

Food Protein-Induced Enterocolitis and Enteropathies

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KEY CONCEPTS

- Food protein-induced enterocolitis and enteropathies are non-IgE-mediated gastrointestinal food allergy disorders.
- Food protein-activated intestinal lymphocytes elaborate inflammatory cytokines that result in increased intestinal permeability, malabsorption, dysmotility, diarrhea, pain, and failure to thrive.
- Food protein-induced enterocolitis syndrome (FPIES) is typically caused by cow's milk and soy; cereal grains (rice, oat, barley), fish, poultry, and vegetables may also cause FPIES.
- Classic infantile food protein-induced enteropathy was caused by cow's milk, soy, and wheat; recent reports describe subtle enteropathy in older children and adults with delayed food allergy to cow's milk and cereal grains as well as in children with multiple IgE-mediated food allergy.
- The majority of FPIES and food protein-induced enteropathies resolve by age 3 years.

Introduction

Allergic reactions to foods affecting the gastrointestinal tract have been known since ancient times. Hippocrates observed that cow's milk caused gastrointestinal symptoms as well as urticaria, and that some infants fed cow's milk developed prolonged diarrhea, vomiting, and failure to thrive that resolved only after removal of cow's milk from their diet. At present, gastrointestinal immune reactions to cow's milk proteins that are mediated by T-lymphocytes with or without contribution of specific IgE antibody are estimated to account for up to 40% of cow's milk-protein hypersensitivity in infants and young children [1–7]. Food protein-induced enterocolitis syndrome (FPIES) and enteropathies represent non-IgE-mediated gastrointestinal food hypersensitivities. Their prevalence is not known but they are well established as distinct clinical entities. Their pathophysiology requires further characterization; current evidence indicates that T-lymphocyte-mediated responses play an important role, whereas IgE antibodies to the offending foods are of minimal or no significance in the pathophysiology of these disorders [8]. In the absence of definitive laboratory tests, diagnosis relies predominantly on clinical responses to elimination

diets with resolution of symptoms, oral food challenges (OFCs) with reappearance of symptoms following ingestion of the offending food; and endoscopy and biopsy findings as well as exclusion of causes such as infections, inflammatory bowel disease, ischemia, metabolic disorders, and others.

Table 16.1 summarizes the most important features of the clinical conditions induced by dietary proteins in children that are reviewed in this chapter, including food protein-induced enterocolitis, enteropathy, and iron-deficiency anemia caused by cow's milk. They were defined using the consensus criteria developed by a workshop jointly sponsored by European Society of Pediatric Gastroenterology, Hepatology and Nutrition and North American Society for Pediatric Gastroenterology and Nutrition in November 1998 [8].

Food protein-induced enterocolitis syndrome

FPIES manifests as profuse vomiting and diarrhea in young infants and is most commonly caused by cow's milk and soy proteins. Other foods such as grains, meats, and fish have been reported; onset of symptoms at older ages may occur with shellfish [8].

Historical perspective

Rubin, in 1940, reported intestinal bleeding due to cow's milk allergy in newborns [9]. Gryboski and Powell *et al.* described

Table 16.1 Comparison of FPIES, food protein-induced enteropathy, and iron deficiency anemia due to cow's milk

	FPIES	Enteropathy	Iron-deficiency anemia
<i>Age at onset</i>	1 day to 1 year	Dependent on age of exposure to antigen; Cow's milk and soy up to 2 years	2–20 months
<i>Food proteins implicated</i>			
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk
Less common	Rice, oat, barley, chicken, turkey, fish, pea	Wheat, egg	
<i>Multiple food hypersensitivities</i>	>50% both cow's milk and soy	Rare	No
<i>Feeding at the time of onset</i>	Formula	Formula	Cow's milk, non-humanized Cow's milk-based formula
<i>Atopic background</i>			
Family history of atopy	40–70%	Unknown	Unknown
Personal history of atopy	30%	22%	Unknown
<i>Symptoms</i>			
Emesis	Prominent	Intermittent	No
Diarrhea	Severe	Moderate	Minimal
Bloody stools	Severe	Rare	No
Edema	Acute, severe	Moderate	Mild
Shock	15%	No	No
Failure to thrive	Moderate	Moderate	Minimal
<i>Laboratory findings</i>			
Anemia	Moderate	Moderate	Moderate
Hypoalbuminemia	Acute	Moderate	Mild
Methemoglobinemia	May be present	No	No
Acidemia	May be present	No	No
<i>Allergy evaluation</i>			
Food prick skin test	Negative*	Negative	Negative
Serum food-allergen IgE	Negative*	Negative	Negative
Total IgE	Normal	Normal	Normal
Peripheral blood eosinophilia	No	No	No
<i>Biopsy findings</i>			
Villous injury	Patchy, variable	Variable, increased crypt length	Mild
Colitis	Prominent		No
Mucosal erosions	Occasional	No	No
Lymphoid nodular hyperplasia	No	No	No
Eosinophils	Prominent	No	No
		Few	
<i>Food challenge</i>	Vomiting in 1–4 hours; diarrhea in 5–8 hours	Vomiting and/or diarrhea in 40–72 hours	Usually not necessary
<i>Treatment</i>	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3–10 days; re-challenge in 1.5–2 years	Protein elimination, symptoms clear in 1–3 weeks, re-challenge and biopsy in 1–2 years	Whole cow's milk-protein elimination, feeding with humanized cow's milk-based formulas
<i>Natural history</i>	Cow's milk: 60% resolved by 2 years Soy: 25% resolved by 2 years	Most cases resolve in 2–3 years	Most cases resolve by 3 years
<i>Reintroduction of the food into the diet</i>	Inpatient food challenge	Home, gradually advancing	Home, gradually advancing

*If positive, may be a risk factor for persistent disease.

infants presenting in the first 6 weeks of life with recurrent vomiting, bloody diarrhea, and abdominal distension while being fed with cow's milk-based formula [10–13]. Many appeared dehydrated and severely ill. Sepsis evaluations were negative but improvement was achieved with intravenous fluids or hydrolyzed casein-based formula but not with soy-based formula. Reintroduction of the cow's milk-based formula had resulted in recurrence of severe emesis and elevation of the peripheral neutrophil count. Subsequently Powell characterized major features of the disorder, established criteria for the diagnosis of cow's milk-induced enterocolitis, and a standard challenge protocol [14]. Reports of a series of infants with food protein-induced enterocolitis by Sicherer *et al.* (16 patients) and Burks *et al.* (43 patients) further characterized clinical features and refined food challenge protocols [15,16]. Additional reports identified solid foods such as cereal grains, vegetables, meats, and fish as triggers for FPIES [17–25].

Clinical characteristics

Cow's milk/soy food protein-induced enterocolitis syndrome

FPIES is most commonly caused by cow's milk or soy proteins in formula-fed infants, with over half reacting to both foods; and onset of symptoms from first days to 12 months of life; later onset is associated with delayed introduction of milk or soy protein in breast-fed infants [12,13]. Interestingly, there are no reports of FPIES in infants exclusively breast-fed and no reports of the reactions to the offending foods in the breast milk, suggesting an important protective role of breast-feeding in FPIES [21]. Lake hypothesized that food protein-induced proctocolitis may be a milder form of FPIES based on the fact that in FPIES, the maximal inflammatory response also involves the rectum [26]. Hence, proctocolitis in formula-fed infants would represent the mildest phenotype, whereas the protective effects of the breast milk such as presence of IgA antibodies and partially processed food proteins would prevent the expression of the full, more severe clinical phenotype in the breast-fed infants. Perhaps IgA or other immunologically active components of breast milk bind with the food allergens and release them in the rectum following cleavage by microbial IgA proteases or via other mechanisms [26].

In the most severe cases, symptoms may manifest within first days of life with severe, bloody diarrhea, lethargy, abdominal distension, hypoactive bowel sounds, weight loss, failure to thrive, dehydration, metabolic acidosis and electrolyte abnormalities, anemia, elevated white blood count with eosinophilia, and hypoalbuminemia [12,27]. Intramural gas may be noted on abdominal radiographs, prompting a diagnosis of necrotizing enterocolitis, sepsis evaluation, and treatment with antibiotics [12,27,28]. Ileus resulting in laparoscopy was reported [29,30]. Overall 75% of infants with FPIES appear acutely ill including 15% who are hypotensive and require hospitalization as well as extensive evaluation before the diagnosis of FPIES is established.

Murray and Christie reported six infants with cow's milk or soy FPIES who presented with acidemia (mean pH, 7.03) and methemoglobinemia (10–37% of total hemoglobin) among 17 infants under 6 months of age hospitalized with diagnosis of cow's milk or soy protein intolerance over a 10-year period [31]. Presence of transient methemoglobinemia was associated with severe reactions and profound acidemia; some infants required treatment with methylene blue and bicarbonate. Murray and Christie postulated that methemoglobinemia was caused by an elevation of nitrites in the intestine resulting from severe intestinal inflammation and reduced catalase activity. An additional report confirmed association of methemoglobinemia with FPIES [15].

Young infants presenting with chronic symptoms while being continuously fed with cow's milk or soy formula improve promptly when placed on intravenous fluids or with casein hydrolysate-based formula. However, upon reintroduction of the offending food, they develop dramatic symptoms, including shock in 15–20%. Based on Powell's experience with 14 positive follow-up challenges in 18 infants, repetitive emesis started within 1–2 hours following ingestion and diarrhea within 2–10 hours (mean onset, 5 hours) with blood, mucous, leukocytes, eosinophils, and increased carbohydrate content in the stool [13]. Peripheral blood neutrophil counts were elevated in all positive challenges, peaking at 6 hours following ingestion with a mean increase, 9900 cells/mm³; range, 5500–16,800 cells/mm³. Clinical features of cow's milk and soy FPIES are summarized in Table 16.2.

Solid food protein-induced enterocolitis syndrome

Rare case reports initially described infants with typical features of FPIES provoked by ingestion of solid foods such as rice, chicken, turkey, egg white, green pea, and peanut [15,17,18,20,32]. Subsequently, larger series of patients with solid food FPIES were published [21–23,25].

In adults, crustacean shellfish (shrimp, crab, and lobster) and fish hypersensitivity may provoke a similar syndrome with severe nausea, abdominal cramps, protracted vomiting, and diarrhea [8]. Among infants with solid food FPIES, 65% were previously diagnosed with cow's milk and/or soy FPIES and were fed with casein hydrolysate- or amino-acid-based formula; 35% were breast-fed at the time of FPIES onset suggesting that breast milk may confer a protective effect against FPIES development [21]. The mean age at onset of solid food FPIES tends to be higher. Infants often present with a history of multiple reactions and have undergone extensive evaluations for alternative etiologies (infectious, toxic, metabolic) before the diagnosis of FPIES is established [21,23,25]. Delayed diagnosis may be explained by common perception that grains, for example rice, and vegetables have low-allergenic potential and are not considered as a cause of severe food-allergic reactions, as well as lack of definitive diagnostic tests and the unusual nature of symptoms. A summary of the current published experience with solid food FPIES is presented in Table 16.3.

Table 16.2 Clinical characteristics of cow's milk/soy FPIES

General		Chronic manifestations during continued ingestion of the food	Acute manifestations following ingestion after a period of avoidance
Age at onset: days – 12 months		Intermittent emesis	Emesis, onset 1–3 hours following ingestion
Allergy to cow's milk and soy:	65%	Chronic watery diarrhea with blood and mucous	Diarrhea, onset about 5 hours following ingestion
FPIES to solid foods:	25%	Carbohydrate malabsorption (stool positive for reducing substances)	Lethargy, dusky appearance
Resolution by age 3 years:			
Cow's milk:	65%	Lethargy	Acidemia, methemoglobinemia, and hypotension in 15%
Soy:	25–35%		
Male:Female:	60:40	Dehydration	Elevated PMN count
Personal history of atopy:		Hypotensive shock (15%)	Frank or occult fecal blood
Atopic dermatitis:	25%	Acidemia	Sheets of leukocytes and eosinophils in stool
Asthma/allergic rhinitis:	20%	Methemoglobinemia/clinical cyanosis	Abdominal distension, hypoactive bowel sounds, ileus (extreme cases, typically newborns and young infants <3 months of age)
Family history of atopy:	80%	Anemia	
Family history of food allergy:	20%	Hypoalbuminemia	
Allergy evaluation:		Elevated white blood count with eosinophilia	
Prick skin test: Negative		Failure to thrive	
Serum food-IgE: Negative		Abdominal distension, hypoactive bowel sounds, ileus	
Tolerated diet: Breast milk, extensively hydrolyzed casein formula, amino acid formula			

Adapted from Sicherer [40], with permission from the American Academy of Allergy, Asthma, and Immunology.

Table 16.3 Clinical characteristics of solid food FPIES

Feature	Cereal [21,23]	Fish [22]	Poultry [21,25]	Legumes* [21,25]
Specific foods (number of patients)	Rice 16 Oat 9 Barley 2	<i>N</i> = 14; hake, sole, cork float	Chicken 5 Turkey 3	Green pea 3 String bean 2 Lentil 1
Age of onset, months; median (range)	6 (3–6)	10.5 (9–12)	6.5 (3–12)	6 (4.5–8)
Sex: % Male	50	42	60	80
# of reactions prior to diagnosis, median (range)	2 (1–5)	3 (2–6)	NS	1 (1–3)
% FPIES to other food from the same group	50	70	33	20
% FPIES to soy	~60	NS	40	80
% FPIES to cow's milk	~30	NS	40	60
% FPIES to both cow's milk and soy	~30	NS	20	40
% FPIES to more than one food	~90	NS	80	80
% Positive prick skin test	0	NS	0	0
% Detectable serum food-IgE	~8(1/13)	~7(1/14)	0	0
% Resolved by age 3 years	Rice 50 (6/12) Oat 66 (4/6)	30% resolved in 1–7 years	20	60

*Other than soybean; NS, not specified.

Diagnosis and management of food protein-induced enterocolitis syndrome

Diagnosis of FPIES relies on history, clinical features, exclusion of other etiologies and OFC (Table 16.4). The vast majority (over 90%) of patients in large series have negative skin prick tests and undetectable allergen-specific IgE antibodies to the offending foods [15,16]. Although OFC is the gold standard for diagnosing FPIES, most infants do not need to undergo confirmatory challenges, especially if they have a classic history of severe reactions and become asymptomatic following elimination of the suspected food. However, OFCs are necessary to monitor when a patient “outgrows” FPIES. In the infants with chronic diarrhea, stool samples test positive for occult blood and show the presence of intact polymorphonuclear neutrophils, eosinophils, and Charcot–Leyden crystals. Some patients develop carbohydrate malabsorption and show reducing substances in the stool.

Recently, the atopy patch test (APT) has been evaluated in a number of studies for diagnosing food disorders with mixed mechanism, IgE mediated and T-cell mediated, such as atopic dermatitis and allergic eosinophilic esophagitis [33–35]. Some reports suggest that APT with food allergens may identify patients in whom T-cell-mediated mechanisms predominate. Subsequently, APT was evaluated in 19 infants (ages, 5–30 months) with FPIES confirmed by an OFC [36]. APT predicted the outcome of an OFC in 28/33 instances; all positive OFCs had a positive APT, but five patients with positive APT did not react to an OFC. Similar results have not been reported by other investigators so at this time, the role of APT in the diagnosis of FPIES requires further rigorous evaluation.

Given the description of the typical constellation of clinical symptoms and strict criteria for a positive OFC, endoscopic examination is not performed routinely in patients with suspected FPIES. However, prior to the establishment of diagnostic criteria, endoscopic evaluations were performed in some very ill infants with cow’s milk and/or soy FPIES and rectal bleeding. Investigators reported rectal ulceration and bleeding with friability of the mucosa in most patients; endoscopy was normal in a minority of such children. Plain radiological imaging or with barium contrast in infants with ongoing chronic symptoms of diarrhea, rectal bleeding, and/or failure

to thrive showed air fluid levels consistent with intestinal obstruction, non-specific narrowing and thumb-printing of the rectum and sigmoid, as well as thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid. Striking, ribbon-like jejunum with loss of valvulae and separation of bowel loops, suggesting thickening of the bowel wall was reported [29,37]. In the extreme cases of ileus, in which laparotomy was performed, distention of small bowel loops and marked thickening of the wall of jejunum distal to Treitz’s ligament with diffuse subserosal bleeding were observed [29,30]. Follow-up studies performed on a restricted diet in asymptomatic patients documented resolution of radiological abnormalities. Radiological findings are non-specific and can be also seen in celiac disease, intestinal lymphangiectasia, immunodeficiency, or Crohn’s disease. However, they may alert the physician to the possibility of allergic colitis in a child presenting with chronic symptoms of diarrhea, failure to thrive, anemia, and hypoalbuminemia.

Oral food challenge in food protein-induced enterocolitis syndrome

OFCs can be used to establish diagnosis of FPIES or to evaluate the possibility that FPIES has been “outgrown” in a patient with known or suspected FPIES. Depending on the clinical severity, follow-up challenges should be performed every 18–24 months to determine tolerance in patients without accidental reactions [38]. Guidelines for preparation and interpretation of the OFC for FPIES are summarized in Table 16.5; Box 16.1 contains a practical example for calculating the quantity of food to use in the challenge.

Box 16.1 Food challenge preparation for FPIES

- 1 Obtain current weight of the patient.
- 2 Calculate the amount of *protein per kg body weight*; range 0.06–0.6 g protein per kg body weight; typically 0.15–0.3 g protein per kg body weight.
- 3 Weigh the equivalent of the calculated protein dose; do not exceed 10 g of the food challenged.
- 4 Mix the amount calculated with a vehicle of choice, such as rice milk for a total weight of 200 ml.
- 5 Administer in three doses over 30–45 minutes.

The child’s weight is 10 kg.

Total dose of milk protein: $0.15 \text{ g} \times 10 \text{ kg} = 1.5 \text{ g} = 42 \text{ ml}$ of skim milk = 1.4 oz skim milk (8 oz = 236.5 ml contains 8.4 g milk protein). Add 42 ml of skim milk to a safe rice milk for a total volume 100 ml* and administer in three doses over 30–45 minutes.

*100 ml is used to simplify calculations. Total amount of food should be the smallest amount needed that will mask the challenge food and will be reasonable for the patient to consume at one sitting.

Vehicles used in the OFCs should be carefully selected to avoid contamination with food allergens to which the patient undergoing challenge is allergic. (Adapted from [39], with permission from the Food Allergy and Anaphylaxis Network.)

Table 16.4 Differential diagnosis of FPIES

Allergic	Non-allergic
Food protein-induced proctocolitis	Necrotizing enterocolitis
Food protein-induced enteropathy	Sepsis
Eosinophilic gastroenteropathies	Gastrointestinal infection (<i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i> sp., parasites)
Cow’s milk-induced gastroesophageal reflux	Hirschprung’s disease Intussusception Volvulus

Table 16.5 OFC in FPIES

<i>Challenge protocol</i>
High-risk procedure, requires immediate availability of fluid resuscitation, secure intravenous access
Baseline peripheral neutrophil count
Gradual (over 1 hour) administration of food protein 0.06*–0.6 g/kg body weight, generally not to exceed total 3 g protein or 10 g of total food for an initial feeding
If no reaction in 2–4 hours, administer a regular age-appropriate serving of the food followed by several hours of observation
Majority of positive challenges require treatment with intravenous fluids and steroids
<i>Criteria for a positive challenge</i>
<i>Symptoms</i>
Emesis (typically in 2–4 hours)
Diarrhea (typically in 5–8 hours)
<i>Laboratory findings</i>
Fecal leukocytes
Fecal eosinophils
Increase in peripheral neutrophil count >3500 cells/mm ³ peaking at 6 hours
<i>Interpretation of the challenge outcome</i>
Positive challenge: three of five criteria positive
Equivocal: two of five criteria positive

*Lower dose recommended in children with history of previous severe reaction.
(Data from [14,38–40].)

OFCs involve the administration of food protein, 0.06–0.6 g/kg body weight, with lower doses (0.06 g/kg) used in children with prior severe reactions [14,15]. Generally, the amount served initially during an OFC does not exceed 3–6 g of food protein or 10–20 g of total food weight (usually less than 100 ml of liquid food such as cow’s milk or infant formula). The calculated amount of food is divided into three equal portions and served over 45 minutes [39]. The patient is observed for 4 hours and if asymptomatic, a second feeding, typically an age-appropriate regular serving amount is given followed by observation for several hours [40]. OFC in FPIES is a high-risk procedure and should be performed under physician supervision with secure intravenous access for fluid resuscitation [15]. Intravenous hydration is the first-line therapy; however, corticosteroids are often used for severe reactions, based on presumed pathophysiology that involves T-cell-mediated intestinal inflammation. Epinephrine should be available for severe cardiovascular reactions with hypotension/shock; however, rapid rehydration with intravenous fluids (up to 20 ml/kg) is the mainstay of therapy and the efficacy of epinephrine in FPIES has not been established.

Dietary management of food protein-induced enterocolitis syndrome

For patients with suspected or confirmed FPIES, strict dietary avoidance of the offending food protein(s) should be

recommended and appropriate guidelines for avoidance provided. Given the high risk of concomitant cow’s milk and soy FPIES (over 60% of cases), extensively hydrolyzed casein formulas are recommended for infants and young children that cannot be breast-fed [13,15,38]. Eighty percent of patients with cow’s milk and/or soy FPIES respond to extensively hydrolyzed casein formula with resolution of symptoms within 3–10 days. Up to 20% of patients require amino-acid-based formula or temporary intravenous therapy [41,42].

Proposed guidelines for solid foods introduction to infants with cow’s milk or soy FPIES (especially those with atopic dermatitis) take into account that up to one-third of these children appear to develop a reaction to solid food and include: (i) delayed introduction of solid foods and (ii) suggested yellow fruits and vegetables instead of cereal grains as first foods [21,40]. Infants with solid food FPIES are at high risk to react to other foods, 80% are reactive to more than one food protein, 65% react to cow’s milk and/or soy, and those with a history of reactions to one grain have at least a 50% chance of reacting to other grains. Empirically, infants with solid food FPIES may benefit from avoidance of grains, legumes, and poultry in the first year of life [40]. Introduction of cow’s milk and soy in infants without prior history of reactivity to these foods may be attempted at the age older than 1 year, preferably under physician supervision. Tolerance to one food from each “high-risk category” such as soy for legumes, chicken for poultry, or oat for grains might be considered as an indication of increased likelihood of tolerance to the remaining foods from the same category [40].

Natural history of food protein-induced enterocolitis syndrome

Sensitivity to milk was lost in 60% and to soy in 25% of patients by age 3 years [15,21]. Rates of resolution of solid food FPIES by age 3 years were 40% for rice, 66% for oat, and 67% for other foods (vegetables). Current experience suggests that soy, cow’s milk, and poultry FPIES may have longest duration [21]. FPIES rarely develops to foods upon first exposure beyond 1 year of age. For example, wheat allergy has not been reported in infants with oat- or rice-induced FPIES, but introduction of wheat was significantly delayed, presumably avoiding the “window of physiologic susceptibility” for FPIES development [21,40]. Sicherer *et al.* noted three patients who initially presented with, and two that developed positive prick skin tests to commercial extracts of cow’s milk and detectable serum milk-specific IgE antibodies (1 and 3 years after the diagnosis) [15]. All five patients remained sensitive to the offending food and showed only symptoms consistent with FPIES. They had no IgE-mediated symptoms of urticaria, wheezing, or anaphylaxis when challenged. Similarly, persistence of oat and soy allergy 2–3 years after the initial reaction was observed in two patients with detectable serum IgE antibodies to these foods [21]. Therefore, initial presence or development of IgE to food

protein may indicate a more protracted course. It may be prudent to include prick skin testing and/or measurement of serum food-specific IgE level in the initial as well as follow-up evaluations, to identify patients at risk for persistent FPIES.

Genetics

The genetics of FPIES and the role of heredity are unknown. FPIES appears to be slightly more frequent in males than females, with a ratio of 60:40. Family history of atopy is positive in 40–80% of patients reported but only rarely family history is positive for food allergy, in about 20% of the cases [15,21,38,40]. In the author's experience, FPIES is uncommonly seen in more than one family member. Approximately 30% of infants with FPIES develop atopic diseases such as atopic dermatitis (23–57%), asthma or rhinitis (20%), or drug hypersensitivity later in life, probably not significantly different than the general population [15,21].

Pathology

Since the diagnosis of FPIES is based on clinical criteria, endoscopy and biopsy are not routinely performed. However, previously, endoscopic evaluations and biopsies were obtained in infants with chronic symptoms of FPIES plus diarrhea, rectal bleeding, and failure to thrive while being fed cow's milk or soy-based formulas. These cases with available biopsy data highlight inflammatory responses in the colon of this subset of patients. Endoscopic evaluation revealed diffuse colitis with variable degrees of ileal involvement; in the most severe cases focal erosive gastritis and esophagitis are found with prominent eosinophilia and villus atrophy. Colon mucosa can be mildly friable to severe spontaneous hemorrhage, and minute ulcers similar to those seen in ulcerative colitis can be found [11,38,44]. Crypt abscesses have been identified in some patients [43].

Jejunal biopsies reveal mild to severe degree of villus atrophy, edema, and increased numbers of lymphocytes, IgM- and IgA-containing plasma cells, eosinophils, and mast cells [43,44].

Pathophysiology

Based on clinical manifestations of severe emesis and dehydration, it is hypothesized that local intestinal inflammation induced upon food-allergen ingestion leads to increased intestinal permeability and fluid shift. In asymptomatic children with suspected egg white FPIES, gastrointestinal absorption of ovalbumin as measured by serum level of ovalbumin was not different between children who subsequently had a positive oral challenge to egg white and those who had no symptoms on egg challenge, suggesting that baseline antigen absorption is normal and does not predispose to FPIES [45].

Cytokines secreted by food-allergen-stimulated T-lymphocytes affect the intestinal permeability. Interleukin-4 (IL-4), interferon- γ (IFN- γ), and tumor necrosis factor- α (TNF- α) synergistically increase intestinal permeability whereas

transforming growth factor- β 1 (TGF- β 1) protects the epithelial barrier of the gut from the penetration of foreign antigens by antagonizing the action of IFN- γ [46–49].

Several original studies investigated lymphocyte responses and cytokine release in the patients with FPIES. Van Sickle *et al.* showed that following *in vitro* stimulation with milk or soy proteins, peripheral blood mononuclear cells (PBMCs) from children with cow's milk or soy-induced FPIES had significantly ($p < 0.01$) higher geometric mean proliferation indices in comparison with children who had negative oral challenges to cow's milk and soy [50]. Hoffman *et al.* reported increased proliferative responses in PBMCs from children with OFC-documented cow's milk allergy (IgE-mediated or cow's milk FPIES) on day 7; however, stimulation indices were not significantly different compared with non-cow's milk-allergic controls [51]. Shek *et al.* found higher-lymphoproliferative response in patients with cow's milk allergy than in control patients but this response was similar in patients with IgE-mediated cow's milk-allergy and in cow's milk FPIES [52].

TNF- α is a potent pro-inflammatory cytokine that induces neutrophil activation and increases intestinal permeability *in vitro* by altering the tight junctions between epithelial cells [53]. Because of these known effects of TNF- α , its role in this gastrointestinal cow's milk hypersensitivity has been investigated in a number of studies that included subsets of infants with cow's milk FPIES. Heyman suggested that TNF- α secreted by circulating milk-protein-specific T-cells increased intestinal permeability, thus contributing to the influx of antigen into the submucosa with further activation of antigen-specific lymphocytes [54]. Lower quantities of intact cow's milk protein required to stimulate TNF- α secretion, and prolonged secretion of TNF- α by PBMCs was reported in patients with active intestinal cow's milk allergy, compared with patients with cutaneous symptoms and those who outgrew cow's milk allergy [55]. Cow's milk-stimulated fecal TNF- α was also found in increased concentrations following positive milk challenges in children with cow's milk allergy.

Investigating local mucosal characteristics, Chung found generally depressed TGF- β expression in duodenal biopsies from all 28 infants with challenge-proven cow's milk FPIES [56]. Expression of type 1 TGF- β receptors was significantly lower in the patients with villous atrophy compared with patients who did not have villous atrophy ($p < 0.001$). This was negatively correlated with the severity of villous atrophy ($r = -0.59$, $p < 0.001$). In contrast to depressed TGF- β , TNF- α expression on epithelial and lamina propria cells was significantly greater in the patients with villous atrophy ($p < 0.01$), suggesting that imbalance in TGF- β /TNF- α may be important in the pathophysiology of FPIES.

Humoral immune responses are generally not considered to be an important mechanism in FPIES. Interestingly, an increase in serum food antigen-specific IgA and IgG

antibody levels has been noted in the FPIES patients [57]. Recently Shek *et al.* found lower levels of serum cow's milk-specific IgG₄ antibody levels ($p < 0.05$) and a trend for higher IgA antibody levels in patients with cow's milk FPIES when compared to the control group [52]. The role of IgG and IgA antibodies in the pathogenesis of FPIES needs to be further explored.

Food protein-induced enteropathy

Food protein-induced enteropathy is a syndrome of small bowel injury with resulting malabsorption, similar to celiac disease although less severe [8].

Historical perspective

The first report of malabsorption syndrome with diarrhea, emesis, and impaired growth induced by cow's milk-feedings in infants was published in 1905 [58]. Subsequent reports, including large series of cow's milk-protein-sensitive Finnish infants, defined clinical features of this disorder [59–65]. The reported incidence of food protein-induced enteropathy peaked in the 1960s in Finland, with virtual disappearance of severe jejunal damage caused by cow's milk protein in the past 20 years [66]. Infant feeding practices have been implicated as a cause of the changing prevalence of food protein-induced enteropathy, with the highest incidence of classic severe enteropathy attributed to feedings with non-humanized, high protein infant formulas and the lowest incidence in breast-fed infants [67–69]. Recently, intestinal enteropathy was reported in older children with delayed type allergic reactions to cow's milk as well as in children with multiple food allergies [70–72].

Clinical features of food protein-induced enteropathy

Food protein-induced enteropathy presents with protracted diarrhea in the first 9 months of life, typically the first 1–2 months, within weeks following the introduction of cow's milk formula. Food proteins such as soybean, wheat, and egg have been confirmed as causes of enteropathy, frequently in children with co-existent cow's milk-protein-induced enteropathy [73–76]. In a single report, "enteropathy" related to fish, rice, and chicken was described in three patients [19]. However, careful analysis of the cases leads to conclusion that the reported condition was consistent with FPIES rather than enteropathy. Given the evolving understanding of the gastrointestinal food hypersensitivity syndromes, the older literature has to be reviewed critically and disorders re-classified on the basis of the consensus guidelines [8].

More than 50% of the affected infants have vomiting and failure to thrive and some present with abdominal distension, early satiety, and malabsorption. In many infants the onset of symptoms is gradual; in others, it mimics acute gastroenteritis with transient emesis and anorexia complicated

by protracted diarrhea. It may be difficult to distinguish food protein-induced enteropathy from post-enteritis-induced lactose intolerance, especially since these two conditions may overlap [76]. Acute small bowel injury caused by viral enteritis has been postulated to predispose children to subsequent food protein-induced enteropathy, or alternatively to unmask underlying food protein hypersensitivity [64,75,77,78]. Diarrhea generally resolves within 1 week following cow's milk-protein elimination, although some infants require prolonged intravenous nutrition [65].

Moderate anemia is present in 20–69% of infants with cow's milk-protein-induced enteropathy [65,66]. Iron deficiency is more common than anemia and malabsorption of iron or folate is likely a major contributing factor [65]. Bloody stools are typically absent but occult blood can be found in 5% of patients [79]. Malabsorption with hypoproteinemia and deficiency of vitamin K-dependent factors have been reported in 35–50%. Moderate steatorrhea manifested by increased fecal fat excretion can be found in over 80%. The absorption of the sugar D-xylose test is abnormal in up to 80% [80]. Lactose can be found in the urine in 55% and in the stool in 52% of cases, typically in the youngest infants. Lactose absorption becomes normal promptly following the elimination of cow's milk protein [64].

Recently, school-age children who developed delayed gastrointestinal symptoms to cow's milk challenge but had no villous atrophy or malabsorption were reported [70]. Twenty-seven children with suspicion of cow's milk-related symptoms, such as history of cow's milk allergy in infancy, abdominal pains, or diarrhea after consumption of dairy products, were placed on strict elimination of cow's milk protein for 2 weeks, followed by a challenge over 1 week. Although all children clinically responded to elimination of cow's milk, only 15 children (mean age, 10 years; range, 6–14) had relapse of symptoms during 1-week challenge. When compared with control children (11 with celiac disease, 12 without gastrointestinal disease), they had a history of significantly higher food allergy at <2 years of age, gastritis and esophagitis on biopsy, as well as lymphonodular hyperplasia of the duodenal bulb. An increase in gamma/delta T-lymphocytes, but of lesser magnitude than in seen celiac disease, was observed. It remains to be established whether these older children represent a milder phenotype of enteropathy or whether they have a different disease caused by cow's milk hypersensitivity.

The prevalence of this problem among school-age children is unknown but subsequent reports confirmed the presence of subtle enteropathy in children with delayed gastrointestinal symptoms following food ingestion [71,81]. Veres *et al.* evaluated seven children with untreated food allergy (mean age, 7.3 years; range, 2–13), seven children with treated food allergy (mean age, 8.1 years; range, 1–14), and five normal pediatric controls with endoscopy and duodenal biopsy (mean age, 11.4 years; range, 4–16) [71]. Diagnosis of food allergy was based on resolution of gastrointestinal symptoms

during 2 weeks of an elimination diet and reappearance in an open food challenge within a median 4.5 days range 1–7 days. Children reacted to cow's milk [8], cereal grains [3], or both [3]. Five of eight children tested had specific serum food-specific IgE >0.7 IU/l or a positive prick skin test. Biopsies showed features of immune activation in the small intestine; over 90% had lymphonodular hyperplasia. In spite of the normal villous structure, the untreated children with food allergy exhibited a higher crypt proliferation rate and HLA-DR crypt staining than those of the controls. Latcham *et al.* reported that in 45 duodenal biopsies obtained from children with both immediate and delayed history of allergy to multiple foods, there was evidence of subtle enteropathy in most, with focal lymphocytic or eosinophilic infiltration, villous blunting, and reduced crypt–villous ratio [72].

Genetics of food protein-induced enteropathy

The infants with enteropathy typically do not have a predisposing family history of cow's milk allergy. Atopic dermatitis and chronic respiratory symptoms may be present in 22% of children, which is similar to the general population [65].

Diagnosis and management of food protein-induced enteropathy

Food protein-induced enteropathy is diagnosed by the confirmation of villous injury, crypt hyperplasia, and inflammation on small bowel biopsy obtained in a symptomatic patient who is being fed a diet containing the offending food allergen [43,82–84]. Elimination of the food allergen should lead to resolution of clinical symptoms within 1–3 weeks [65]. Villous atrophy should improve within 4 weeks but complete resolution may take up to 1.5 years. Infants with severe initial manifestations may require prolonged bowel rest and parenteral nutrition for days or weeks. Diagnostic confirmatory challenges and measurement of specific serologies for celiac disease may be necessary to distinguish between food protein enteropathy and celiac disease, or to identify multiple food allergens. In the clear-cut cases, oral challenges are not absolutely required for confirmation of the diagnosis. The OFCs should be performed periodically to assess the development of oral tolerance.

Immunologic studies have shown increased levels of milk IgA in 74% and milk IgG precipitins in 65% of infants. Milk IgA levels decrease following cow's milk dietary elimination [65]. However, the diagnostic utility of these tests is unknown, particularly in view of the high prevalence of positive results in many other gastrointestinal inflammatory disorders in childhood. Classically, food-specific IgE antibodies are undetectable and skin prick tests are negative [85]. Several studies suggested that patch skin tests may be a useful screen for gastrointestinal food hypersensitivity (cow's milk, wheat) [33]. However, biopsies were not obtained and the association of positive patch tests with gastrointestinal changes remains to be determined.

Recently, serum concentrations of granzymes A (GrA) and B (GrB), soluble Fas, and CD30 were analyzed in children with cow's milk-sensitive enteropathy confirmed by endoscopy and biopsy [86]. These markers reflect activation of cytotoxic lymphocytes that have been shown to be upregulated in the local intestinal mucosa in food-sensitive enteropathy [86–88]. Serum concentrations of GrA and GrB were significantly higher in the 18 untreated children with food allergy and in the 20 untreated celiac disease patients as compared with the control subjects. Measurable serum GrB was present in only 20% of the control subjects but in 100% of patients with cow's milk-sensitive enteropathy. CD30 was similarly increased in both untreated cow's milk-sensitive enteropathy and celiac disease cases, whereas in the treated patients the concentrations were not different from control subjects. All groups showed similar levels of soluble Fas. The numbers of duodenal CD3+, $\alpha\beta$ -, and $\gamma\delta$ -TCRs correlated with the serum granzyme and CD30 levels. These preliminary results are very encouraging but have to be confirmed in a larger number of patients before measurement of serum markers of intestinal cytotoxic lymphocyte activation may be routinely used.

Natural history of food protein-induced enteropathy

Food protein-induced enteropathy resolves clinically in the majority of children by age 1–2 years, however the proximal jejunal mucosa may be persistently abnormal at that time [65]. Mucosal healing continues during feeding with the implicated food once clinical tolerance is achieved [82]. In the children with less severe disease who were diagnosed at an older age, tolerance also developed at an older age, however, most became tolerant by 3 years [68]. Of note, 5 of 54 infants with challenge-confirmed cow's milk-induced enteropathy were ultimately diagnosed with celiac disease that persisted beyond infancy [65]. In contrast, transient wheat enteropathy with or without associated cow's milk-protein-induced enteropathy has been reported in a number of studies, including transient wheat enteropathy following enteritis [77,89,90]. Strict criteria for the diagnosis of transient wheat-induced enteropathy were established and include evidence of small bowel villous injury, resolution with gluten avoidance and persistent normal small bowel mucosa for 2 or more years after reintroducing gluten to the diet [91]. The course of food protein-induced enteropathy in older children has not been characterized.

Pathologic features of food protein-induced enteropathy

The degree of villous injury is variable, ranging from severe to mild, with most biopsy specimens revealing patchy, subtotal villous atrophy [43,65,82–84]. In the more recent reports, patterns of enteropathy are more subtle, without obvious villous atrophy but with noticeable villous blunting, and reduced crypt–villous ratio [71,72,81]. Intestinal mucosa is thin and

crypts can be elongated [65,68,71,92] (Fig. 16.1). Intraepithelial lymphocytes (IELs) are prominent, while infiltration with eosinophils is inconsistent [71,81,92–94]. Lymphocytes can also be found in the lamina propria. Increased apoptosis of duodenal IELs can be found [95].

Mucosal lipid content may be increased [96]. Columnar cells of the normal jejunum are replaced by crypt cells of a more cuboidal, immature type [61]. The epithelial cells bear short microvilli that contain large aggregates of lysozymes and abnormal nuclei [83]. The basement membrane is un-evenly thickened. The epithelial cell renewal rate is markedly increased as a result of the increased mitotic rate [97,98]. Immunohistochemical studies of the mucosal biopsies in untreated and challenge-positive infants demonstrate a non-specific increase in mucosal IgA, IgG, and IgM, with inconsistent increase in IgE [99,100]. The histologic features of soybean- or cereal-induced enteropathy are similar to those noted for cow's milk [71,73,75,101,102].

Pathophysiology of food protein-induced enteropathy

T-lymphocytes appear to play a central role in the pathophysiology of food protein-induced enteropathy. Activated T-cells in the lamina propria of the fetal human small intestine have been shown to produce crypt hypertrophy and villous atrophy [103,104]. Increased IELs are predominantly CD3+ α/β suppressor/cytotoxic CD8+ T-cells [105]. However in some series, between 50% and 100% of patients with severe enteropathy have increased density of γ/δ T-cells in the epithelium, similar to celiac disease and autoimmune enteropathy [106,107]. Similar increases were also detected in older children with delayed gastrointestinal symptoms of cow's milk allergy [70,71,108,109]. In the lamina propria, the numbers of lymphocytes (predominantly CD4+ T-cells), plasma cells, and eosinophils are increased [92,94,105]. Many T-cells express HLA-DR, suggestive of an activated state. Following cow's milk-elimination diet, these cells diminish [71,105,109]. Increased numbers of cytotoxic

IELs expressing T-cell-restricted intracellular antigen (TIA1) are found in biopsies from infants as well as from school-age children [86–88]. Activation of cytotoxic duodenal IELs is also confirmed by analysis of expression of cytotoxic granule components, such as perforin and GrA and GrB in duodenal IELs [88,108].

Mononuclear cells from biopsies of children with cow's milk enteropathy have significantly higher expression of VCAM-1 than that of control children [44]. The number of lymphocytes positive for gut homing receptor $\alpha 4/\beta 7$ is increased in the lamina propria in adults and untreated children with delayed food allergy [71,110]. These patients also show higher numbers of ICAM-1+ cells in the lamina propria.

In addition to lymphocytic infiltration, electron microscopy shows edema of the lamina propria and of the endothelium of small blood vessels, as well as degranulation of mast cells, eosinophils, and macrophages [84]. Mucosal histamine content is high suggesting activation of the mast cells [111]. In a series of 21 patients with cow's milk enteropathy, there was significantly increased eosinophil degranulation as evidenced by localization of extracellular major basic protein (MBP), compared with the non-cow's milk-induced enteropathy control groups. The severity of villous atrophy was positively correlated with the deposition of MBP ($r=0.79$, $p<0.001$). The numbers of IgA- and IgM-bearing cells in the lamina propria increase significantly (average 2.4 times) following positive cow's milk challenge. In contrast, in specimens from asymptomatic patients, the IgA cells increase 1.5-fold, whereas the IgM cell numbers do not change during a 4- to 6-week consumption of cow's milk in the diet. An elimination diet following a positive challenge results in decreased densities of IgA- and IgM-containing cells [112]. Similar changes in IgA and IgM cells were observed in soy-induced enteropathy following an oral challenge with soy and reinstitution of an elimination diet [101].

Presence of IgE in the mucosal biopsies was reported by two groups but was not confirmed in large series of infants [113]. In a mouse model of allergic enteropathy, evidence of local



Figure 16.1 Biopsy of duodenal mucosa obtained from a 6-month-old infant with cow's milk-protein-induced enteropathy. Hematoxylin and eosin stain, original magnification 200 $\times$. Villous blunting, elongated crypts, and numerous lymphocytes can be seen in the intestinal epithelium. (Slide and description were generously provided by Dr. Keith Benkov, Division of Pediatric Gastroenterology, Mount Sinai School of Medicine, New York.)

IgE was prominent. The ovalbumin 23-3 T-cell receptor transgenic mice that were fed with egg white developed weight loss and jejunal inflammation characterized by villous atrophy and goblet cell hyperplasia [114]. Tissue sections showed significant infiltration of specific IgE-positive cells and IgE-positive degranulating mast cells. Higher levels of IL-4 and significant levels of histamine were detected in the tissues. However, RAG-2-deficient transgenic mice that lacked mature B-cells and were defective in local and serum IgE responses developed a similar degree of weight loss and jejunal inflammation, suggesting that specific T-cells are indispensable in the development of enteropathy in this murine model.

Following stimulation with cow's milk protein *in vitro*, a higher proportion of cells isolated from jejunal specimens of patients with enteropathy secreted IFN- γ and IL-4 than from control subjects, with IFN- γ secreting cells being 10 times more numerous than IL-4 secreting cells [115]. IL-10 secreting cells were reduced, further implicating a predominance of the Th1-type responses involved. The numbers of cells secreting IL-5 were not different between two groups of specimens. Spontaneous cytokine release from duodenal biopsy samples of children with delayed cow's milk allergy was recently reported [81]. Children with cow's milk allergy secreted more

IFN- γ than the controls ($p=0.006$) and the children with celiac disease ($p=0.006$). Children with untreated cow's milk allergy secreted less TGF- β than those who avoided dietary cow's milk ($p=0.05$) and more IL-4 and IL-10 than healthy controls ($p=0.016, 0.059$).

Intestinal cytokine mRNA expression was significantly different in children with delayed cow's milk allergy than in children with celiac disease [116]. IL-2 and IL-18 mRNA expression was lower in the duodenum (both $p=0.055$) and CCR-4 and IL-6 mRNA expression was higher in the terminal ileum ($p=0.055, 0.016$) compared with the controls. In contrast, children with celiac disease had slightly higher expression of IFN- γ and CCR-4 mRNA, and lower expression of IL-18 mRNA compared with the controls. The mRNA expression of IL-10 and TGF- β was similar in these groups. However, Perez-Machado *et al.* found reduced amounts of TGF- β 1 producing lymphocytes in the epithelium and lamina propria in duodenal biopsies from 30 children (8 with IgE-mediated and 22 with non-IgE-mediated multiple food allergy) by flow cytometry [117]. Reduction of TGF- β 1 expression was confirmed in mononuclear cells and epithelium by immunohistochemistry and *in situ* hybridization. Table 16.6 summarizes the most important

Table 16.6 Summary of pathologic and immunologic features of food protein-induced enteropathy

Characteristics	Infantile enteropathy	Older child/adult-type enteropathy
<i>Offending foods</i>	Cow's milk, soybean, wheat	Cow's milk, cereal grains
<i>Pathology</i>		
Villous atrophy	Patchy, mild to severe	Villous blunting, reduced crypt-villous ratio
Intra-epithelial and lamina propria lymphocytes	Increased	
Eosinophilic infiltration	Variable	
Mucosal lipid content	Increased	
Crypt cells	Immature, cuboidal	
Basement membrane	Unevenly thickened	
Epithelial cell renewal rate	Increased	
Mucosal IgA, IgG, IgM	Non-specific increase	
Mucosal IgE	Inconsistent increase	
<i>Pathophysiology</i>		
IELs-cytotoxic CD8+ phenotype	Predominantly α/β , fewer γ/δ	α/β and γ/δ
Increased markers of CD8+ activation	HLA-DR T-cell-restricted intracellular antigen	HLA-DR T-cell-restricted intracellular antigen Perforin, GrA CD1d
High expression of lymphocyte adhesion molecules	VCAM-1, ICAM-1, $\alpha 4/\beta 7$	ICAM-1, $\alpha 4/\beta 7$
Mast cells activation	High mucosal histamine content	
Eosinophil activation	Deposits of extracellular MBP	
Cytokine patterns upon stimulation of cells isolated from jejunal biopsies with cow's milk <i>in vitro</i>	Increased IFN- γ >> increased IL-4 Reduced IL-10	
Spontaneous cytokine release in duodenal biopsy samples		Increased IFN- γ , IL-4, and IL-10, decreased TGF- β
Intestinal cytokine mRNA expression		Decreased IL-2 and IL-18 in the duodenum Increased CCR-4 and IL-6 in the terminal ileum Decreased TGF- β 1 in the epithelium and lamina propria

pathologic and immunologic features of food protein-induced enteropathy.

Iron-deficiency anemia

Infants with cow's milk-protein-induced occult rectal bleeding, anemia, hypoproteinemia, and respiratory signs were originally reported by Wilson *et al.* in 1962 [118]. Symptoms manifested between 2 and 20 months of age, frequently following the transition from breast-feeding or formula to regular cow's milk. Hypoproteinemia was caused by increased intestinal protein leakage, but malabsorption and growth retardation were absent [119]. Subsequently, cow's milk-induced anemia and hypoproteinemia were reported in 1 in 7000 infants in a large prospective study from Scandinavia [120].

Whole cow's milk was associated with iron depletion in a large proportion (27%) of infants from 4 to 12 months, mostly attributable to reduced iron absorption [121]. Heat treatment of pasteurized cow's milk reduced the incidence of occult fecal blood loss from 40% to less than 10% in 6-month-old infants, whereas feeding with humanized cow's milk-based formula completely prevented fecal blood loss [122]. Pathophysiology of this disorder is unknown; the limited biopsy data reveal minimal lymphocytic infiltrates and cytotoxicity, and no significant increase in local antibody synthesis [123].

Pulmonary hemosiderosis has been reported in children with cow's milk-induced anemia and respiratory symptoms of chronic cough, hemoptysis, recurrent lung infiltrates, wheezing, and persistent rhinitis [124–130]. Recently, a single case of buckwheat-induced hemosiderosis and melena was described [131]. Respiratory symptoms and anemia resolved upon elimination of the offending food and relapsed following oral challenge. Iron-laden macrophages were recovered from bronchial or gastric washings or at lung biopsy. Prick skin tests and serum food-specific IgE levels were negative but high titers of serum milk and buckwheat precipitins were reported. Increased lymphoproliferative responses of PBMCs upon stimulation with buckwheat flour were observed in one patient with buckwheat-induced pulmonary hemosiderosis [132]. Biopsy specimens of the lung revealed deposits of IgG, IgA, and complement components, without evidence of IgE [128]. Pulmonary symptoms tend to be persistent, with relapses described in 6- and 8-year olds but the natural history of food protein-induced pulmonary hemosiderosis is unknown. Considering the seriousness of pulmonary hemorrhage, diagnostic OFCs must be done with extreme caution under close physician supervision in the hospital setting and *only* when potential benefits outweigh the risks, such as identification of an offending food in a patient with ongoing symptoms or determination of tolerance after a long period of food avoidance without accidental reactions.

Conclusion

Food protein-induced enterocolitis, enteropathy, and anemia in infants and children have been reviewed. Invariably, they respond well to strict dietary elimination of the offending food protein. Most are outgrown within 3 years of life but subtle enteropathy in school-age children and adults with symptoms of delayed food allergy is being increasingly recognized. In addition, occasional cases of FPIES persisting into the teenage years are being seen. Considering the increasing prevalence of allergic disease in general, as well as food hypersensitivities specifically, one may anticipate increasing frequency of these disorders [133,134]. As more insight into the pathophysiology of these disorders is gained, non-invasive diagnostic tests may become available. Heightened awareness and increased attention should lead to early, accurate diagnosis and management.

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