Case study

Food protein-induced enterocolitis syndrome: Case presentations and management lessons

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Enterocolitis induced in infants by cow's milk and/or soy protein has been recognized for decades. Symptoms typically begin in the first month of life in association with failure to thrive and may progress to acidemia and shock. Symptoms resolve after the causal protein is removed from the diet but recur with a characteristic symptom pattern on re-exposure. Approximately 2 hours after reintroduction of the protein, vomiting ensues, followed by an elevation of the peripheral blood polymorphonuclear leukocyte count, diarrhea, and possibly lethargy and hypotension. The disorder is generally not associated with detectable food-specific IgE antibody. There are increasing reports of additional causal foods, prolonged clinical courses, and onset outside of early infancy, leading to description of a food protein-induced enterocolitis syndrome. The disorder poses numerous diagnostic and therapeutic challenges. The purpose of this report is to delineate the characteristic clinical features and review the possible pathophysiologic basis to frame a rational strategy toward management. (J Allergy Clin Immunol 2005;115:149-56.)

Key words: *Food allergy, food protein-induced enterocolitis syndrome*

Abbreviations used
CM: Cow's milk
FPIES: Food protein-induced enterocolitis syndrome

CASE PRESENTATION

A female patient presented at the age of 14 months for evaluation of possible allergy to cow's milk (CM) and soy proteins. The patient was a full-term female infant initially breast-fed. At 4 weeks of age, a CM-based formula was used to supplement breast-feeding, and over a 2-week period, the patient developed frequent episodes of vomiting, poor weight gain, and small specks of blood in her stools. Soy-based formula was substituted but was discontinued in 2 days because of continued vomiting. The patient was then exclusively breast-fed until 1 feeding with a CM-based formula at 12 weeks of age. Approximately 90 minutes after the feeding, she developed repetitive vomiting and became lethargic. Emergency department evaluation included blood, urine, stool, and cerebrospinal fluid cultures; toxicology; and metabolic screening. She received intravenous fluid resuscitation and antibiotics and was observed in the hospital for 3 days. Blood-tinged diarrhea was noted only the first hospital day. She tolerated an extensively hydrolyzed casein formula and was discharged after 3 days when cultures were negative. She avoided CM and soy and tolerated several solid foods introduced from 5 to 7 months of age without symptoms until a jarred infant food containing cheese was given. Similar to the previous episode, 90 minutes after ingestion, she developed repetitive vomiting and lethargy and required intravenous fluid resuscitation. CM and soy proteins were excluded from the diet to the time of allergy consultation.

CASE DISCUSSION

It is clear that the physicians caring for this infant with vomiting and lethargy were initially considering possible infection. Even if the reader has neglected to note the title of this article, suspicion that this infant actually had a food-allergic disorder should be high. Indeed, the child became ill on 3 occasions when CM protein was ingested (and possibly when soy was substituted) and was well when not ingesting these proteins. This infant had 2 somewhat distinct patterns of reaction: she initially had chronic vomiting, diarrhea and poor growth when ingesting CM protein; later, after resolution of the chronic symptoms, she had 2 episodes with severe symptoms and a more discrete onset. This single food hypersensitivity disorder with 2 clinical faces has been described for decades as infantile milk/soy-induced enterocolitis and has been variably termed a milk allergy or intolerance.[1-4] More recently, the clinical entity has been expanded to include a broadening range of triggers, advanced age of presentation, and the possibility of persistence beyond infancy.[5-8] The clinical presentations and severity of the disorder present the allergist with a host of challenges for diagnosis

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Disclosure of potential conflict of interest: None disclosed.
Received for publication September 8, 2004; revised September 23, 2004; accepted for publication September 28, 2004.
Available online November 19, 2004.

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0091-6749/$30.00

doi:10.1016/j.jaci.2004.09.033

TABLE I. Clinical features of FPIES (CM, soy-induced)

General features	Symptoms/laboratory findings during continued ingestion of the causal food	Symptoms/laboratory findings following ingestion after a period of avoidance
Onset: early infancy	Vomiting	Vomiting onset: ~2 h after ingestion
Rate of allergy to both milk and soy: 50%	Diarrhea (blood, reducing substances positive)	Diarrhea onset ~5 h after ingestion
Tests: negative for IgE to causal proteins	Lethargy/septic appearance	Lethargy
Course: usually resolves by age 2-3 y	Dehydration	Possible progression to (~15%) acidemia, methemoglobinemia, hypotension
Sex: 60% male	Hypotension	Elevated PMN count
Family history atopy: 75%	Methemoglobinemia	
Family history food allergy: 20%		
Atopic dermatitis: 25%	Hypoalbuminemia	
Asthma/rhinitis: 20%		
Tolerate: breast milk, extensively hydrolyzed casein formula	Failure to thrive	

and management. In this case-based review, the clinical features and meager understanding of the pathophysiology of this disorder are discussed to provide the allergist with a framework for rational diagnosis and management.

Infantile milk/soy-induced enterocolitis: historical perspectives

In 1940, Rubin[9] reported an infant with severe bloody diarrhea responsive to CM elimination. In 1967, Gryboski[10] described 21 children diagnosed with various gastrointestinal symptoms proven by oral challenge to be associated with ingestion of CM. Among them were 11 with growth failure and 7 who had symptoms of shock after reintroduction of CM. A decade later, Powell[2] described 2 premature infants with symptoms of recurrent vomiting, bloody diarrhea, and abdominal distension suspected of having necrotizing enterocolitis. However, no bacterial pathogens or other causes of necrotizing enterocolitis could be identified, and their symptoms were diet-responsive.

The major features of this disorder where characterized by Powell[1] in a subsequent case series. Nine infants were described with severe, protracted diarrhea and vomiting that developed 4 to 27 days after birth (mean, 11 days) while on a CM formula. Switching to a soy formula resulted in transient improvement, but symptoms generally recurred in 7 days. Seven infants were below birth weight, 8 presented with dehydration, and 8 appeared acutely ill and underwent negative sepsis evaluations. All infants were noted to have low serum albumin and an elevated PMN count, and stools were positive for heme and reducing substances. The hospitalized infants improved while on intravenous fluids but had recurrence of dramatic symptoms with reintroduction of soy or CM formula, including shock in several.

Powell[1] undertook follow-up oral challenges in these infants at a mean age of 5.5 months. Fourteen of the 18 challenges were positive: 10 resulted in vomiting (onset 1-2.5 hours after ingestion; mean, 2.1 hours), and all had diarrhea (onset, 2-10 hours; mean, 5 hours), with blood, leukocytes, eosinophils and increased carbohydrate in the stool. There was a rise in PMN count in all positive challenges, peaking at 6 hours after ingestion with a mean rise of 9900 cells/mm^3 (range, 5500-16,800 cells/mm^3).

Additional clinical features of food protein-induced enterocolitis syndrome

The clinical features and natural course of the disorder have been elucidated through many reports, usually of single cases or small case series, of various types of CM/soy reactions.[1,4,11,12] In addition, similar reaction patterns are reported for other foods, such as rice or poultry.[13,14] Case series have shown that infants with milk/soy enterocolitis have negative skin prick tests and/or serum food-specific IgE tests.[6,15] These reports also showed approximately half of the infants reacted to both milk and soy, and sensitivity to milk was lost in 60% and to soy in 25% of the patients 2 years from the time of presentation. The possibility that reactions are severe has been underscored.[1,6] Murray and Christie[16] reported 6 infants who presented with acidemia (mean pH, 7.03) and methemoglobinemia (including clinical cyanosis) from among 17 presenting with food protein-induced enterocolitis syndrome (FPIES). Methemoglobinemia was hypothesized to result from increased heme oxidation caused by an elevation of nitrites in the intestine because of reduced catalase activity during inflammation. Considering the expanding range of causal foods and the stereotypical clinical features, the term FPIES has been increasingly used to describe the disorder.[6,17] A summary of the clinical features are listed in Table I.

Atypical FPIES

Powell[3] noted that her suggested criteria to describe infantile milk/soy enterocolitis (which included criteria of oral food challenge) would potentially exclude some patients who might have a similar clinical presentation but with differences in particular specific features or severity. Although IgE antibody to the causal food is typically not detected, there are reports of clinical FPIES in which children had detectable IgE to the causal protein either at presentation or during follow-up.[6] These children

TABLE II. Clinical differentiation of allergic gastrointestinal disorders of infancy from FPIES

Disorder	Key features	Distinction from FPIES
Dietary protein proctitis	Blood-streaked stools	No vomiting, usually breast-fed, no constitutional symptoms
Dietary protein enteropathy	Diarrhea, vomiting, edema, failure to thrive	No acute reaction on re-exposure, vomiting less prominent, diarrhea nonbloody
Milk-induced reflux	Vomiting	No lower intestinal symptoms
Eosinophilic gastroenteropathies	Depends on sites of inflammation; may include vomiting, obstruction, gastric, or colonic bleeding	More common to involve multiple foods and positive tests for IgE; no acute (~2 h) onset of gastrointestinal and systemic symptoms

had a prolonged course of allergy and, in some cases, progression to typical reactions, reflecting IgE-mediated sensitivity (eg, urticaria). Case series of patients with FPIES also indicate a high rate of atopic disease.[7,8] Therefore, it is prudent for purposes of following the course of FPIES to include screening for IgE to the suspected foods. Until more specific differentiation is possible, FPIES in association with IgE to the triggering food may be termed atypical. Although a role for IgE in the pathophysiology of the disorder has not been established, it has not been completely excluded.[18]

HISTOLOGY

Infantile FPIES is a diagnosis that is generally made clinically; therefore, there are no series in which biopsies are performed solely in patients with this diagnosis. However, several case series include patients who fulfill criteria for a diagnosis of FPIES and describe varied and nonspecific histologic features.[4,10,11,19-21] Colonic biopsies in symptomatic patients reveal crypt abscesses and a diffuse inflammatory cell infiltrate with prominent plasma cells; small bowel biopsies reveal edema, acute inflammation, and mild villus injury. In some cases, focal erosive gastritis and esophagitis is found with prominent eosinophilia and villus atrophy.

PATHOPHYSIOLOGY

Van Sickle et al[22] noted that *in vitro* stimulation of PBMCs with the causal antigen in children with FPIES resulted in greater cell proliferation than in children with negative challenges, an observation that in retrospect indicated the response as immune-mediated (allergy) rather than intolerance. Hoffman et al[23] also showed a proliferative response in affected children, but the stimulation index was not significantly different compared with controls, and the test result could not reliably distinguish affected patients. An increase in serum antigen specific IgA was noted in the patients of McDonald et al.[24] However, the pathophysiologic ramifications and clinical implications of these findings remain unclear.

Recent studies have focused on the role of T cells and the importance of TNF-α. Heyman et al[25] demonstrated that TNF-α secreted by circulating CM protein-specific T cells increased intestinal permeability, thus possibly contributing to the influx of antigen into the submucosa with further activation of antigen-specific lymphocytes. Fecal TNF-α was also found in increased concentrations after positive milk challenge in patients with CM-induced gastrointestinal reactions.[26,27] Benlounes et al[28] showed that significantly lower doses of intact CM protein stimulated TNF-α secretion from PBMCs of patients with active intestinal CM allergy compared either with patients whose sensitivity resolved or with those with skin, rather than intestinal, manifestations of CM hypersensitivity. In addition, *in vitro* kinetic studies differed in these groups, with those having active disease showing 2 peaks in TNF-α elaboration. The second peak occurred later during culture.[29] Chung et al[17] examined the presence of TNF-α in duodenal biopsy specimens by using immunostains in infants with FPIES. Semiquantitative analyses revealed higher staining for TNF-α in affected infants with villus atrophy compared with those without atrophy and compared with normal controls. Taken together, these studies support the notion that TNF-α plays a role in the acute and chronic symptoms of FPIES. It is also known that the regulatory cytokine TGF-β1 acts to protect the epithelial barrier of the gut from the penetration of foreign antigens.[30,31] Chung et al[17] demonstrated that the type 1, but not type 2, receptor for TGF-β1 was decreased in duodenal biopsy specimens in patients with FPIES compared with controls. Although much more work is needed to elucidate the immunologic basis of this disorder, a deficit in TGF-β1 response and overzealous TNF-α response may be important factors.

DIFFERENTIAL DIAGNOSIS

A full discussion of the many disorders that could result in infants variably experiencing vomiting, diarrhea, and poor growth, possibly progressing to dehydration, lethargy, and shock, are beyond the scope of this discussion. In regard to nonallergic causes, infection is the one most likely, and most importantly, considered. Metabolic disorders and necrotizing enterocolitis, particularly for newborn, preterm infants, should also be considered. Several gastrointestinal disorders may present in infancy with diarrhea that is nonbloody and possibly with growth failure, but these disorders are not associated

TABLE III. Oral food challenges for FPIES according to Powell[3] criteria

Preparatory steps	Observe/test for criteria*
Emergency therapies in place, consider intravenous access	Vomit, diarrhea
Verify normal weight gain and lack of symptoms while avoiding potential causal protein	Fecal blood (frank or occult)
Baseline (verify no blood) and follow-up stool samples	Fecal leukocytes
Baseline peripheral blood PMN count	Fecal eosinophils
Repeat peripheral blood PMN count 6 h after ingestion	Rise in PMN count (>3500 cells/mm^3)

*Challenge is considered positive if 3 or more criteria are met, equivocal if 2, and negative if 0-1; see text for additional issues in interpretation.

with inflammation, and stools are typically heme-negative. For infants presenting with bloody stools (occult or gross), considerations include infection, Hirschsprung disease, and intussusception. Many of the aforementioned disorders would have been considered before an allergy consultation. In regard to food hypersensitivity, several gastrointestinal disorders of infancy include symptoms that overlap those of CM/soy-induced enterocolitis. These disorders are contrasted with protein-induced enterocolitis in Table II.[32,33]

DIAGNOSIS

Skin prick tests are typically negative, but if positive, the risk for a reaction, including typical anaphylaxis, is greater and may require an alteration in diagnostic approach.[2,6] Assessment of *in vitro* lymphocyte responses to food stimulation for diagnosis has not reached clinical utility.[22,29] Hypothetically, the atopy patch test, used with variable clinical utility for atopic dermatitis[34,35] or eosinophilic gastroenteritis,[36] may have a role in diagnosis of gastrointestinal allergy without evidence of IgE[37] but has not been sufficiently evaluated in this disorder.

Powell[3] suggested specific criteria for the diagnosis of milk/soy enterocolitis based on oral challenge. However, it is also clear that a confirmatory challenge would not be needed when the typical symptoms occur after ingestion of the food (particularly more than once) and there are no alternative explanations for the symptoms. Therefore, the need for an oral food challenge to confirm the diagnosis must be determined on clinical grounds. Otherwise, this modality is more typically used to monitor the development of tolerance.

Oral challenge

Oral challenges should be undertaken with personnel and facilities prepared to manage allergic reactions, hypotension, and shock, and the general approach is reviewed elsewhere.[38,39] For FPIES in particular, strong consideration must be given for insertion of an intravenous line before challenge, because reactions may require treatment with intravenous fluids and intravenous access may be difficult if hypotension has occurred. The amount of protein given for challenge has been recommended at 0.6 g protein per kilogram of body weight, but this was generally calculated for young infants.[1,3] After noting reactions at lower doses, a lower total amount of protein (0.15-0.3 g protein per kilogram of body weight or lower) was recently recommended, particularly if the infant or child has a history of a severe reaction after a small ingestion.[6,7] We generally do not exceed 3 g protein or 10 g total food weight for a challenge (usually less than 100 mL). To calculate doses, one would need to determine the protein concentration of the product used. For example, for a 15-kg child who is to receive 0.15 g/kg protein (eg, 2.3 g), 66 mL whole milk (0.034 g protein/mL) would be given. We generally administer the dose gradually in 3 feedings over a period of 45 minutes. If there are no symptoms in 4 hours, a second feeding is given, generally with a serving size amount, and the child is observed for several more hours. Symptoms are monitored and interpreted as shown in Table III, which presents Powell's[3] criteria for a positive challenge (which would require stain for fecal eosinophils). These criteria have not been systematically validated, and an argument could be made for including additional clinical symptoms (hypotension) or valuing clinical (vomiting) over laboratory (fecal eosinophils) ones. Equivocal challenges, eg, abdominal pain with increased PMN counts, may need to be repeated using higher doses. Reactions are treated with fluid resuscitation (eg, a bolus of normal saline) and possibly intravenous steroids to quell the presumed T-cell–mediated response. In the author's experience, epinephrine has not been needed in these controlled challenges. Patients are monitored until they are hemodynamically stable, able to take fluids on their own. Additional therapies may be needed depending on symptoms (eg, vasopressors).

CASE REPORT: CLINICAL COURSE

The patient presented was evaluated at 14 months of age. Skin prick tests were negative to CM and soy. The patient was tolerating a variety of solid foods. We chose to perform an oral food challenge to soy because only approximately 50% who are reactive to milk also react to soy.[6,7] Further, the clinical history was not very clear for a soy reaction; she tried soy for only 2 days and may have been experiencing residual symptoms from the milk reaction. It was only 7 months since her latest reaction to CM protein, so tolerance of this food was less likely.[1,6] She was admitted to the hospital, an intravenous line was placed, and an oral food challenge to soy was performed with no reaction, and this food was added to her diet. At

TABLE IV. Clinical features of FPIES induced by solid foods[7,8]

Feature	Solid food FPIES (n = 20)	CM/soy FPIES (n = 30)
Foods reported	CM: 40% Soy: 50% Both: 30% Solids only: 35% Solids: US (n = 16): rice (71%), oat (64%), barley/pea/string bean (14% each), squash, sweet potato, poultry (7% each), >1 grain 50% Israel (n = 7):poultry (71%), lentil, pea (29% each)	CM: 80% Soy: 53% Both: 33%
Resolved by age 3 y (calculated per food, n = 3-24 patients per food)	CM: 75%	CM: 63%
	Soy: 38%	Soy: 25%
	Oat: 66%	
	Rice: 40%	
	Barley: 100%	
	Poultry: 100%	
	Others: 67%	
Age introduction of solids (median)	5.5 mo	4.3 mo
Diet at time of reaction	Breast-fed: 9 Soy: 3 Casein hydrolysate: 7 Amino acid–based: 1	NA
Age introduction of CM (median), US data	11 mo	0.8 mo*
Personal history of atopic dermatitis	57%	23%*

*$P < .05$.

age 30 months, an oral food challenge to milk was performed. One hour and 20 minutes later, she began to vomit repetitively and had a decrease in blood pressure. A complete blood count performed before challenge (6300/mm^3; 28% PMNs) compared with one performed 5 hours later (10,300/mm^3; 79% PMNs) indicated an increase of 6370 cells/mm^3 in absolute neutrophil count. She was treated with intravenous hydration and steroids and discharged home to avoid milk. Diarrhea was noted the following day (tested heme-positive).

ANOTHER CASE PRESENTATION

A male patient was initially breast-fed with no maternal dietary restriction. He had mild reflux symptoms, and at age 5 months, an H-2 blocker was prescribed, and rice was added to breast milk on occasion to thicken the feedings. At 6 months of age, he developed repetitive vomiting and lethargy and was admitted to the hospital for a sepsis evaluation. During the hospitalization, he had several mucous, bloody stools. With intravenous hydration, he improved clinically, and all cultures were negative. He was discharged with a diagnosis of viral gastroenteritis, tolerating breast milk. One week later, he developed a similar constellation of symptoms and was treated similarly. At that time, his mother indicated that both episodes developed approximately 2 hours after oat cereal was given (mixed with expressed breast milk). The pediatrician performed a serum test for oat-specific IgE that was negative. Another diagnosis of viral gastroenteritis was entertained, and the mother was instructed to add oat to the diet. She insisted on doing this in the pediatric office. Ninety minutes after the feeding, recurrent vomiting and lethargy developed that was treated with intravenous hydration. Allergy consultation was then sought.

FEATURES OF FPIES CAUSED BY SOLID FOODS

There are increasing reports of FPIES induced by foods other than CM and soy.[6-8,13,14] Nowak-Wegrzyn et al[7] reported 14 patients identified over a 5-year period from 2 US academic centers, and Levy and Danon[8] reported 6 patients over a 7-year period from an allergy clinic in Israel. Clinical features of these 21 patients are partly summarized in Table IV. Of note, 65% of these patients already had FPIES from milk or soy. Delayed diagnosis is particularly common for these patients, probably attributable to the uncommon nature of the disorder, lack of a specific diagnostic laboratory test, symptoms that overlap episodes of sepsis, and the concept that foods such as oat, rice, and chicken are not considered to be significantly allergenic.

An interesting hypothesis emerges from review of the causal foods and time course of reactions noted for the infants with FPIES from solid foods compared with those with soy/milk reactions.[7] Virtually all of the patients who were not being breast-fed at the time of the development of the solid food FPIES already required a casein hydrolysate formula because of the intolerance of CM

TABLE V. Examples of management decision making for FPIES*

Situation	Approach	Rationale
Infant diagnosed with milk FPIES: first-year management	Liquid: feed with extensively hydrolyzed casein formula or breast milk	50% risk to react to soy
	Solid: consider delay and avoid grains as first foods	As much as 32% risk for reaction to solids. Most fruits and vegetables not implicated. More concern if atopic dermatitis
Infant diagnosed with solid food FPIES: first-year management	Liquid: feed with extensively hydrolyzed casein formula or breast milk	Solid food reaction typically occurs in child already avoiding milk/soy; 65% react to milk/soy
	Solid: no grains, legumes or poultry	50% risk for another grain 80% reactive to >1 food protein
1-year-old with history of FPIES	Liquid: consider challenge first to high-risk foods not otherwise tried but excluded per above to clear food category; wait to approximately 18 months or more post reaction to perform challenge to reactive food	After age 1 y, new-onset FPIES to a food not previously ingested is not commonly reported (but not well studied, and is possible); presume longer delay of introduction, more likely tolerated; see Table IV for resolution data
		Presume negative challenge to 1 food in a category (eg, soy for other beans; rice or oat for grains; chicken for other poultry) increases likelihood that related items would be tolerated

*These strategies represent only 1 of many possible courses of action and would require alterations in approach depending on numerous factors, including severity of previous reactions, clinical judgment, nutritional needs, and patient preferences. Foods that are clinically tolerated should not be removed from the diet. See text for further discussion

or soy-based formula in the first month of life. These infants manifested their predisposition for food hypersensitivity in the first months of life and evidently remained at high risk for similar reactions to whole food proteins introduced during an apparent window of immunologic susceptibility (facilitated by a hyperpermeable gut barrier of infancy). The potential toward FPIES was unrealized early on in the breast-fed infants who were not exposed to infant formula before the introduction of solid foods. Another related hypothesis, demonstrated in an animal model of food hypersensitivity,[40] is that the use of an antacid may facilitate sensitization because the intact proteins likely to induce reactions[28] are able to evade digestion further.

Applying the principle of a window of immunologic vulnerability to the patient presented here, we suggested continued breast-feeding or, if needed, weaning to an extensively hydrolyzed casein formula and avoidance of all major food allergens, eg, milk, egg, wheat, and soy, but also those causing FPIES such as other grains (except rice that was already tolerated), poultry, and, of course, oat.

What should be done for this child at age 1 year? The length of physiologic susceptibility for allergy to food proteins has not been established. In our patient series,[7] none developed FPIES to CM and/or soy after age 1 year, and the oldest age for the onset of solid food-induced FPIES was 7 months. However, our data are confounded by the fact that after the onset of solid food FPIES, subsequent introduction of food proteins was delayed (eg, wheat was not introduced until after age 1 year). We also reported a child with IgE antibody mediated food allergies and atopic dermatitis with atypical poultry-induced FPIES that began at 2 years of age, but this child did not have FPIES during infancy.[6] The series of patients reported by Levy and Danon[8] generally had their first reaction at or before age 1 year. Still, the patient presented here had no clinical history to evaluate in regard to certain foods, and we would not know whether administration of milk or soy would stimulate a reaction. It was too early at age 1 year to perform an oat challenge (just 6 months since the reaction). All skin tests were negative at age 1 year, and there was no personal atopic disease. We chose to perform a CM challenge at 13 months with the assumption that if it were tolerated, then a soy reaction would also be unlikely. The child tolerated both foods. An oat oral food challenge resulted in a reaction at 18 months and again at 36 months. In the interim, wheat and chicken were introduced under observation and tolerated. Persistence of FPIES beyond the age of 4 years has been reported but is uncommon.[5]

GENERAL MANAGEMENT APPROACHES

As illustrated by the 2 cases presented here and the available literature as summarized in Table IV, an approach to diet must take into consideration the reaction history, age of the child, number of foods involved, results of tests for IgE antibody, and results of oral food challenges. Data are limited, and on the basis of a few case series and reports, it is not possible to suggest a specific course of action applicable to all situations. Presented here are the authors' opinions based on the available data, but this should not be construed to suggest that there is just 1 course of action. Certainly, no food already tolerated would be restricted. The clinician must determine a reasonable sequence, timing, and modality of administration from among options such as an oral food challenge with or without intravenous access in place or

routine addition to the diet at home. Some examples of decision making are shown in Table V. For infants, an extensively hydrolyzed casein formula is usually tolerated, but if not, an amino acid–based formula should be tolerated.[41,42] Although it is recognized that infants may react to maternally ingested proteins passed into breast milk,[43] this problem has generally not been noted in FPIES. Dietary avoidance must be reviewed in detail, including careful label reading and concern for cross contact of the allergen during food preparation. Excellent resources on this subject are available from the Food Allergy & Anaphylaxis Network (http://www.foodallergy.org; 800-929-4040).

Reactions to accidental exposures can be severe, so instructions on emergency management should be given. On the basis of the only partially understood pathophysiology of the immune response (T-cell–mediated) and observations of the clinical symptoms (lethargy, dehydration, shock), several suggestions can be made for emergency care that are based on response to treatments in studies reporting results of oral food challenges.[3,6,7] If an ingestion is known to have occurred, the patient should be instructed to present to medical attention for observation. Intravenous fluid resuscitation may be needed. For patients with a history of severe reaction and onset of any symptoms, consideration should be given for administration of corticosteroids to quell a presumed T-cell–mediated reaction, and this treatment could be considered for any patient with more than minimal symptoms. The reaction can include symptoms of shock that may presumably respond to epinephrine, but our experience has been that intravenous hydration and steroids are the only medications typically required. Theoretically, fluid loss from the gastrointestinal symptoms is partly responsible for the hypotension, so epinephrine without intravenous hydration may be less efficacious, as would be expected in any form of shock. Prescription of self-injectable epinephrine may be considered, but the time course of the reaction in the face of a diagnosis already made should render the need for this drug virtually nil, because patients have approximately 2 hours to seek medical attention if an accidental ingestion is known, and symptom progression to shock is not likely to occur as quickly as it can for IgE-mediated anaphylaxis. The role for and efficacy of antihistamines are unknown. Understanding the rare and underrecognized nature of the allergy and the overlap of symptoms with other disorders, I generally provide patients with a letter explaining the disorder for use in the event they present for medical evaluation of a reaction, and an example skeleton letter is available in the Journal's Online Repository (Fig E1 at www.mosby.com/jaci).

SUMMARY AND UNRESOLVED ISSUES

Pediatricians and other primary care providers are at the front line in the diagnosis of FPIES, and efforts to educate them are underway.[44] The characteristic clinical pattern of reactions can aid the allergist in verifying a diagnosis, and partnership with a gastroenterologist can be helpful in ruling out other entities. Ultimately, oral food challenges are needed to confirm the diagnosis in some cases, and certainly to evaluate for tolerance. Clinical data have been summarized here to assist the clinician in making decisions regarding management, but much more research is needed to determine the best course of dietary management, develop laboratory tests to avoid the need for oral food challenges, address prevention, and determine specific treatment modalities. These goals will most likely be reached through more intensive laboratory investigation of the immunopathologic basis of the disorder. More work also needs to be done to determine whether disorders with similar symptoms (Table II) are pathophysiologically distinct from FPIES or part of a spectrum with a similar etiology whose clinical expression varies with environmental influences.

REFERENCES

1. Powell GK. Milk- and soy-induced enterocolitis of infancy. J Pediatr 1978;93:553-60.
2. Powell GK. Enterocolitis in low-birth-weight infants associated with milk and soy protein intolerance. J Pediatr 1976;88:840-4.
3. Powell G. Food protein-induced enterocolitis of infancy: differential diagnosis and management. Compr Ther 1986;12:28-37.
4. Halpin TC, Byrne WJ, Ament ME. Colitis, persistent diarrhea, and soy protein intolerance. J Pediatr 1977;91:404-7.
5. Busse P, Sampson HA, Sicherer SH. Non-resolution of infantile food protein-induced enterocolitis syndrome (FPIES) [abstract]. J Allergy Clin Immunol 2000;105:S129.
6. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. J Pediatr 1998;133:214-9.
7. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. Pediatrics 2003;111:829-35.
8. Levy Y, Danon YL. Food protein-induced enterocolitis syndrome—not only due to cow's milk and soy. Pediatr Allergy Immunol 2003;14:325-9.
9. Rubin M. Allergic intestinal bleeding in the newborn. Am J Med Sci 1940;200:385-7.
10. Gryboski J. Gastrointestinal milk allergy in infancy. Pediatrics 1967;40:354-62.
11. Fontaine J, Navarro J. Small intestinal biopsy in cow's milk protein allergy in infancy. Arch Dis Child 1975;50:357-62.
12. Hill DJ, Firer MA, Shelton MJ, Hosking CS. Manifestations of milk allergy in infancy: clinical and immunological findings. J Pediatr 1986;109:270-6.
13. Vandenplas Y, Edelman R, Sacre L. Chicken-induced anaphylactoid reaction and colitis. J Pediatr Gastroen Nutri 1994;19:240-1.
14. Vitoria JC, Camarero C, Sojo A, Ruiz A, Rodriguez-Soriano T. Enteropathy related to fish, rice and chicken. Arch Dis Child 1982;57:44-8.
15. Burks AW, Casteel HB, Fiedorek SC, Williams LW, Pumphrey CL. Prospective oral food challenge study of two soybean protein isolates in patients with possible milk or soy protein enterocolitis. Pediatr Allergy Immunol 1994;5:40-5.
16. Murray K, Christie D. Dietary protein intolerance in infants with transient methemoglobinemia and diarrhea. J Pediatr 1993;122:90-2.
17. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor beta1, transforming growth factor type I and II receptors, and TNF-alpha in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2002;109:150-4.
18. Lin XP, Magnusson J, Ahlstedt S, Dahlman-Hoglund A, Hanson LL, Magnusson O, et al. Local allergic reaction in food-hypersensitive adults

despite a lack of systemic food-specific IgE. J Allergy Clin Immunol 2002;109:879-87.
19. Goldman H, Provjanksy R. Allergic proctitis and gastroenteritis in children. Am J Surg Pathol 1986;10:75-86.
20. Jenkins HR, Pincott JR, Soothill JF, Milla PJ, Harries JT. Food allergy: the major cause of infantile colitis. Arch Dis Child 1984;59: 326-9.
21. Coello-Ranurez P, Larrosa-Haro A. Gastrointestinal occult hemorrhage and gastroduodenitis in cow's milk protein intolerance. J Pediatr Gastroenterol Nutri 1984;3:215-8.
22. Van Sickle GJ, Powell GK, McDonald PJ, Goldblum RM. Milk- and soy protein- induced enterocolitis: evidence for lymphocyte sensitization to specific food proteins. Gastroenterology 1985;88:1915-21.
23. Hoffman KM, Ho DG, Sampson HA. Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of allergy to cow's milk. J Allergy Clin Immunol 1997;99:360-6.
24. McDonald PJ, Goldblum RM, Van Sickle GJ, Powell GK. Food protein-induced enterocolitis: altered antibody response to ingested antigen. Pediatr Res 1984;18:751-5.
25. Heyman M, Darmon N, Dupont C, Dugas B, Hirribaren A, Blaton MA, et al. Mononuclear cells from infants allergic to cow's milk secrete tumor necrosis factor alpha, altering intestinal function. Gastroenterology 1994; 106:1514-23.
26. Kapel N, Matarazzo P, Haouchine D, Abiola N, Guerin S, Magne D, et al. Fecal tumor necrosis factor alpha, eosinophil cationic protein and IgE levels in infants with cow's milk allergy and gastrointestinal manifestations. Clin Chem Lab Med 1999;37:29-32.
27. Majamaa H, Aittoniemi J, Miettinen A. Increased concentration of fecal alpha1-antitrypsin is associated with cow's milk allergy in infants with atopic eczema. Clin Exp Allergy 2001;31:590-2.
28. Benlounes N, Dupont C, Candalh C, Blaton M-A, Darmon N, Desjeux J-F, et al. The threshold for immune cell reactivity to milk antigens decreases in cow's milk allergy with intestinal symptoms. J Allergy Clin Immunol 1996;98:781-9.
29. Benlounes N, Candalh C, Matarazzo P, Dupont C, Heyman M. The time-course of milk antigen-induced TNF-alpha secretion differs according to the clinical symptoms in children with cow's milk allergy. J Allergy Clin Immunol 1999;104:863-9.
30. Planchon S, Fiocchi C, Takafuji V, Roche JK. Transforming growth factor-beta1 preserves epithelial barrier function: identification of receptors, biochemical intermediates, and cytokine antagonists. J Cell Physiol 1999;181:55-66.
31. Planchon S, Martins C, Guerrant R, Roche J. Regulation of intestinal epithelial barrier function by TGF-beta 1. J Immunol 1994;153:5730-9.
32. Sampson HA, Anderson JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. J Pediatr Gastroenterol Nutr 2000; 30(suppl):S87-94.
33. Sampson HA. 9. Food allergy. J Allergy Clin Immunol 2003;111(suppl): S540-7.
34. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. J Allergy Clin Immunol 1996;97:9-15.
35. Perackis K, Celik-Bilgili S, Staden U, Mehl A, Niggemann B. Influence of age on the outcome of the atopy patch test with food in children with atopic dermatitis. J Allergy Clin Immunol 2003;112:625-7.
36. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. J Allergy Clin Immunol 2002;109:363-8.
37. De Boissieu D, Waguet JC, Dupont C. The atopy patch tests for detection of cow's milk allergy with digestive symptoms. J Pediatr 2003;142: 203-5.
38. Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol 1988;82:986-97.
39. Sicherer SH. Food allergy: when and how to perform oral food challenges. Pediatr Allergy Immunol 1999;10:226-34.
40. Untersmayr E, Scholl I, Swoboda I, Beil WJ, Forster-Waldl E, Walter F, et al. Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy model in BALB/c mice. J Allergy Clin Immunol 2003;112:616-23.
41. Sicherer SH. Food protein-induced enterocolitis syndrome: clinical perspectives. J Pediatr Gastroenterol Nutr 2000;30(suppl):S45-9.
42. Kelso JM, Sampson HA. Food protein-induced enterocolitis to casein hydrolysate formulas. J Allergy Clin Immunol 1993;92:909-10.
43. Jarvinen KM, Makinen-Kiljunen S, Suomalainen H. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. J Pediatr 1999;135:506-12.
44. Sicherer SH. Clinical aspects of gastrointestinal food allergy in childhood. Pediatrics 2003;111:1609-16.