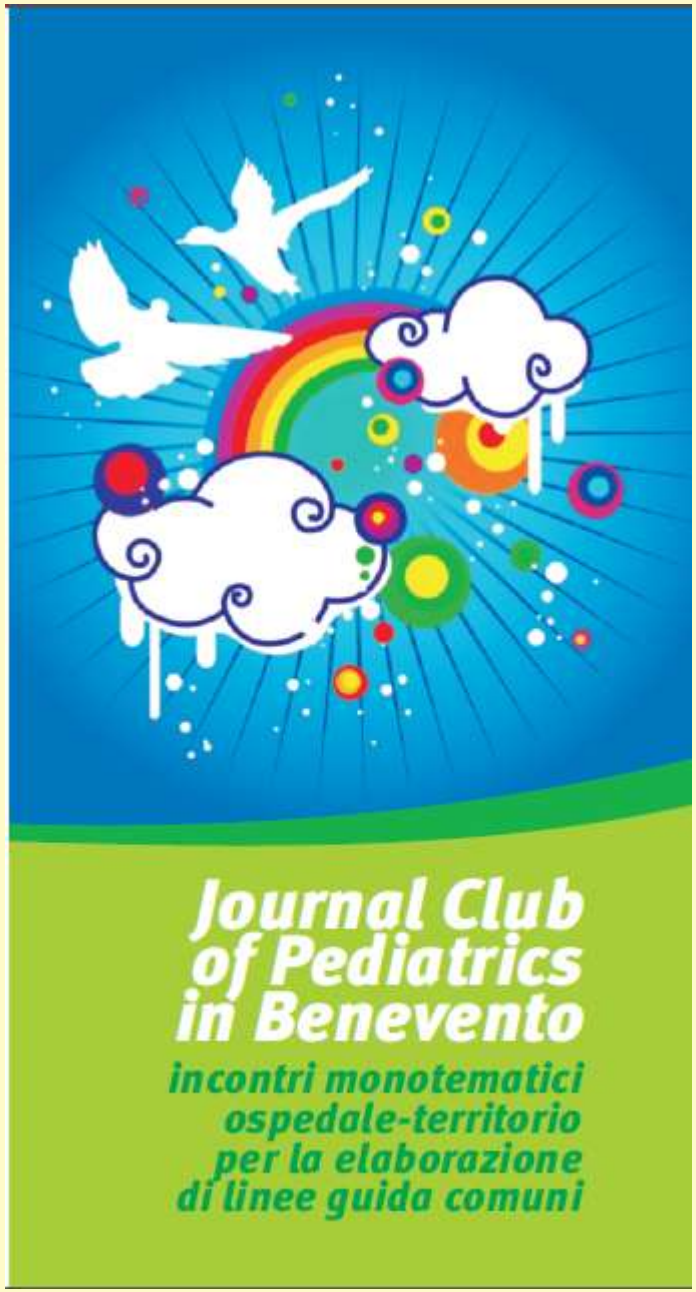
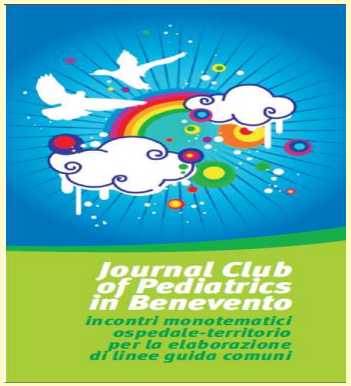


24 Maggio 2014

LE ALLERGIE ALIMENTARI NON IgE-MEDIATE

Iride Dello Iacono

Unità Operativa di Pediatria ed Allergologia
Ospedale Fatebenefratelli
Benevento



FOOD ALLERGY

IgE-mediated reactions

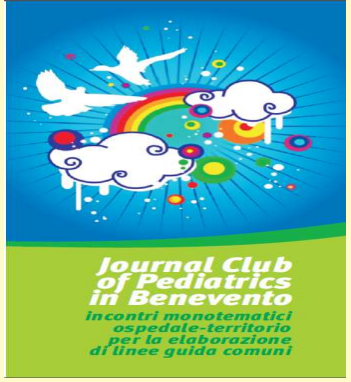
Non IgE-mediated reactions or cell-mediated reactions

Combined IgE and cell-mediated reactions

J Allergy Clin Immunol. 2012 Apr;129(4):906-20. Epub 2012 Feb 23.

ICON: food allergy.

Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA.



FOOD ALLERGY

IgE-mediated reactions

IgE-mediated reactions are characterized by an acute onset of symptoms generally within 2 hours after ingestion of or exposure to the trigger food.

IgE-mediated reactions to foods typically involve the skin, gastrointestinal tract, and respiratory tract.

Allergic sensitization occurs when food-specific IgE (sIgE) antibodies are produced by plasma cells that have differentiated from allergen-specific B lymphocytes.

J Allergy Clin Immunol. 2012 Apr;129(4):906-20. Epub 2012 Feb 23.

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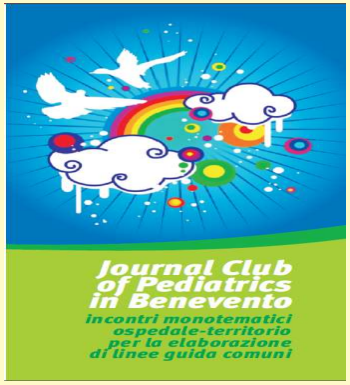

FOOD ALLERGY

IgE-mediated reactions

The sIgE antibodies bind to the surface of tissue mast cells and blood basophils, and on reexposure to the food, antigenic proteins in the food bind to and cross-link these cell surface–bound sIgE antibodies, which triggers the release of symptom-causing mediators, such as histamine and leukotrienes.

J Allergy Clin Immunol. 2012 Apr;129(4):906-20. Epub 2012 Feb 23.

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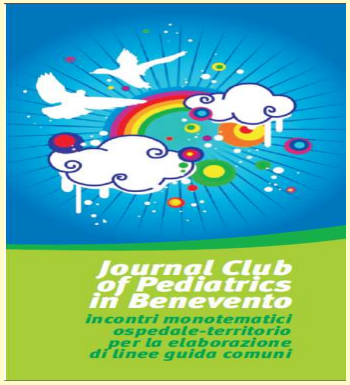
Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA.



FOOD ALLERGY

IgE-mediated reactions

Subjects can have allergic sensitization (production of sIgE) to food allergens <u>without having clinical symptoms of an allergic reaction on exposure.</u>

<u>Thus sensitization alone is not sufficient to define food allergy.</u>

An sIgE-mediated food allergy requires both the presence of sensitization and the development of specific signs and symptoms on exposure to that food.

J Allergy Clin Immunol. 2012 Apr;129(4):906-20. Epub 2012 Feb 23.

ICON: food allergy.

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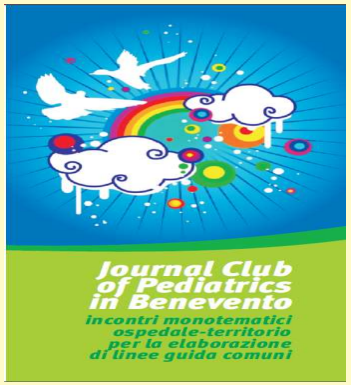
Sensibilizzazione allergica

non equivale ad

ALLERGIA



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Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA.

Specific food-induced allergic conditios

IgE mediated (acute onset)	Acute urticaria/angioedema	Food commonly causes acute (20%) but rarely chronic urticaria.	Primarily "major allergens" (see text)
	Contact urticaria	Direct skin contact results in lesions. Rarely this is due to direct histamine release (nonimmunologic).	Multiple
	Anaphylaxis	Rapidly progressive, multiple organ system reaction can include cardiovascular collapse.	Any but more commonly peanut, tree nuts, shellfish, fish, milk, and egg
	Food-associated, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion is followed temporally by exercise.	Wheat, shellfish, and celery most often described
	Oral allergy syndrome (pollen-associated food allergy syndrome)	Pruritus and mild edema are confined to oral cavity and uncommonly progress beyond the mouth (~7%) and rarely to anaphylaxis (1% to 2%). Might increase after pollen season.	Raw fruit/vegetables; cooked forms tolerated; examples of relationships: birch (apple, peach, pear, carrot), ragweed (melons)
	Immediate gastrointestinal hypersensitivity	Immediate vomiting, pain	Major allergens

FOOD ALLERGY

Non IgE-mediated reactions

Non–IgE-mediated immunologic reactions (eg, cell mediated) include food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes.

These conditions primarily affect infants or young children who present with abdominal complaints, such as vomiting, abdominal cramps, diarrhea, and occasionally blood in the stool and failure to thrive or poor weight gain.

J Allergy Clin Immunol. 2012 Apr;129(4):906-20. Epub 2012 Feb 23.

ICON: food allergy.

Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA.

J Allergy Clin Immunol. 2012 Apr;129(4):906-20. Epub 2012 Feb 23.

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Specific food-induced allergic conditios

Cell mediated (delayed onset/chronic)	Food protein–induced enterocolitis syndrome	Primarily affects infants; chronic exposure: emesis, diarrhea, poor growth, lethargy; re-exposure after restriction: emesis, diarrhea, hypotension (15%) 2 hours after ingestion	Cow's milk, soy, rice, oat, meat
	Food protein–induced allergic proctocolitis	Mucus-laden, bloody stools in infants	Milk (through breast-feeding)
	Allergic contact dermatitis	Often occupational because of chemical moieties, oleoresins. Systemic contact dermatitis is a rare variant because of ingestion	Spices, fruits, vegetables
	Heiner syndrome	Pulmonary infiltrates, failure to thrive, iron deficiency anemia	Cow's milk

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ICON: food allergy.

Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA.

Specific food-induced allergic conditios

Combined IgE and cell mediated (delayed onset/chronic)	Atopic dermatitis	Associated with food allergy in ~35% of children with moderate-to-severe rash	Major allergens, particularly egg, milk
	Eosinophilic esophagitis	Symptoms might include feeding disorders, reflux symptoms, vomiting, dysphagia, and food impaction.	Multiple
	Eosinophilic gastroenteritis	Vary on site(s)/degree of eosinophilic inflammation; might include ascites, weight loss, edema, obstruction	Multiple

Allergo et Immunopathol. 2009;37(1):36-42

ELSEVIER DOYMA

Allergologia et immunopathologia

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REVIEW

Allergic proctocolitis, food-induced enterocolitis: immune mechanisms, diagnosis and treatment

J. Boné[a], Á. Claver[a], I. Guallar[a], A.M. Plaza[b,*]

Table I. Classification of gastrointestinal food hypersensitivity

IgE	→	Non-IgE
Immediate GI hypersensitivity Oral allergy syndrome		
	Eosinophilic allergic esophagitis Eosinophilic allergic gastritis Eosinophilic allergic gastroenterocolitis	
		Enterocolitis induced by proteins Proctocolitis induced by proteins Enteropathy induced by proteins Celiac disease

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J. Boné[a], Á. Claver[a], I. Guallar[a], A.M. Plaza[b,*]

Proctocolitis is characterized by the presence of red blood mixed with the stools in healthy breastfed infants or infants receiving artificial formulas, and subsides after withdrawal of the milk proteins, or upon introducing special formulas (with hydrolysed proteins, or based on amino acids). The underlying mechanism is not known, though IgE is clearly not implicated. Endoscopy is known to show focal or diffuse colitis, with oedema and erosions. The biopsy reveals eosinophil infiltration and occasionally lymphoid nodular hyperplasia.

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REVIEW

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Allergic proctocolitis

Allergic proctocolitis was first described by Rubin[18] in 1940, and subsequently by Gryboski[19,20] in 1966 and 1967. This disorder is characterized by inflammatory alterations of the colon and rectum, secondary to an immune reaction triggered by the ingestion of foreign proteins. The prevalence and natural history of allergic proctocolitis is not clear, though its frequency appears to be increasing in our setting, even in infants who are exclusively breastfed.[21]

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REVIEW

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The clinical picture develops in the first weeks or months of life (neonates and infants between 2 days and 3 months old, and practically always within the first 6 months of life). The symptoms are always gastrointestinal and comprise rectal bleeding, in most cases associated to diarrhoea with mucus — although the stools may also appear normal. Haemorrhage can range from small spots of blood mixed with the stools to abundant bleeding (rectorrhagia). Bloody stools can increase gradually, with the erratic appearance of blood for several days, followed by the presence of blood in most bowel movements, until the causal agent is withdrawn. The general condition of the child is not affected, there is no arrest or loss of body weight, and abdominal palpation reveals no alterations.[10,21,22]

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REVIEW

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The laboratory test results are normal in most infants, though it is possible to detect discrete alterations in the form of anaemia, hypoalbuminaemia or peripheral eosinophilia in isolated cases.

A number of foods have been associated to allergic colitis (soy, fish, egg, wheat, etc.), although cow's milk is implicated in almost all cases. Approximately 60% of all cases of proctocolitis are found in breastfed children.[23-26] The triggering allergens in these cases are CMPs excreted in breast milk after the ingestion of dairy products by the mother. As a rule, the most allergenic protein is β-lactoglobulin.[27] The rest of the affected patients correspond to infants fed formulas containing CMPs or soy. Odze[28] reported that up to 30% of all patients are allergic to both proteins (i.e., CMPs and soy).

Allergo et Immunopathol. 2009;37(1):36-42

ELSEVIER DOYMA

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REVIEW

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J. Boné[a], Á. Claver[a], I. Guallar[a], A.M. Plaza[b,*]

The risk factors for the development of allergic colitis are an immature immune system, altered intestinal permeability and other factors that activate focal immune function, such as genetic susceptibility in combination with particularly sensitising foods (milk, egg, fish, nuts, soy).[26]

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Unfortunately, there are no non-invasive, specific diagnostic tests, and the existing laboratory or biochemical techniques lack the required specificity and sensitivity. Ultrasound is able to evidence thickening of the mucosa. The skin tests and specific IgE titres are negative. The diagnosis is fundamentally based on a detailed case history and patient response to the elimination of suspect proteins from the diet (generally cow's milk), after ruling out other possible explanations for the clinical manifestations such as infection, necrotizing enterocolitis, or anal fissures or invagination. Most cases are diagnosed and treated on an empirical basis. In these children, re-exposure (provocation test) should be contemplated in order to confirm the diagnosis. Xantacos[29] confirmed allergic proctocolitis via endoscopy and biopsy in only 64% of healthy infants consulting for rectal bleeding. Rectosigmoidoscopy and biopsy are not required on a routine basis, provided that the patient responds well to withdrawal of the protein in question. If this is not the case, however, then at least endoscopy must be carried out. The endoscopic findings comprise an oedematous and erythematous mucosa with possible superficial erosions or ulcerations, bleeding and lymphoid nodular hyperplasia. The affected surfaces (particularly descending zones and sigmoid colon) alternate with healthy areas (patched lesions). The histological study of the rectal biopsy reveals an eosinophilic infiltrate in the full thickness of the mucosa and *lamina propria* (over 20 cells per high-magnification field) and, less frequently, cryptic abscesses.[24,26]

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Treatment consists of eliminating the suspect proteins from the diet (generally CMPs). In the case of breastfed infants, if the desire is to maintain breastfeeding, the suppression of dairy products from the maternal diet will gradually resolve the symptoms in most patients. In isolated cases a soy and egg exclusion diet is also needed. If the condition does not begin to subside within 48-72 hours, a hydrolysed protein infant formula should be considered, and if this does not improve the situation then an elemental amino acid-based formula is indicated. In infants fed artificial formulas, the introduction of a special formula is indicated. The recommendation in this case is a hydrolysed protein formula (it should be remembered that 30% of all patients with reactions to CMPs also react to soy proteins), and if this proves ineffective, then an elemental formula (amino acids) is advised.

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These treatment measures are only temporary, since it must be taken into account that proctocolitis is a benign and self-limiting disease in which the infants by one year of age are able to tolerate a free diet, and the long-term prognosis is excellent[30] (Table II).

FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME (FPIES)

- **Enterocolite allergica o *food protein-induced enterocolitis syndrome: un pò di storia……***

- Nel 1940, Rubin descrisse un bambino con severa diarrea ematica responsiva alla dieta priva di LV .

  Rubin M. *Allergic intestinal bleeding in the newborn.* Am J Med Sci 1940;200: 385-7.

- Nel 1967 Grybosky descrisse 21 bambini in cui challenges orali dimostrarono sintomi gastrointestinali associati ad ingestione di LV .

  Gryboski J. *Gastrointestinal milk allergy in infancy.* Pediatrics 1967;40:354-62.

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME (FPIES)

Powell GK.

Milk-and soy-induced enterocolitis in infancy.

J Pediatr 1978;93:553-60

- **Powell propose i seguenti criteri per definire la enterocolite allergica infantile:**

1. **inizio dei sintomi prima dei due mesi di vita**
2. **una risposta positiva al challenge eseguito durante i primi nove mesi di vita**
3. **la cessazione della diarrea con l'eliminazione della proteina sospetta e**
4. **la ricorrenza dei sintomi dopo ingestione della proteina offending.**

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Sicherer SH, Eigenmann PA, Sampson HA.

Clinical features of food protein-induced enterocolitis syndrome.

J Pediatr 1998:133:214-9.

Nel 1998 Sicherer puntualizzò le caratteristiche cliniche della enterocolite allergica in una review di 16 pazienti e definì la sindrome *Food protein induced enterocolitis syndrome (FPIES),*

***ampliando* i criteri iniziali proposti da Powell e includendo pazienti che avevano un'età superiore ai 2 mesi al momento della diagnosi.**

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Segni tipici di FPIES secondo Sicherer:

- età inferiore ai 9 mesi alla diagnosi iniziale;
- la ripetuta esposizione all'alimento incriminato suscitava diarrea e/o vomito ripetuto entro 24 ore senza nessuna altra causa dei sintomi;
- non vi erano sintomi, oltre a quelli gastrointestinali, provocati dall'alimento incriminato;
- la rimozione delle proteine offending dalla dieta comportava la risoluzione dei sintomi;
- un challenge orale standardizzato provocava diarrea e/o vomito entro 24 ore dalla somministrazione dell'alimento;
- se monitorato durante un challenge, un aumento della conta assoluta di neutrofili al di sopra di 3550/mm^3 a 5 ed 8 ore dal challenge costituiva un segno evidente addizionale di una risposta positiva.

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Tipicamente i soggetti descritti da Sicherer erano negativi alla ricerca delle IgEs nei confronti degli alimenti offending (principalmente LV e soia).

Sei ulteriori soggetti, che soddisfacevano i criteri clinici di FPIES, ma che avevano più di 9 mesi di età alla diagnosi o che presentavano anticorpi IgE verso l'alimento incriminato erano considerati avere una **FPIES "atipica".**

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Sono stati segnalati reports di FPIES che rispondevano ai criteri clinici,

in cui i bambini mostravano IgE nei confronti delle proteine causali, sia alla presentazione che durante il follow-up.

Questi bambini avevano un decorso più prolungato dell'allergia, non potendosi escludere la progressione verso reazioni tipiche che riflettono la sensibilità IgE-mediata.

Sicherer ritiene, pertanto, prudente che, nel seguire il decorso della FPIES, si includa lo screening delle IgE per gli alimenti sospetti.

Scott H, Sicherer. *Food protein-induced enterocolitis syndrome: case presentations and management lessons. J Allergy Clin Immunol* 2005;115:149-56.

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

PATOGENESI

Recenti studi hanno evidenziato il ruolo delle cellule T e l'importanza del *tumor necrosis factor (TNF)-α nella patogenesi dell'affezione.*

Heyman et al. hanno dimostrato che l'α-interferon, secreto da cellule T proteinospecifiche nei confronti del LV, è in grado di incrementare la permeabilità intestinale, contribuendo, in tal modo, al passaggio di antigeni nella sottomucosa, con successiva attivazione di linfociti antigene-specifici.

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.**

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

PATOGENESI

Si è, infine, ipotizzato, un deficit di risposta di β-*transforming growth factor (TGF),* fattore citochino-regolatore, che agisce nella protezione della barriera epiteliale dell'intestino dalla penetrazione di antigeni estranei, accanto ad una eccitata risposta α-TNF, nella patogenesi immunitaria della malattia.

Chung HL, Hwang JB, Park JJ, Kim SG. ***Expression of transforming growth factor beta1, transforming growth factor type i and ii receptors, and tnf-alfa in the mucosa of the small intestine in infants with foodprotein-induced enterocolitis syndrome. J Allergy*** **Clin Immunol 2002;109;150-4.**

REVIEW

OPEN

CURRENT OPINION

Definition, etiology, and diagnosis of food protein-induced enterocolitis syndrome

Elizabeth Feuille and Anna Nowak-Węgrzyn

Curr Opin Allergy Clin Immunol 2014, 14:222–228

Table 1. Studies that investigated T-cell responses in food protein-induced enterocolitis syndrome and non-IgE-mediated food allergy

Study	Findings
Van Sickle *et al.* [32]	In children with confirmed FPIES, peripheral blood mononuclear cell (PBMC) stimulation by the causal antigen induced greater cell proliferation than in children with negative oral food challenge
Hoffman *et al.* [33]	Higher lymphocyte proliferative response in affected children was observed, but the stimulation index was not significantly different compared with the control group
Heyman *et al.* [34]	The high level of TNF-α released by antigen-specific T cells acts synergistically with IFN-γ to increase intestinal permeability. This may contribute to the influx of antigens into the submucosa with further activation of antigen-specific T cells
Benlounes *et al.* [35]	Intact rather than intestinally processed proteins stimulate PBMC to release TNF-α. The threshold for PBMC reactivity to milk antigens decreases considerably during active cow's milk allergy with intestinal symptoms compared with patients whose sensitivity resolved or with those with skin rather than intestinal manifestation of cow's milk hypersensitivity. In-vitro kinetic studies differed in these groups, with those having active disease showing two peaks in TNF-α elaboration. The second peak occurred after 5 days of culture
Chung *et al.* [36]	There was higher staining for TNF-α in infants with FPIES and with villous atrophy compared with those without villous atrophy, and with the control group. Type 1, but not type 2, receptor for TGF-β was decreased in duodenal biopsy specimens in FPIES patients compared with controls
Mori *et al.* [37]	In a case of FPIES to rice, authors described an increase in IL-4 and decrease in IFN-γ expression in T cells after a positive oral challenge with rice. After the patient had acquired tolerance, there was an increase in IL-10 expression in $CD3^+$ cells, as well as an increase in IFN-γ before and after the challenge
Karlsson *et al.* [38]	Children outgrowing non-IgE-mediated hypersensitivity to cow's milk following a period of dairy-free diet were compared to children with active non-IgE-mediated hypersensitivity to cow's milk protein. The results revealed a higher frequency of circulating $CD4^+CD25^+$ Treg cells specific for cow's milk protein in children outgrowing non-IgE-mediated hypersensitivity to cow's milk protein. The suppressive action of cow's milk-specific Treg cells was exerted partly by direct cell–cell contact and partly by production of TGF-β

Guidelines for the Diagnosis and Management of Food Allergy in the United States

National Institute of Allergy and Infectious Diseases

2010

DIAGNOSIS

The NIAID Food Allergy Guidelines recommend using the medical history and OFC to establish a diagnosis of FPIES . However, when history indicates that infants or children have experienced hypotensive episodes or multiple reactions to the same food, a diagnosis may be based on a convincing history and absence of symptoms when the causative food is eliminated from the diet.

The original diagnostic criteria as proposed by Powell
were as follows:
- exposure to the incriminating food elicits repetitive vomiting and/or diarrhea within 4 h, without any other cause for the symptoms;
- symptoms are limited to the gastrointestinal tract;
-avoidance of the offending protein from the diet results in resolution of symptoms;
- a standardized OFC or isolated reexposure elicits the typical symptoms

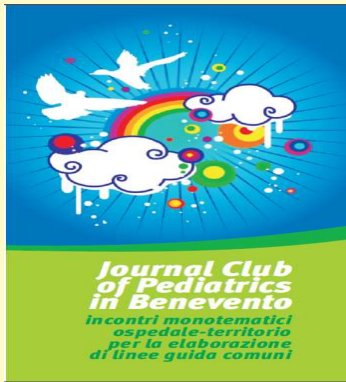
Expert Rev Clin Immunol. 2013 Aug;9(8):707-15. doi: 10.1586/1744666X.2013.814418.

Food protein-induced enterocolitis syndrome, from practice to theory.

Miceli Sopo S[1], Greco M, Monaco S, Tripodi S, Calvani M.

In a review published in 2013, Miceli Sopo et al. proposed criteria to aid the clinician in diagnosis, which include the following:

- less than 2 years of age at first presentation (not mandatory);
-exposure to trigger food elicits repetitive vomiting, pallor, and lethargy within 2–4 h, and usually last less than 6 h;
- absence of symptoms that suggest an IgE-mediated reaction;
- avoidance of offending protein from the diet results in resolution of symptoms;
- recurrence of typical symptoms within 2–4h of reexposure.



DIAGNOSI DI FPIES

La FPIES infantile è una diagnosi clinica

- **Non sono, infatti, riportati studi in cui biopsie intestinali siano state eseguite unicamente per questa diagnosi.**
- **Tuttavia, in alcuni case reports di soggetti che rispondevano ai criteri clinici di una FPIES, biopsie del colon effettuate in pazienti sintomatici, hanno rivelato ascessi criptici ed un diffuso infiltrato cellulare infiammatorio con predominanti plasmacellule; biopsie intestinali del piccolo intestino, hanno mostrato edema, infiammazione acuta e lieve insulto sui villi.**
- **In alcuni casi,sono state descritte una gastrite erosiva focale ed una esofagite con una predominante eosinofilia.**

Goldman H, et al. Allergic proctitis and gastroenteritis in children. Am J Surg Pathol 1986;10:75-86

DIAGNOSI DI FPIES

La FPIES infantile è una diagnosi clinica

Murray e Christie hanno riportato sei bambini che si sono presentati con acidosi, metaemoglobinemia e con cianosi evidente clinicamente su circa 17 FPIES.

La metaemoglobinemia si ipotizzava fosse il risultato dell'incremento della eme-ossidazione, causata da una elevazione di nitriti nell'intestino per la ridotta attività catalasica durante l'infi ammazione

Murray K, Christie D. ***Dietary protein intolerance in infants with transient methemoglobinemia and diarrhea. J Pediatr 1993;122:90-2.***

ORAL FOOD CHALLENGE IN FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

The OFC remains the gold standard for an initial diagnosis of FPIES as well as for monitoring the resolution of FPIES.

Table 2. Oral food challenge in food protein-induced enterocolitis syndrome

Basic requirements	Physician supervision
	Secure intravenous (i.v.) access
	Immediate availability of fluid resuscitation
Baseline laboratory tests	Peripheral neutrophil count (CBC with differential)
Challenge administration	Food amount is calculated as 0.06–0.6 g/kg body weight in three equal doses, generally not to exceed total 3 g protein or 10 g of total food (100 ml of liquid) for an initial feeding[a]
	Food is divided in three equal portions and fed over 30 min if food-specific IgE is negative
	Modification of the challenge and more incremental dosing is used for patients with positive food-specific IgE

ORAL FOOD CHALLENGE IN FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

The OFC remains the gold standard for an initial diagnosis of FPIES as well as for monitoring the resolution of FPIES.

Table 2. Oral food challenge in food protein-induced enterocolitis syndrome

Treatment of the reaction	Fluid resuscitation: 20 ml/kg i.v. boluses of 0.9% sodium chloride (NaCl)
	Steroids: methylprednisolone 1 mg/kg IV, max 60–80 mg
	A majority (>50%) of positive challenges require treatment with i.v. fluids and steroids
	The role of intravenous ondansetron in the management of acute FPIES reactions is being currently evaluated
	Epinephrine and antihistamines are not effective in FPIES
Postchallenge laboratory tests	Peripheral neutrophil count (CBC with differential): at 6 h if the patient reacted or at discharge if the patients tolerated the challenge
	If stool sample available: test for occult blood and stool smear for leukocytes
Postchallenge observation	About 6 h after the resolution of symptoms or 4 h after feeding in case of no symptoms

ORAL FOOD CHALLENGE IN FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

The OFC remains the gold standard for an initial diagnosis of FPIES as well as for monitoring the resolution of FPIES.

Table 3. Interpretation of the food protein-induced enterocolitis syndrome oral food challenge results

Symptoms	1. Emesis (onset 1–3 h)
	2. Diarrhea (onset 2–10 h, mean 5 h)
Laboratory	3. Elevated neutrophil count (>3500 cells/ml, peaks at 6 h)
	4. Fecal leukocytes
	5. Fecal eosinophils
Positive challenge	Three of five criteria met
Equivocal challenge	Two of five criteria met

Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

Ann Allergy Asthma Immunol. 2011;107:95–101.

MANAGEMENT

Management of FPIES consists of removing the offending food from the diet

For infants, exclusively breastfeeding can be protective.

If this is not possible or the infant is exclusively formula-fed, casein hydrolysate-based formulais recommended due to frequent concomitant cow's milk and soy FPIES

Rarely, amino acid formula or, in severe cases, intravenous fluids are need

Fiocchi et al. Italian Journal of Pediatrics 2011, 37:53
http://www.ijponline.net/content/37/1/53

ITALIAN JOURNAL OF PEDIATRICS

COMMENTARY Open Access

DRACMA one year after: Which changes have occurred in diagnosis and treatment of CMA in Italy?

Alessandro Fiocchi[1*], Holger Schunemann[2], Luigi Terracciano[1], Marco Albarini[1], Alberto Martelli[1], Massimo Landi[3], Enrico Compalati[4] and Giorgio Walter Canonica[4]

Table 1 Reference Guide to the Recommendations [14]

Clinical presentation	1st choice	2nd choice	3rd choice
Anaphylaxis	AAF+	eHF#§	SF
Acute urticaria or angioedema	eHF§♭	AAF^/SF°	
Atopic dermatitis	eHF§♭	AAF^/SF°	
Immediate gastrointestinal allergy	eHF§♭	AAF^/SF°	
Allergic eosinophilic oesophagitis	AAF		
Gastroesophageal reflux disease (GERD)	eHF♭	AAF	
Cow's milk protein-induced enteropathy	eHF§♭	AAF	
Food protein-induced enterocolitis syndrome (FPIES)	eHF*	AAF	
CM protein-induced gastroenteritis and proctocolitis	eHF♭	AAF	
Severe irritability (colic)	eHF♭	AAF	
Constipation	eHF♭	AAF	Donkey milkX
Milk-induced chronic pulmonary disease (Heiner's syndrome) **	AAF^	eHF	SF

La storia di Giulia

Giulia, 4 mesi, viene condotta in PS per la comparsa di stato letargico ed ipotonia generalizzata insorti dopo vomito a getto, profuso.

La piccola, secondogenita, nata a termine da PS, con PN di Kg 3.200, si è regolarmente accresciuta, con esclusivo allattamento al seno.

Da qualche giorno assume integrazione con LVA, che non sembra gradire molto

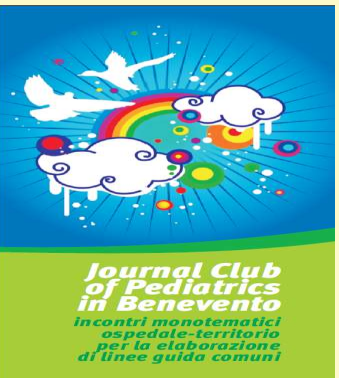
La storia di Giulia

Quali ipotesi diagnostiche possiamo fare

di fronte ad una storia come questa?

La storia di Giulia

Poco prima del ricovero Giulia ha presentato 3 episodi di vomito a getto, seguiti da sonnolenza, insorti dopo circa tre ore dal pasto abituale di LM integrato con LVA (60 ml) e, in pochi minuti, è diventata sempre meno reattiva; per tale motivo è stata condotta in PS.



La storia di Giulia

L'esame clinico mostra una bambina compromessa nello stato generale: colorito cutaneo grigiastro, estremità fredde, lieve cianosi periorale, tempo di Refil > 2 secondi, FC = 160', PA = 50/20; iporeattività, ipotonia generalizzata.

Il nostro orientamento è per un quadro settico.

Si incannula una vena periferica e vengono eseguite indagini ematologiche e colturali in urgenza.
Frattanto si inizia ad infondere soluzione fisiologica alla dose di 20 ml/Kg PC in ½ ora + Flebocortid: 10 mg/kg PC e.v. per combattere lo shock.

La storia di Giulia

Perviene immediatamente l'EAB che evidenzia un quadro di acidosi metabolica: pH = 7,25, BE= -8 mmol/l, glicemia= 60 mg/dl; Na+= 124 mmol/l; K+= 6 mmol/l.

L'Emocromo rivela una leucocitosi neutrofila: G.B. = 22.000 con 70% di neutrofili, PCR = 1,2 mg/dl.

Il sospetto di una sepsi sembra confermato ed iniziamo terapia con Ceftriaxone e.v.

La storia di Giulia

Dopo circa un'ora dall'arrivo in PS, già solo con l'infusione di fluidi ed il trattamento cortisonico, Giulia si mostra più reattiva, anche se persiste pianto sofferente. La PA è 70/50, il colorito cutaneo appare meno grigiastro; frattanto, tuttavia, inizia a mostrare una distensione addominale con ipertimpanismo.

Esplorazione rettale negativa, con fuoriuscita solo di feci liquide e maleodoranti. Nelle 3 ore successive lo stato generale della piccola migliora e, gradatamente, ritorna alla normale reattività, sebbene persista il pianto sofferente ed un addome disteso.

L'EAB a tre ore: pH = 7,32 con BE = -6 mmol/L; Na+=132 mmol/l; glicemia = 80 mg/dl. Dopo sei ore dall'ingresso Giulia presenta una evacuazione abbondante, acquosa con emissione di una discreta quantità di sangue, gelatina di ribes.

La storia di Giulia

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La storia di Giulia

Cosa avreste fatto a questo punto?

La storia di Giulia

In urgenza, nel sospetto di invaginazione intestinale, si esegue ecografia addome: negativa.

Dopo 12 ore deciso miglioramento delle condizioni generali, colorito cutaneo roseo, normale reattività, EAB: pH = 7,35; BE = -2 mmol/l ; Na+= 135 mmol/l.

Giulia, nelle successive 12 ore, presenta ancora tre evacuazioni liquide, la prima con muco striato di sangue, le altre due senza sangue evidente.

Si effettua esame citologico del muco fecale che evidenzia granulociti eosinofili e neutrofili.

La storia di Giulia

Quali ulteriori esami avreste eseguito?

La storia di Giulia

SPT per lattoalbumina, beta-lattoglobulina e caseina sono negativi.

Prick by Prick LV: negativo

IgEs per LV < 0,35 KUA/L.

Si conferma l'orientamento di una sepsi a partenza gastrointestinale.

La storia di Giulia

Voi avreste ipotizzato altre patologie con questa storia clinica e con le indagini laboratoristiche e strumentali in nostro possesso?

La storia di Giulia

Dopo 24 ore Giulia riprende un'alimentazione con Nutramigen (per prudenza) e presenta pieno recupero delle condizioni generali.

Dopo qualche giorno dimettiamo la piccola con il consiglio di effettuare, dopo 6 settimane, TPO con latte formulato, ma ci scontriamo con il rifiuto della madre, la quale è, comunque, convinta che tutta la sintomatologia sia stata una conseguenza dell'alimentazione con LVA ; lei ritiene, infatti, che sua figlia, questo alimento, non lo abbia mai ben tollerato.

La storia di Giulia

Considerate giusta la scelta di dimettere la bambina con idrolisato di proteine del LV pur non avendo posto diagnosi di APLV?

La storia di Giulia

.

Giulia, pertanto, si dimette con Nutramigen e non presenta più alcuna manifestazione clinicamente importante.

Viene svezzata secondo le indicazioni del pediatra curante senza problemi, inserendo nella dieta tutti i cibi solidi e continuando solo alimentazione priva di latte e derivati.

La storia di Giulia

Avreste effettuato un TPO a Giulia, dopo sei settimane di dieta?

La storia di Giulia

.

A 15 mesi effettua TPO presso la nostra Unità Operativa volto a valutare una eventuale acquisita tolleranza.

Si somministra LV alla dose di 0,6 g/Kg PC, in tre dosi frazionate, in 60 minuti.

Dopo 2 ore dall'ultima somministrazione Giulia presenta vomito a getto, sonnolenza ed ipotensione. Viene trattata con fluidi e.v e cortisonici. Dopo circa sei ore diarrea muco-ematica con presenza di eosinofili nel muco fecale. Resterà a ricovero per due giorni.

La storia di Giulia

Food Protein-Induced Enterocolitis Syndrome

o

Enterocolite Allergica.

IL CASO DI AKRAM

- 9 mesi, accesso in DEA per la comparsa di

  VOMITI ripetuti (9 episodi)

  DIARREA, numerose scariche

  insorti dopo circa 3 ore dal pasto (LM + LA)

IL CASO DI AKRAM

- anamnesi familiare: positiva per atopia
- anamnesi personale:

  PS a 39 W, PN 3.770 g, Apgar 9/10

  LM esclusivo dalla nascita, divezzamento a 6 mesi

  età di 9 mesi: integrazione LA per riduzione LM

- 3 ore dopo il primo pasto con LM + LA (50 ml): vomiti ripetuti
- dopo 5 ore: persistono i vomiti, compare la diarrea

IL CASO DI AKRAM

- in DEA:
  - lieve iporeattività
  - cute rosea, non segni di disidratazione
  - T 36°7 C
  - FC 137', satO2 in AA: 99%

- terapia infusiva EV (SF 40 ml/h)
- esami ematochimici urgenti

IL CASO DI AKRAM

EGA: modesta acidosi metabolica
(PH 7.34, BE -5.7 mmol/l, $HCO3^-$ 19.1 mmol/l)
Na+ 130 mmol/l glicemia 74 mg/dl

EMOCROMO: leucocitosi neutrofila, piastrinosi
(WBC 24510, PMN 63.8%; PLTs 577000)

PCR: nella norma

graduale ripresa della reattività dopo infusione EV

si ricovera in osservazione

IL CASO DI AKRAM

- in OB:

  rapida normalizzazione condizioni generali

  ancora 3 evacuazioni diarroiche

  non più vomiti *(a 2 ore dall'arrivo in DEA)*

proseguita infusione

EGA e Na+ normalizzatisi dopo 24 ore

diarrea cessata *(dopo 48 ore dall'arrivo in DEA)*

pasti regolari con LM

IL CASO DI AKRAM

- dopo 48 ore dal ricovero in OB:

  DIMISSIONE (diagnosi: GASTROENTERITE)

- raccomandazioni:

  LM esclusivo per alcuni giorni

  graduale integrazione con LA; fermenti lattici

IL CASO DI AKRAM

DA FEBBRAIO 2009 A LUGLIO 2009

ALTRI 10 EPISODI ANALOGHI

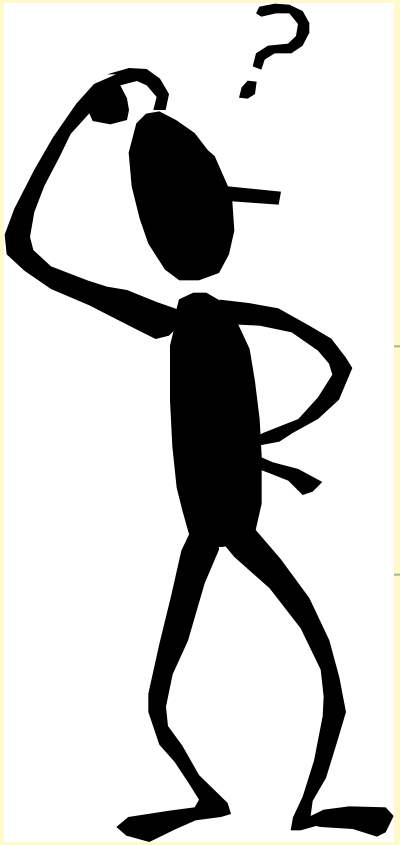
SEMPRE 3-4 ORE DOPO

L'ASSUNZIONE DI LATTE VACCINO O DERIVATI

SEMPRE CON ACCESSO IN DEA

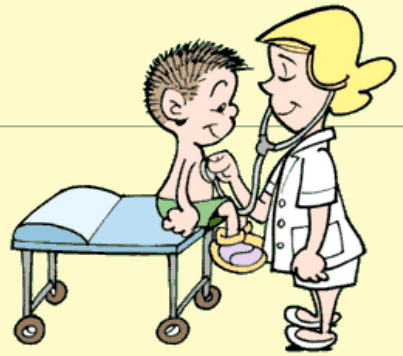
E DIAGNOSI DI GASTROENTERITE

IL CASO DI AKRAM



finché…

IL CASO DI AKRAM: LA DIAGNOSI



- età 14 mesi:
  - ultimo accesso in DEA
  - raccolta anamnesi accurata
  - richiesto ricovero per sospetta APLV

- in reparto:
  - ripresa dell'alimentazione (LM + Nutramigen)
  - SPT e PbP per proteine del latte: NEGATIVI
  - APT per latte: POSITIVI +++

IL CASO DI AKRAM

- si decide per TPO con latte vaccino

  dose: 0.6 g/Kg, in tre dosi frazionate, in 60 minuti

- dopo aver bevuto 75 ml di LV

  RIFIUTO A PROSEGUIRE l'assunzione

- a 3 ore dall'ultima dose:

  DIARREA (1 scarica, feci lievemente sfatte)

  nelle ore successive il bambino sta bene, beve il LM

IL CASO DI AKRAM

- il giorno successivo riprende il TPO

- dopo aver bevuto 10 ml di LV

  RIFIUTO A PROSEGUIRE l'assunzione

- a 3 ore dall'ultima dose:

  VOMITI A GETTO, profusi (6 episodi)

IL CASO DI AKRAM

- a 5 ore dall'ultima dose:

  DIARREA (2 episodi)

EGA: modesta acidosi metabolica

(PH 7.33, BE -4 mmol/l, $HCO3^-$ 20.6 mmol/l)

Na+ 137 mmol/l

EMOCROMO: leucocitosi neutrofila

(WBC 15340, PMN 68.4%; PLTs 437000)

- terapia infusiva EV

  SF 20 ml/Kg in 30’

  idrocortisone 10 mg/Kg

pronta risposta alla terapia

EGA e Na+ normalizzatisi dopo 4 ore

pasti regolari con LM

IL CASO DI AKRAM

DIAGNOSI:

Food Protein- Induced Enterocolitis Syndrome
alias
Enterocolite Allergica

da allergia alle proteine del latte vaccino

The prevalence and natural course of food protein–induced enterocolitis syndrome to cow's milk: A large-scale, prospective population-based study

Yitzhak Katz, MD,[a,b] Michael R. Goldberg, MD, PhD,[a] Nelly Rajuan, MSc,[b] Adi Cohen, MD,[a] and Moshe Leshno, MD, PhD[c] *Zerifin and Tel Aviv, Israel*

J Allergy Clin Immunol 2011;127:647-53

Methods: In a prospective study the feeding history of 13,019 infants was obtained. Infants with probable adverse reactions to cow's milk protein (CMP) were clinically examined, skin prick tested, and challenged orally. Diagnostic criteria for CMP-induced FPIES included age less than 9 months, delayed recurrent vomiting (usually with nausea), and lethargy after exposure to CMP in the absence of other IgE-mediated symptoms, such as rash, urticaria, and respiratory symptoms. In addition, a positive challenge response to milk resulted in the above-mentioned gastrointestinal symptoms, removal of milk from the diet resulted in the resolution of those symptoms, or both.

The prevalence and natural course of food protein–induced enterocolitis syndrome to cow's milk: A large-scale, prospective population-based study

Yitzhak Katz, MD,[a,b] Michael R. Goldberg, MD, PhD,[a] Nelly Rajuan, MSc,[b] Adi Cohen, MD,[a] and Moshe Leshno, MD, PhD[c] *Zerifin and Tel Aviv, Israel*

Results: Ninety-eight percent of the cohort participated in the study. The cumulative incidence for FPIES was 0.34% (44/13,019 patients). The most common symptoms were recurrent vomiting (100%), lethargy (77%) diarrhea (25%), pallor (14%), and bloody diarrhea (4.5%). All patients had FPIES within the first 6 months of life. By the age of 3 years, 90% of the patients had recovered. We did not detect any concomitant reaction to soy. Eight patients with FPIES had IgE-mediated cow's milk allergy (IgE-CMA).
Conclusions: The prevalence of FPIES is significant, and its clinical presentation is distinct from that of IgE-CMA. Most patients with FPIES recover, although a proportion might convert to IgE-CMA. The likelihood for a cross-reactivity to soy in this population was less than previously estimated. (J Allergy Clin Immunol 2011;127:647-53.)

Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

Table 1. Clinical Features of Food Protein–Induced Enterocolitis Syndrome

Chronic	Acute
Symptoms	*Symptoms*
Intermittent, chronic emesis	Repetitive emesis onset 1–3 hours after ingestion
Chronic, watery diarrhea with blood/mucus	Diarrhea onset about 5 hours after ingestion
Lethargy	Lethargy
Dehydration	Pallor
Abdominal distension	Dehydration
Weight loss	Hypotension
Failure to thrive	Hypothermia
Laboratory	Abdominal distension
Anemia	*Laboratory*
Hypoalbuminemia	Elevated neutrophil count
Elevated white count: left shift eosinophilia	Thrombocytosis
Metabolic acidosis	Metabolic acidosis
Methemoglobinemia	Methemoglobinemia
Stool-reducing substances	Fecal leukocytes and eosinophils
Radiology	Frank or occult fecal blood
Intramural gas	Increased carbohydrate content in stool
Air-fluid levels	Elevated gastric juice leukocytes

Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

Overall, approximately 75% of infants with FPIES symptoms appear acutely ill, and 15% develop hypotension and require hospitalization.[6] Infants presenting with chronic symptoms usually improve within 3 to 10 days of switching to a casein hydrolysate–based formula with or without temporary intravenous fluids. In our experience from a food allergy referral center, severe chronic FPIES is uncommon nowadays, likely due to ready availability if hypoallergenic formulas. Early introduction of hypoallergenic formula for mild, non-specific gastrointestinal symptoms may prevent the expression of full FPIES. Food reintroduction induces acute symptoms, typically emesis beginning within 1 to 3 hours and diarrhea within 2 to 10 hours (mean onset, 5 hours) of ingestion, with stool containing blood, mucus, sheets of leukocytes and eosinophils, and increased carbohydrate content.[16] Peripheral blood neutrophil counts are usually elevated in patients with positive challenge results and peak at 6 hours. Not all patients with acute reactions develop diarrhea. In a study of 66 acute episodes in 35 children, emesis was present in 100% of episodes, lethargy in 85%, pallor in 67%, diarrhea in 24%, and hypothermia (temperature $<36^{\circ}C$) in 24%.[4]

Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

Acute vomiting, diarrhea, and dehydration may mimic a gastrointestinal viral illness or food poisoning. The absence of fever and sick contacts will be seen in cases of FPIES, although this may also occur in acute viral illness. Often it is the reoccurrence of repetitive emesis hours after ingestion of a particular food that points to food intolerance and not an acute microbial illness. Acute dehydration and lethargy may also mimic sepsis on presentation to an acute care facility.

OPEN

CURRENT OPINION

Epidemiology of food protein-induced enterocolitis syndrome

Sam Mehr[a], Katie Frith[b], and Dianne E. Campbell[a,c]

2014

Whereas earlier studies focused on chronic FPIES , the majority of published series now describe the acute phenotype.

Chronic FPIES may have become a less common entity, because of improved and earlier recognition by pediatricians that cow milk/soy can induce allergic gastrointestinal reactions in newborns and the availability of hydrolyzed formulas for treatment of such presentations.

Based on cases presenting to pediatric allergy outpatients, the yearly prevalence of FPIES in two series was approximately 1% .

Katz et al. were the first to perform a population-based case study.

The prevalence of cow milk FPIES over a 2-year period in this Israeli population was 0.34%.

CURRENT OPINION

Epidemiology of food protein-induced enterocolitis syndrome

Sam Mehr[a], *Katie Frith*[b], *and Dianne E. Campbell*[a,c]

2014

Table 2. Onset of food protein-induced enterocolitis syndrome in months.[a]

Study	All triggers	Cow milk and soy	Solids	Individual solids
Ruffner *et al.* [30▪] (USA)	–	7 (0.7)	12.1 (1.1)	Rice 7.4 (5.1)
				Oats 9.3 (6.2)
				Egg 11.3 (9.6)
				Wheat 11.9 (9.5)
				Chicken 17.6 (12.3)
Nowak-Wegrzyn *et al.* [9] (USA)	–	1 (2 days–12 months)[a]	5.5 (3–7 months)	–
Frith *et al.* [25] (Australia; unpublished data)	6.2 (3.4)	3.8 (2.6)	7.5 (3.3)	Rice 6.3 (3.3)
				Chicken 6.7 (1.3)
				Oats 7.1 (1.4)
				Wheat 7.5 (0.7)
				Fruits 7.8 (3.0)
				Vegetables 9 (2.8)
				Egg 8.4 (2.1)
				Fish 10.9 (3.6)
Mehr *et al.* [29] (Australia)	5.6 (2.7)	4.9 (2.6)	6.1 (1.7)	Rice 5.2 (0.8)[b]
				Oat 5.7 [1]
Sopo *et al.* [31▪] (Italy)	5.7 (5.1)	3.5 (2.4)[c]	10.6 (6.7)	–

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Diagnosi Differenziale (Sampson et al. 2000)

Malattia	Sintomi fondamentali	Segni differenziali da FPIES
Proctite da proteine dietetiche	Feci striate di sangue	Non vomito, usualmente allattati al seno, assenza di sintomi costituzionali
Enteropatia da proteine dietetiche	Diarrea, vomito, edema, perdita di peso	Nessuna reazione acuta con la riesposizione, vomito meno evidente, diarrea non ematica
Reflusso latte-indotto	Vomito	Non sintomi del basso intestino
Gastroenteropatia eosinofila	Dipende dai siti di infiammazione; può includere vomito, ostruzione, sanguinamento gastrico o colico	Più comunemente riguarda alimenti plurimi. Test + per IgE. Nessun inizio acuto dei sintomi gastrointestinali e sistemici

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.

Pediatr Allergy Immunol. 2006 Aug;17(5):351-5.

Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome.

Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM.

- **Atopy Patch test (APT) per la diagnosi di FPIES**

- **Si tratta di uno studio prospettico, non controllato, volto a valutare se l'APT è in grado di predire i risultati del TPO, gold standard della diagnosi di FPIES.**

- **L' APT viene considerato un esame in grado di valutare una reazione di ipersensibilità ritardata, non cutanea.**

- **19 pazienti, di età compresa tra 5 e 30 mesi hanno partecipato allo studio . I pazienti venivano inclusi nello studio se rispondevano ai criteri clinici proposti da Sicherer per la FPIES "tipica".**

Pediatr Allergy Immunol. 2006 Aug;17(5):351-5.

Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome.

Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM.

- **Atopy Patch test (APT) per la diagnosi di FPIES**

- **Entro 2 mesi dall'APT veniva effettuato un challenge orale, non cieco, per accertare se i pazienti avessero FPIES. Durante questi due mesi i pazienti erano istruiti ad evitare tutti gli alimenti che erano positivi all'APT.**

- **I risultati dell'APT e del TPO venivano comparati ed usati per calcolare sensibilità e specificità dell'APT**

Pediatr Allergy Immunol. 2006 Aug;17(5):351-5.

Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome.

Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM.

- ✓ **L'analisi statistica dei risultati di questi 19 pazienti , fece concludere per:**

  - un valore predittivo positivo del 75%,

  -valore predittivo negativo del 100%

  -sensibilità del 100%

  -specificità del 71%

✓Qualora in studi ulteriori, standardizzando l'esecuzione del test, tali risultati dovessero essere riconfermati, 'APT sembrerebbe essere un esame diagnostico promettente per la diagnosi di FPIES.

Ann Allergy Asthma Immunol. 2012 September ; 109(3): 221–222. doi:10.1016/j.anai.2012.06.020.

Poor utility of atopy patch test in predicting tolerance development in food protein-induced enterocolitis syndrome

Kirsi M. Järvinen, MD, PhD[*,†], **Jean-Christoph Caubet, MD**[*,‡], **Laura Sickles, BA**[*], **Lara S. Ford, MD, MPH**[*], **Hugh A. Sampson, MD**[*], and **Anna Nowak-Węgrzyn, MD**[*]

In conclusion, APTs to common food allergens have poor utility in the follow-up prediction of outgrowing FPIES in children.

Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

Although OFC is the criterion standard for diagnosis of FPIES, infants do not usually require confirmatory challenges for initial diagnosis if they have a classic history and symptoms resolve after removal of the offending food from their diet. Physician-supervised OFCs are necessary if the history is unclear, and to determine whether FPIES has resolved before a food is reintroduced into the diet.

Quando si acquisisce la tolleranza nella *food protein-induced enterocolitis syndrome da LV o da soia?*

Arch Dis Child. 2009 Jun;94(6):425-8. doi: 10.1136/adc.2008.143289. Epub 2008 Oct 1.

Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome.

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✓ **23 bambini, alimentati con LV o Soia o con alimentazione mista (latte vaccino o soia + LM), ricoverati per vomito e/o diarrea, segni clinici iniziali di perdita di peso, acidosi metabolica, ipoalbuminemia sierica e metaemoglobinemia, sospetti di FPIES .**

✓**Sottoposti a 2 o più TPO, a partire dai 6 mesi, seguiti fino all'età di 2 anni.**

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✓**Gli AA concludono che, nella FPIES, il primo challenge dovrebbe essere eseguito, con la soia, a 6-8 mesi e con il LV ad oltre i 12 mesi di età**

✓**Guarigione in genere entro i primi 2 anni di vita**

LA FPIES E' INDOTTA SOLO DA LV E DA SOIA?

Pediatr Allergy Immunol. 2003 Aug;14(4):325-9.

Food protein-induced enterocolitis syndrome--not only due to cow's milk and soy.

Levy Y, Danon YL.

Pediatrics. 2003 Apr;111(4 Pt 1):829-35.

Food protein-induced enterocolitis syndrome caused by solid food proteins.

Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH.

Allergol Immunopathol (Madr). 2005 Nov-Dec;33(6):312-6.

Food-protein-induced enterocolitis syndrome caused by fish.

Zapatero Remón L, Alonso Lebrero E, Martín Fernández E, Martínez Molero MI.

Arch Dis Child. 2009 Mar;94(3):220-3. doi: 10.1136/adc.2008.145144. Epub 2008 Oct 28.

Rice: a common and severe cause of food protein-induced enterocolitis syndrome.

Mehr SS, Kakakios AM, Kemp AS.

-Riso (n=14)
-Soia (n=12)
-Latte Vaccino (n=7)
-Vegetali e frutta (in totale n=3, di cui 1 reagì alla banana)
-Carni (n=2)
-Avena (n=2)
-Pesce (n=1).

Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

Ann Allergy Asthma Immunol. 2011;107:95–101.

MANAGEMENT

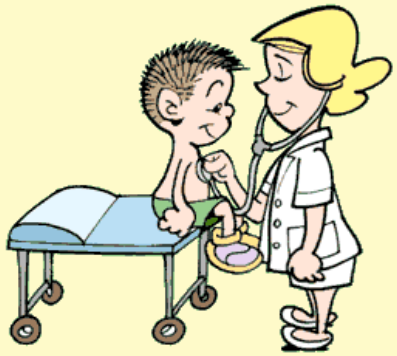
Management of FPIES consists of removing the offending food from the diet. For infants, exclusively breastfeeding can be protective. If this is not possible or the infant is exclusively formula-fed, casein hydrolysate–based formula is recommended due to frequent concomitant cow's milk and soy FPIES. Rarely, amino acid formula or, in severe cases, intravenous fluids are needed. An example of a typical cow's milk and soy FPIES case is presented in Table 4.

Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

An 8-month-old girl was initially breastfed and supplemented with a cow's milk–based formula. From birth she had issues with increased gas and appeared uncomfortable. She also had recurrent vomiting, which typically would occur soon after eating, and intermittent bloody streaks in her stool, which were green in color and often very loose.

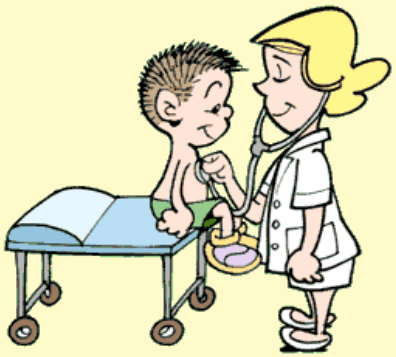
Her symptoms did not improve when a short trial of soy formula was given at 2 weeks of age. At 3 weeks of age she was prescribed ranitidine and formula was changed to a casein hydrolysate–based formula with resolution of vomiting and improvement in her symptoms.



Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

At 4 months of age she was given soy formula and within 1 hour developed repetitive vomiting, became lethargic and pale, and her parents described her as nonresponsive. Emergency services were called, and she was brought to the emergency department, where she was treated with oral rehydration. Her brother had diarrhea around the same time, and it was thought that the infant's symptoms could be secondary to viral gastroenteritis.

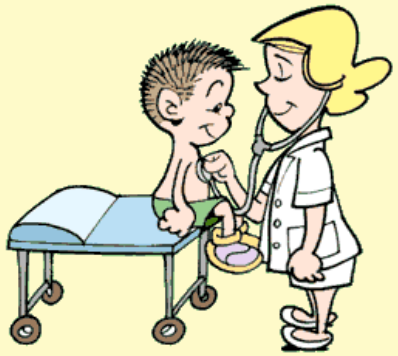


Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

She was seen by an allergist, and food allergy testing was performed. The results of skin testing to milk, soy, and egg were negative at the time, and specific IgE was undetectable to milk, soy, egg, wheat, and peanut. Because of negative test results, an attempt was made to slowly reintroduce soy into her diet at home. She was given a bottle with 1 oz of soy formula and 7 oz of casein hydrolysate–based formula and did not complete the bottle.

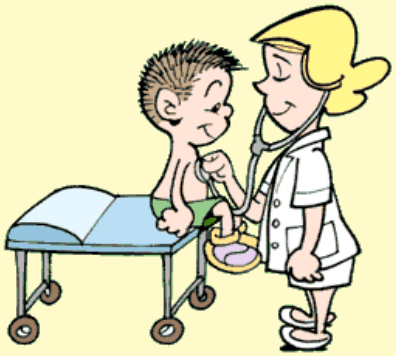
Within 2 hours, she developed repetitive vomiting but was not pale or lethargic and she recovered within 1 hour. She did not have any shortness of breath, rash, or angioedema with any of these reactions.



Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

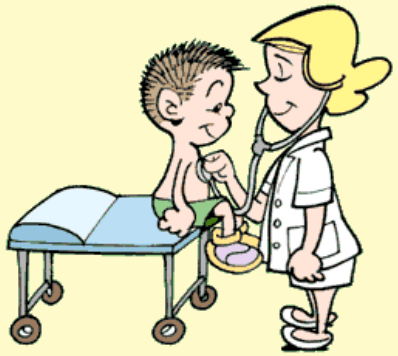
Her diet currently includes hydrolyzed casein formula, grains (rice, wheat and oat), several fruits and vegetables, and chicken.
She has dry patches of skin on her legs at times but has never been diagnosed as having eczema. She has no history of asthma or wheezing. There is a strong family of history of allergy, including cousins with food allergy and eczema, as well as her father with a history of allergic rhinitis.



Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

This infant's history is consistent with milk and soy food protein– induced enterocolitis.
A plan was made to continue with a casein hydrolysate–based formula and avoid soy and milk. A follow-up in 1 year was recommended to consider performing a physician-supervised food challenge to milk or soy at approximately 2 years of age.
This challenge would be done with intravenous access in place and rapid hydration available.



Quando si acquisisce la tolleranza nella *food protein-induced enterocolitis syndrome da LV o da soia?*

Arch Dis Child. 2009 Jun;94(6):425-8. doi: 10.1136/adc.2008.143289. Epub 2008 Oct 1.

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Food protein–induced enterocolitis syndrome: an update on natural history and review of management

Stephanie A. Leonard, MD*; and Anna Nowak-Węgrzyn, MD*

NATURAL HISTORY

Resolution of FPIES appears to be population dependent, particularly for cow's milk and soy. Although in our experience based on a referral allergy population, cow's milk FPIES resolves in approximately 60% by 3 years of age, the Korean cohort showed more than 60% resolution by 10 months of age and the Israeli birth cohort showed 90% resolution by 3 years of age.[3,5,21,24] More striking, in our population we have seen that only 25% of soy FPIES resolves by 3 years of age, whereas in the Korean cohort, more than 90% of children showed resolution of soy FPIES by 10 months of age.[5,24] This difference may be explained by the higher proportion of subjects with detectable food-specific IgE levels and atopic dermatitis who were referred to a major allergy center in our population compared with the Israeli and Korean populations. There are not as many data for resolution of solid food FPIES. In our studies on solid food FPIES, resolution by 3 years of age occurred in 67% for vegetables, 66% for oat, and 40% for rice. Atypical FPIES (associated with food-specific IgE) may be more severe and/or protracted. Because patients initially presenting with or later developing food-specific IgE antibodies are at risk for persistent FPIES, including skin prick testing and/or measurement of serum food-specific IgE levels in the initial and follow-up evaluations is useful.

CASE REPORT | EUR ANN ALLERGY CLIN IMMUNOL | VOL 43, N 1, 00-00, 2011

R. ONESIMO[1], I. DELLO IACONO[2], V. GIORGIO[1], M. G. LIMONGELLI[2], S. MICELI SOPO[1]

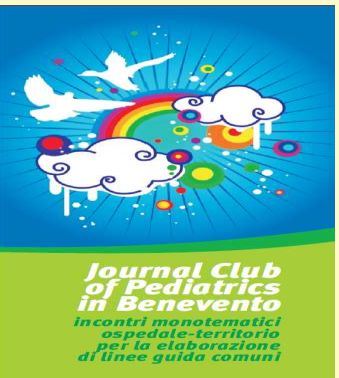
Can food protein induced enterocolitis syndrome shift to immediate gastrointestinal hypersensitivity? A report of two cases

[1]Department of Pediatrics, Catholic University - Rome - E-mail: smicelisopo@rm.unicatt.it
[2]Department of Pediatrics, Fatebenefratelli Hospital - Benevento

FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME

CASO CLINICO

- S. è un secondogenito con anamnesi familiare e personale negativa per malattie allergiche.
- A 40 giorni di vita, per una ipogalattia materna, assume integrazione con formula presentando, la prima volta, vomito a getto **dopo due ore** dall'ingestione di circa 60 ml, senza compromissione dello stato generale e, la seconda volta, vomito profuso ed "abbattimento" dopo circa tre ore dall'introduzione.



FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME

- La Pediatra curante esegue: skin prick test (SPT) con lattalbumina, beta-lattoglobulina e caseina: negativi; prick by prick latte formulato: negativo. Si orienta per una allergia alle proteine del latte vaccino (APLV) non (Ig)E-mediata e pone il piccolo a dieta con latte di soia.
- Dopo sei settimane S. giunge alla nostra osservazione. Si conferma la negatività dei test cutanei e delle IgEs per latte vaccino (LV) e si effettua test di provocazione orale (TPO): 0,3 g di proteine di LV/kg PC in un'ora. **Dopo circa 20 minuti dalla dose bolo, S. presenta vomito profuso e ipotensione lieve, risolti rapidamente con infusione di soluzione fi siologica.**
- Nei giorni successivi presenterà diarrea striata di sangue.

FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME

- Confermiamo il sospetto diagnostico di enterocolite allergica da latte vaccino e prescriviamo prosecuzione della dieta di esclusione dell'alimento.
- S. ritorna alla nostra osservazione dopo 18 mesi per ripetere TPO.
- SPT con lattalbumina e caseina risultano negativi; SPT con beta-lattoglobulina è positivo: **5 mm diametro medio; prick by prick LV fresco positivo: 7 mm; IgEs LV: 10 KUA/l.**

FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME

- Effettua secondo TPO, seguendo lo schema della graduale somministrazione poiché risulta, allo stato attuale, IgE positivo.
- Nessuna manifestazione clinica fino alla dose bolo di 100 ml che evoca, in successione:

- **vomito profuso**
- **edema della glottide**
- **stato letargico e**
- **shock** (pressione arteriosa 50/20). Si somministra adrenalina i.m., cortisonico ed idratazione massiva e.v.

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Prima descrizione in età adulta

J Allergy Clin Immunol. 2012 Nov;130(5):1199-200. doi: 10.1016/j.jaci.2012.06.017. Epub 2012 Jul 24.

Food protein-induced enterocolitis syndrome can occur in adults.

Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A.

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

FPIES TRASMESSA ATTRAVERSO LATTE MATERNO

J Allergy Clin Immunol. 2012 Mar;129(3):873, author reply 873-4. doi: 10.1016/j.jaci.2011.12.1000. Epub 2012 Jan 31.

Food protein-induced enterocolitis syndrome in an exclusively breast-fed infant-an uncommon entity.

Tan J, Campbell D, Mehr S.

J Allergy Clin Immunol. 2011 Mar;127(3):679-80. doi: 10.1016/j.jaci.2010.10.017. Epub 2010 Dec 13.

Food protein-induced enterocolitis syndrome by cow's milk proteins passed through breast milk.

Monti G, Castagno E, Liquori SA, Lupica MM, Tarasco V, Viola S, Tovo PA.

doi: 10.1111/j.1365-2222.2012.04027.x

Clinical & Experimental Allergy, **42**, 1257–1265

ORIGINAL ARTICLE Clinical Allergy

A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes

S. Miceli Sopo[1], V. Giorgio[1], I. Dello Iacono[2], E. Novembre[3], F. Mori[3] and R. Onesimo[1]

[1]*Department of Pediatrics, University of Sacred Heart Agostino Gemelli Rome, Rome, Italy,* [2]*Unit of Paediatrics, Fatebenefratelli Hospital, Benevento, Italy and* [3]*Allergy and Clinical Immunology Unit, Anna Meyer Children's Hospital, Department of Paediatrics, University of Florence, Florence, Italy*

Background Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated paediatric disorder triggered by the ingestion of specific food proteins. Many features of this syndrome are not yet well defined.

Objective The aim of our study was to describe demographic features, causative agents, clinical features, treatments and outcomes of children suffering from acute FPIES at three Italian of Pediatric Allergology Centers.

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Methods A retrospective study was performed over a 7-year period (2004–2010). Hospital medical record databases and hospital outpatient electronic charts were screened for the diagnosis of FPIES. Information on the first and subsequent FPIES' episodes was collected. *Results* We diagnosed 66 children with FPIES. The number of diagnoses significantly increased between 2008 and 2010 ($P < 0.001$). We collected a total of 165 FPIES episodes (median per child 2, range 1–10). Cow's milk was the most common trigger food (65%), followed by fish, egg, rice, soy, corn, poultry and goat's milk. Fifty-six (85%) children reacted to a single food. Mean documented time from ingestion to symptom onset was 2.4 h (SD 0.7 h). Vomiting was the most common symptom (98%). Among patients diagnosed with OFC, 78% reacted after eating a whole serving size of the trigger food per age. Skin prick tests (SPT) for trigger foods were negative in 97% of cases. Thirty-two/66 children (48%) achieved tolerance at a mean age of 29 months (SD 17 months). Age of achieved tolerance for cow's milk was significantly lower compared to that of other foods (24 ± 8 vs. 53 ± 17 months, $P < 0.0006$).

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Conclusion and Clinical Relevance This article provides new insights on FPIES in Italy by describing its largest series, and shows how a significant increase in the FPIES diagnosis has been observed in the last few years. We also discussed selected management aspects of this syndrome where different phenotypes can be found.

REVIEW

OPEN

CURRENT OPINION

Clinical management of food protein-induced enterocolitis syndrome

Stefano Miceli Sopo[a], *Iride Dello Iacono*[b], *Monica Greco*[a], *and Giovanna Monti*[c]

Curr Opin Allergy Clin Immunol 2014, 14:240–245

Curr Opin Allergy Clin Immunol 2014, 14:240–245

CLINICAL CASE NUMBER 1

- When Gabriele was 1 year old, he received a diagnosis of egg-FPIES; he had already experienced three severe acute episodes. Rigorous avoidance of dietary egg was prescribed, and the parents were given an action plan of instructions to be followed in case of accidental egg ingestion; this could be shown to the medical personnel in case of emergency.
- Some months later, Gabriele accidentally ate a small piece of omelet at nursery school, without anyone noticing.

Curr Opin Allergy Clin Immunol 2014, 14:240–245

CLINICAL CASE NUMBER 1

- Two hours later his fourth acute FPIES episod occurred. The child presented with repetitive and profuse vomiting, pallor, and severe lethargy.
- He was immediately taken to the emergency department, where his parents produced the action plan; intravenous fluids and steroids were immediately administered.
- Six hours after the onset of symptoms, he had recovered fully.

Curr Opin Allergy Clin Immunol 2014, 14:240–245

KEY POINTS

- Severe and acute FPIES episodes, such as those that can occur in the case of accidental ingestion of a culprit food, must be treated with intravenous fluids and steroids. Epinephrine usage is debated; ondansetron appears promising, but further studies are required. Mild acute attacks can be resolved with oral rehydration, without drugs.
- Elimination of the culprit food from the baby's diet must be very strict. The same is true of the breast-feeding mother if the relation between breast milk intake and the baby's symptoms is proven. The possibility that processed (baked) offending foods may be tolerated is not yet well established. In the case of fish-FPIES, it is possible that patients tolerate species of fish other than the causative one.
- In the case of cow's milk-FPIES, an OFC to test achievement of tolerance can be performed when the patient is between 18 and 24 months. With regard to FPIES induced by other foods, there is not yet sufficient information; it may be suggested to perform an OFC yearly.

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CLINICAL CASE NUMBER 2

- Carmen suffers from atopic eczema; she has been exclusively breast-fed. From her second month of life she presented frequent episodes of vomiting and diarrhea, sometimes watery; her growth was normal.
- When she was 5 months, she drank 70ml of cow's milk formula; 2 h later she presented with repetitive and profuse vomiting, pallor, lethargy, and watery stools.
- Two hours later the symptoms resolved, and this episode was diagnosed as a viral gastroenteritis.
- After 2 weeks, she again drank 90ml of cow's milk formula, and 2 h later suffered a similar acute episode. After the symptoms had improved, she still had episodes of regurgitation, colic, and occasional diarrhea.

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CLINICAL CASE NUMBER 2

- When Carmen reached the age of 6months, her mother, who was still breast-feeding the baby, exceptionally drank a larger than usual quantity of cow's milk (500 ml) as she had to take a breath test.
- Twelve hours later, Carmen presented with a worsening of her chronic symptoms: increased regurgitation, diarrhea with bloody stools, and colic.
- An allergist now formulated a diagnosis of FPIES and eliminated cow's milk proteins from the diet of both the child and the mother. Gradually, regurgitation, colic, and diarrhea disappeared. Carmen started to eat other foods but, when she ate cream of rice (that does not contain cow's milk), the diarrhea reappeared; this occurred twice, and rice was eliminated from her diet.

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LONG-TERM DIETARY MANAGEMENT AND INTRODUCTION OF AT-RISK FOODS

- Carmen's story clearly exemplifies the chronic FPIES phenotype, which is rare. This case can be considered even rarer, because the culprit food affected her after passing through the breast milk. Although chronic FPIES is less frequent than acute FPIES, its long-term management is very similar: both require the culprit food to be eliminated from the patient's diet, a point on which all experts agree.

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LONG-TERM DIETARY MANAGEMENT AND INTRODUCTION OF AT-RISK FOODS

- Whereas in the case of IgE-mediated food allergies management is moving toward decreasing dietary restrictions, albeit with great caution (e.g. administration of baked milk or egg, ora immunotherapy), and although the current standard of care continues to entail strict avoidance of the food allergen for food allergy patients, in the case of FPIES patients, avoidance of culprit foods is compulsory, and surrounded by little or no doubt.

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LONG-TERM DIETARY MANAGEMENT AND INTRODUCTION OF AT-RISK FOODS

This certainty is due to at least three reasons:

- first, most FPIES patients achieve tolerance spontaneously before their fifth year of life, an important reason making oral immunotherapy less attractive;
- second, for the individual patient, it is difficult to know the minimal dose of culprit food that may cause an adverse reaction; it may even be infinitesimal. This is due to the latency of symptoms; the child can finish the meal before any symptoms appear. It is thus very difficult to formulate an oral immunotherapy program with an initial dose that will almost certainly be tolerated;

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LONG-TERM DIETARY MANAGEMENT AND INTRODUCTION OF AT-RISK FOODS

- third, although the immunopathogenic mechanisms are not as yet fully clear, the most convincing hypothesis assigns an important role to the T lymphocytes and their inflammatory cytokines; this would mean that pathogenic chemical bonds involve sequential peptides that are so small that any heating process, as for example in baking food, will be irrelevant in terms of the immune system's recognition of epitopes.

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LONG-TERM DIETARY MANAGEMENT AND INTRODUCTION OF AT-RISK FOODS

- In the case of cow's milk-FPIES, if breast milk is lacking, the use of an extensively hydrolyzed casein formula is usually recommended, whereas soy milk should be avoided.
- These recommendations were developed on the basis of studies observing some clinical cohorts some years ago in the USA; the studies showed that 50% of children affected by cow's milk-FPIES had adverse reactions to soy.
- More recently, Ruffner et al. confirmed these data in a study likewise conducted on U.S. children. However, Israeli, Italian, and Australian reports have not found the same association between cow's milk-FPIES and soy-FPIES.
- .

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- More recently, Ruffner et al. confirmed these data in a study likewise conducted on U.S. children. However, Israeli, Italian, and Australian reports have not found the same association between cow's milk-FPIES and soy-FPIES.
- Soy milk may thus be considered as a cow's milk substitute, but only after having performed an OFC, to ensure that no adverse events will occur. In rare cases, it may be necessary to use an amino-acid formula.

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Two hypothetical liberalization in the diet

- It has been reported that culprit foods (in particular, cow's milk and hen's egg) may be tolerated if baked; this runs counter to the theory of an exclusively cell-mediated pathogenesis of FPIES, and provides support for a role played by specific IgEs, as has been hypothesized.
- However, very few studies have addressed this point, so that in expectation of further research, the current recommendation is still to avoid culprit food even if baked.
- In this case, too, possible tolerance of baked culprit food should be verified by means of an OFC.

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Two hypothetical liberalization in the diet

- In the case of fish-FPIES, which is the commonest form of solid-food-induced FPIES in Italy, it may not be necessary to eliminate all kinds of fish from the diet.
- Sopo et al. reported that three of eight children who reacted to one or more types of fish tolerated other fish (e.g. tuna, swordfish, salmon).
- It is known that cross-reactivity between species of fish is not absolute in IgE-mediated fish allergy; this may also be true for fish-FPIES.
- Be that as it may, tolerance to other types of fish must
- in all cases be verified via an OFC.

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- **Should a restrictive diet be prescribed to breast-feeding mothers?**

- **Considering the rarity of FPIES passing through breastmilk, the more tolerant approach is currently preferable**

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CONCLUSION

- In 2005, Sicherer [1] wrote: '. . . 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 are pathophysiologically distinct from FPIES or part of a spectrum with a similar cause whose clinical expression varies with environmental influences.' In 2014, we still agree with those conclusions.

MESSAGES

- **La FPIES rappresenta una sindrome non ancora perfettamente conosciuta e ciò spiega il numero elevato di indagini che, abitualmente, vengono eseguite in PS e di diagnosi errate effettuate prima che sia posta la diagnosi corretta.**

- **Si tratta di una diagnosi prevalentemente clinica. I criteri di Sicherer, se soddisfatti, sono in grado di far formulare correttamente la diagnosi.**

CONCLUSIONI

- **Un TPO diagnostico è superfluo nei casi “tipici”, che soddisfino tutti i criteri clinici.**

- **Il TPO, allorquando se ne valuti l’opportunità di esecuzione, va effettuato in ambiente attrezzato e con personale esperto a fronteggiare eventuali gravi reazioni.**

- **L’acquisizione della tolleranza totale verso l’alimento responsabile si verifica nella stragrande maggioranza dei casi**

BENEVENTO

VIII GIORNATA DI ALLERGOLOGIA ED IMMUNOLOGIA PEDIATRICA

20-22 Novembre 2014