Latest insights on Food Protein-Induced Enterocolitis Syndrome: an emerging medical condition

Short title: Latest insights on FPIES

Author: Leticia Vila Sexto, MD, PhD. Pediatric Allergy Department. Children's Hospital Teresa Herrera. La Coruña. Spain.

Address to correspondence:
Leticia Vila Sexto
Pediatric Allergy Department. Children's Hospital Teresa Herrera. La Coruña. Spain.
Xubias s/n 15006. A Coruña, Spain
e-mail: leticia.vila.sexto@sergas.es

Author has no financial or personal relationship which could result in a conflict of interest with regard to the published article.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0192

ABSTRACT

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated gastrointestinal food hypersensitivity, characterized by profuse vomiting, frequently associated to pallor or/and lethargy that appears within 1 to 3 hours after ingestion of the offending food. There is a less frequent chronic form of FPIES, presenting with protracted vomiting, diarrhea or both, accompanied by poor growth.

Although FPIES is considered a rare allergic disorder, in the last few years there have been an increasing number of reports about it indicating if not a real increase in incidence, at least an increased awareness of this condition by pediatricians.

Foods more frequently implicated are CM, soy formula, grains and fish, depending on the different areas of the world. Diagnosis is based on clinical manifestations and it requires a high index of suspicion, since we still lack a diagnostic laboratory tool. Early recognition of FPIES and removal of the offending food are mandatory. Recently international consensus guidelines have been published regarding diagnosis and management. Prognosis is usually good, with most children tolerating foods before 6 years of age.

Key words: FPIES, Food-Induced Enterocolitis, Food Allergy, Ondansetron, Oral Food Challenge, Cow's Milk, Fish.

RESUMEN

La enterocolitis inducida por proteínas de alimentos es un tipo de enfermedad alérgica gastrointestinal no mediada por IgE. Se caracteriza por vómitos profusos, frecuentemente asociados a palidez y/o letargia que aparece 1-3 horas después de la ingesta del alimento al que el paciente se encuentra sensibilizado. Existe otra forma menos frecuente y más larvada o crónica, caracterizada por vómitos persistentes y/o diarrea, asociados a fallo de medro. Aunque se considera una patología alérgica infrecuente, en los últimos años se ha incrementado el número de publicaciones sobre este tema, indicando si no un incremento real en su incidencia, al menos un incremento en el conocimiento que los pediatras y alergólogos tienen sobre esta enfermedad. Los alimentos implicados con mayor frecuencia son leche de vaca, soja, cereales y pescado, dependiendo de las distintas zonas geográficas. El diagnóstico se fundamenta en la clínica y por tanto requiere un alto índice de sospecha, dado que no existe ninguna prueba de laboratorio que sea definitiva. Una vez establecido el diagnóstico, es fundamental retirar el alimento de la dieta. Recientemente ha sido publicado un consenso internacional de expertos, en el que se revisa en profundidad el diagnóstico y tratamiento de la enterocolitis. El pronóstico suele ser bueno, ya que la mayoría de los niños llegan a tolerar el alimento antes de los 6 años.

Palabras clave: FPIES, Enterocolitis Inducida por Alimentos, Alergia Alimentaria, Ondansetron, Prueba de Exposición Controlada Oral, Leche de Vaca, Pescado.

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated gastrointestinal food hypersensitivity, characterized in its acute form by profuse vomiting, frequently associated to pallor or/and lethargy that appears within 1 to 3 hours after ingestion of the offending food. Chronic FPIES presents with protracted vomiting, diarrhea or both, accompanied by poor growth.

We could consider that this is a relatively new condition since first clinical reports are from the late 60s of the last century. In 1967, Gryboski [1] described a series of infants presenting during the first 6 weeks of life with recurrent vomiting, bloody diarrhea, abdominal distension and occasionally dehydration, while being fed with cow's milk-based formula. Patients improved with hydrolyzed casein-based formula and they experienced recurrence of severe emesis 1 to 3 hours after reintroduction of cow's milk-based formula. In 1978, Powell [2] described 9 newborns presenting with projectile vomiting and severe diarrhea after ingestion of cow's milk and soy-based formulas. Patients recovered on a CM and soy free diet and symptoms recurred from 1 to 10 hours during food challenge, confirming the diagnosis. Based on his experience, Powel proposed clinical diagnostic criteria for FPIES and a standard challenge protocol [2] that has been modified over time by other authors.

Epidemiology

Although FPIES is considered a rare allergic disorder, in the last few years there have been an increasing number of reports about it indicating if not a real increase in incidence, at least an increased awareness of this condition by pediatricians.

Large population studies to assess the overall prevalence of FPIES are lacking. Katz et al [3] were the first to perform a population-based case study with more than 13.000 Israeli infants prospectively enrolled. They reported a cumulative incidence of cow's milk (CM) FPIES at 0,34% compared with 0,5% of IgE-mediated CM allergy, diagnosed during the first year of life.

Ludman et al [4] reported an incidence of 0,36% in the UK after performing a retrospective audit of patients presenting to a tertiary London pediatric allergy

doi: 10.18176/jiaci.0192

service. Still in Europe, Sopo et al [5] estimated a prevalence of FPIES around 1% based on cases presenting to the pediatric allergy outpatients clinic in Italy. Recently, an Australia-wide survey undertaken through the Australian Paediatric Surveillance Unit, reports an incidence of FPIES in children less than 2 years of age of 15,4/100.000/y [6].

Although FPIES is considered a pediatric disease, typically presenting during infancy and at some degree during childhood, there are reports of adults, indicating that it may develop at any age [7].
Most case series report a slight male predominance.
Regarding the atopic background, there are differences based on geographical areas. In Europe, specifically in Spain and Italy, up to 20-42,7% of patients report family history of atopy (FHA) [5, 8, 9, 10] while in the United States and Australia, this percentage is higher. In the US, Caubet et al [11] and Nowak-Wegrzyn et al [12] reported 77% and 71% of children with FHA, respectively. In Australia, Mehr et al [6] reported that 57% of children present FHA.
Regarding personal atopic background, eczema has been reported in 9-65% of FPIES subjects, asthma in 6% to 28% and IgE mediated food allergy in 11-34% of patients [5, 8, 9, 10, 12, 13, 14].

Clinical presentation

The first manifestations of FPIES usually develop after the first or second introduction of the offending food into the infant's diet [3, 5, 6, 15], although it is only after a mean of 2 episodes (range 1-6) that the actual diagnosis is finally made [9, 10, 12, 16].
FPIES may present in an acute or chronic form. Acute FPIES is the commonest type and it usually presents in older infants, children and adults after intermittent ingestion of the offending food. It is characterized by profuse, projectile and repetitive emesis frequently accompanied by pallor and lethargy, beginning 1 to 4 hours after food ingestion, although it may develop as soon as half an hour or as late as 6 hours after food intake. Diarrhea may follow within 2 to 10 hours, especially in severe reactions [17, 18]. Stools may contain blood and mucous.

Most common symptoms of acute FPIES are summarized in Table 1.
Chronic FPIES occurs when the culprit food is introduced early in life, usually during the first 4 moths of life, and there is a daily intake. In this form of presentation, CM and soy-based formulas are the most frequently implicated foods. Patients develop intermittent emesis, bloody diarrhea, lethargy, dehydration, abdominal distension, hypoalbuminemia and failure to thrive. Avoidance of the offending food leads to resolution of symptoms in days and reintroduction of the food induces an acute FPIES reaction.
FPIES in exclusively breastfed infants is rare and few cases of CM or soy FPIES in exclusively breastfed infants have been described [6,19-21]. It has been proposed that breast milk may have a protective effect based on the presence of immunoglobulin A, that the food is highly processed and/or that the amount of the food present in breast milk may no be enough to elicit symptoms.

Foods causing FPIES.

CM is the most frequent cause of FPIES along de world. Soy formula is other common trigger of FPIES in the US [11,14], but not in other areas of the world as Europe [5,8,9,22], Australia [6,15] or Israel [3].
Regarding solids, cereals are the principal solid foods causing FPIES in the US (oats and rice) [11,12,14] and Australia (rice) [6,13,24], while in Europe, especially in Spain and Italy, fish is the most reported solid food causing FPIES [4, 5,8,10,22]. A wide variety of foods have also been reported: egg, poultry meat, vegetables (sweet potato, squash, pumpkin, corn, carrots), legumes (green pea, peanut, lentil, kidney bean), fruits (banana, orange, pineapple, apple, tomato, strawberry) [23], mushrooms [25], and even the probiotic Saccharomyces boulardii [2]. Seafood and egg seem to be the main foods eliciting FPIES in adults [7, 27, 28].
Most common food triggers in cohort studies are summarized in Table 2.
Patients with CM and soy FPIES present earlier than those with solid food FPIES, since formulas are introduced before solids in infants' diet.
Threshold doses of foods causing FPIES are usually in the gram range, contrary to IgE-mediated food allergy. However there are children that react to

doi: 10.18176/jiaci.0192

casein in hydrolyzed formula and to CM that passes through breast milk as previously mentioned.

Multiple foods causing FPIES

In the US, Ruffner et al [14] and Caubet et al [11] reported that 43,5% and 35% of CM FPIES respectively also reacted to soy. These observations differ from those made in Israel, Spain, Italy and Australia, where most patients with CM FPIES tolerate soy [3, 5, 6, 8,15]

Regarding the number of foods involved, there are also geographical differences. In the US, Nowak-Wegrzyn [12] reported that 80% of infants reacted to more than one food, being 65% of them previously diagnosed with CM and/or soy FPIES. In Australia and Europe only 7-33% of infants with solid food FPIES reacted to more than one type of food [6,23]. In Spain, we found only 2 patients out of 21 reacting to two different foods and Vazquez et al [8] reported only 1 child out of 81 with FPIES reacting to more than 1 food. Recently, Mehr et al [6] reported that infants with FPIES to grains were likely to have co-associated FPIES to fruits, vegetables or both.

Percentage of patients with FPIES reacting to 2 or more foods are summarized in Table 3.

Differences in FPIES triggers between countries may be explained at least in part by feeding practices. Soy formula is much more commonly used in the US compared to Europe and Australia, and Australian and European feeding guidelines do not recommend the use of soy formula under 6 months of age, whereas American guidelines make no restriction [29].

On the other hand, rice is one of the first solid foods introduced in the infants diet but FPIES caused by rice is reported mainly in Australia and the US, but not in Europe, where fish is the main solid food causing FPIES. Thus, other environmental or genetic factors could be involved in this geographical variability regarding FPIES triggers.

Katz et al [3] and Sopo et al [5] support the theory of different phenotypes of FPIES that would explain differences in food triggers, prevalence of allergic family histories and range of severity of reactions.

Pathophysiology

FPIES is presumed to be caused by protein component of foods, based in the reports by Freier et al [30] and Kuitunen et al [31]. Freier et al [30] observed that 5 out of 6 infants presenting with vomiting related to CM formula reproduced these symptoms after being challenged with isolated beta-lactoglobulin (BLG). One infant reacted only to bovine serum albumin. Also, they described one infant having a severe reaction after being challenged with BLG that had been boiled for 70 minutes and suggested that conformational epitopes do not play a role in FPIES. However, there are patients with CM and egg FPIES that tolerate these foods in baked form [32].

In their study, Kuitunen et al [31] included 54 children with diarrhea and failure to thrive related to CM formula. Eight infants were challenged with CM proteins, being casein and BLG the main ones eliciting clinical manifestations.

The immune mechanisms responsible for FPIES remain unclear. FPIES is considered a T-cell-mediated disorder where ingestion of food allergens cause local inflammation leading to increased intestinal permeability and fluid shift.

Mucosal biopsies from children with enteropathy/FPIES show a number of inflammatory features after food challenge, as increased number of intraepithelial lymphocytes, CD4+T cells and plasma cells producing IgM and IgA [33] as well as clusters of eosinophils [34,35]. Eosinophils and Charcot-Leyden crystals in stool samples have also been reported [36].

Moreover, a reduction in the expression of TGF-β receptor 1 in the intestinal epithelium of children with challenge proven CM-FPIES has been described compared to controls [34]. TGF-β is a cytokine that induces T-cell suppression, promotes B-cell switching to IgA production and preserves epithelial barrier function.

TNF-α is a pro-inflammatory molecule that induces intestinal permeability. Studies *in vitro* have shown that peripheral blood mononuclear cells (PBMC) from children with FPIES produce more TNF-α that those from control subjects [37] or patients that had outgrown FPIES.

González-Delgado et al [37] also demonstrated a higher increased in expression of the HLA-DR molecule in dendritic cells (DC) from patients with fish-induced FPIES in the presence of two different fish extracts, compared to controls.
Recently, Goswami et al [38] found an activation of cells of the innate immune system after food challenge, as monocytes, neutrophils, eosinophils and natural killer cells. This activation was not observed in children who had outgrown FPIES. Also, a global loss of lymphocytes from the peripheral circulation after positive food challenge was observed as well as activation of CD4+, CD8+ and γδ-lymphocytes, probably in response to cytokines and other mediators released during the acute reaction.

Regarding the humoral immune profile, there are contradictory data. Konstantinou et al [39] found significantly lower levels of casein specific IgA, casein specific IgG and casein specific IgG4 in infants with CM FPIES after CM challenge, compared to controls. Caubet et al [40] also reported lower levels of CM and casein- specific IgG and casein specific IgG4 in patients with active CM FPIES versus those patients tolerating CM. Shek et al [41] also observed significantly lower levels of CM-specific IgG4 in patients with CM-FPIES compared to controls. In contrast, McDonald and cols reported an increased in specific IgA and IgG in infants who reacted to CM, egg and soy on food challenge compared to those who tolerated these foods [42].

Interestingly, IL-10 levels have been found to be significantly higher in patients with resolved CM-FPIES, suggesting that IL-10 expression could be associated with the development of tolerance in these patients [40]. Nevertheless, Kimura et al [43] have found rise of serum IL-10 in 2 positive OFC.
An increased in serum IL-8 in patients with positive OFC compared with patients with a negative OFC result has been also reported [40, 43]. IL-8 is a potent chemoattractant of neutrophils from peripheral blood into tissues and it is also secreted by neutrophils. Their finding supports the role of neutrophils in the pathogenesis of FPIES. Also higher casein-specific production of IL-9 was

doi: 10.18176/jiaci.0192

found in children with CM-FPIES compared with children with IgE-CMA. IL-9 may participate in FPIES pathogenesis by increasing intestinal mast cell numbers and influencing intestinal permeability [40].

Recently, increased serum levels of IL-2 and IL-5 were found after positive open food challenge (OFC). IL-2 is a representative Th1 cytokine, while IL-5 is a Th2 cytokine that enhances the proliferation of eosinophils and promotes de development of eosinophilic inflammation in allergic disorders [43].

Furthermore, IL-2 and IL-8 induce fever and increased of CRP. Elevation of both citokynes might explain why some patients show fever after positive OFC [43].

Further studies are needed to elucidate the role of these cytokines in the pathogenesis of FPIES.

Pathologic findings in patients with FPIES are summarized in Table 4.

Diagnosis

Affected infants suffer from 2 to 3 reactions (range 1-10) before FPIES is considered. A mean delay of 12 months for the diagnosis of FPIES has been reported [4]. Diagnosis of FPIES especially to solid foods, can be challenging and it is often delayed probably due to a low index of suspicion, absence of a diagnostic tests and the fact that many culprit foods are traditionally not considered allergenic, as vegetables, rice or poultry meat.

Evolution of clinical diagnostic criteria for FPIES over time are summarized in Table 5.

Powell [2] initially proposed diagnostic criteria for the chronic form of FPIES, modifying them few years later, incorporating features of the acute form of FPIES [44]. In 2013, Sopo et al [45] updated them, mainly for the acute form of FPIES, and they suggested that the diagnostic could be established after two typical episodes of FPIES. The first international consensus guidelines on diagnosis and management of FPIES have been recently published. At the present time, the diagnosis of FPIES is based on a clinical history of typical characteristic signs and symptoms with improvement after withdrawal of the

suspected trigger food. Open food challenge (OFC) would be considered to help confirm the diagnosis if the history is unclear and there is a favorable risk/benefit ratio [46].

A variety of protocols for FPIES-related OFC have been published.

Zapatero et al [9] start the challenge with the eight portion of a normal serving size amount per age, that it is increased every 30 min to a full serve. Patients remain under supervision for 3 hours. This protocol is similar to the one we perform in our daily practice. We do not place an intravenous (iv) line before.

Sopo and cols [5] describe three different protocols in Italy. Only one medical team placed an intravenous access before OFC. In this case, 0,4gr/kg of protein divided in three equal doses is administered over 3 hours and if no adverse reaction, a whole meal with the offending food is given and the patient is under observation for 2 hours. A second protocol consists in the administration of 50% of a serving size per age followed by 2-hour observation. If tolerance is confirmed, a second dose of 100% of the serving per age is given, followed by 4-hour observation. The last protocol starts with 25% of the serving size per age followed by a 4-h clinical observation; then a dose equal to 50% of the serving size per age is given, followed by another 4-h observation. Finally, the whole meal is given the day after, followed by a 4-h clinical observation.

Vazquez-Ortiz et at [8] administer 0,3gr protein/kgr body weight, 3gr as maximal dose, divided in 3 equal doses given at 90-min intervals, except for CM in which 7 consecutive doses are given at 90-min intervals. Intravenous access is placed before start.

Current consensus is to administer 0,06 to 0,6gr of protein/kg of body weight (0,15 to 0,3g protein/kg body if the patient had a history of severe reaction, in three equal doses over 30 minutes in order not to exceed a total dose of 3 grams of protein or 10 grams of total food (100ml of liquid). Patients are observed for 4 to 6 hours [46]. Intravenous hydration readily available is advised during this procedure [46], although in our experience and others [3, 5], most reactions can be managed by oral rehidration.

Although serum specific-IgE as well as skin prick tests with the suspected food are negative in the majority of patients, some patients present food specific IgE. This has been called “atypical FPIES” and it has been reported more frequently in the US and UK. Thus, in the US Caubet et al [11] reported 37% of patients with this form of FPIES and Ludman et al [4] 33% in UK. In Italy and Spain, it is rarely reported: Sopo et al [5] found 3% of “atypical FPIES” in Italian children while in Spain, Ruiz et al [22] found 1 patient out of 16 to have food-specific IgE; Zapatero et al, reported 1 out of 14 [9] and Vazquez-Ortiz et al [8] reported no “atypical FPIES” in a large series of 81 patients. According to these observations, we also found negative SPT and serum specific IgE in 21 children with FPIES caused by solid foods [10].

Patients with “ atypical FPIES” have a more protracted course as well as an increased risk to develop immediate allergic reactions after ingestion of the offending food [3,5,11]. Therefore testing specific IgE for trigger food would be interesting on follow up, before performing OFC, in patients with comorbid conditions, such as IgE-mediated food allergy to other foods and atopic dermatitis believed to be influenced by a food allergen, but this is not recommended at the initial evaluation for a FPIES trigger. In patients with CM-induced FPIES, CM IgE levels should be measured before performing OFC, given the risk of conversion to IgE mediated CM allergy [46]. In cases of positive food specific IgE, more gradual administration of increasing doses of food during OFC is recommended, with a longer observation period [47].

Given FPIES is presumably T-cell mediated, atopy patch testing (APT) was thought initially as a rentable tool for the diagnosis of FPIES. In a series of 19 patients Fogg et al [48) reported APT to have high SE (100%) and SP (71%). A subsequent study by the same group APT showed a 45% false-negative rate and they concluded that APT was not useful for the diagnosis of FPIES [14]. Järvinen and Nowak-Wegrzyn [49] performed APT on children with FPIES before OFC to monitor tolerance development. APT yielded low sensitivity (11,8%), positive predictive value of 40% and negative predictive value of

54,5%. So up to date, more studies are needed to determine the usefulness of APT for the diagnosis of FPIES.
Other studies as stool testing or endoscopy and biopsy are not recommended routinely in patients with suspected FPIES since the diagnostic is based in clinical criteria [46].

During the acute FPIES reaction if the diagnosis of FPIES is not established yet, the ill appearance of the patient may warrant laboratory studies that may help narrowing the differential diagnosis, which includes sepsis, gastroenteritis, bowel obstruction, celiac disease, inborn errors of metabolism, necrotizing enterocolitis and even anaphylaxis. Leukocytosis with neutrophilia is a common finding in acute FPIES reactions [12, 50]. Other findings are thrombocytosis [15], eosinophilia [51], metabolic acidosis and metahemoglobinemia [52]. Recently, a time-dependent significant increased of C-reactive protein during acute episodes of FPIES has been reported [50]. Stool samples may reveal leukocytes, frank or occult blood and eosinophils. All these changes are within normal ranges once the reaction has resolved.
Chronic FPIES has to be distinguished from eosinophilic gastroenteritis, celiac disease, allergic proctocolitis and food protein-induced enteropathy.
Differential diagnosis of FPIES is summarized in Table 6.

Management

Acute management of FPIES is based on rehydration. Oral rehydration at home or at a medical facility when possible is preferred, but in severe cases with protracted emesis, lethargy, hypotension or acidosis, intravenous hydration is mandatory. In some cases, supplemental oxygen, vasopressors and even methylene blue may be necessary.
Traditionally and based on that FPIES is a cell mediated condition, intravenous methylprednisolone (1mg/kg) is administered during the acute, severe reaction although no studies support this recommendation [53].
Recently, two small series of case reports by Holbrook et al [54] and Sopo et al [55] suggested a role for parenteral ondansetron in controlling acute symptoms.

Ondansetron is a serotonin 5-HT3 receptor antagonist used classically to prevent postquirurgic and chemotherapy-induced nausea and vomiting. It also is being used to control vomiting during acute gastroenteritis [56].

In fact serotonin is mostly produced at the gatrointestinal tract and it induces vomiting through vagal peripheric and central reflexes and stimulates peristalsis, gastric emptying and secretion of liquid and electrolytes to intestinal light.

The only relevant side effect of ondansetron is the risk of prolonged QT interval which can lead to Torsade de Pointes, a potentially fatal arrhythmia. This is a dose-dependent side effect so it has been recommended than >32mg single intravenous dose should be avoided. Patients with bradyarrithmias or taking concomitant medications that prolong the QT interval are in greater risk [57].

Sopo et al [58] conducted a study comparing parenteral ondansetron with traditional therapy (iv fluids and methylprednisolone 1 mg/kg/dose), finding that only 19% of children treated with ondansetron continued vomiting versus 93% of children treated with traditional therapy. And, although it did not reached statistical significance, non-responder patients treated with ondansetron had less episodes of vomiting than those receiving traditional therapy. Also, the percentage of children admitted overnight to hospital was significantly lower in the ondasetron group. Thus, authors conclude that parenteral ondansetron is more effective than iv steroids in resolving acute symptoms of FPIES. Moreover, there were no significant differences between intramuscular and intravenous routes of administration of ondansetron.

Leonard reported effectiveness of liquid ondansetron used at home in these patients [23]. Our personal experience with this route of administration is positive in 7 patients who developed vomiting on OFC at our clinic. Only one of them kept vomiting after the first dose of ondansetron and had to be admitted to the emergency room for oral rehydration. Proposed dosage is extrapolated from that recommended for acute gastroenteritis (Table 7).

Long term management and prognosis

Strict avoidance of the trigger food is the cornerstone of long term management. After elimination of the offending food, acute FPIES usually resolves within 4-12 hours, whereas chronic FPIES resolves within 3 to 10 days [59].

In infants with CM/soy-FPIES breastfeeding should be encouraged and an extensive hydrolyzed casein-based formula is usually recommended although up to 11-40% of infants may not tolerate it and require an aminoacid based formula [11,12]. Regarding baked egg and milk, since there are only small case series reporting tolerance to them [32], it is recommended to introduce them in the clinical setting under physician supervision.

Regarding solid foods, there are patients that tolerate other foods belonging to the same family as the offending one. We [10] as well as Sopo et al [5] have reported that 60% and 21%, respectively, of children with fish-FPIES tolerated fish other than the one causing the reaction. Based in our experience and especially in the case of fish-induced FPIES, OFC at diagnosis with other foods from the same family as the offending food would help to avoid unnecessary dietary restrictions.

Prognosis is good, with most children tolerating the offending food over time. There are some differences though depending on the type of food. Children with fish –induced FPIES outgrow it later than those with CM, soy or rice-induced FPIES [3, 5, 8-11,13,14,16,24, 35, 55], although as reported by Caubet and cols [11], soy FPIES may be outgrown as late as 6 years of age (Table 8). OFC every 1,5-2 years is recommended to confirm achievement of tolerance to the offending food although deferring egg and fish challenges until age 5 years has been suggested [24].

Recently Kimura et al [60] studied 32 patients with FPIES caused by CM. They found a significant positive correlation between the time of tolerance acquisition and the level of serum C-reactive protein (CRP) at onset, and a significant negative correlation with the percentage of eosinophils in peripheral blood at

onset, suggesting the CRP could be a useful parameter of poor prognosis as well as eosinophilia could be used as a marker of good prognosis.
Older age at initial FPIEs episode and diagnosis and presence of specific IgE to the triggering food have been associated with slower association of tolerance [11, 24].
There is controversy over whether common FPIES foods should be profilactically avoided in infants with a previous history of FPIES.
Owing to the high rates of CM and soy co-sensitization in the US, Ruffner et al [14] and Caubet et al [11], recommend avoidance of soy formulas in infants with CM-induced FPIES. Cohorts from Australia, Italy and Israel report much lower rate of simultaneous CM and soy FPIES, suggesting that soy could be an alternative for infants with CM-FPIES [62].
Children with CM- or soy-induced FPIES can also have an increased likelihood of reacting to a solid foods, most commonly rice and oat and although it has been suggested to avoid grains, legumes and poultry in the first year of life [62], current early feeding guidelines do not recommend delay in introducing complementary foods past 6 months of life because of a history of previous FPIES [46]. A sequence of introduction of solid foods after 6 months of age starting with fruits and vegetables, followed by red meats and then cereal grains (considering poultry, banana, green pea, rice and oat as high risk foods) has been proposed [46,59]. Sopo [46] proposes supervised OFCs to a mixture of several solids as a way of excluding the risk of severe reactions to small amounts, followed by gradual build up toregular age-appropriate serving size at home.

It is not recommended that mothers avoid trigger foods when nursing unless a reaction after breast-feeding has been documented [63].

In summary, FPIES is a non-IgE mediated gastrointestinal food hypersensitivity that predominantly affects infants and young children. Foods more frequently implicated are CM, soy formula, grains and fish, depending on the different areas of the world. Diagnosis is based on clinical manifestations and it requires

a high index of suspicion, since we still lack a diagnostic laboratory tool. Early recognition of FPIES and removal of the offending food are mandatory to avoid new acute episodes and/or chronic manifestations as failure to thrive.
Prognosis is usually good, with most children tolerating foods before 6 years of age. More protracted courses are seen in infants with fish induced FPIES and in those patients who develop food specific IgE.
Further study on pathophysiology, diagnosis tools and natural course of FPIES area warranted.

ACKNOWLEDGEMENTS

I want to thank Maria Jesus Fernandez Hermida and Isabel Cabanas for their great job with oral food challenges and for their dedication to the patients.

REFERENCES

1. Gryboski J. Gastrointestinal milk allergy in infancy. Pediatrics 1967; 40:354-362

2. Powell GK . Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. J Pediatr 1978;93: 553- 560

3. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to CM: a large-scale, prospective population-based study. J Allergy Clin Immunol 2011; 127: 647-653.e1-3

4. Ludman S, Harmon M, Whiting D, du Toit G. Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom. Ann Allergy Asthma Immunol 2014; 113 (3): 290-294

5. Sopo M, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicenter retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. Clin Exp Allergy 2012; 42:1257-1265

6. Mehr S, Frith K, Barnes E, Campbell D of behalf of the FPIES Study Group. Food protein-induced enterocolitis syndrome in Australia: a population-based study, 2012-2014. J Allergy Clin Immunol 2017, Apr 18. pii: S0091-6749(17)30588-2. doi: 10.1016/j.jaci.2017.03.027

7. Fernandes B, Boyle R, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. J Allergy Clin Immunol 2012;130 (5): 1199-200

8. Vazquez-Ortiz M, Machinena A, Dominguez O, Alvaro M, Calvo-Campoverde K, Giner MT, et al. Food protein-induced enterocolitis syndrome to fish and egg usually resolves by age 5 years in Spanish children. J Allergy Clin Immunol Pract 2017; 5(2): 512-515.

9. Zapatero Remón L, Alonso Lebrero E, Martín Fernández E, Martínez Molero MI. Food protein-induced enterocolitis syndrome caused by fish. Allergol et Immunopathol 2005; 33 (6):312-6

10. Vila L, Garcia V, Rial MJ, Novoa E, Cacharron T. Fish is a major trigger of solid food protein-induced enterocolitis syndrome in Spanish children. J Allergy Clin Immunol Pract 2015;3(4):621-3.

11. Caubet JC, Ford LS, Sickles L, Jarvinen KM, Sicherer SH, Sampson HA. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol 2014; 134: 382-9

12. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins Pediatrics 2003; 111:829-835

13. Mehr SS, Kakakios AM, Kemp AS. Rice: a common and severe cause of food protein-induced enterocolitis syndrome. Arch Dis Child 2009;94:220-223

14. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. J Allergy Clin Immunol Pract 2013;1:343-9

16. Sopo SM, Monaco S, Badina L, Barni S, Longo G, Novembre E, et al. Food protein-induced enterocolitis syndrome caused by fish and/or shellfish in Italy. Pediatric Allergy Immunology 2015; 26: 731-736

17. Hwang JB, Sohn SM, Kim AS. Prospective follow-up food challenge in food protein-induced enterocolitis syndrome. Arch Dis Child 2009;94:425-428

18. Nomura I, Morita H, Hosokawa S, Hoshina H, Fukuie T, Watanabe M, et al. Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms. J Allergy Clin Immunol 2011;127:685-8 e1-8

19. Miceli Sopo S, Monaco S, Greco M, Scala G. Chronic food protein-induced enterocolitis syndrome caused by cow's milk proteins passed through breast milk. Int Arch Allergy Immunol. 2014;164(3):207-9.

20. Kaya A, Toyran M, Civelek E, Mirishoglu ED, Kirsaclioglu CT, Kocabas CN. Food protein-induced enterocolitis syndrome in two exclusively breastfed infants. Pediatr Allergy Immunol 2016; 27(7): 749-750.

21. Tan J, Campbell D, Mehr S. Food protein-induced enterocolitis syndrome in an exclusively breast-fed infant- un uncommon entity. J Allergy Clin Immunol 2012;129:873

22. Ruiz-García M, Escudero Díaz C, Sánchez García S, Rodriguez del Río P, Ibañez MD. Diagnosis and natural history of food protein-induced enterocolitis syndrome in children from a tertiary hospital in Central Spain. J Invest Allergol Clin Immunol 2014; 24 (5):352-370.

23. Leonard S, Nowak-Wegrzyn A. Food Protein-Induced Enterocolitis Syndrome. Pediatr Clin N Am 2015; 62: 1463-1477

24. Lee E, Campbell D, Barnes E, Mehr S. Resolution of acute food protein-induced enterocolitis syndrome in children. J Allergy Clin Immunol Pract 2016; 5(2): 486-488.e1

25. Serafini S, Bergman M, Nowak-Wegrzyn A, Eigenmann P, Caubet C. A case of food protein-induced enterocolitis syndrome to mushrooms challenging currently used diagnostic criteria. J Allergy Clin Immunol Pract 2014; 3(1): 136-137

26. Hwang JB, Kang KJ, Kang YN, Kim AS. Probiotic gastrointestinal allergic reaction caused by Saccharomyces boulardii. Ann Allergy Asthma Immunol 2009; 103 (1):87-8

27. Zubrinich C, Hew M, O'Hehir R.Egg provoked food protein-induced enterocolitis-like syndrome in adults. Clin Case Rep 2016; 4(9): 899-901

28. Tan JA, Smith WB. Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults. J Allergy Clin Immunol Pract 2014;2: 355-357.e1

29. Mehr S, Frith K, Campbell D. Epidemiology of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol 2014;14: 208-216

30. Freier S, Kletter B, Gery I, Lebenthal E, Geifman M. Intolerance to milk protein. J Pediatrics 1969, 75;4: 623-631

31. Kuitunen P, Visakorpi JK, Savilahti E, Pelkonen P. Malabsorption syndrome with cow's milk intolerance. Clinical findings and course in 54 cases. Arch Dis Child 1975, 50:351-356

32. Sopo M, Buonsenso D, Monaco S. Food protein-induced enterocolitis syndrome (FPIES) and well cooked foods: a working hypothesis. Allergol Immunopathol (Madr) 2013;41: 346-348

33. Nagata S, Yamashiro Y, Ohtsuka Y. Quantitative analysis and immunohistochemical studies on small intestinal mucosa of food sensitive enterophaty. J Pediatr Gastroenterol Nutr 1995;20 (1): 44-48

34. Fontaine JL, Navarro J. Small intestinal biopsy in cow's milk protein allergy in infancy. Arch Dis Child 1975;50:357-362.

35. Savilahti E. Immunochemical study of the malabsortion syndrome with cow's milk intolerance. Gut 1973; 14: 491-501

36. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor b1, transforming growth factor type I and II receptors and TNF-alfa in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2002; 109: 150-154

37. González-Delgado P, Caparrós E, Moreno MV, Clemente F, Flores E, Velásquez L, et al. Clinical and immunological characteristics of a pediatric population with food protein-induced enterocolitis syndrome (FPIES) to fish. Pediatr Allergy Immunol 2016;27: 269-275

38. Goswami R, Blazquez AB, Kosy R, Rahman A, Nowak-Wegrzyn A, Berin C. Systemic innate immune activation in food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2017;139:1885-1896

39. Konstantinou G, Bencharitiwong R, Grishin A, Caubet JC, Bardina L, Sicherer S, et al. The role of casein-specific IgA and TGF-beta in children with food-protein-induced enterocolitis syndrome to milk. Pediatr Allergy Immunol 2015; 25: 651-656

40. Caubet JC, Bencharitiwong R, Ross A, Sampson HA, Berin MD, Nowak-Wegrzyn A. Humoral and cellular responses to casein in patients with food protein-induced enterocolitis to cow's milk. J Allergy Clin Immunol. 2017;139(2):572-583

41. 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;60: 912-919

42. McDonald PJ, Goldblum RM, Van Sickle GJ, Powell GK. Food protein-induced enterocolitis: altered antibody response to ingested antigen. Pediatr Res 1984;18: 751-755

43. Kimura M, Ito Y, Shimomura M, Morishita H, Meguro T, Adachi Y, Seto S. Cytokine profile after oral food challenge in infants with food protein-induced enterocolitis syndrome. Allergol Int. 2017 doi: 10.1016/j.alit.2016.12.001

44. Powell GK. Food protein-induced enterocolitis of infancy: differential diagnosis and management. Compr Ther 1986;12:28-37

45. Sopo M, Greco M, Monaco S, Tripodi S, Calvani M. Food protein-induced enterocolitis syndrome: from practice to theory. Exp Rev Clin Immunol 2013;9:707-715

46. Nowak-Wegrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2017;139:1111-26

47. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123: S365-38

48. Fogg MI, Brown-Whitehorn TA, Pawlowski NA et al. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2006;17:351-355

49. Järvinen KM, Nowak-Wegrzyn A, Caubet JC, Sickles L, Ford LS, Sampson HA, et al. Poor utility of atopy patch test in predicting tolerance development in food protein-induced enterocolitis syndrome. Ann Allegy Clin Immunol 2012;109: 221-222

50. Pecora V, Prencipe G, Valluci R, Dahdah L, Insalaco A, Cianferoni A, et al. Inflammatory events during Food Protein-Induced Enterocolitis Syndrome reactions. Pediatr Allergy Immunol. 2017 Apr 4. doi: 10.1111/pai.12723

51. Kimura M, Shimomura M, Morishita H, Meguro T, Seto S. Eosinophilia in infants with food protein-induced enterocolitis syndrome in Japan. Allergol Int 2016.pii:S1323-8930 (16) 30109-5

52. Murray K CD. Dietary protein intolerance in infants with transient methemoglobinemia and diarrhea. J Pediatr 1993;122: 90-2

53. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J Allergy Clin Immunol 2005;115: 149-156

54. Holbrook T, Keet CA, Frischmeyer-Guerreiro PA, Wood RA. Use of ondasetron for food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2013; 135 (5): 1219-1220

55. Sopo SM, Battista A, Greco M, Monaco S. Ondansetron for food protein-induced enterocolitis syndrome. Int Arch Allergy Immunol 2014; 164: 137-139

56. Tomasik E, Ziółkowska E, Kołodziej M, Szajewska H. Systematic review with meta-analysis: ondansetron for vomiting in children with acute gastroenteritis. Aliment Pharmacol Ther. 2016 Sep;44(5):438-46

57. Doggrell SA1, Hancox JC. Cardiac safety concerns for ondansetron, an antiemetic commonly used for nausea linked to cancer treatment and following anaesthesia. Expert Opin Drug Saf. 2013 May;12(3):421-31

58. Sopo SM, Bersani G, Monaco S, Cerchiara G, Lee E, Campbell D, et al. Ondansetron in acute food protein-induced enterocolitis syndrome, a retrospective case-control study. Allergy 2016; DOI: 10.1111/all.13033

59. Nowak-Wegrzyn A, Jarocka-Cyrta E, Moschione Castro. Food Protein-Induced Enterocolitis Syndrome. J Invest Allergol Clin Immunol 2017; 27(1): 1-18

60. Kimura M, Shimomura M, Morishita H, Meguro T. Prognosis of infantile food protein-induced enterocolitis syndrome in Japan. Pediatr Int. 2017 Apr 22. doi: 10.1111/ped.13305

61. Karefylaki S, Gustafsson D. Recovery from food protein-induced enterocolitis syndrome caused by fish. Pediatr Allergy Immunol 2016; 27: 105-6

62. Järvinen KM, Nowak-Wegrzyn A. Food Protein-Induced Enterocolitis Syndrome (FPIES): Current Management Strategies and Review of the literature. J Allergy Clin Immunol Pract 2013; 1: 317-22

63. Leonard S, Chehade M. Food Protein-Induced Enterocolitis Syndrome. J Allergy Clin Immunol Pract 2017

64. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. J Pediatr 1998; 133:214-9

Table 1. Clinical manifestations of FPIES

	Katzl[3] (n=44)	Sopo[5] (n=66)	Sicherer[6] [4] (n=22)	Ruiz-García[22] (n=16)	Ludman[4] (n=54)	Caubet[11] (n=74)	Nowak-Wegrzyn[11] (n= 14)	Vila[10] (n=21)	Zapatero [9] (n=14)
Vomiting	100 (44)	98 (65)	95 (21)	100 (16)	81 (44)	96 (70)	100 (14)	100 (21)	85 (12)
Lethargy	77 (34)	-	36 (8)	25 (4)	17 (9)	7 (5)	71 (10)	66 (14)	21 (3)
Pallor	14 (6)	80 (53)	-	19 (3)	15 (8)	-	-	52 (11)	-
Hypotension	-	77 (51)	9 (2)	-	-	19 (14)	21 (3)	-	-
Diarrhea	25 (11)	54 (36)	72 (16)	56 (9)	37 (20)	7 (5)		33 (7)	35 (5)

Values: percentage (number of subjects)

Table 2. Most common food triggers of FPIES in cohort studies.

	Caubet[11] (n=160)	Ruffner[14] (n=462)	Sicherer[64] (n=22)	Ludman[4] (n=54)	Ruiz-García[22] (n=16)	Sopo[5] (n=66)	Vazquez-Ortiz[8] (n=81)	Vila[10] (n=21)	Mehr[15] (n=35)
CM	44 (70)	67 (309)	59 (13)	46 (25)	44 (7)	67 (44)	25,9 (21)	-	20 (7)
Soy	41(66)	41 (189)	63 (14)	11 (6)	6 (1)	4 (3)	-	-	34 (12)
Rice	23 (36)	19 (88)		2 (4)	6 (1)	4 (3)	7,4 (6)	9,5(2)	40 (14)
Oat-	16 (26)	16 (74)	-	6 (3)	-	-	-	4,7(1)	6 (2)
Fish	-	-	-	15 (8)	31 (5)	12 (8)	54,3 (44)	85,7(18)	3 (1)
Poultry	-	4,5 (21)	4,5 (1)	-	6 (1)	3 (2)	-	-	3 (1)
Wheat	1 (2)	10 (46)	-	11 (6)	6 (1)	-	-	4,7(1)	-
Egg	-	11 (51)	-	13 (7)	-	6 (4)	9,8 (8)	-	-

Values are: percentage (number of subjects)

Tabla 3. Percentage of patients with FPIES reacting to 2 or more foods.

USA	Caubet [10]	35%
USA	Nowak-Wegrzyn [11]	80%
USA	Ruffner [13]	43%
Australia	Mehr [14]	17%
Spain	Vila [9]	9%
Spain	Ruiz-García [21]	7%
Spain	Vazquez-Ortiz	1,2%
Italy	Sopo [5]	15%
United Kingdom	Ludman [4]	30%

Table 4. Pathologic findings in patients with FPIES

Cellular findings	Peripheral blood eosinophilia, clusters of eosinophils in intestinal biopsies, eosinophils and Charcot-Leyden crystals in stool samples [34] Increased number of intraepithelial lymphocytes, increased number of CD4+, plasma cells producing IgM and IgA [36] Increased expression of HLA-DR in dendritic cells [35] Increased plasma cells producing IgM and IgA and eosinophils during milk exposure in the gastrointestinal tract [32,33] Activation of cells of the innate immune system (monocytes, eosinophils, NK cells, neutrophils) [38] Pan-T-cell activation and redistribution from the circulation after positive food challenge [38]
Humoral responses	Lower levels of casein-IgG4 and casein-IgG in patients with active CM-FPIES than those who tolerate CM [36, 37] Contradictory results regarding food specific-IgA: increased [42] /decreased [39]
Cytokines	Lower secretion of IL-10 [40] Increased secretion of IL-8 [43) and IL-9 [40] Increased TNF-α [36,37, 43] Decreased expression of TGF-β receptors and decreased production of TGF-β [37,41] Increased IP-10 [40] Increased IL-2 and IL-5 [43]

Table 5. Evolution of clinical diagnostic criteria for FPIES over time and actual proposed criteria

Powell, 1978 [2]

1. Onset before 2 months of age.
2. Manifestations: watery stools with mucus, blood and leukocytes. Peripheral polymorphonuclear leukocytosis.
3. Clinical manifestations resolve when the offending food is eliminated
4. Reintroduction of offending food (OFC) leads to:
    a. Diarrhea within 24h of challenge
    b. Stools contain blood and leukocytes
    c. Leukocytosis over 4000cells/mm3, 6 to 8 hours postchallenge.

Powell, 1986 [44]

1. Removing of the offending food leads to disappearance of vomiting and diarrea and of leukocytes and blood in stools.
2. No other causes for the colitis.
3. Symptoms do not recur and weight gain is normal for ne month on a low-antigen formula as the only dietary source.
4. Challenge with the offending food reproduce symptoms of vomiting within 1-3 hours and/or diarrea within 4-10 hours.

Leonard, 2012 [23]

1. Less than 9 months of age at initial diagnosis.
2. Repeated exposure to the offending food elicits gastrointestinal symptoms without alternative cause.
3. Absence of symptoms suggesting an IgE-mediated reaction.
4. Removal of causative food results in resolution of symptoms.
5. Re-exposure to the offending food elicits typical symptoms within 4 hours.

Sopo, 2013 [45]

1. Age of presentation less than 2 years.
2. Exposure to the offending food elicits repetitive vomiting, pallor, lethargy within 2-4 hours. Diarrhea may be present but later. Symptoms usually resolve within 6 hours.
3. Absense of symptoms suggesting an IgE-mediated reaction.
4. Avoidance of the offending food results in resolution of symptoms.
5. Re-exposure to the offending food elicits typical symptoms within 2-4 hours. Two typical episodes are needed to establish the definitive diagnosis without the need to perform an OFC.

Consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome (Nowak-Wegrzyn et al, 2017 [46]

Acute FPIES

Major Criterion

Vomiting in the 1-4 hour period after ingestion of the offending food and absence of classic IgE-mediated allergic skin or respiratory symptoms.

Minor Criteria

1. A second (or more) episode of repetitive vomiting after eating the same suspected food
2. Episode of repetitive vomiting 1-4 hours after eating a different food
3. Extreme lethargy with any suspected reaction
4. Marked pallor with any suspected reaction
5. Need for emergency room visit with any suspected reaction
6. Need for intravenous fluid support with any suspected reaction
7. Diarrhea within 24h (usually 5-10 hours)
8. Hypotension
9. Hypothermia

The diagnosis of FPIES requires the major criterion and at least 3 minor criteria.

Chronic FPIES

Severe presentation: when the offending food is ingested in on a regular basis (eg. infant formula): intermittent and progressive vomiting and diarrhea (occasionally with blood) can develop, sometimes with dehydration and metabolic acidosis.

Milder presentation: lower doses of the culprit food (eg solid foods or food allergens in breast milk) lead to intermittent vomiting, and/or diarrhea, usually with poor weight gain/failure to thrive, but without dehydration of metabolic acidosis).

The most important criterion for chronic FPIES diagnosis is resolution ofthe symptoms within days after elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 h, diarrhea in 24 h (usually 5-10 h).

Table 6. Differential diagnosis of FPIES

Acute FPIES	Chronic FPIES
Gastrointestinal viral infection Sepsis Anaphylaxis Inborn errors of metabolism Intussuception Necrotizing enterocolitis	Celiac disease Proctocolitis Food protein-induced enteropathy Eosinophilic gastroenterophaties Inborn errors of metabolism

Table 7. Proposed doses of ondansetron as treatment of acute FPIES

	Intravenous	**Intramuscular**	**Iv/im**	**Oral (lingual)**
Holbrook et al [54]	0,08-0,1-0,15-0,2 mg/kg			
Sopo et al [55]		0,2 mg/kg		
Sopo et al [58]			0,15-0,2mg/kg	
Vila et al (personal communication)				Body weight Dose 8-15kg 2mg 16-30kg 4mg >30kg 8mg

Table 8. Age of FPIES resolution by cohort population

	Cow's milk	**Soy**	**Rice/grains**	**Fish**	**Egg**
González-Delgado et al [35]				> 6 years	
Sopo et al [5]	2 years			9 years	
Vila et al [9]				> 5 years	
Ruffner et al [13]			3,5 years		
Vazquez-Ortiz et al [8]	2,4 years			5 years	> 5 years
Nowak-Wegrzyn et al [11]	2 years	> 3years	2 years		
Caubet et al [10]	5 years	6,7 years	4,7 years		
Katz et al [3]	3 years				
Mehr et al [14]			3 years		
Lee et al [24]	4 years		4 years	> 5 years	> 5 years
Huang et al [16]	1 year		7,8 months		
Karefylaki et al [55]				> 4 years	