



Emerging triggers of food protein–induced enterocolitis syndrome

Lessons from a pediatric cohort of 74 children in the United States

Andrea C. Blackman, MD ^{*,†}; Sara Anvari, MD, MS ^{*,†}; Carla M. Davis, MD ^{*,†}; Aikaterini Anagnostou, MD, PhD ^{*,†}

^{*} Section of Pediatric Immunology, Allergy, and Rheumatology, Baylor College of Medicine, Houston, Texas

[†] Department of Pediatrics, Section of Immunology, Allergy, and Rheumatology, Texas Children's Hospital, Houston, Texas

ARTICLE INFO

Article history:

Received for publication December 11, 2018.

Received in revised form January 23, 2019.

Accepted for publication January 31, 2019.

ABSTRACT

Background: Food protein–induced enterocolitis syndrome (FPIES) is an infrequent non–IgE-mediated gastrointestinal allergic disorder that occurs mostly in infants and young children. FPIES food triggers vary among different geographic locations, and the condition is still underdiagnosed and underrecognized.

Objective: To identify the triggers, characteristics, and management of FPIES in a pediatric US population of 74 children presenting to a tertiary center during a 3-year period.

Methods: We performed a retrospective electronic record review of all pediatric patients with a diagnosis of FPIES who presented to Texas Children's Hospital emergency centers and clinics.

Results: Most of our patients were white, and 65% had a positive family history of atopy. The median age at the first FPIES episode was 5 months (interquartile range, 4–6 months), and the median age at diagnosis was 11 months (interquartile range, 7–16 months). Grains (88%), cow's milk (49%), and vegetables (43%) were the most common food triggers in our cohort. Of the fruits, banana (24%) and avocado (16%) were predominantly reported. More than half of our patients experienced FPIES to multiple food triggers.

Conclusion: In our cohort, rice (53%) was the most common individual food trigger, surpassing cow's milk and soybean, previously reported as the most prevalent FPIES triggers in the United States. Banana (24%) and avocado (16%) rates were also much higher than in other studied populations, likely a reflection of different dietary and weaning habits in our area. Time from disease presentation to diagnosis was delayed, potentially because of difficulties in disease recognition. We noted a significant percentage of multiple-food FPIES in contrast to other populations.

© 2019 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Food protein–induced enterocolitis syndrome (FPIES) is a rare non–IgE-mediated gastrointestinal food–induced allergic disorder that occurs predominantly in infants and young children. Common food triggers and the natural history of FPIES vary according to geographic location. It is a serious condition that is still under-recognized, resulting in a delay in diagnosis and appropriate management. FPIES is characterized by delayed onset of repetitive vomiting that occurs approximately 1 to 4 hours after food

ingestion. Symptoms can include lethargy and pallor and may be followed by watery or bloody diarrhea. As many as 15% of patients develop hemodynamic instability.¹ Management of mild to moderate FPIES may occur at home and consists mainly of oral rehydration. Severe acute FPIES should be managed as a medical emergency, and treatment includes intravenous fluid resuscitation as first-line treatment. In selected cases, intravenous corticosteroids and/or 5-HT₃ antagonists (eg, ondansetron) may also be beneficial.² Maternal food elimination while breastfeeding is not routinely recommended in FPIES.²

Epidemiologic data on FPIES are limited. A recent population-based study from Australia reported the estimated incidence of FPIES to be 15.4 per 100,000 infants per year in infants younger than 2 years,³ and a prospective birth cohort study from Israel identified 0.34% of infants with cow's milk FPIES during a 2-year period.⁴ We sought to identify the triggers, characteristics, and

Reprints: Aikaterini Anagnostou, MD, PhD, Department of Pediatrics, Section of Immunology, Allergy, and Rheumatology, Texas Children's Hospital, 1102 Bates Ave, Ste 330, Houston, TX 77030; E-mail: aikaterini.anagnostou@bcm.edu.

Disclosures: Authors have nothing to disclose.

Funding: None.

<https://doi.org/10.1016/j.anai.2019.01.022>

1081-1206/© 2019 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

management of FPIES in a pediatric US population of 74 children presenting to a tertiary center during a 3-year period.

Methods

Design

We performed a retrospective electronic record review of all pediatric patients 0 to 17 years of age who presented to Texas Children's Hospital emergency centers and affiliated clinics for clinical symptoms of FPIES during a 3-year period between January 2015 and December 2017. The study was approved by the institutional research board committee at Baylor College of Medicine.

Selection of Participants

Electronic medical records were searched for pediatric patients with all diagnoses related to FPIES. The *International Classification of Diseases, Tenth Edition* codes K52.xx (including code K52.2, which is specific for FPIES) were searched for the 3-year period (2015–2017).

Medical records were reviewed, and patients with a clinical diagnosis of FPIES, as defined in the international guidelines,² were included in the analysis. The following information was recorded: race, ethnicity, sex, feeding method at birth, family history of atopy, atopic comorbidities, age of first episode, age at diagnosis, number of FPIES episodes, number of trigger foods, positive skin prick test (SPT) and/or specific IgE test results to the trigger food, clinical presentation, emergency department visits, dietetic consultation, rate of hospitalizations, and abnormal laboratory findings.

Statistical Analysis

Descriptive statistics were used for analysis. Continuous data were described as median and interquartile range (IQR). The Fisher exact test was performed using GraphPad Prism for Windows, version 7.0 (GraphPad Software, La Jolla California). $P < .05$ was considered statistically significant.

Results

Demographics and Characteristics

We identified 74 cases of FPIES during a 3 year-period. The female to male ratio was 1:1. A total of 67 of 74 patients (90%) were white. Only 3 patients (4%) were African American. In terms of ethnicity, 59 of 74 (80%) were non-Hispanic, whereas 8 of 74 (11%) were Hispanic. In this cohort, 65% had a positive family history of atopy. A family history of atopy was defined as 1 or more close family members (mother, father, or sibling) with a diagnosis of food allergy, asthma, eczema, or allergic rhinitis. A total of 46% of infants had atopic dermatitis, 19% had allergic rhinitis, 7% had concomitant asthma, and 5% had an IgE-mediated food allergy. The median age of the first episode was 5 months (IQR, 4–6 months), and the median age at diagnosis was 11 months (IQR, 7–16 months). With regard to the number of FPIES episodes, 4% of the patients had only 1 episode, 11% had 2 episodes, 7% had 3 episodes, 11% had 4 episodes, and 15% had 5 or more episodes before the diagnosis was confirmed. In 53%, this information was unrecorded. Sixty-five percent were exclusively breastfed since birth until at least the first 4 months of life, whereas 13% were bottle fed, 8% were mixed fed, and 13% had an unrecorded mode of feeding (Table 1).

Triggers

Grains (88%), cow's milk (49%), vegetables (43%), fruits (40%), soy (31%), meat (13%), nuts (3%), and fish (1%) were the food triggers identified in our cohort (Table 2). For grains, rice was a food trigger in 53%, oats in 35%, wheat in 5%, and quinoa in 4%. No patients in our

Table 1

Demographic Characteristics of the Study Patients

Characteristic	No. (%) of patients (N = 74)
Race	
White	67 (90)
Black	3 (4)
Unrecorded	4 (5)
Ethnicity	
Non-Hispanic	59 (80)
Hispanic	8 (11)
Sex	
Female	38 (51)
Male	36 (49)
Family history of atopy	
Yes	48 (65)
No	18 (24)
Unrecorded	8 (11)
Eczema	
Yes	34 (46)
No	40 (54)
Allergic rhinitis	
Yes	14 (19)
No	60 (81)
IgE-mediated food allergy	
Yes	4 (5)
No	70 (95)
Asthma	
Yes	5 (7)
No	69 (93)
Feeding method at birth	
Breastfed	48 (65)
Bottle fed	10 (13)
Mixed fed	6 (8)
Unrecorded	10 (13)
No. of episodes	
1	3 (4)
2	8 (11)
3	5 (7)
4	8 (11)
≥5	11 (15)
Unrecorded	39 (53)

cohort reacted to barley or millet. Rice was a single trigger in 10 of 74 patients (14%) only because it mostly occurred as multi-food FPIES (29 [39%]). Cross-reactivity between rice and oat was seen in 18 of 74 patients (24%). Oat was encountered as a single trigger in 1 patient (1%) only. Thirty patients (41%) had both milk and a solid food trigger. Of the fruits, banana (24%), avocado (16%), apple (11%), pear (9%), blueberry (3%), mango (3%), peach (1%), strawberry (1%), and plum (1%) were reported. Meat was found as a trigger in 13% of the patients (chicken, 5; beef, 1; pork, 1; turkey, 2; and bison, 1). In 31% of patients, only 1 trigger food was identified, whereas 18% of patients had 2 food triggers, and 51% had 3 or more food triggers.

When comparing infants with 1 or 2 triggers to those with multiple food triggers (defined as ≥ 3 food triggers), no significant difference was found in age at onset, family history of atopy ($P = .47$), presence of eczema ($P = .35$), any IgE-mediated food allergy ($P = .35$), or mode of feeding (breastfeeding vs bottle-feeding for the first 4 months of life) ($P = .26$). Rice and milk were less likely associated with multiple-food FPIES (>1 –2 triggers) than fruits and vegetables (Table 3).

Clinical Presentation and Management

All patients in this cohort presented with vomiting, 51 (69%) had diarrhea, 48 (65%) had lethargy, and 20 (27%) had pallor. Dehydration was found in 37 (50%) of the patients, whereas 6 (8%) developed hypovolemic shock. Hypotension was recorded in 10 (13%) and failure to thrive in 16 (22%). A total of 18 patients (24%) required hospitalization for dehydration (11 of 18), hypovolemic shock (5 of 18), hypotension (1 of 18), or profound lethargy (1 of 18).

Table 2
Trigger Foods

Trigger food	No. (%) of patients (N = 74)
Grains	65 (88)
Rice	39 (53)
Oats	26 (35)
Wheat	4 (5)
Quinoa	3 (4)
Cow's milk	36 (49)
Vegetables	32 (43)
Sweet potato	16 (22)
Squash	9 (12)
Potato	6 (8)
Corn	5 (7)
Carrots	5 (7)
Green beans	4 (5)
White potato	3 (4)
Pea	3 (4)
Beet	1 (1)
Fruits	30 (40)
Banana	18 (24)
Avocado	12 (16)
Apple	8 (11)
Pear	7 (9)
Blueberry	2 (3)
Mango	2 (3)
Peach	1 (1)
Strawberry	1 (1)
Plum	1 (1)
Soy	23 (31)
Meat	10 (13)
Chicken	5 (7)
Turkey	2 (3)
Beef	1 (1)
Pork	1 (1)
Bison	1 (1)
Nuts	2 (3)
Fish	1 (1)
Other ^a	2 (3)
No. of trigger foods	
1	23 (31)
2	13 (18)
3	12 (16)
4	6 (8)
≥5	20 (27)

^aIncludes bean and goat's milk.

Patients with reported failure to thrive were reviewed in detail. In 6 cases, malnutrition was identified during the dietetic consultation because of suboptimal oral intake and limited food choices related to the FPIES diagnosis. In 4 patients, a knowledge deficit related to food protein–induced enterocolitis syndrome food introduction guidelines was identified, and the infant or child was considered at risk of malnutrition. In the remaining patients, the failure to thrive diagnosis was previously made by the pediatrician for reasons unrelated to FPIES.

Most patients (74%) had a negative SPT result to their FPIES trigger food, and 66% had negative specific IgE test result to their trigger food. A dietetic consultation was received by 76%. A total of 54% required an emergency department visit, and 24% required hospitalization. Sepsis workup was performed in 22% of patients visiting the emergency department, and abnormal laboratory test results were found in 5%. These abnormal results included an elevated white blood cell count in 1 case, increased liver enzyme levels in 1 patient, and the presence of metamyelocytes in 2 other patients (Fig 1).

Discussion

We report on 74 patients with FPIES who presented to our pediatric tertiary center during a period of 3 years (2015–2017). Median age of disease onset in our cohort was 5 months, in line with

Table 3Comparison of Group Reacting to 1 to 2 Trigger Foods With Group Reacting to 3 or More Trigger Foods^a

Variable	Group reacting to 1–2 food triggers (n = 36)	Group reacting to ≥3 food triggers (n = 38)
Age at first episode, median, mo	5	5
Sex, No.		
Male	19	19
Female	17	19
Family history of atopy	25/36 (69)	23/38 (60)
Eczema	19/36 (53)	15/38 (39)
IgE-mediated food allergy	3/36 (8)	1/38 (3)
Breastfed exclusively (first 4 months)	22/36 (61)	26/38 (68)
Bottle fed exclusively (first 4 months)	5/36 (14)	5/38 (13)
Most common trigger foods	Rice (17/36 [47%]) and milk (13/36 [36%])	Vegetables (27/38 [71%]) and fruits (24/38 [63%])

^aData are presented as number (percentage) of patients unless otherwise indicated.

previously published studies reporting an age at onset between 2 and 7 months.^{2–6}

Our city is one of the most ethnically diverse in the nation, and according to the US Census 2000, the racial makeup of Houston included 49.3% white, 25.3% black or African American, and 37% Hispanic or Latino of any race. Our tertiary care center is mostly reflective of this race and ethnicity distribution. However, this diversity was not observed in our FPIES cohort, which mostly consisted of non-Hispanic white patients, suggesting that FPIES may be a disease that affects certain races and/or ethnicities more than others.

The most commonly reported FPIES food triggers in the United States include cow's milk and soybean, followed by grains, especially rice and oat.² In our cohort (Southwestern United States), rice (53%) was the most common individual food trigger, surpassing cow's milk. We identified only a few patients reacting to other grains, such as wheat (5%) and quinoa (4%), which should be reassuring for the practitioner when addressing food introduction. Cross-reactivity between rice and oat was low (24%) in our cohort. More than half (53%) of our patients with cow's milk FPIES also had soy as a trigger, a higher percentage when compared with other populations; Caubet et al⁵ identified 23% of infants with combined milk and soy FPIES during a 10-year period, whereas Ruffner et al⁷ report that 43.5% of their population with cow's milk FPIES also reacted to soy during a 5-year period. Interestingly, we also identified a significant number of our patients (40%) reacting to fruits, with banana (24%) and avocado (16%) the most frequent; this is also a much higher rate than in other studied populations, reinforcing the observation that FPIES is a heterogeneous disorder with significant geographic variations.² A recent Australian study reports a rate of 10% for fruits and only 4% for banana and 2% for avocado.³ In contrast, a brief report from the Southwestern area of the United States recently highlighted avocado as an emerging FPIES trigger in areas where this food is used more frequently given as an early weaning solid food for infants.⁸ Despite our geographic proximity to the Gulf Coast, fish was an uncommon trigger in our cohort compared with other coastal areas, such as in Italy and Spain.^{6,9} We hypothesize that the reason for this low incidence may be dietary and weaning habits, with other foods preferred as weaning foods, rather than fish, which is likely introduced into the diet much later in the Southwestern United States. Another possible explanation

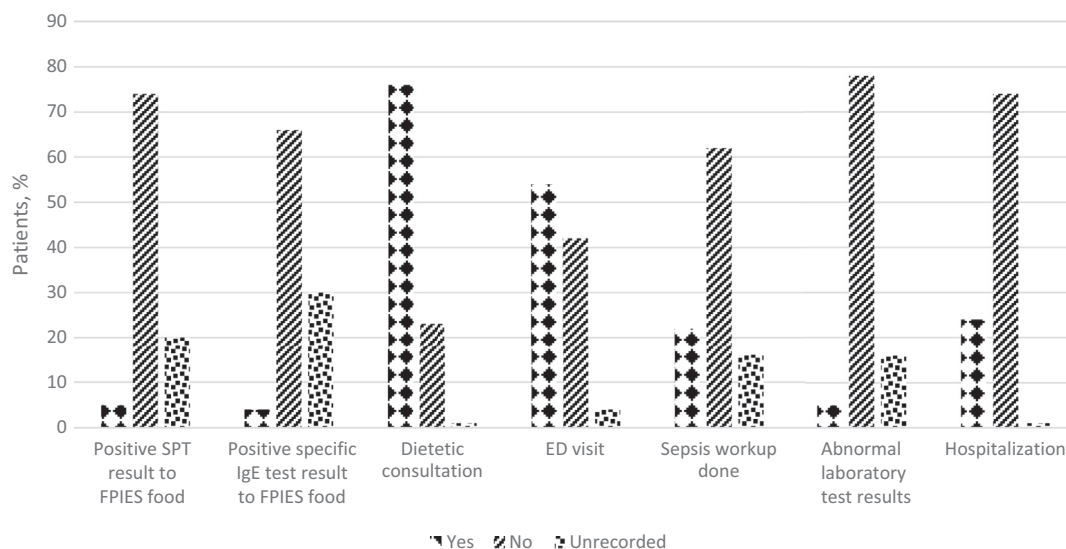


Figure 1. Management of food protein–induced enterocolitis syndrome (FPIES), including skin prick tests (SPTs), specific IgE tests, dietetic input/consultation, emergency department (ED) visit, sepsis workup, abnormal laboratory results, and hospitalization as a result of the episode.

could be the differences in how trigger foods are identified among studies: typical history of an FPIES reaction³ vs oral food challenges.^{5,6}

One-third of our cohort had a single food trigger; 18% reacted to 2 different foods, but more than 50% had 3 or more recorded triggers, and solid food FPIES was noted at a younger age in our study. This is an unusual finding because most studies report most infants having 1 or 2 food triggers; for example, a multicenter study combining data from the United States and Europe during a 10-year period report only 9% of infants with 3 or more triggers.⁵ Multiple food triggers were identified in only 12% in a large Australian study,³ whereas a single-center study from Philadelphia identifies 30% of patients reacting to 3 or more foods.⁷ We hypothesize that our high rate of solid food and multiple-foods FPIES is a reflection of our patient population as a large tertiary pediatric hospital, which may invite referrals of a more complex or unusual nature. We found no significant difference in age at onset, family history of atopy ($P = .47$), presence of eczema ($P = .35$), any IgE-mediated food allergy ($P = .35$), or mode of feeding ($P = .26$) when comparing infants with 1 or 2 triggers to those with multiple food triggers (defined as ≥ 3 food triggers). The only observed difference between the groups were the trigger foods; rice and milk in the first group vs fruits and vegetables in the second (multiple-food FPIES) group.

In terms of investigations, most of our patients had negative skin test results (76%) and undetectable serum specific IgE (64%) for their food triggers. We identified only 5% of cases with concomitant positive test results to their FPIES trigger(s). Studies in the United States and Australia have reported that approximately 2% to 20% of FPIES patients may have coexisting IgE sensitization to the food(s) that trigger their FPIES, a condition also known as atypical FPIES.^{2,4} Patients with atypical FPIES were observed to have a more protracted course of their disease compared with those without IgE sensitization.^{2,5,10,11} Although testing for IgE sensitization is not routinely recommended in patients with FPIES, a supporting clinical history of atopy and coexisting IgE-mediated food allergy may warrant the need for testing. In our cohort, 46% of patients with FPIES had a diagnosis of atopic dermatitis, a finding in accordance with US and Australian studies, which observed atopic dermatitis in up to 57% of cases.^{3,5,7,12} Family history of atopy is also common in patients with FPIES,^{3,10} and we noted that 65% of our patients had a documented family history of atopy.

We observed a 6-month median delay in the diagnosis of FPIES (from first episode to confirmed diagnosis), suggesting that this condition is still underrecognized and may remain undiagnosed for many months. It has been reported that patients with FPIES may have multiple episodes before the diagnosis is made. Mehr et al¹⁰ highlight that 20% of their cohort had up to 4 episodes before diagnosis. In our cohort, the rate was even higher, with 32% of infants experiencing up to 4 episodes before diagnostic confirmation. The delay in disease recognition could be largely attributed to the combination of nonspecific symptoms, lack of confirmatory diagnostic testing, and lack of familiarity of the disease, making recognition difficult. A 2014 online survey described poor understanding of this condition among allergists,¹³ but recent international guidelines have provided some necessary insight into disease diagnosis and management.² Parents report facing significant challenges before and after disease diagnosis, including poor quality of life, emotional upheaval, and relief after long periods of doubt and confusion, when the diagnosis is confirmed.¹⁴

More than half of our patients visited the emergency department after an acute FPIES episode, with 22% receiving a sepsis workup. Hospitalization rates for our cohort were low (24%) compared with other studies that reported rates of 64%.¹⁰ Less than a quarter of infants needed to be admitted, and most were hospitalized because of dehydration rather than sepsis concerns. Dietetic evaluation was provided in most cases in our cohort. Malnutrition related to the FPIES diagnosis (restricted food choices) was identified in 8%, whereas 5% were found at risk for malnutrition as a consequence of limited knowledge on how to introduce safe foods. It is therefore important to highlight the crucial role of appropriate nutritional input during infancy and the first few years of life as part of the long-term management of this condition. This management consists of avoidance of the culprit food(s) and includes advice on the consumption of suitable safe foods that will ensure sufficient nutritional intake, growth, and development.¹⁵ The role of the dietician is important in providing education to the families and ensuring that a variety of tastes and textures are introduced in a timely fashion in weaning infants to promote normal eating behavior.¹⁵

The strength of our work lies in the large number of cases, which provide an updated assessment of the presentation and management of FPIES in a single institution. Novel findings include the

frequency of diagnosis of fruit-triggered FPIES and multiple-foods FPIES, the low cross-reactivity between rice and oat, and the identification of malnutrition risk as a result of limited food choices related to FPIES. The significant delay in the diagnosis is also important to note because this condition has been generally described as presenting a diagnostic challenge. Limitations of our work include the retrospective design, data from a single institution, and some incomplete documentation, resulting in missing data, because of variations in recording by different health care professionals.

In summary, we identified 74 cases of FPIES during a 3-year period, with rice being the most frequent trigger. We report multiple infants with fruit-triggered and multiple-food FPIES. No significant differences were identified when comparing infants with 1 or 2 triggers with those with multiple food in terms of age at onset, family history of atopy, presence of eczema, presence of an IgE-mediated food allergy, or mode of feeding. Time from disease onset to diagnosis was delayed by 6 months in our cohort, likely reflecting continuing difficulties in disease recognition. Because FPIES is a clinical diagnosis without confirmatory testing in the acute care setting, practitioners should have a better understanding of its presentation and maintain a high level of suspicion for this condition.

References

1. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update - 2014. *J Allergy Clin Immunol*. 2014;134(5):1016–1025.e43.
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 & Immunology. *J Allergy Clin Immunol*. 2017;139(4):1111–1126.e4.
3. Mehr S, Frith K, Barnes EH, Campbell DE. Food protein-induced enterocolitis syndrome in Australia: a population-based study, 2012–2014. *J Allergy Clin Immunol*. 2017;140(5):1323–1330.
4. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *J Allergy Clin Immunol*. 2011;127(3):647–653.
5. 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.
6. Sopo SM, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. *Clin Exp Allergy*. 2012;42(8):1257–1265.
7. 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.
8. Cherian S, Neupert K, Varshney P. Avocado as an emerging trigger for food protein-induced enterocolitis syndrome. *Ann Allergy Asthma Immunol*. 2018;121(3):369–371.
9. Vila L, García V, Rial MJ, Novoa E, Cacharron T. Fish is a major trigger of solid food protein-induced enterocolitis syndrome in Spanish children. *J Allergy Clin Immunol Pract*. 2015;3(4):621–623.
10. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. *Pediatrics*. 2009;123:e459–e464.
11. Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. *Arch Dis Child*. 2009;94(6):425–428.
12. Fogg MI, Brown-Whitehorn T, Pawlowski N, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. *Pediatr Allergy Immunol*. 2016;17(5):351–355.
13. Greenhawt M, Bird JA, Nowak-Węgrzyn AH. Trends in provider management of patients with food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol Pract*. 2017;5(5):1319–1324.e12.
14. Schultz F, Westcott-Chavez A. Food protein-induced enterocolitis syndrome from the parent perspective. *Curr Opin Allergy Clin Immunol*. 2014;14(3):263–267.
15. Venter C, Groetch M. Nutritional management of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol*. 2014;14(3):255–262.