

# ADVERSE FOOD REACTIONS

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## Disclosures

- u I do not have any relevant financial or commercial interests to disclose.
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## Learning objectives

- ◆ To identify the differences between IgE-mediated and non-IgE-mediated adverse food reactions
- ◆ Evaluation and management of IgE-mediated food allergy
- ◆ Evaluation and management of food protein-induced enterocolitis syndrome
- ◆ Evaluation and management of food protein-induced allergic proctocolitis
- ◆ Evaluation and management of eosinophilic esophagitis

## Categories of adverse food reactions

- ◆ Food allergy: abnormal immunologic response to a food
  - ▶ May be IgE- and/or non-IgE-mediated
- ◆ Food intolerance: non-immunologic reaction to a food caused by a metabolic, pharmacologic and/or toxic mechanism
  - ▶ Examples: lactose intolerance, scromboid poisoning, sulfite sensitivity



<https://utswmed.org/medblog/kids-food-allergies-can-affect-gi-tract-symptoms-parents-should-know/>

## Types of food reactions

- ◆ IgE-mediated:
  - ▶ **IgE-mediated hypersensitivity to food protein**
  - ▶ IgE-mediated hypersensitivity to food-associated carbohydrate
  - ▶ **Oral allergy syndrome**
- ◆ Non-IgE-mediated:
  - ▶ **Food protein-induced proctitis/proctocolitis**
  - ▶ Food protein-induced enteropathy
  - ▶ **Food protein-induced enterocolitis syndrome (FPIES)**
  - ▶ Food-induced pulmonary hemosiderosis (Heiner syndrome)
  - ▶ Celiac disease
- ◆ Mixed IgE and non-IgE-mediated:
  - ▶ Atopic dermatitis
  - ▶ **Eosinophilic gastrointestinal disorders (EGID)**

Slide courtesy of Tim Moran

## Clinical Case #1

- ♦ A 6 month old full-term male presents to clinic for facial rash after ingesting peanut butter for the first time

## Clinical Case #1

- ◆ PMH: History of eczema— controlled with topical corticosteroids
- ◆ PSH: none
- ◆ Family Hx: Dad has seasonal allergies and mom had eczema as a child
- ◆ Additional information pertaining to reaction:
  - ◆ *How much was ingested?*
  - ◆ *Was this the first exposure?*
  - ◆ *How quickly after eating the food did symptoms occur?*
  - ◆ *Any additional symptoms (hives, swelling, vomiting, diarrhea or respiratory)?*

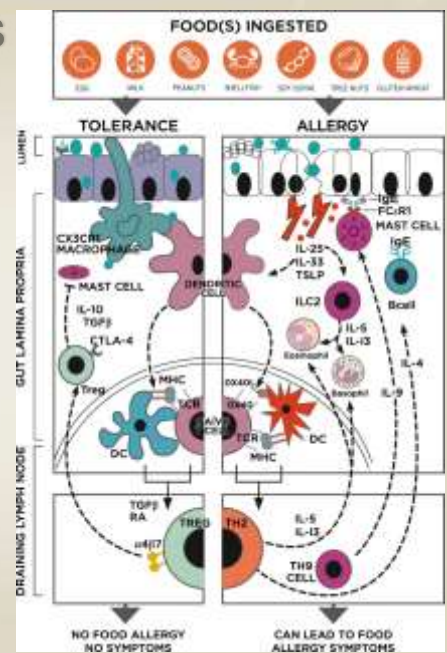
## Initial Allergy & Immunology clinic visit

- ◆ He was referred to our clinic after food panel was drawn with the following results:
  - ◆ *Peanut* sIgE 4.5 , *Egg white* sIgE 3.3, *Cow's milk* sIgE 5.5 , *Wheat* sIgE 2.1
  - ◆ *Cashew* sIgE 3.7 , *Pistachio* sIgE 2.4, *Pecan* sIgE 5.1, *Walnut* sIgE 6.3, *Hazelnut* sIgE 0.9, *Almond* sIgE 1.7
- ◆ On further history, he previously consumed egg and yogurt without issue (was instructed by PCP to stop eating these foods due to positive results) but he has never had wheat or tree nuts
- ◆ SPT was performed for further evaluation to peanut (8 mm), tree nuts (cashew 3 mm, pistachio 2 mm, pecan 4 mm, walnut 4 mm, hazelnut 3 mm and almond 5 mm) and wheat (3 mm)



## IgE-mediated food allergy versus sensitization

- ♦ Sensitization: presence of allergen-specific IgE bound mast cells to the offending allergen
  - ♦ Does not always result in an allergic disorder
- ♦ When sensitization and allergic clinical symptoms are both present, we diagnosis allergy.
- ♦ In patients with a food allergy, upon exposure to the offending allergen the mast cells with specific IgE bind to allergens causing local inflammation and allergic symptoms.



<https://link.springer.com/article/10.1007/s12016-018-8710-3/figures/3>

## Next steps

- ◆ How would you advise the family?
  - ◆ Depending on comfort level of the family, I would recommend at home introduction to foods previously tolerated
  - ◆ If family was hesitant to reintroduce, then we would proceed with an in office challenge
  - ◆ For positive testing with foods that he has not consumed, we would schedule an in office challenge
  - ◆ I recommend continued avoidance of peanut with repeat testing in 1 year
    - ◆ EpiPen prescribed

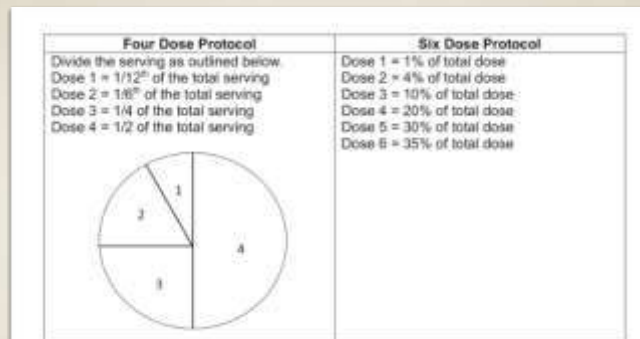
TABLE V. Age appropriate portion sizes for open DFC

Allergen	Food	Portion content per serving size	Age				
			4-11 mo	1-3 y	4-6 y	9-10 y	10+ y
Egg	Fresh (use 11 egg per 1 slice of bread)	4 g if made with 1 large egg	1/2 slice	1/2 slice	1 slice	1-2 slices	1-2 slices
	Hard-boiled or scrambled egg	4 g/1 large egg	1/2 egg	1/2 egg	1 egg	1-2 eggs	1-2 eggs
Fish	Cooked fish	4 g/1 oz	1/2 oz	1 oz	1 oz	2-3 oz	3-4 oz
Cheese	Cooked cereal	3 g per 1/4 cup dry oatmeal or Cream of Wheat	1/2 cup	1/2 cup	1/2-1 cup	1/2 cup	1/2 cup
	Cooked pasta/rice	3 g per 1/2 cup	1/2 cup	1/2 cup	1/2-1 cup	1/2 cup	1/2 cup
	Infant cereal	1-2 g per 1/4 cup	1/2 cup	1/2 cup	1/2 cup	1/2 cup	1/2 cup
	Muffin or roll (small)	4-6 grams/roll or half	1/2 piece	1/2 piece	1/2 piece	1 piece	1 piece
	Ready-to-eat cereal	3-4 g/1 cup	1/2 cup	1/2 cup	1/2 cup	1/2 cup	1/2 cup
	Slice bread	2-4 grams	1/2 slice	1/2 slice	1/2 slice	1-2 slices	2 slices
Milk	Infant formula	2-3 g/1 oz	4-8 oz	4-8 oz	4-8 oz	8 oz	8 oz
	Milk	8 g/1 oz	4-8 oz	4-8 oz	4-8 oz	8 oz	8 oz
	Cottage cheese	10-14 g/1 oz	1/2 cup	1/2 cup	1/2 cup	1/2 cup	1 cup
	Hard cheese	6-8 g/1 oz	1/2 oz	1/2 oz	1 oz	1 oz	1/2 oz
	Yogurt (NOT Greek style)	8 g/1 oz	1/2 cup	1/2 cup	1/2 cup	1/2 cup	1/2 cup
Peanut	Peanut (solid)	2 g/1-4 pieces	10 pieces	10 pieces	10 pieces	10 pieces	10 pieces
	Peanut butter	3 g/1 tbsp	1 rounded tsp	1-2 tbsp	1-2 tbsp	2 tbsp	2 tbsp
	Peanut flour or peanut butter powder	3 g/1 tbsp mixed or 2.25 g/1 tbsp chocolate form	1 rounded tsp	1-2 tbsp	1-2 tbsp	2 tbsp	2 tbsp
	Paranickel-type candy cups (half-size)	0.075 g/1 cup	1-2 candy cups	1-2 candy cups	2-3 candy cups	2-3 candy cups	
Shellfish	Shellfish	2 g/1 oz	1/2 oz	1 oz	1 oz	2-3 oz	3-4 oz
Soy/legumes	Infant formula	2-3 g/1 oz	4-8 oz	4-8 oz	4-8 oz	8 oz	8 oz
	Soy beverage	2 g/1 oz	4-8 oz	4-8 oz	4-8 oz	8 oz	8 oz
	Cooked beans (black, chickpea, lentil)	1/4 g per 1/2 cup	1/2 cup	1/2 cup	1/2 cup	1/2 cup	1 cup
	Tofu	8 g/1 oz firm tofu	1/2 oz	1 oz	1 oz	2-3 oz	3-4 oz
	Yogurt	8 g/1 oz	1/2 cup	1/2 cup	1/2 cup	1 cup	1 cup
Tree nut	Almond	3 g/1 whole nut	1 piece	1 piece	1 piece	1 piece	1 piece
	Almond butter (flavorless butter form)	3 g/1 tbsp	1-2 tsp	1-2 tsp	1-2 tsp	1-2 tsp	1-2 tsp
	Walnut nut	3 g/1 nut	1 piece	1 piece	1 piece	1 piece	1 piece
	Cashew	3 g/1 whole nut	1 piece	1 piece	1 piece	1 piece	1 piece
	Coconut flake	3 g/1 cup	1-2 tsp	1-2 tsp	1-2 tsp	1-2 tsp	1-2 tsp
	Coconut milk	3 g/1 oz	1 oz	1 oz	1 oz	1 oz	1 oz
	Macadamia	3 g/1 nut (shell-on) or flaked nut	1 piece	1 piece	1 piece	1 piece	1 piece
	Peanut (solid)	3 g/1 nut	10-12 halves	10 halves	10 halves	10 halves	10 halves
	Peanut butter	3 g/1 tsp pure nut	3 tsp	3-4 tsp	3-4 tsp	3-4 tsp	3-4 tsp
	Peanut	3 g/20 whole nut	10 pieces	10 pieces	10 pieces	10 pieces	10 pieces
	Walnut (solid)	3 g/10 halves	10 halves	10 halves	10 halves	10 halves	10 halves

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Bird et al JACI 2009

## Oral food challenge protocol



**FIGURE 1.** Dosing options for an in-office open OFC.<sup>1</sup> The clinician may choose to perform a 4-dose OFC or a 6-dose OFC depending on the prechallenge probability of reacting and inherent patient risk factors. Doses are typically administered 15 to 30 minutes apart.

Bird et al JACI 2009

## Clinical Case #2

- ◆ An 8 month old full-term female who presented to the ER with numerous episodes of projectile vomiting and lethargy.
- ◆ Mom denies sick contacts and reports that she does not attend daycare.
- ◆ Mom reports giving her baby oatmeal a few hours prior to symptoms.

## Additional history

- PMH: born full-term via SVD
- PSH: none
- Family hx: paternal cousin with celiac disease
- Developmental hx: age-appropriate
- Social history: lives with parents and older brother
- ROS: + vomiting, lethargy and decreased PO
- Immunizations: UTD

## Hospital admission

- Laboratory evaluation:
  - CBC w/diff: WBC 14.4, Hgb 10.8, *Plt* 491
  - Stool occult blood: *negative*
  - GI pathogen panel: *none*
- She was discharged home from the ER after receiving fluids

## Differential diagnosis

- Food protein-induced enterocolitis syndrome
- Infectious gastroenteritis
- Sepsis
- Food aversion
- Inborn errors of metabolism
- Neurologic disorders (cyclic vomiting)
- GERD
- Food protein-induced enteropathy
- Eosinophilic gastroenteropathies
- Celiac disease
- Immune enteropathies
- Obstruction problems



## Initial Allergy & Immunology clinic visit

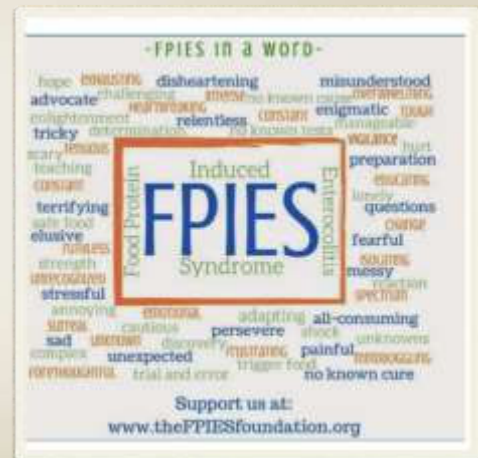
- A 12 month old female with well-controlled eczema presented to our clinic for an initial evaluation of repetitive projectile vomiting at 8 months old concerning for food protein-induced enterocolitis syndrome
- Parents introduced a variety of food into her diet without issue including green beans, pumpkin, banana, avocado, carrots, squash, cow's milk and soy
- Treatment plan:
  - Continue avoidance of rice and oatmeal.
  - Continue age appropriate food introductions.
  - Recommend skin testing for oat at 26 months old or older. If negative, proceed with at home introduction of oatmeal. If skin testing positive, proceed with in office food challenge to oatmeal.

## Non-IgE mediated food reactions

- ◆ Generally present with delayed or chronic GI symptoms
- ◆ Severity can range from mild to severe
- ◆ Diagnosis is generally based on clinical findings
  - ▶ Reproducible clinical symptoms upon exposure to a food with resolution upon specific food avoidance
  - ▶ Food sIgE may be present, but symptoms are not consistent with immediate hypersensitivity reaction

# FPIES Clinical presentation

- Usually presents in infancy
- Early infancy: CM/soy (when introducing formula)
- At 4-6 months: solid foods
- Rare for adult onset (fish/shellfish)
- Incidence ranges 0.015-0.7%
- Slight male predilection (52 to 60%)
- Reports of FPIES in siblings of an affected child are rare
- Can present with chronic and/or acute symptoms



**Table 1** Common food co-allergies in children with FPIES [1]

FPIES to	Clinical cross-reactivity/ co-allergy	Observed Occurrence <sup>a</sup>
Cow's milk	Soy	<30–40%
	Any solid food	<16%
Soy	Cow's Milk	<30–40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	Cow's milk or soy	<25%
Legumes <sup>a</sup>	Soy	<80%
Grains: rice, oats, etc. <sup>a</sup>	Other grains (including rice)	about 50%
Poultry <sup>a</sup>	Other poultry	<40%

<sup>a</sup>where a child already tolerates a food type in a particular group (e.g. beans), clinical reactions to other members of the **same** group (e.g. other legumes) are unlikely. Caution is warranted in interpreting these data as they were derived from single centers and from patient populations skewed towards the more severe phenotype of FPIES and may overestimate the actual risk of co-allergy

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# Infant food introduction guidelines

Ages and Stages	Lower risk foods <sup>1</sup>	Moderate risk foods <sup>2</sup>	Higher risk foods <sup>3</sup>
<p><b>4-6 months (as per AAP, CoN)</b> If developmentally appropriate and safe and nutritious foods are available:</p> <ul style="list-style-type: none"> <li>➤ Begin with smooth, thin, purees and progress to thicker purees.</li> <li>➤ Choose foods that are high in iron.</li> <li>➤ Add vegetables and fruits.</li> </ul>	Broccoli, cauliflower, parsnip, turnip, pumpkin	<p><b>Vegetables</b></p> Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
<p><b>6 months (as per WHO)</b> Complementary feeding should begin no later than 6 months of age:</p> <ul style="list-style-type: none"> <li>➤ In the breast fed infant, high iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 months of age.</li> <li>➤ Continue to expand variety of fruits, vegetables, legumes, grains, meats and other foods as tolerated.</li> </ul>	Blueberries, strawberries, plum, watermelon, peach, avocado	<p><b>Fruits</b></p> Apple, pear, orange	Banana
<p><b>8 months of age</b> or when developmentally appropriate:</p> <ul style="list-style-type: none"> <li>➤ Offer soft-cooked and bite-and-dissolve textures from around 8 months of age or as tolerated by infant.</li> </ul>	Lamb, fortified quinoa cereal, millet	<p><b>High iron foods</b></p> Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Higher iron foods: Fortified infant rice and oat cereals.
<p><b>12 months of age</b> or when developmentally appropriate:</p> <ul style="list-style-type: none"> <li>➤ Offer modified tolerated foods from the family table-chopped meats, soft cooked vegetables, grains and fruits.</li> </ul>	Tree nuts and seed butters <sup>4</sup> (sesame, sunflower, etc.) <sup>4</sup> Thinned with water or infant puree for appropriate infant texture and to prevent choking	<p><b>Other</b></p> Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

**Table 3** Diagnostic criteria for patients presenting with possible FPIES [1]**Acute FPIES****Major criterion:**

Vomiting in the 1–4 h 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 h 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 h (usually 5–10 h)
8. Hypotension
9. Hypothermia

**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 completely 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.

**Chronic FPIES**

**Severe presentation:** when the offending food is ingested in on a regular basis (e.g., infant formula). Intermittent 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/fall or no thrive, but without

The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days following elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1–4 h, diarrhea in 24 h (usually 5–10 h). Without confirmatory challenge, the diagnosis of chronic FPIES remains presumptive.

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# Acute FPIES management

**Table 5** Management of acute FPIES episode at home [1]

Current episode	Mild <sup>a,b</sup>	Moderate-severe
Symptoms	1-2 episodes of emesis No or mild lethargy	More than 3 episodes of emesis and moderate-severe lethargy
Management	Attempt oral re-hydration at home (e.g., breast-feeding or clear fluids)	Call 911 or go to the emergency room

<sup>a</sup>Child with history of severe FPIES reaction: call 911 or go to the emergency department if the triggering food was definitely ingested, even in the absence of symptoms or with any symptoms regardless of severity

<sup>b</sup>Child with no history of severe FPIES reaction

**FPIES Emergency Plan**

Re: @NAME@  
DOB: @DOB@

Dear healthcare provider,

@NAME@ 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 isolated gastrointestinal symptoms.

The symptoms of this type of allergic reaction include repetitive vomiting that may not start for a few hours (e.g., two hours) following ingestion of the food to which the child is allergic. Even trace amounts can trigger a reaction. There is often diarrhea that starts later (after 6 hours). In some cases (~20%), the reaction includes hypotension and lethargy. The treatment is symptomatic and can include **intravenous fluids** (e.g., normal saline bolus, hydration), **ondansetron** 0.1 to 0.15 mg/kg IV (maximum single dose 16 mg) and steroids (e.g., **methylprednisolone** 1 mg/kg IV, maximum daily dose 80 mg) for significant symptoms. The latter is given because the pathophysiology is that of a T-cell response.

This information is being given so that this could be considered in the differential diagnosis for this patient in event of symptoms. Of course, this illness 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., symptomatic such as epinephrine for shock, antibiotics for presumed infections, etc.).

If you have any questions, please contact the on-call UNC Pediatric Allergist at 919-966-4131.

Sincerely,



## Follow-up Allergy & Immunology visit

- Pt is now 30 months old and presented back to clinic to discuss next steps for possible oat reintroduction.
  - Introduced a variety of other foods including avocado, egg, peanut, tree nuts, vegetables and fruits
- Since she has been avoiding oat since she was 8 months old, evaluation for development of an IgE-mediated allergy prior to introduction of oat is warranted.
- Skin prick testing was negative to oat
- Plan to proceed with at home introduction of oat

## Food protein-induced proctitis/proctocolitis

- Typically presents as rectal bleeding in otherwise healthy infant within the first few months of life
- Cow's milk and soy are most common triggers
- No specific laboratory testing
- Allergy testing NOT recommended
- Management is avoidance of trigger food
  - If breastfed, complete elimination of milk from mother's diet
  - If formula fed or no improvement with maternal elimination diet, then give extensively hydrolyzed formula
- Trigger foods can usually be gradually reintroduced at 1 year of age
  - If symptoms recur after reintroduction, wait 6 months and then try again

**Formula options for infants with dietary protein-induced conditions**

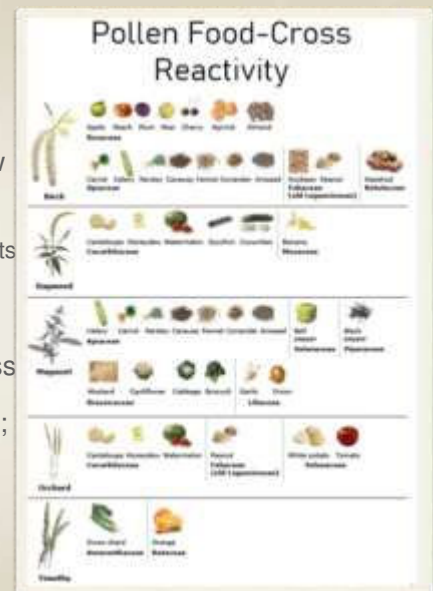
	Manufacturer
<b>Extensively hydrolyzed casein-based formulas</b>	
Infant Nutrigen	Heal Johnson Nutrition
Infant Nutrigen with Infyns 100	Heal Johnson Nutrition
Proposed 100 and 400	Heal Johnson Nutrition
Similac Expert Care Alimentum <sup>®</sup> *	Abbott Nutrition
<b>Extensively hydrolyzed whey-based formulas</b>	
Gerber Soy-based HA	Gerber
<b>Amino acid-based formulas</b>	
Neocate for infants	Abbott Nutrition
Neocate Infant DHA/ARA	Nutricia
Neocate Syneo Infant	Nutricia
PurKare DHA/ARA	Heal Johnson Nutrition
Alfama Infant	Nestle

LOO: L-lysine/lysine monohydrochloride; DHA: docosahexaenoic acid; ARA: arachidonic acid.  
\*The ready-to-feed form of Similac Expert Care Alimentum is cow free. All of the other formulas on this list, including the powder form of Similac Expert Care Alimentum, contain cow.

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# Oral allergy syndrome

- Oral allergy syndrome: form of contact allergic reaction that occurs upon contact of the mouth and throat with certain raw fruits and vegetables in individuals with allergic rhinitis.
  - Driven by cross-reacting allergens found in both pollen and raw fruits/vegetables and some tree nuts in sensitized individuals.
- Cooked forms of fruit and vegetable are often tolerated because the proteins are distorted during the heating process
- Treatment: recommend avoidance of foods in the fresh form; some evidence that allergen immunotherapy can alter reactions



## Clinical case #3

- ◆ 14 year old male with history of allergic rhinitis and eczema presents with poor weight gain and abdominal discomfort
- ◆ On further discussion, he reports limiting meats and starchy foods due to discomfort and feels that food gets stuck in his throat
- ◆ Family reports he does cut food into small pieces and takes longer than everyone else to eat

## Eosinophilic esophagitis

- ◆ What are the symptoms?
  - ◆ Infants: GERD-like symptoms (reflux, feeding refusal, poor weight gain)
  - ◆ Children: abdominal pain, gagging/choking, growth delay, dysphagia, abdominal pain, food impaction
  - ◆ Young adults: dysphasia, heartburn, impaction, strictures
- ◆ Demographics:
  - ◆ occurs more often in school-aged boys with atopy
- ◆ Diagnostic criteria:
  - ◆ Presence of clinical symptoms of EoE
  - ◆ Esophageal biopsy  $\geq 15$  eosinophils/hpf



Figure 2. Mucosal edema, loss of vascular pattern, and linear furrows in a patient with eosinophilic esophagitis.  
 From Adamiak T, Pleśki KJ. Pediatric esophageal disorders: diagnosis and treatment of reflux and eosinophilic esophagitis. *Pediatr Rev.* 2018;39(3):392-409.

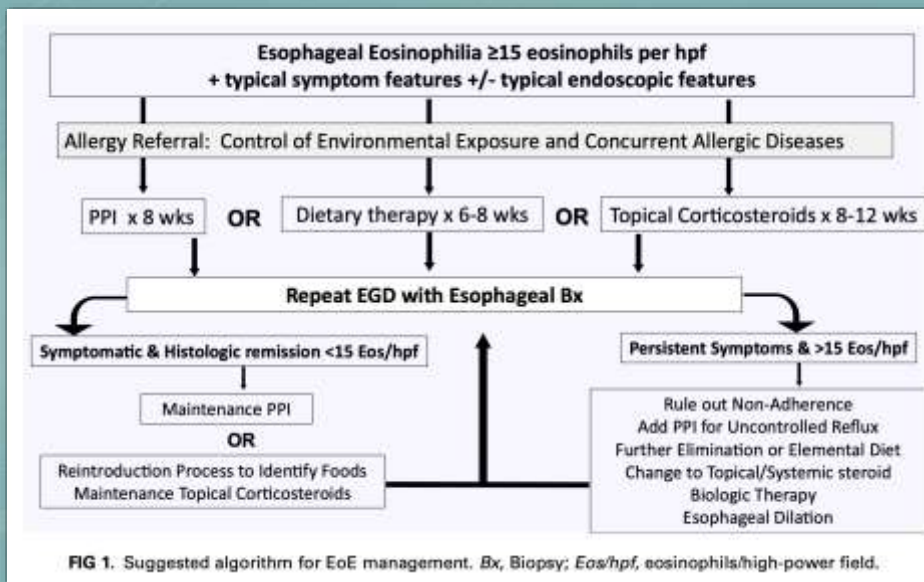
# Eosinophilic esophagitis treatment

- ◆ Diet
- ◆ Oral medications
- ◆ Biologic



Photo courtesy of Allergic Living





## Eosinophilic esophagitis diet

- ◆ Guided diet:
  - ◆ Allergy tests of foods that cause reactions are done by blood or skin prick
  - ◆ After the tests are done, the foods that cause a reaction may be removed from the diet.
- ◆ Non-guided diet:
  - ◆ Foods that cause EoE are taken out of the diet. Sometimes even when allergy tests are negative they are removed.
    - ◆ Milk, soy, egg, peanut/tree nut, wheat and seafood (6FED, 4FED or single food)
- ◆ Complete (Elemental Diet):
  - ◆ These formulas are pre-digested and “invisible” to the immune system. The formula has all the nutrition needed for growth and development. Often a large amount must be given (sometimes via feeding tube).



## Eosinophilic esophagitis medications

- ◆ Anti-reflux medications (proton pump inhibitor)
- ◆ Topical steroids: swallowed Flovent® from an inhaler or drinking thickened Pulmicort® flavored with Splenda®
- ◆ The Food and Drug Administration (FDA) recently approved dupilumab (Dupixent) for treatment of adults and children 1 year and older who weigh at least 15 kg with eosinophilic esophagitis.
- ◆ These do not cure the disease but improve symptoms

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