

Table 1

History of Eczema, Serum Total IgE, and Severity of Inpatient Asthma Admission Outcomes

	N	Outcomes	P Value
Eczema	20	Length of stay (days)	4.6 ± 1.8
		Hours of continuous albuterol	8.7 ± 10.5
		Mean total IgE (IU/mL)	1166 ± 1439
No eczema	28	Length of stay (days)	3.5 ± 1.4
		Hours of continuous albuterol	3.5 ± 7.1
		Mean total IgE (IU/mL)	562 ± 837

Abbreviation: IgE, immunoglobulin E.

In summary, we found that children who were hospitalized for asthma had a more severe hospital course when there is a history of eczema, as compared with those without a history of eczema. Our study is limited by a small sample size. Larger studies are needed to confirm these findings.

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References

- [1] Newth CJ, Meert KL, Clark AE, et al. Fatal and near-fatal asthma in children: the critical care perspective. *J Pediatr*. 2012;161:214–221.
- [2] Akinbami LJ, Sullivan SD, Campbell JD, et al. Asthma outcomes: healthcare utilization and costs. *J Allergy Clin Immunol*. 2012;129:S49–S64.
- [3] Sherenian MG, Wang Y, Fulkerson PC. Hospital admission associates with higher total IgE level in pediatric patients with asthma. *J Allergy Clin Immunol Pract*. 2015;3:602–603.
- [4] Lee JK, Han D. Atopic dermatitis is an important comorbidity in severe asthma. *Ann Allergy Asthma Immunol*. 2018;120:661–662.
- [5] Malka J, Mauger DT, Covar R, et al. Eczema and race as combined determinants for differential response to step-up asthma therapy. *J Allergy Clin Immunol*. 2014;134:483–485.
- [6] Ong PY, Ferdman RM, Church JA. Association of microbial IgE sensitizations with asthma in young children with atopic dermatitis. *Ann Allergy Asthma Immunol*. 2012;108:212–213.
- [7] Tanaka A, Suzuki S, Ohta S, et al. Association between specific IgE to *Staphylococcus aureus* enterotoxins A and B and asthma control. *Ann Allergy Asthma Immunol*. 2015;115:191–197.
- [8] Uong P, Curran-Everett D, Leung DYM. *Staphylococcus aureus* colonization is associated with increased inhaled corticosteroid requirements in patients with atopic dermatitis and asthma. *J Allergy Clin Immunol Pract*. 2017;5:1782–1783.

FPIES in adults

Non-immunoglobulin E (IgE)-mediated food allergic disorders are poorly characterized in adults. Some adult patients report gastrointestinal (GI) symptoms that recur consistently after ingestion of specific foods, in the absence of cutaneous, respiratory, or cardiovascular manifestations. These patients have no evidence of food-specific IgE by either in vivo or in vitro testing. These patients may have an adult variant of food protein–induced enterocolitis syndrome (FPIES), which is a non-IgE-mediated food hypersensitivity, generally diagnosed in infants.¹ According to the FPIES guidelines,² FPIES is diagnosed based on a supportive medical history, resolution of symptoms by elimination of the causative food, and, where the history is unclear, confirmation with an oral food challenge (OFC). We report a cohort of 20 adults with recurrent non-IgE-mediated GI symptoms to specific foods.

We conducted a retrospective chart review of patients seen in an allergy practice at a university teaching hospital from 2008 to 2015. Electronic records were searched using key words including “non-IgE” and “non-immunologic.” We included subjects 18 years or older reporting at least 2 episodes of exclusively GI symptoms triggered by a specific food, with an onset at least 60 minutes after food ingestion, resolution of symptoms after food elimination, and no evidence of IgE-sensitization to the food trigger. Alternative diagnoses must have been ruled out, including lactose intolerance, fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) intolerance,

inflammatory bowel disease, and celiac disease. This study was approved by the research ethics board of St. Michael's Hospital.

Twenty patients met inclusion and exclusion criteria. Eighteen (90%) were female, and 2 (10%) were male. The median age at the time of symptom onset was 38.5 years (range, 16–67 years). A median delay of 1 year (mean, 3.59 years) from the onset of symptoms to diagnosis of non-IgE-mediated food allergy was seen. Asthma was noted in 1 of 20 patients, eczema in 4 of 20, and urticaria (independent of their GI symptoms) in 2 of 20. Serologic testing was done during the consumption of wheat, for celiac disease; tissue transglutaminase IgA antibody was negative in all 3 patients with wheat hypersensitivity. Lactose intolerance was ruled out in 4 of 4 of patients with dairy allergies. Patients were equally symptomatic with foods with high lactose content (eg, milk and ice cream) and low lactose content (eg, hard aged cheeses) dairy products. Allergy skin tests with commercial extracts and the corresponding fresh foods (for 20/20 patients) and ImmunoCAP tests (Thermo Fisher Scientific, Toronto, Ontario, Canada; for 17/17 patients) for food-specific-IgE were negative.

The median time from food ingestion to the onset of symptoms was 3 hours (range, 1–11 hours). Symptoms lasted from 48 minutes to 27 hours (median, 3 hours). The most commonly reported GI symptoms were severe crampy abdominal pain (90%; 18/20), vomiting (55%; 11/20), and diarrhea (50%; 10/20); 6 of 20 patients (30%) experienced all 3 symptoms, and 6 of 20 patients (30%) reported symptoms induced by more than 1 food. None of these patients had cutaneous, respiratory, genitourinary, or cardiovascular

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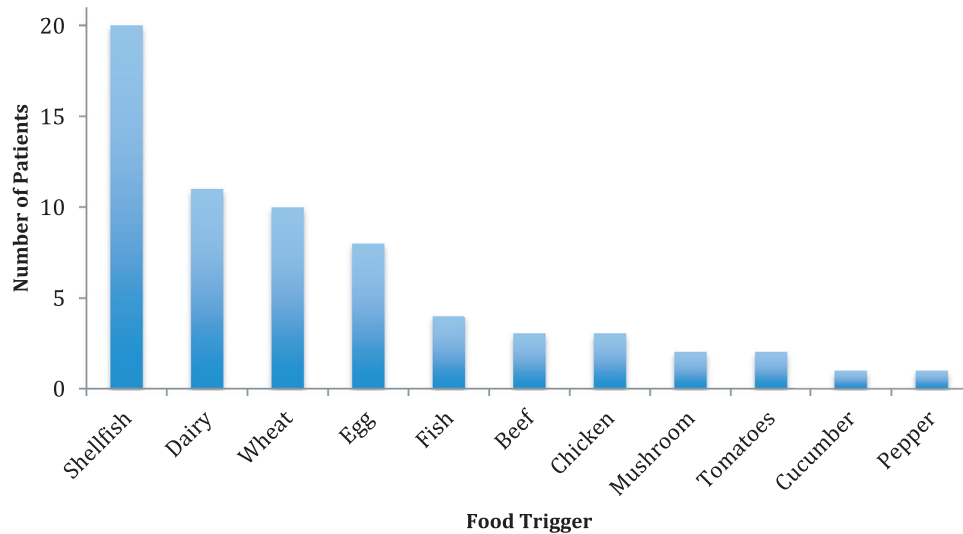


Figure 1. Foods that induce non-IgE-mediated GI symptoms in adults.

manifestations. Patients had a median of 3 (range, 2–7) separate reactions, with typical symptoms triggered by the same food.

The most common triggers were shellfish (65% of patients), followed by dairy products (20%), wheat (20%), and egg (15%), followed by less common foods (Fig 1).

Typically, FPIES begins in infancy and manifests as recurring vomiting, pallor, lethargy, abdominal pain, and diarrhea; in severe cases, acidosis and hypotension are seen.³ Symptoms are reproducible and begin within 1 to 4 hours of food ingestion. The diagnosis of FPIES is confirmed when 2 or more reactions with typical symptoms to the same food occur,² and symptoms resolve when the causative food is removed from the diet. The FPIES generally resolves between the ages of 1 and 5 years.⁴

In recent years, non-IgE-mediated food allergies have been described in adults.^{1,5} Symptoms may be provoked most commonly by seafoods (crustacean, mollusc shellfish, and fish),^{6,7} hen's egg,⁸ and infrequently by other foods such as mushroom.⁷ Patients included in these studies had delayed reactions, with pronounced abdominal pain, vomiting, or diarrhea.^{5,7} In our study, the long interval between ingestion of the trigger food and the onset of symptoms is typical for non-IgE mediated allergic reactions.³ Negative allergy skin tests (using both commercial extracts and fresh foods) and in vitro food-specific IgE tests, as well as reproducible symptoms in every patient, are consistent with a non-IgE-mediated mechanism. None of the patients had worsening of their reactions with self-administered rechallenge, and none had extra-GI manifestations that progressed to anaphylactic reactions.

In a previous study⁷ of 31 adult patients with non-IgE mediated GI food hypersensitivities consistent with FPIES, most of the patients were females, with a median age of disease onset of 29 years. Shellfish was the most common trigger, followed by egg, producing the gastrointestinal symptoms mentioned previously.⁷ Interesting similarities were noted between their patients and infants with FPIES. In general, patients reported symptoms of abdominal pain, vomiting, or diarrhea within 4 hours after ingestion of a specific food without any other explanation for symptoms.⁹

Patients usually develop FPIES in early infancy and become tolerant to the food with age.⁹ However, 1 case has been published of FPIES in a 53-year-old man who developed symptoms in adulthood.¹ In comparing adults in our study with children with FPIES, some common features are noted, including the time of symptom onset and the most common symptoms (vomiting, abdominal pain, and diarrhea). However, we noted a few differences. The foods most commonly implicated in causing FPIES in

infants were milk, soy, rice, and oat, whereas the most common food triggers in our population were shellfish, wheat, dairy products, and egg. Most infants with FPIES are males,⁹ whereas females make up the majority of our adult group.

Our study is limited by potential recall bias and lack of a confirmatory OFC. We did not perform OFC in our patients because they had already rechallenged themselves multiple times, either purposefully or unintentionally, with consistent and reproducible symptoms, and they were unwilling to undergo a formal OFC procedure. As well, we may have inadvertently included patients with non-celiac gluten sensitivity among those reporting symptoms to wheat.

These 20 adults exhibit non-IgE-mediated symptoms of abdominal pain, vomiting, and diarrhea most commonly triggered by ingestion of shellfish, dairy, wheat, and egg, highly suggestive of the FPIES diagnosis. Treatment is avoidance of the specific foods and reassurance that these patients are not at risk for anaphylaxis. Prospective studies are needed to describe the natural history and potential comorbidities of non-IgE-mediated GI food allergic disorders in adults.

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References

- [1] Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. *J Allergy Clin Immunol*. 2012;130(5):1199–1200.

- [2] Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 2017;139(4):1111–1126.
- [3] Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update—2014. *J Allergy Clin Immunol*. 2014;134(5):1016–1025.
- [4] Caubet JC, Bencharitiwong R, Ross A, Sampson HA, Berin MC, Nowak-Węgrzyn A. Humoral and cellular responses to casein in patients with food protein-induced enterocolitis to cow's milk. *J Allergy Clin Immunol*. 2016;139(2):572–583.
- [5] Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol Pract*. 2013;1(4):343–349.
- [6] Gleich GJ, Sebastian K, Firszt R, Wagner LA. Shrimp allergy: gastrointestinal symptoms commonly occur in the absence of IgE sensitization. *J Allergy Clin Immunol Pract*. 2015;4(2):316–318.
- [7] Tan JA, Smith WB. Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults. *J Allergy Clin Immunol Pract*. 2014;2(3):355–357.
- [8] >Zubrinich C, Hew M, O'Hehir R. Egg provoked food protein-induced enterocolitis-like syndrome in an adult. *Clin Case Rep*. 2016;4(9):899–901.
- [9] Caubet JC, Ford LS, Sickles L, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol*. 2014;134(2):382–389.

Chronic rhinosinusitis with severe nasal polyposis in hyper-IgE syndrome



Autosomal-dominant hyperimmunoglobulin E (hyper-IgE) syndrome (AD-HIES) is a rare multisystem disorder that is characterized by eczema, infections with staphylococcal and fungal organisms, increased total serum IgE level, and skeletal and connective tissue involvement. The transcription factor signal transducer and activator of transcription 3 (STAT3) plays a crucial role in the development and differentiation of T-helper cell type 17 (T_H17) cells and mutations in *STAT3* cause AD-HIES.¹ Patients with AD-HIES are reported to have markedly decreased or absent circulating T_H17 cells.^{2,3} This T-cell subset appears to be critically important for generating protective immunity to selected bacterial (*Staphylococcus aureus*) and fungal (*Candida albicans*) pathogens.⁴ Similarly, *STAT3* deficiency confers susceptibility to molds, especially *Aspergillus* species, and particularly in association with parenchymal lung damage as in bronchiectasis or pneumatocoeles.⁵ T_H17 cells also play an important role in the host response to *Aspergillus fumigatus* infections.⁶

The diagnosis of AD-HIES depends on a combination of clinical features, testing for *STAT3* mutations, and quantification of circulating T_H17 cells.^{7,8} A scoring system developed by investigators at the National Institutes of Health (NIH) incorporates assessment of clinical features, including skin abscesses, episodes of pneumonia, parenchymal lung anomalies, retained primary dentition, eczema, and serious infections, and laboratory studies, including highest serum IgE level and highest blood eosinophil count.⁹ Points are assigned for the presence and severity of clinical and laboratory features. A score higher than 40 is strongly suggestive of AD-HIES.

An 11-year-old girl presented for evaluation of a chronic facial rash and recurrent infections. Present sporadically since she was 1 year of age, the rash was diagnosed as “eczema” and was characterized by pruritus and somewhat disfiguring erythematous, maculopapular, and multinodular lesions, with nodules up to 1 cm that affected her face, neck, and scalp. The nodules did not drain and were not cultured. Her eczema seemed to decrease with topical steroids and bleach washes, but it never cleared completely. In areas not affected, her facial skin texture appeared rough and superficially wrinkled. She did not have the characteristic coarse facial features of AD-HIES. She had a history of recurrent aphthous oral ulcers, recurrent clinical pneumonias, hyperlaxity of shoulder joints, and delayed shedding of primary dentition. She did not display evidence, previously or currently, of mucocutaneous or systemic candidiasis. Her family history was negative for features suggestive of AD-HIES.

At 13 years of age, she developed marked nasal congestion. In addition to chronic rhinosinusitis with bilateral nasal polyposis, allergic fungal rhinosinusitis was diagnosed. The diagnosis was made on the presence of significant nasal obstruction and congestion,

computed tomographic findings of near complete mucosal obliteration of sinuses with extensive nasal polyposis and areas of increased density in multiple sinuses bilaterally, visualization of eosinophilic mucin within multiple sinus cavities during sinus surgery, noninvasive fungal hyphae observed on pathology of mucin, and increased specific IgE to *Aspergillus* and *Alternaria* species. She underwent functional endoscopic sinus surgery after failed medical management. Eventually her sinus disease required 2 additional functional endoscopic sinus surgical procedures to clear, in addition to systemic steroids, nasal steroids, and itraconazole suppressive therapy.

The patient's highest serum IgE level was 2,001 kU/L when she was 15 years of age and she had eosinophilia to 14.2% (absolute eosinophil count 980 cells/ μ L). Other laboratory studies showed normal levels of serum IgG, IgA, and IgM and protective antibody levels to tetanus toxoid, *Haemophilus influenza* polysaccharide, and 23 of 23 pneumococcal serotypes after Pneumovax (Merck & Co, West Point, Pennsylvania) administration. The patient's NIH AD-HIES clinical score for HIES was 44, which predicted that a *STAT3* mutation was likely. *STAT3* sequencing showed a variant, c.1003C>T, that results in a p.Arg335Try missense mutation, a finding that was reported previously in AD-HIES.² Office spirometry and chest radiographs for the patient did not suggest chronic lung disease or anatomic anomalies. Measurement of circulating T_H17 cells (Diagnostic Immunology Laboratory, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio) showed a normal percentage of T_H17 cells expressed as a percentage of CD4⁺ T cells (0.33%, reference range 0.31–1.80) and a normal percentage of interleukin-17A–positive (IL-17A⁺) cells expressed as a percentage of CCR6⁺CD45RA⁺ cells (3.1%, reference range 1.2–4.6). Repeat testing 5 months later confirmed normal percentages of T_H17 cells and IL-17A⁺ cells (T_H17 0.49% and IL-17A⁺ 4.3%, respectively).

We hypothesize that having a normal level of T_H17 cells cannot rule out a clinical diagnosis of AD-HIES and that having an adequate number of T_H17 cells contributed to our patient's limited history of serious bacterial infections and absent history of invasive fungal infections. In a study by Renner et al,² all 17 patients tested had low or absent T_H17 cells and it was suggested that this could be useful for screening for AD-HIES. However, fewer than half the subjects in the report had their T_H17 cells tested. Our patient is the only case to our knowledge that has a documented normal T_H17 cell number with a known clinically relevant *STAT3* mutation. Thus, the mechanism in patients with *STAT3* mutations that prevents the normal generation of T_H17 cells, as described by Milner et al,³ might need to be reconsidered. The same *STAT3* mutation as described in our patient occurred in a father and daughter with AD-HIES.² Interestingly, these 2 patients had relatively low NIH clinical scores (42 and 43), similar to our patient, indicating a relatively mild clinical phenotype. However, their levels of T_H17 cells were not reported. To date, although there are defined scoring systems available for AD-HIES, there does not

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