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Practice Point

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Practice Point

Non-IgE-mediated food allergy: Evaluation and management

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Abstract

The most common types of non-IgE-mediated food allergy are food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP). FPIES presents with delayed refractory emesis, while FPIAP presents with hematochezia in otherwise healthy infants. Acute management of FPIES includes rehydration or ondansetron, or both. No acute management is required for FPIAP. Long-term management of both disorders includes avoidance of the trigger food. The prognosis for both conditions is a high rate of resolution within a few years' time.

Keywords: *Allergy; Food allergy; Food protein-induced enterocolitis syndrome; Food protein-induced allergic proctocolitis*

Several disorders are classified as non-immunoglobulin E(IgE)-mediated food allergies, including food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPE), and other conditions (1). This practice point focuses on FPIES and FPIAP as the most common of these conditions. The largest prospective study of infants with non-IgE-mediated food allergy reported a cumulative incidence for FPIES of 0.34% (2), and for FPIAP of 0.16% (3). However, the estimated prevalence of FPIES and FPIAP varies among studies (4), and are probably underestimated overall (1). The pathophysiologies of FPIES and FPIAP are poorly understood but both conditions are believed to be caused by T-cell-mediated inflammation (1,5).

CLINICAL MANIFESTATIONS

Food protein-induced enterocolitis syndrome: FPIES

FPIES generally presents in infants between 2 and 7 months of age, often in association with the introduction of formula or solids into the diet (although this disorder can also occur into adulthood) (1,2,5,6). Acute FPIES is characterized by profuse, repetitive vomiting, often accompanied by pallor or lethargy (or both) and typically occurring 1 to 4 hours after ingesting the trigger food (1,5,7). Signs may occur on first exposure to the trigger food or after a period of tolerance (8). Associated diarrhea, which often represents a more severe form of FPIES, can occur 5 to 10 hours later (8). In rare severe cases, infants may experience associated hypothermia, hypotension, loss of consciousness, hypotonia, acidemia, or methemoglobinemia (1,5,9).

In contrast to IgE-mediated allergy, there are no associated cutaneous or respiratory symptoms with FPIES. It is important to include FPIES in the differential diagnosis for an infant presenting to the emergency room with acute onset emesis, because presentation can be easily confused with viral gastroenteritis, sepsis, or other conditions.

Chronic FPIES is poorly described, uncommon, and requires more research for further characterization. Chronic FPIES occurs in the context of ongoing ingestion of the trigger food.

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Symptoms are nonspecific and may include failure to thrive, anemia, chronic diarrhea or emesis, and malabsorption (1). Symptoms resolve with elimination of the trigger food from the infant diet.

Food protein-induced allergic proctocolitis: FPIAP

FPIAP presents with intermittent, slow-in-onset hematochezia in an otherwise healthy, growing infant, generally in the first 6 months of life (typical onset is in the first 1 to 4 weeks post-delivery) (9). There is no associated emesis, diarrhea, or failure to thrive (1). Symptoms resolve with elimination of the trigger food from maternal or infant diet.

ACUTE MANAGEMENT

FPIES

History-taking should focus on infant feeding patterns, including introduction of formula or solids (or both), that are temporally associated with reactions. In acute FPIES, signs of dehydration may be present.

When blood work is performed acutely, infants with FPIES can also have leukocytosis, neutrophilia, thrombocytosis, methemoglobinemia, or metabolic acidosis. However, blood tests are neither sensitive nor specific for FPIES (10,11). In acute FPIES, dehydration can lead to hemodynamic instability, indicating a medical emergency (5). Management in the acute care setting includes intravenous (IV) fluid boluses (10 to 20 mL/kg of normal saline [NS] may be required) (10). There is increasing evidence that IV or intramuscular (IM) ondansetron (one dose of 0.15 mg/kg; typically 2 mg for patients weighing 8 to 15 kg; 4 mg for those weighing 15 to 30 kg; and 8 mg for those >30 kg) may resolve ongoing emesis and reduce the risk of dehydration when used for acute FPIES (12–14). When FPIES is severe, IV corticosteroids (e.g., methylprednisolone 1 mg/kg to a maximum of 60 to 80 mg) may be considered, although there are no studies demonstrating the efficacy of this strategy (10).

FPIAP

In general, the physical examination and blood work will be normal. No acute intervention, including blood work, is required.

LONG-TERM MANAGEMENT

FPIES

Primary management consists of eliminating the trigger food from the infant's diet (Table 1) (11,15). Identification of the trigger food relies largely on clinical history. There is no validated diagnostic testing for FPIES other than an oral food challenge by an allergist (using observed ingestion in the office [OFC]). An OFC would only be recommended if the infant's history is unclear, such as in the absence of a clear trigger food, an atypical symptom time course, or lack of symptom resolution with trigger food elimination (5,16). For infants with a clear history, the OFC is mainly indicated to assess whether FPIES has been outgrown. Stool testing, endoscopy, and radiography are not recommended (5,10).

In contrast to IgE-mediated allergy, there is no need to avoid food products with precautionary (e.g., 'may contain') labelling and, in most cases, no need for maternal elimination of trigger foods while breastfeeding (5,7). Nor is having an epinephrine autoinjector required (7).

Infants with FPIES may react to multiple food triggers. The prevalence of multiple food FPIES varies by geographic location but is estimated to affect up to about 30% of infants with FPIES (11,15). In the absence of a history of reaction, however, avoiding common FPIES triggers during infancy is not recommended (15). Although some guidelines suggest delaying introduction of additional common allergens empirically to prevent FPIES, this approach is not recommended. Because IgE-mediated food allergy is more prevalent and generally more difficult to outgrow, the risk of developing an IgE-mediated allergy to foods such as peanut or egg outweighs the benefit of delayed introduction to manage or prevent FPIES (17). Rather, introducing commonly

Table 1. Food triggers for FPIES, from most to least common

Food Category	Specific foods	Rates
Milk		67%
Soy		41%
Grains	Rice > Oat > Wheat > Corn > Barley	25.3%
Egg		11%
Meats/Fish	Chicken > Turkey > Beef > Pork > Lamb > Salmon > Crab	<10%
Vegetables	Sweet potato > Pea > Potato > Carrot > Squash > Kidney bean > Green bean	<10%
Fruits	Banana > Apple > Pear > Peach > Plum > Strawberry > Watermelon > Avocado	<10%
Peanut/Tree nut	Peanut > Tree nut	<10%

Adapted from reference (15).

allergenic solids at around 6 months of age (and not before 4 months), especially if the child is at risk for IgE-mediated allergy, is recommended (17).

When an infant has cow's milk FPIES, extensively hydrolyzed formula should be considered as a feeding alternative (11,18). Recent data suggest that cross-reactivity between cow's milk and soy-based formulas is low, such that soy-based formula can be considered as an alternative for feeding infants over 6 months of age (2). A minority of infants trialed on extensively hydrolyzed formula appear to require an amino acid-based formula (5,10). When the trigger food is rice or oat, avoiding both these grains is recommended because of the high rate of cross-reactivity between the two. Attempting to introduce other grains into the diet of infants who react to either rice or oat is reasonable (10).

Especially in the context of multiple food FPIES, growth and nutrition must be closely monitored (5).

FPIAP

When an infant is breastfed, FPIAP typically resolves with the elimination of cow's milk (and often soy) from the maternal diet. Other possible triggers are egg and corn, which can be removed from maternal diet when symptoms do not resolve with cow's milk and soy elimination (7,19). In formula-fed infants, FPIAP typically resolves with transition to an extensively hydrolyzed formula (7,19,20). Only rarely is an amino acid-based formula required (19,20).

PROGNOSIS

FPIES

The natural history of FPIES is a high spontaneous rate of resolution, often in early childhood. A large review of FPIES in childhood noted rates of resolution of 35% by 2 years of age, 70% by 3 years of age, and 85% by 5 years of age (15). Solid food-related FPIES may resolve later than cow's milk or soy FPIES (5,11,15). Medically supervised OFCs may be considered as early as 12 to 18 months after the most recent reaction (1). They should be conducted in a medical setting with ready access to IV fluids, although data suggest that infants who require IV fluids tend to be younger or have severe FPIES (5,21). Different protocols for OFCs exist, with variability of protein amounts and observation periods (5).

FPIAP

FPIAP typically resolves by 1 year of age (1). Milk and soy can then be introduced into both the mother's and the infant's diet, one at a time, in an age-appropriate way (7). It is not known whether cow's milk and soy need to be introduced slowly, but this approach may be considered for practical reasons.

WHEN TO REFER TO AN ALLERGIST

FPIES

In general, young children with FPIES should be referred to an allergist who can offer OFCs for evaluation, especially before reintroducing a trigger food into the diet. Only an OFC can safely identify when a child has outgrown FPIES. Early referrals can help to ensure timely access to OFCs. Referral is also warranted when the family is hesitant to introduce new foods that have not been tried before.

Some guidelines recommend that allergists perform skin prick testing to measure food-specific IgE levels for a trigger food, because such tests can have prognostic implications (e.g., prolonged course) and identify children at risk for future IgE-mediated reactions (7). However, skin prick tests are highly susceptible to false positive results. Such tests should only be conducted with allergist guidance, and OFCs remain the procedure of first line.

Limited access to appropriate test settings in Canada may prompt health care providers to consider other factors. For example, in rural areas, a local paediatrician with admitting privileges may be comfortable conducting an OFC, after consultation with a paediatric allergist remotely. Specialist allergy involvement is not always necessary for infants whose trigger food has been clearly identified and whose family diet has not been otherwise restricted, provided that both the family and clinician are comfortable with ongoing nutritional management.

FPIAP

Infants with uncomplicated FPIAP may not require allergy referral. However, any infant with FPIAP should be evaluated if the trigger cannot be identified, or if the symptoms do not respond to typical trigger food eliminations.

PRACTICE POINTS

- Acute management of FPIES includes fluid resuscitation or IV/IM ondansetron (or both). No acute management of FPIAP is necessary.
- Long-term management of both FPIES and FPIAP involves eliminating the trigger food from the infant's diet.
- Avoiding cross-reactive foods and precautionary labelling are generally not required.
- Using an epinephrine autoinjector is not required for FPIES or FPIAP.
- Closely monitoring nutrition and growth, especially when there are multiple trigger foods or food avoidances, is essential.
- Both FPIAP and FPIES have high rates of resolution in early childhood. Reintroducing a trigger food at home can occur with FPIAP. For FPIES, reintroduction should occur under medical supervision.

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