

Tackling Food Allergy in Infancy



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KEYWORDS

• Food allergy • Infancy • Atopic dermatitis • Prevention • Oral food challenge

KEY POINTS

- Adverse food reactions, including immunoglobulin E (IgE)-mediated and non-IgE-mediated food allergy, are common in infancy.
- IgE-mediated food allergy diagnosis is based on clinical history and confirmed with skin prick or serum-specific IgE testing. US guidelines currently only recommend proactive screening for peanut sensitization prior to oral introduction in infants with severe atopic dermatitis and/or egg allergy.
- Unless an infant has experienced symptoms after breastfeeding, there are no recommendations regarding maternal dietary modification for the treatment or prevention of food allergy.
- Evidence suggests that IgE-mediated food allergy is preventable through the earlier introduction of allergenic food; however, this is not yet a broad recommendation for all foods and populations of infants.

INTRODUCTION

Adverse food reactions are a common concern in infancy. Nonimmune-mediated susceptibilities are referred to as food intolerances.^{1,2} Food allergies are defined as adverse health effects arising from a specific immune response that occurs reproducibly upon exposure to a specific food.^{2,3} These immune responses can be categorized based on the immune system components involved: non-immunoglobulin E (IgE)-mediated and IgE-mediated food allergies.^{3,4}

With recent changes to infant feeding recommendations, attention has shifted to IgE-mediated food allergy in the infant population. Infancy is often defined as 0 to 12 months of age, a time of tremendous change both clinically and with respect to the immune system. Now, allergists are frequently seeing infants in their clinics for

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food allergy evaluation, either for suspected allergic reactions or proactively in the context of atopic dermatitis (AD) or a positive family history.

The following case will be referred to throughout this article to address the assessment and management of infants with suspected food allergy. A 4 month-old male infant with AD was referred to allergy prior to solid food introduction. His AD began around 2 months of age and has been visible daily with intermittent flares. He is bathed 1 to 2 times per day, applying a petroleum-based emollient several times per day, and using prescribed topical steroids twice per day to flares throughout the week. He has had a superinfection requiring oral antibiotics and has disrupted sleep because of pruritus. He spits up frequently and used to cry for an hour every evening, but is now only intermittently fussy. He is gaining weight normally and overall has a happy disposition. He is exclusively breastfed, and the maternal diet has been unrestricted. On examination, his AD affects greater than 50% of his body surface area, and appears erythematous, lichenified, and excoriated. The parents wonder if his regurgitation and fussiness are caused by a particular food his mother is consuming. In addition, the parents have heard about associations between AD and food allergy and are concerned he may already have a food allergy.

DISCUSSION

Non-IgE-mediated Food Allergy

Commonly encountered non-IgE-mediated food allergies in infancy include food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES), and food protein-induced enteropathy (FPE) (Table 1).^{5–9} Other non-IgE-mediated adverse food reactions include eosinophilic esophagitis (EoE), celiac

Table 1 Characteristics of non-immunoglobulin E-mediated food allergies			
	FPIAP	FPIES	FPE
Typical age of onset	Days to 6 months	Days to 12 months	2–24 months
Typical symptoms	Painless, bloody and/or mucous-containing stools in an otherwise healthy infant	• Acute: severe vomiting, pallor, and lethargy; sometimes diarrhea • Chronic: chronic diarrhea and/or vomiting that can lead to nutritional deficiencies and failure to thrive (FTT)	Chronic diarrhea, malabsorption, anemia, hypoproteinemia, FTT
Timing of symptoms in relation to food ingestion	6–72 h	• Acute: vomiting in 1–4 h; diarrhea within 5–10 h	40–72 h
Most common culprit foods	Cow’s milk (CM), soy, egg, wheat	CM, soy, rice, oat	CM, soy, egg, wheat
Natural history	Usually resolves by age 1 y	Varies by allergen, but generally resolves by age 3–4 y	Usually resolves by age 1–2 y

Data from Refs.^{7–9,14}

disease, and lactose intolerance; these have been reviewed elsewhere.^{10–12} Symptoms of non-IgE-mediated allergies typically involve the gastrointestinal system and are usually delayed in onset and/or chronic.^{5–8} Diagnosis is based on history, without any role for skin prick testing (SPT) or serum-specific IgE (sIgE) testing, given their non-IgE-mediated pathogenesis.^{5–8} Diagnosis is aided by a trial elimination diet with improvement in symptoms, with oral food challenge (OFC) acting to confirm the diagnosis following symptom resolution or to determine if tolerance has been achieved.^{7,8} Management of non-IgE-mediated food allergies (ie, FPIAP, FPIES, and FPE) is through strict elimination of the culprit food(s); although foods with precautionary allergen labeling (eg, "may contain trace," "processed in a facility," etc.) may still be consumed.⁸ Breastfeeding may continue if the mother is willing to eliminate the food(s) from her diet.⁸ Elimination of multiple foods from the maternal diet may not only affect the nutritional health of the mother, but also may impact the nutritional profile of her breastmilk.¹³ Thus, strong consideration should be made prior to recommending a multiple food elimination diet for a breastfeeding mother, and, if it is deemed necessary, involvement of a nutritionist is recommended.

Gastroesophageal reflux (GER) and colic are common pediatric disorders that may be seen in the allergist's office, although the role of food allergy in their pathogenesis is less clear. GER is the physiologic passage of gastric contents into the esophagus, and may occur at least 30 times a day in healthy infants, decreasing with age.^{15,16} Symptoms include intermittent vomiting, spitting up, coughing, and food aversion.¹⁷ Most infants with GER have a normal examination and do not require treatment.¹⁸ CM sensitivity or intolerance has been implicated in 40% to 50% of infants with GER, based on elimination of CM and OFC.^{19,20} For infants with frequent and/or severe regurgitation, food aversion, and FTT, a few week trial elimination of CM can aid in diagnosis of food-related GER, especially if subsequent reintroduction is performed confirming the diagnosis.

Infantile colic is described as unexplained episodes of inconsolable crying early in life.²¹ Colic has largely been attributed to intestinal immaturity, hypermotility, alterations in the fecal microbiome, and faulty feeding techniques.²² Although studies have shown benefits from hydrolyzed formula, soy formula, and low-allergenic maternal diets in breastfed infants with colic, the transient nature and spontaneous improvement of colic render true confirmation of the effect of food elimination difficult.²³ The history of the infant presented previously is consistent with colic, now resolved, and normal GER, which does not require intervention.

IgE-Mediated Food Allergy

IgE-mediated food allergy is a type I hypersensitivity reaction.⁵ During sensitization, B cells are directed to produce allergen-specific IgE, which binds to high-affinity FcεRI receptors on mast cells and basophils. Upon re-exposure to the allergen, surface-bound IgE is cross-linked, resulting in mast cell and basophil degranulation and the release of preformed mediators, including histamine and tryptase. There is also rapid synthesis of cytokines and lipid mediators.^{24,25} This swift response leads to onset of clinical symptoms within minutes. Signs and symptoms of IgE-mediated reactions have variable severity and affect multiple organ systems (**Table 2**). These signs and symptoms may be more subjective and subtle in the infant population. Anaphylaxis is a "severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance," and may result in death if not treated appropriately.²⁶ Clinical criteria center around symptoms in more than 1 organ system and/or hypotension following ingestion of an allergen.²⁶

The prevalence of IgE-mediated food allergy among children ages 0 to 2 years in the United States is 6.3%.²⁷ Allergy to CM is the most common (2.0%) in this age group,

Table 2 Systems-based manifestations of immunoglobulin E-mediated food allergies in infants	
Organ System	Manifestations
Skin/mucous membranes	• Erythema • Pruritus • Urticaria • Angioedema • Ear picking or rubbing • Sticking out and rubbing tongue or putting a hand in the mouth
Gastrointestinal	• Emesis • Diarrhea
Respiratory	• Rhinorrhea and/or congestion • Sneezing • Stridor • Cough • Increased work of breathing • Wheezing
Cardiovascular	• Syncope • Hypotension/tachycardia
Neurologic/behavior	• Change in demeanor (ie, irritability, clinging to parent, or inconsolable crying) • Change in mental status or somnolence • Food refusal and/or aversion

followed by peanut (1.4%), egg (1.0%), shellfish (0.5%), fish (0.3%), soy (0.3%), wheat (0.3%), and tree nut (0.2%).²⁷ IgE-mediated allergy to food appears within the first 2 years of life and may increase or decrease, with decreases associated with tolerance of the food.²⁸ The likelihood of resolution depends on the allergen. Approximately 70% to 80% of milk, egg, wheat, and soy allergies are outgrown by adolescence,^{29–32} with roughly 50% of milk and egg allergies resolved by age 6.³³ Peanut and tree nut allergies are often life-long, with only 20% and 10% resolving, respectively.^{34–36}

Diagnosis of IgE-mediated food allergy is driven by clinical history, which informs testing based on the suspected trigger, symptoms experienced, and timing.^{5,6} Testing can involve SPT, in vitro serum sIgE testing, and OFC. Skin prick and sIgE testing are used to confirm diagnosis, but alone, these cannot be considered diagnostic for food allergy.^{5,6} Specific IgE-based testing using allergen extracts, whether by skin prick or serum, is highly sensitive for food allergy but poorly specific; the presence of food sIgE merely indicates sensitization and cannot predict individuals at risk for clinical reactivity. Prior studies in infants and children show that only 30% to 70% of sensitized patients will display symptoms following exposure to the food in question.^{37–40} For patients sensitized to a particular food, size of the SPT wheal or magnitude of the sIgE cannot be used to predict reaction severity and can only serve to determine the likelihood a reaction will occur.^{36,39–45} However, most reference values for these purposes have not been standardized for infants.^{46,47} In addition, variability in testing results can occur because of differences in SPT technique, biologic composition and quality of extracts, and laboratory methods.^{48–50}

Infants are often subjected to indiscriminate testing for food sIgE in an attempt to catch food allergy prior to initial exposure for various reasons, including AD, family history of food allergy, and caregiver anxiety.⁵¹ Unfortunately, indiscriminate testing often leads to further testing, unnecessary food avoidance, and concern for adequate

nutrition and growth.^{5,52–54} In turn, these consequences can dramatically impact an infant's development and cause undue family stress.^{55–60}

Oral Food Challenges in Infants

OFC remains the most accurate tool to diagnose food allergy.^{5,6,61,62} However, OFCs require time, trained personnel, and access to emergency resources; additionally, they impart significant risk to the patient. OFCs in infants carry unique concerns. Infants are unable to use words to express discomfort or symptoms, and instead develop changes in demeanor or behavior that may be interpreted as a reaction or normal behavior.^{57,63,64} Increased vigilance from the providers administering the OFC is needed to perceive subtle signs of a reaction (see [Table 2](#)).⁶⁵ Another challenge is that infants who are still developing feeding skills can have difficulty consuming standard OFC doses,^{57,64,66} either because of satiety or time constraints. An infant who does not react to 50% of the OFC dose but does not consume the complete dose may be still be advised to avoid the food in question, leading some to propose supervised challenges with lower, age-appropriate doses, with continued incorporation of the food into the diet and further dose increases at home, or arbitrarily determining that the infant has eaten enough to rule out the diagnosis of IgE-mediated food allergy.^{64,66}

Despite these obstacles, infant OFCs are safe and can be used to diagnose food allergy or determine tolerance. Infants appear to have a low rate of anaphylaxis, with most reactions being mild and cutaneous.^{38,39,66–71} Efforts should be made to create an infant-friendly environment including the use of high chairs, the child's own cups and/or utensils, as well as books, toys, and other entertainment. The dose should be age-appropriate and the vehicle, food form, and food texture should be familiar and should not pose a choking hazard. Ample time (eg, 4–6 hours) should be planned for feeding and observation. Ideally, the OFC should be scheduled for a time of day when the infant is usually awake, to avoid complications with feeding or interpretation of the results. The infant should be without signs of illness that could interfere with interpreting signs and symptoms of a reaction and/or could increase the risk of reaction. Infant OFCs should be performed in a monitored setting, with emergency medications available, and by providers familiar with infant vital signs and with clear indications for stopping the OFC, administering treatment, and transferring the patient to more advanced care.^{57,61,63,64} If OFC is tolerated, guidance should be given to aim for an age-appropriate serving size of the food at a regular frequency in the diet.^{57,64,68,70} If OFC is not tolerated, the infant should be managed in accordance with established food allergy treatment guidelines⁷² and the family given counseling to help maintain a healthy perspective on the infant's diagnosis.⁶⁴

Atopic Dermatitis and IgE-Mediated Food Allergy

AD is among the most common pediatric dermatologic conditions, with a reported prevalence in infants and toddlers of 14%.⁷³ AD is often a reason for referral to an allergist, particularly in the infant population.⁷⁴ Among infants with moderate to severe AD, up to a third may have IgE-mediated food allergy.⁷⁵ Although acute reactions (see [Table 2](#)) can be seen with exposure to a suspected allergen, individuals with food-triggered AD may also describe nonimmediate AD flares associated with ingestion of the suspected allergen.

If the infant's history is consistent with an IgE-mediated food allergy, targeted testing should proceed as already reviewed. SPT is typically pursued first given its high negative predictive value and tolerability; however, serum sIgE testing

may be required in the case of extensive and severe AD.⁷⁵ Both testing modalities are limited by a high rate of false positives, particularly among individuals with AD.⁷⁶ In a clinical trial studying infants with AD, sIgE levels to common food allergens were measured, and, based on clinical history, were found to have poor positive predictive value ($\leq 30\%$).⁷⁷ Up to 50% of infants with AD will have evidence of sensitization to food allergens, despite consumption of the food without a history of a reaction or no history of oral exposure, with highest sIgE found among those with early onset AD and more severe AD.⁷⁸ If a patient is found to have positive testing, but the history is inconsistent or unclear, an OFC should occur. Of 364 OFCs performed for the diagnosis of food allergy at a tertiary care center among 125 children (96% with AD), 89% were negative.⁷⁹ Forty-four children in this study were avoiding 111 foods because of positive testing results, and 93% of OFCs performed in this context were negative.⁷⁹

Data describing OFC-proven delayed AD flares triggered by food are limited. In a retrospective study of 106 OFCs conducted in 64 children with AD, 6 OFCs resulted in isolated delayed AD flares (>24 hours), and 50% of these were triggered by wheat consumption.⁸⁰ However, of 364 OFCs performed among 125 children (120 with AD), there were no AD flares in the 24 hours following the OFC.⁷⁹ If the patient's history is consistent with a delayed AD flare following consumption of a particular food, it is of utmost importance that the patient's AD regimen be optimized prior to proceeding with any diagnostic tests or diets (Fig. 1).

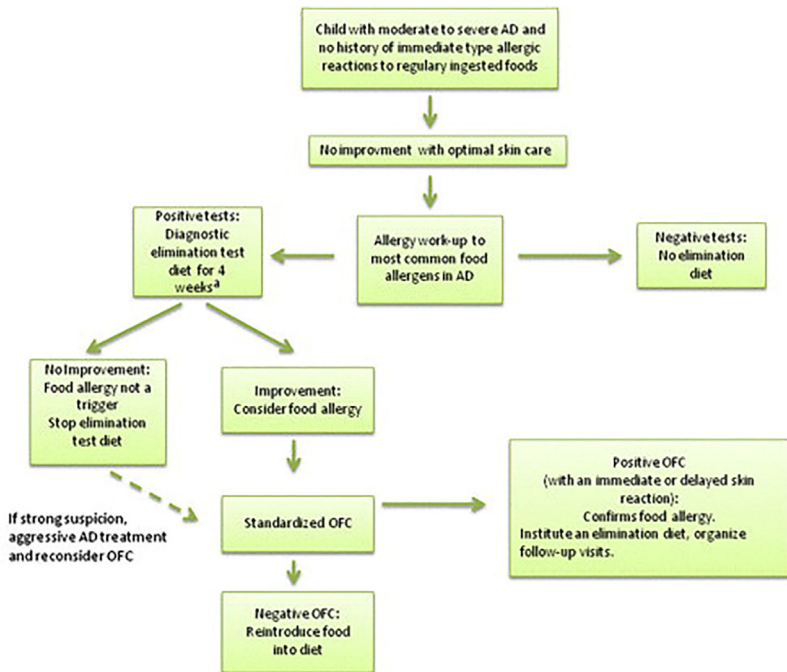


Fig. 1. Algorithm proposed for approach to patients with moderate-severe AD and concern about potential food trigger. ^a (see additional comments in text). (From Bergmann MM et al. Evaluation of food allergy in patients with atopic dermatitis. *J Allergy Clin Immunol Pract.* 2013;1(1):25; with permission.)

The decision to prescribe an elimination diet for AD in an infant is challenging, particularly amidst evidence for earlier introduction of allergenic foods as a means of primary food allergy prevention. Elimination diets are not without risk. Among 183 subjects diagnosed with food-triggered AD, nearly 19% developed an immediate reaction to a food without having a previous history of such, and most reactions were triggered by foods being actively avoided.⁸¹ If an elimination diet is prescribed to assess the role of a food in the patient's AD, this should be considered only for a few weeks and, if there is no improvement, the food should be readily reintroduced.⁷⁵ If there is improvement in the patient's AD, an OFC should be considered and a conversation about the risks and benefits of an avoidance diet should ensue. The infant presented earlier is at high risk for an IgE-mediated food allergy given the onset and severity of his AD. Prior to evaluating the role of food in his AD, an aggressive skin care regimen should be prescribed and compliance with the regimen emphasized.

Management of IgE-Mediated Food Allergy in Infants

Once an IgE-mediated food allergy has been diagnosed, strict avoidance of the implicated food is of utmost importance. For breastfed infants, questions arise regarding modification of the maternal diet during lactation. Allergenic protein is detectable in the breastmilk of some nursing mothers; however, the quantity and timing are variable.^{82,83} The allergenic protein content of breast milk seems to correlate with maternal dietary ingestion⁷⁴ and may be immunologically functional; peanut protein found in breast milk can bind peanut-specific IgE and elicit effector cell responses.⁸⁴ Among breastfed infants with IgE-mediated food allergy, some may react when exposed to their allergen through maternal milk, whereas others may be tolerant.⁸⁵ The reason behind this discrepancy has not been thoroughly studied. Thus, guidelines for maternal dietary avoidance in the setting of a breastfed infant with an IgE-mediated food allergy have not been developed, and recommendations regarding maternal dietary adjustment should be made on a case-by-case basis by a provider familiar with this evolving literature base (Fig. 2). The effect of ongoing exposure to allergenic protein through maternal milk on tolerance and sensitization is unclear. An analysis of data from the Canadian Asthma Primary Prevention Study found peanut sensitization at 7 years of age was lower in children whose mothers consumed peanut during lactation and who were orally exposed to peanut before 1 year of age, suggesting the combination of peanut consumption by both the mother and young children may prevent sensitization.⁸⁶

Although a peanut oral immunotherapy (OIT) product has been US Food and Drug Administration (FDA)-approved for peanut allergic individuals aged 4 years and older in the United States, these products have not been thoroughly studied in the infant population. A study of peanut OIT in 9- to 36-month-old peanut-allergic subjects found that the OIT promoted tolerance to peanut in 80% of the subjects, resulting in their ability to freely introduce peanut-containing foods into the diet 4 weeks after the cessation of therapy. The effect of OIT on long-term peanut tolerance in this age group is not yet known.⁸⁷

Primary Prevention of IgE-Mediated Food Allergy

Given the increased incidence of food allergy, recent research has focused on strategies for primary prevention. After the discovery that peanut allergy rates were lower in communities whose children consumed peanut earlier in life, the Learning Early About Peanut Allergy (LEAP) trial was conducted.^{68,88} This clinical trial of early peanut introduction in a group of infants with AD and/or egg allergy found a significant reduction in the incidence of peanut allergy among infants randomized to early, regular peanut

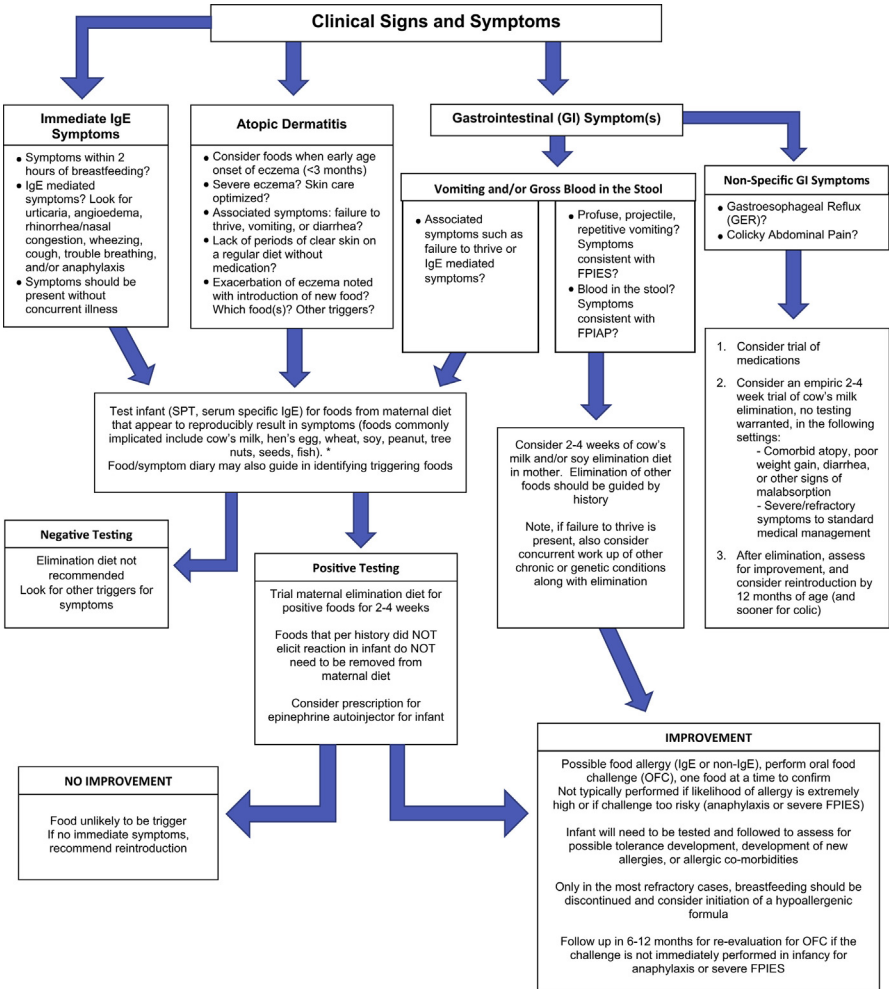


Fig. 2. Algorithm proposed for approach to infants with an adverse food reaction following breastfeeding. (From Rajani PS et al. Presentation and Management of Food Allergy in Breastfed Infants and Risks of Maternal Elimination Diets. *J Allergy Clin Immunol Pract.* 2020;8(1):61; with permission.). * Recommend advising against proceeding with panel testing.

consumption.⁶⁸ A subsequent trial of 3-month-old, exclusively breastfed infants randomized to early introduction of multiple allergenic foods or standard consumption of allergenic foods after 6 months of age found that among the infants able to comply with the early allergenic food diet, the prevalence of egg and peanut allergy was significantly lower.⁷⁰ Follow-up clinical trials of early egg introduction have had variable results; however, a systematic review and meta-analysis of allergenic food introduction did conclude that early egg introduction is beneficial for the prevention of egg allergy (Fig. 3).⁸⁹ A recent randomized trial of CM-based formula introduction at 1 to 2 months of age while breastfeeding showed a decreased incidence of OFC-proven CM allergy at 6 months of age,⁹⁰ providing further evidence that earlier introduction of allergenic foods may prevent the development of food allergy.

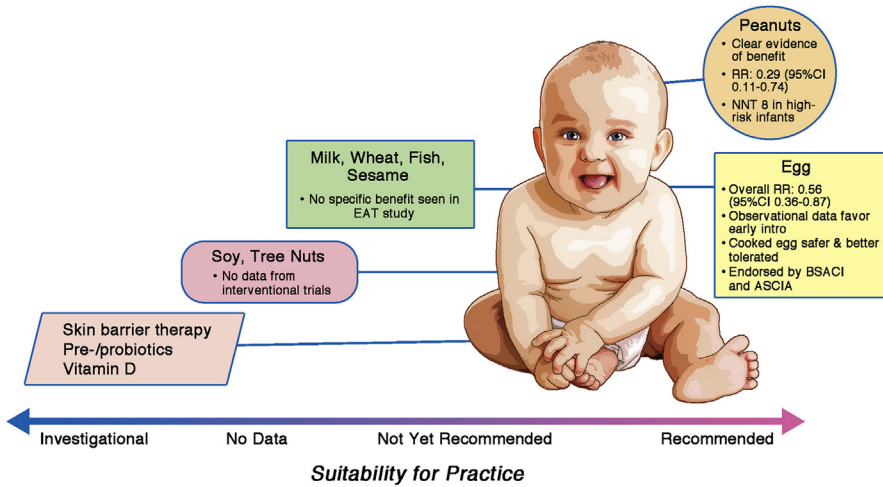


Fig. 3. Status of interventions for the primary prevention of food allergy in infancy. (From Bird JA et al. Prevention of food allergy: Beyond peanut. *J Allergy Clin Immunol.* 2019;143(2):546; with permission.)

With these critical findings, professional societies and experts authored guidelines to change infant feeding recommendations. In the United States, it is now recommended that infants with severe AD and/or egg allergy undergo screening for peanut sensitization prior to its oral introduction and, if possible, oral peanut introduction should occur by 4 to 6 months of age.⁹¹ Among infants with mild-moderate AD, oral peanut introduction should occur by 6 months of age.⁹¹ However, these recommendations differ by country. In Australia, experts recommend introduction of allergenic foods within the first year of life, regardless of the presence of atopic diagnoses conveying increased risk.⁹² The British Society of Allergy and Clinical Immunology has provided similar recommendations.⁹³ The infant presented in the previously mentioned clinical vignette should be screened for the presence of peanut-specific IgE with SPT and, if negative, peanut should be introduced and maintained in the diet.

Although the American Academy of Pediatrics (AAP) recommends exclusive breastfeeding as the primary source of nutrition until 6 months of age, breastfeeding has not been shown to prevent food allergy. Modification of the pregnant or lactating mother's diet in an effort to prevent food allergy is not recommended. The AAP previously recommended the use of partially or extensively hydrolyzed formula in infants at high risk for atopy who are unable to be breastfed in an attempt to prevent the development of allergy. Recently, these recommendations were overturned, and hydrolyzed formulas are no longer recommended for the prevention of atopy.⁹⁴

Citing the dual-allergen exposure hypothesis, efforts have ensued attempting to prevent food allergy by targeting the skin.⁹⁵ A randomized trial of aggressive emollient application in early life and allergenic food introduction at 3 to 4 months of age found that neither intervention prevented the development of AD by 1 year of age.⁹⁶ Similar studies of early emollient application have shown a protective effect against the development of AD^{97,98}; however, protective effects against the development of allergic sensitization were not seen.⁹⁸

SUMMARY

Infants may experience IgE-mediated or non-IgE-mediated adverse food reactions. Diagnoses are made based on the clinical history. Signs and symptoms of IgE-

mediated food allergy may be different in the infant population, and providers must be aware of subtle manifestations. The epidemiology of food allergy in infancy is likely to change in the coming years, with changes to early life feeding practices and the focus shifting to prevention. Strong evidence supports the early introduction of peanut among infants with AD or egg allergy in attempts to prevent the development of a peanut allergy. There continue to be many unanswered questions regarding food allergy in the infant population, including the effect of breastfeeding and maternal diet on food allergy outcomes, whether early introduction guidelines apply to other allergenic foods, and how current testing modalities utilized for IgE-mediated food allergy perform in the infant population.

CLINICS CARE POINTS

- Both IgE-mediated and non-IgE mediated food allergies can be seen in infancy, and the patient's clinical history is a crucial element in making this distinction.
- The OFC is an important tool for food allergy diagnosis. Providers should be aware of the differences and challenges of conducting these procedures in the infant population.
- Increasing evidence strongly suggests that IgE-mediated food allergy may be preventable with earlier oral introduction of allergenic foods.

DISCLOSURE

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