

Food Protein-Induced Enterocolitis Syndrome: Consensus Recommendations for Diagnosis and Treatment

Japanese Research Group for Neonatal, Infantile Allergic Disorders

Ichiro Nomura, Mitsuaki Kimura, Tetsuya Takamasu, Akihiko Terada, Manabu Takenaka, Misa Watanabe, Hiroaki Hoshina, Toshio Katsunuma, Komei Ito, Izumi Kimoto, Shin-ichi Hosokawa, Norikazu Ohtsuka, Arata Isozaki, Tetsuo Syouda, Kaori Mishina, Masashi Kondo, Tatsuki Fukuie, Hiroko Watanabe, Susumu Manki, Akemi Manki, Yukihiro Ohya, Akira Akasawa, Katsuhiko Arai, Satsuki Kakiuchi, Naoki Ito, Yushi Ito, Hideaki Morita, Kenji Matsumoto, Jun Abe and Hirohisa Saito.

Contact; Ichiro Nomura, MD, PhD.

Division of Allergy, National Center for Child Health and Development,

Okura 2-10-1, Setagayaku, Tokyo, Japan, Zip 157-8535

Phone; +81-3-3416-0181, Fax; +81-3-3416-2222

e-mail; nomura-i@ncchd.go.jp

Revised: September 27, 2008

Introduction

In Japan, the number of reported cases of food protein-induced enterocolitis syndrome (FPIES) has increased dramatically since 1995. FPIES occurs in neonates and infants after drinking milk or breast milk. Gastrointestinal symptoms such as vomiting and diarrhea are common, but some patients may only show nonspecific symptoms, including decreased suckling and lethargy. IgE is not generally required for the pathogenesis, and the absence of detection of milk-specific IgE antibodies often makes diagnosis difficult. If diagnosis and treatment of FPIES are delayed, ileus and impaired development can occur. Therefore, the Food Protein-Induced Enterocolitis Syndrome Research Group has established guidelines to enable prompt diagnosis and treatment of FPIES.

FPIES Diagnosis and Treatment Guidelines

Diagnosis and treatment are divided into 5 steps:

Step 1: Suspicion of FPIES based on symptoms

Step 2: Differential diagnosis from other disorders based on laboratory data

Step 3: Switch to therapeutic milk

Step 4: Verify body weight gain

Step 5: Challenge test to confirm diagnosis and start weaning.

Step 1. Suspicion of FPIES based on symptoms

FPIES should be suspected in neonates and infants who after starting milk develop lethargy, abdominal distension, vomiting, bilious vomiting, decreased oral intake, diarrhea, or bloody stools. (In a child only with bloody stools who otherwise appears healthy, the term “food protein-induced proctocolitis” is used. This is a less urgent condition to be described later.)

Step 2. Differential diagnosis from other disorders based on laboratory examinations

Evaluation should include blood tests (blood count, differential, clotting parameters), biochemical screening, blood gases, complement, CRP, total IgE, milk-specific IgE), stool mucous cytology, stool culture, ova and parasites, imaging studies, and if necessary, colonoscopy and tissue biopsy, to differentiate FPIES from the following disorders.

Necrotizing enterocolitis	Meckel’s diverticulum
Bacterial enteritis	Volvulus
Pseudomembranous colitis	Intussusception
Hemolytic uremic syndrome	Pyloric stenosis
Parasitic disease	Hirschsprung's disease
Lactose intolerance	Crohn’s disease
Neonatal melena	Ulcerative colitis

FPIES is characterized by the following findings, but clinical diagnosis is often difficult. In many cases, treatment (change in nutrition) should be started before the establishment of a diagnosis, and symptoms and signs should be monitored for improvement.

- (a) Elevated values on a high quality lymphocyte stimulation test.
- (b) Clumps of eosinophils on fecal examination.
- (c) Increased eosinophils on intestinal mucosal biopsy (≥ 20 per field; 400 x)
- (d) Peripheral eosinophilia.
- (e) Milk-specific IgE antibody (33.8% positive rate at FPIES onset).¹⁰

If (a), (b), or (c) are positive, this is “highly suspicious.” If (a), (b), and (c) are all negative, or not performed, but both (d) and (e) are positive, this is also “highly suspicious.” If either (d) or (e) is positive, this is “suspicious.” If (d) and (e) are both negative, this is “slightly suspicious.”

Step 3. Switch to therapeutic milk

If FPIES is suspected based on the above findings, the child should be switched to therapeutic milk. If FPIES is the correct diagnosis, symptoms will often rapidly resolve. If cow’s milk causes symptoms, breast feeding is possible. If breast milk causes

symptoms, select hydrolyzed milk or amino acid milk. When inflammation is chronic, symptoms may persist for several weeks, and steroid therapy may be required. Allergic symptoms have also been reported with hydrolyzed milk. Therefore, in severe FPIES, starting with amino acid milk is a reasonable option. If breast feeding is possible, mothers can restrict their own intake of milk products and nurse infants for 1 week to see what effect this has on symptoms.

Step 4. Verify body weight gain

With a switch to breast milk, hydrolyzed milk, or amino acid milk, symptoms should resolve promptly, and weight gain should be observed in every month.

Step 5. Challenge test to confirm diagnosis and start weaning (baby food)

At age 5 to 7 months (may be earlier in some cases), a milk tolerance test is performed to confirm the diagnosis. If symptoms were severe at onset, hospitalization of the infant is advisable. Parental or guardian consent is necessary to perform tolerance test. Prick test and specific IgE test are done beforehand in order to assess the risk of type I allergy. Challenge test is performed over 1 week. (Example) For regular milk, gradually increase: Monday 5 mL, Tuesday 10 mL, Wednesday 20 mL, Thursday 40 mL, Friday 80 mL, Saturday 80 mL, and Sunday 80 mL.

Evaluate the following:

- Symptoms of vomiting, diarrhea, bloody stools, fever, and rashes (symptoms are most sensitive).
- Before and after blood tests for peripheral eosinophils and CRP (low sensitivity).
- Stool eosinophils before and after challenge (low sensitivity).

In addition, infants with FPIES may also have allergies to rice, soybeans, and wheat. Challenge test should also be performed to identify these potential allergens, which are usually found in the home.

History

Bloody stools in infants after cow's milk ingestion, with symptom resolution after the milk is stopped, was first reported in 1949. Gryboski later reported similar findings in 21 patients. During the 1970s and 1980s, Powell et al. coined the term "food protein-induced enterocolitis of infancy," which is currently used in Western countries. Powell et al. also established diagnostic criteria based on development of peripheral neutrophilia after a milk challenge test. Some twenty years later, the same criteria are being used, but updates and revisions are needed.

In Japan, the number of reported cases has increased dramatically since 1995, but guidelines for diagnosis and treatment do not exist. Thus, clinical management is basically left to the discretion of each medical institution.

Epidemiology

No statistically controlled studies have been reported to date. The National Center for Child Health and Development estimates an annual incidence of 1000 new cases of FPIES in Japan.

Pathogenesis of FPIES⁹

Allergic reactions are broadly divided into immediate-type reactions mediated by specific IgE antibodies and nonimmediate-type reactions not mediated by IgE. The most well known type of milk allergy is an immediate-type response mediated by IgE with symptoms such as urticaria, dyspnea, and vomiting. Mixed types involving both immediate and nonimmediate reactions with symptoms of eczema also occur. FPIES is generally a nonimmediate-type allergic reaction. The exact pathophysiologic mechanism is not known, but cellular immunity, namely, antigen presenting cells, allergen specific lymphocytes, eosinophils, and epithelial cells, plays an important role.

Possible fetal sensitization

About one half of infants develop symptoms 1 to 7 days after birth and ingestion of cow's milk.¹⁰ Sensitization usually takes a minimum of 10 days to develop. This suggests the possibility of fetal sensitization in FPIES. T cells can recognize 6 peptides as a foreign body, and milk protein fragments of this size can cross the placenta and cause sensitization.

This has led some to believe that restricting milk products in pregnant women is beneficial, but this is incorrect. Despite even very limited ingestion of milk products during pregnancy, there is no preventive effect because many infants still develop FPIES. In fact, the lack of induction of immune tolerance may have an adverse effect.

Of course, there are also many infants who first become sensitized after birth.

Symptoms

Data collected by our research group¹⁰ shows that 86.5% of FPIES patients have at least one of the following symptoms: vomiting, bloody stools, or diarrhea. However, 12.4% only had nonspecific symptoms, including poor weight gain and not doing well.

The incidence of each symptom was: vomiting 58.4%, bilious vomiting 24.7%, bloody stools 51.7%, diarrhea 27.0%, abdominal distension 36%, poor weight gain 24.7%, apneic episodes 4.5%, fever 5.6%, and rash 10.1%.

Food-protein induced proctocolitis (discussed later), characterized by bloody stools only, but an otherwise healthy appearance, was diagnosed in 6.7% of cases.

Severe FPIES is diagnosed based on the following symptoms.

- <1> Frequent vomiting
- <2> Low blood pressure
- <3> Apneic episodes
- <4> Acidosis
- <5> Ileus

<6> Poor weight gain

<7> Other severe symptoms

One or more of the above suggests severe FPIES. These infants should be hospitalized when the food-challenge test is performed.

Complications

Complications of FPIES include ileus, shock, and impaired development. Intestinal perforation has also been reported. But in neonates, hypoxemia, circulation failure, and necrotizing enterocolitis can occur from another pathogenic mechanism. It is difficult to conclude that allergy is the cause of these severe complications. Therefore, doctors must be very careful when assessing such problems.

Prognosis

In the absence of severe ileus and impaired development, the prognosis is usually good. Most patients acquire tolerance by age 2 years, although intolerance persists in some until age 3.

Laboratory findings

Effective laboratory tests only when GI symptoms such as vomiting and bloody stools are present.

1. Peripheral eosinophils¹⁰

Peripheral eosinophil counts (as percent total cells) are elevated in about one half of patients at initial diagnosis, with values $\geq 20\%$. However, 21% of patients have normal eosinophils counts $< 5\%$. Eosinophilia may persist for a while after milk has been discontinued. Although not very specific, eosinophilia is an important clue in diagnosing FPIES.

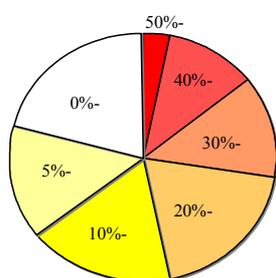


Figure: Peripheral eosinophils; initial diagnosis, maximum values in each patient.¹⁰

2. CRP¹⁰

Strongly positive CRP values ≥ 5 are present in 6.7% of patients, and 37.1% have a positive CRP ≥ 0.5 . This may be mistaken for bacterial infections. This differs from the traditional concept of allergic inflammatory diseases. Strong expression of TNF-alpha in inflamed intestinal tissue may be a reason for elevated values. On the other hand, CRP is negative in 58.4% of cases.

3. Acidosis occurs in some cases.

4. Mucus stool eosinophils

Cytological examination of stool mucus usually shows cluster of eosinophils and Charcot-Leyden crystals. This has high diagnostic value, but technique can affect the results, and positivity rates vary in different reports. The most important point is to obtain a mucous part of the stool.

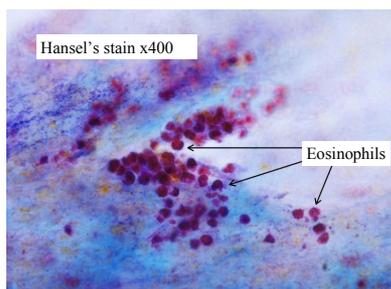


Fig. Cluster of eosinophils in stool mucous of the FPIES

According to a report from Chiba University, some eosinophils can also be seen in normal babies in the first month after birth. Therefore, “cluster” of many eosinophils is an important clue in diagnosis. Samples of mucus stool should be thinly smeared on microscope slides. These are rapidly dried and stained with Wright’s or Giemsa’s stain for microscopic examination of eosinophils. If staining is not performed immediately, the sample slides should be stored in a bottle of methanol.

5. Imaging studies

Evaluation with plain abdominal x-rays, ultrasound, CT, upper and lower GI series, and scintigraphy have been reported. Intestinal dilation is a common but nonspecific finding. Case reports include necrotizing enterocolitis based on intestinal wall gas on plain abdominal x-rays, gastric rupture suspected from pneumoperitoneum and diagnosed on emergency laparotomy, and gastric inflammation only noticed on gallium scintigraphy.

6. Intestinal mucosal biopsy

Intestinal mucosal biopsy shows extensive eosinophilic infiltration. Although not investigated on a global basis, we believe this study is useful given the large number of eosinophils on fecal examination. Histologic examination of the mucosa shows large numbers of eosinophils (≥ 20 per field; 400 x). The presence of eosinophilic degranulation is a helpful finding. Colonoscopy in premature and newborn infants should be performed by an experienced physician. However, examination of the colonic mucosa may miss the diagnosis if only the stomach and/or small bowel are involved.

Effective tests even after symptom resolution

7. Milk specific IgE

FPIES is a delayed type allergic reaction (cell-mediated, non-IgE)⁹, so the absence of milk-specific IgE does not rule out the diagnosis. However, milk-specific IgE is positive in 33.8% of cases (\geq class 1) on initial diagnosis,¹⁰ and in about 90% of cases sometime during the clinical course. On the other hand, milk-specific IgE is detectable in some normal newborns, so further investigation is needed to determine its usefulness in the diagnosis of FPIES.

8. Milk-specific lymphocyte stimulation responses reflect underlying pathology and may be highly useful.

9. Challenge test¹⁰

At 5 to 7 months of age, before weaning, challenge test for milk should be done to

confirm FPIES. Challenge test for allergic reactions to rice, soybeans, and wheat is also recommended. Before challenge test, a prick test (or patch test) and measurement of serum specific IgE should be performed to predict and avoid a possible severe reaction. In patients with a severe onset of symptoms, hospitalization for test is mandatory. A heparin lock is placed to secure a parenteral route of administration, and milk is ingested over about 1 hour. The amount used for challenge is gradually increased, for example, from Monday to Friday. Samples may be collected before and after completion of challenge test to measure blood count, CRP, peripheral eosinophils, and stool eosinophils. Test is considered positive if <1> symptoms such as vomiting, diarrhea, bloody stools, eczema, or fever develops and if <2> CRP and stool eosinophils are positive (those examinations are less sensitive than symptoms). Recommended (final) amounts of test foods are: rice (gruel 30 g), soybeans (tofu 30 g or soy milk 50 mL), wheat (udon paste 30 g) and milk (regular milk 50 mL). Increase the amount of each food gradually. (Examples) For regular milk: Monday 5 mL, Tuesday 10 mL, Wednesday 20 mL, Thursday 40 mL, Friday 80 mL, Saturday 80 mL, and Sunday 80 mL. For rice: Monday 5 g, Tuesday 10 g, Wednesday 20 g, Thursday 30 g, and Friday to Sunday 30 g.

In patients with a mild onset of symptoms, challenge test need not be performed in a hospital setting. Test for rice, soybeans, and wheat may be performed at home. Each test food should be gradually increased to the amounts indicated above, including the same final amount for several days. The absence of symptoms within 7 to 10 days is evidence of acquired tolerance. Patients should be carefully monitored during this time for any severe symptoms such as vomiting, bloody stools, or loss of appetite.

Some infants may outgrow this disorder by age 5 to 6 months, and challenge tests may become negative during this time. In these patients, the diagnosis cannot be confirmed.

Challenge test during the neonatal period can also be performed if there is an adequate interval after symptom resolution. Care must be taken to avoid complications like intestinal perforation.

Points to consider in differential diagnosis

Necrotizing enterocolitis

This mainly occurs in low birth weight infants and is commonly associated with failure to thrive, bloody stools, and abdominal bloating. Abdominal x-rays often show pneumatosis intestinalis.

Bacterial enteritis

Symptoms include fever, bloody diarrhea, and failure to thrive. Blood tests reveal inflammatory changes. Stool cultures are necessary to identify the causative organism.

Pseudomembranous colitis

Colitis develops due to antibiotics, with symptoms of watery or bloody diarrhea. A history of antibiotic use within the previous 3 months may suggest the diagnosis. Failure to thrive, leukocytosis, and an elevated CRP are common. Detection rates of *Clostridium difficile* (CD) in stool cultures are usually low. The identification of CD toxin in stool is diagnostic. CD colonization can occur in infants, so diagnosis is based on the clinical picture. Colonoscopy may be useful in suspected cases.

Lactose intolerance

Diarrhea, vomiting, and abdominal distension after lactose ingestion occur due to lactase deficiency. Bloody stools do not occur. Transient development due to damage of small intestinal villi associated with gastroenteritis can occur. The medical history is important in the diagnosis. A breath test performed after lactose ingestion is useful in confirming the diagnosis. Symptoms improve with a lactose-free diet.

Neonatal melena

Upper gastrointestinal bleeding may occur with hematemesis and tarry stools. Patients should be evaluated for clotting abnormalities such as vitamin K deficiency and a bleeding tendency. Treatment consists of nasogastric tube placement and identification of the bleeding site.

Hemolytic uremic syndrome

This is characterized by hemolytic anemia, thrombocytopenia, and renal failure after an episode of bacterial enteritis. Stool cultures often reveal pathogens such as *E. coli* O-157 and *Shigella*.

Meckel's diverticulum

This is characterized by painless passage of relatively copious amounts of reddish-brown to maroon colored stools. Meckel's scintigraphy can be useful in diagnosis.

Volvulus

Volvulus must be considered in infants with failure to thrive and bilious vomiting. Abdominal x-rays show abnormal gas patterns. Abdominal ultrasound and an upper GI series are also useful in diagnosis. Urgent surgical consultation is necessary.

Intussusception

Intussusception is characterized by intermittent abdominal pain, vomiting, and

jelly-like stools, but the combination of all these symptoms is rarely present. Ultrasound typically reveals a target sign. A barium enema is performed for the treatment and diagnosis.

Pyloric stenosis

Severe nonbilious vomiting is common, and arterial blood gases show hypochloremic metabolic alkalosis. Ultrasound typically reveals thickening of the pyloric muscle (≥ 4 mm).

Hirschsprung's disease

Symptoms include vomiting and bloody diarrhea due to enteritis. Infants presenting with enteritis have a poorer prognosis, and antibiotics should be started as soon as possible (including coverage of *Clostridium difficile*). A history of dyschezia (difficulty defecating) in a neonate is an important clue. The diagnosis is confirmed by rectal biopsy, which shows a marked reduction in the number of ganglion cells. Abdominal x-rays and a barium enema are also useful in differential diagnosis.

Other related disorders

Food protein-induced proctocolitis (allergic colitis)

The term proctocolitis refers to inflammation of both the colon and rectum. Unlike FPIES, which also involves the small bowel, inflammation in food protein-induced proctocolitis is limited to the large bowel. Bloody stools are the only symptom; there is no malabsorption. This is a less urgent condition. Treatment consists of removing the offending food allergen.

Allergic eosinophilic gastroenteritis (AEG)

The diagnostic criteria set forth by the American Academy of Allergy, Asthma, and Immunology (AAAAI) for AEG includes detection of milk-specific IgE antibody. The pathogenesis involves a combination of IgE, mast cells, and cellular immunity. EGE can affect all age groups. Debate still exists whether AEG differs substantially from FPIES.

Treatment

Definitive diagnosis is difficult when infants are still symptomatic. If FPIES is suspected, start treatment first and monitor changes in symptoms. Challenge test to confirm the diagnosis should be deferred until after symptoms have resolved and weight gain is restored.

If symptoms are severe, stop all feeding and begin intravenous fluids. After symptoms have subsided, feeding can be resumed.

Three types of milk are used for treatment.

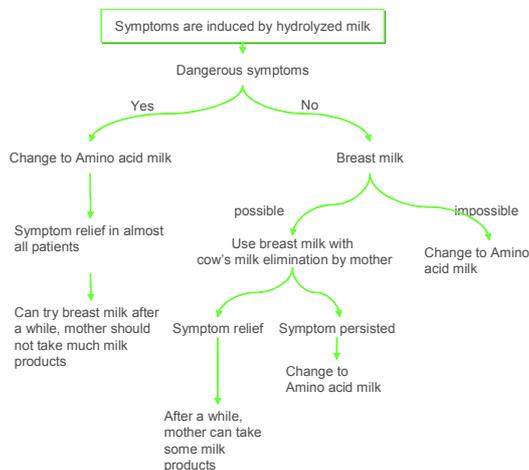
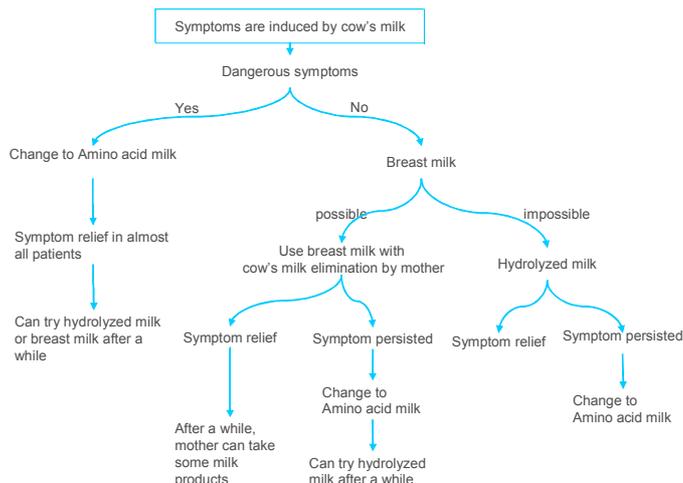
<1> Breast milk: This is the most preferable because it is rich in nutrients such

as taurine. In addition, infants ingest small amounts of food antigen through breast milk, which helps to induce immune tolerance in Peyer's patches of the small intestine. This may prevent the development of other food allergies. However, in infants with allergic reactions to very small amounts of antigen, breast milk may not be suitable.

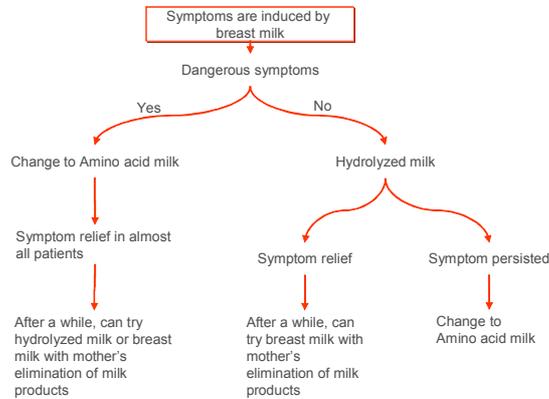
<2> Hydrolyzed milk: Formulas such as MA-1 are available. But in infants with allergic reactions to very small amounts of cow's milk antigen, hydrolyzed milk may not be suitable.

<3> Amino acid milk: Elental P and other elemental formulas are effective in almost all infants. However, some nutritional factors are lacking, so from the standpoint of development and growth, this is less than ideal.

If the cause is cow's milk, then breast milk or hydrolyzed milk like MA-1 can be selected. When symptoms are severe, mothers may breast feed infants if they limit their own intake of milk products. However, caution is required, because about 20% of infants will have recurrent symptoms with breast milk or hydrolyzed milk. In these cases, use amino acid milk.



If the cause is breast milk, then hydrolyzed milk or amino acid milk must be given.



For Elental P and other elemental formulas, begin at a 10% concentration and gradually increase to 17%. Even with hydrolyzed milk, recurrent symptoms sometimes occur, so caution is required.

When amino acid milk alone is used, sufficient amounts of biotin, selenium, carnitine, choline, and iodine are lacking. Oral supplements of biotin and selenium should be given. Requirements for the other 3 are currently under investigation.

In Japan, provisional recommendations for biotin are 10 µg/day in early infancy and 15 µg/day in late infancy. Elental P contains biotin, eliminating the need for supplements.

The NRC (United States National Research Council) recommendations are:

Biotin: Early infancy, 35 µg/day; late infancy, 50 µg/day

Selenium: 6 to 8 µg/day

Carnitine: Under consideration

Choline: Under consideration

Iodine: Under consideration

Other

Added fats: Under consideration

Dietary fiber: Under consideration

Lactobacillus: Under consideration

References

1. [Powell GK](#). Food protein-induced enterocolitis of infancy: Differential diagnosis and

management. *Compr Ther*. 1986 Feb;12(2):28-37. (establishment of diagnostic criteria by Powell)

2. [Powell GK](#). Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. *J Pediatr*. 1978 Oct;93(4):553-60. (report of challenge test by Powell)

3. [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 Jan;109(1):150-4. (report of TNF-alpha production by intestinal mucosal epithelium and inflammatory cells in infants with FPIES)

4. [Sicherer SH](#), [Eigenmann PA](#), [Sampson HA](#). Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr*. 1998 Aug;133(2):214-9. (overview of FPIES)

5. [Sicherer SH](#). Food protein-induced enterocolitis syndrome: Clinical perspectives. *J Pediatr Gastroenterol Nutr*. 2000;30 Suppl:S45-9. Review. (overview of FPIES)

6. [Dupont C](#), [Heyman M](#). Food protein-induced enterocolitis syndrome: Laboratory perspectives. *J Pediatr Gastroenterol Nutr*. 2000;30 Suppl:S50-7. Review. (overview of FPIES)

7. [Nowak-Wegrzyn A](#), [Sampson HA](#), [Wood RA](#), [Sicherer SH](#). Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics*. 2003 Apr;111 (4 Pt 1):829-35. (incidence of involvement of foods other than milk)

8. [Shek LP](#), [Bardina L](#), [Castro R](#), [Sampson HA](#), [Beyer K](#). Humoral and cellular responses to cow milk proteins in patients with milk-induced IgE-mediated and non-IgE-mediated disorders. *Allergy*. 2005 Jul;60(7):912-9. (results of humoral immunity and lymphocyte stimulation tests in FPIES)

9. [Sampson HA](#). Update on food allergy. *J Allergy Clin Immunol*. 2004 May;113(5):805-19 (update of food allergy; best overview)

10. Evaluation of 89 patients with food protein-induced enterocolitis syndrome. 4th Meeting of the Food Protein-Induced Enterocolitis Syndrome Research Group. March 30, 2008. Tokyo International Forum.