemic reactions in two small studies although skin reactions did occur [14, 15]<br>Soap and water, and commercial hand wipes are effective in cleaning hands; alcohol and non-alcohol-based hand sanitizers are not [16]<br>Soap and water, commercial cleaners, and commercial wipes were effective in cleaning table tops [16]<br>Young children frequently place their hands and objects in their mouth (age 1–2:80x/h; age 2–5:40x/h) [21]<br>Adults touch their eyes, nose, and mouth regularly (15x/h) [28] | Handwashing in young grades can take 20–30 minutes<br>Resources and manpower available to clean allergens and prevent cross-contact will vary school by school and classroom by classroom<br>Some non-edible items contain some food Allergens; finger paint, play dough, shaving cream, paste, bean bags, furniture, pet food, bird feed, as well as others [29]<br>Skin exposure can result in mucosal exposure in adults and children | Hand washing with soap/water or wipes before and after eating is optimal<br>Appropriate cleaning of eating areas decreases risk<br>Curricular activities can be food free, or comparable but alternate activities can be provided for children with life-threatening food allergies attention to avoid allergens with crafts/lessons/pets is optimal<br>Establish a cleaning protocol to avoid cross-contact |
| | | *Additional consideration for pre-school/early elementary* | |
| | | Skin exposure that can quickly turn into mucosal exposure or oral ingestion<br>Less effective cleaning skills (hands or eating surfaces) | In some cases food-free classrooms or selective allergen restriction in lower age groups may be appropriate and practical<br>Adult supervision of hand cleaning is optimal<br>Adult have responsibility for cleaning surfaces, toys, etc |
| Inhalation exposure | Aerosolized proteins in cooking are the most common cause of allergic reactions by inhalation [30]<br>Odors are caused by volatile organic compounds, not protein, and odors alone do not cause allergic reactions | Experiments involving burning/heating of allergens create risk<br>Some field trips are in areas where foods are actively cooking or aerosolized<br>Some activities involve using food powders or grinding/crushing fresh foods | Use caution with cooking foods, flours, powders, and other small particles of food that can go up in the air<br>Avoid food in curricular science experiments or classroom activities. All field trips to have prior assessment from school nurse to determine need for special accommodations |

Adapted with permission from Pistiner, AllergyHome.org/schools [23]. Also published in Pistiner and Devore [4] and Pistiner et al. [7]

## Ensure Readiness to Treat Allergic Reactions

Unfortunately, allergen avoidance is not always fool-proof; therefore, readiness to treat allergic reactions is also essential. School staff must be able to recognize anaphylaxis, have epinephrine available, and be capable of administering it. All states have passed/pending policies to allow and encourage stock epinephrine auto-injectors in schools [31]. Epinephrine prescriptions from health care providers are still necessary at school. Helping schools obtain epinephrine and training on how to use it is essential. Data from school nurses demonstrated that most schools have stock epinephrine (81.7%) and training (96.7%) in place [32]. Significant reactions can occur very quickly after allergen exposure, and rapid, early epinephrine use is associated with improved outcomes, such as decreased risk of hospitalization and of requiring multiple doses of epinephrine [33, 34]. In a national survey of over 5000 schools, 11% reported at least one

instance of anaphylaxis in the 2013/14 school year and 1% reported three or more cases [35]. Data from the US Peanut and Tree Nut Allergy Registry indicates that 16% (of ~4500) reported reactions happened at school, with the majority of reactions occurring in the classroom and 12% in lunchrooms [29]. Reactions also occurred in other settings such as field trips in addition to the school playground, with nearly 25% of reactions occurring during special occasions such as a birthday celebration [8]. Several studies suggest that this is a significant problem warranting attention as rates of epinephrine use in schools has reported to be increasing in recent years [36, 37].

Food-induced anaphylaxis can be life threatening and deaths have occurred in schools. However, this is rare. The primary risk factor for poor outcomes in anaphylaxis is the delay or lack of administration of epinephrine [38–40].

Recognition of reactions can be difficult at times. Not all cases of anaphylaxis present with skin symptoms [41]. Young children lack of self-awareness or may be unable to verbalize what they are feeling; symptoms may not be specific for anaphylaxis. For children with asthma, symptoms of an allergic reaction may be mistaken for an asthma exacerbation.

Another pitfall that schools must contend with is that the first allergic reaction for a child may occur at school so the child and family is unaware of the allergy risk. Close to 25% of administrations of epinephrine are to those without an allergy history that was known by the school [42]. Adults on school premises can also have food-allergic reactions, so schools need to be prepared to treat both children and adults. Plans must be in place to treat both those with and without known food allergies and other potentially severe allergies (Table 15.2).

**Table 15.2** School strategies for management of allergic emergencies

| Strategies for KNOWN history of food allergy | Strategies for UNKNOWN food allergy |
|---|---|
| Identification of students with life-threatening allergies via medical documentation<br>Food Allergy Emergency Care Plan based on medical orders<br>Updated at least annually, reviewed periodically, always accessible<br>Shared on a need to know basis with all staff in a supervisory role, with education in its use given by an appropriate health professional<br>Child-specific dual pack auto-injectors kept with supervising adult, or in a known and secure but accessible, location<br>Delegate medication administration[a]<br>School nurse trains non-licensed staff to administer auto-injector and arrange immediate transportation to ED when school nurse is not immediately available | Designee stock epinephrine administration[a]<br>School nurse trains select non-licensed staff to administer auto-injector to those with no known history of potentially life-threatening allergy and arrange immediate transportation to ED when school nurse is not immediately available<br>Full-time school nurse<br>In some states currently only licensed professionals can administer epinephrine to those experiencing anaphylaxis without a prior known allergy[a]<br>Standing epinephrine orders[a]<br>Stock epinephrine[a]<br>Supervisory staff trained to rapidly identify allergic reactions and immediate contact of school nurse and/or 911 (especially if nurse not immediately available) and/or give non-patient specific epinephrine auto-injector if appropriately trained |
| Strategies for ALL students and staff (with known and unknown history of life-threatening allergies) | |
| School physician in every district, full-time school nurse in every building<br>Universal staff training<br>Include anaphylaxis emergency in periodic school/staff-wide emergency preparedness drills<br>Written non-patient specific medical orders and emergency procedures or emergency action plans familiar to all staff to include when and how to give epinephrine auto-injectors, importance of keeping child from raising to an upright position, calling 911<br>Communication access for all staff in supervisory roles available to contact 911 for ambulance transport to emergency department and school nurse, if available | |

Adapted with permission from Pistiner, AllergyHome.org/schools [23]. Also published in Pistiner and Devore [4] and Pistiner et al. [7]

[a]Regulations and guidance will vary state by state. Confirm that school practices conform with state and local regulations and guidance

### Understand Individualized Healthcare Plans (IHCPs) and 504s

Individualized healthcare plans (IHCPs) and 504s are created for the individual student and help ensure that food allergy management strategies are implemented. IHCPs are documents created by a school nurse to manage individual students' school health needs. These plans are based on the healthcare provider's diagnosis, medications, medication orders, and treatment/management plans given to the specific patient that they manage. IHCPs are nursing tools that, while not a legal document, are best practice [4, 7].

A 504 is a legally binding care plan that can be utilized when a medical diagnosis may interfere with a student's ability to learn. It serves to delineate necessary accommodations according to a health care provider's recommendation. These plans are particularly useful in situations where a lack of resources, such as lack of a school nurse, may necessitate a student-specific plan that will ensure adequate food allergy management and allow for an equal education. Initial steps in creating a 504 are taken by the parents by submitting a request to the school district in writing. In the Chicago Public School system, only half of children with food allergy had a plan in place with their schools [43]. Clinicians caring for the patient provide the medical documentation communicating the student's needs [4, 7].

### Support the Social and Emotional Well-Being of Students with Food Allergy

Increasingly, more data demonstrate the impact of food allergy on the social and emotional development of school-age children. Due to the concerns about allergen exposure, children and family can experience (or choose to place) limitations on social activities and feel anxiety about the possibility of reactions. Peanut-allergic children demonstrate lower quality of life in school compared to their non-food-allergic siblings [8, 44]. In a survey of 251 families, food-related bullying, teasing, or harassing was reported by nearly one-third, with 60% of events occurring in school [45]. The incidents noted not only include verbal acts, but also include physical acts such as having the allergen waved in the face. Of note, perpetrators are not only classmates and other students, but include teachers and school staff as well [46]. Awareness of these and other social and emotional impacts is important to ensure safe environments for food-allergic learners [8]. Clinicians should ask patients and families about food allergy-related teasing, harassment or bullying and should be prepared to provide educational resources [8].

Clinicians should provide guidance and empower children to engage in developmentally appropriate food allergy management. Their gradually increasing participation, while still supervised by knowledgeable adults, allows for age-appropriate practice and skill development. As children mature, they can begin taking increased responsibility for their food allergy management. The ultimate goal is for the child to self-manage with skill and confidence when not under the care of an adult. Multiple resources for schools and students have been developed through research to support students and their peers in understanding and managing food allergy [47]. Organizations working to help schools with training and resources for their staff and students such as *AllergyHome* and *Code Ana* should also be encouraged.

Sound and practical school-wide policies coupled with school community education and awareness serve to keep students with food allergies safe and maintain quality of life without negatively impacting them or their peers [9].

## Additional Roles of the Clinician

All clinicians have an opportunity to advocate for students with food allergies. Advocacy occurs at the individual, school/district, and state and federal levels. Clinicians support individual patients by partnering with families and schools to ensure that students are thriving. In addition, clinicians can help intervene and facilitate appropriate evaluation and resource allocation when needed. At the school/school district level, clinicians can support sound food allergy school policies by

sharing of evidence-based resources and assisting in training school staff.

Clinicians who are interested in advocacy at the state and federal levels can provide support to the department of public health, department of education, and/or state legislatures to develop guidelines and policies. Medical societies including the AAP, AAAAI, and ACAAI have councils and committees focused on advocacy on all levels by improving access to available data that can be used to establish and implement sound policy and improve school management of students with food allergies. Furthermore, non-profit organizations and other advocacy groups assist in evidence-based policy creation and implementation and advocate for increased school nurse presence.

## Conclusion

Clinicians play a key role in food allergy management in schools. This starts with providing students and their families with accurate diagnoses and evidence-based recommendations regarding allergen avoidance and preparedness to treatment of allergic reactions. Collaboration and open communication between clinicians, families, and schools are essential. Clinicians have the opportunity to support not only their individual patients when it comes to food allergy management, but also serve students in their school districts and beyond. Participation in education and advocacy can extend the reach of the clinician into the school environment, supporting their patients where they spend vast amounts of time and giving them the opportunity to learn in safe learning environments.

## References


1. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.
2. Sicherer SH, Mahr T, American Academy of Pediatrics Section on A, Immunology. Management of food allergy in the school setting. Pediatrics. 2010;126(6):1232–9.
3. Young MC, Munoz-Furlong A, Sicherer SH. Management of food allergies in schools: a perspective for allergists. J Allergy Clin Immunol. 2009;124(2):175–82, e1–4; quiz 83–4.
4. Pistiner M, Devore CD. The role of pediatricians in school food allergy management. Pediatr Ann. 2013;42(8):334–40.
5. Wang J, Sicherer SH. Section on allergy and immunology. Guidance on completing a written allergy and anaphylaxis emergency plan. Pediatrics. 2017;139:e20164005.
6. Sicherer SH, Simons FE. Section on a, immunology. Epinephrine for first-aid Management of Anaphylaxis. Pediatrics. 2017;139:e20164006.
7. Pistiner M, Devore CD, Schoessler S. School food allergy and anaphylaxis Management for the Pediatrician--Extending the medical home with critical collaborations. Pediatr Clin North Am. 2015;62(6):1425–39.
8. Wang J, Bingemann T, Russell AF, Young MC, Sicherer SH. The Allergist's role in anaphylaxis and food allergy Management in the School and Childcare Setting. J Allergy Clin Immunol Pract. 2018;6(2):427–35.
9. CDC. Voluntary guidelines for managing food allergies in schools and early care and education programs. In: US Department of Health and Human Services, editor. Washington, DC; 2013.
10. Pistiner M, Mattey B. A universal anaphylaxis emergency care plan: introducing the new allergy and anaphylaxis care plan from the American Academy of Pediatrics. NASN Sch Nurse. 2017;32(5):283–6.
11. USDA-FNS. Accommodating Children with Disabilities in the School Meal Programs Guidance for School Food Service Professionals United States Department of Agriculture Food and Nutrition Service. https://fns-prod.azureedge.net/sites/default/files/cn/SP40-2017a1.pdf (2017 Jul 25).
12. US Equal Employment Opportunity Commission. ADA Amendments Act of 2008. http://www.eeoc.gov/laws/statutes/adaaa.cfm (2018 Sept). Accessed September 2018.
13. US Department of Agriculture. Food and Nutrition Service. Accommodating children with food and special dietary needs in the school nutrition programs. Guidance for School Food Service Staff. www.fns.usda.gov/sites/default/files/special_dietary_needs.pdf; https://fns-prod.azureedge.net/sites/default/files/special_dietary_needs.pdf (2001 Fall). Accessed Sept 2018.
14. Simonte SJ, Ma S, Mofidi S, Sicherer SH. Relevance of casual contact with peanut butter in children with peanut allergy. J Allergy Clin Immunol. 2003;112(1):180–2.
15. Wainstein BK, Kashef S, Ziegler M, Jelley D, Ziegler JB. Frequency and significance of immediate contact reactions to peanut in peanut-sensitive children. Clin Exp Allergy. 2007;37(6):839–45.

16. Perry TT, Conover-Walker MK, Pomes A, Chapman MD, Wood RA. Distribution of peanut allergen in the environment. J Allergy Clin Immunol. 2004;113(5):973–6.
17. Johnson RM, Barnes CS. Airborne concentrations of peanut protein. Allergy Asthma Proc. 2013;34(1):59–64.
18. Patel DR, Upton JEM, Wang J, Harada L, Guffey D, Minard CG, et al. Quality of life for parents of children with food allergy in peanut-restricted versus peanut-free schools in the United States and Canada. J Allergy Clin Immunol Pract. 2018;6(2):671–3 e7.
19. Banerjee DK, Kagan RS, Turnbull E, Joseph L, St Pierre Y, Dufresne C, et al. Peanut-free guidelines reduce school lunch peanut contents. Arch Dis Child. 2007;92(11):980–2.
20. Bartnikas LM, Huffaker MF, Sheehan WJ, Kanchongkittiphon W, Petty CR, Leibowitz R, et al. Impact of school peanut-free policies on epinephrine administration. J Allergy Clin Immunol. 2017;140(2):465–73.
21. Tulve NS, Suggs JC, McCurdy T, Cohen Hubal EA, Moya J. Frequency of mouthing behavior in young children. J Expo Anal Environ Epidemiol. 2002;12(4):259–64.
22. Simons E, Sicherer SH, Simons FE. Timing the transfer of responsibilities for anaphylaxis recognition and use of an epinephrine auto-injector from adults to children and teenagers: pediatric allergists' perspective. Ann Allergy Asthma Immunol. 2012;108(5):321–5.
23. Pistiner M. Food allergen exposure in the school setting and school strategies in place for management of allergic emergences. Available on AllergyHome.org
24. Munoz-Furlong A. Daily coping strategies for patients and their families. Pediatrics. 2003;111(6 Pt 3):1654–61.
25. Ford LS, Taylor SL, Pacenza R, Niemann LM, Lambrecht DM, Sicherer SH. Food allergen advisory labeling and product contamination with egg, milk, and peanut. J Allergy Clin Immunol. 2010;126(2):384–5.
26. Maloney JM, Chapman MD, Sicherer SH. Peanut allergen exposure through saliva: assessment and interventions to reduce exposure. J Allergy Clin Immunol. 2006;118(3):719–24.
27. Nowak-Wegrzyn A, Conover-Walker MK, Wood RA. Food-allergic reactions in schools and preschools. Arch Pediatr Adolesc Med. 2001;155(7):790–5.
28. Nicas M, Best D. A study quantifying the hand-to-face contact rate and its potential application to predicting respiratory tract infection. J Occup Environ Hyg. 2008;5(6):347–52.
29. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. The US Peanut and tree nut allergy registry: characteristics of reactions in schools and day care. J Pediatr. 2001;138(4):560–5.
30. Roberts G, Lack G. Relevance of inhalational exposure to food allergens. Curr Opin Allergy Clin Immunol. 2003;3(3):211–5.
31. Allergy & Asthma Network. School stock epinephrine laws. https://www.allergyasthmanetwork.org/advocacy/current-issues/stock-epinephrine/ (2019).
32. Kao LM, Wang J, Kagan O, et al. School nurse perspectives on school policies for food allergy and anaphylaxis. Ann Allergy Asthma Immunol. 2018;120(3):304–9.
33. Fleming JT, Clark S, Camargo CA Jr, Rudders SA. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. J Allergy Clin Immunol Pract. 2015;3(1):57–62.
34. Hochstadter E, Clarke A, De Schryver S, LaVieille S, Alizadehfar R, Joseph L, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal. Canada J Allergy Clin Immunol. 2016;137(6):1888–90 e4.
35. White MV, Hogue SL, Bennett ME, Goss D, Millar K, Hollis K, et al. EpiPen4Schools pilot survey: occurrence of anaphylaxis, triggers, and epinephrine administration in a U.S. school setting. Allergy Asthma Proc. 2015;36(4):306–12.
36. Wright BL. Anaphylaxis and epinephrine in North Carolina public schools. Ann Allergy Asthma Immunol. 2015;115(1):75–7.
37. Feuille E, Lawrence C, Volel C, Sicherer SH, Wang J. Time trends in food allergy diagnoses, epinephrine orders, and epinephrine administrations in new York City schools. J Pediatr. 2017;190:93–9.
38. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 2001;107(1):191–3.
39. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001–2006. J Allergy Clin Immunol. 2007;119(4):1016–8.
40. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 1992;327(6):380–4.
41. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47(4):373–80.
42. McIntyre CL, Sheetz AH, Carroll CR, Young MC. Administration of epinephrine for life-threatening allergic reactions in school settings. Pediatrics. 2005;116(5):1134–40.
43. Gupta RS, Rivkina V, DeSantiago-Cardenas L, Smith B, Harvey-Gintoft B, Whyte SA. Asthma and food allergy management in Chicago public schools. Pediatrics. 2014;134(4):729–36.
44. King RM, Knibb RC, Hourihane JO. Impact of peanut allergy on quality of life, stress and anxiety in the family. Allergy. 2009;64(3):461–8.

45. Shemesh E, Annunziato RA, Ambrose MA, Ravid NL, Mullarkey C, Rubes M, et al. Child and parental reports of bullying in a consecutive sample of children with food allergy. Pediatrics. 2013;131(1):e10–7.
46. Lieberman JA, Weiss C, Furlong TJ, Sicherer M, Sicherer SH. Bullying among pediatric patients with food allergy. Ann Allergy Asthma Immunol. 2010;105(4):282–6.
47. Jiang J, Gallagher JL, Szkodon JW, et al. The development and evaluation of peer food allergy education videos for school-age youth. Ann Allergy Asthma Immunol. 2019;123(1):107–8.

# Oral Tolerance and Prognosis in Food Allergy

16

David R. Stukus

## Introduction

A diagnosis of IgE-mediated food allergy is life altering. As discussed in detail earlier in this book, children with food allergies need to strictly avoid their allergen at all times. Successful avoidance requires communication with food handlers and caregivers and reading labels on packaged products. In addition, families with food-allergic children need to be well versed in the recognition and treatment of allergic reactions. This can result in significant burden, cost, psychosocial impact, and decreased quality of life [1].

While the overarching themes surrounding successful management of IgE-mediated food allergies are similar regardless of specific food, the prognosis differs greatly. A deeper understanding of IgE-mediated food allergies demonstrates that prognosis can differ greatly for one child compared with another. This is an important area for physicians and families to understand as a diagnosis of food allergy during childhood should not be communicated as an absolute need for lifelong avoidance. As with any chronic medical condition, food allergies should be monitored routinely with at least annual office visits to review management strategies, accidental exposures, and to discuss anticipatory guidance, which varies based upon age, specific food allergen, and circumstances specific to each family (Table 16.1). In addition, repeat skin prick or serum food-specific IgE testing should be performed over time to help determine prognosis and identify those children who will naturally develop oral tolerance.

This chapter discusses specific aspects that can help predict which child may develop tolerance to their food allergen over time. Most of the research surrounding this topic has been conducted for a few specific highly allergenic foods including peanut, milk, and egg, but general concepts can be applied to children with other food allergies.

## Case Study

A 9-month-old boy developed facial hives and two episodes of emesis after eating scrambled egg for the first time. Symptoms resolved without any treatment. Follow-up skin prick testing 2 months later revealed a 10-mm wheal to egg and his family was instructed on avoidance measures. He returns for follow-up evaluation at 24 months of age. Parents report successful avoidance of any egg-containing foods, and he has not had reactions suggestive for food allergy to any other foods. At this visit, parents inquire about ongoing

D. R. Stukus (✉)
Division of Allergy and Immunology, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, OH, USA
e-mail: david.stukus@nationwidechildrens.org



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_16

**Table 16.1** Food allergy discussion topics at annual physician visits

| Age | Topic |
|---|---|
| *All* | Accidental ingestion or reactions since last visit<br>Prior test results and consideration for repeat testing<br>Challenges in management, including exclusion from social interactions, reading labels, dining out at restaurants<br>Signs/symptoms of an allergic reaction<br>Indications for using epinephrine<br>Proper epinephrine auto-injector technique with hands-on-practice through a training device<br>Misconceptions surrounding epinephrine<br>Update written food allergy/anaphylaxis treatment plan |
| *Infant/ toddler* | Allergen exposure in the home<br>Normal development/exploration of environment with mouths<br>Discussion points with caregivers, babysitters, family members<br>Comorbid conditions such as atopic dermatitis |
| *School age* | Management in the classroom and cafeteria<br>Preparation for new school year, teachers, nurses<br>Classroom celebrations with food<br>School bus, field trips |
| *Teenagers* | Self-carry of epinephrine<br>Peer pressure, communication with friends and significant others<br>Common occurrence and risks of not having epinephrine available at all times<br>Practice scenarios involving dining out, dating, alcohol<br>Preparation for transition to independent living |

avoidance of all egg products, or if they can try to introduce baked egg into his diet. They also have questions about repeat skin prick testing and if he will ever be able to eat egg without having a reaction.

- What is the best advice regarding baked egg in a child with egg allergy?
- What is the natural history of egg allergy in the majority of children?

## Differences Between Food Allergens

While any food can potentially cause an IgE-mediated food allergy, the eight most common allergenic foods (cow's milk, hen's egg, soy, wheat, peanut, tree nut, finfish, and shellfish) account for more than 90% of all reactions. Food allergies can be transient for many children, particularly to milk, egg, wheat, and soy [2]. Approximately 85% of children with these food allergies will naturally develop oral tolerance, often by school age. Recent research has demonstrated that egg and milk allergies may be more persistent than previously believed, and some children are not developing tolerance until adolescence [3]. Additionally, milk seems to persist into adolescence and adulthood frequently and is reported to be the second most common food allergy among both children and adults [4]. Unfortunately, only about 20% of children with peanut, tree nut, or seafood allergy will develop tolerance with age [3]. There are limited, if any, data surrounding most other foods, or adults who develop food allergies later in life. Thus, the prognosis for a child diagnosed with allergies to foods including seeds, fruits, vegetables, grains, poultry, and red meat remains largely unknown.

## Factors Associated with Prognosis

While it is generally accepted that milk, egg, wheat, and soy allergies are the most likely to be transient, and peanut, tree nut, fish, and shellfish allergies are more likely to remain lifelong, the ability to predict which child may or may not develop tolerance remains challenging. In general, children with a history of severe early-onset atopic dermatitis, multiple food allergies, and severe anaphylactic reactions to their food allergen are most likely to have persistent food allergies [2]. At the time of initial food allergy diagnosis, it is important to discuss prognosis with every family. Thus, an understanding of how

the natural history differs by food allergen and factors associated with development of tolerance is useful. Physicians should anticipate questions from families regarding long-term prognosis, future need for repeat testing, and the manner of determining whether tolerance has occurred.

The specific size of initial skin prick and serum food-specific IgE testing that predicts future tolerance have not been established for any food allergen. However, in general, when the initial IgE test result is very elevated, this suggests that it is less likely for tolerance to develop over time. Ongoing assessment is useful to detect trends in IgE levels. For milk, egg, peanut, and tree nuts, skin prick wheal diameter >15 mm and/or serum IgE >25 kU/L suggests persistent allergy. Conversely, some children only demonstrate mild elevations in IgE testing, regardless of the severity of their reaction, and maintain persistent food allergy for years. As discussed in the section regarding food allergy diagnosis, the clinical history is the most important "test" to consider and can also help guide discussion regarding the potential for developing tolerance. Children who experience severe reactions (respiratory distress, anaphylaxis, need for epinephrine) are less likely to develop tolerance in the future compared with those who have mild symptoms such as skin rash or who have never experienced a clinical reaction but were diagnosed through testing alone.

The monitoring of serum IgE testing over time is more indicative of prognosis and future tolerance compared with skin prick testing [3]. Several studies have evaluated the usefulness of comparing food-specific IgE levels with prior test results to determine suitability for reintroduction. It merits mention that the research studies evaluating this concept vary widely according to population, methodology, cutoff points, and use of oral food challenges. In an ideal research setting, every child with food allergy would be followed longitudinally and undergo a supervised oral food challenge at specific intervals as they age along with skin prick and serum food-specific IgE testing at the time of challenge. This is the best way to not only determine prognosis and acquisition of tolerance, but to develop predictive cutoff values that may offer benefit on a population level. Unfortunately, this approach is not feasible for many reasons.

The HealthNuts study, a large prospective longitudinal cohort of thousands of food-allergic children in Australia, offers one of the best attempts at this approach and has revealed useful information about the natural history of peanut, egg, and milk allergy [5]. HealthNuts researchers evaluated patients longitudinally through serial IgE measurements and oral food challenges. Among 1-year-old infants with challenge-confirmed peanut allergy ($n$ = 156) enrolled in this cohort, 103 underwent repeat oral challenge and IgE measurements at 4 years of age [6]. They found that peanut allergy resolved in 22% of children by age four and a decreasing wheal size on skin testing predicted tolerance, whereas an increasing wheal size predicted unsuccessful challenge on persistent allergy. Thresholds for 95% positive predictive value (PPV) of peanut allergy at 1-year of age were a ≥13 mm wheal and serum IgE ≥5 kU/L. At 4 years of age, these 95% PPV thresholds were wheal size ≥8 mm and serum IgE ≥2.1 kU/L.

The HealthNuts researchers took a similar approach for children with egg allergy ($n$ = 140) who were challenged at both 1 and 2 years of age [7]. They found that egg allergy resolved in 47% of children by 2 years of age. Interestingly, the development of tolerance varied according to the ability to ingest baked egg, which will be discussed later in this chapter. At 1 year of age, infants with a skin prick wheal size ≥4 mm or serum IgE ≥1.7 kU/L were more likely to have persistent egg allergy at age 2.

A large research network in the United States employed a similar approach in determining the natural history of milk and egg allergy [8, 9]. The Consortium of Food Allergy Research enrolled 293 children with milk allergy between 3 and 15 months of age and followed them longitudinally. In this cohort, milk allergy resolved in 53% of participants at a median age of 63 months. Smaller skin prick (<5 mm compared with ≥10 mm) and serum IgE (<2 kU/L compared

with ≥10 kU/L) milk levels at baseline were associated with higher likelihood for developing tolerance. Among infants enrolled with egg allergy ($n = 213$), 49% experienced resolution at a median age of 72 months. Similar to milk, smaller skin prick (<5 mm compared with ≥10 mm) and serum IgE (<2 kU/L compared with ≥10 kU/L) egg levels at baseline were associated with higher likelihood for developing tolerance.

## Diagnostic Testing

The most commonly used and widely available food-specific IgE tests use commercial extracts that contain combinations of multiple proteins within each food. However, not all proteins are associated with the same risk for clinical food allergy reaction. Both over diagnosis and misdiagnosis of food allergies occur based upon IgE testing alone, particularly through the use of widely marketed food allergy panel testing, which includes various numbers of unrelated foods which can be analyzed through one blood sample [10]. Newer component testing can isolate the specific protein that IgE is directed towards and is available for a few specific foods. The most widespread example of component testing is for peanut. Patients who have IgE directed towards the proteins Ara h 1, 2, or 3 are at highest risk for clinical allergy compared with those who are sensitized towards Ara h 8, which represents cross-sensitization with birch tree pollen [11]. As component testing becomes more widely available for peanut and other foods, these tests must be used and interpreted in the proper context [12]. For instance, it is not useful to obtain peanut component testing on a patient who has already had clear anaphylaxis from peanut ingestion as the component test will not predict future tolerance or severity of future reactions. Most importantly, component testing should not be routinely obtained in the diagnosis or follow-up of food allergy. Use of these tests warrants careful consideration of their cost, limitations, performance characteristics, differing results in various populations, and always must be interpreted in the proper clinical context.

The proteins in cow's milk and egg offer two examples of how testing beyond the routine commercial testing reagents may offer insight into prognosis. Markers for persistent cow's milk allergy include children with higher IgE binding towards casein as compared with whey [13]. Markers for persistent egg allergy include children with higher IgE towards ovomucoid compared with egg white, egg yolk, ovalbumin, and lysozyme [14]. In addition, patients may react to three-dimensional conformational epitopes, whereas others react to linear segments which are much more resistant to degradation through cooking or food production. It is well established that egg and milk allergic children may only react to conformational epitopes, which can be destroyed through extensive heating [15]. Recent research conducted in infants with peanut allergy found that those with persistent allergy developed specific IgE towards linear epitopes, as opposed to conformational epitopes [16]. At this time, there are no commercially available tests to distinguish conformational versus linear epitopes, but this concept is important to understand for future applications and individualized management options.

## Can the Natural Development of Oral Tolerance Be More Rapidly Acquired?

Other chapters in this textbook address the use of immunotherapy to assist the development of tolerance to food allergens. However, the question that many parents and researchers have asked is: Can we help a child who will naturally develop tolerance to a food allergen achieve this more rapidly? The alternate question that may be asked is: Are there factors that may slow the development of tolerance? To answer the second question, there do not appear to be any factors that will hasten natural resolution. As discussed at the end of this chapter, oral food challenges are the best predictors for resolution of food allergy. However, not all food challenges are successful and may induce reactions in children with ongoing allergy. Fortunately, there is no evidence that unsuccessful food challenges, or reactions to foods through accidental ingestion, will cause someone to "hold onto" their food allergy any

longer than they would through strict avoidance. This is useful information to share with parents who may be concerned that they harmed their child through a supervised challenge or accidental exposure at some point. One study demonstrated that the mean age of reported outgrown food allergy is 5.4 years old and children that experienced earlier allergy onset were more likely to report developing food allergy tolerance compared to later onset [17]. While it is discouraged to counsel patients they have a "mild" allergy due to concern they will not follow stringent avoidance measures, patients with a milder phenotype exist [11]. These are likely the same patients that have transient IgE-mediated food allergies and naturally develop oral tolerance over time. Given our limitations in reliably identifying these individuals at this time, we are relegated to offer the same management strategies of strict avoidance for anyone with a diagnosis of IgE-mediated food allergy. However, as our understanding of mechanisms involved in the pathogenesis and manifestations of food allergy continues to evolve, a more individualized approach to management may be applicable in the near future.

## Baked Milk and Baked Egg

Milk and egg allergies are two of the most common IgE-mediated food allergies in young children. Dietary avoidance can be challenging given the ubiquitous nature of these food proteins as ingredients in a wide variety of products. As discussed previously, the natural history of milk and egg allergy is favorable with most patients developing oral tolerance by later in childhood. However, the ability to incorporate these foods into the diet in some form has many positive advantages.

Interestingly, approximately 70% of children with milk and egg allergies can tolerate these proteins in the baked, or extensively heated, form [18]. As introduced earlier, some food allergies are caused by three-dimensional conformational epitopes as opposed to linear structures. These conformational epitopes are subject to degradation through heating. This change in conformation alters the recognition by the immune system and in many cases no longer causes an IgE-mediated reaction. It is recommended that only foods cooked at high enough temperatures, such as 350 degrees Fahrenheit, in an oven for 30 minutes be considered safe for ingestion. Stove top preparation, boiling, or frying has not been demonstrated to sufficiently heat or denature these proteins. In addition, the interactions with other ingredients involved in the food matrix that constitutes a food product appears to be of significance, thus boiling milk alone is not likely enough to denature the proteins rendering it safe for consumption.

The predominant protein in egg allergy is ovalbumin, which is a heat-labile conformational epitope. The other major allergen is ovomucoid, which is a heat-resistant linear epitope. Similarly, whey proteins in cow's milk allergy are heat labile whereas casein is heat resistant. Interestingly, the level of specific IgE towards these specific proteins may predict which child is more likely to have persistent allergy but have not been shown to be as reliable at predicting which child may tolerate baked milk (Table 16.2) or baked egg (Table 16.3).

**Table 16.2** Predictors of baked milk tolerance [18]

| Specific IgE (kU/L) NPV | Specific IgE (kU/L) PPV | Skin prick test wheal (mm) NPV | Skin prick test wheal (mm) PPV |
|---|---|---|---|
| [19] Cow's milk <0.35, 100% | Cow's milk ≥0.35, >50% | Cow's milk <5, 100% | Cow's milk ≥15, >5 0% |
| [20] casein <0.35, 100%<br>Casein 0.94, 95%<br>Casein 4.95, 89%<br>Cow's milk 1.21, 94%<br>Cow's milk 9.97, 86% | Casein 20.2, 69%<br>Cow's milk 24.5, 69% | N/A | N/A |
| [21] casein 0.9, >90%<br>Cow's milk 1.0, >90% | Casein >10.3, 100%<br>Cow's milk >20.6, 100% | Casein <9, 92%<br>Cow's milk <7, 100%<br>Cow's milk <13, 91% | Casein >15, 100% |

Reprinted from Leonard et al. [18], with permission from Elsevier
*NPV* negative predictive value, *PPV* positive predictive value

**Table 16.3** Predictors of baked egg tolerance [18]

| Specific IgE (kU/L) NPV | Specific IgE (kU/L) PPV | Skin prick test wheal (mm) NPV | Skin prick test wheal (mm) PPV |
|---|---|---|---|
| [22] OM <0.35, 10% | OM 50, 90%<br>EW 25, 30%<br>EW 50, 40%<br>EW 75, >50% | N/A | EW 0, 5%<br>EW 15, 60% |
| [23] EW 0.85, 96%<br>OM 1.16, 97% | EW 30.7, 84%<br>OM 10.8, 88% | N/A | N/A |
| [24] EW 2.5, 89%<br>EW 5, 77%<br>EW 10, 71% | EW 10, 60% | N/A | N/A |
| [25] N/A | N/A | N/A | OM ≥11, 100% |
| [26] EW 6, >90%<br>OM 0.35, >90% | EW 9.65, 59%<br>OM 3.38, 42% | EW <3, 100%<br>EW <11, >90% | N/A |

Reprinted from Leonard et al. [18], with permission from Elsevier
*NPV* negative predictive value, *PPV* positive predictive value, *OM* ovomucoid, *EW* egg white

In addition, the size of skin prick wheal or serum IgE testing to egg or milk also does not reliably predict which children may tolerate in the baked form, i.e., children with very large skin test reactions may tolerate and vice versa.

Given the limited predictive capabilities of available testing and the potential for approximately 30% of children with milk or egg allergy to react upon ingestion of baked forms, there is debate as to whether it is safe to introduce at home or if it should always be done in an office setting through an oral food challenge. For children who have already eaten and tolerated baked forms, they should be encouraged to continue to expand their diet with these foods at home. Other considerations for at home versus in office introduction include the severity of prior reactions, size of IgE testing, comorbid conditions such as severe atopic dermatitis that may make interpretation of potential reaction difficult, and parental comfort. Any child with a history of anaphylaxis, respiratory or severe gastrointestinal symptoms, or underlying asthma should have baked milk or egg introduced under physician supervision in the office setting.

Once a child is tolerating baked milk or egg, parents should be instructed to maintain it in the child's diet. There are several published recipes [7] that ensure sufficient amounts of baked protein both during challenge and once at home. Store-bought baked products can be included in the diet as well, so long as milk or eggs are not the first or second ingredient listed. Parents should be counseled to continue to read labels and avoid stove top or raw forms of milk and egg to prevent reactions from occurring.

In addition to liberalizing the diet and affording additional choices for feeding children with milk and egg allergy, inclusion of baked milk and egg into the diet may offer additional benefits. Tolerance of baked milk and egg is safe and does not increase the risk of reaction for children with milk or egg allergy. In addition, studies have shown that this may accelerate development of tolerance to unheated milk and egg. Whether the inclusion of baked milk and egg acts as a form of immunotherapy or marks children who are "less allergic" to begin with, this discussion should be a routine part of management of all children with milk and egg allergy [27]. Ongoing evaluation of existing milk and egg allergy should continue to occur in children who tolerated baked milk and baked egg along with the same provisions for repeat testing and consideration for supervised oral food challenge to determine future tolerance.

## Case Study

A 12-month-old boy develops rapid onset emesis and generalized hives after ingestion of yogurt. Skin prick testing 1 month later reveals an 11-mm wheal diameter. The family is counseled regarding milk avoidance and he does well

without any accidental ingestion or subsequent reactions. Follow-up skin prick testing at 2, 3, and 4 years of age reveals a slightly declining wheal diameter of 9 mm, 8 mm, and then 6 mm. He is now 5 years old and parents would like to clarify his milk allergy diagnosis prior to starting kindergarten.

- What other tests can be considered to help determine his need to continue milk avoidance?

## Long-Term Follow-Up

Every child who is diagnosed with IgE-mediated food allergies should have at least annual follow-up visits to discuss food allergen avoidance, challenges with management, and to repeat testing (Table 16.1). There are no well-established guidelines regarding the use of repeat skin prick or serum IgE tests in patients who have established food allergy but it is important to consider the utility and limitations of both types of tests. In general, the trends of IgE values over time are useful in predicting the likelihood that allergy may be dissipating. If skin prick and/or serum IgE levels increase over time, this indicates persistent allergy. If these levels decrease over time, or if they are relatively low at baseline and remain low with increasing age, this indicates possible tolerance.

As discussed previously in this book, neither skin prick or serum IgE tests by themselves are diagnostic for food allergy. Neither test result can predict the severity of future reactions. Both tests are associated with high rates of falsely elevated results and must be used and interpreted with caution and in the proper clinical context. The availability and use of each test will vary by physician, access to allergists, and parental preference. The positive and negative predictive values for skin prick and serum IgE tests have not been well established other than for the most highly allergenic foods and also vary significantly by food. Most clinicians who manage food allergy use established 95% PPV cutoffs to determine not only the likelihood of a food allergy being present at the time of diagnosis, but also whether tolerance may be possible over time (Table 16.4) [28, 38]. Unfortunately, cutoff values have only been established for a few select foods. A general approach to long-term monitoring of children with food allergy is highlighted in Fig. 16.1.

**Table 16.4** Predictive values of IgE testing [28–36]

| | >95% PPV | | ~50% NPV | |
|---|---|---|---|---|
| Food | Serum IgE | Skin prick (mm) | Serum IgE | Skin prick (mm) |
| *Egg white* | ≥7 | ≥7 | ≤2 | ≤3 |
| | ≥2 if age <2 years old | | | |
| *Cow's milk* | ≥15 | ≥8 | ≤2 | |
| | ≥5 if age <1 years old | | | |
| *Peanut* | ≥14 | ≥8 | ≤2 = prior reaction | ≤3 |
| | | | ≤5 = no prior reaction | |
| *Fish* | ≥20 | | | |

Reprinted from Sampson et al. [37], with permission from Elsevier [28]
*PPV* positive predictive value, *NPV* negative predictive value

There are several nuances to the data surrounding cutoffs that must be appreciated prior to application in clinical practice [39]. Previous studies have significant limitations in methodology including lack of food challenges to confirm diagnosis, retrospective application of cutoff levels, and variances in study population, age of participants, and length of time between follow-up visits. In addition, the diagnostic cutoffs were established in children of different ages, and clinical applicability will vary by age. Studies investigating PPV and NPV of skin prick and serum IgE testing to peanut, egg, and milk found variable results or no correlation of test results with the development of tolerance. Most studies reliably determined the persistence of allergy to these foods through higher skin prick/serum IgE values but could not reliably identify cutoff values that demonstrated tolerance. Ultimately, this circles back to the need for longitudinal studies that incorporate serial food challenges and skin prick/serum IgE testing at various ages. In the meantime, skin prick and serum IgE tests can be utilized to determine trends over time and

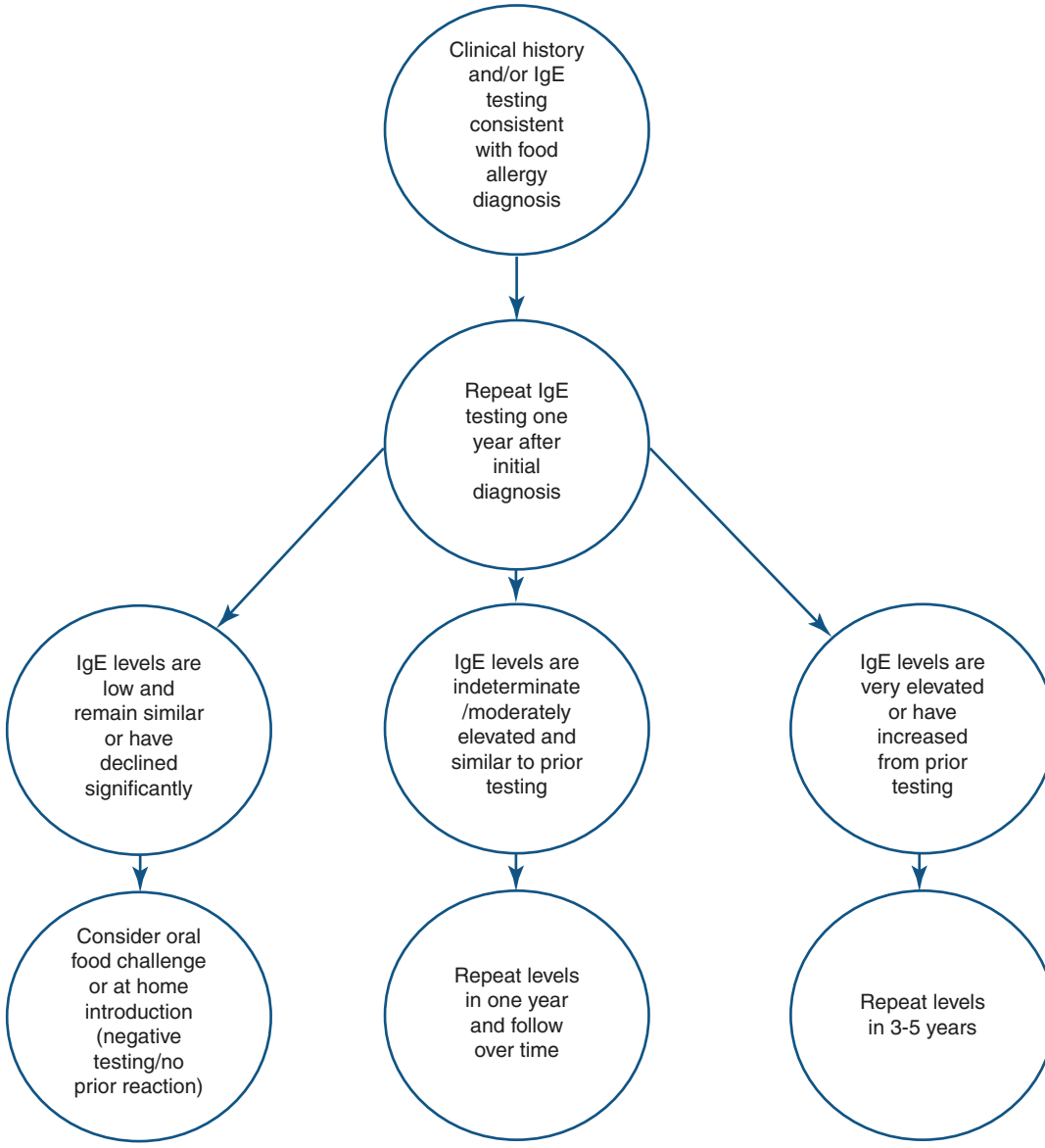



**Fig. 16.1** Approach to long-term follow-up and repeat IgE testing

patients with decreasing values should be considered the best candidates to develop tolerance with age.

## Oral Food Challenges

The only manner to truly determine if oral tolerance has developed is through ingestion of the food. For children who have had prior clinical reactions and/or IgE testing that highly suggests likelihood for clinical reaction, reintroduction of the food is safest through a physician-supervised oral challenge. During this procedure, small amounts of the food are ingested with gradual increases in the amount given until a cumulative dose of 6–10 grams (or 1–2 servings) are eaten. Medical supervision is important in case signs or symptoms of an allergic reaction occur. Physicians who administer oral food challenges must be versed in the recognition

and treatment of anaphylaxis, have resuscitation equipment immediately available in their office including epinephrine, and should obtain informed written consent from families prior to administration of the first dose.

Reasons to consider an oral food challenge include determining if a prior food allergy has resolved, as suggested by reassuring and declining repeat IgE testing over time. Oral food challenges are useful at the time of initial diagnosis as well, particularly when the clinical history and/or IgE test results are indeterminate. At times, patients who are likely to react with ingestion may still wish to undergo an oral food challenge. An example is an adolescent who has not ingested or reacted to a food for years but desires to better understand if they are still allergic or what signs/symptoms may occur during a reaction.

In clinical practice, most oral food challenges are open with both the patient and provider knowing what food is being ingested. This is the easiest method for conducting a challenge. The potential downside for the open challenge is the development of subjective symptoms in a patient who is very anxious. Children and families should be counseled ahead of time that anxiety is a normal and expected occurrence during oral food challenges, as well as what to expect during the challenge. Blinded challenges mask the food being ingested so the patient is not aware of what they are ingesting. If symptoms occur after ingestion of a placebo dose, this can assist the patient and family in better understanding the role that anxiety is contributing to their suspected reactions. Double-blind oral food challenges are considered the gold standard but are often limited to research studies due to the technical demands of preparation and lack of necessity for the majority of patients.

Consideration of whom and when to perform an oral food challenge varies, and conversations should be individualized. See Table 16.5 for talking points to consider in this discussion with patients and their families. There are many benefits to oral food challenges. If no symptoms occur, then the patient can incorporate the food back into their diet and no longer needs to follow strict avoidance measures. Even when symptoms occur, including anaphylaxis and the need for epinephrine, patients and families benefit by increasing their understanding of how a reaction will present, observing how rapidly symptoms improve with proper treatment, and confirming that they need to continue ongoing avoidance of that food. When done properly under medical supervision with small starting doses and gradual escalation, the oral food challenge is a safe and beneficial procedure to consider and is the gold standard method to determine the development of oral tolerance.

**Table 16.5** Discussion points to determine readiness for an oral food challenge

| |
|---|
| How severe was the prior reaction? |
| How long has it been since the last reaction? |
| Has there been accidental ingestion and if so, what happened? |
| What do the most recent IgE results predict? |
| Is the patient interested and/or willing to ingest the food and incorporate it into their diet? |
| Does the family have significant anxiety or decreased quality of life due to food avoidance? |
| How much of a burden is it to avoid the food(s)? |
| What are the patient/family reasons for wanting or not wanting to pursue an oral food challenge? |

## Summary

IgE-mediated food allergies have a heterogeneous clinical presentation, severity, and prognosis. The majority of children with milk, egg, wheat, and soy allergies are expected to develop oral tolerance as they age, whereas those with peanut, tree nut, and seafood allergies are more likely to have persistent allergies. Unfortunately, our ability to accurately predict which children with existing food allergy have developed tolerance is limited by current research and imperfect performance characteristics of IgE testing. Each child who has been diagnosed with food allergy should be monitored longitudinally with repeat IgE testing and consideration of an oral food challenge when results indicate that their food allergy may no longer be present. An informed and comprehensive approach can assist families in better understanding their child's food allergy, prognosis, and ongoing management.

## References


1. DunnGalvin A, Dubois AE, Flokstra-de Blok BM, Hourihane JO. The effects of food allergy on quality of life. Chem Immunol Allergy. 2015;101:235–52.
2. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention and management. J Allergy Clin Immunol. 2018;141:41–58.
3. Savage J, Sicherer S, Wood R. The natural history of food allergy. J Allergy Clin Immunol Pract. 2016;4(2):196–203.
4. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. JAMA Netw Open. 2019;2(1):e185630.
5. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Thiele L, Tang ML, et al. The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. Clin Exp Allergy. 2010;40(10):1516–22.
6. Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. J Allergy Clin Immunol. 2015;135(5):1257–66.
7. Peters RL, Dharmage SC, Gurrin LC, Koplin JJ, Ponsonby AL, Lowe AJ, et al. The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study. J Allergy Clin Immunol. 2014 Feb;133(2):485–91.
8. Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of milk allergy in an observational cohort. J Allergy Clin Immunol. 2013;131(3):805–12.
9. Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of egg allergy in an observational cohort. J Allergy Clin Immunol. 2014;133(2):492–9.
10. Bird JA, Crain M, Varshney P. Food allergy panel testing often results in misdiagnosis of food allergy. J Pediatr. 2015;166(1):97–100.
11. Baker MG, Sampson HA. Phenotypes and endotypes of food allergy: a path to better understanding the pathogenesis and prognosis of food allergy. Ann Allergy Asthma Immunol. 2018;120(3):245–53.
12. Sicherer S, Wood RA. Advances in diagnosing peanut allergy. J Allergy Clin Immunol Pract. 2013;1(1):1–13.
13. Chatchatee P, Jarvinen KM, Bardina L, Beyer K, Sampson HA. Identification of IgE- and IgG-binding epitopes on alpha(s1)-casein: differences in patients with persistent and transient cow's milk allergy. J Allergy Clin Immunol. 2001;107:379–83.
14. Jarvinen KM, Beyer K, Vila L, Bardina L, Mishoe M, Sampson HA. Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. Allergy. 2007;62:758–65.
15. Bloom KA, Huang FR, Bencharitiwong R, Bardina L, Ross A, Sampson HA, et al. Effect of heat treatment on milk and egg proteins allergenicity. Pediatr Allergy Immunol. 2014;25(8):740–6.
16. Suarez-Farinas M, Gimenez G, Grishina, G. et al. Peanut epitope-specific IgE binding in the first 2 years of life can predict clinical peanut allergy. Presented at European Academy of Allergy and Clinical Immunology, Helsinki, 20 June 2017.
17. Gupta RS, Lau CH, Sita EE, Smith B, Greenhawt MJ. Factors associated with reported food allergy tolerance among US children. Ann Allergy Asthma Immunol. 2013;111(3):194–198.e194.
18. Leonard SA, Caubet JC, Kim JS, Groetch M, Nowak-Wegrzyn A. Baked milk-and egg-containing diet in the management of milk and egg allergy. J Allergy Clin Immunol Pract. 2015;3(1):13–23.
19. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol. 2008;122:342–7.
20. Caubet JC, Nowak-Wegrzyn A, Moshier E, Godbold J, Wang J, Sampson HA. Utility of casein-specific IgE levels in predicting reactivity to baked milk. J Allergy Clin Immunol. 2013;131:222–4.
21. Bartnikas LM, Sheehan WJ, Hoffman EB, Permaul P, Dioun AF, Friedlander J, et al. Predicting food challenge outcomes for baked milk: role of specific IgE and skin prick testing. Ann Allergy Asthma Immunol. 2012;109:309–13.
22. Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. J Allergy Clin Immunol. 2008;122:977–83.
23. Ando H, Moverare R, Kondo Y, Tsuge I, Tanaka A, Borres MP, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. J Allergy Clin Immunol. 2008;122:583–8.
24. Alessandri C, Zennaro D, Scala E, Ferrara R, Bernardi ML, Santoro M, et al. Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation. Clin Exp Allergy. 2012;42:441–50.
25. Lieberman JA, Huang FR, Sampson HA, Nowak-Wegrzyn A. Outcomes of 100 consecutive open, baked-egg oral food challenges in the allergy office. J Allergy Clin Immunol. 2012;129:1682–4.
26. Tan JW, Campbell DE, Turner PJ, Kakakios A, Wong M, Mehr S, et al. Baked egg food challenges—clinical utility of skin test to baked egg and ovomucoid in children with egg allergy. Clin Exp Allergy. 2013;43:1189–95.
27. Dang TD, Peters RL, Allen KJ. Debates in allergy medicine: baked egg and milk do not accelerate tolerance to egg and milk. World Allergy Organ J. 2016;9:2.

28. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014;134(5):1016–25.
29. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clin Exp Allergy. 2000;30:1540–6. (IIb).
30. Verstege A, Mehl A, Rolinck-Werninghaus C, Staden U, Nocon M, Beyer K, et al. The predictive value of the skin prick test weal size for the outcome of oral food challenges. Clin Exp Allergy. 2005;35:1220–6. (III).
31. Pucar F, Kagan R, Lim H, Clarke AE. Peanut challenge: a retrospective study of 140 patients. Clin Exp Allergy. 2001;31:40–6. (III).
32. Saarinen KM, Suomalainen H, Savilahti E. Diagnostic value of skin-prick and patch tests and serum eosinophil cationic protein and cow's milk-specific IgE in infants with cow's milk allergy. Clin Exp Allergy. 2001;31:423–9. (IIb).
33. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. Pediatr Allergy Immunol. 2004;15:435–41. (III).
34. Knight AK, Shreffler WG, Sampson HA, Sicherer SH, Noone S, Mofidi S, et al. Skin prick test to egg white provides additional diagnostic utility to serum egg white-specific IgE antibody concentration in children. J Allergy Clin Immunol. 2006;117:842–7. (III).
35. Nolan RC, Richmond P, Prescott SL, Mallon DF, Gong G, Franzmann AM, et al. Skin prick testing predicts peanut challenge outcome in previously allergic or sensitized children with low serum peanut-specific IgE antibody concentration. Pediatr Allergy Immunol. 2007;18:224–30. (IIb).
36. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. J Allergy Clin Immunol. 2009;123(suppl):S365–83. (IV).
37. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update. J Allergy Immunol. 2014;134(5):1016–1025.e43.
38. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol. 2001;107(5):891–6.
39. Peters RL, Gurrin LC, Dharmage SC, Koplin JJ, Allen KJ. The natural history of IgE-mediated food allergy: can skin prick tests and serum IgE predict the resolution of food allergy? Int J Environ Res Public Health. 2013;10(10):5039–61.

# Part V

# Therapies for Food Allergy

# Oral Immunotherapy (OIT)

17

Jay A. Lieberman and Julie Wang

## Introduction

Food allergy has become a global health burden in recent years [1]. The true prevalence is difficult to ascertain as studies use various methods and definitions for food allergy, but it is clear that in industrialized nations, such as the United States, the prevalence appears to have increased in the last few decades [2]. Unfortunately, to date, there is no approved therapy for the treatment of food allergy. Current guidelines continue to recommend avoidance of known allergens and to have epinephrine readily available for the treatment of severe reactions in the case of ingestion of an allergen [3, 4]. To that end, there has been a large amount of research conducted over the past few decades attempting to develop therapies for food allergy. The majority of this research has focused on IgE-mediated food allergies, with most studies examining differing forms of desensitization strategies. This chapter focuses on oral immunotherapy (OIT) as a treatment strategy for IgE-mediated food allergies, examining the history and evolution of the treatment, its possible mechanisms of action, the data from the larger, randomized trials for individual foods including efficacy and adverse effects, and possible novel strategies and adjuvants that have been investigated in order to improve efficacy or to decrease adverse effects.

## History

Since the first report by Noon, allergen-specific immunotherapy has been a mainstay of therapy for IgE-mediated allergies [5]. For respiratory and venom-induced allergies, immunotherapy is classically given by the subcutaneous route. Often overlooked, this route was actually reported to be effective for IgE-mediated food allergies by Noon's successor, John Freeman, as early as 1930 [6]. There was little immunotherapy research for food allergy reported in the literature unfortunately for the next several decades, and it was not until the 1990s when this therapy was re-examined in well-designed trials. In that decade, two studies suggested that peanut subcutaneous immunotherapy (SCIT) could be beneficial for the treatment of peanut allergy [7, 8]. These studies suggested that peanut SCIT could increase the peanut-reactive dose during challenges. Unfortunately, the subcutaneous route led to frequent and often severe adverse reactions and, thus, was not pursued as a reasonable therapy for food allergy. As an alternative,

J. A. Lieberman
Department of Pediatrics, The University of Tennessee Health Science Center and LeBonheur Children's Hospital, Memphis, TN, USA
e-mail: jlieber1@uthsc.edu

J. Wang (✉)
Department of Pediatrics, Division of Allergy and Immunology, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: julie.wang@mssm.edu



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_17

other routes of allergen delivery have since been examined with well-designed trials examining oral, sublingual, and epicutaneous routes of immunotherapy [9]. All forms have been shown to be effective in desensitizing patients with IgE-mediated food allergy, presumably with a similar mechanism of action. Currently available data suggest that the oral route likely provides the highest degree of desensitization but may be associated with a higher frequency of adverse events when compared to the sublingual and epicutaneous routes [9].

No matter the route of exposure, there are specific themes and terms used when examining efficacy of food allergy immunotherapy. *Desensitization* typically refers to the state achieved when the individual on therapy can tolerate the therapy without limiting side effects and ingest a certain amount of antigen (typically assessed by an observed food challenge) without a reaction as long as they are maintained on the therapy. This may be a temporary state that is lost if the patient stops the therapy. *Sustained unresponsiveness* (SU) typically refers to the ability to tolerate the food without a reaction after completing the desensitization protocol and then stopping the immunotherapy regimen for a prolonged time. Typically, SU is determined after discontinuing the therapy for 1–2 months after achieving desensitization (although varying durations have been used). SU may or may not be a permanent state.

## Mechanism of Action

The mechanism of action of OIT to foods is thought to be similar to that of SCIT for inhalant allergens [10] For example, like with SCIT for inhalant allergens, food OIT leads to a gradual increase in food-specific IgG4 and concomitant decrease in food-specific IgE [11]. While this change in humoral immune response to the antigen is associated with OIT, it is unclear whether the IgG4 plays a mechanistic role or simply reflects increased exposure to the antigen. Data from mouse models suggest that the IgG induced by OIT can suppress IgE-mediated responses and is indeed functional [12]. However, there is at least some human data to suggest that responders and non-responders to OIT both have similar increases in OIT-specific IgG4, and thus this may not be functional or play an actual role in tolerance development [13, 14].

Examination of basophil reactivity in patients undergoing OIT suggests that both spontaneous and allergen-induced basophil histamine release and expression of CD63 are suppressed during OIT [15]. Much of this was transient however, and thus it is not clear if differing mechanisms are involved in transient (desensitization) versus a more permanent response (sustained unresponsiveness).

To date, there are few studies that have examined sustained unresponsiveness, and no definitive mechanistic studies in this group of patients. One study examining SU after a peanut OIT protocol found no differences in peanut IgG4 levels or peripheral T-regulatory cells between treatment responders and non-responders. The only difference between the groups was that responders had lower peanut IgE levels, smaller peanut skin test responses, and lower ratios of peanut-specific IgE/total IgE at baseline and end of study [14]. Another study of SU to peanut OIT showed no difference in peanut-IgE, -IgG4, or basophil reactivity in responders versus non-responders [13]. In that study, the only parameter able to differentiate sustained responders was demethylation of forkhead box protein 3 (FOXP3) CpG sites in antigen-induced regulatory T cells, suggesting that perhaps T-regulatory cells play a role in SU, although the numbers of patients analyzed in this study was small [13].

## Clinical Studies of Oral Immunotherapy

While the exact mechanism of action of desensitization and sustained unresponsiveness remain unclear, the clinical results from multiple trials consistently show that clinical efficacy can be achieved in the majority of patients, no matter the food. Achieving desensitization has been accomplished with various protocols. One common food OIT protocol involves starting with

a very small dose of the food (typically a dose lower than the patient has reacted to during a challenge or a dose lower than would be expected to lead to a reaction). The patient then ingests that dose daily at home, increasing the dose (usually by 50–100%) every 1–2 weeks. Dose increases are performed under supervision in a health care setting. Once the patient reaches a pre-defined maintenance dose, the patient continues to ingest that dose daily. The more rigorous research protocols will perform oral food challenges at baseline and after at least 3–6 months of daily maintenance therapy to assess efficacy.

The first reported case series of oral immunotherapy that included patients with challenge-proven food allergies were from a single center and included various foods [16, 17]. Since that time, the most well-designed and informative studies have focused on single foods (or major food allergens).

## Milk

In the earliest cohort of milk OIT that enrolled only clinically reactive patients with a positive baseline double-blind placebo-controlled food challenge (DBPCFC), 71% of the subjects were able to tolerate a daily dose of 200 mL of cow's milk daily at the end of a 6-month desensitization protocol [18].

Since that time, several studies have examined milk OIT utilizing randomized studies [19–23]. Details of these studies are outlined in Table 17.1. The maintenance doses in these studies varied greatly and ranged from 500 to 7000 mg of cow's milk protein. In all but one of these studies, the majority (67–100%) of subjects were considered responders and were able to complete the protocol and ingest the goal dose of milk (or milk protein) on a daily basis.

The majority of the protocols utilized a desensitization regimen that slowly increased the daily

**Table 17.1** Select milk OIT studies

| Study | Design | Subjects | Form | Updosing | Goal dose | Adverse events | Clinical outcomes |
|---|---|---|---|---|---|---|---|
| Meglio et al. [18] | Open label | 21 subjects<br>Ages 5–10 years | Cow's milk | Every 7 days up to 2 ml then every 16 days | 200 mL | 10/21 had AEs during updosing<br>3/21 dropped out of protocol | 71.4% achieved desensitization to 200 mL cow's milk |
| Longo et al. [24] | Randomized open label (1/2 subjects enrolled randomized to 1 year milk-avoidance diet) | 60 subjects enrolled<br>30 randomized to OIT<br>Ages 5–17 years<br>Positive challenge to 0.8 mL of milk at baseline | Cow's milk | 10 day in-hospital rush updosing to 20 mL cow's milk<br>Increasing by 1 mL at home every second day after rush updosing | 150 mL | Almost all subjects experience AEs<br>3/30 in active treatment dropped out of protocol<br>4 subjects received epinephrine during rush updosing and 1 during home dosing | 36% achieved desensitization to 150 mL of cow's milk<br>54% were able to tolerate lower daily doses, ranging from 5 to 150 mL |
| Staden et al. [25] | Open label | 9 subjects<br>Ages 3–14 years<br>Positive DBPCFC | Cow's milk | Rush OIT in hospital with doubling doses every 2 hours (3–5 doses per day) | 120 mL | All subjects experienced AEs<br>No subject required epinephrine | 67% achieved desensitization to 120 mL of cow's milk in 3–7 days |

(continued)

**Table 17.1** (continued)

| Study | Design | Subjects | Form | Updosing | Goal dose | Adverse events | Clinical outcomes |
|---|---|---|---|---|---|---|---|
| Skripak et al. [19] | Randomized, double-blind, placebo-controlled | 20 subjects enrolled<br>13 randomized to OIT<br>Ages 6–21 years<br>Positive DBPCFC | Dry nonfat powdered milk | 0.4–50 mg in study center on day 1<br>Weekly or every 2-week dose increase at study center | 500 mg protein | 35% of doses led to reaction in the active group (1% in placebo group)<br>4 subjects required epinephrine | 100% tolerated 2540 mg at 1 year randomized double-blind placebo-controlled food challenge (RDBPCFC)<br>31% tolerated max dose challenge at 1-year DBPCFC |
| Pajno et al. [20] | Randomized, single-blind | 30 subjects enrolled<br>15 randomized to OIT<br>Ages 4–10 years<br>Positive DBPCFC | Cow's milk | Weekly updosing in clinic<br>No-daily home dosing | 200 mL | 10/13 had adverse events<br>3/13 had protocol terminated due to AE | 77% in per-protocol (67% in intention-to-treat) analysis achieved desensitization to 200 mL of cow's milk |
| Martorell et al. [21] | Randomized open label (1/2 subjects enrolled randomized to 1 year milk-avoidance diet) | 60 subjects enrolled<br>30 randomized to OIT<br>Ages 2–3 years<br>Positive DBPCFC | Cow's milk | 2-day in hospital updosing to 2.5 mL<br>Weekly updosing in clinic | 200 mL | 80% of subjects had AE in active group<br>15% of doses led to reaction in active group<br>2 subjects required epinephrine | 90% achieved desensitization to 200 mL of cow's milk<br>10% in avoidance group tolerated 200 mL after 1 year during challenge |
| Salmivesi et al. [23] | | 28 subjects enrolled<br>18 randomized to OIT<br>Ages 6–14 years | Cow's milk | Starting at 0.06 mg protein and increasing every 2–4 days on average<br>All doses given at home except eight doses once a week at start of OIT regimen | 200 mL | All subjects in active arm experienced AE<br>2/18 subjects dropped out due to AE | 78% achieved desensitization to 200 mL of cow's milk |

dose over months. However, some protocols utilized a rush desensitization (e.g., doubling the dose every 2 hours in a hospital setting with 3–5 doses per day, achieving 120 mL of cow's milk in 6–7 days), suggesting that this is an alternative requiring close observation due to the concern for higher risk of adverse events [24, 25].

One study of milk-allergic subjects examined milk-OIT versus milk sublingual immunotherapy (SLIT). In that study, subjects were initially treated with a minimum of 4 weeks of SLIT and then randomized to SLIT or to one of two doses of OIT [22]. That study suggested that OIT was more efficacious for desensitization to milk than SLIT alone but was accompanied by more systemic side effects. Sustained unresponsiveness was examined for those who passed an 8 g challenge after 60 weeks of maintenance therapy. Six

of 15 subjects experienced some loss of desensitization, with two having regaining reactivity after 1 week off OIT.

## Egg

Soon after the publication of the initial milk OIT trials, data from trials examining egg OIT followed, with the first open-label trial being published in 2007 [26]. Since then, numerous well-designed studies have examined egg OIT, with some examining sustained unresponsiveness after cessation of therapy [27–35] (Table 17.2). Similar to studies for milk, these trials have varied in course (rush versus non-rush), egg preparation (raw egg, egg powder, etc.), maintenance dose, and duration of immunotherapy; however, they have all shown that desensitization to egg can be achieved in the majority (~56–100%) of subjects who can complete the protocol.

Two studies utilized a randomized, double-blind, placebo-controlled study design and followed subjects who achieved desensitization to assess sustained unresponsiveness by challenge after stopping egg consumption for 2 or 3 months [30, 32]. These studies perhaps give the best assessment of effectiveness of the therapy and the likelihood of achieving sustained unresponsiveness in egg-allergic children. The first study, out of the United States, reported that desensitization was achieved in 22/40 (55%) at 10 months and 30/40 (75%) at 22 months, and the second study, reported from Italy, desensitization was achieved by 16/17 (94%) at 4 months [30, 32]. Following the children that achieved desensitization, the US study had children avoid egg for 2 months and then challenged them to assess for sustained unresponsiveness. With this protocol, 11/40 (28%) assigned to egg OIT passed the challenge after stopping egg ingestion and were considered to achieve sustained unresponsiveness [30]. The Italian study had children stop egg ingestion for 3 months, and 5/17 (29%) achieved sustained unresponsiveness [32]. Thus, from these well-designed, yet small studies, it appears that about 25–30% of subjects who start an egg OIT protocol can achieve sustained unresponsiveness. However, one must realize that there is no way to assure that the participants did not ingest egg on their own during the timeframe that they were supposed to be avoiding all egg, and, thus, measurements of sustained unresponsiveness will always carry the caveat that it is possible that at least some of these subjects continued to only be desensitized.

## Peanut

Data from select peanut OIT trials are detailed in Table 17.3. The original open-label studies were published from 2009 to 2010 and all showed high rates of desensitization, 64–93%, depending on the study and the definition used [36–38]. The first randomized, double-blind, placebo-controlled study was published in 2011 [39]. In that study, 19 subjects (3–10 years of age) were randomized to peanut OIT and 9 subjects (2–9 years of age) were randomized to placebo. Out of those randomized to peanut, 3/19 (16%) dropped out due to adverse effects. Of the 16 remaining, all completed the study and passed the 5000 mg peanut protein challenge at the end of the study. None of those randomized to placebo tolerated 5000 mg at study end (median tolerated dose in placebo group was 280 mg).

There has been one study specifically examining peanut OIT in younger children [40]. In that open-label study, 40 subjects with a median age of 28.5 months were enrolled, and 37 of them were randomized to peanut OIT with a goal daily dose of either 300 mg/day (low dose) or 3000 mg/day (high dose) of peanut protein. Five subjects dropped out of the study (three due to adverse effects and two due to non-adherence). In the intention-to-treat analysis, 17/20 (85%) of subjects in the low dose and 13/17 (76%) in the high dose were considered desensitized. The investigators then had subjects discontinue OIT and avoid peanut for 4 weeks to assess for sustained unresponsiveness. In the low-dose group, 17/20 (85%) achieved sustained unresponsiveness and 12/17 (71%) achieved sustained unre-

**Table 17.2** Select egg OIT studies

| Study | Design | Subjects | Form | Updosing | Goal dose | Adverse events | Clinical outcomes |
|---|---|---|---|---|---|---|---|
| Buchanan et al. [26] | Open label | 7 subjects enrolled<br>Ages 1–7 years | Powdered egg white | Initial 1-day rush updosing in hospital up to 200 mg egg protein<br>Home dosing with in-clinic updosing every 2 weeks | 300 mg egg protein | All subjects had mild symptoms during 1-day rush updosing | 100% of subjects were able to reach the 300 mg daily dose<br>57% passed 8 g blinded and open egg challenges at 24 months<br>2/4 of the subjects passing the 24-month challenge, also passed SU challenge 3 months off therapy |
| Burks et al. [30] | Randomized, double-blind, placebo-controlled | 55 subjects enrolled<br>40 randomized to egg OIT<br>Ages 5–11 years<br>Positive DBPCFC | Powdered egg white | Initial 1-day updosing up to 50 mg<br>Home dosing with in-clinic updosing every 2 weeks up to 2000 mg<br>Maintenance up to 40 weeks<br>Open-label maintenance for additional 12 months<br>Additional challenge at 2 months off therapy in desensitized subjects | 2000 mg egg white powder | 25.0% of active doses led to AE<br>3.9% of placebo doses led to AE<br>5/40 in active treatment dropped out of protocol<br>4 subjects received epinephrine during rush updosing and 1 during home dosing | 55% of subjects who received egg OIT passed the blinded 5 g egg OFC at 10 months<br>75% of subjects who received egg OIT passed the blinded 10 g egg OFC at 22 months<br>28% of subjects randomized to egg OIT passed 10 g blinded OFC and open challenge at 24 months while off therapy suggesting sustained unresponsiveness |
| Meglio et al. [31] | Randomized, open label | 20 subjects enrolled<br>10 randomized to egg OIT<br>10 randomized to observation<br>Ages 4–15 | Raw hen's egg | All doses at home<br>Dosing started at 1 drop raw hen's egg (yolk and white) mixed with water (1:100)<br>Doses increased at home every few days achieving a doubling every 8 days until day 80, then every 16 days up to 25 ml raw egg over 6 months | 25 ml raw egg | 70% of subjects in egg OIT reported symptoms during dosing<br>1/10 subjects in egg OIT dropped out | 80% of subjects enrolled to egg OIT achieved desensitization to 25 ml raw egg<br>20% in observation group tolerated 25 ml in DBPCFC to egg at 6 months |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Caminiti et al. [32] | Randomized, double-blind, placebo-controlled | 31 subjects enrolled<br>17 randomized to egg OIT<br>Ages 4–11<br>Positive DBPCFC | Dehydrated egg white | Weekly updosing (~doubling each week) in clinic<br>Goal dose of 4000 mg in 16 weeks<br>No home doses<br>6-month egg-containing diet for those who passed DBPCFC at 16 weeks<br>3-month egg avoidance after 6-month ingestion | 4000 mg dehydrated egg white | 18% subjects in active group had AE during desensitization<br>No AE in placebo arm<br>1 subject received epinephrine during desensitization<br>1/17 subjects in active arm dropped out due to AE | 94% of subjects enrolled to egg OIT achieved desensitization to 4000 mg dehydrated egg white<br>94% in active group and 0% in control group passed DBPCFC at 16 weeks<br>29% enrolled to egg OIT achieved sustained unresponsiveness |
| Akashi et al. [34] | Randomized, open label | 36 subjects enrolled<br>18 randomized to egg OIT<br>18 randomized to observation<br>Ages 3–15 | Dry powdered egg | All doses at home<br>Starting at 0.1 mg dry powdered egg<br>Doses increased at home every 3–4 days to a goal dose of 4000 mg over ~6 months | 4000 mg dry powdered egg | 94% in OIT group experienced AEs<br>3/18 withdrew from study<br>No subjects received epinephrine | 56% achieved desensitization to 4000 mg dry powdered egg<br>44% in egg OIT group passed challenge at 6 months<br>0 in observation group passed challenge |
| Perez-Rangel et al. [35] | Randomized, open label (with crossover for those in observation group) | 33 subjects enrolled<br>19 randomized to egg rush OIT<br>14 randomized to observation<br>Ages 5–18 | Dehydrated egg white | 5-day rush OIT done on outpatient basis<br>Starting 0.04 mg dehydrated egg white<br>Goal dose 3600 mg by the end of day 5<br>Maintenance was ingestion of 1 undercooked egg at home 2–3 times per week (~5 months) | 3600 mg dehydrated egg white | 97.5% receiving OIT experienced AEs<br>68.8% experienced AE during rush build-up phase<br>2/19 randomized to egg OIT withdrew form study<br>2 subjects received epinephrine | 90% in active group (0 in observation group) achieved desensitization |

**Table 17.3** Select peanut OIT studies

| Study | Design | Subjects | Form | Updosing | Goal dose | Adverse events | Clinical outcomes |
|---|---|---|---|---|---|---|---|
| Varshney et al. [39] | Randomized, double-blind, placebo-controlled | 28 subjects enrolled<br>19 randomized to peanut<br>Ages 2–11 years | Peanut flour | 1 day updosing from 0.1 to 6 mg<br>In-clinic updosing every 2 weeks with daily home dosing | 4000 mg | 1.2% of home doses led to AE<br>2/19 subjects in active treatment received epinephrine (all on initial updosing day)<br>1/9 subjects in placebo arm received epinephrine during home dosing | 16/19 subjects in active group reached 4000 mg<br>16/19 subjects in active group passed 5000 mg OFC<br>0 placebo subjects tolerated 5000 mg OFC (median = 280 mg) |
| Vickery et al. [40] | Randomized, double-blind, dosing study | 37 subjects enrolled<br>20 randomized to low-dose IT (300 mg)<br>17 randomized to high-dose IT (3000 mg)<br>Ages 9–36 months | Peanut flour | 1 day updosing<br>Home dosing with in-clinic updosing every 2 weeks up to 300 or 3000 mg<br>Off product × 4 weeks for SU challenge | 300 vs. 3000 mg peanut protein | 95% of subjects experienced AEs<br>0.8% per dose rate<br>1/20 withdrew from LOW dose<br>4/17 withdrew from high dose | 85% in the low-dose group tolerated 5 g challenge at the end of treatment<br>76% in high-dose group tolerated 5 g challenge at the end of treatment<br>85% in low-dose group achieved SU<br>71% in high-dose group achieved SU |
| Bird et al. [41] | Randomized, double-blind, placebo-controlled | 56 subjects enrolled<br>29 randomized to peanut<br>Ages 4–21<br>Had to react to <144 mg cumulative peanut protein in OFC | AR101 (peanut flour) | 1 day updosing from 0.5 to 6 mg<br>In-clinic updosing every 2 weeks with daily home dosing | 300 mg peanut protein | 96.6% of subjects in active group had AE<br>84.6% of subjects in placebo group had AE<br>6/29 in active group withdrew | 79% in active group tolerated 443 mg cumulative dose at end of study<br>19% in placebo group tolerated 443 mg cumulative dose at end of study<br>62% in active group tolerated 1043 mg cumulative dose at end of study<br>0 in placebo group tolerated 1043 mg |

sponsiveness in the high-dose group [40]. Data from this trial suggests several things. Efficacy may be impacted by age at starting OIT and/or baseline peanut IgE levels. In addition, low-dose OIT (at least in young children) may be as effective as high-dose OIT.

Finally, there is a single report to date examining the safety and efficacy of a peanut OIT product (AR101), which is characterized and manufactured so that it could meet US Federal Drug Administration standards for a biologic if effective [41]. In this phase II randomized, double-blind, placebo-controlled trial, 56 subjects ages 4–21 years were randomized to AR101 ($n$ = 29) or to placebo ($n$ = 27). After initial dose escalation to 3 or 6 mg peanut protein in 1 day, subjects took daily home doses with dose increases occurring in the office setting

every 2 weeks to a goal maintenance dose of 300 mg peanut protein over 24–30 weeks. In the intention-to-treat analysis, 23 (79%) randomized to AR101 tolerated the goal dose of 443 mg peanut protein during blinded challenge at the end of the study compared to 5 (19%) in the placebo group ($p < 0.01$). In addition, 18 (62%) in the AR101 group and 0 in the placebo group tolerated the maximum dose (1043 mg peanut) during the exit challenge ($p < 0.01$). Six subjects (21%) in the active group dropped out (four due to adverse events). The phase III results have only been reported in abstract form at this time but suggest similar outcomes.

## Other Foods

Because the mechanism of action for OIT appears to be the same no matter the food studied, OIT theoretically should work for all IgE-mediated food allergies. The largest amount of data for other foods has come from case series and open-label trials examining wheat OIT [42–45]. These reports suggest that wheat OIT can successfully lead to desensitization similar to other foods. However, none of these studies were placebo controlled and some did not have a post-treatment challenge. The only randomized, placebo-controlled study of wheat OIT has only been published in abstract from to date [46]. This multi-center study enrolled 46 wheat-allergic subjects 4–22 years of age to wheat OIT (with a goal dose of 1445 mg wheat protein) or placebo. After 1 year of OIT, 12/23 (52.2%) of those in the active group achieved desensitization (tolerating ≥4443 mg wheat protein during challenge) versus 0/23 (0%) in the placebo group. After 2 years of wheat OIT, only 7/23 (30.4%) subjects were desensitized and 3/23 (13.0%) achieved sustained unresponsiveness. Those in the placebo were then given 1 year of a higher dose of wheat OIT (goal dose of 3870 mg wheat protein), and 14/21 (66.7%) achieved desensitization [46]. Thus, based on limited data, wheat OIT appears to be slightly less effective than other foods, however due to the limited data, it is difficult to draw definitive conclusions.

## Long-Term Studies

There are very few long-term (e.g. >2 years) outcomes studies of OIT [14, 33, 47, 48]. One study followed subjects enrolled in one of the early, open-label peanut trials for up to 5 years with questionnaires [14]. In that follow-up study, 24/39 (62%) of the originally enrolled subjects had evaluable data for follow-up. Twelve of the original 39 (31%) achieved sustained unresponsiveness based on challenges 4 weeks off of therapy. Following the subjects who achieved sustained unresponsiveness with questionnaires over a median of 40 months, the investigators found that the majority incorporated peanut into the diet ad lib a few days per week without reactions. However, one of the subjects that achieved sustained unresponsiveness stopped eating peanut for "personal reasons," which was associated with increases in both his peanut skin test size (0.5–16 mm) and his serum peanut IgE level (3.56–11.5), suggesting that sustained unresponsiveness is not permanent in at least some patients. In addition, 57% of parents reported difficulty in getting their child to willingly eat peanut in their diets.

Following subjects in a long-term study of egg OIT, Jones et al. showed that rate of sustained unresponsiveness increased with the duration of egg OIT, increasing from 27% at year 2, 45% at year 3, and 50% at year 4 [33]. However, this was offset in some ways with increased drop-out rates over time, with seven subjects withdrawing from the study in years 0–2 (most due to allergic reactions) and another eight withdrawing in years 2–4 (most due to "patient decision").

Finally, in a long-term follow-up study of milk OIT subjects, Keet et al. followed 32 subjects who had completed one of two prior OIT studies [19, 22, 48]. Subjects were followed a median of 3.2 years and 4.5 years after completion of their original study using questionnaires and clinic visits. In this report, 22% reported limiting their consumption because of symptoms, 9% because of anxiety, and 13% because of taste. In addition, 25% limited milk ingestion with exercise and 6% with illness. In examining risk factors for poor outcomes, they found subjects who were not able to consume at least one serving of milk without

symptoms had either a baseline milk IgE levels of greater than 75 kU/L, respiratory symptoms with more than 2% of doses, or a posttreatment food challenge threshold of less than 4 g was [48].

Thus, there is still much to be learned about how this therapy will actually be incorporated in lives of patients on a long-term basis in the real-world setting.

## Multi-Food OIT

Though the exact prevalence of patients with more than one food allergy is not known, various studies suggest that about one-third of food-allergic patients are avoiding more than one food [49]. In addition, quality of life for patients with food allergies appears to be lower for multiple food allergies compared to single food allergy [50]. Since food OIT appears to be food-specific, [51] undergoing OIT to a single food will not protect against exposures to the other foods to which the patient is allergic, and it is questionable whether single food OIT will improve the patients' quality of life, if they remain allergic to other foods.

There are little data published to date assessing the safety and efficacy of performing OIT to multiple foods at the same time. The first multi-food OIT study published compared peanut OIT to multi-food OIT [52]. This was an open-label study in which patients who had confirmed peanut allergy were then challenged to other foods. Those with only peanut allergy were assigned to open-label peanut OIT, and those with other foods allergies were assigned to peanut + other food OIT based on challenge results (up to five total foods). A total of 25 subjects were assigned to multi-food OIT, and 15 were assigned to peanut OIT. Results suggested that multi-food OIT was as safe as peanut OIT, showing similar reaction rates both at home and during updosing. However, one patient in the multi-food OIT arm did have to drop out due to worsening eczema, while none in the peanut group dropped out due to side effects. Interestingly, the study did not report on efficacy, but reported data suggested that fewer subjects in the multi-food OIT arm reached the goal maintenance dose of 4000 mg of allergen as compared to those in the peanut-only OIT arm [52].

The same group also reported data on long-term outcomes of subjects undergoing their multi-food OIT regimen [53]. This study was observational in that it allowed subjects to essentially choose between a "lower" or "higher" maintenance dose of allergen, there was no placebo group, and there was no set time for follow-up challenges to determine desensitization. Thus, these results are difficult to interpret, but based on reported data, it appears that all participants on the long-term maintenance dosing of multi-food OIT were able to tolerate challenges with 2 g of each food allergen at the end of the follow-up (median follow-up of 48 months on maintenance dose) [53].

From a mechanistic standpoint, multi-food OIT seems like a reasonable approach to patients with multiple food allergies. Clearly, more data will be needed to know if it is a reasonable clinical approach however, and many questions remain regarding its implementation.

## Adverse Events

One common finding in almost all studies of food OIT is that adverse events are frequent during the course of OIT. Unfortunately, there is no uniform reporting system for adverse events, and thus a quantitative analysis is difficult. From pooled analysis of milk OIT studies, 97 out of 106 (92%) subjects treated with milk OIT experienced at least one symptom. While most adverse events (~60–90% of those reported) were local and mild, for every 11 patients receiving milk OIT, one required intramuscular epinephrine [54]. Pooled analysis of egg OIT suggested slightly lower rates of adverse events, with 69% of the participants reporting adverse events and 5 of the 100 participants receiving egg OIT requiring epinephrine [55]. Finally, pooled analysis from a single center on peanut OIT reported that 80% of subjects experienced at least one adverse event and 12% of subjects received epinephrine [56].

Examining randomized, placebo-controlled studies of food OIT, it is clear that adverse events are more common in the active group. For example, for egg OIT, adverse events were associated with 25.0% of active doses and only 3.9% of placebo doses in the largest trial [30]. For milk OIT, adverse events were associated with 45.4% of active doses and 11.2% of placebo doses [19]. In addition, drop-out rates due to reactions have been higher in active groups as compared to placebo groups [30].

There have been various attempts to evaluate risk factors associated with adverse events. These can be best summarized as follows.

## Baseline Characteristics Predicting Those with Adverse Events

In a pooled analysis of peanut OIT from a single center, there were two baseline factors associated with a higher frequency of adverse events. Baseline allergic rhinitis predicted a higher rate of adverse events and a higher rate of systemic reactions, and baseline peanut skin prick test wheal size predicated a higher rate of adverse events and, specifically, a higher rate of gastrointestinal adverse events [56]. One other group has examined baseline characteristics in children undergoing egg and milk OIT groups, looking for factors associated with more persistent symptoms [57, 58]. For milk, higher milk-specific serum IgE levels (≥50 kU/L), larger milk skin prick test wheal size (≥9 mm), and more severe reactions at baseline challenge were independent risk factors for persistence of adverse events [57]. For egg allergy, a baseline diagnosis of asthma, higher egg-specific serum IgE levels, and lower threshold of egg leading to reaction at baseline challenge were all associated with early discontinuation or more severe adverse events during OIT [58].

## Factors Associated with Adverse Events During Home Dosing

There have been various findings associated with adverse events to doses at home, i.e., reactions to doses formerly tolerated. These risk factors include concurrent illness (typically illnesses associated with fever), suboptimal control of concomitant asthma, taking doses on an empty stomach, exercise or physical exertion after dosing, and dosing during menses [25, 59]. Therefore, some protocols call for changes in dosing to accommodate for these conditions and suggest decreased adverse event rates with these precautions [59].

## Factors Associated with Severe Adverse Events

Two groups have reported that baseline asthma is associated with more severe adverse events during OIT [60, 61]. In one study of milk OIT, patients with asthma, regardless of severity, had more anaphylactic reactions, ED visits, and hospital admissions as compared to patients without asthma. Another study of milk and egg OIT reported three life-threatening adverse events due to OIT, and all three were in adolescents with moderate-severe asthma. Two of the three required invasive mechanical ventilation and the other required non-invasive mechanical ventilation [60]. Thus, it appears caution should be taken when considering OIT as a treatment option for asthmatics, or at least asthmatics that are poorly controlled or that require higher doses of inhaled corticosteroids to control their symptoms. Interestingly, some of the larger, randomized controlled trials added uncontrolled asthma as an exclusion criterion.

## Persistent Gastrointestinal (GI) Symptoms and Eosinophilic Esophagitis (EoE)

Gastrointestinal adverse events are frequent in studies of OIT and appear not to be dependent on the food studied [62]. In one pooled analysis of peanut OIT studies, half of the subjects that dropped out did so due to GI symptoms [56]. Of interest, some of the subjects with persistent GI symptoms have been diagnosed with EoE while

being on treatment. In a meta-analysis examining this phenomenon, it was estimated that approximately 2.7% of subjects developed EoE after initiating OIT, and it occurred to a variety of foods [63]. It is unknown if these subjects had EoE prior to being enrolled in the study (as endoscopy is not performed at enrollment); however, symptoms developed while in the study, EoE was confirmed with biopsy, and resolution of symptoms occurred with cessation of therapy. Interestingly, one group has suggested that peripheral eosinophilia can be a marker of persistent GI symptoms, suggesting values of absolute eosinophil counts that can help predict those who have GI symptoms from a single cohort of subjects [62]. Thus, if OIT becomes a more mainstream treatment option for food allergies, practitioners will have to be aware of GI symptoms and, hopefully, biomarkers will be identified that are able to predict who will be at risk and who may need to stop therapy.

## Adjuvants

Given the frequency, and possible severity, of adverse events, studies have examined the utility of adjuvants to OIT regimens. Not only could adjuvants allow for improved safety of OIT, but this could, in turn, allow for a more rapid updosing phase. In addition, adjuvants have been added in an attempt to further modulate immune response to increase the efficacy of the therapy. The two main adjuvants studied in food OIT clinical trials to date are anti-IgE therapy and probiotics.

### Anti-IgE Therapy

Several studies have examined the utility of adding the anti-IgE monoclonal antibody omalizumab to OIT protocols [64–68]. These studies have added omalizumab (dosed per package insert for asthma) 8–12 weeks prior to initiating either a milk or peanut OIT protocol and stopped the omalizumab during the updosing or maintenance phase. All studies used different updosing protocols and control groups (if used at all). The initial report examined omalizumab in an open-label, pilot study with a milk OIT protocol [64]. This study enrolled 11 subjects (median age 8 years) and showed that 10/11 tolerated an initial 1-day, rush updosing schedule up to 1000 mg of milk protein. Those subjects then continued dosing at home with increases in the research unit every 2 weeks. Nine out of those 10 subjects achieved desensitization to the goal dose of 2000 mg (over 7–11 weeks), suggesting that omalizumab could facilitate a rapid updosing schedule. Since that time, two controlled studies have examined the utility of omalizumab in food OIT protocols. The first study randomized 57 subjects to omalizumab or placebo starting 4 months prior to initiating a milk OIT desensitization protocol over 22–40 weeks [66]. Omalizumab was continued throughout the OIT treatment. Results from this study showed that subjects in the omalizumab arm reached the goal maintenance dose of milk in fewer doses (i.e., it allowed for a shorter updosing phase), and omalizumab-treated subjects had a higher percentage of symptom-free doses during updosing (91.5%) as compared to placebo-treated subjects (73.9%). However, there was no significant difference in the percentage of subjects that passed the desensitization challenge or the sustained unresponsiveness challenge between the groups.

One study has examined omalizumab in conjunction with peanut OIT in a randomized and blinded fashion [67]. In this study, 37 subjects were randomized to omalizumab or placebo (4:1) for 12 weeks prior to a rapid 1-day updosing to a maximum dose of 250 mg peanut protein. This was followed by weekly updosing to 2000 mg (stopping study drug at either week 19 or week 25) with eventual challenge around week 26. Those subjects randomized to omalizumab were able to tolerate a higher dose during the 1-day rush updosing (250 mg versus 22.5 mg in the placebo arm) and were more likely to pass a 2000 mg challenge at ~week 26 (79% versus 12% in the placebo arm). There was a non-significant trend to suggest that reactions occurred less frequently in the omalizumab-treated group (7.8% of doses) versus the placebo group (16.8% of doses) despite the omalizumab group ingesting higher doses of peanut on average.

Based on the available data, omalizumab appears to be able to facilitate a more rapid updosing protocol and may decrease adverse effects associated with OIT. However, whether it allows for increased efficacy or a change in the mechanism of OIT is unclear. After all, data from prior studies have shown that anti-IgE therapy alone can increase the threshold of reaction to peanut [69, 70]. Thus, perhaps addition of omalizumab simply allows for higher tolerated doses early in therapy, which, in turn, allows for earlier maintenance dosing only, but no change in long-term outcomes.

## Probiotics

Adjuvants can be added to allergy immunotherapy to help potentiate immune response and shift immune response from a Th2 phenotype to a Th1 phenotype, thereby augmenting the efficacy (and possibly the safety) [71]. Probiotics are one candidate adjuvant in this regard, having been shown to induce Th1 and/or regulatory T cells when administered with allergy immunotherapy in various murine models [71].

There has been a single report to date on the utility of adding probiotics to an OIT regimen for food allergy [72]. In this study, 62 children (1–10 years of age) were randomized 1:1 to receive either peanut OIT + *Lactobacillus rhamnosus* ($2 \times 10^{10}$ colony-forming units) or placebo. They were treated for a total of 18 months (maintenance dose of 2000 mg peanut protein in the active group) and then challenged while on therapy, and again within 2–5 weeks off therapy to assess for sustained unresponsiveness. Desensitization was achieved in 89.7% of those in the active arm and in 7.1% of those in the placebo arm. Sustained unresponsiveness was reported to occur in 82.1% of those in the active arm and 3.6% of those in the placebo arm. Adverse events were common in this study with at least one severe AE being reported in 45.2% of children in the active arm and in 32.3% of those in the placebo arm. From this single study, it is clear that addition of a probiotic to a food allergy OIT regimen has no negative effects on the efficacy of the OIT regimen. However, whether it augments OIT can only be answered with a protocol comparing OIT to OIT plus a probiotic.

## Quality of Life

In the studies discussed above, the efficacy of the therapy was determined by desensitization or sustained unresponsiveness. For many patients and parents though, another important outcome may be quality of life (QoL). While likely influenced by the clinical efficacy of the therapy, improvement in QoL can be independent of "curing the allergy." For example, even if the patient is not able to tolerate ingestion of the goal dose upon food challenge while on therapy, if they can tolerate more allergen, or enough that would give families confidence of protection in the case of accidental ingestion of small amounts of the allergen, this may be enough impact QoL. In fact, about one-third of parents of food-allergic children reported willingness to undergo OIT trials with the desired outcome of protection against accidental ingestion, not ability to eat the food ad lib [73].

Surprisingly, very few of the food OIT studies to date have included QoL as an outcome measure. In one crossover study of peanut OIT, parents filled out a standardized QoL questionnaire for any 7–12-year-old subject in the study [74]. After completion of the OIT regimen, there was a significant improvement in QoL based on parent reported scores. However, as there was no placebo group, it is difficult to know if just undergoing any treatment at all could have this affect. After all, evidence exists to suggest that QoL can improve even after a child fails an oral food challenge [75]. Thus, perhaps the challenge procedures, alone or frequent, and regular contact with health care providers at study visits could positively impact QoL.

There are a few reports specifically examining QoL before and after open OIT regimens [76, 77]. These reports both showed overall improvement in QoL scores in subjects undergoing food OIT. However, very interestingly, not all subjects had improvement, and some even had a decrease

in QoL after undergoing OIT. One report showed that QoL improved significantly in those with poor QoL scores at baseline, and that this drove the overall change in the cohort. However, in those patients with better QoL scores at baseline, many had deterioration in QoL [77]. This would suggest that the overall daily burden and adverse effects of OIT may actually make QoL worse in some patients who are less impacted by their food allergy at baseline.

Other aspects of OIT may play a role when considering the impact it may have on patients' QoL. For example, the goal dose, updosing schedule (length of time it takes to reach maintenance), the maintenance target dose, and the maintenance dosing schedule (daily, every other day, three times per week, etc.) may all contribute to QoL. In addition, the frequency and severity of adverse events effect drop-out rates, and thus may impact QoL. From a clinical standpoint, it is important to take patient/parent preference into account when considering the option of OIT.

## Conclusion

Over the past few decades, oral immunotherapy has increasingly been researched as a possible treatment strategy for IgE-mediated food allergies. From these trials, it is clear that the majority of patients can achieve desensitization and that a portion of these can achieve sustained unresponsiveness. In addition, the therapy may improve quality of life at least for some. However, adverse events are common in all studies with a small number of these being severe and some leading to cessation of therapy. Unfortunately, there is no known set of parameters or risk factors that can predict who will achieve desensitization and/or sustained unresponsiveness and who will experience dose-limiting adverse effects. In addition, there is no standardized OIT protocol or food material, and thus there is little unity among the studies for comparison and understanding. These issues will be important to facilitate the transition to clinical practice.

## References


1. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Food and Nutrition Board; Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy. In: Oria MP, Stallings VA, editors. Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy. Washington, DC: National Academics Press; 2016.
2. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. NCHS Data Brief. 2013;(121):1–8. PubMed PMID: 23742874.
3. Panel NI-SE, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1–58.
4. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008–25.
5. Noon L. Prophylactic inoculation against Hay fever. Lancet. 1911;177(4580):1572–3.
6. Freeman J. "Rush" inoculation, with special reference to Hay-fever treatment. Lancet. 1930;215(5562):744–7.
7. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol. 1992;90(2):256–62.
8. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol. 1997;99(6 Pt 1):744–51.
9. Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. J Allergy Clin Immunol. 2018;141(1):1–9.
10. Nowak-Wegrzyn A, Albin S. Oral immunotherapy for food allergy: mechanisms and role in management. Clin Exp Allergy. 2015;45(2):368–83.
11. Vickery BP, Lin J, Kulis M, Fu Z, Steele PH, Jones SM, et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. J Allergy Clin Immunol. 2013;131(1):128–34.e1–3.
12. Burton OT, Logsdon SL, Zhou JS, Medina-Tamayo J, Abdel-Gadir A, Noval Rivas M, et al. Oral immunotherapy induces IgG antibodies that act through FcgammaRIIb to suppress IgE-mediated hypersensitivity. J Allergy Clin Immunol. 2014;134(6):1310–7.e6.
13. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead

box protein 3 (FOXP3). J Allergy Clin Immunol. 2014;133(2):500–10.
14. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol. 2014;133(2):468–75.
15. Gorelik M, Narisety SD, Guerrerio AL, Chichester KL, Keet CA, Bieneman AP, et al. Suppression of the immunologic response to peanut during immunotherapy is often transient. J Allergy Clin Immunol. 2015;135(5):1283–92.
16. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. Hepato-Gastroenterology. 1998;45(19):52–8.
17. Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Pasquale T, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. Aliment Pharmacol Ther. 2003;17(3):459–65.
18. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy. 2004;59(9):980–7.
19. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122(6):1154–60.
20. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol. 2010;105(5):376–81.
21. Martorell A, De la Hoz B, Ibanez MD, Bone J, Terrados MS, Michavila A, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011;41(9):1297–304.
22. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012;129(2):448–55.e1–5.
23. Salmivesi S, Korppi M, Makela MJ, Paassilta M. Milk oral immunotherapy is effective in school-aged children. Acta Paediatr. 2013;102(2):172–6.
24. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121(2):343–7.
25. Staden U, Blumchen K, Blankenstein N, Dannenberg N, Ulbricht H, Dobberstein K, et al. Rush oral immunotherapy in children with persistent cow's milk allergy. J Allergy Clin Immunol. 2008;122(2):418–9.
26. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol. 2007;119(1):199–205.
27. Itoh N, Itagaki Y, Kurihara K. Rush specific oral tolerance induction in school-age children with severe egg allergy: one year follow up. Allergol Int. 2010;59(1):43–51.
28. Vickery BP, Pons L, Kulis M, Steele P, Jones SM, Burks AW. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. Ann Allergy Asthma Immunol. 2010;105(6):444–50.
29. Garcia Rodriguez R, Urra JM, Feo-Brito F, Galindo PA, Borja J, Gomez E, et al. Oral rush desensitization to egg: efficacy and safety. Clin Exp Allergy. 2011;41(9):1289–96.
30. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233–43.
31. Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. Pediatr Allergy Immunol. 2013;24(1):75–83.
32. Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, et al. Oral immunotherapy for egg allergy: a double-blind placebo-controlled study, with postdesensitization follow-up. J Allergy Clin Immunol Pract. 2015;3(4):532–9.
33. Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. J Allergy Clin Immunol. 2016;137(4):1117–27.e10.
34. Akashi M, Yasudo H, Narita M, Nomura I, Akasawa A, Ebisawa M, et al. Randomized controlled trial of oral immunotherapy for egg allergy in Japanese patients. Pediatr Int. 2017;59(5):534–9.
35. Perez-Rangel I, Rodriguez Del Rio P, Escudero C, Sanchez-Garcia S, Sanchez-Hernandez JJ, Ibanez MD. Efficacy and safety of high-dose rush oral immunotherapy in persistent egg allergic children: a randomized clinical trial. Ann Allergy Asthma Immunol. 2017;118(3):356–64.e3.
36. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009;124(2):292–300.e1–97.
37. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010;126(1):83–91.e1.
38. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. Clin Exp Allergy. 2011;41(9):1273–81.
39. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011;127(3):654–60.

40. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139(1):173–81.e8.
41. Bird JA, Spergel JM, Jones SM, Rachid R, Assa'ad AH, Wang J, et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. J Allergy Clin Immunol Pract. 2018;6(2):476–85.e3.
42. Pacharn P, Siripipattanamongkol N, Veskitkul J, Jirapongsananuruk O, Visitsunthorn N, Vichyanond P. Successful wheat-specific oral immunotherapy in highly sensitive individuals with a novel multirush/maintenance regimen. Asia Pac Allergy. 2014;4(3):180–3.
43. Rodriguez del Rio P, Diaz-Perales A, Sanchez-Garcia S, Escudero C, do Santos P, Catarino M, et al. Oral immunotherapy in children with IgE-mediated wheat allergy: outcome and molecular changes. J Investig Allergol Clin Immunol. 2014;24(4):240–8.
44. Sato S, Utsunomiya T, Imai T, Yanagida N, Asaumi T, Ogura K, et al. Wheat oral immunotherapy for wheat-induced anaphylaxis. J Allergy Clin Immunol. 2015;136(4):1131–3.e7.
45. Kulmala P, Pelkonen AS, Kuitunen M, Paassilta M, Remes S, Schultz R, et al. Wheat oral immunotherapy was moderately successful but was associated with very frequent adverse events in children aged 6–18 years. Acta Paediatr. 2018;107(5):861–70.
46. Nowak-Wegrzyn AH, Wood RA, Nadeau KC, Pongracic JA, Henning A, Beyer K, et al. Randomized placebo-controlled multicenter clinical trial of wheat oral immunotherapy. J Allergy Clin Immunol. 2017;139(2, Supplement):AB378.
47. Narisety SD, Skripak JM, Steele P, Hamilton RG, Matsui EC, Burks AW, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. J Allergy Clin Immunol. 2009;124(3):610–2.
48. Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2013;132(3):737–9.e6.
49. Wang J. Management of the patient with multiple food allergies. Curr Allergy Asthma Rep. 2010;10(4):271–7.
50. Lieberman JA, Sicherer SH. Quality of life in food allergy. Curr Opin Allergy Clin Immunol. 2011;11(3):236–42.
51. Meglio P, Giampietro PG, Gabriele I, Carello R, Avitabile S, Galli E. Oral desensitisation with food is food-specific and protein-specific. Int J Immunopathol Pharmacol. 2011;24(3):803–11.
52. Begin P, Winterroth LC, Dominguez T, Wilson SP, Bacal L, Mehrotra A, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. Allergy Asthma Clin Immunol. 2014;10(1):1.
53. Andorf S, Manohar M, Dominguez T, Block W, Tupa D, Kshirsagar RA, et al. Feasibility of sustained response through long-term dosing in food allergy immunotherapy. Allergy Asthma Clin Immunol. 2017;13:52.
54. Yeung JP, Kloda LA, McDevitt J, Ben-Shoshan M, Alizadehfar R. Oral immunotherapy for milk allergy. Cochrane Database Syst Rev. 2012;11:CD009542.
55. Romantsik O, Bruschettini M, Tosca MA, Zappettini S, Della Casa Alberighi O, Calevo MG. Oral and sublingual immunotherapy for egg allergy. Cochrane Database Syst Rev. 2014;11:CD010638.
56. Virkud YV, Burks AW, Steele PH, Edwards LJ, Berglund JP, Jones SM, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol. 2017;139(3):882–8.e5.
57. Vazquez-Ortiz M, Alvaro-Lozano M, Alsina L, Garcia-Paba MB, Piquer-Gibert M, Giner-Munoz MT, et al. Safety and predictors of adverse events during oral immunotherapy for milk allergy: severity of reaction at oral challenge, specific IgE and prick test. Clin Exp Allergy. 2013;43(1):92–102.
58. Vazquez-Ortiz M, Alvaro M, Piquer M, Dominguez O, Machinena A, Martin-Mateos MA, et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg-allergic children. Clin Exp Allergy. 2014;44(1):130–41.
59. Varshney P, Steele PH, Vickery BP, Bird JA, Thyagarajan A, Scurlock AM, et al. Adverse reactions during peanut oral immunotherapy home dosing. J Allergy Clin Immunol. 2009;124(6):1351–2.
60. Vazquez-Ortiz M, Alvaro M, Piquer M, Giner MT, Dominguez O, Lozano J, et al. Life-threatening anaphylaxis to egg and milk oral immunotherapy in asthmatic teenagers. Ann Allergy Asthma Immunol. 2014;113(4):482–4.
61. Elizur A, Goldberg MR, Levy MB, Nachshon L, Katz Y. Oral immunotherapy in cow's milk allergic patients: course and long-term outcome according to asthma status. Ann Allergy Asthma Immunol. 2015;114(3):240–4.e1.
62. Goldberg MR, Elizur A, Nachshon L, Appel MY, Levy MB, Golobov K, et al. Oral immunotherapy-induced gastrointestinal symptoms and peripheral blood eosinophil responses. J Allergy Clin Immunol. 2017;139(4):1388–90.e4.
63. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014;113(6):624–9.
64. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol. 2011;127(6):1622–4.
65. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol. 2013;132(6):1368–74.
66. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind,

placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol. 2016;137(4):1103–10.e11.
67. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol. 2017;139(3):873–81.e8.
68. Takahashi M, Soejima K, Taniuchi S, Hatano Y, Yamanouchi S, Ishikawa H, et al. Oral immunotherapy combined with omalizumab for high-risk cow's milk allergy: a randomized controlled trial. Sci Rep. 2017;7(1):17453.
69. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003;348(11):986–93.
70. Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, double blind, parallel group, placebo controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol. 2011;127(5):1309–10.e1.
71. Moingeon P. Adjuvants for allergy vaccines. Hum Vaccin Immunother. 2012;8(10):1492–8.
72. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol. 2015;135(3):737–44.e8.
73. Kao LM, Greenhawt MJ, Warren CM, Siracusa M, Smith BM, Gupta RS. Parental and parent-perceived child interest in clinical trials for food allergen immunotherapy. Ann Allergy Asthma Immunol. 2018;120(3):331–3.e1.
74. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297–304.
75. Soller L, Hourihane J, DunnGalvin A. The impact of oral food challenge tests on food allergy health-related quality of life. Allergy. 2014;69(9):1255–7.
76. Factor JM, Mendelson L, Lee J, Nouman G, Lester MR. Effect of oral immunotherapy to peanut on food-specific quality of life. Ann Allergy Asthma Immunol. 2012;109(5):348–52.e2.
77. Rigbi NE, Goldberg MR, Levy MB, Nachshon L, Golobov K, Elizur A. Changes in patient quality of life during oral immunotherapy for food allergy. Allergy. 2017;72(12):1883–90.

# Epicutaneous Immunotherapy

18

Allison G. Hicks and David M. Fleischer

## Introduction

Food allergy is defined by the National Institute of Allergy and Infectious Diseases expert panel as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [1]. True food allergy prevalence in the United States is difficult to assess, as food challenges have not been performed in US prevalence studies to confirm IgE-mediated food allergy; rather food allergy is patient or parent reported. Self-reported prevalence in adults approaches 19% [2], but using stricter diagnostic criteria, adult food allergy is estimated to be nearly 11% [2] while food allergy among children is estimated to be between 4% and 8% [1, 3–6]. Prior studies have also indicated that the prevalence is increasing [3].

Current treatment measures for food allergy are limited to strict avoidance, which is known to have a negative impact on quality of life [7] and is also often hard for patients to adhere to, leading to accidental exposures to known food allergens [8, 9]. Fortunately, emerging treatment options are nearing FDA approval for the treatment of peanut allergy, including epicutaneous immunotherapy (EPIT), discussed in this chapter, and oral immunotherapy (OIT), which will be discussed in another chapter.

## Proposed Mechanism of Epicutaneous Immunotherapy

EPIT was first studied as a method to treat allergic rhinitis [10], but given the increasing prevalence and attention to the treatment of food allergy over the last several decades, efforts were shifted to EPIT for food allergy, starting within a murine model. Mouse models have shown that applying an antigen via an epicutaneous route modulates TH2 immune responses. This occurs via antigen-driven activation of dendritic cells that then prompt further immune modulation in draining lymph nodes (Fig. 18.1) [11].

## Current EPIT Products

Most animal models, as well as all human trials, have used a product developed by DBV Technologies called Viaskin. Viaskin consists of a central, translucent polyethylene membrane surrounded by an adhesive polyester crown for adherence to the skin (Fig. 18.1). The delivery system creates an occlusive chamber on the skin which creates moisture, allowing a dry layer of the allergenic material to be

A. G. Hicks (✉) · D. M. Fleischer
Department of Pediatrics, Section of Allergy and Immunology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: allison.hicks@childrenscolorado.org; david.fleischer@childrenscolorado.org


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_18

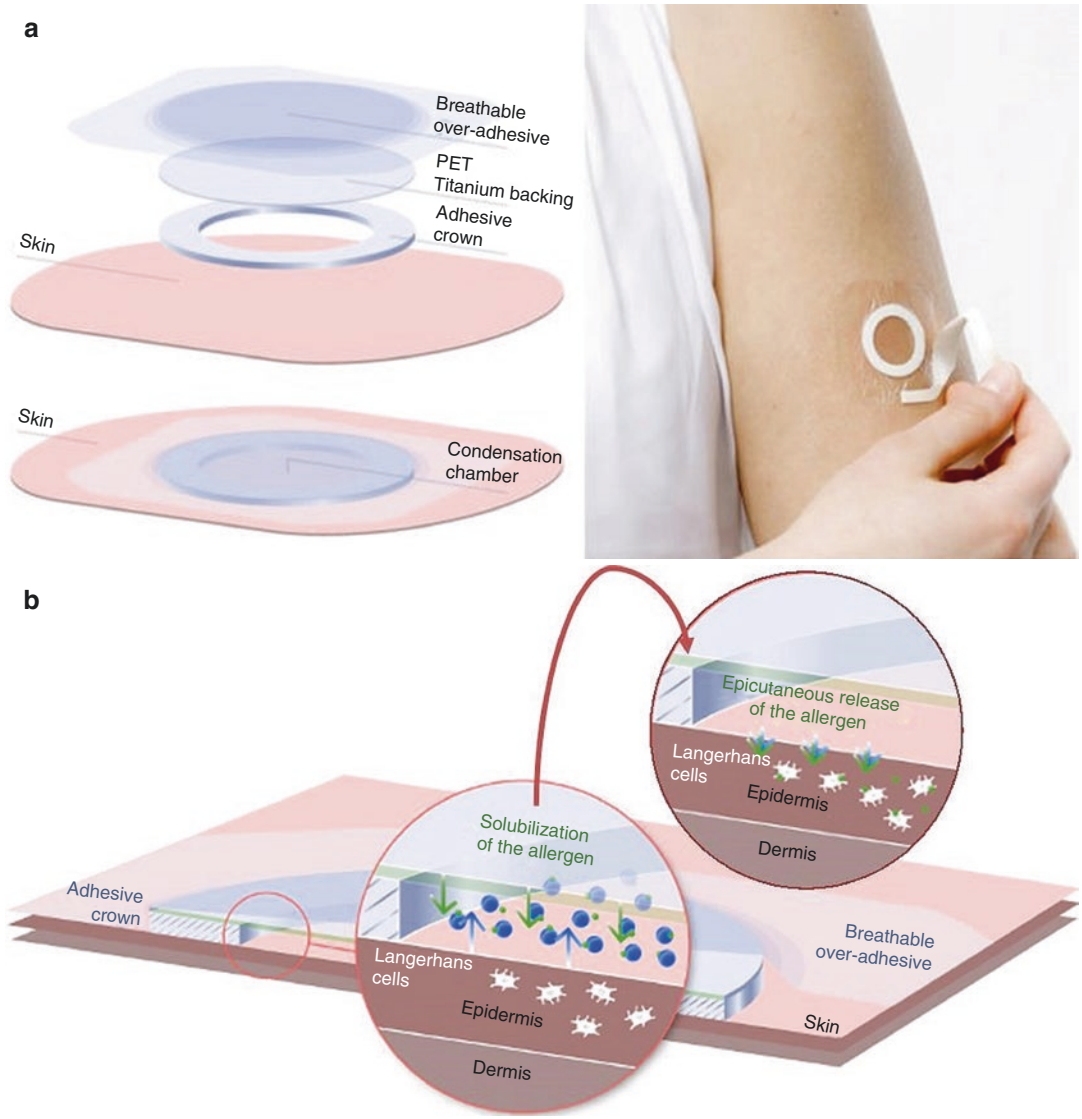



**Fig. 18.1** Viaskin patch (**a**) Illustration of patch layers and its application on the skin (**b**) Schematic of the solubilization of allergen leading to epicutaneous release of the allergen and uptake by Langerhans cells in the epidermis. (Figure used with permission of DBV Technologies)

released. This allergenic material then diffuses across the skin [11] and is primarily absorbed by the epidermis but in a small amount by the dermis as well. The Viaskin patch (hereafter referred to as the patch) is applied in a rotating fashion every 24 hours to six sites on the interscapular space in children younger than 11 years of age and in past peanut clinical trials on the upper arm in participants 12 years and older [12].

## Treatment Regimens

As opposed to other emerging treatment options, including OIT, increasing doses of the allergen in question within the patch are not used. Instead, patches contain a fixed amount of protein in micrograms (μg), and the amount of time wearing the single-dose patch is increased at home to the maintenance goal of a 24-hour application; this is notably different than updosing that occurs

in OIT every 2 weeks under medical supervision until a maintenance dose is achieved after several to many months depending on the amount of protein desired for maintenance dosing. The patch is first applied for 3 hours under medical supervision, and then patients wear the patch for 6 hours a day during the first week, followed by 12 hours during the second week, and then from the third week onward, the patch is applied for 24 hours every day. Some patients may have more skin reactivity at the initiation of treatment; these local skin reactions usually decrease over time, but some patients may have difficulty with intense itching. In these cases, the patch can be removed and titration to the goal of 24-hour wearing can be longer than the 2 weeks proposed. Antihistamines or topical corticosteroids can be used to treat significant pruritus or local skin reactions. For persistent patch-site reactions, patients are instructed to remove the patch and to return to the last duration that was tolerated for 3 days. The patient could then increase patch duration every 3–4 days until they were again tolerating 24 hours per day [12]. Patches may fall off or may be removed by patients purposefully before 24 hours; the patch is only reapplied to the same site if it fell off within 2 hours of application.

## Current Evidence in Humans

Clinical trials have been performed assessing the use of EPIT in cow's milk (CM) and peanut-allergic patients. The current evidence, including information from available manuscript publications as well as abstracts presented at scientific meetings, is presented for each below.

### Cow's Milk

A pilot study using EPIT for cow's milk allergy (CMA) by Dupont et al. was published in 2010 [13]. Nineteen children between the ages of 3 months to 15 years were randomized to a placebo or a CM EPIT. To be included, participants had to have a history of systemic symptoms to CM protein, serum-specific IgE to CM >0.35 kilounits per liter (kU/L), and/or a skin prick test (SPT) to CM protein with a wheal greater than 3 mm. Prior to randomization, patients had to have a positive oral food challenge, with a cumulative tolerated dose of less than 10 mL of CM.

Treatment consisted of three 48-hour applications of the patch per week for 3 months applied to the interscapular area. Active patches contained 1 mg of skimmed CM powder, and placebo patches contained 1 mg of glucose. Patients in the active EPIT group had a non-statistically significant increase in their cumulative tolerated dose. The study's failure to demonstrate a statistically significant improvement was felt to be due to the short duration of the study, 3 months, and they proposed future studies with an extended treatment period, i.e., 12 months, to demonstrate an effect. As discussed in more detail in the safety section, they were able to demonstrate patient tolerability and safety of the patch, encouraging further studies.

Recently, a Phase I/II safety and efficacy study was completed for EPIT in IgE-mediated CM-allergic children (MILES study) [14]. Per DBV's press release of the initial results, the study enrolled 198 participants in two age groups: children aged 2–11 years and adolescents aged 12–17 years [15]. Participants were randomized 1:1:1:1 into four treatment arms comparing placebo to 150, 300, and 500 μg patches. Patients underwent a double-blind, placebo-controlled food challenge (DBPCFC) at screening and again after 12 months of treatment.

The primary efficacy endpoint of the study was the percentage of patients who responded to treatment, which was defined as either (1) a 12-month cumulative reactive dose (CRD), defined as the total dose of allergen administered in the DBPCFC prior to occurrence of an allergic reaction, of ≥1444 mg (approximately 45 mL of CM) or (2) a tenfold or greater change in baseline in DBPCFC CRD and tolerance of at least 144 mg (4.5 mL) of CM protein. The study found a statistically significant response in the 300-μg arm of the 2–11 years of age group, with a response rate of 57.9% compared to 32.5% in placebo ($p = 0.042$). There was not a statistically significant response

in any dosage level in the adolescent age group or at other dosage levels in the younger group. An open-label extension with conversion of all participants to the 300-μg dose and active treatment for up to 3 years has been proposed, with a Phase III clinical trial being planned.

## Peanut

Initial studies were performed at multiple sites in France, entitled the Arachild study. Dupont et al. enrolled 54 pediatric participants (ages 5–17 years, median 10.5) with a peanut IgE level greater than 5 kU/L and SPT greater than 8 mm to peanut who reacted during a screening DBPCFC to a CRD dose of <300 mg peanut protein. Patients were randomized 1:1 to either a 100-μg peanut protein patch for a total of 18 months vs. 6 months of placebo followed by 12 months of active treatment. Desensitization was monitored by DBPCFCs every 6 months. Treatment response was defined as a ≥tenfold increase in the CRD from baseline or a dose threshold of ≥1000 mg. Patients in the arm receiving 18 months of active treatment showed a treatment response of 40% overall, with the subpopulation of children aged 5–11 years (15 children) showing a 67% response rate. In this subpopulation, the mean CRD increased over time: baseline: 24.27 ± 29.98 mg; 6 months: 122.6 ± 239.2 mg; 12 months: 308.3 ± 673.9 mg; 18 months: 357.7 ± 542.9 mg, with a p value of <0.001 between serial measurements of participants CRD. Peanut IgG4 levels showed a progressive increase over time, with a mean value of 5.13 ± 5.9 mg/L at 18 months ($p < 0.001$) [16].

A follow-up study by Sampson et al. assessed different dosages of the peanut patch, entitled the VIPES randomized controlled trial [17, 18]. Two hundred twenty-one participants aged 6–55 years were randomized 1:1:1:1 to 1 year of patches at either 50-μg, 100-μg, 250-μg, or placebo. Inclusion criteria were similar, with participants having to demonstrate an allergic reaction to peanut during a screening DBPCFC to an eliciting dose (ED) of ≤300 mg. The primary endpoint was the proportion of respondents with a ≥tenfold increase in their ED, defined as the last single food challenge dose administered prior to development of objective clinical symptoms, or achieving a posttreatment eliciting dose of ≥1000 mg. CRDs were also measured but were not the primary endpoints as in the Arachild Study.

The overall primary endpoint was met but only with the 250-μg dose (total 56 participants, 28 children). After 12 months of treatment, 50.0% of participants in the 250-μg dose were responders vs. 25% ($n = 14$) in the placebo group (difference in response rates 25%, $p = 0.01$); this corresponded to a number-needed-to-treat of 4. Again, the younger subpopulation, children aged 6–11 years, demonstrated the only statistically significant response; in this age group, 53.6% ($n = 15$) of those on the 250-μg patch responded vs. 19.4% for the placebo participants of the same age range (difference in response rates 34.2%, $p = 0.008$). Adolescents and adults showed no difference between any active dose and placebo. The mean CRD at month 12 was greater for the 250-μg dose (1117.8 mg) compared to placebo (469.3 mg) (least squares [LS] mean difference, 336.2 mg); for the children subpopulation, mean CRDs were 1211.9 mg and 239.2 mg, respectively (LS mean difference 333.7).

The placebo response rate was much higher than the study's projected 10% and higher than that reported in other studies. The authors argue this could have been due to the use of PRACTALL DBPCFC guidelines, which initiate food challenges as very small doses [19]. Given these small starting doses, it was proposed that more placebo arm patients were able to meet the primary endpoint of a tenfold increase from their baseline challenge than if higher initiating doses were used. A progressive increase in IgG4 was again noted over the 12-month period, but the increase was only statistically significant for the 250-μg group and was most robust in the youngest age range. At month 12, mean peanut IgG4 levels were greater for the 250-μg patch than for placebo (LS mean difference 2.2, $p < 0.001$). Compliance with patch application was greater than 95%, and dropout for adverse events was less than 1%, with no serious adverse events occurring related to treatment.

Sampson et al. then completed an open-label 24-month extension of the participants in the prior dose-range study, the Open-Label Follow-up Study or OLFUS-VIPES [18, 20]. Of the 207 participants who completed the VIPES trial, 171 (82.6%) entered the open-label extension, 97 children (85.8%) and 74 adolescents/adults (68.5%). All participants were transitioned to the 250-μg patch within 6 months of completing the Phase 2b trial. All patients underwent DBPCFCs at months 12 and 24 of the extension, and the primary endpoint was unchanged from the Phase IIb blinded trial. For the overall study population, per-protocol response rates after 12 and 24 months of additional therapy were 63.3% and 68.4% in children, respectively, and 54.2% and 57.8%, respectively, in adolescents/adults. The mean CRD of 21 children originally on the 250-μg patch in the blinded Phase IIb trial continued to increase from mean of 1067.8 mg at 12 months of treatment to 1883.5 mg at 24 months (OLFUS-year 1) and to 2453.9 mg at 36 months (OLFUS-year 2) of treatment. Furthermore, of the 18 of these 21 participants who were challenged at 36 months of active treatment, 39 (7/18) were able to consume a CRD of ≥5040 mg. Of note, 31.7% of the patients in the open-label extension discontinued for various reasons, with only two patients (1.2%) discontinuing due to adverse events, one of which was a treatment-emergent adverse event (TEAE). Compliance rates and rate of patch-related adverse reactions in the 24-month extension were similar to the initial 12-month study.

While previous trials discussed to date have only focused on efficacy related to desensitization, defined as a transient, reversible state of decreased threshold reactivity while receiving therapy, one of the efficacy analyses in OLFUS-VIPES investigated sustained unresponsiveness (SU), defined as sustained reduced clinical reactivity determined by a food challenge after a period of cessation of therapy [21]. Participants in the OLFUS-VIPES trial who tolerated a cumulative dose of ≥1440 mg of peanut protein during the month 24 DBPCFC were invited to enroll in a SU assessment with another DBPCFC at month 26 after stopping EPIT treatment for 2 months. Twenty-nine participants, 21 children and 8 adolescents/adults, completed 24–36 months of EPIT with 250-μg and were unresponsive to a cumulative dose of ≥1440 mg peanut protein at the month 24 OLFUS DBPCFC. Of the 29, 25 participants, 19 of which were children and 6 were adolescents/adults, completed the 2-month period without treatment and underwent the subsequent DBPCFC. Eighty percent (20/25) were able to consume the cumulative dose of ≥1440 mg at 26 months without reaction, thus being labeled as developing SU to this cumulative dose. Further studies investigating SU with EPIT are required, but this initial report is promising in regard to its ability to induce a more lasting response.

A concurrent Phase II study was conducted by Jones et al. within the Consortium of Food Allergy Research (CoFAR) group [12]. Seventy-four participants between the ages of 4–25 years (median age 8.2 years) were randomized to either a placebo patch, a 100-μg patch, or a 250-μg patch for a period of 52 weeks. Inclusion criteria varied slightly compared to the previously discussed studies, requiring a peanut-specific IgE of >0.35 kU/L, a SPT wheal size ≥3 mm greater than the saline control, and a positive baseline DBPCFC to a cumulative dose of 1044 mg or less of peanut protein.

The primary endpoint was the proportion of participant responders after 52 weeks of treatment, defined as either passing a DBPCFC with 5044 mg of peanut protein at week 52 or by a ≥ tenfold increase in the successfully consumed dose (SCD). At 52 weeks, compared to placebo, in which three placebo arm participants (12%) met the primary endpoint, treatment success was obtained in 11 100-μg patch participants (46%, $p = 0.005$) and 12 250-μg patch participants (48%, $p = 0.003$). There was a statistically significant difference in the median change of SCDs in both the 100-μg and 250-μg patches, 43 mg and 130 mg of protein, respectively, compared to placebo (0 mg change). Similar to the studies previously discussed, treatment success was higher among younger children (4–11 years of age): compared to placebo, treatment success was achieved in 1 (6%) placebo-treated participant, 10 (59%) 100-μg treated participants, and

11 (61%) 250-μg treated participants ($p < 0.001$ and $p < 0.001$, respectively). A statistically significant increase in peanut-specific Ig4 levels over time between treatment groups ($p < 0.001$) was again noted among the 100-μg patch and 250-μg patch groups compared to placebo.

DBV is now completing Phase III trials regarding their peanut patch, titled Peanut EPIT Efficacy and Safety Study (PEPITES) and Real Life Use and Safety of EPIT (REALISE). PEPITES was a multi-center, international, randomized, double-blind, placebo-controlled study where pediatric participants ages 4–11 years were randomized 2:1 to either a 250-μg peanut patch or placebo patch [22]. Participants underwent a baseline DBPCFC, and the primary combined endpoint was based on responder analysis after 12 months of treatment. For participants who had a baseline ED of ≤10 mg, a responder was labeled as a participant with an ED of ≥300 mg of peanut protein after 12 months of treatment. In patients who had a baseline ED >10 mg, a responder was defined as a 12-month ED of ≥1000 mg. To assess the degree of benefit in favor of peanut-patch, a threshold of ≥15% on the lower bound of a 95% confidence interval around the responder rate difference was prespecified.

PEPITES Topline results found a statistically significant response, with 35.3% of participants in the 250-μg patch arm responding vs. 13.6% of participants in the placebo arm (difference in response rate 21.7%; $p < 0.001$; 95% confidence interval (CI) = 12.4%-29.8%) [23]. The lower bound of the 95% CI of the difference extended below the prespecified lower limit of 15%. CRD was a secondary endpoint and showed that participants treated with the 250-μg patch for 12 months reached a mean CRD of approximately 900 mg vs. 360 mg in the placebo arm. The mean baseline CRD was 210 mg in both groups, and the 250-μg patch arm's increase was statistically significant compared to placebo ($p < 0.001$).

An open-label extension trial, titled the PEPITES Open Label Extension Study (PEOPLE), is following the participants from PEPITES for a 36-month open-label treatment period: 300 of the 323 (93%) participants from the 12-month blinded trial have enrolled in the open-label extension [24]. Participants who had received the 250-μg patch for the initial 12 months continue for an additional 24 months of treatment, while those initially on placebo will complete a total of 36 months of open-label treatment with the 250-μg patch. DBPCFCs will be performed after 36 months of treatment.

The REALISE study was initiated in 2016 to assess the safety and efficacy of the peanut patch in routine clinical practice [25]. It is a multicenter, randomized, double-blind, placebo-controlled Phase III study where participants age 4–11 years initially were randomized 3:1 to a 250-μg patch or placebo for a 6-month blinded period. After 6 months, participants in both arms were invited to join an open-label extension with the plan to monitor participants for a total of 36 months of active treatment. Serological markers were followed over time as well as scores from a Food Allergy Quality of Life Questionnaire (FAQLQ). Given its intent to mirror clinical practice, no entry oral food challenge was required to enroll in the REALISE study. Participants were selected based on medical history of IgE-mediated reactions to peanut as well as baseline peanut-specific immunologic markers. The blinded portion of the study was completed in 2017, and of 393 participants enrolled, 383 (97.5%) continued into the open-label portion of the study, which is ongoing [26]. The initial results from the blinded portion showed a similar safety profile of prior studies, which is discussed further below [27].

A summary of the different phase trials using the peanut patch is provided in Table 18.1.

## Safety

The primary objective of many of the initial studies previously outlined has been to assess safety and tolerability of EPIT in humans. Evidence is again outlined for both CM and peanut below.

**Table 18.1** Summary of the different phase trials using the peanut patch

| Phase | Study name | Reference | Design | N | Age (y) | Peanut treatment arm dose(s) (μg) | Duration | Results of primary outcome |
|---|---|---|---|---|---|---|---|---|
| Phase I | | Jones [28] | Randomized, double-blind | 100 | 5–60 | 20, 100, 250, 500 | 2 weeks | 52% of patients in treatment arms had at least one TEAE, 41.3% mild severity, 11.3% moderate severity, no severe TEAES |
| Phase II | CoFAR | Jones [12] | Randomized, double-blind | 74 | 4–25 | 100, 250 | 12 months | 46% in 100 μg and 48% in 250 μg patch with either tenfold increase in SCD or passed DBPCFC of 5044 mg |
| | ARACHILD | Dupont [16] | Randomized, double-blind | 54 | 5–17 | 100 | 18 months | 40% of 18-month treatment group had a ≥ tenfold increase in CRD or a dose threshold of ≥1000 mg |
| | VIPES | Sampson [17] | Randomized, double-blind | 221 | 6–55 | 50, 100, 250 | 12 months | 50% of the 250 μg group had a ≥ tenfold increase in ED and/or reached ≥1000 mg peanut protein vs. 25% of placebo ($p = 0.01$) |
| | OLFUS-VIPES | Sampson [20] | Open-label extension | 171 | 6–55 | 250 | 24 months | 68.4% of children and 57.8% of adults had a ≥ tenfold increase in ED and/or reached ≥1000 mg peanut protein after 24 months of additional treatment |
| | OLFUS-VIPES – SU | Brown-Whitehorn [21] | Sustained unresponsiveness extension | 29 | 6–55 | 2 months off 250 | 2 months | 80% (20/25) tolerated a DBPCFC of ≥1440 mg off of therapy for 2 months |
| Phase III | PEPITES | DBV [22, 23] | Randomized, double-blind | 323 | 4–11 | 250 | 12 months | 35.3% responders (either increase from ≤10 mg to ≥300 mg or from >10 mg to ≥1000 mg) vs. 13.6% of placebo ($p < 0.001$) |
| | PEOPLE | DBV [24] | Open-label extension | 300 | 4–11 | 250 | 36 months | Results pending |
| | REALISE | DBV [26] | Blinded, followed by open-label | 393 | 4–11 | 250 | 36 months | Data from initial 6 month blinded period with adverse events mostly mild/moderate. 3 SAEs in treatment group vs. 2 in placebo |
| | EPITOPE | DBV [29] | Randomized, double-blind | 331 | 1–3 | 100, 250 | 15 months | Results pending |

## Cow's Milk

Dupont et al.'s initial pilot study [13] of CM patches defined local adverse events as local reactions exceeding simple erythema, with or without local pruritus, and associated erythema, edema, and infiltration using the International Contact Dermatitis Research Group classification grade I [30]. Of the 19 participants, local adverse events were reported for 4 of 10 children in the active group and 2 of the 8 participants in the placebo group. In the intention-to-treat population, 24 systemic adverse reactions occurred in the active group and 8 in the placebo group. However, no reactions were classified as anaphylaxis, and reported symptoms, including bronchitis, diarrhea, and fever, were unlikely to be due to treatment, and no participant interrupted treatment because of an adverse event.

Interim safety reports from the MILES study have also had minimal significant safety concerns [14]. In Part A, an initial 18 participants, with a median age of 8 years at entrance, were randomized to receive either a placebo patch or a 150, 300 or 500 μg CM patch to assess safety before opening the trial for further recruitment. At time of the interim report, no serious adverse events had been reported, and no epinephrine had been required for a drug-related adverse event. Most participants reported local itching (83.3%), redness (83.3%) or swelling (72.2%) with at least one patch application. One case of erythema and papules required treatment with 2% topical hydrocortisone. Three other cases of drug-related adverse reactions were reported and were all skin reactions of mild to moderate intensity, i.e., application site urticaria or bruising. Preliminary results from Part B, which looked at the safety and efficacy of the three doses of a CM patch in 198 patients, also reported no treatment-related serious adverse events [15]. Most reported adverse events were mild to moderate application site reactions, and there was a low dropout rate of 1.5% due to adverse events.

## Peanut

Initial Phase 1 safety trials in peanut involved 100 participants ages 6–50 years with peanut allergy, including 30 adult participants deemed to have severe peanut allergy [28]. A severe peanut allergy was defined as positive SPT with a wheal greater than or equal to 8 mm, a serum IgE greater than 0.7 kU/L and a history of allergy to peanuts with anaphylaxis of grade 4 or 5 using a standardized food-induced anaphylaxis grading scale [31]. Participants were randomized 4:1 to receive peanut patches in doses of 20, 100, 250, and 500 μg or placebo. The patch was applied to the upper arm or interscapular space at either 24- or 48-hour periods during a 2-week period followed by a 1-week follow-up period. Safety and tolerability were assessed by evaluating the presence and severity of TEAEs and local- treatment-emergent adverse events (L-TEAEs), which were limited to the patch site. TEAEs were overall mild, and there were no differences in TEAEs between treatment groups. In those on active treatment, 52.5% (42/80) reported at least one TEAE, 41.3% of which were mild in severity and 11.3% were moderate. In the placebo arm, 45% (9/20) reported at least one TEAE, 30% of mild severity, and 15% of moderate severity. There was no statistical difference in the proportion of participants reporting a TEAE in the placebo vs. active treatment arms or when comparing participants with severe vs. non-severe peanut allergy. There were no reports of severe TEAEs, severe adverse events or epinephrine use. The product and study were also well tolerated, with only 4 of 100 participants discontinuing, 3 because of TEAEs, and 2 of which were participants on active treatment.

The CoFAR Phase II EPIT trial assessed safety as well as clinical response over a 52-week period [12]. Participants were monitored for patch-site reactions during scheduled visits and as needed. Skin changes at the patch site were scored as grade 0–4. Extension of symptoms outside the patch site or involvement of systemic reactions was recorded using the CoFAR grading system for allergic reactions [12]. Overall, 14.4% of placebo doses resulted in a reaction vs. 79.8% in active doses (100-μg and 250-μg). The majority of reactions were mild and limited to the patch site. Grade 2 or greater patch-site reactions occurred with 1.6% of placebo doses vs. 18.7% of 100-μg doses and 23.4% of 250-μg

doses. There was report of one grade 4 reaction in a 12-year-old participant, resulting in discontinuation of this participant by predetermined criteria. Reactions that extended beyond the patch occurred in 1.5% of placebo participants, 8.9% of 100-μg patches, and 16.2% of 250-μg patches. Non-patch-site reactions were uncommon, being reported in 0.2% of placebo and 100-μg doses and 0.1% of 250-μg doses. No participants had a severe or life-threatening reaction. Treatment of reactions most commonly consisted of topical corticosteroids, followed by oral antihistamines. The median percentage of doses per participant with a treated reaction was 0% for the placebo group compared to 8.9% for the 100-μg patch and 16.2% for the 250-μg patch. No epinephrine was used for treatment of symptoms. High compliance of 97.1% demonstrated good tolerance of the product.

The VIPES and OLFUS-VIPES studies presented further reassuring safety data for peanut, similar to that found in the CoFAR trial and with those of CM [18]. Participants graded application site skin reactions (i.e., erythema, pruritus, and edema) or cutaneous symptoms on a daily basis with a scale from 0 (absent) to 3 (severe) for the first 3 months of the study and whenever symptoms occurred for the remaining 9 months. Occurrence of all TEAEs and event rates were balanced between all peanut patch groups (50-, 100-, or 250-μg). TEAEs related to the investigational product occurred twice as often in the peanut-patch groups compared to placebo (96.2% for 250, 94.6% for 100, 96.4% for 50, and 48.2% for placebo), primarily during the first months of treatment. Local skin reactions were the most common adverse symptoms reported, and symptoms of grade 1–3 occurred during the first month of treatment in most participants, but such symptoms lasted less than 3 months in half of the participants. The rate of more generalized reactions was approximately 25%, including mostly cutaneous reactions extending beyond borders of patch (18%) There was one case of non-serious, moderate anaphylaxis possibly related to treatment, and 20 serious AEs were recorded in 17 participants, none related to study drug. The patch was overall well tolerated, with only 3 in 165 discontinuing because of an AE, 1 for an unrelated AE and 2 for local dermatitis, 4 and 9 months after initiating the patch. Similar results were seen during the open-label extension period.

In the REALISE study [27], the most commonly reported adverse events were local application site reactions that were mostly mild or moderate in nature. A similar number of serious adverse events were observed in the active and placebo arms (3 events vs. 2 events, respectively): 1 episode in the treatment arm was labeled as moderate anaphylaxis probably related to treatment. In the 6-month blinded period, the discontinuation rate was 2.5% with a 1.0% dropout related to adverse events, with a mean participant compliance above 95%.

Overall, data collected thus far regarding the safety of the patch for EPIT have been reassuring. Although the rate of local erythema and pruritus is quite high, especially at the initiation of EPIT, studies to date have shown a decrease in severity and frequency of symptoms over time with prolonged use, a high level of tolerability and compliance, and a low risk of more serious side effects. Furthermore, increased reactions have not been seen with exercise or patch application while the participant is ill with an infection (e.g., URI, influenza); an increased risk of reaction during these scenarios has been noted in OIT studies [32–35]. Families should also be consulted on proper application of the patch product as some of the more systemic adverse events in the trials previously outlined may have been due to accidental transfer of allergen from the patch to mucous membranes during application as opposed to a reaction from the patch itself [28].

## Comparison of Other Treatment Methods

EPIT is not the only emerging treatment for IgE-mediated food allergy, and thus before starting any new therapy, a consideration of EPIT compared to other immunotherapy methods is warranted. Clinical trials to date have focused on other forms of food immunotherapy, primarily OIT and sublingual immunotherapy (SLIT) (Note: the safety and efficacy of OIT will be

covered in greater detail in Chap. 17) [5, 36]. This section will focus more on the general differences with respect to advantages and disadvantages among the therapies with respect to efficacy, safety, and practicality.

## Oral Immunotherapy

OIT has been studied most extensively in the form of single-allergen therapy, primarily with CM, egg, and peanut, although multi-allergen OIT is also under investigation [37]. With respect to efficacy, OIT studies have reported ranges of desensitization at rates ranging from 40% to 90% and a rate of SU of 27%–50%, with varying doses of maintenance therapy, length of treatment on therapy, and with amount of time off therapy [38]. Studies to date, in general, demonstrate increased desensitization and SU in OIT compared to EPIT. However, this higher degree of efficacy is not unexpected when orally consumed doses are commonly given at a maintenance dose of 300 mg of protein (or in previous non-industry studies in 2–4 gram daily doses) compared to 250–300 μg of protein applied topically. To put this into scale, 250–300 mg is the protein content of approximately one peanut; 250 μg is a 1000-fold less difference in daily protein amounts. In fact, over the course of a 3-year study of daily application of a 250-μg patch, the total dose of this daily application, approximately 273 mg, is less than 1 day of 300 mg protein taken orally.

However, with the higher doses taken orally comes a higher side effect profile, resulting in higher dropout rates in OIT compared to EPIT. As seen in EPIT where local skin reactions occur in over 90% of patients, overall approximately 90% of participants in clinical trials for OIT experienced mild, localized adverse events [36]. The most common symptoms with OIT are oral pruritus and abdominal pain that are generally mild and do not require treatment. However, more moderate symptoms occur with OIT in a small percentage of patients, such as wheezing, vomiting, and urticaria; while these may only occur in a small percentage of patients, the fact that larger doses are given orally over an extended period of time makes this risk for each patient more significant. More severe reactions requiring treatment, including epinephrine, have been reported with OIT, especially during dose escalation (build-up to maintenance dose), although they can occur as well during maintenance dosing. Gastrointestinal side effects are most common in OIT and can be intolerable in up to 20% of receiving active therapy, leading to a much higher rate of therapy discontinuation in OIT compared to EPIT or SLIT: 15–20% withdrawal rate in OIT studies compared to 1–5% in EPIT and SLIT studies. Also concerning is that patients on OIT who have previously been tolerating therapy can unpredictably and suddenly have a severe reaction with certain cofactors such as exercise or infection, e.g., febrile illnesses.

Another area of concern for OIT is the reported incidence of eosinophilic esophagitis (EoE). EoE is an immune-mediated chronic disease with wide-ranging symptoms, most commonly abdominal pain, vomiting, reflux, dysphagia, and food impaction, as well as eosinophilic infiltration of the esophagus on biopsy [39]. A recent review of OIT clinical trials attempted to quantify the rate of EoE [40]. Direct correlation is difficult given endoscopy with biopsies are not performed prior to initiation of OIT, and thus presence of EoE at baseline cannot be ruled out. Furthermore, most patients who develop GI-related symptoms that may be attributed to EoE do not undergo endoscopy with biopsy to prove the presence of it, but rather stop OIT with resolution of symptoms. This review both assessed symptoms that could be concerning for the presence of EoE, which can be difficult given their prevalent and vague nature as well as confirmed cases of EoE. Overall rates of symptoms possibly related to EoE were 34% for general GI symptoms, 32% for abdominal pain, and 12% for vomiting. In 18 studies, there were confirmatory endoscopies with biopsies performed when there was concern for EoE in 35 cases, making a rate of developing EoE of 5.3% in patients receiving OIT. A systematic review with meta-analysis performed in 2014 found a lower prevalence of EoE of 2.7% [41], but a prospective study of 128 patients undergoing OIT reported a prevalence of 4.69% [42]. Given the chronic nature of EoE and

its impact on nutrition and quality of life, this risk should be discussed with potential patients and families considering treatment options for IgE-mediated food allergy.

Another consideration in the clinical setting is the titrating protocol in OIT vs. EPIT. OIT protocols have varied but usually consist of three phases: initial day escalation, build-up, and maintenance. Initial day escalation consists of escalating doses of the allergen until attainment of a prespecified minimum dose, usually 3–6 mg [43]. The build-up phase follows with incremental increases of allergen every 2 weeks until a maintenance dose is reached. This build-up can take nearly a year to achieve if daily maintenance doses of 2–4 grams are desired, which can be difficult if moderate to severe symptoms develop with up-dosing that can result in prolongation of the build-up phase. More recent studies have used lower maintenance doses of 300 mg, thus shortening the build-up time. As opposed to the fairly quick and simple increasing at-home time over several weeks to wear the fixed dose of EPIT patch for 24 hours, the dose escalation of OIT is more time intensive, with observation time in a medical office usually of 1–2 hours if no symptoms develop, with longer observation periods if they do. If more than two doses in a row are missed during the build-up phase, patients are recommended to return to have the current dose given under medical supervision or a decreased dose if 5–7 days are missed. Patients taking doses of OIT are instructed to take the dose as part of a meal and preferably in the evening, but not within 2 hours of bedtime, when a patient can be supervised for several hours by a parent/guardian. They are also instructed not to exercise or take a hot shower or bath within 3 hours of taking the dose and are warned about possible allergic reactions when patients are sick with upper respiratory infections or other potentially febrile illnesses. Thus, the possibly earlier and greater clinical desensitization seen with OIT vs. EPIT must be balanced by the relative increased safety and overall convenience of EPIT, and different patients and families will likely prefer different treatments depending on their child's school and sports commitments and treatment goals.

## Sublingual Immunotherapy

SLIT for IgE-mediated food allergy has also focused on single allergen treatment, including CM, peanut, tree nuts, and fresh fruits [5]. Studies to date have demonstrated clinical efficacy with a moderate allergen-specific desensitization. Two double-blind, placebo-controlled studies of peanut SLIT have been published. In a double-blind, placebo-controlled single-center study by Kim et al., 18 children age 1–11 years completed 12 months of SLIT followed by a DBPCFC [44]. At the end of 12 months, participants in the treatment group were able to ingest 20 times more peanut protein than placebo group (median mg ingested of 1710 mg vs. 85 mg in placebo group, $p = 0.011$). In a randomized, double-blind, placebo-controlled multi-center trial of patients aged 12–40 years, the CoFAR group was able to demonstrate responders in 14 of 20 (70%) participants in the active treatment arm after 44 weeks of SLIT compared to 3 of 20 (15%) of participants in the placebo arm ($p < 0.001$), with responders defined as those who could consume either a cumulative dose of 5 grams of peanut powder or a tenfold increase in the amount of peanut powder compared with baseline DBPCFC [45]. The median dose tolerated increased from 3.5 to 496 mg in the peanut SLIT responders. In the open-label extension of the study participants, 4 of 37 (10.8%) were fully desensitized to 10 g of peanut powder after 3 years of SLIT [46]. This group of participants was also able to achieve SU, defined as the ability to consume 10 grams of peanut powder, followed by an open-feeding of peanut without dose-limiting symptoms 8 weeks after discontinuing SLIT [44].

SLIT has also been noted to have a low side effect profile, with dosing symptoms limited to mostly oropharyngeal pruritus. In the CoFAR study, 59.9% of peanut SLIT doses were symptom-free during the study's first 44 weeks blinded phase, and with exclusion of oral-pharyngeal symptoms, 94.7% of doses were symptom free. Only 127 (1.1%) of the total 11,854 doses required treatment during the first phase, 125 of which required oral antihistamines only, with one requiring albuterol only, and the

**Table 18.2** Summary of the advantages and disadvantages among EPIT, OIT, and SLIT

| | Advantages | Disadvantages |
|---|---|---|
| Oral immunotherapy (OIT) | Can achieve larger doses (grams) than SLIT/EPIT (mg/μg)<br>Relatively greater efficacy after 1 year of treatment compared to SLIT/EPIT | Increased risk of systemic reactions<br>Not tolerated in 15–20% of subjects<br>Risk of inducing EoE (2–5%)<br>Less convenient than EPIT (time and labor-intensive dosing/up-dosing)<br>Compliance: ↑ risk of rxn with missed doses and with concomitant exercise/illnesses |
| Sublingual immunotherapy (SLIT) | Relatively fewer side effects than OIT: more local oropharyngeal symptoms but less systemic reactions | Only able to reach small doses (<10 mg daily)<br>Not tolerated in 5% of subjects<br>Relatively less efficacy than OIT |

other antihistamine and epinephrine. However, adherence over time in the CoFAR trial of adolescents and adults was difficult for participants, with greater than 50% of participants discontinuing therapy, resulting in limited interpretation of its effectiveness [45].

A summary of the advantages and disadvantages among EPIT, OIT, and SLIT is provided in Table 18.2.

## Clinical Approach to Use

As new treatment methods become available for IgE-mediated food allergy, clinicians must be comfortable with their use and which patient populations would be best served as possible candidates. As previously summarized, the most promising use of EPIT may be in younger patients, likely prior to the age of 11 years, and possibly most effective under 1–3 years of age, which will be studied in the EPIT in Toddlers with Peanut Allergy (EPITOPE) trial [29]. Prior confirmatory testing for an IgE-mediated food allergy as well as supporting clinical history consistent with a food allergy should be obtained as is discussed in more detail in other chapters of this book. In clinical practice as opposed to a clinical trial, an oral food challenge may not be required prior to initiation of EPIT.

Prior to initiation of any food allergy immunotherapy, medical providers must discuss patient and family goals of treatment. It should be discussed with families that the use of EPIT, or other therapies including OIT and SLIT, is unlikely to "cure" an individual of their IgE-mediated food allergy. Their primary indication for FDA approval will be as treatments that can induce a level of desensitization to the allergen of concern over that of SU and possibly true tolerance. This desensitized state may prevent patients from either any allergic reaction or possibly a less severe reaction due to a cross-contamination or other small accidental exposure to an allergen; its primary intended use would not allow a patient to eat a larger amount of an allergen. The decreased risk of any or a less severe reaction due to a cross-contamination may be very appealing to families, as the risk of these types of reactions can cause a significant amount of stress, and the ability to open the diet to these precautionary labeled products may improve patient and family quality of life [47]. Along this line, a recent study by Baumert et al. determined that achieving thresholds of 300 mg of peanut protein was clinically relevant, and that the risk for peanut-allergic patients who achieve this increased threshold via immunotherapy had a decreased risk of an allergic reaction due to cross-contamination of about 99% [48]. Longer treatment may result in SU or possibly tolerance, but longer-term follow-up of patients will be needed to determine this.

The length of treatment should also be discussed with patients and families prior to initiation. Studies to date show an improved response to treatment with prolonged use of EPIT, with significant increases in amount of peanut protein

tolerated with 24–36 months of total treatment; thus, families should be aware that in order to achieve effectiveness in most patients, EPIT (and other therapies) may need to be a longer-term therapy than just 12 months. The exact duration of treatment that will be recommended has yet to be determined, and it will vary from patient to patient, but it may be many years to a lifetime, especially in peanut-allergic patients since they less commonly outgrow their peanut allergy. Lastly, the side effect profile and relative convenience of EPIT compared to the other therapies under investigation must be discussed with families. As discussed earlier, EPIT is overall well tolerated, but local, mild skin irritation is common and should be expected. Discussing side effects prior to treatment initiation will likely better prepare a family of what to expect and may increase tolerability and compliance.

Once treatment with EPIT is initiated, follow-up may initially be quite frequent at 3–6-month intervals based on previous clinical trials, but this may eventually be spaced to 6–12 months unless concerns arise. Monitoring of effectiveness may include food-specific IgE and IgG4 levels to peanut as well as intermittent repeat skin prick testing. When a food challenge should occur to clinically assess effectiveness is also yet to be determined, but mechanistic data that may predict a response to therapy or signal when to perform a food challenge are being investigated.

Finally, it should be noted that none of these food immunotherapies are intended to replace the current standards of care for management of patients with food allergies. Patients who are placed on food immunotherapy should continue to read food product labeling for their allergens and always carry emergency medicines, such as epinephrine auto-injectors, at all times in case of an accidental ingestion leading to an allergic reaction. While these therapies, and the subsequent desensitization induced by them, may potentially reduce the risk of any allergic reaction or its severity from occurring upon accidental ingestion of a trigger food, the same precaution patients and families instituted prior to starting immunotherapy must remain intact.

## Future Directions and Conclusions

Given the initial clinical success of EPIT, new uses are being explored. Initial trials have been performed for peanut and CM as discussed above, but EPIT will likely extend to other common allergens, including egg and possibly other foods in the near future. EPIT's future use also extends beyond IgE-mediated food allergy. Initial studies in non-human models have found that after piglets were induced to have EoE, use of EPIT for 3 months reduced the median IgE and significantly reduced gastric mucosal lesions and eosinophil counts compared to placebo [49]. Similarly, studies in mice with induced esophageal eosinophilia demonstrated that EPIT reduced Th2 immunologic responses as well as esophageal eosinophilia ($p = 0.05$) [50].

A double-blind placebo-controlled, randomized pilot trial in human patients aged 4–17 years with milk-induced EoE to study the efficacy and safety of CM EPIT has been completed and awaiting publication of results; if results are promising, further phase trials may be performed [51]. Initial studies have also found utility of EPIT in vaccines, with evidence of reactivated vaccine-induced pertussis immunity with a single application of a patch containing detoxified pertussis toxin [52]. There has also been collaboration between DBV technologies and Nestle Health Science regarding use of EPIT as a standardized diagnostic tool in non-IgE-mediated CMA [53].

Future questions remain regarding EPIT and other forms of food immunotherapy, including targeting the optimal patients for its use, the length of treatment, and monitoring parameters. However, given EPIT's demonstrated efficacy, safety, and practicality of use in peanut- and CM-allergic patients, its future is promising as a treatment method for IgE-mediated allergy. Its use in other non-IgE mediated diseases, such as EoE and non-IgE-mediated food allergy, and its use in vaccinations are also promising future directions for this relatively new treatment modality.

## References


1. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1–58.
2. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. JAMA Netw Open. 2019;2(1):e185630.
3. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009;124(6):1549–55.
4. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6). pii: e20181235.
5. Scurlock AM, Jones SM. Advances in the approach to the patient with food allergy. J Allergy Clin Immunol. 2018;141(6):2002–14.
6. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Food and Nutrition Board; Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy. In: Oria MP, Stallings VA, editors. Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy. Washington, DC: National Academics Press; 2016.
7. Walkner M, Warren C, Gupta RS. Quality of life in food allergy patients and their families. Pediatr Clin N Am. 2015;62(6):1453–61.
8. Clark S, Espinola J, Rudders SA, Banerji A, Camargo CA Jr. Frequency of US emergency department visits for food-related acute allergic reactions. J Allergy Clin Immunol. 2011;127(3):682–3.
9. Fleischer DM, Perry TT, Atkins D, Wood RA, Burks AW, Jones SM, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. Pediatrics. 2012;130(1):e25–32.
10. Pautrizel R, Cabanieu G, Bricaud H, Broustet P. Allergenic group specificity & therapeutic consequences in asthma; specific desensitization method by epicutaneous route. La semaine des hopitaux: organe fonde par l'Association d'enseignement medical des hopitaux de Paris. 1957;33(22):1394–403.
11. Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, Benhamou PH, et al. Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and downregulates the allergen-specific response in sensitized mice. J Immunol (Baltimore, Md:1950). 2011;186(10):5629–37.
12. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol. 2017;139(4):1242–52.e9.
13. Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol. 2010;125(5):1165–7.
14. Rutault K, Agbotounou W, Peillon A, Thébault C, Vincent F, Martin L, et al. Safety of Viaskin milk epicutaneous immunotherapy (EPIT) in IgE-mediated cow's milk allergy (CMA) in children (MILES study). J Allergy Clin Immunol. 2016;137(2):AB132.
15. DBV technologies announces results from PHASE II study of Viaskin milk in milk- allergic patients [2018 press release]. 2/26/2018.
16. Dupont C, Bourrier T, de Blay F, Guénard-Bilbault L, Sauvage C, Cousin M-O, et al. Peanut epicutaneous immunotherapy (EPIT) in peanut-allergic children: 18 months treatment in the Arachild study. J Allergy Clin Immunol. 2014;133(2):AB102.
17. Sampson HA, Agbotounou W, Thébault C, Charles R, Martin L, Yang WH, et al. Epicutaneous immunotherapy (EPIT) is effective and safe to treat peanut allergy: a multi-national double-blind placebo-controlled randomized Phase IIb trial. J Allergy Clin Immunol. 2015;135(2):AB390.
18. Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. JAMA. 2017;318(18):1798–809.
19. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130(6):1260–74.
20. Sampson HA, Agbotounou W, Thébault C, Ruban C, Martin L, Sussman GL, et al. Enhanced efficacy and confirmed safety of a two-year epicutaneous immunotherapy (EPIT) treatment of peanut allergy with Viaskin® peanut: the continuation of the Vipes Phase IIb randomized controlled trial (RCT). J Allergy Clin Immunol. 2016;137(2):AB408.
21. Brown-Whitehorn T, Sampson H. Sustained unresponsiveness following long-term epicutaneous immunotherapy (EPIT) with VIASKIN peanut: results of the OLFUS-VIPES Phase IIb study. EAACI congress 2018, Munich, 26–30 May 2018, 2018.
22. DBV technologies announces initiation of the Phase III study of Viaskin peanut for the treatment of peanut allergy children [2015 press release]. www.dbv-technologies.com, 12/7/2015.

23. DBV technologies announces topline results of Phase III clinical trial in peanut-allergic patients four to 11 years of age [2017 press release]. www.dbv-technologies.com, 10/20/2017.
24. DBV technologies announces completion of enrollment in Phase III extension study of Viaskin peanut [2017 press release]. www.dbv-technologies.com, 8/29/2017.
25. DBV technologies announces expansion of clinical program of Viaskin peanut for the treatment of peanut allergy [2016 press release]. www.dbv-technologies.com, 8/1/2016.
26. DBV technologies announces completion of blinded period in REALISE study of Viaskin peanut [2017 press release]. www.dbv-technologies.com, 10/12/2017.
27. DBV technologies announces positive topline safety results from REALISE Phase III trial of Viaskin peanut for the treatment of peanut-allergic patients [2017 press release]. www.dbv-technologies.com, 11/20/2017.
28. Jones SM, Agbotounou WK, Fleischer DM, Burks AW, Pesek RD, Harris MW, et al. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: a phase 1 study using the Viaskin patch. J Allergy Clin Immunol. 2016;137(4):1258–61.e10.
29. DBV technologies initiates Phase III study of Viaskin peanut in peanut-allergic patients one to three years of age [2017 press release]. www.dbv-technologies.com, 8/2/2017.
30. Turjanmaa K, Darsow U, Niggemann B, Rance F, Vanto T, Werfel T. EAACI/GA2LEN position paper: present status of the atopy patch test. Allergy. 2006;61(12):1377–84.
31. Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111(6 Pt 3):1601–8.
32. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol. 2009;124(2):286–91.e1–6.
33. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297–304.
34. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122(6):1154–60.
35. Narisety SD, Skripak JM, Steele P, Hamilton RG, Matsui EC, Burks AW, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. J Allergy Clin Immunol. 2009;124(3):610–2.
36. Wood RA. Food allergen immunotherapy: current status and prospects for the future. J Allergy Clin Immunol. 2016;137(4):973–82.
37. Begin P, Winterroth LC, Dominguez T, Wilson SP, Bacal L, Mehrotra A, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. Allergy Asthma Clin Immunol. 2014;10(1):1.
38. Wood RA. Oral immunotherapy for food allergy. J Investig Allergol Clin Immunol. 2017;27(3):151–9.
39. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128(1):3–20.e6; quiz 1–2.
40. Petroni D, Spergel JM. Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy. Ann Allergy Asthma Immunol. 2018;120(3):237–40.e4.
41. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014;113(6):624–9.
42. Echeverria-Zudaire LA, Fernandez-Fernandez S, Rayo-Fernandez A, Munoz-Archidona C, Checa-Rodriguez R. Primary eosinophilic gastrointestinal disorders in children who have received food oral immunotherapy. Allergol Immunopathol (Madr). 2016;44(6):531–6.
43. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233–43.
44. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127(3):640–6.e1.
45. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131(1):119–27.e1–7.
46. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, et al. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol. 2015;135(5):1240–8.e1–3.
47. Taylor SL, Baumert JL. Cross-contamination of foods and implications for food allergic patients. Curr Allergy Asthma Rep. 2010;10(4):265–70.
48. Baumert JL, Taylor SL, Koppelman SJ. Quantitative assessment of the safety benefits associated with increasing clinical peanut thresholds through immunotherapy. J Allergy Clin Immunol Pract. 2018;6(2):457–65.e4.
49. Mondoulet L, Kalach N, Dhelft V, Larcher T, Delayre-Orthez C, Benhamou PH, et al. Treatment of gastric eosinophilia by epicutaneous immunotherapy

in piglets sensitized to peanuts. Clin Exp Allergy. 2017;47(12):1640–7.
50. Mondoulet L, Dioszeghy V, Larcher T, Ligouis M, Dhelft V, Puteaux E, et al. Epicutaneous immunotherapy (EPIT) blocks the allergic esophago-gastro-enteropathy induced by sustained oral exposure to peanuts in sensitized mice. PLoS One. 2012;7(2):e31967.
51. ClinicalTrials.Gov. Milk patch for eosinophilic esophagitis (SMILEE) 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02579876?term=SMILEE&rank=1
52. Gavillet BM, Mondoulet L, Dhelft V, Eberhardt CS, Auderset F, Pham HT, et al. Needle-free and adjuvant-free epicutaneous boosting of pertussis immunity: preclinical proof of concept. Vaccine. 2015;33(30):3450–5.
53. DBV Technologies. Pipeline – diagnostics. Available from: https://www.dbv-technologies.com/pipeline/

# 19 Emerging Food Allergy Therapies

Luanna Yang and Edwin H. Kim

## Introduction

IgE-mediated food allergy is a rapidly growing health problem affecting millions of individuals, both children and adults alike, worldwide. In the United States alone it is estimated that 15 million Americans, of which 5.9 million are children under 18 years of age, are affected by food allergy. Epidemiologic studies suggest that there has been an increase in prevalence over the past two decades that mirrors the increase in other atopic diseases like atopic dermatitis [1–5].

Food allergy is thought to be caused by a loss of oral tolerance or a delay in the development of oral tolerance, or both. There are likely genetic and environmental factors that play a role in the development of atopic disease [6, 7]. Current standard therapy for the management of IgE-mediated food allergies involves strict avoidance of the offending food(s) and immediate treatment of allergic reactions, including the use of epinephrine, due to accidental ingestion. This can be anxiety provoking to patients and their families and quality of life can be significantly affected [8, 9]. Prevention and treatment of allergic reactions can also place a financial burden on patients, families, and society (estimated at $24.8 billion per year) as the maintenance of strict avoidance can prove difficult [10]. Unfortunately, there are no FDA-approved treatments for food allergy to date and significant resources are being directed towards finding potential preemptive treatments and cure [11–13].

In this chapter, we first focus on reviewing food-allergen-specific treatment techniques that are under clinical investigation. Several types of immunotherapy are actively being studied for the treatment of food allergies, including oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). As OIT and EPIT have been covered in depth in prior chapters, the current chapter will begin with a focus on SLIT. A number of other food-specific therapies will also be discussed including peptide-based vaccines, recombinant allergen vaccines, allergen DNA vaccinations, and transgenic plants, which have less supportive clinical study data available but which present exciting possible treatment modalities that warrant further investigation. Finally, non-allergen-specific therapies including anti-IgE treatment, traditional Chinese medicine, and probiotics will then be reviewed.

L. Yang
University of North Carolina at Chapel Hill, Department of Pediatrics, Division of Allergy, Immunology, and Rheumatology, Chapel Hill, NC, USA

E. H. Kim (✉)
University of North Carolina at Chapel Hill, Department of Medicine, Division of Rheumatology, Allergy and Immunology, Chapel Hill, NC, USA
e-mail: edwinkim@email.unc.edu


R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_19

## Concepts of Desensitization, Sustained Unresponsiveness, and Tolerance in Immunotherapy

Although allergen avoidance is an effective form of management of food allergy, it is not equivalent to a true treatment or cure. To mitigate the risk of reacting to allergens, several investigational therapies are currently being studied. Currently, the most-studied form of disease-modifying treatment is allergen immunotherapy, which for the purposes of treatment in food allergies, is administered via three main routes: sublingual (SLIT), oral (OIT), and epicutaneous (EPIT) [12–15]. Treatment regimens consist of daily, incremental doses of whole-allergen extracts which are administered over the course of months to several years (Fig. 19.1). The over-arching goal of immunotherapy is to induce sustained immunologic and clinical tolerance to an allergen following cessation of therapy.

In order to evaluate immunotherapy and other emerging therapies for food allergy, it is important to understand the concepts of clinical desensitization, sustained unresponsiveness, and tolerance. *Desensitization* is defined as a temporary increase in the dose threshold required to trigger an allergic reaction while receiving active therapy. Desensitization may confer a level of protection in case of accidental ingestion but is usually achieved only after months of therapy and is dependent upon continued treatment. Loss of desensitization is not unusual, either in food allergy therapy or in the treatment of other allergic diseases, such as environmental allergies or hymenoptera venom allergy. The ideal therapy would, of course, be curative and allow an individual to ingest any amount of allergen without symptoms even in the presence of activating factors (such as acute illness or exercise). This is termed *tolerance*, which is not thought to depend upon continued allergen exposure. Clinical studies often assess whether an increased threshold of reactivity to an allergen is lost during a period off therapy or whether a temporary remission or *sustained unresponsiveness* (SU) can be maintained. Achieving SU appears to require years of therapy and has only been evaluated and identi-

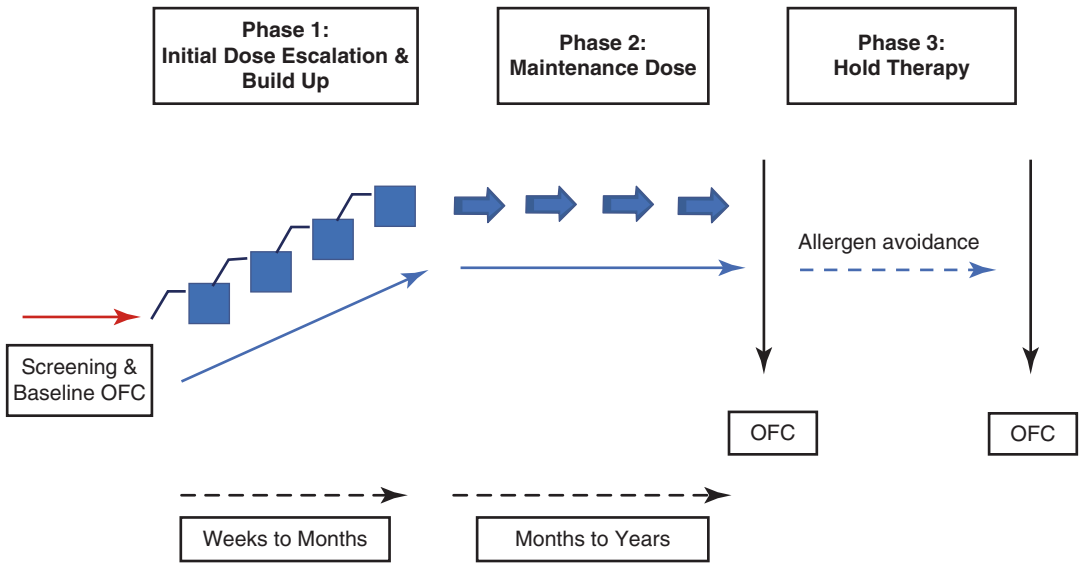



**Fig. 19.1** General food immunotherapy administration protocol used in clinical studies. Subjects are first screened and have a baseline oral food challenge (OFC) performed to verify allergy and evaluate for threshold reactivity. Treatment begins with the build-up phase (+/− initial dose escalation with OIT) involving daily home dosing with observed dosage increases every 1–2 weeks. Once the maintenance dose is achieved, dosing continues for months to years and concludes with an OFC to evaluate for desensitization. Certain protocols then include a period of treatment avoidance lasting up to several months followed by an OFC to evaluate for sustained unresponsiveness

fied in subsets of treated individuals [16–19]. The biologic mechanisms underlying desensitization, sustained unresponsiveness, and tolerance are not well understood, and the achievement of true clinical and immunologic tolerance following active treatment of food allergy requires further investigation [12, 17, 20].

## Allergen-Specific Immunotherapies

### Sublingual Immunotherapy

The sublingual route of allergen administration is of significant interest given its success in achieving tolerance in individuals suffering from environmental allergies [21]. SLIT in food allergies involves administration of an allergen extract in liquid form to the sublingual space where it is held for 2–3 minutes to promote absorption and then swallowed. Dosing protocols for SLIT do not include the initial multi-dose escalation day commonly seen in OIT protocols. Rather, subjects begin treatment in the biweekly dose escalation phase receiving their first dilution of SLIT under clinical observation. If the dose is well tolerated, then subjects repeat the dose daily at home with dose escalations every 2 weeks until maintenance dosing is reached. Some SLIT protocols allow for weekly updosing and for some updosing to be performed at home, which offers a significant advantage over OIT in decreasing the time and cost associated with frequent clinic visits. This type of dosing schedule is in contrast to EPIT where only a single dose patch is required. The dose is instead controlled by a prescribed patch application time which is gradually increased over a few weeks until application for 24 hours/day is reached and only intermittent clinical monitoring is needed. Notably, dosing in SLIT is usually on the order of micrograms to milligrams, which is higher than with EPIT but much lower than with OIT dosed in milligrams to grams (Table 19.1). Maintenance SLIT therapy

**Table 19.1** Comparison of food immunotherapies under current clinical investigation

| | OIT | SLIT | EPIT |
|---|---|---|---|
| Allergens studied | Peanut, milk, egg, wheat, and multi-food regimens | Peanut, milk, hazelnut, peach | Peanut, milk |
| Observed dosing | Updosing under observation | Updosing under observation | Initiation and periodically afterwards |
| Typical maintenance dose | 300–4000 mg | 2–7 mg | 50–500 μg |
| Typical protocol | Initial dose escalation over 1–2 days, then build-up with dose increases every 2 weeks until maintenance | Build-up with dose increases every 1–2 weeks until maintenance | Increasing patch application duration every 1–2 weeks until 24 hrs/day maintenance administration |
| Restrictions around dosing | Administer with food; avoid physical activity for 2 hours; do not take within 2 hours of bedtime; hold during acute illness | No eating for 30 minutes following dosing; hold during acute illness | Administer to intact skin; hold during acute illness |
| Immune modulation | ↑ Food-specific IgG4<br>↓ Food-specific IgE<br>↓ Skin testing and basophil reactivity | ↑ Food-specific IgG4<br>↓ Food-specific IgE<br>↓ Skin testing and basophil reactivity | ↑ Food-specific IgG4<br>↓ Food-specific IgE<br>↓ Skin testing |
| Common side effects | Gastrointestinal (abdominal pain, nausea), oral (local) | Oropharyngeal (local) | Skin (local) |
| Advantages | Higher reaction thresholds achieved compared to SLIT and EPIT | Moderate reaction thresholds, less frequent adverse effects | Simple administration, no taste aversion, strong safety profile |
| Disadvantages | Frequent office visits for updosing, common GI adverse events, risk of EoE, restrictions around dosing | Wider range of responses than OIT, medicinal taste, lack of phase III studies | Lower median reaction thresholds than OIT and SLIT after 12 months |

then continues for a period of months to years and has been associated with clinical desensitization and changes in antigen-specific immune responses [15].

It is believed that SLIT works through allergenic interaction with Langerhans cells, which are the major dendritic cell population in oral mucosal tissues. Evidence suggests that allergen binding of oral Langerhans cells displays saturation kinetics that are dependent on both the allergen dose and exposure time, which is further supported by prior studies performed in mouse models and humans evaluating the safety and efficacy of sublingual immunotherapy in the treatment of allergic rhinitis [22–24]. Following antigen binding, Langerhans cells migrate to local lymph nodes where interactions with T-cells promote immune modulation through enhanced production of immunosuppressive cytokines, TGF-β and IL-10, and induction of Tregs [25].

The study of SLIT in clinical trials for the treatment of food allergy has primarily focused on peanut, although a few other foods including milk, hazelnut, peach, and kiwi have been evaluated with promising results [26–29]. In a multicenter, randomized, double-blind, placebo-controlled trial looking at the efficacy of 44 weeks of peanut SLIT, 14 of 20 subjects (70%) were able to consume either 5 g or had at least a tenfold increase in the amount of peanut powder they could consume compared to baseline [29]. Subjects were subsequently followed in a long-term extended maintenance phase where SLIT demonstrated a good safety profile. More than 98% of doses were administered without reported side effects aside from mild oropharyngeal tingling/itching. No doses of epinephrine were required. Immunological changes suggesting modulation of the allergic response including decreased peanut-specific basophil activation and skin prick testing persisted for the duration of study [14].

These results suggest that SLIT therapy may be an efficacious and safe treatment option for food allergy in the future, but larger clinical trials are still ongoing to try to answer additional questions regarding its use. For now, SLIT remains an investigational therapy and is not yet available to the public in the United States.

## Sublingual Versus Oral Immunotherapy

Studies looking at direct comparisons of OIT versus SLIT in terms of efficacy and safety are limited. A retrospective comparison of SLIT versus OIT in peanut allergy in children found more significant changes in peanut-specific IgE and IgG4 levels in those treated with OIT. These patients were also three times more likely to pass a desensitization food challenge compared to those undergoing SLIT therapy [30].

A double-blind, placebo-controlled study evaluated 21 patients with confirmed peanut allergy who were randomized to either peanut SLIT with placebo OIT or peanut OIT with placebo SLIT. Following dose build-up, the daily maintenance dose (3.7 mg of peanut protein for SLIT and 2000 mg of peanut protein for OIT) was continued for 12 months. Oral food challenges were performed after 6 and 12 months of maintenance therapy at which time the subjects and investigators were unblinded. Those individuals that completed the 12-month challenge with mild or no symptoms discontinued therapy for 4 weeks and were then re-challenged. Subjects who were symptomatic at the 12-month challenge proceeded to an unblinded study phase where they were offered peanut OIT or SLIT for another 6 months. Subjects that were able to consume 5–10 grams of peanut protein prior to developing symptoms continued their prior therapy (either SLIT or OIT) for 6 more months. Those subjects that developed symptoms at less than 5 grams of peanut protein continued their prior treatment and had either active OIT or SLIT added on. At the end of this unblinded phase, a cumulative 10,000 mg oral food challenge was performed and those who successfully completed the challenge with minimal or no symptoms were taken off therapy for 4 weeks before being re-challenged.

Out of 21 enrolled subjects, 16 completed 12 months of therapy followed by an OFC. All subjects, regardless of treatment group, demonstrated increased challenge thresholds, and seven subjects (78%) of the active SLIT group and seven subjects (100%) of the active OIT group

exhibited at least a tenfold increase in the amount of peanut protein they could tolerate compared to baseline. However, the OIT group had a greater threshold increase compared to the SLIT group (141-fold versus 22-fold) after 12 months of therapy. Following unblinding, all nine patients on active SLIT continued on their therapy and had OIT added on, but two were unable to complete OIT build-up due to side effects. The other seven individuals completed 6 months of active OIT add-on treatment and were re-challenged, demonstrating a significantly increased tolerated dose (median OFC dose of 10,000 mg) compared to the amount tolerated following 12 months of SLIT alone. Out of the patients on active OIT, one individual passed the OFC at the end of 12 months and was taken off therapy, three individuals stayed on OIT alone for 6 more months, and three individuals continued OIT and had active SLIT added on for 6 months. All three patients that were on extended OIT therapy alone passed the 10,000 mg challenge at the end of treatment. For those on OIT with SLIT added on, a median tolerated OFC cumulative dose of 10,000 mg was achieved which was not significantly different compared to the amount tolerated following 12 months of OIT alone.

Although this study is limited in its sample size, the results suggest that both OIT and SLIT are effective at inducing desensitization with a greater level of desensitization achieved with OIT compared to SLIT. However, the potential advantage in efficacy afforded by OIT should be weighed against safety concerns. In this study, the proportion of doses administered that were associated with adverse reactions was significantly higher in the OIT versus the SLIT group (43% versus 9% of doses, respectively). A total of five doses of epinephrine were required to treat systemic reactions in four patients in the active OIT group while none were needed in the SLIT group [13, 31].

The dosing and efficacy of SLIT can be limited by the volume that can be held in the small sublingual space, but at the same time, lower dosing can confer the advantages of better tolerability and safety while still maintaining an acceptable level of desensitization [32]. These data support that SLIT, with its balance of safety and efficacy, may provide a viable alternative to OIT.

## Peptide-Based Vaccines

One disadvantage of immunotherapy using whole native allergens in the treatment of food allergy (as is the case with OIT, SLIT, and EPIT) is the risk of anaphylaxis due to the food allergen binding and cross-linking IgE. By utilizing small peptide fragments containing short (usually ~8–16 amino acids in length), synthetic peptides made up of allergen-derived T-cell epitopes, one theoretically avoids the risk of cross-linking IgE on mast cells or basophils which can elicit immediate-type adverse reactions [33]. A T-cell epitope is the specific part of an antigen or allergen that is immunogenic and antigenic, so these peptides are still able to stimulate T-cell responses and lead to suppression and/or downregulation of the Th2 pathway, which is the primary goal of allergen immunotherapy. Peptide-based food allergy vaccination is a proposed method of treatment of food allergies that is still under early investigation but may offer an improved safety profile compared with classic immunotherapy techniques [34, 35].

In order to manufacture a peptide vaccine, all potential T-cell epitopes must first be identified. Epitope mapping requires the ability to sequence an allergen and to identify allergen-specific T-cell lines from large donor cohorts. These T-cell lines are screened for reactivity against synthetic peptides modeled after the target allergen. Once identified, precise epitope sequences are evaluated for their ability to stimulate T-cells, and those with the strongest immunogenicity are selected for immunotherapy. Peptide modification is sometimes required to improve solubility and stability in manufacturing of the final product. The efficacy of peptide immunotherapy has been demonstrated in studies of perennial and bee venom allergies, but its use in food allergy has not been widely explored [36–38].

Yang et al. investigated the therapeutic potential of peptide immunotherapy using synthetic peptides manufactured from three epitope

sequences that were identified in a previous study in a BALB/c mouse model of allergy to ovalbumin (Gal d2), which is one of the major allergens associated with egg allergy [39, 40]. In this study, mice were sensitized to ovalbumin with repeated oral feedings and then stratified into treatment or placebo groups. The treatment groups were given single synthetic peptide doses (AG-15, AI-15, or SL-15) or a mixture containing all three peptides. Following a three-week treatment period of subcutaneous immunotherapy where injections were administered three times a week, the mice were given oral challenges with high doses of ovalbumin to trigger anaphylaxis. Mice given multiple epitope-containing peptides achieved lower anaphylaxis scores and lower serum histamine and OVA-specific IgE levels compared to single-peptide treated or placebo-treated mice. The co-administration of three OVA T-cell epitopes also produced significantly higher mRNA expression of FOXP3 and TGF-beta in intestinal tissues compared to placebo or single-peptide treated mice. FOXP3 expressing T-cells are known for their inhibitory effects on Th2-allergic responses while TGF-beta inhibits effector T-cells and acts as a regulator in the induction of FOXP3 expression in regulatory T-cells. This suggests a potential modulatory effect of the T-cell response [40]. The authors concluded that ovalbumin peptide immunotherapy utilizing the administration of multiple T-cell epitopes led to suppressive effects in egg allergy in a mouse model that may be used to better understand mechanisms of peptide immunotherapy in food allergy in humans.

Similar research is being conducted in peanut allergy where Ara h 1, Ara h 2, and Ara h 3 are the major peanut allergens that have been identified as potential targets for peptide immunotherapy. Ongoing research into the identification of T-cell epitopes in these peanut allergens is crucial to isolating peptide targets for eventual use in peptide-based immunotherapy [41–44].

## Recombinant Allergen Vaccines

The use of recombinant native allergens has also been considered for use in immunotherapy for food allergy, but the major concern in their use is the risk of inducing severe hypersensitivity reactions due to reactivity of the allergens with IgE. The best designed recombinant food allergens have a decreased or eliminated ability to bind IgE while retaining the ability to stimulate T-cell responses that is comparable to native proteins. The use of recombinant allergens in immunotherapy has the potential to induce desensitization with shorter courses of treatment as higher doses can be administered with little or no dose escalation required. In the production of recombinant allergens, IgE reactivity is mitigated through denaturation of the recombinant wild-type allergen, production of recombinant fragments, or formation of mosaics through reassembly of allergen fragments that leads to reduced IgE binding and decreased allergenic potential [45]. On the other hand, the allergen T-cell epitopes are preserved, which allows for IgG antibody production and promotion of regulatory and Th1 immunomodulatory effects. Support for the use of recombinant allergens in immunotherapy primarily stems from prior studies looking at the safety and efficacy of their use in treatment of environmental allergies to various allergens including Birch and Timothy grass pollens [46, 47].

Ara h 1, Ara h 2, and Ara h 3 are three major peanut allergens whose T-cell epitopes have been mapped out using synthetic peptides and sera from a large cohort of peanut-allergic individuals. Additionally, the amino acid sequences needed for IgE binding by these epitopes have been identified, allowing for the production of recombinant hypoallergenic variants of Ara h 1, Ara h 2, and Ara h 3 in *Escherichia coli*. In vitro studies have shown that modified peanut allergens exhibit decreased IgE binding compared to wild-type allergens while still retaining the ability to stimulate T-cell proliferation [48, 49].

Bacterial adjuvants are potent stimulators of the Th1 immune response and can be co-administered with hypoallergenic peanut proteins to help bolster the desensitization effect. The efficacy and safety of this technique has been explored in several studies. The effects of

three times weekly subcutaneous administration of heat-killed *Listeria monocytogenes* (HKLM) with a combination of three modified peanut allergens (mAra h 1, mAra h 2, and mAra h 3) over a period of 4 weeks was investigated by Li, et al. in a murine model of peanut allergy. Mice given the combination of modified allergens plus HKLM not only had reduced serum histamine and peanut-specific IgE levels, but when undergoing a peanut challenge, they had decreased incidence and severity of anaphylaxis compared to placebo mice. The incidence and severity of anaphylaxis in mice treated with mAra h 1–3 proteins alone were also reduced but to a lesser degree than the mAra h 1–3 plus HKLM group [50].

Another study utilized heat-killed *Escherichia coli* that produced engineered Ara h 1, 2, and 3 proteins (HKE-MP123) and administered this mixture rectally to mice and, following an intragastric peanut challenge, found that mice treated with HKE-MP123 exhibited significantly reduced plasma histamine levels and anaphylactic symptoms compared to sham-treated mice. This protective effect lasted up to 10 weeks after treatment was discontinued [51].

Given these encouraging results, a suspension comprised of three recombinant peanut allergens (Ara h 1, 2, and 3) encapsulated within inactivated *E. coli* was developed for human use and named EMP-123. Its safety and efficacy were assessed in a phase I non-randomized, open-label trial. EMP-123 was given rectally in weekly dose escalations from 10 to 3063 μg over 10 weeks in 10 peanut-allergic adults followed by three biweekly doses of 3063 μg. Of the 10 patients, 5 patients (50%) experienced adverse reactions severe enough to prevent them from completing the trial. The other five patients experienced mild or no symptoms. Assessing immunologic differences between the two patient groups revealed that that median baseline peanut-specific IgE and Ara h2-specific IgE levels were significantly higher in those individuals who were unable to complete the trial. Due to the high frequency of adverse reactions, the trial authors concluded that additional modifications to the allergens or dosing regimen would be needed [52].

## DNA-Based Vaccines

Another distinct therapeutic approach is to completely discount the administration of protein altogether in favor of allergen exposure in the form of DNA. The concept of vaccinations using genetic material came about from studies showing that injections with a plasmid DNA (pDNA) vector could induce humoral and cellular responses to the encoded antigen. The pDNA sequence is taken up by antigen-presenting cells (APCs) which transcribes and translates the antigen-specific DNA into protein product and presents it on the cell surface to T-cells via MHC complexes [53, 54]. Since genetic vaccination preferentially induces a Th1 immune response, its use in allergic disease has been investigated in different mouse models since a weighted imbalance towards a Th2 immune response has been thought to be a major causative factor in the development of atopic disease [55, 56].

In a murine model, oral gene delivery using Ara h 2 pDNA complexed with chitosan, which is a nonimmunogenic polysaccharide that improves gene adhesion and transport in the gut, led to gene expression in intestinal epithelium. Immunized AKR mice showed a significant reduction in peanut-induced hypersensitivity symptoms following a period of sensitization and subsequent challenge with Ara h 2 protein compared to controls as observed using specific symptom measurements of anaphylaxis, serum peanut-specific IgE levels, and serum histamine levels. The study authors concluded that chitosan-pDNA nanoparticles could represent an oral option for the prevention of the development of food allergies [57]. In another study by Li et al., different mouse strains were administered intramuscular injections of plasmid DNA encoding Ara h 2. Following three weeks of immunization, injections of Ara h 2 elicited anaphylactic reactions in C3H/HeJ mice while immunized ARK/J and BALB/c mice remained asymptomatic. These studies highlight concerns that there is a strain-dependent response to pDNA-based immunizations which may translate to significant interindividual variations in efficacy in the treatment of food hypersensitivity in humans [58].

Additionally, results from human trials using DNA-based vaccines have suggested somewhat disappointing immunomodulatory effects [59].

In an attempt to enhance the efficacy of DNA vaccines, lysosomal-associated membrane protein-1 (LAMP-1) has been included in DNA plasmids to elicit enhanced immunomodulatory effects via greater production of antibodies and cytokines. In a study of Japanese Red Cedar (JRC) allergy, the DNA sequence of either CryJ1 or CryJ2, which are the immunodominant allergens to JRC, were fused to LAMP-1 and administered to BALB/c mice. Resulting data showed high IgG2a and low IgE titers as well as high IFN-gamma production, suggesting an enhanced Th1 response [60]. This suggests that LAMP-DNA vaccines may have therapeutic potential in the treatment of allergic disease. An ongoing phase 1 randomized, placebo-controlled trial is currently underway to assess the safety and efficacy of ASP892 (ARA LAMP Vax), a multivalent peanut (Ara h1, h2, h3) LAMP-DNA plasmid vaccine, in peanut-allergic adults (NCT02851277).

### Transgenic Plants

One proposed method of combating the increasing incidence of food allergy is through reduction or abolishment of allergen expression in plants, which has been made possible with advances in biotechnology. In 1996, using antisense RNA technology, the expression of allergenic proteins found in seeds from several transgenic rice plants was found to be significantly lower than wild-type rice [61]. Herman et al. was able to completely suppress the accumulation of Gly m Bd 30 K, which is the major identified allergen in soybean, in soybean plants and their seeds through the use of transgene-induced gene silencing. There were no observed differences in composition, development, structure, or phenotype in the transgenic plants compared to controls [62]. In another study, RNA interference (RNAi) technology was used to decrease expression of the allergenic protein Lyc e 3 in tomatoes. There was decreased skin reactivity with prick-to-prick skin testing using fruits harvested from first- and second-generation transgenic plants compared to wild-type controls, suggesting decreased allergenic potential [63].

But the difficulty with attempts to produce hypoallergenic plants, even with utilization of the aforementioned approaches, lies in the fact that several allergenic proteins are oftentimes involved in IgE binding. Alteration in enough allergens to make the target food less likely to cause an allergic reaction may affect aspects of plant health and viability or even characteristics that would make the food less palatable, like taste and texture [64].

## Nonspecific Allergen Immunotherapies

### Anti-IgE

Non-allergen-specific approaches to the treatment of food allergy have been discussed, including the use of anti-human IgE IgG1 antibodies, which can be advantageous over traditional immunotherapies in being able to treat individuals who may be allergic to multiple foods or possess allergies to foods for which targeted immunotherapy has not yet been studied. Anti-IgE therapy is based on the concept that anti-IgE antibodies bind to the constant region of IgE molecules which prevents their binding to high-affinity FcεRI receptors on the surfaces of mast cells and basophils. This leads to a reduction in free IgE molecules and inhibition of IgE-mediated hypersensitivity reactions [12, 32, 46].

The first study looking at anti-IgE therapy in food allergy was a double-blind, placebo-controlled trial using TNX-901, a humanized IgG1 monoclonal antibody against IgE, performed by Leung, et al. in 2003. Results showed that subcutaneous administration of TNX-901 every 4 weeks for 4 doses in subjects with confirmed peanut allergy increased the mean reactivity threshold to peanut during oral challenge compared to placebo in a dose-dependent manner; however, the increase was only statistically significant in the group receiving the highest monthly dosing of 450 mg. Additionally, about 25% of treated subjects in the

450 mg monthly group showed no change in the threshold dose, suggesting that a subset of patients may not benefit from anti-IgE therapy or would require more frequent or higher doses to see a protective benefit [65].

Further studies using TNX-901 were discontinued following an agreement between pharmaceutical companies involved in developing anti-IgE therapies [66]. Subsequent studies utilized omalizumab (Xolair), a humanized monoclonal anti-IgE antibody that has shown promise in human studies of asthma and has been approved for treatment of severe, persistent allergic asthma. A phase II, double-blind, placebo-controlled trial performed in 2011 looked at the use of omalizumab in the treatment of peanut allergy. The study intended to randomize 150 subjects with confirmed peanut allergy and to compare changes in peanut tolerability thresholds before and after therapy. Unfortunately, the study was terminated early due to two severe anaphylactic reactions that occurred during the initial screening and enrollment process before omalizumab was actually initiated. Prior to trial discontinuation, 26 subjects had been randomized to omalizumab or placebo with 14 subjects completing 24 weeks of therapy followed by a double-blind, placebo-controlled oral peanut challenge. Four (44.4%) of omalizumab-treated subjects could tolerate at least 1 gram of peanut flour following completion of therapy compared to one (20%) placebo-treated subject. A large proportion of subjects did not achieve the primary endpoint, experiencing reactions at <1 gram of peanut flour; however, there was a shift towards greater peanut tolerability in omalizumab-treated subjects compared to those receiving placebo [67].

In addition to its limited clinical efficacy data as a monotherapy, anti-IgE therapy poses some significant disadvantages including the need for regular clinic administered injections and the high cost associated with treatment. Given the recent dramatic increase in studies examining immunotherapy protocols for food allergies, the use of anti-IgE therapy as an adjunct to other food-specific therapies has gained increasing attention [66]. In particular, administration of omalizumab with OIT may offer protective effects against IgE-mediated reactions, allowing for safer dose escalation and better treatment tolerability. In a randomized, placebo-controlled study, 37 peanut-allergic children were initially treated with either 12 weeks of omalizumab or placebo. They then underwent rapid one-day desensitization up to a cumulative dose of 490.5 mg of peanut protein, which represented a dramatic increase from the 6 mg maximum dose more typical of OIT protocols. The highest tolerated dose was administered daily at home followed by weekly updosing up to 2000 mg of peanut protein rather than the usual biweekly dosing schedule. The anti-IgE study drug was then discontinued and subjects continued on 2000 mg of peanut protein daily, if tolerated. An oral food challenge with a cumulative dose of 4000 mg peanut protein was performed 12 weeks following anti-IgE study drug discontinuation and, if tolerated, the 4000 mg daily dose was continued thereafter. The median peanut dose tolerated during rapid one-day desensitization was 250 mg for omalizumab-treated patients compared to 22.5 mg for placebo-treated patients. There were 23 out of 29 (79%) subjects in the omalizumab group that tolerated 2000 mg of peanut protein following omalizumab discontinuation compared to one out of eight subjects (12%) on placebo, which was a statistically significant difference. All 23 subjects on omalizumab passed the 4000 mg open challenge compared to only one subject on placebo. This suggests that the addition of omalizumab may allow for rapid OIT desensitization and offer protective benefits up to 6 weeks after the drug is discontinued [68]. Several other studies on the use of omalizumab with desensitization protocols to various foods have been performed with encouraging results [69–72], but one important question to consider is whether the rate of adverse reactions with continued OIT increases at some point after omalizumab has been discontinued. In a study by Nadeau et al., there were two reported adverse reactions graded "moderate" in severity and treated with epinephrine autoinjectors following omalizumab cessation in two patients (out of a total of 11) who were receiving cow's milk maintenance OIT [70]. This is a concern that requires further investigation.

## Traditional Chinese Medicine

Herbs and herbal mixtures have been utilized in traditional Chinese medicine for centuries for the treatment of various ailments. Western countries have also developed interest in the use of alternative or complementary therapies including herbs for different diseases, such as asthma, but no prior research into the use of herbal remedies in food allergy had been conducted until relatively recently [46, 73].

The first study on the use of herbs to treat food hypersensitivity in a murine model of peanut allergy utilized Food Allergy Herbal Formula-1 (FAHF-1), which is a formulation containing 11 different herbs. Mice were started on 7 weeks of therapy with FAHF-1 after being sensitized to peanut. Following therapy, the mice were challenged to peanut and had anaphylactic symptoms, body temperatures, plasma histamine, and peanut-specific IgE levels measured. Results showed that FAHF-1 completely blocked peanut-induced anaphylactic symptoms and reduced mast cell activation and histamine release. Serum IgE levels were also significantly reduced compared to controls. There were no observed toxic effects on the liver or kidneys, even at high doses [46, 74].

Following this study, FAHF-1 was reformulated to a nine-herb regimen after two herbs were removed to improve safety as they had potentially toxic properties if processed incorrectly. This simplified formula was named FAHF-2, and its safety was demonstrated in a study where mice were administered 24 times the effective daily dose. Several blood tests were obtained 2 weeks after the dose was given with no abnormalities noted in blood counts and renal or hepatic function. Histology of all major organs was normal as well [75]. The efficacy of FAHF-2 was then assessed using a murine model of multiple food allergy. Mice were orally sensitized to peanut, codfish, and egg and given daily orally administered FAHF-2 for 7 weeks afterwards. Following the completion of therapy, the mice underwent separate oral food challenges with peanut, codfish, and egg. Mice treated with FAHF-2 were completely protected from anaphylaxis based on symptom scores, body temperature, and serum histamine levels after challenge with each allergen, suggesting that FAHF-2 offers protection from anaphylaxis in an allergen non-specific manner [76].

Based on the encouraging data from mouse models displaying effective and safe protection from anaphylaxis with FAHF-2, a phase II, double-blind, placebo-controlled trial to examine its safety and efficacy in humans was recently conducted. Sixty-eight subjects with a history of peanut, tree nut, sesame, fish, or shellfish allergy were assigned randomly to either treatment with FAHF-2 or placebo. Although many subjects had allergies to multiple foods, only one food allergen was studied during the trial for each participant. After 6 months of therapy, an oral challenge with 5 grams of allergen protein was performed. Although treatment with FAHF-2 was well tolerated, significantly more placebo-treated subjects had improvements from baseline in the amount of allergen able to be consumed following treatment compared to FAHF-2 treated subjects. In contrast, in vitro studies looking at FAHF-2 effects on cytokine levels in peripheral blood mononuclear cells (PBMCs) showed that incubation with FAHF-2 and food allergen produced significantly less IL-5, greater IL-10, and increased regulatory T-cells compared to untreated cells, suggesting favorable immunomodulatory effects. The study authors suggested that further research into optimization of the treatment dose and duration of FAHF-2 and consideration of combination therapy with concurrent allergen exposure (such as with OIT) may result in improved clinical efficacy [77]. A phase II, double-blind, placebo-controlled clinical trial investigating the use of FAHF-2 as an adjunct to multi-food OIT and omalizumab is currently underway (NCT 02879006).

## Probiotics

The "hygiene hypothesis" suggests that a lack of early childhood exposures to infections or microorganisms may contribute to the abnormal development of immune tolerance, leading to an increasing incidence of allergic disease [78,

79]. Support for this hypothesis comes from studies performed on germ-free mice that reveal that immune tolerance does not develop appropriately in the absence of a gut microbiota. The microbiome of the GI tract is a major source of microbial exposure and differences in bacterial colonization, which can be affected by geographical or other environmental factors, may play a role in observed differences in disease prevalence throughout the world. This has prompted researchers to study the use of probiotics as a potential solution to the allergic epidemic.

Several clinical studies have been conducted to evaluate the efficacy of probiotics for the prevention or treatment of different allergic diseases with conflicting results [78, 80–86]. There have been few trials looking at the use of probiotics in the treatment of food allergy that utilize oral food challenges in their study design. A trial looking at the use of *Lactobacillus casei* and *Bifidobacterium lactis* on the acquisition of oral tolerance in milk allergic children did not show a difference between children treated with probiotics for 12 months versus children on placebo [87]. However, treatment with *Lactobacillus rhamnosus* combined with extensively hydrolyzed casein formula increased the rate of milk allergy resolution in children compared to control subjects that received only hydrolyzed formula alone [88, 89].

The use of probiotics as an adjuvant to OIT has also been evaluated. In a double-blind, placebo-controlled trial, *Lactobacillus rhamnosus* was administered with peanut OIT in children with confirmed peanut allergy. Subjects were treated for approximately 18 months and had sustained unresponsiveness (SU) assessed with 4 g oral peanut challenge performed 2–5 weeks after the completion of therapy. About 82% of subjects treated with OIT and probiotics achieved SU compared to 3.6% in the placebo group, which was statistically significant. However, due to the lack of an OIT-only or probiotic-only control group, it is unclear through this trial alone how much additional effect the use of probiotics adds to the use of OIT alone [90].

If a benefit to the use of probiotics exists, it is likely that the benefits of supplementation are strain specific, but there is insufficient evidence to support the use of one particular bacterial strain over another at this time. Other factors that could influence responsiveness to treatment include individual differences in bacterial colonization or immune development which can be affected by things like genetics, susceptibility to bacterial colonization, maternal flora, or diet [78, 91]. More research into these individual differences in food allergic patients could aid in the development of future randomized clinical trials that can focus on the appropriate probiotics to use in people with food allergy.

## Considerations for Future Use of Immunotherapy in Clinical Practice

Food allergen immunotherapy is not currently a recommended part of routine clinical care, given persistent safety concerns, questions regarding appropriate dosing and treatment schedules, accurate identification of responders, and ultimately the lack of an FDA-approved product. However, as more information is being gathered and questions clarified through ongoing research, the landscape of food allergy treatment is changing and immunotherapy in the form of OIT, SLIT, and EPIT to treat IgE-mediated hypersensitivity reactions to major food allergens seems likely to be a standard part of food allergy management in the near future.

An important inclusion in treatment guidelines should be recommendations on how to select appropriate patients to undergo therapy. Currently, no strict criteria exist to help providers determine which patients might be too high risk to receive treatment, but factors like extreme sensitization to a food or a history of anaphylaxis would need to be taken into consideration prior to starting treatment. Immunotherapy trials almost always exclude individuals with a history of severe anaphylaxis, uncontrolled asthma, or other conditions that would place them at increased risk for a serious adverse reaction, and so data on immunotherapy response is not available in this subset of patients and individuals that fall in this category may not be appropriate to undergo food

immunotherapy. Other factors that may increase the risk for more frequent and severe adverse reactions include a lower tolerated threshold dose at initial study screening, higher food-specific serum IgE levels, higher food-specific serum IgE to total IgE ratios, larger skin prick testing wheal diameter, and a personal history of asthma or allergic rhinitis. Studies have shown that these factors can affect treatment adherence and attainment of desensitization and SU [92, 93]. But not enough is known at this point to provide specific recommendations on how immunotherapy dose or schedule adjustments should be made in patients with these associated risk factors.

Individual patient preferences will also need to be taken into consideration when deciding whether or not immunotherapy is appropriate. Some patients and their families may find the risks associated with immunotherapy to be unacceptable. Other individuals may be hesitant or unwilling to treat potential reactions with an epinephrine autoinjector or be unwilling to avoid cofactors around the time of dosing that can lower the reactivity threshold, like exercise. For safety reasons, these patients should be excluded from treatment. Other potential roadblocks to treatment could include issues with adherence due to patient or family anxiety about dose administration, taste or food aversions, or a lack of resources for appropriate monitoring and follow-up.

With the possibility that multiple forms of immunotherapy will eventually be available for public use, clinician knowledge about the risks and benefits of different delivery routes for immunotherapy and how they compare with each other will be key to selecting the appropriate type of treatment for each patient. Combination therapy, such as having a patient start with SLIT and transitioning to OIT at a later time, or the use of adjunctive therapies like omalizumab may also be viable strategies to improve tolerability and adherence. It will be important that an open discussion about personal and family goals, ability to adhere to therapy, appropriate expectations, potential outcomes, and possible adverse effects be conducted with each patient while taking into consideration each individual's specific history and preexisting risk factors.

## Future Directions

While the availability of an FDA-approved, readily accessible, safe, and effective treatment for food allergy appears to be on the near horizon, standardized protocols are needed to guide clinicians on implementation of such therapies into daily practice. Nearly 40% of children with persistent food allergies are also allergic to multiple foods, so the development of treatments for other common food allergens including milk, egg, wheat, fish, and shellfish are needed in addition to a safe approach to combine therapies to concomitantly address these issues [4]. Ways to improve safety and enhance efficacy of immunotherapy or achieve permanent oral tolerance through the use of DNA-based vaccines, recombinant allergen vaccines, adjunctive therapies, or combination therapy need to be further studied. Current clinical trials on food allergy therapies also exclude patients with a history of severe anaphylaxis, but it could be argued that this subset of patients is in most need for a safe and effective treatment. Although much progress has been made, further research into desensitization and tolerance needs to be performed to find a permanent cure for food allergy.

## References

1. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol. 2011;127(3):594–602. https://doi.org/10.1016/j.jaci.2010.11.044.
2. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009;124(6):1549–55. https://doi.org/10.1542/peds.2009-1210.
3. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014;134(5):1016–25 e43. https://doi.org/10.1016/j.jaci.2014.05.013.
4. Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.
5. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. JAMA Netw Open. 2019;2(1):e185630-e185630.
6. Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance rel-

evant to food allergy. J Allergy Clin Immunol. 2011;127(3):576–84;. quiz 85-6. https://doi.org/10.1016/j.jaci.2010.12.1116.
7. Berin MC, Shreffler WG. Mechanisms underlying induction of tolerance to foods. Immunol Allergy Clin N Am. 2016;36(1):87–102. https://doi.org/10.1016/j.iac.2015.08.002.
8. Lieberman JA, Sicherer SH. Quality of life in food allergy. Curr Opin Allergy Clin Immunol. 2011;11(3):236–42. https://doi.org/10.1097/ACI.0b013e3283464cf0.
9. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JSA. Management of nut allergy influences quality of life and anxiety in children and their mothers. Pediatr Allergy Immunol. 2010;21(4p1):586–94. https://doi.org/10.1111/j.1399-3038.2009.00975.x.
10. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013;167(11):1026–31. https://doi.org/10.1001/jamapediatrics.2013.2376.
11. Anvari S, Anagnostou K. The nuts and bolts of food immunotherapy: the future of food allergy. Children (Basel). 2018;5(4):47. https://doi.org/10.3390/children5040047.
12. Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. J Allergy Clin Immunol. 2018;141(1):1–9. https://doi.org/10.1016/j.jaci.2017.11.004.
13. Chen M, Land M. The current state of food allergy therapeutics. Hum Vaccin Immunother. 2017;13(10):2434–42. https://doi.org/10.1080/21645515.2017.1359363.
14. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, et al. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol. 2015;135(5):1240–8 e1-3. https://doi.org/10.1016/j.jaci.2014.12.1917.
15. Sampath V, Sindher SB, Zhang W, Nadeau KC. New treatment directions in food allergy. Ann Allergy Asthma Immunol. 2018;120(3):254–62. https://doi.org/10.1016/j.anai.2018.01.004.
16. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol. 2014;133(2):468–75.e6. https://doi.org/10.1016/j.jaci.2013.11.007.
17. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. J Allergy Clin Immunol. 2014;133(2):318–23. https://doi.org/10.1016/j.jaci.2013.12.1040.
18. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233–43. https://doi.org/10.1056/NEJMoa1200435.
19. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012;129(2):448–55, 55 e1–5. https://doi.org/10.1016/j.jaci.2011.10.023.
20. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S116–25. https://doi.org/10.1016/j.jaci.2009.08.028.
21. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J. 2014;7(1):6. https://doi.org/10.1186/1939-4551-7-6.
22. Didier A, Malling HJ, Worm M, Horak F, Jager S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol. 2007;120(6):1338–45. https://doi.org/10.1016/j.jaci.2007.07.046.
23. Kildsgaard J, Brimnes J, Jacobi H, Lund K. Sublingual immunotherapy in sensitized mice. Ann Allergy Asthma Immunol. 2007;98(April):366–72.
24. Malling HJ, Lund L, Ipsen H, Poulsen L. Safety and immunological changes during sublingual immunotherapy with standaradized quality grass allergen tablets. J Investig Allergol Clin Immunol. 2006;16(3):162–8.
25. Allam JP, Wurtzen PA, Reinartz M, Winter J, Vrtala S, Chen KW, et al. Phl p 5 resorption in human oral mucosa leads to dose-dependent and time-dependent allergen binding by oral mucosal Langerhans cells, attenuates their maturation, and enhances their migratory and TGF-beta1 and IL-10-producing properties. J Allergy Clin Immunol. 2010;126(3):638–45 e1. https://doi.org/10.1016/j.jaci.2010.04.039.
26. de Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. Allergy. 2006;61(10):1238–9. https://doi.org/10.1111/j.1398-9995.2006.01196.x.
27. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol. 2005;116(5):1073–9. https://doi.org/10.1016/j.jaci.2005.08.027.
28. Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, Diaz de Durana MD, Garcia BE, Gonzalez-Mancebo E, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009;64(6):876–83. https://doi.org/10.1111/j.1398-9995.2008.01921.x.
29. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131(1):119–27 e1-7. https://doi.org/10.1016/j.jaci.2012.11.011.
30. Chin SJ, Vickery BP, Kulis MD, Kim EH, Varshney P, Steele P, et al. Sublingual versus oral immunotherapy

for peanut-allergic children: a retrospective comparison. J Allergy Clin Immunol. 2013;132(2):476–8 e2. https://doi.org/10.1016/j.jaci.2013.02.017.
31. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol. 2015;135(5):1275–82 e1-6. https://doi.org/10.1016/j.jaci.2014.11.005.
32. Bublin M, Breiteneder H. Developing therapies for peanut allergy. Int Arch Allergy Immunol. 2014;165(3):179–94. https://doi.org/10.1159/000369340.
33. Cook QS, Burks AW. Peptide and recombinant allergen vaccines for food allergy. Clin Rev Allergy Immunol. 2018;55:162. https://doi.org/10.1007/s12016-018-8673-4.
34. Ali FR, Larche M. Peptide-based immunotherapy: a novel strategy for allergic disease. Expert Rev Vaccines. 2005;4(6):881–9.
35. Lieberman JA, Nowak-Węgrzyn A. Vaccines and immunomodulatory therapies for food allergy. Curr Allergy Asthma Rep. 2011;12(1):55–63. https://doi.org/10.1007/s11882-011-0232-5.
36. Prickett SR, Rolland JM, O'Hehir RE. Immunoregulatory T cell epitope peptides: the new frontier in allergy therapy. Clin Exp Allergy. 2015;45(6):1015–26. https://doi.org/10.1111/cea.12554.
37. Muller U, Akdis C, Fricker M, Akdis M, Blesken T, Bettens F, et al. Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A2 includes specific T cell anergy in patients allergic to bee venom. J Allergy Clin Immunol. 1998;101(6 Pt 1):747–54.
38. Alexander C, Tarzi M, Larche M, Kay AB. The effect of Fel d 1-derived T-cell peptides on upper and lower airway outcome measurements in cat-allergic subjects. Allergy. 2005;60(10):1269–74. https://doi.org/10.1111/j.1398-9995.2005.00885.x.
39. Yang M, Mine Y. Novel T-cell epitopes of ovalbumin in BALB/c mouse: potential for peptide-immunotherapy. Biochem Biophys Res Commun. 2009;378(2):203–8. https://doi.org/10.1016/j.bbrc.2008.11.037.
40. Yang M, Yang C, Mine Y. Multiple T cell epitope peptides suppress allergic responses in an egg allergy mouse model by the elicitation of forkhead box transcription factor 3- and transforming growth factor-beta-associated mechanisms. Clin Exp Allergy. 2010;40(4):668–78. https://doi.org/10.1111/j.1365-2222.2009.03442.x.
41. Glaspole IN, de Leon MP, Rolland JM, O'Hehir RE. Characterization of the T-cell epitopes of a major peanut allergen, Ara h 2. Allergy. 2005;60(1):35–40. https://doi.org/10.1111/j.1398-9995.2004.00608.x.
42. Prickett SR, Voskamp AL, Dacumos-Hill A, Symons K, Rolland JM, O'Hehir RE. Ara h 2 peptides containing dominant CD4+ T-cell epitopes: candidates for a peanut allergy therapeutic. J Allergy Clin Immunol. 2011;127(3):608–15.e5. https://doi.org/10.1016/j.jaci.2010.09.027.
43. Prickett SR, Voskamp AL, Phan T, Dacumos-Hill A, Mannering SI, Rolland JM, et al. Ara h 1 CD4+ T cell epitope-based peptides: candidates for a peanut allergy therapeutic. Clin Exp Allergy. 2013;43(6):684–97. https://doi.org/10.1111/cea.12113.
44. Ramesh M, Yuenyongviwat A, Konstantinou GN, Lieberman J, Pascal M, Masilamani M, et al. Peanut T-cell epitope discovery: Ara h 1. J Allergy Clin Immunol. 2016;137(6):1764–71 e4. https://doi.org/10.1016/j.jaci.2015.12.1327.
45. Valenta R, Linhart B, Swoboda I, Niederberger V. Recombinant allergens for allergen-specific immunotherapy: 10 years anniversary of immunotherapy with recombinant allergens. Allergy. 2011;66(6):775–83. https://doi.org/10.1111/j.1398-9995.2011.02565.x.
46. Nowak-Wegrzyn A, Sampson HA. Future therapies for food allergies. J Allergy Clin Immunol. 2011;127(3):558–73;. quiz 74-5. https://doi.org/10.1016/j.jaci.2010.12.1098.
47. Pauli G, Larsen TH, Rak S, Horak F, Pastorello E, Valenta R, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2008;122(5):951–60. https://doi.org/10.1016/j.jaci.2008.09.017.
48. Bannon GA, Cockrell G, Connaughton C, West CM, Helm R, Stanley JS, et al. Engineering, characterization and in vitro efficacy of the major peanut allergens for use in immunotherapy. Int Arch Allergy Immunol. 2001;124:70–2.
49. King N, Helm R, Stanley JS, Vieths S, Luttkopf D, Hatahet L, et al. Allergenic characteristics of a modified peanut allergen. Mol Nutr Food Res. 2005;49(10):963–71. https://doi.org/10.1002/mnfr.200500073.
50. Li XM, Srivastava K, Huleatt JW, Bottomly K, Burks AW, Sampson HA. Engineered recombinant peanut protein and heat-killed Listeria monocytogenes coadministration protects against peanut-induced anaphylaxis in a murine model. J Immunol. 2003;170(6):3289–95. https://doi.org/10.4049/jimmunol.170.6.3289.
51. Li X-M, Srivastava K, Grishin A, Huang C-K, Schofield B, Burks W, et al. Persistent protective effect of heat-killed Escherichia coli producing "engineered," recombinant peanut proteins in a murine model of peanut allergy. J Allergy Clin Immunol. 2003;112(1):159–67. https://doi.org/10.1067/mai.2003.1622.
52. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, et al. A phase 1 study of heat/phenol-killed, E. coli-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. Allergy. 2013;68(6):803–8. https://doi.org/10.1111/all.12158.

53. Tang D, DeVit M, Johnston SA. Genetic immunization is a simple method for eliciting an immune response. Nature. 1992;356:152.
54. Keet CA, Wood RA. Emerging therapies for food allergy. J Clin Investig. 2014;124(5):1880–6. https://doi.org/10.1172/jci72061.
55. Weiss R, Scheiblhofer S, Gabler M, Ferreira F, Leitner WW, Thalhamer J. Is genetic vaccination against allergy possible? Int Arch Allergy Immunol. 2006;139(4):332–45. https://doi.org/10.1159/000091946.
56. Burks W, Kulis M, Pons L. Food allergies and hypersensitivity: a review of pharmacotherapy and therapeutic strategies. Expert Opin Pharmacother. 2008;9(7):1145–52. https://doi.org/10.1517/14656566.9.7.1145.
57. Roy K, Mao HQ, Huang SK, Leong KW. Oral gene delivery with chitosan–DNA nanoparticles generates immunologic protection in a murine model of peanut allergy. Nat Med. 1999;5(4):387–91.
58. Li X-M, Huang C-K, Schofield B, Burks AW, Bannon G, Kim K-H, et al. Strain-dependent induction of allergic sensitization caused by peanut allergen DNA immunization in mice. J Immunol. 1999;162:3045–52.
59. Liu MA. DNA vaccines: an historical perspective and view to the future. Immunol Rev. 2011;239:62–84.
60. Su Y, Connolly M, Marketon A, Heiland T. CryJ-LAMP DNA vaccines for Japanese red cedar allergy induce robust Th1-type immune responses in murine model. J Immunol Res. 2016;2016:4857869. https://doi.org/10.1155/2016/4857869.
61. Nakamura R, Matsuda T. Rice allergenic protein and molecular-genetic approach for hypoallergenic rice. Biosci Biotechnol Biochem. 1996;60(8):1215–21. https://doi.org/10.1271/bbb.60.1215.
62. Herman EM, Helm RM, Jung R, Kinney AJ. Genetic modification removes an immunodominant allergen from soybean. Plant Physiol. 2003;132(1):36–43. https://doi.org/10.1104/pp.103.021865.
63. Lorenz Y, Enrique E, Lequynh L, Fotisch K, Retzek M, Biemelt S, et al. Skin prick tests reveal stable and heritable reduction of allergenic potency of gene-silenced tomato fruits. J Allergy Clin Immunol. 2006;118(3):711–8. https://doi.org/10.1016/j.jaci.2006.05.014.
64. Burks AW. Peanut allergy. Lancet. 2008;371(9623):1538–46. https://doi.org/10.1016/s0140-6736(08)60659-5.
65. Leung DY, Sampson HA, Yunginger JW, Burks AW, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003;348(11):986–93.
66. Lieberman JA, Chehade M. Use of omalizumab in the treatment of food allergy and anaphylaxis. Curr Allergy Asthma Rep. 2012;13(1):78–84. https://doi.org/10.1007/s11882-012-0316-x.
67. Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, double-blind, parallelgroup, placebocontrolled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol. 2011;127(5):1309–10 e1. https://doi.org/10.1016/j.jaci.2011.01.051.
68. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol. 2017;139(3):873–81.e8. https://doi.org/10.1016/j.jaci.2016.08.010.
69. Begin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. Allergy Asthma Clin Immunol. 2014;10(1):7. https://doi.org/10.1186/1710-1492-10-7.
70. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol. 2011;127(6):1622–4. https://doi.org/10.1016/j.jaci.2011.04.009.
71. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol. 2016;137(4):1103–10. e11. https://doi.org/10.1016/j.jaci.2015.10.005.
72. Feuille E, Nowak-Wegrzyn A. Allergen-specific immunotherapies for food allergy. Allergy Asthma Immunol Res. 2018;10(3):189–206. https://doi.org/10.4168/aair.2018.10.3.189.
73. Wang J. Treatment of food anaphylaxis with traditional Chinese herbal remedies: from mouse model to human clinical trials. Curr Opin Allergy Clin Immunol. 2013;13(4):386–91. https://doi.org/10.1097/ACI.0b013e3283615bc4.
74. Li XM, Zhang TF, Huang CK, Srivastava K, Teper AA, Zhang L, et al. Food allergy herbal Formula-1 (FAHF-1) blocks peanut-induced anaphylaxis in a murine model. J Allergy Clin Immunol. 2001;108(4):639–46. https://doi.org/10.1067/mai.2001.118787.
75. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. J Allergy Clin Immunol. 2005;115(1):171–8. https://doi.org/10.1016/j.jaci.2004.10.003.
76. Srivastava KD, Bardina L, Sampson HA, Li XM. Efficacy and immunological actions of FAHF-2 in a murine model of multiple food allergies. Ann Allergy Asthma Immunol. 2012;108(5):351–8. e1. https://doi.org/10.1016/j.anai.2012.03.008.
77. Wang J, Jones SM, Pongracic JA, Song Y, Yang N, Sicherer SH, et al. Safety, clinical, and immunologic efficacy of a Chinese herbal medicine (Food Allergy Herbal Formula-2) for food allergy. J Allergy Clin Immunol. 2015;136(4):962–70 e1. https://doi.org/10.1016/j.jaci.2015.04.029.
78. Prescott SL, Bjorksten B. Probiotics for the prevention or treatment of allergic diseases. J Allergy Clin Immunol. 2007;120(2):255–62. https://doi.org/10.1016/j.jaci.2007.04.027.

79. Lynch S. Gut microbiota and allergic disease. Ann Am Thorac Soc. 2016;13(Supplement 1):S51–S4. https://doi.org/10.1513/AnnalsATS.201507-451MG.
80. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2007;119(1):192–8. https://doi.org/10.1016/j.jaci.2006.09.009.
81. Marschan E, Kuitunen M, Kukkonen K, Poussa T, Sarnesto A, Haahtela T, et al. Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. Clin Exp Allergy. 2008;38(4):611–8. https://doi.org/10.1111/j.1365-2222.2008.02942.x.
82. Abrahamsson TR, Jakobsson T, Bottcher MF, Fredrikson M, Jenmalm MC, Bjorksten B, et al. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2007;119(5):1174–80. https://doi.org/10.1016/j.jaci.2007.01.007.
83. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. J Allergy Clin Immunol. 1997;99(2):179–85.
84. Rosenfeldt V, Benfeldt E, Nielsen S, Michaelsen K, Jeppesen D, Valerius N, et al. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. J Allergy Clin Immunol. 2003;111(2):389–95.
85. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. J Allergy Clin Immunol. 2007;119(1):184–91. https://doi.org/10.1016/j.jaci.2006.08.036.
86. Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. Allergy. 2005;60(4):494–500. https://doi.org/10.1111/j.1398-9995.2004.00514.x.
87. Hol J, van Leer EH, Elink Schuurman BE, de Ruiter LF, Samsom JN, Hop W, et al. The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. J Allergy Clin Immunol. 2008;121(6):1448–54. https://doi.org/10.1016/j.jaci.2008.03.018.
88. Berni Canani R, Nocerino R, Terrin G, Coruzzo A, Cosenza L, Leone L, et al. Effect of Lactobacillus GG on tolerance acquisition in infants with cow's milk allergy: a randomized trial. J Allergy Clin Immunol. 2012;129(2):580–2, 2 e1-5. https://doi.org/10.1016/j.jaci.2011.10.004.
89. Berni Canani R, Nocerino R, Terrin G, Frediani T, Lucarelli S, Cosenza L, et al. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. J Pediatr. 2013;163(3):771–7 e1. https://doi.org/10.1016/j.jpeds.2013.03.008.
90. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol. 2015;135(3):737–44 e8. https://doi.org/10.1016/j.jaci.2014.11.034.
91. Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ, Nadeau KC. Molecular and cellular mechanisms of food allergy and food tolerance. J Allergy Clin Immunol. 2016;137(4):984–97. https://doi.org/10.1016/j.jaci.2016.02.004.
92. Virkud Y, Burks AW, Steele PH, Edwards LJ, Berglund JP, Jones SM, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol. 2017;139(3):882–8. https://doi.org/10.1016/j.jaci.2016.07.030.
93. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139(1):173–81. https://doi.org/10.1016/j.jaci.2016.05.027.

# Correction to: Epidemiology and Racial/Ethnic Differences in Food Allergy

Jialing Jiang, Christopher M. Warren, and Ruchi S. Gupta

**Correction to: Chapter 1 in: R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_1**

A typographical error in the chapter has been corrected. The line "Specifically, peanut allergy was more prevalent among Jewish infants…" has now been changed as "Specifically, peanut allergy was less prevalent among Jewish infants…"

The updated version of this chapter can be found at https://doi.org/10.1007/978-3-030-33292-1_1



R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1_20

# Index




R. S. Gupta (ed.), *Pediatric Food Allergy*, https://doi.org/10.1007/978-3-030-33292-1