Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology

The consensus document provides the first international evidence-based guidelines to improve the diagnosis and management of patients with FPIES. It also identifies the unmet needs and future directions for research. Research on prevalence, pathophysiology, diagnostic markers, and future treatments is necessary to improve the care of patients with FPIES. These guidelines will be updated periodically, as more evidence becomes available.

SUMMARY STATEMENTS

SS 1: Recognize FPIES as a potential medical emergency, which presents as delayed onset of protracted emesis and/or watery/bloody diarrhea, which culminates in hemodynamic instability and hypotension in at least 15% of reactions.

SS 2: Recognize that the symptom phenotype in FPIES is determined by the frequency of food ingestion. [Strength of Recommendation: Strong; Evidence strength Ia; Evidence grade B]

SS 3: Recognize that onset of FPIES to cow’s milk and soy may occur at younger ages compared to FPIES to solid foods. Patients may have a single trigger or multiple triggers.

SS 4: Consider specific-IgE testing of children with FPIES to their trigger food, as co-morbid IgE-mediated sensitization to triggers such as CM may infer greater chance of persistent disease.

SS 5: Do not recommend any specific pre-natal or post-natal food introduction/avoidance, health behaviors, or advise patients regarding any specific genetic factors known to moderate the risk of an individual developing FPIES.

SS 6: Consider FPIES as a heterogeneous disorder associated with a number of geographic variations in the features of disease, representing a spectrum of “syndromes” as opposed to a uniform “syndrome”.

SS 7: Diagnose FPIES primarily upon a clinical history of typical characteristic signs and symptoms, with improvement following withdrawal of the suspected trigger food. Exclude other potential etiologies and use OFC to help confirm the diagnosis if the history is unclear and there is a favorable risk to benefit ratio.

SS 8: Conduct OFCs in patients with suspected FPIES in medically supervised settings where access to rapid fluid resuscitation is available and prolonged observation can be provided if necessary.

SS 9: Do not routinely perform testing for food-sIgE to identify food trigger FPIES, as FPIES is not an IgE-mediated process. However, since some patients with FPIES may exhibit co-existing IgE-mediated allergies, testing may be considered in patients with certain comorbid conditions. Assessment of chemistry or blood count can help rule-out other causes of symptoms if obtained in the acute setting.

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Diagnostic criteria for patients presenting with possible FPIES

**Acute FPIES**

Major criterion: Vomiting in the 1-4 hour period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms

Minor criteria:
1. A second (or more) episode of repetitive vomiting after eating the same suspect food
2. Repetitive vomiting episode 1-4 hours after eating a different food
3. Extreme lethargy with any suspected reaction
4. Marked pallor with any suspected reaction
5. Need for emergency room visit with any suspected reaction
6. Need for intravenous fluid support with any suspected reaction
7. Diarrhea in 24 hours (usually 5-10 hours)

**Chronic FPIES**

Severe presentation: when the offending food is ingested in on a regular basis (e.g., infant formula) intermittently, but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis.

Milder presentation: lower doses of the problem food (e.g., solid foods or food allergens in breast milk) lead to intermittent vomiting, and/or diarrhea, usually with poor weight gain failure to thrive, but without dehydration or metabolic acidosis.

The diagnosis of FPIES requires that a patient meets the major criterion and at least 3 minor criteria. If only a single episode has occurred, a diagnostic oral food challenge should be strongly considered to confirm the diagnosis, especially since viral gastroenteritis is so common in this age group. Further, while not a criteria for diagnosis, it is important to recognize that acute FPIES reactions will typically resolve over a matter of hours, compared to the usual several day time course of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.

Diagnostic criteria for the interpretation of oral food challenges in patients with a history of possible or confirmed FPIES

**Major criterion**

Vomiting in the 1-4 hour period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms,

**Minor criteria**

- Lethargy
- Pallor
- Diarrhea in 5-10 hours after food ingestion
- Hypotension
- Hypothermia
- Increased neutrophil count of at least 1500 neutrophils above the baseline

The OFC will be considered diagnostic of FPIES, i.e. positive, if the major criterion is met with at least two minor criteria. However, we would suggest two important caveats to these criteria: 1) with the rapid use of ondansetron, many of the minor criteria, such as repetitive vomiting, pallor and lethargy may be averted; and 2) not all facilities performing challenges have the ability to perform neutrophil counts in a timely manner. Therefore, the treating physician may decide that a challenge be considered diagnostic in some instances even if only the major criterion was met. However, in challenges performed for research purposes, stringent criteria for challenge positivity should be adhered to.

Management of acute FPIES episode at the medical facility

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<thead>
<tr>
<th>Mild Symptoms</th>
<th>Moderate Symptoms</th>
<th>Severe Symptoms</th>
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<tbody>
<tr>
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<tr>
<td>1. Attempt oral re-hydration (e.g., breast-feeding or clear fluids)</td>
<td>1. If age older than 6 months: administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose</td>
<td>1. Place a peripheral intravenous line and administer normal saline bolus 20 mL/kg rapidly, repeat as needed to correct hypotension</td>
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<td>2. If age 6 months and older: Consider ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose</td>
<td>2. Consider placing a peripheral intravenous line for normal saline bolus 20 mL/kg, repeat as needed</td>
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<td>3. Monitor for resolution about 4-6 hours from the onset of a reaction</td>
<td>3. Transfer the patient to the emergency department or intensive care unit in case of persistent or severe hypotension, shock, extreme lethargy, or respiratory distress</td>
<td>3. If placement of intravenous line is delayed due to difficult access and age is 6 months or older administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose</td>
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**Clinicopathologic features**

- Correct methemoglobinemia if present
- Monitor vital signs
- Discharge after 4-6 hours from the onset of a reaction when the patient is back to baseline and is tolerating oral fluids
- Transfer the patient to the emergency department or intensive care unit for further management in case of persistent or severe hypotension, shock, extreme lethargy, respiratory distress

**Follow-up**

- Oral challenges in the physician’s office can be considered in patients with no history of a severe FPIES reaction, although caution should be urged as there are no data that can predict future severity of FPIES reactions.

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Strong consideration should be kept in performing food challenges in children with history of severe FPIES in the hospital or other monitored setting with immediate availability of intravenous resuscitation. Oral challenges in the physician’s office can be considered in patients with no history of a severe FPIES reaction, although caution should be urged as there are no data that can predict future severity of FPIES reactions.