

EDUCATIONAL REVIEW (NON COMMISSIONED)

Perioperative considerations for the food-allergic pediatric patient

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Summary

Patients with a history of food allergy and food intolerance are common in the pediatric population and are encountered frequently in the perioperative setting by pediatric anesthesiologists. Perioperatively, food allergy can present on a spectrum ranging from minor acute urticaria to more severe hypovolemia and anaphylactic shock. Allergy to foods including fruits, fish, egg, soy, and peanut are most concerning for their potential to cross-react with perioperative medications. There is little in the anesthesia literature that focuses on the perioperative management of children with food allergies. This educational review will provide a brief overview of classic immunoglobulin E (IgE)-mediated food allergies, less common non-IgE food allergies, and present perioperative considerations for these patients. An audio summary of this topic is included as Supplementary Audio S1.

Introduction

Adverse food reactions can be classified as immune-mediated, nonimmune-mediated, and toxic reactions (Fig. 1). Immune-mediated reactions can further be divided into food allergy, which will be the focus of this review, and celiac disease. Food allergy reactions include IgE-mediated, non-IgE-mediated (food protein-induced enterocolitis syndrome, food protein-induced proctocolitis, and food protein-induced enteropathies), and mixed type (cow's milk protein allergy, eosinophilic esophagitis, and eosinophilic gastroenteritis). Nonimmune-mediated reactions are often termed food intolerance syndromes and include those produced by enzyme deficiencies (lactose/fructose malabsorption) and pharmacological agents (caffeine and tyramine), as well as nonspecific gut and nongut reactions to food (irritable bowel syndrome and behavioral or psychological factors).

IgE-mediated food allergy

Overview

Severe food allergies are immediate sensitivity reactions mediated by IgE; they include food-induced anaphylaxis,

immediate gastrointestinal (GI) hypersensitivity, acute urticaria, and oral allergy syndrome.^{1,2} While many foods have been identified as being allergenic, the majority of hypersensitivities can be attributed to eight foods: cow's milk, egg, peanut, tree nut, soy, wheat, fish, and shellfish.¹ Accurate estimates of prevalence of food allergy are a challenge, as emphasized in a recent publication by *The National Academies Press*.¹ Studies examining prevalence vary widely with respect to study design, patient cohort, and even the definition of food allergy, resulting a prevalence ranging from 0.02% to 30% depending upon the study.¹ Children at elevated risk for developing food allergy are those with a history of atopic dermatitis, asthma, allergic rhinitis, or a family history of atopy.¹

The natural history of food allergy varies with specific foods. Hypersensitivity to milk, egg, soy, and wheat tend to manifest in childhood (often before 2 years of age) and all are likely to resolve. By contrast, peanut and tree nut allergy can develop at any point in life, while allergy to fish and shellfish is more likely to develop in adulthood; all of these typically result in lifelong hypersensitivity. With respect to severity, peanut and tree nut allergies are among the most concerning, accounting for greater than 90% of fatalities due to anaphylactic reactions.³

Pathophysiology and clinical manifestations

The allergy and immunology literature defines a “complete allergen” as a substance capable of inducing sensitization and triggering a clinical reaction. With respect to food allergy, small, water-soluble, heat- and acid-resistant glycoproteins are typically complete allergens. Furthermore, it is unlikely for anyone to be sensitized to a carbohydrate or fat component of foods, and thus, these components do not typically lead to allergic reactions. IgE-mediated food allergy is the result of abnormal sensitization leading to development of antibodies to harmless food proteins that trigger a type I hypersensitivity reaction. The mechanism for this is not fully understood but genetic and environmental factors likely play a role.

Type I hypersensitivity reactions are initiated when an allergen cross-links two IgE antibodies coating the surface of mast cells or basophils. Cross-linking generates a signal cascade within the mast cell or basophil resulting in release of chemical mediators culminating in physiologic consequences. IgE-mediated reactions can be classified as either immediate (within minutes) or delayed (within 2–4 h) and the timing of symptoms is a reflection of the actions of different chemical mediators. Mediators and their physiologic consequences are summarized in Table 1.

Clinical symptoms elaborated via the actions of chemical mediators can manifest in various organ systems including cutaneous, respiratory, cardiovascular, and gastrointestinal. Oral food challenge (OFC) studies reveal that cutaneous symptoms such as hives are the most common manifestation of food allergy.⁴ Furthermore, reactions to certain allergens are more likely to present in specific organ systems compared to other

allergens.⁴ For example, peanut allergy is more likely to impact the respiratory system while egg allergy more commonly impacts the GI tract.⁴ Anaphylaxis occupies the severe end of the clinical spectrum as a rapid manifestation of multisystem involvement resulting in laryngeal edema and cardiovascular collapse.

Diagnosis and management

Diagnosis of IgE-mediated food allergy is dependent upon a combination of history, allergen-specific serum-IgE (sIgE) levels, skin prick test (SPT), and oral food challenges. Sensitization describes the presence of allergen-specific IgE as determined by SPT or sIgE levels. One can be sensitized to a particular food allergen but not manifest clinical symptoms upon exposure to the allergen. This difference between sensitization and clinical allergy is dependent upon several variables of the IgE antibody itself including its quantity in the serum,

Table 1 Mast cell mediators of type I hypersensitivity (*PAF = platelet-activating factor)

	Vasodilation	Vascular Leak	Smooth Muscle Spasm	Leukocyte Extravasation
Histamine	×	×	×	
PAF*	×	×	×	
Leukotriene C4, D4, and E4	×	×	×	
Prostaglandin D2	×	×	×	
Cytokines				×

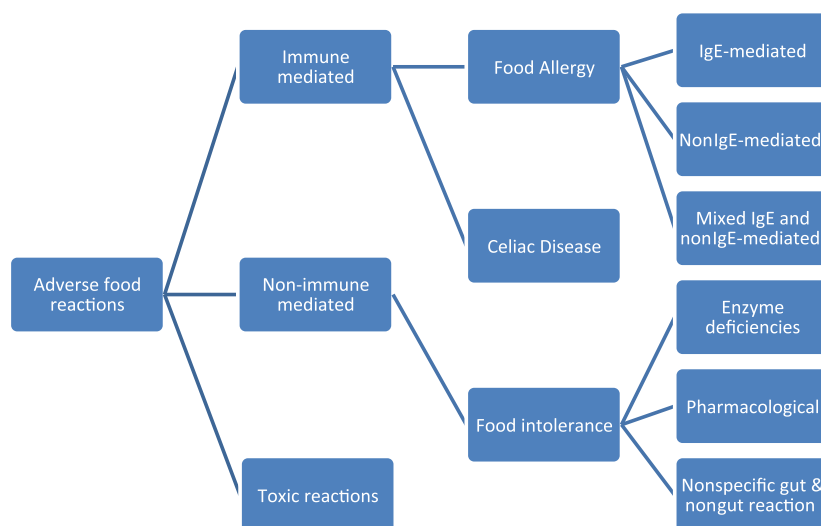


Figure 1 Classification of adverse food reactions.

affinity for the allergen, and specificity for certain sub-components of the allergen.^{1,2}

Management of IgE-mediated food allergy requires a comprehensive plan that includes strict avoidance of allergens through diet modification as well as immediate recognition and treatment of symptoms should exposure occur. Avoidance of the allergen requires education of parents and children about reading food labels and vigilance about cross-contamination in uncontrolled environments such as restaurants or parties. Should an exposure occur, treatment is focused on halting the effects of chemical mediators and preventing their further release. Given that histamine is the primary mediator, antihistamines (both H1 and H2 receptor blockers) are useful for mitigating the effect of histamine. Epinephrine stabilizes mast cell degranulation and is thus the single most important intervention for severe reactions, as it will prevent further histamine release. For this reason, epinephrine autoinjectors are often prescribed.

Epinephrine autoinjectors (EAI) are deemed first-line emergency management and should be used in concert with calling for emergency medical help. However, not every child with a food allergy needs them. Guidelines for prescribing an EAI for food allergy vary among different countries. In the USA, the National Institutes of Allergy and Infectious Disease (NIAID) expert panel recommends prescribing *two* autoinjectors for: a history of systemic allergic reaction; food allergy plus asthma; known allergy to peanut, tree nut, fish, or shellfish; and consideration should be given in all IgE-mediated food allergy.² Experts from the British Society for Allergy and Clinical Immunology (BSACI) recommend EAI prescription be *considered* in food allergy for: history of a severe systemic reaction to an allergen that cannot be easily avoided, allergy to high-risk allergens (nuts) in the setting of other comorbidities (asthma), and history of reaction to trace amounts of allergen.⁵ The BSACI guidelines further emphasize risk assessment by an allergist to determine need for an EAI. Such risk assessment not only includes clinical risk evaluation but also considers social factors such as remoteness from medical help, which lowers the threshold for prescribing this emergency medication.⁵ Although the British experts advise that most patients should require only a single autoinjector, they do recognize that the aforementioned allergist risk assessment may deem it necessary to prescribe two autoinjectors (i.e., prior need for two doses, obesity or geographic isolation).⁵ BSACI guidelines also stress the importance of routine follow-up to reassess risk as food allergies may resolve over time—making an autoinjector no longer indicated. Despite some differences between the USA and British recommendations, both emphasize

the importance of patient and family education with respect to establishing a written emergency action plan and proper use of EAIs.

A final point regarding EAIs is important to address: should children who are prescribed EAIs have them available during their perioperative journey? We agree it is important that patients prescribed EAIs carry them at all times; therefore, bringing them to the hospital should not be an exception. These devices should be available in the unlikely event that a reaction occurred on the trip to or from the hospital; however, making them available to anesthesia providers perioperatively is unnecessary and potentially problematic for several reasons. First, as epinephrine is a standard component of pediatric advanced life support interventions, it is readily available to anesthesia staff in modern operating rooms and easily obtainable elsewhere in the hospital. Second, if a patients' autoinjector were used while in the hospital, the patient would be obligated to re-fill this prescription in order to have it available to them while at home, which is an unnecessary burden. Finally, if used while in the hospital, the significant cost of EAIs in the USA (generic \$300 two-pack) saddles families with a very real financial burden. For both these reasons, utilization of these devices while patients are in a hospital setting is unnecessary.

Non-IgE-mediated food allergy

Overview

While IgE-mediated food allergy can lead to immediate and severe symptoms, non-IgE-mediated food allergies universally result in a delayed symptom response affecting the GI tract and are often underrecognized or misdiagnosed. Classic cutaneous and respiratory symptoms resulting from IgE-mediated hypersensitivity are uncommon in non-IgE reactions.⁶ In descending order of clinical severity, non-IgE food allergy includes: food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy, and food protein-induced allergic proctocolitis.⁷ FPIES is the most severe of these and will be explored further.

The typical onset of FPIES is during the first year of life and is rarely diagnosed thereafter.⁸ The exact prevalence of FPIES is unknown; but in a large Israeli study, the prevalence of FPIES due to cow's milk was 0.34%, while the prevalence of IgE-mediated allergy to cow's milk was 0.5% in the same study population.⁸ The prevalence of FPIES to other foods is largely unknown.⁸ Most patients (65%) are sensitive to one food, 26% react to two foods, 9% react to three or more foods, and very few react to six or more.⁷ An atypical form (24% of

cases) exists in patients who have the classic features of FPIES but have detectable IgE levels to the offending foods. These patients usually have a more protracted course that can last for years.⁷ Risk factors include delivery by cesarean section, male gender (54–60%), FPIES to another food, and early introduction of cow's milk.⁸ Similar to IgE-mediated food allergy, 30% of FPIES patients are atopic.⁸

FPIES is most commonly triggered by cow's milk and soy, with rice and oat being second most common. Other foods include eggs, poultry (chicken and turkey), meat, beans, vegetables (white potato, sweet potato, and squash), tomato, fruits, legumes (peanut, green pea, lentil, string bean), different cereals, and seafood.⁷ Similar to IgE-mediated allergy, FPIES triggered by fish and other seafood are seen mainly in older children and adults.⁸

Pathophysiology and clinical manifestations

The exact mechanism of FPIES is not completely understood but it may represent a defect in the protective and immunological function of the intestinal tract.⁷ It is believed that ingestion of food allergens leads to T-cell activation and release of proinflammatory mediators such as TNF- α and INF- γ , which cause intestinal inflammation. Inflammation enhances intestinal penetrability of the offending allergens and their presentation to the immune system.⁷ Activation of other cells such as peripheral mononuclear cells, regulatory T cells, eosinophils, neutrophils, and thrombocytes has also been observed.^{7,8}

In addition to the inflammatory cascade, involvement of humoral and neuroendocrine pathways has been postulated. While the details of humoral involvement are yet to be fully elucidated, biopsy data have shown elevated IgA and decreased IgG4 antibodies in patients with FPIES. A neuroendocrine mechanism was suggested because of the effectiveness of ondansetron in treating FPIES symptoms. Ondansetron, which is a 5-HT₃ antagonist, reduces central and peripheral vagus nerve activity.⁸ The vagus nerve is increasingly recognized as an important mediator in the inflammation process. Its afferent fibers sense the inflammatory signals and convey them to the brain. At the same time, the efferent fibers modulate the inflammatory response by controlling acetylcholine release from T cells. These cholinergic signals activate $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) on immune cells.⁹

Clinical manifestations of FPIES depend on the dose and frequency of the triggering food ingested. An acute attack occurs if the patient is exposed to the allergenic food for the first time, reintroduced to it after a period

of abstinence, or following an OFC test. The acute severe FPIES attack manifests as profuse, repetitive, and sometimes projectile vomiting (10–20 episodes) often with diarrhea, leading to severe dehydration and possibly shock. The onset of vomiting is typically 1–3 h, while diarrhea is delayed 5–10 h after culprit food ingestion. Vomiting is the most common (95–100%) presentation followed by lethargy, pallor, dehydration, diarrhea, and hypothermia (Table 2).^{7,8}

Chronic FPIES develops upon ingestion of the allergenic food on a regular basis leading to intermittent vomiting, diarrhea, malabsorption, dehydration, weight loss, and failure to thrive. Anemia and hypoalbuminemia are frequently encountered in these patients. Despite the severe reaction that may occur during the acute attack, FPIES can be considered a self-limiting disease as patients are asymptomatic if they are not exposed to the offending food.^{7,8}

Diagnosis and management

Delay in diagnosis may result from the nonspecific clinical features, lack of specific allergic tests, broad differential diagnosis, the perception that grains and vegetable proteins are hypoallergenic, and the unfamiliarity of this condition among treating healthcare providers. There are no pathognomonic biomarkers or radiologic findings specific to diagnose FPIES. Thus, it is a diagnosis of exclusion, largely based on history, clinical criteria, and an OFC test. Diagnostic features include: (i) Age <9 months, (ii) predictive repetitive vomiting and/or diarrhea within 24 h of exposure to trigger food, (iii) only GI symptoms, and (iv) resolution of symptoms within 24 h of avoiding exposure.¹⁰ Table 3 summarizes the diagnostic tests and their relevance. Severe cases may present similar to an acute abdomen, but characteristically the patient improves significantly with exclusion of the food allergen and the workup for sepsis is negative.

Table 2 Differences are noted between acute and chronic presentation of FPIES

Acute FPIES	Chronic FPIES
Repetitive vomiting (95–100%)	Intermittent vomiting
Lethargy (75–85%)	Diarrhea
Pallor (67%)	Lethargy
Dehydration (15–20%)	Pallor
Diarrhea (25–40%), bloody if severe	Dehydration
Hypotension and shock (if severe) (15–20%)	Weight loss
Abdominal distension (if severe)	Failure to thrive
Metabolic acidosis (if severe)	Abdominal distension
Hypothermia <36 °C (<25%)	Limpness
Cyanosis	Dusky appearance

Table 3 Comparison of diagnostic tests for FPIES

Diagnostic test	Comments
Oral food challenge (OFC)	Gold standard (not indicated for initial diagnosis with typical symptoms and/or hypotension, but are necessary for follow-ups and for food reintroduction)
Leukocytosis	Nonspecific but is a prominent finding in acute FPIES
Thrombocytosis	Nonspecific but found in 63% of patients
Food-specific IgE antibody	Undetectable (except in 25% of patients who later convert to IgE-specific food allergy)
Skin prick tests	Not indicated (negative in up to 90% of cases)
Atopy patch tests	Mixed results (not typically used for diagnosis)
Fecal tests	Nonspecific
Intestinal biopsies	Not routinely required except in persistent severe chronic disease or to exclude other GI pathology. Nonspecific findings (diffuse inflammation, friable hemorrhagic mucosa with ulcers, edema, villous atrophy, absent lymphonodular hyperplasia, and eosinophils clusters)
Methemoglobinemia	Positive in severe acute attacks. Produced by increased heme oxidation caused by the elevation of nitrites which is the result of reduced catalase activity associated with severe intestinal inflammation
Metabolic acidosis	Nonspecific and also present in sepsis like illness
C-reactive protein	Nonspecific
Radiologic findings	Nonspecific. Include air-fluid gut levels, nonspecific narrowing and thumb printing of the rectum and the sigmoid, thickening of the plicae circulares, and intramural gas. Resemble acute abdominal pathology. Resolve with elimination of the offending food
Gastric juice leukocytosis	Currently, it is a research tool rather than a diagnostic test
Anemia and hypoalbuminemia	Common in chronic FPIES
Peripheral blood eosinophilia	Typically absent

Management of severe acute FPIES is one of supportive care and begins with vigorous intravenous (IV) resuscitation ($10\text{--}20\text{ ml}\cdot\text{kg}^{-1}$) of balanced electrolyte solution for severe attacks or oral rehydration if tolerated for mild symptoms. Methylprednisolone, $1\text{ mg}\cdot\text{kg}^{-1}$ (maximum $60\text{--}80\text{ mg}$), is recommended for severe reactions in order to decrease presumed cell-mediated intestinal inflammation. Bicarbonate is used to treat metabolic acidosis. Vasopressors, such as epinephrine, are given for severe hypotension or shock, but they are not effective in improving the symptoms of vomiting and lethargy. Ondansetron, $0.2\text{ mg}\cdot\text{kg}^{-1}$ per dose, has

been shown effective in treating emesis along with IV fluids. Methemoglobinemia results from increased heme oxidation caused by elevation of nitrites and reduced catalase activity associated with severe intestinal inflammation.⁷ Methylene blue, $1\text{--}2\text{ mg}\cdot\text{kg}^{-1}$, should be administered to treat methemoglobinemia.⁸ Oxygen supplementation is indicated in patients with cyanosis, shock, or those with severe methemoglobinemia.⁸ Temporary bowel rest and parenteral nutrition may be needed in the most severe cases.

The mainstay of management for chronic FPIES is avoidance of the culprit food. Due to the unfamiliarity of FPIES in urgent care centers, letters explaining the presentation and management of FPIES, provided by families to healthcare providers, can be helpful.

Perioperative considerations

Preoperative

Children with food allergy may present for anesthetic care at any time for the full spectrum of surgical or diagnostic procedures. Given that certain allergies are more common in childhood, it is conceivable that the pediatric anesthesiologist may encounter these patients more frequently compared to adult anesthesiologists. Factors impacting both the patient and anesthesia provider should be considered preoperatively when caring for these patients. With respect to the patient, children with atopy may be at greater risk of developing adverse respiratory reactions under general anesthesia because of the increased risk of laryngospasm, bronchospasm, breath holding, and desaturation. A discussion on a patient's allergy history should not be limited to medication allergies because certain aspects of food allergy are potentially relevant. Anesthesia providers should also consider their own potential exposure to allergens throughout the day (i.e., nut exposure during a lunch break) as this could impact highly sensitive patients. A logical question might be: how should anesthesia providers respect these food allergies as we care for patients? It is plausible to assume we can all be exposed to these allergens during lunch breaks. We will look to the nut allergy literature for the answer.

Anesthesia provider contamination with food allergens

Peanut allergy accounts for the majority of severe, life-threatening food allergy, and as a result, much of the literature regarding minimum threshold allergen exposure and how to disinfect allergens from surfaces focuses on nut allergens. Food allergy experts have aimed to identify the lowest observed adverse-effect level (LOAEL) for common food allergens in order to inform the food

industry on detection of contaminants as well as to determine protective measures for patients who are most sensitive. The gold standard for determining such thresholds, the double-blind placebo controlled food challenge (DBPCFC), was recently used to establish the minimum quantity of peanut allergen required for a reaction in patients with peanut hypersensitivity.¹⁰ Briefly, the DBPCFC involves ingestion of increasing doses of a food allergen matrix (or placebo) until a clinically objective or subjective reaction occurs. Using this method, investigators found the dose of peanut allergen likely to elicit a response in 10% of the study population (ED_{10}) was 2.8 mg (equivalent to 11.2 mg of peanut seed).¹⁰ An important application of this knowledge, relevant to perioperative care of patients, is how best to decontaminate this minimum dose of allergen from surfaces.

Typically, ingestion of peanut allergen is required to trigger a severe reaction, and casual contact or inhalation of allergen does not pose a significant risk.¹¹ However, guidelines pertaining to the proper decontamination of surfaces exposed to peanut allergen are available for wide use.^{12,13} Perry and colleagues showed that the most common peanut allergen, Ara h 1, is easily cleaned from hands by using soap and water and from tabletops using common household cleaners.¹² Interestingly, antibacterial hand sanitizer was not adequate to remove all contaminant in this study.¹² Based upon this evidence, it seems prudent that perioperative implementation of these decontamination measures, many of which are presumably included in current sanitizing processes, is likely to result in very low risk of allergen exposure to at risk patients. We recommend washing hands with soap and water after eating, as it is a simple and sensible thing that all anesthesia providers can do prior to resuming patient care to further reduce risk. The Centers for Disease Control (CDC) has established guidelines for schools to create a safe environment with respect to food allergies.¹³ Although they suggest instituting “nut-free zones” in schools, the establishment of “nut-free” hospitals seems unnecessary if not impractical given that hospitals arguably are a more controlled environment where decontamination practices can be easily followed.

Preoperative considerations in non-IgE-mediated food-allergic patients

While classic IgE-mediated food allergy patients are unlikely to present for elective procedures during an acute hypersensitivity reaction; the less obvious presentation of non-IgE-mediated food allergy, especially FPIES, can present perioperative challenges. The greatest challenge comes from an infant with an unknown severe case of FPIES that presents as an acute abdomen. Surgery may be performed in these cases, exposing these infants to

unnecessary procedures. In this context, history of marked symptom improvement after culprit food exclusion and intravenous hydration should alert clinicians to reconsider the diagnosis of a surgical abdomen. In acute known FPIES cases, surgery is contraindicated except if there is a strong suspicion of another underlying pathology.

In addition, due to the rare nature of FPIES, adverse reactions to anesthesia drugs in such populations are largely unknown. Of potential concern might be propofol due to its egg and soy components. The use of propofol in egg- and soy-allergic patients will be discussed in detail later. To date, no case reports in the literature have documented an adverse drug reaction in FPIES patients; but, this could be due to underreporting or unrecognized reactions. Therefore, due to the inherent nature of delayed symptoms, history should include any complications from anesthesia that extended beyond the immediate PACU stay into the postoperative period. For example, in outpatient surgery situations, symptoms of vomiting and diarrhea will not typically be seen until 4 hours after discharge, which is well beyond the patient's PACU stay. In this regard, parents and previous anesthesia records documenting medication given serve as a great source of information.

Preoperative food allergy reactions and elective surgery

Finally, one might wonder about the timing of surgery in the context of a recent food allergy reaction—specifically, what type of a reaction might warrant cancellation of an elective procedure? Unfortunately, there is nothing in the literature to help guide us on this. As mentioned above, it is sensible to delay an elective surgery in the setting of a severe food allergy reaction resulting in life-threatening symptoms (hypovolemia or bronchospasm), or during an acute FPIES reaction resulting in hypovolemia. However, for more mild reactions, as seen with urticaria, the clinical decision-making process is far less obvious. Given the limited data, extrapolating from the immunization literature might be a source of insight for basic recommendations. With regard to immunization, some vaccinations may elicit adverse reactions in certain subsets of children. These symptoms could potentially be misinterpreted as perioperative hypersensitivity reactions if they occur within a certain window of exposure to anesthetic or perioperative medications. While there is no current evidence to contraindicate immunization of healthy children immediately prior to surgery, some recommend that elective procedures be postponed for up to 3 weeks after receiving a live attenuated vaccination. This recommendation came about after Judith Short and colleagues conducted an international survey to assess the level of concern anesthesiologists had about the timing of vaccination with respect to elective

surgery.¹⁴ With this in mind, similarly, it may be practical to postpone an elective surgery in the setting of a recent mild allergic reaction if there is concern that the preoperative presence of these symptoms might be confused with an allergic reaction secondary to medication administration perioperatively. Although ideally postponing surgery until urticarial symptoms resolve, the lack of evidence ultimately leaves this decision to the clinical discretion of the anesthesia provider.

Intraoperative

The potential for cross-sensitivity between food allergy and certain medications pediatric patients may be exposed to intraoperatively is controversial. It is well documented that the most likely culprits resulting in a perioperative hypersensitivity reaction are neuromuscular blockers (NMBs), latex, and antibiotics.¹⁵ Hypersensitivity reactions to iodinated substances, protamine, and propofol are also relevant to our discussion of intraoperative care. Quaternary ammonium ions are the presumed sensitizing entity with respect to NMBs and there is no evidence in the literature linking these to specific food allergies. Of the remaining substances, iodinated media, protamine, latex, and propofol are the only ones pertinent to further discussion involving potential cross-sensitivity with food allergy. Available literature does not substantiate an association with these agents and an increased risk for allergic reaction in patients with food allergies, except for potential concern with protamine.

Seafood and fish allergy: Iodinated media and protamine

Pediatric patients can be exposed to iodinated media and protamine intraoperatively. Exposure to iodinated substances may occur as a part of sterile surgical preparation or via imaging studies in the form of radiocontrast media (i.e., iopamidol for epidurogram). Protamine is routinely used for reversal of heparin, most commonly in the cardiac operating room or catheterization laboratory. We discuss these items together as there has been a theoretical concern regarding cross-sensitivity with fish or seafood allergy for both.

The risk of iodine administration in patients with seafood allergy is a misconception among patients and physicians alike. Esteban Schabelman and Michael Witting evaluated the roots of this myth in a review of the literature published in 2010.¹⁶ The authors trace the origins of this link between seafood allergy and radiocontrast to studies published in the 1970s that reported a hypersensitivity to iodine contrast in patients who also had other allergies, not just food allergy. They further explain that somehow this reaction to iodine became wrongly perpetuated as an “allergy to iodine”. A position statement by

the American Academy of Allergy, Asthma and Immunology further demystifies this issue with three key points: (i) reactions to iodine radiocontrast media are mediated by an anaphylactoid mechanism that does not involve IgE and is not evidence of allergy to iodine, (ii) contact dermatitis to iodinated antiseptics is not an IgE-mediated response triggered by iodine and (iii) protein components of seafood including parvalbumin and tropomyosin are responsible for hypersensitivity to seafood, not iodine.¹⁷ In summary, there is no evidence in the literature linking seafood allergy and iodinated agents.

Unfortunately, the data concerning protamine and potential cross-sensitivity with fish allergy are less straightforward. The connection between fish allergy and protamine stems from the fact that commercial formulations of protamine are derived from salmon milts (sperm). Protamine is a simple, low molecular weight protein and therefore could result in IgE-mediated hypersensitivity. The package insert from one manufacturer includes allergy to fish as risk factor in its boxed warning (Fresenius-Kabi, Germany). However, this manufacturer does not include fish allergy as a contraindication, acknowledging that while “patients with a history of allergy to fish may develop hypersensitivity reactions to protamine... to date no relationship has been established between allergic reactions to protamine and fish allergy.” Indeed, our appraisal of the literature did not reveal any definitive connection, but only isolated case reports of potential cross-sensitivity between fish allergy and protamine in adults. As previously detailed, fish allergy is more likely to develop later in life, and thus, is of less concern in pediatric patients. Nevertheless, because it is conceivable that prior sensitization to fish could result in an IgE-mediated reaction to protamine, a medication made from a fish-derived protein, we cannot definitively rule out this possible connection. If there is sufficient concern, patients should be allergy tested for fish and protamine prior to planned exposure to protamine. If such testing were positive, alternatives to heparin, such as direct thrombin inhibitors (i.e., bivalirudin), could be considered and have been used in adults for this very reason.

Banana, avocado, and kiwi: latex-fruit syndrome

Allergic reactions triggered by exposure to natural rubber latex (NRL) in the healthcare setting can impact healthcare workers and patients alike. NRL is well established as both a contact allergen and aeroallergen with multiple proteins implicated.¹⁸ The potential for severe reactions has led to the implementation of latex-free strategies that are nearly ubiquitous in modern healthcare settings. While establishment of a latex-free healthcare environment has helped decrease the risk, a

well-documented cross-sensitivity between allergy to NRL and certain fruit is relevant to our discussion.

Latex-fruit syndrome (LFS), first defined by Carlos Blanco in 1994, is a clinical entity whereby IgE antibodies recognizing latex proteins cross-react with similar epitopes found in fruits.^{18,19} Rates of cross-sensitivity with fruit among NRL allergic patients range from 21% to 58% with the most common fruits being banana, avocado, kiwi, and chestnut.¹⁷ Similar to the wide range of prevalence is a wide range of severity with certain foods (i.e., papaya) more likely to cause severe reactions like anaphylaxis.¹⁷ An important question is: what comes first? For example, does an allergy to NRL establish cross-sensitivity to avocado or should a patient with a known avocado allergy be placed on latex precautions despite no documented clinical latex hypersensitivity? The answer seems to be that either can occur. Data show that patients with avocado allergy are likely to have IgE-mediated sensitivity to latex and people with occupational exposure to certain foods are at increased risk for NRL allergy.¹⁷ With this in mind, latex precautions should be considered for children with hypersensitivity to banana, avocado, kiwi, and chestnut as these are the most frequently implicated foods.

Egg, soy, and peanut allergy: propofol

As an induction agent, propofol is of potential concern because of its egg and soy contents. As a result, package inserts of all propofol formulations contraindicate its use in patients with egg and soy allergy, while European package inserts also warn about use in peanut allergy due to potential cross-sensitivity with soy. Propofol is an alkylphenol derivative (2,6-di-isopropyl-phenol) containing soybean oil (10%) and egg lecithin (1.2%). Lecithin, a highly purified egg yolk phosphatide, is not the allergenic component in IgE-mediated egg allergy. Most patients with egg allergy are allergic to the protein components of egg, most commonly ovomucoid. The soy oil is highly refined during propofol preparation by removing allergenic proteins. Curiously, while the fat emulsion, Intralipid, also contains soybean oil and egg yolk lecithin, identical to that found in propofol, its package insert does not mention any contraindication in patients with egg, soy, or peanut allergy.

Data in the literature with respect to propofol and food allergies include case reports and retrospective studies focusing on its use in patients hypersensitive to egg, soy, and peanut. Multiple case reports published between 1992 and 2010 attempted to implicate propofol in perioperative allergic reactions, specifically in egg-allergic patients. These were met with similar criticism including unclear details of the egg allergy history, lack of follow-up confirmatory allergy testing to propofol,

and patient exposure to confounders such as NMBs or latex. Interestingly, the earliest such case reports did not even attempt to link food allergy and a potential reaction to propofol. Documented anaphylactic reactions to propofol have been attributed to its isopropyl or phenol groups rather than its egg or soy contents.

A retrospective case review published by Murphy and colleagues identified 28 pediatric patients with known egg allergy who were also given propofol as part of an anesthetic.²⁰ Among these patients, only one had a documented perioperative allergic reaction, resulting in 98% of these patients being exposed to propofol without incident.²⁰ The single reaction was urticaria in a patient who had history of anaphylaxis to egg leading the authors to caution the use of propofol in patients with history of egg anaphylaxis. However, the authors did conclude that propofol is likely safe in the majority of egg-allergic children. Another retrospective study in 2014 looked at propofol administration in adult eosinophilic esophagitis (EoE) patients.²¹ Eighty-six percent of these patients were sensitized to egg, soy, or peanut, and underwent a combined 404 anesthetics, including propofol, for upper endoscopy.²¹ The authors found no allergic adverse events and concluded that propofol can be safely administered in adult EoE patients with known egg, soy, or peanut sensitivity.²¹

In January 2016, a group in Denmark performed the largest study to date. This study included two parts—"Study A," retrospectively examined the frequency of propofol allergy in patients being evaluated for suspected perioperative allergic reactions in the Danish Anesthesia Allergy Center, and "Study B," retrospectively evaluated patients with known sensitivities to egg, soy, or peanut and reviewed medical records for a documented sensitivity reaction in those who were given propofol.²² Study A identified four patients with a positive test to propofol, none had a history of egg, soy, or peanut allergy nor did any of them test positive for IgE to egg or soy.²² Study B identified 544 patients evaluated by an allergist as IgE positive for egg, soy, or peanut but none of those who were also exposed to propofol had any documented concern for perioperative hypersensitivity reactions.²² The authors concluded that there was no connection between allergy to propofol and allergy to egg, soy, or peanut and that the current practice of modifying anesthetic plans to avoid propofol in such patients should be reconsidered.²² Finally, collaborators from Children's Hospital Colorado looked at propofol use in the pediatric EoE population.²³ In this retrospective, observational study, they found that while propofol tended to be used less in egg- or soy-allergic patients when it was used there was no difference in complication rates related to propofol use.²³

These retrospective studies all emphasize a lack of evidence for avoiding propofol in patients with egg, soy, and peanut allergy. A statement by the American Academy of Allergy Asthma & Immunology corroborates this: "Patients with soy or egg allergy can receive propofol without any special precautions. Any patient whether soy or egg-allergic or not, who has an apparent allergic reaction to propofol should be evaluated by an allergist."²⁴

Current evidence does not support a concern for any food allergy and cross-sensitivity with common anesthetic medications. However, such atopic patients should be monitored with elevated vigilance and deemed a higher risk for reaction whether they have a food allergy or not. If appropriate, the preoperative period could be used as a time to educate patients and parents about the safety of these medications despite food allergy. Reasonable concessions for patients (or parents) adamant about avoiding certain anesthetic agents should be entertained. All other induction and inhalation agents are considered safe.

Postoperative

While we contend that cross-reaction between food allergy and perioperative substances is highly unlikely, a discussion of postoperative allergy management is important to address. Lene Garvey of the Danish Anaesthesia Allergy Centre described a systematic approach to perioperative allergy in a recent review.²⁵ Thorough evaluation of the hypersensitivity reaction is a key postoperative component and ideally involves collaboration between the anesthesiologist of record and an allergist. In an effort to provide an accurate history, any suspected perioperative allergic reaction should be well documented in the anesthetic record with attention to symptoms and their timing relative to medication administration. As a guideline, any intravenous substance administered within 1 h of a reaction and any substance given by another route within 2 h of a reaction should be investigated.²⁵ Knowledge of potential causes for the perioperative reaction should then prompt referral to an allergist for definitive evaluation. It is prudent to await the results of this evaluation before a new substance is added to a patient's allergy list in their medical record in order to ensure the allergy record is as accurate as possible. Given the potential for life-threatening reactions triggered by some food allergies, these reactions should be documented and given attention in handoffs and perioperative evaluations, no different than drug allergies. As described earlier, the risk of a significant reaction occurring likely requires ingestion of allergen, but all hospital staff can easily introduce an allergen if they do not effectively remove contaminants by washing their hands prior to patient contact.

Conclusion

Food allergy in pediatric patients can present in the form of classic IgE-mediated reactions or non-IgE-mediated food intolerance. These patients may present for anesthetic care for a variety of reasons. All anesthesia providers should wash their hands with soap and water after eating to minimize allergen exposure to the most sensitive patients. With the possible exception of concern for fish allergy and protamine administration, there is no evidence in the literature supporting avoidance of anesthetic agents with respect to potential cross-sensitivity with food allergy. Patients with certain fruit allergies should be considered at risk for reaction to natural rubber latex. All patients with food allergy should be considered atopic and at greater risk for hypersensitivity reactions, and appropriate perioperative vigilance should be employed.

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Learning points

- Classification of different types of adverse food reactions.
- Identification of different pathophysiological mechanisms of IgE- and non-IgE-mediated food allergies.
- Discussion of perioperative considerations in children with food allergy.
- Considering the implications of a child's food allergies when developing an anesthetic plan.

Reflective questions

- What components of foods are most likely to result in IgE-mediated hypersensitivity?
- Why are iodinated medications not a concern in patients with allergy to fish or seafood?
- How might you alter your anesthetic plan for a patient with egg or soy allergy after reading this review?
- What is an important component of postoperative management following a suspected and resolved perioperative hypersensitivity reaction?
- After reading this article, would you use propofol in children with FPIES to egg and soy?

Disclosures

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Additional Supporting Information may be found in the online version of this article:

Audio S1. Audio file provides a summary of the salient points of the manuscript highlighted by the first author.

Supporting information

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