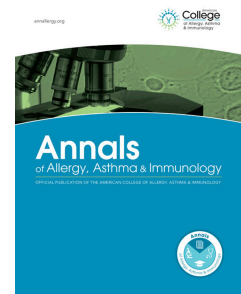


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Management of Acute FPIES Emergencies at Home and in a Medical Facility

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Conflict of Interests

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Key Words: FPIES, food protein-induced enterocolitis syndrome, food allergy

Abbreviations:

EAI: epinephrine auto-injectors
FPIES: Food protein-induced enterocolitis syndrome
IgE: immunoglobulin E
IL-2: interleukin-2
IL-8: interleukin-8
IM: intramuscular
IV: intravenous
OFC: oral food challenge
NK-1: neurokinin-1
sIgE: specific IgE
SPT: skin prick testing
TGF- β : transforming growth factor- β
T_H2: T helper cell type 2
TNF- α : Tumor necrosis factor- α

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Objective : Acute food protein-induced enterocolitis syndrome (FPIES) is characterized by delayed repetitive vomiting after ingestion of a trigger food, and severe reactions may lead to dehydration, hypotension, and shock.

Data Sources : This review summarizes the clinical context, pathophysiology, presentation, and treatment of FPIES emergencies. We provide recommendations on management of FPIES emergencies in a medical facility versus at home. **Study Selections :** We referred to the 2017 International Consensus Guidelines for the Diagnosis and Management of FPIES, and performed a literature search identifying relevant recent primary articles and review articles on clinical management.

Results : Management of FPIES emergencies in a medical facility is based on severity of symptoms and involves rehydration, ondansetron and corticosteroids. A proactive approach for reactions occurring at home involves prescribing oral ondansetron and providing an individualized treatment plan based on the evolution of symptoms and severity of past reactions. Better understanding of the pathophysiology of FPIES could lead to more targeted treatments.

Conclusion : Children with FPIES are at risk for severe symptoms constituting a medical emergency. Management of FPIES emergencies is largely supportive, with treatment tailored to the symptoms, severity of the patient's condition, location of reaction, and reaction history.

1 Introduction

2 Food protein-induced enterocolitis syndrome (FPIES) is a non-Immunoglobulin E (non-IgE)
3 mediated food allergy with primary gastrointestinal involvement that typically presents in
4 infancy. There are chronic and acute forms, the latter being most recognizable. An acute FPIES
5 reaction may be considered mild when there are 1-2 episodes of vomiting and no lethargy.¹
6 Moderate acute FPIES presents with ≥ 3 episodes of vomiting and mild to moderate lethargy.
7 Severe acute FPIES presents with ≥ 3 episodes of vomiting and severe lethargy, hypotonia, or a
8 grey/ashen appearance. Patients with severe FPIES are at risk for dehydration, hypotension,
9 shock, methemoglobinemia, and metabolic acidosis, constituting a medical emergency.² This
10 review summarizes the clinical context, pathophysiology, presentation, and treatment of FPIES
11 emergencies, and provides recommendations on management in a medical facility versus at
12 home.

14 Clinical context

15 Acute FPIES is characterized by profuse, repetitive, often projectile vomiting, that usually
16 develops within 1 to 4 hours of food ingestion, and may be associated with concurrent lethargy,
17 pallor, hypotonia, and/or hypothermia.³ Diarrhea may follow within 5 to 10 hours. Symptoms
18 usually resolve within 24 hours. Severe acute FPIES may result in dehydration, metabolic
19 acidosis, hypotension, and hypovolemic shock necessitating emergent medical management.³
20 No deaths have been reported following an acute FPIES reaction, however admissions to the
21 intensive care unit have occurred.⁴ Children with acute FPIES are well in between the episodes
22 and grow and develop normally.³ Chronic FPIES most often presents in young infants fed cow's

milk or soy-based formula and causes intermittent but progressive gastrointestinal symptoms.² Chronic FPIES may culminate in the same dramatic symptoms of shock, metabolic acidosis, and dehydration over the course of days to weeks, with the additional findings of abdominal distention, weight loss, anemia, hypoalbuminemia and hypoproteinemia.^{2, 5}

A subset of children with FPIES have positive skin prick test (SPT) and/or serum food allergen-specific IgE (sIgE) to their FPIES food trigger, referred to as atypical FPIES.⁶⁻⁸ Positive testing is not usually seen at initial presentation, but may develop and has been associated with a protracted course of FPIES and possible transition to acute IgE-mediated reactions.^{6, 7, 9} Caubet et al. reported 24% (n=39) of cohort subjects had detectable food allergen-specific IgE to their FPIES trigger food, of which 82% had FPIES to milk, soy or both.⁷ Transition to classic IgE-mediated reactions was demonstrated in 41% of patients with detectable milk-specific IgE. Other series, however, have found evidence of IgE sensitization in as few as 3% of patients.⁹

Acute FPIES in infants and young children are most commonly triggered by cow's milk, soy, and grains, such as rice and oat.² In addition, egg, vegetables, fruits, peanut, meats, and seafood have also been reported as triggers. Theoretically, any food can be a trigger for FPIES, and geographic differences have been observed.^{9, 10} The majority of infants (65-80%) with FPIES react to a single food, although multiple food FPIES does occur.^{2, 7, 11} Co-allergy between milk and soy FPIES, and oat and rice FPIES are common (<30-40%) in some populations.¹²

Diagnosis

Diagnosis of acute FPIES requires a high index of suspicion and relies on knowledge of the condition and its common triggers, careful history of any prior similar episodes, and exclusion of other diagnoses. A delay in diagnosis is common, and infants often experience multiple reactions before an FPIES diagnosis is considered.¹³ Patients may not react on their first known exposure to the trigger food; hence, a history of tolerating several previous ingestions does not rule out an FPIES diagnosis.¹⁴ The 2017 International Consensus Guidelines has proposed criteria for acute FPIES (Table 1).² The major criterion of delayed vomiting and three minor criteria are required to make a diagnosis.

There are no current tests, other than an oral food challenge (OFC), that can confirm an FPIES diagnosis.² When the history of a reaction meets diagnostic criteria, particularly in patients who have had two or more acute FPIES reactions, it is unnecessary to confirm FPIES with an OFC. There are situations in which a diagnostic OFC can be useful, including if the vomiting is not repetitive¹, if the vomiting does not resolve within a matter of hours, or if only one FPIES episode has occurred and it was not severe. A peculiar feature of acute FPIES is acute onset followed by quick resolution of symptoms. The level of suspicion for FPIES should be high to defer a diagnostic OFC if only one episode has occurred since other conditions may mimic acute FPIES, particularly if symptoms are mild.²

Separate diagnostic criteria are proposed for OFCs in patients with a history of possible or confirmed FPIES (Table 2). It is suggested that the presence of minor criteria is not critical in the OFC setting for making a diagnosis^{2,4}, acknowledging that the use of ondansetron may improve

symptoms such as vomiting, pallor and lethargy, and that not all facilities may be able to perform a prompt neutrophil count. Although the presence of neutrophilia, leukocytosis, and/or thrombocytosis supports the diagnosis of acute FPIES, these laboratory features are present in less than 50% of cases and may also be present during infection - the magnitude of neutrophilia in FPIES can be as high as that seen in bacterial sepsis.¹³

Differential diagnosis

In cases of suspected FPIES, clinicians should consider ruling out other diagnoses (Table 3). For example, infectious etiologies, gastrointestinal conditions, and anaphylaxis should be ruled out when acute FPIES is suspected.^{2, 15} It may be difficult to distinguish acute sepsis in an infant from the first few hours of an initial episode of acute FPIES. Infants experiencing an FPIES reaction may appear very sick with dehydration, lethargy, pallor and weakness. A diagnosis of FPIES is favored over infection if there is rapid resolution of symptoms within hours of presentation (although diarrhea may occur over the next 24 hours), an absence of fever, and a lack of a significant rise in C-reactive protein in the very first hours after symptom onset.¹⁶

Long term management

Once the diagnosis of FPIES has been made, strict elimination of the food trigger is recommended.³ It is important to assure parents that a majority of children will only have one food trigger and that the disease in infants and young children has a good prognosis.^{3, 4} Avoiding foods with precautionary labeling is not routinely recommended, unless a patient has

demonstrated reactivity to a low threshold.² Exclusion of the triggering food in the maternal diet while breastfeeding is also not required unless the infant is symptomatic.^{3, 4, 12}

The 2017 International Consensus Guidelines² promote the introduction of low-risk foods and recommend delaying introduction of high-risk foods that are more likely to trigger a reaction in infants with a diagnosis of FPIES. Supervised food introductions may be considered by the clinician in cases of high-risk food introductions or family concerns and/or anxieties.¹⁵ Patients with FPIES should be evaluated at regular intervals to monitor growth and diet history, and to consider the ideal time for an OFC to assess disease resolution.

Prognosis

Overall, FPIES has been shown to resolve by school age for the majority of patients.¹⁷ The natural history of FPIES varies, depending on the trigger food and country of origin.² A good rule to follow for reintroductions is waiting at least 12-18 months since the patient's last reaction to consider an OFC.² The development of a tolerance to cow's milk and soy appears to occur earlier than to grains or other foods.² However, in children initially diagnosed with FPIES in infancy, OFCs to assess tolerance could be considered with a reasonable chance of success to cow's milk, soy and rice by 18 to 24 months of age^{9, 18}, to egg by 30 months of age^{18, 19}, and to fish after 5 years of age.^{18, 20}

Pathophysiology

Although the subject of intense investigation, a clear understanding of the pathophysiology of FPIES has been elusive. Unlike other food allergies, it does not appear that IgE plays a significant role in mediating FPIES reactions. Instead, studies appear to suggest a role for pan-leukocyte activation, cytokine release, innate immune system activation, and increased gastrointestinal permeability.^{2, 21-24} (Figure 1) C-reactive protein, not involved in the acute phase, tends to rise 24-48 hours after food exposure, particularly after a severe FPIES reaction, testifying to a late involvement of the inflammatory mechanisms.²³

The role of T lymphocytes in the pathophysiology of FPIES has been a subject of great interest as it has long been speculated that FPIES is a cell-mediated process, although clear evidence to support this theory is still lacking.²⁵ Increased expression of CD69 and elevation in serum IL-2 in symptomatic patients supports T cell activation.^{22, 26, 27} Multiple groups have reported increases in T cell-derived cytokines, particularly TNF- α .^{24, 27, 28} It is thought that the increase in TNF- α , combined with a decrease in TGF- β , which has been shown to preserve gut integrity, is critical to FPIES pathophysiology.^{29, 30}

In patients with acute FPIES symptoms, basic laboratory evaluation often reveals a leukocytosis, and specifically an increase in circulating neutrophils.^{7, 22, 25, 31, 32} A study of patients with symptoms upon supervised OFC demonstrated neutrophil activation, and increases in IL-8 have been reported.^{22, 26, 28} In addition to the effects of IL-8 on inducing neutrophilia by promoting migration, Shimomura proposed that the dramatic vomiting that occurs during active FPIES reactions causes a stress response, including an increase in cortisol, which may contribute to

neutrophilia.³³ Eosinophil activation has also been demonstrated,^{22, 34} and patients with a symptomatic FPIES challenge have been noted to experience a decrease in serum eosinophils.^{7, 22} Chung et al demonstrated significant extracellular deposition of eosinophil major basic protein in the lamina propria, supporting the involvement of eosinophils in the mucosal damage that occurs during FPIES reactions.³⁵

Treatment of Acute FPIES Emergencies

The treatment of children with acute FPIES symptoms is supportive and tailored to the severity of symptoms.^{1, 2} (Figure 2) The first priority should be hemodynamic support given the risk for dehydration or even shock with progressive FPIES symptoms. Vasopressors may be needed for hypotension not immediately responsive to fluid resuscitation.^{36, 37} Because of the presumed cell-mediated pathophysiology, patients with severe symptoms have been treated with corticosteroids; however, no study to date has demonstrated clear benefit from this intervention.⁸ Although not common, patients with severe reactions may experience shock and resulting hypoxemia requiring support with supplemental oxygen, positive pressure, or mechanical ventilation.² In severe cases, patients may experience laboratory abnormalities such as electrolyte derangements, metabolic acidemia, and methemoglobinemia. Electrolytes should be repleted, bicarbonate given for patients with acidemia, and methylene blue administered for patients with methemoglobinemia.^{36, 38}

To mitigate symptoms, administration of an antiemetic such as ondansetron can be considered for children older than 6 months.² Small studies of intravenous (IV) and intramuscular (IM)

ondansetron demonstrated rapid symptom resolution (generally <15 minutes) with no adverse effects.^{39, 40} A larger retrospective study revealed that among children undergoing a symptomatic OFC, vomiting persisted in 19% of children treated with parenteral ondansetron vs. 93% of children treated with IV fluids and steroids alone, and that children treated with ondansetron were less likely to be admitted to the hospital overnight.⁴¹ As a more accessible and less invasive alternative, there is interest in examining the role of oral ondansetron in the treatment of FPIES reactions. A recent case series demonstrated prompt symptom resolution following oral ondansetron administration in 5 out of 7 symptomatic food challenges, all of which involved mild to moderate symptoms; the other two required IV doses of ondansetron for recurrent vomiting.⁴² Ondansetron has been associated with QT prolongation, so caution has been recommended for children with cardiac disease.^{2, 43} However, in a study of children without cardiac co-morbidities, no significant QT prolongation has been noted following a single dose of IV ondansetron.⁴⁴

Treatment of Acute FPIES in a Medical Facility

The risks of an acute FPIES reaction include dehydration, hypotension and, if severe, shock. Symptoms of shock are thought to be due to third-spacing or hypovolemia caused by severe vomiting and diarrhea. It is not known why lethargy, pallor, and hypotonia are part of acute FPIES, and these symptoms may indicate that other mediators are at play. Placement of IV access is guided by the patient's overall presentation, including signs of dehydration, presence of lethargy, low blood pressure, and inability to tolerate oral fluids.

For patients with mild symptoms, it is appropriate to attempt oral rehydration with breastfeeding or formula for infants and clear liquids for older children. (Figure 2) If the patient is > 6 months old, ondansetron may be considered. The suggested dose is 0.15 mg/kg (maximum 16 mg), given IM or IV.² For patients with moderate symptoms, an IM or IV injection of ondansetron can be given and IV fluid boluses considered. The bioavailability of IM vs. IV ondansetron is equivalent, although peak plasma concentration occurs sooner when given IV.⁴⁵ Having an IM option for ondansetron administration is useful in an outpatient setting where peripheral IVs are not typically placed. Vital signs should be monitoring closely, and the patient can be discharged if symptoms resolve and they are able to tolerate oral liquids.

Epinephrine is not indicated for acute FPIES treatment and epinephrine auto-injectors (EAI) are not prescribed for patients with classic FPIES. Atypical FPIES manifesting as anaphylaxis is rare and EAI are not routinely prescribed unless SPT or sIgE testing is predictive of possible IgE-mediated allergy, or the patient has asthma or other IgE-mediated food allergies.

For patients with severe symptoms, such as hypotension and shock, emergency care and IV fluid resuscitation are indicated. In these cases, isotonic fluid boluses (20 ml/kg normal saline) and a maintenance dextrose saline infusion should be administered.⁴⁶ Ondansetron and corticosteroids should be given IV. Although there are no data to support the use of corticosteroids in an acute FPIES reaction, they may be given for presumed gastrointestinal inflammation.¹² The suggested dose of corticosteroids is one single IV administration of 1 mg/kg methylprednisolone (maximum 60-80 mg).² Vital signs should be checked regularly, and

patients should be monitored for severe lethargy, hypotension, and/or shock. Electrolyte abnormalities should be corrected, and blood pressure support given if needed. Patients with severe symptoms may require hospital admission for further care.

Preparing for Acute FPIES Reactions During Oral Food Challenges

Whether FPIES OFCs are performed for diagnostic purposes or to assess for resolution, they should be conducted in a hospital setting due to the risk of severe symptoms.³ In one study, the severity of OFC symptoms did not correlate with reported severity of initial reaction symptoms.⁷ Because the severity of reactions is not predictable and there are no diagnostic tests that can indicate when a patient has outgrown FPIES, it is not recommended to perform OFCs at home. If a patient passes a supervised OFC to a food in a certain category, such grains or legumes, then trying other foods in the same category may be considered at home as long as there is no history of a severe reaction to those particular foods. Otherwise, FPIES OFCs should be performed in a facility where prompt access to IV fluid resuscitation and prolonged monitoring is possible.²

Some protocols recommend placement of IV access prior to an FPIES OFC. This may depend on the severity of past reactions and the location of the OFC (office vs. hospital). It is recommended that OFCs be conducted with an IV in place and occur in a hospital setting for patients who have a history of severe symptoms after low doses of food ingestion, or those who required IV fluid resuscitation and/or prolonged hospitalization and support during an FPIES reaction. If the OFC is deemed to be of mild risk (for example, history of mild symptoms

in a patient who recovered at home, low suspicion of FPIES, or the OFC is done for food introduction without a history of reactivity to that food) it can be performed in an outpatient setting and prior IV placement does not seem necessary. If an FPIES OFC is performed in an outpatient setting, a plan for rapid transfer of the patient to an emergency department should be in place. In these cases, or if IV access is not immediately available, treatment may begin with an IM dose of ondansetron.

Nowak-Wegrzyn et al. suggest monitoring the patient for at least 4 hours after the last ingested dose of an age-appropriate serving is ingested.³ The observation period may be extended based on a history of a longer duration between ingestion and onset of symptoms. In patients with a history of severe FPIES, smaller initial doses and a longer time between doses may be considered. If a smaller serving is attempted at first and no symptoms develop within 2-3 hours, a full serving should subsequently be administered, and the patient monitored for at least 4 hours.

Testing milk FPIES patients for the presence of milk-specific IgE prior to an FPIES OFC is prudent due to the higher rate of positivity. Testing other food allergens may be considered, particularly if the patient has risk factors for IgE-mediated food allergies, such as a history of eczema or other IgE-mediated food allergies, although atypical FPIES to foods other than milk has been infrequently described. If food allergen-specific IgE is identified but low enough to support an OFC to assess for tolerance, a graded IgE-mediated OFC should be used with a longer observation time to capture an FPIES reaction.³ While a majority of atypical FPIES retain FPIES

phenotype it is important to have medications, including epinephrine, and equipment to treat anaphylaxis available in case the FPIES has transitioned to an IgE-mediated food allergy.

Management of Acute FPIES Occurring at Home

It is important to review management of acute FPIES reactions at home (Figure 3) with families since most patients are infants still being introduced to new foods, and developing FPIES to multiple foods is not uncommon. Reviewing signs of dehydration, hypotension, and shock may also be useful. Based on clinical experience, it is recommended that FPIES patients are prescribed oral ondansetron to be tried at home in case of an acute reaction.⁴⁷ A dose of ondansetron may be repeated if the patient vomits within 10 minutes of the first dose.

The recent pandemic has provided an opportunity to consider individualized care plans based on the severity of previous FPIES reactions, where not every patient may need to seek medical attention during an acute reaction.⁴⁷ If initial symptoms during an acute FPIES reaction at home are mild and there is a history of mild reactions where the patient recovered at home, then oral rehydration may be attempted 20 minutes after emesis and increased as tolerated. (Figure 3) If the patient does not improve after oral ondansetron or cannot tolerate oral liquids, the family should go to the emergency department. If initial symptoms are moderate or there is a history of a reaction requiring IV fluids in the past, it is recommended that the patient seek medical care in an emergency department. If initial symptoms are severe or there is a history of a severe reaction requiring prolonged hospitalization and support, emergency medical services should be activated.

263

264 Although awareness of FPIES is increasing, patients may continue to get extended work-ups in
265 emergency settings if the provider is unfamiliar. Fortunately, dehydration, hypotension and
266 shock can be treated without knowing the underlying cause, and most FPIES patients recover
267 quickly with fluid resuscitation. Ondansetron is often given for vomiting in general and can
268 shorten time to recovery. It is recommended that patients diagnosed with FPIES be given a
269 letter explaining what FPIES is and recommendations for treatment. See eSupplement 1 for an
270 example of an FPIES emergency letter. Families may also want to bring extra clothes for patient
271 and caregiver in case of additional vomiting, as well as breastmilk or formula and a bottle or
272 sippy cup for oral fluid trials in infants.

273

274 *Post Emergency Care*

275 Patients can resume safe foods when they are back to baseline. Many reactions resolve within a
276 few hours and almost all within 24 hours. If diarrhea occurs later or lasts >24 hours,
277 concentrate on fluids and try small amounts of bland foods. The family should discuss with
278 patient's physician when to restart trials of new foods. Infants and toddlers may have less
279 interest in eating or trying new foods for a time period after an acute reaction. They should be
280 monitored for food refusal and trying a new food may be delayed in these cases. Some infants
281 who have experienced severe or multiple acute FPIES reactions may require nutrition
282 evaluation or feeding therapy for feeding issues.

283

284 **Future directions**

Understanding the pathophysiology of FPIES could lead to the development of diagnostic testing and improved management of acute FPIES. Current data are suggestive of a T cell-mediated response with some T_H2 skewing, which may help explain the significant incidence of atopic dermatitis in children with FPIES, as well as the tendency for transformation to IgE-mediated food allergy in some patients.^{2, 7, 27} Increased inflammatory cytokines noted in some studies, such as IL-2 and TNF- α , may explain the characteristic vomiting and lethargy, but not the lack of fever or relatively quick resolution. Neutrophilia may be a bystander effect due to increased IL-8 and cortisol. Without evidence of hypotension, the underlying cause of marked pallor or ashen color during acute FPIES reactions is unclear. Clarifying which immunologic factors are causative rather than in response to inflammatory stress will be an important distinction and could potentially suggest an anti-inflammatory therapy. The benefits seen in some studies with administration of ondansetron, a serotonin inhibitor, introduces another potential pathway.

More data on safety and efficacy of acute FPIES treatment would be valuable in the management of emergencies. Randomized trials on the use of oral ondansetron by parents at home, and on an IM vs. IV route of ondansetron in a hospital setting may impact recommendations on the treatment of acute FPIES. Given that ondansetron may not work in each case, other antiemetic agents with different mechanisms of action, such as aprepitant, a neurokinin-1 (NK-1) receptor antagonist, could be considered. NK-1 receptor antagonists have anti-nausea and anti-vomiting properties that get relayed through a central blockade in the area postrema, nucleus tractus solitarius, and visceral afferent nerves. NK-1 receptors mediate

most of the central and peripheral effects of substance P, which is released by the intestinal enterochromaffin cells.

Randomized trials on the use of steroids may elucidate whether or not they are beneficial in acute FPIES. In chemotherapy, combination of ondansetron and dexamethasone is more effective than ondansetron alone. It is unknown at this time whether patients could be desensitized to their FPIES trigger food, as is possible in IgE-mediated food allergy. Finally, understanding the immunologic changes that occur when children naturally outgrow FPIES could possibly lead to a cure.

Conclusion

Acute FPIES is characterized by delayed repetitive vomiting after ingestion of a trigger food, often presenting with lethargy and pallor. Severe reactions may lead to dehydration, hypotension, and shock. Management of FPIES emergencies is largely supportive and based on severity of symptoms and location of reaction (under medical supervision vs. at home). Hemodynamic support is of critical importance, either with oral rehydration or IV fluid resuscitation. The use of ondansetron during reactions has been associated with shorter duration of vomiting, and it may prevent the development of more severe symptoms. Corticosteroids are recommended for severe reactions due to presumed cell-mediated inflammation. A proactive approach for reactions occurring at home involves prescribing oral ondansetron and providing an individualized plan based on severity of past reactions. Patient education and dietary management with close follow-up are important for acute and long term

329 FPIES management. A better understanding of the pathophysiology of FPIES could lead to more
330 targeted treatments.

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Figure legends**Figure 1:**

Food ingestion activates cells of the innate and adaptive immune system including T cells, neutrophils, natural killer cells, and eosinophils. C-reactive protein is particularly involved in severe events suggesting an important role of inflammation in more severe forms of FPIES. PO – oral, IV - intravenous

Figure 2:

Management of acute FPIES in a medical facility.

IM – intramuscular, PIV – peripheral intravenous catheter, NS – normal saline, IV - intravenous

Figure 3:

Management of acute FPIES at home.

Table 1 – International consensus diagnostic criteria for patients presenting with possible acute FPIES*

Major criterion

- Vomiting (1-4 h after ingestion of the suspected food) and absence of classic IgE-mediated allergic skin or respiratory symptoms

Minor criteria (3 or more)

- A second (or more) episode of repetitive vomiting after eating the same suspect food
- Repetitive vomiting episode 1-4 h after eating a different food
- Extreme lethargy with any suspected reaction
- Marked pallor with any suspected reaction
- Need for emergency department visit with any suspected reaction
- Need for intravenous fluid support with any suspected reaction
- Diarrhea in 24 h (usually 5-10 h)
- Hypotension
- Hypothermia

FPIES = Food protein-induced enterocolitis syndrome.

*Adapted with permission from Nowak-Wegrzyn et al.³

Table 2 - Diagnostic criteria for the interpretation of oral food challenges in patients with a history of possible or confirmed FPIES*

Major criterion

- Vomiting (1-4 h after ingestion of the suspected food) and absence of classic IgE-mediated allergic skin or respiratory symptoms

Minor criteria (3 or more)

- Lethargy
 - Pallor
 - Diarrhea 5-10 h after food ingestion
 - Hypotension
 - Hypothermia
 - Increased neutrophil count of
 - >1500 neutrophils above the baseline count
- The treating physician might decide that a challenge be considered diagnostic even if only the major criterion was met if: (1) ondansetron was given, which may prevent additional vomiting or other symptoms from developing, or (2) prompt laboratory evaluation of neutrophil count was not feasible.
-

OFC = Oral food challenge; FPIES = Food protein-induced enterocolitis syndrome.

*Adapted with permission from Nowak-Wegrzyn et al.³

TABLE 3 - Differential diagnosis of acute FPIES

Condition	Features that can distinguish from FPIES
Infectious gastroenteritis	Fever, sick contacts, symptoms last for days not hours.
Sepsis	Fluid resuscitation alone is not effective
Anaphylaxis	Skin or respiratory symptoms, responsive to epinephrine, positive allergy testing.
Gastrointestinal obstruction	Not related to specific food intake, evidence of obstruction on radiologic studies
Necrotizing enterocolitis	Newborns and younger infants, rapid escalation of symptoms, bloody stools, shock, intramural gas on abdominal radiographs
Inborn errors of metabolism	Developmental delay, neurologic manifestations, organomegaly, reaction to fruits
Neurologic disorders (e.g., cyclic vomiting)	No relation to specific food intake
Food poisoning	Others eating the same food develop symptoms.

FPIES = Food protein-induced enterocolitis syndrome.

*Adapted with permission from Nowak-Wegrzyn et al.³

Figure 1.

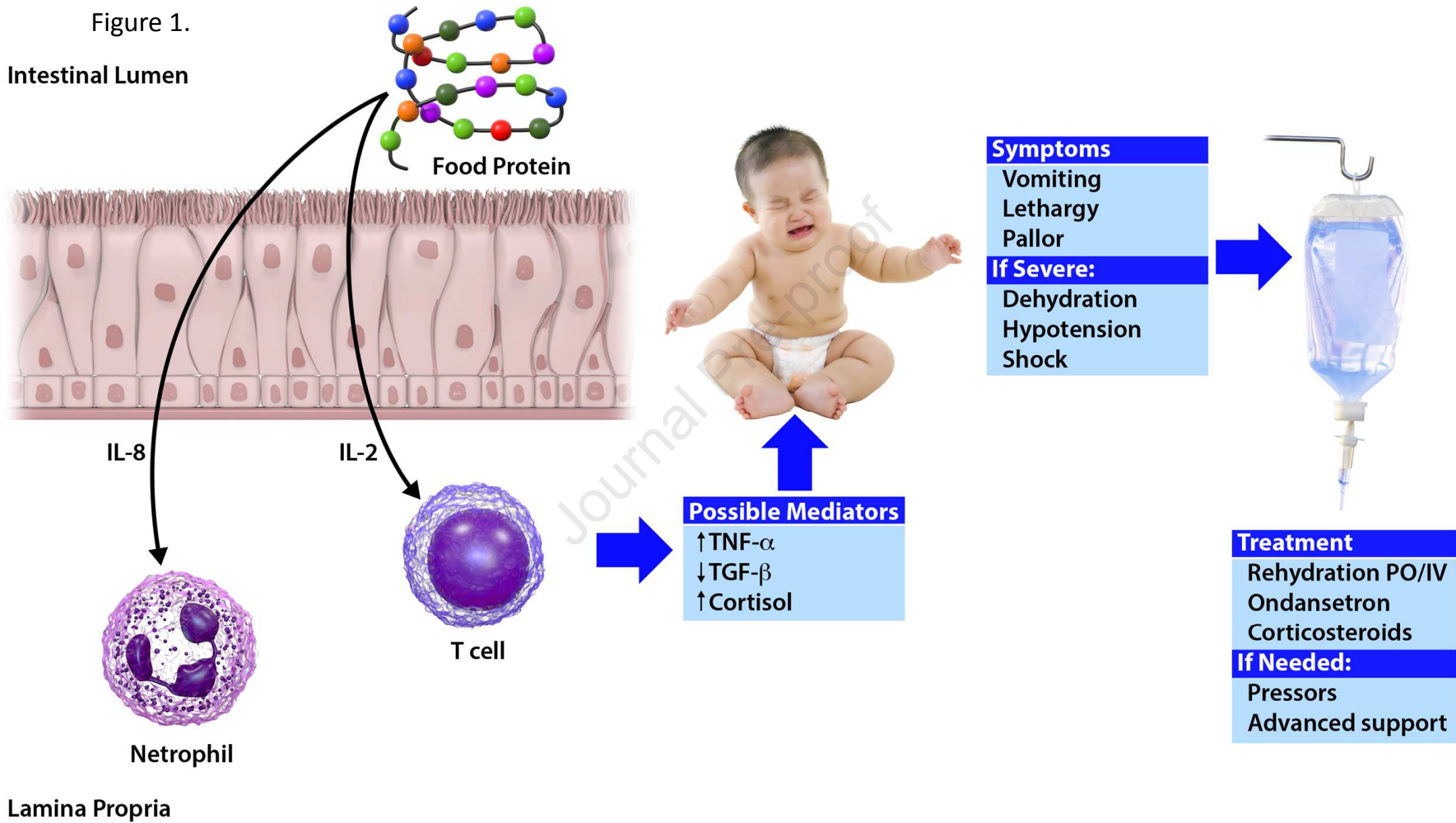
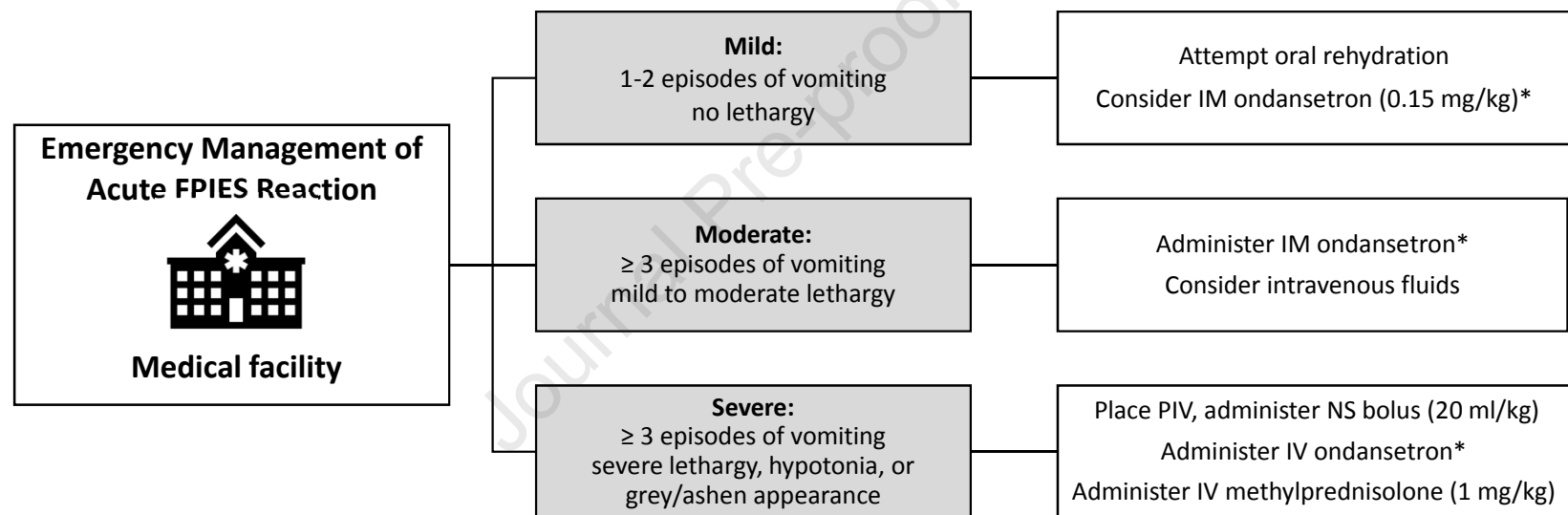
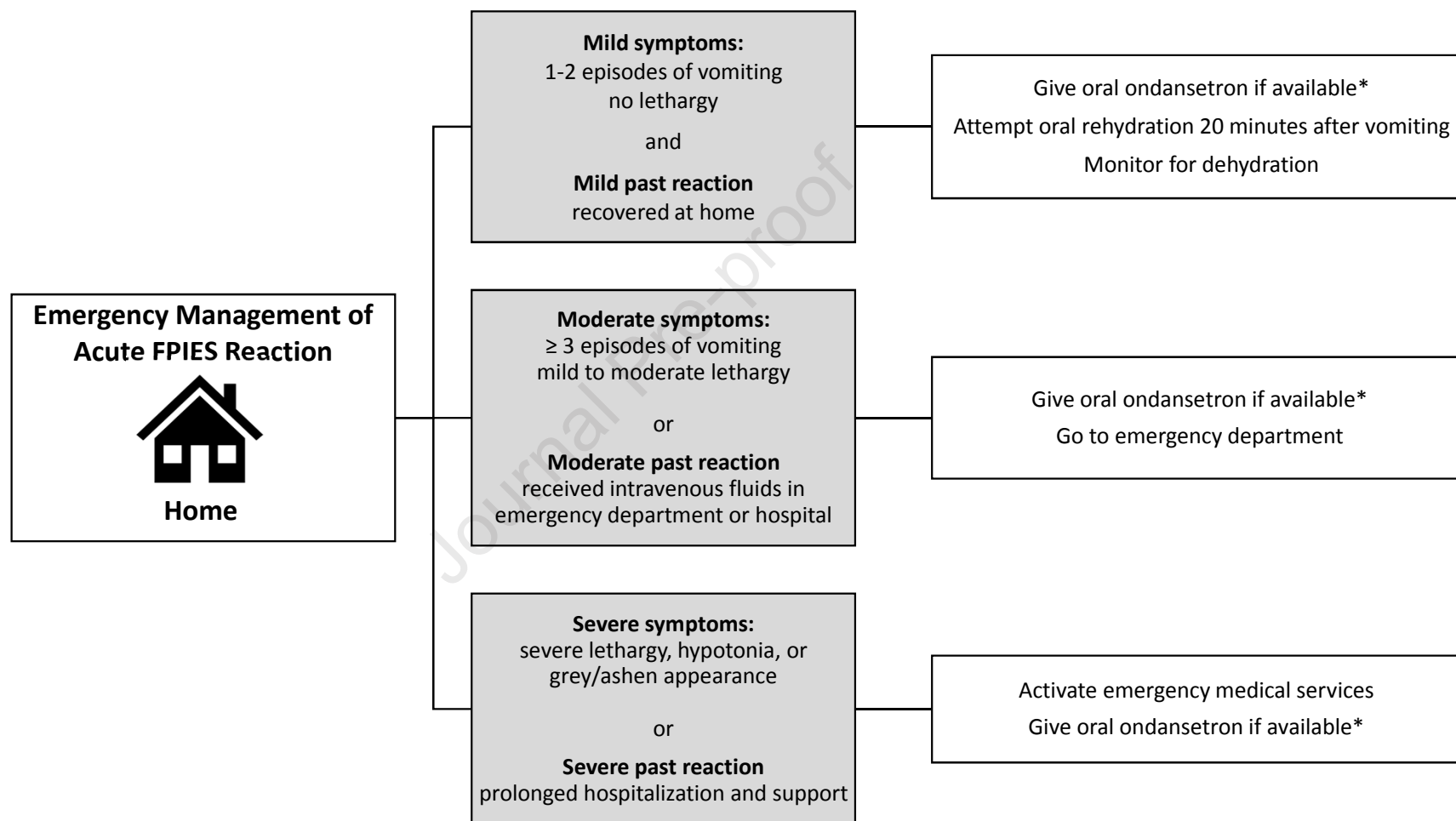


Figure 2.



* ≥ age 6 months

Figure 3.



* ≥ age 6 months, may repeat once if patient vomits within 10 minutes of first dose

Key Messages

1. Patients with moderate to severe FPIES reactions are at risk for dehydration, hypotension and shock, constituting a medical emergency.
2. Management of FPIES emergencies in a medical facility is based on severity of symptoms and involves rehydration, ondansetron and corticosteroids.
3. Management of FPIES reactions that begin at home can be personalized depending on history of reaction severity, and families benefit from individualized treatment plans that take into account the patient's symptoms and reaction history.
4. In case of acute reaction at home, it is recommended that FPIES patients are prescribed oral ondansetron, which can shorten the duration of vomiting and may prevent the development of more severe symptoms. However, efficacy of ondansetron is variable and in severe reactions, intravenous hydration is necessary.

eSupplement 1. Example of an FPIES emergency letter

Dear Doctor (To Whom It May Concern),

The patient named above has a food allergy called food protein-induced enterocolitis syndrome (FPIES). This is a type of allergy that usually does not result in typical "allergic" symptoms such as hives or wheezing, but rather with isolated gastrointestinal symptoms.

The foods this child is avoiding include _____.

The symptoms of this type of allergic reaction include delayed vomiting that typically does not start for hours following ingestion of the food to which the child is allergic. Even trace amounts can trigger a reaction. Diarrhea and lethargy may also be present. In some cases, the reaction includes hypotension. The treatment is symptomatic and can include ondansetron (> age 6 months, 0.15 mg/kg, max 16 mg/dose), intravenous fluids (e.g. normal saline boluses 20 ml/kg) and steroids (e.g. methylprednisolone 1 mg/kg, max 60-80 mg/dose) for significant symptoms. The latter is given because the pathophysiology is thought to involve T cell response.

This information is being given so that this could be considered in the differential diagnosis for this patient in the event of symptoms. This condition *does not* preclude the possibility of other illness (e.g. infection) or even other types of allergic reactions leading to symptoms, so it is up to the evaluating physician to consider all possibilities. Similarly, the treating physician is encouraged to pursue any other treatments deemed necessary (e.g. such as pressors for shock, antibiotics for presumed infection, etc.).

Please feel free to contact us for any further assistance.

Sincerely,