



# Food Allergy and Adverse Reactions to Foods

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# Food Allergy and Adverse Reactions to Foods

- Adverse reactions to foods consist of any untoward reaction following the ingestion of a food or food additive and are classically divided into
- ١- Food intolerances (e.g., lactose intolerance ), which are adverse physiologic responses
- ٢- Food allergies, which are adverse immunologic responses and can be

IgE mediated

Non-IgE mediated

**Table 176.1    Adverse Food Reactions**

**FOOD INTOLERANCE** (non-immune system mediated, nontoxic, noninfectious)

**Host Factors**

Enzyme deficiencies—lactase (primary or secondary), sucrase/isomaltase, hereditary fructose intolerance, galactosemia  
Gastrointestinal disorders—inflammatory bowel disease, irritable bowel syndrome, pseudoobstruction, colic  
Idiosyncratic reactions—caffeine in soft drinks ("hyperactivity")  
Psychologic—food phobias, obsessive/compulsive disorder  
Migraines (rare)

**Food Factors (Toxic or Infectious or Pharmacologic)**

Infectious organisms—*Escherichia coli*, *Staphylococcus aureus*, *Clostridium perfringens*, *Shigella*, botulism, *Salmonella*, *Yersinia*, *Campylobacter*  
Toxins—histamine (scombroid poisoning), saxitoxin (shellfish)  
Pharmacologic agents—caffeine, theobromine (chocolate, tea), tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)  
Contaminants—heavy metals, pesticides, antibiotics

**FOOD ALLERGY**

**IgE Mediated**

Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial  
Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis  
Respiratory—acute rhinoconjunctivitis, bronchospasm  
Generalized—anaphylactic shock, exercise-induced anaphylaxis


**Mixed IgE Mediated and Non-IgE Mediated**

Cutaneous—atopic dermatitis, contact dermatitis  
Gastrointestinal—allergic eosinophilic esophagitis and gastroenteritis  
Respiratory—asthma

**Non-IgE Mediated**

Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)  
Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease  
Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)  
Unclassified



- As with other atopic disorders, food allergies appear to have increased over the past 3 decades, primarily in countries with a Western lifestyle.
- Worldwide, estimates of food allergy prevalence range from 1–10%; food allergies affect an estimated 3/5% of the U.S. population.
- Up to 6% of children experience food allergic reactions in the 1st 3 yr of life, including approximately 2/5% with cow's milk allergy, 2% with egg allergy, and 2–3% with peanut allergy. 
- Peanut allergy prevalence tripled over the past decade.
- Most children “outgrow” milk and egg allergies, with approximately 50% doing so by school-age. In contrast, 80–90% of children with peanut, tree nut, or seafood allergy retain their allergy for life.

# Genetics

- Family history confers a 2-10-fold increased risk
- HLA-DQ locus (HLA-DQB1\*02 and DQB1\*06:03P), filaggrin, interleukin-10, STAT4, and FOXP3 genes are associated with food allergy, although the results are inconsistent across different populations
- Differential methylation at the HLA-DR and -DQ regions was associated with food allergy
- Epigenetic studies implicate DNA methylation effects on interleukins 4, 5, and 10 and interferon (IFN)-γ genes and in the mitogen activated protein kinase (MAPK) pathway.

# Pathogenesis

- IgE mediated
  - In susceptible individuals exposed to certain allergens, food specific IgE antibodies are formed that bind to Fc $\epsilon$  receptors on mast cells, basophils, macrophages, and dendritic cells. When food allergens penetrate mucosal barriers and reach cell-bound IgE antibodies, mediators are released that induce vasodilation, smooth muscle contraction, and mucus secretion, which result in symptoms of immediate hypersensitivity (allergy).

- Activated mast cells and macrophages may release several cytokines that attract and activate other cells, such as eosinophils and lymphocytes, leading to prolonged inflammation.
- Symptoms elicited during acute IgE-mediated reactions can affect the skin (urticaria, angioedema, flushing), gastrointestinal (GI) tract (oral pruritus, angioedema, nausea, abdominal pain, vomiting, diarrhea), respiratory tract (nasal congestion, rhinorrhea, nasal pruritus, sneezing, laryngeal edema, dyspnea, wheezing), and cardiovascular system (dysrhythmias, hypotension, loss of consciousness).



# Pathogenesis

- Non-IgE food allergies
  - Lymphocytes, primarily food allergen-specific T cells, secrete excessive amounts of various cytokines that lead to a “delayed,” more chronic inflammatory process affecting the skin (pruritus, erythematous rash), GI tract (failure to thrive, early satiety, abdominal pain, vomiting, diarrhea), and respiratory tract (food-induced pulmonary hemosiderosis).
- Mixed IgE and cellular responses to food allergens can also lead to chronic disorders, such as atopic dermatitis, asthma, eosinophilic esophagitis, and gastroenteritis.

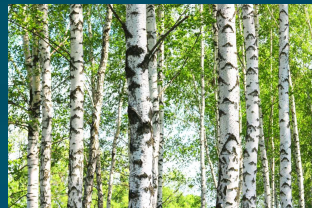


- Children who develop IgE-mediated food allergies may be sensitized by food allergens penetrating the GI barrier, referred to as class 1 food allergens ,
- Or by food allergens that are partially homologous to plant pollens penetrating the respiratory tract, referred to as class 2 food allergens .

- Any food may serve as a class 1 food allergen, but egg, milk, peanuts, tree nuts, fish, soy, and wheat account for 90% of food allergies during childhood. Many of the major allergenic proteins of these foods have been characterized. There is variable but significant cross-reactivity with other proteins within an individual food group. Exposure and sensitization to these proteins often occur very early in life. Virtually all milk allergies develop by 12 mo of age and all egg allergies by 18 mo, and the median age of 1st peanut allergic reactions is 14 mo.



- Class ٢ food allergens are typically vegetable, fruit, or nut proteins that are partially homologous with pollen proteins .With the development of seasonal allergic rhinitis from birch, grass, or ragweed pollens, subsequent ingestion of certain uncooked fruits or vegetables provokes the oral allergy syndrome .
- Intermittent ingestion of allergenic foods may lead to acute symptoms such as urticaria or anaphylaxis, whereas prolonged exposure may lead to chronic disorders such as atopic dermatitis and asthma.
- Cell-mediated sensitivity typically develops to class ١ allergens.



## Clinical Manifestations

- From a clinical and diagnostic standpoint, it is most useful to subdivide food hypersensitivity disorders according to the predominant target organ and immune mechanism.



**Table 176.4 Symptoms of Food-Induced Allergic Reactions**

TARGET ORGAN	IMMEDIATE SYMPTOMS	DELAYED SYMPTOMS
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper respiratory	Nasal congestion Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough, dyspnea, wheezing
Gastrointestinal (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	
Gastrointestinal (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	
Miscellaneous	Uterine contractions Sense of "impending doom"	

# Gastrointestinal Manifestations

- GI food allergies are often the 1st form of allergy to affect infants and young children
- Irritability, vomiting or “spitting-up,” diarrhea, and poor weight gain.
- Cell-mediated hypersensitivities without IgE involvement predominate
- Skin-prick tests and in vitro tests for food-specific IgE antibodies of little diagnostic value.

# Food protein–induced enterocolitis syndrome (FPIES)

- 1st several mo of life
- Irritability, intermittent vomiting, and protracted diarrhea and dehydration .Vomiting generally occurs 1-4 hr after feeding, and abdominal distention, bloody diarrhea, anemia, and failure to thrive.
- Symptoms are most often provoked by cow's milk or soy protein–based formulas.



# Food protein–induced enterocolitis syndrome (FPIES)

- In older infants and children from rice, oat, wheat, egg, peanut, nut, chicken, turkey, or fish.
- Hypotension occurs in approximately 15% of patients after allergen ingestion and may initially be thought to be caused by sepsis.
- FPIES usually resolves by age 3-5 yr.



# Food protein–induced allergic proctocolitis (FPIAP)

- Presents in the 1st few mo of life as blood-streaked stools in otherwise healthy infants.
- 6-9% of cases occur among breastfed infants
- The remainder largely among infants fed cow's milk or soy protein–based formula.
- Occasionally produce anemia



# Food protein–induced enteropathy (FPE)

- 1st several mo of life
- Protracted diarrhea, steatorrhea vomiting in up to 95% of cases, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemia occur occasionally.
- Cow's milk sensitivity is the most common cause of FPE in young infants,
- Soy, egg, wheat, rice, chicken, and fish in older children.
- Celiac disease, the most severe form of FPE, occurs in about 1 per 100 U.S. population, although it may be “silent” in many patients

# Food protein–induced enteropathy (FPE)

## Celiac Disease

- Extensive loss of absorptive villi and hyperplasia of the crypts,
- Malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption may occur.
- Genetically susceptible individuals (HLA-DQ $\alpha$  or HLA-DQ $\beta$ ) demonstrate a cell-mediated response to tissue transglutaminase deamidated gliadin (a fraction of gluten), which is found in wheat, rye, and barley.



# Eosinophilic esophagitis (EoE)

- May appear from infancy through adolescence, more frequently in boys
- Cell mediated + IgE Mediated
- GERD, vomiting, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional GER medications.
- EoE is a clinicopathologic diagnosis.
- 15 eosinophils per high-power field are seen on esophageal biopsy following treatment with PPIs.
- Eosinophilic gastroenteritis occurs at any age and causes symptoms similar to those of EoE, as well as prominent weight loss or failure to thrive, both of which are the hallmarks of this disorder. More than 50% of patients with this disorder are atopic; however, food-induced IgE-mediated reactions have been implicated only in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked protein losing enteropathy.

# Oral allergy syndrome (pollen-associated food allergy syndrome)

- IgE mediated
- Older children
- Birch and ragweed pollen-induced allergic rhinitis.
- Oropharynx ,rapid onset of oral pruritus; tingling and angioedema of the lips, tongue, palate, and throat; and occasionally a sensation of pruritus in the ears and tightness in the throat.
- Symptoms are generally **short lived** and are caused by local mast cell activation following contact with fresh raw fruit and vegetable proteins that cross-react with **birch pollen** (apple, carrot, potato, celery, hazel nuts, peanuts, kiwi, cherry, pear), **grass pollen** (potato, tomato, watermelon, kiwi), and **ragweed pollen** (banana, melons such as watermelon and cantaloupe).



Fig. 2. Asthmatic patient with OAS. Swelling of the tongue and itching after eating a peach.



## Symptoms of Oral Allergy Syndrome



Symptoms typically  
subside within minutes



Can be treated with an  
over-the-counter antihistamine

- Lips tingling
- Mouth itching





## Acute gastrointestinal allergy

- Generally manifests as acute abdominal pain, vomiting, or diarrhea that accompanies IgE-mediated allergic symptoms in other target organs.

**Table 176.5** Food Protein–Induced Gastrointestinal Syndromes

	<b>FPIES</b>	<b>PROCTOCOLITIS</b>	<b>ENTEROPATHY</b>	<b>EOSINOPHILIC GASTROENTEROPATHIES*</b>
Age at onset	1 day–1 year	1 day–6 months	Dependent of age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
Food proteins implicated				
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy, egg white, wheat, peanut
Less common	Rice, chicken, turkey, fish, pea	Egg, corn, chocolate	Wheat, egg	Meats, corn, rice, fruits, vegetables, fish
Multiple food hypersensitivities	>50% both cow's milk and soy	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breastfeeding	Formula	Formula
Atopic background				
Family history of atopy	40–70%	25%	Unknown	~50% (often history of eosinophilic esophagitis)
Personal history of atopy	30%	22%	22%	~50%
Symptoms				
Emesis	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate



**Table 176.5****Food Protein–Induced Gastrointestinal Syndromes**

	<b>FPIES</b>	<b>PROCTOCOLITIS</b>	<b>ENTEROPATHY</b>	<b>EOSINOPHILIC GASTROENTEROPATHIES*</b>
Age at onset	1 day–1 year	1 day–6 months	Dependent of age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
Laboratory findings				
Anemia	Moderate	Mild	Moderate	Mild-moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild-severe
Methemoglobinemia	May be present	No	No	No
Allergy evaluation				
Food skin-prick test	Negative <sup>†</sup>	Negative	Negative	Positive in ~50%
Serum food allergen IgE	Negative <sup>†</sup>	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
Biopsy findings				
Colitis	Prominent	Focal	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation, and basal zone hyperplasia
Food challenge	Vomiting in 1-4 hr; diarrhea in 5-8 hr	Rectal bleeding in 6-72 hr	Vomiting, diarrhea, or both in 40-72 hr	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge under supervision in 1.5-2 yr	Protein elimination, symptoms clear in 3 days with casein hydrolysate; resume/continue breastfeeding on maternal antigen-restricted diet; reintroduce at home after 9-12 mo of age	Protein elimination, symptoms clear in 1-3 wk; rechallenge and biopsy in 1-2 yr	Protein elimination, good response to casein hydrolysate, excellent response to elemental diet; symptoms clear in 2-3 wk, excellent acute response to steroids; rechallenge by introducing food at home and biopsy in 1-2 yr
Natural history	Cow's milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr	Resolved by 9-12 mo	Most cases resolve in 2-3 yr	Typically a prolonged, relapsing course
Reintroduction of the food	Supervised food challenge	At home, gradually advancing from 1 oz to full feedings over 2 wk	Home, gradually advancing	Home, gradually advancing

## Diagnosis

- A thorough medical history is necessary to determine whether a patient's symptomatology represents an adverse food reaction ,whether it is an intolerance or food allergic reaction, and if the latter, whether it is likely to be an IgE-mediated or a cell-mediated response .



- The following facts should be established:
  - (١) The food suspected of provoking the reaction and the quantity ingested,
  - (٢) The interval between ingestion and the development of symptoms,
  - (٣) The types of symptoms elicited by the ingestion,
  - (٤) Whether ingesting the suspected food produced similar symptoms on other occasions,
  - (٥) Whether other inciting factors, such as exercise, are necessary,
  - (٦) The interval from the last reaction to the food.

- Skin-prick tests and RAST tests are useful for demonstrating IgE sensitization
- Many fruits and vegetables require skin-prick testing with fresh produce
- A negative skin test result virtually excludes an IgE-mediated form of food allergy.
- Conversely, most children with positive skin test responses to a food do not react when the food is ingested, so more definitive tests, such as quantitative IgE tests or food elimination and challenge, are often necessary to establish a diagnosis of food allergy.

- In the absence of a clear history of reactivity to a food and evidence of food-specific IgE antibodies, definitive studies must be performed before recommendations are made for avoidance or the use of highly restrictive diets that may be nutritionally deficient, logistically impractical, disruptive to the family, expensive, or a potential source of future feeding disorders. IgE-mediated food allergic reactions are generally very food specific, so the use of broad exclusionary diets, such as avoidance of all legumes, cereal grains, or animal products, is not warranted

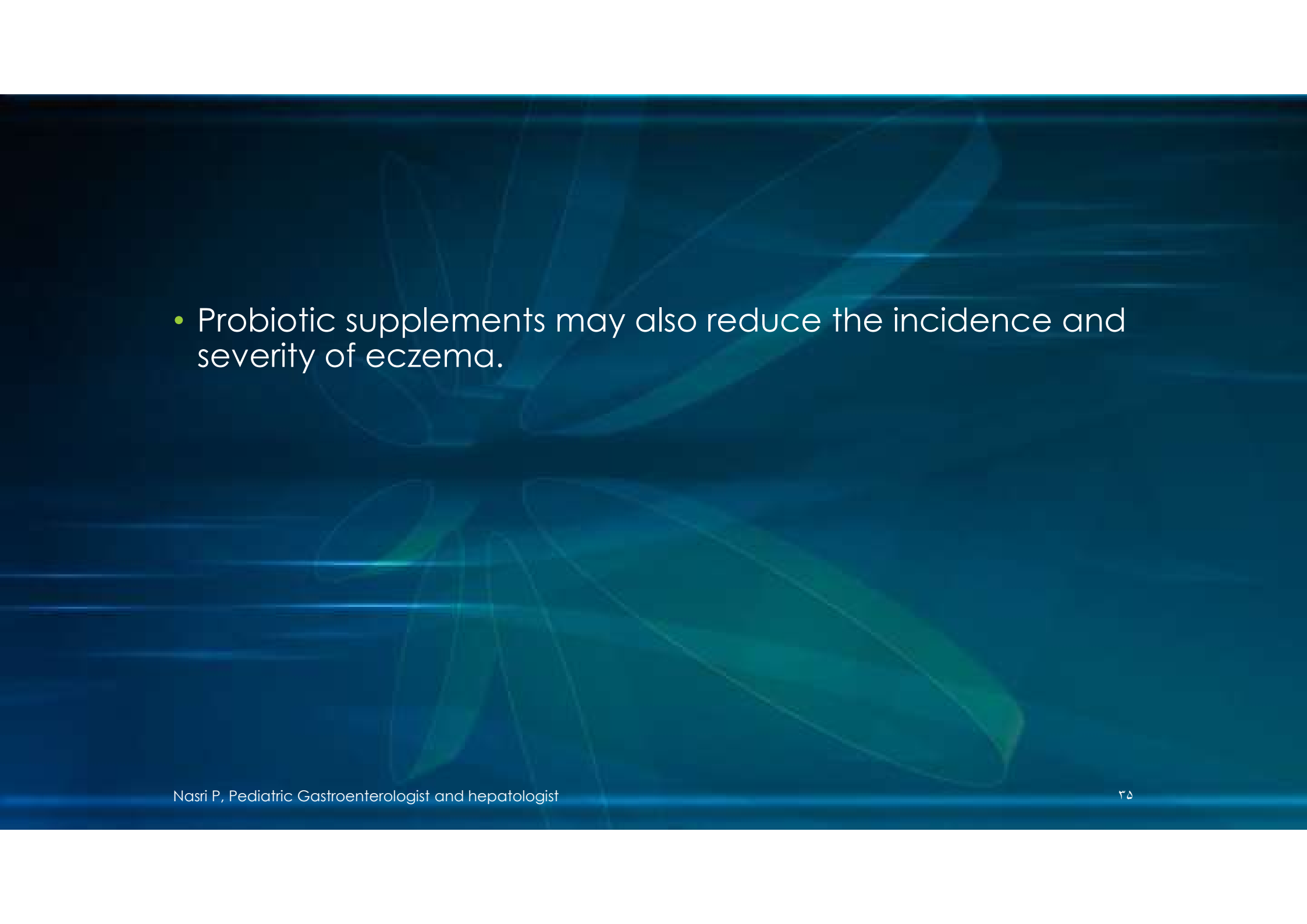
- There are no laboratory studies to help identify foods responsible for cell mediated reactions.
- Consequently, elimination diets followed by oral food challenges are the only way to establish the diagnosis.
- Allergists experienced in dealing with food allergic reactions and able to treat anaphylaxis should perform food challenges.
- Before a food challenge is initiated, the suspected food should be eliminated from the diet for 10-14 days for IgE-mediated food allergy and up to 1 wk for some cell-mediated disorders, such as EoE.
- Some children with cell mediated reactions to cow's milk do not tolerate hydrolysate formulas and must receive amino acid-derived formulas.
- If symptoms remain unchanged despite appropriate elimination diets, it is unlikely that food allergy is responsible for the child's disorder.

# Treatment

- Appropriate identification and elimination of foods responsible for food hypersensitivity reactions are the only validated treatments for food allergies.
- Complete elimination of common foods (milk, egg, soy, wheat, rice, chicken, fish, peanut, nuts) is very difficult because of their widespread use in a variety of processed foods.
- Food Allergy Research and Education (FARE , [www.foodallergy.org](http://www.foodallergy.org) )
- Consortium of Food Allergy Research ([www.cofargroup.org](http://www.cofargroup.org) ).



- Because many food allergies are outgrown, children should be reevaluated periodically by an allergist to determine whether they have lost their clinical reactivity.

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- Probiotic supplements may also reduce the incidence and severity of eczema.

## References:

- Nelson Textbook of Pediatrics ۲۰۲۰.

Thanks