Differential diagnosis of food protein-induced enterocolitis syndrome

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Purpose of review
To assess all the possible differential diagnosis of food protein-induced enterocolitis syndrome (FPIES), both in acute and chronic presentation, reviewing the data reported in published studies.

Recent findings
There is an increase of reported cases of FPIES in recent years. As the disease presents with nonspecific symptoms, it can be misunderstood in many ways. The differential diagnosis includes, in acute presentations, the following: sepsis, other infectious diseases, acute gastrointestinal episodes, surgical emergencies, food allergies. In its chronic forms, FPIES may mimic malabsorption syndromes, metabolic disorders, primary immunodeficiencies, neurological conditions, coagulation defects, and other types of non-IgE-mediated food allergy.

Summary
A thorough clinical evaluation, including symptoms, signs, and laboratory findings, is necessary to lead the clinicians toward the diagnosis of FPIES. The major reason for delayed diagnosis appears to be the lack of knowledge of the disease.

Keywords
chronic diarrhea, dehydration, differential diagnosis, food protein-induced enterocolitis syndrome

INTRODUCTION
Among the mysteries that surround the FPIES, pathogenesis is the most intriguing. Several hypotheses have been proposed, attributing the responsibility to cell-mediated or humoral-specific immunologic alterations, or to neutrophils, platelets, and/or eosinophils dysfunction. Some mediators, such as serotonin, may be involved [1]. Whatever the mechanism(s) is, the presentation of the disease is often explosive and the disease is severely hampering the patient’s quality of life [2]. Thus, the condition must not go unnoticed, and a diagnosis is called for. However, because of several reasons, the first diagnosis is seldom the right one [3].

Although the differential diagnosis of FPIES has been considered an important issue for many years [4], a complete review of the conditions possibly confused with FPIES is lacking. Misdiagnoses may delay the identification of FPIES for months, exposing the children to the repetition of acute episodes [5], or even leading to dramatically incorrect diagnostic/therapeutic interventions [6]. Yet, FPIES is indicated as a possible manifestation of food allergy in all the guidelines on the topic [7–9].

The present article aims to review the possible diagnostic hypotheses proposed for FPIES before its correct identification.

THE DIAGNOSIS IS OFTEN DELAYED
The diagnosis of FPIES is often difficult and delayed, and patients may undergo extensive workups...
for their symptoms. This is very common in non-IgE-mediated food allergies [10], but particularly typical of this syndrome: FPIES does not have an identification biomarker nor an unequivocal, typical symptom.

In a retrospective study [3] of children with FPIES over the course of 16 years at Children’s Hospital in Sydney, 35 children presented with 66 acute episodes of FPIES. Only two of the 19 children who presented to the emergency department with their initial reaction were discharged with the correct diagnosis. Additional tests were common for patients who presented with FPIES in the hospital, with 34% of them undergoing abdominal imaging studies, 28% a septic evaluation, and 22% a surgical consultation. Patients experienced more episodes before the correct diagnosis was made. If this happens in the acute form of the disease, one can imagine that the delayed forms are even less frequently diagnosed.

**KEY POINTS**

- The clinical presentation of FPIES is often misdiagnosed, particularly in chronic form.
- FPIES patients with an incorrect diagnosis undergo unnecessary and, sometimes, risky therapeutic interventions.
- It is mandatory to raise pediatricians’ awareness of clinical aspects characterizing FPIES.

**DIFFERENTIAL DIAGNOSIS OF FPIES**

FPIES may present in either acute or chronic form (Bahna [11]). In its acute form, FPIES occurs 1–3 h after every ingestion of the causative food, with somewhat more severe presentation than in the chronic form. FPIES usually presents with profuse diarrhea, vomiting, acute dehydration, and possible episodes of circulatory collapse and shock in about 20% of patients. Other possible symptoms are pallor, hypotension, hypothermia, and abdominal distension. Given its clinical characteristics, acute FPIES often takes the family to the nearest emergency room where the pediatrician is faced with a patient with an acute episode of vomiting, hypotension, and dehydration. Her first diagnostic orientation will assess the gastrointestinal tract for vomiting, diarrhea, or both. Other possible causes are listed in the following paragraphs. Sepsis is the most commonly diagnosed condition in this phase (Table 1 [3,6,12–30,31**,32–37]).

Chronic FPIES is an ill-defined condition characterized by intermittent vomiting, watery or mucous diarrhea, poor weight gain, and dehydration. The differential diagnosis is particularly important in chronic FPIES, as this is an ‘exclusion’ diagnosis. Thus, in order to label a child with ‘chronic’ FPIES, a huge diagnostic workload is necessary.

**DIFFERENTIAL DIAGNOSIS OF ACUTE FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME**

When presenting at an emergency room, the patient with acute FPIES is most often misdiagnosed with sepsis. This diagnosis has been considered in 20 publications of case series or reports, more frequently at younger ages (mean age at presentation: 11 months, range 0.5–48 months; Table 1). Sepsis and acute FPIES may share a sudden onset of weakness, vomiting, hyperpnea, tachycardia, neurological impairment, oliguria, and hypotension. Although fever is a cardinal symptom of sepsis, not present in acute FPIES, it can happen that in sepsis – particularly when severe – the body temperature falls below normal values. Laboratory features in acutely presenting FPIES may also mislead to sepsis, as they include extreme leukocytosis, elevated neutrophil count, thrombocytosis, metabolic acidosis, and methemoglobinemia. However, inflammatory indices are normal or slightly elevated, differentiating the two conditions. Faced with a clinical suspicion of a septic status, the emergency room physician will treat the child promptly and aggressively, as indicated in such cases [38]. The treatment will include antibiotics – even before test results confirm the etiologic diagnosis – intravenous fluids to sustain blood pressure, dopamine or epinephrine, oxygen, and sometimes plasma infusion. Of these treatments, the only really effective therapy for FPIES is fluid infusion. However, no complaints by patient parents are reported for overtreatment in the published case series. In our opinion, treating as sepsis an acute presentation of FPIES in an undiagnosed patient, based on the worst case scenario, is wise – at least until rapid diagnostic tests, FPIES-specific, can be developed.

Such ‘therapeutically aggressive’ approaches can become dangerous when the suspicion is an acute surgical abdominal condition. At least two FPIES children are reported being mistakenly diagnosed as having intussusception, which led to non-diagnostic laparotomies [6,12].

The second reported differential diagnosis is acute dehydration from gastroenteritis (16 publications). This condition again occurs normally with fever, starts with vomiting, and ends in diarrhea. Etiologic agents can be identified in the stools [39]. In FPIES there is no fever, sometimes no diarrhea, and stool studies for viruses and bacteria are...
negative. The clinical evolution of acute FPIES is much more serious and rapid, leading to a severe impairment of the general conditions in a short time. Supportive treatment is all that is needed for most gastrointestinal patients, with oral or intravenous rehydration in particular in infants.

When FPIES occurs in neonates in the first weeks of life, the differential diagnosis with necrotizing enterocolitis (NEC) has been reported. Common symptoms include instability, lethargy, vomiting, diarrhea, and acidosis. In the most severe cases of NEC, the infant develops shock and DIC [40]. As NEC must be treated aggressively with parenteral nutrition, wide-spectrum antibiotics and surgical resection in case of perforated or necrotic intestine, it is important to distinguish it from FPIES. Epidemiologic considerations can be of help: NEC is more common in premature, low birth weight infants; other risk factors include respiratory distress, congenital heart disease, and formula-milk feeding. The pathognomonic sign of NEC is the radiologic finding of pneumatosis intestinalis.

Another condition occasionally reported in the FPIES caseloads is pyloric stenosis, suspected when symptoms of projectile and repetitive vomiting, eventually leading to dehydration and shock, occur in the first week of life [41]. Sometimes pyloric stenosis is associated, at physical examination, with the presence of a firm and nontender mass in the right upper quadrant, described as an ‘olive’. The diagnostic confirmation derives from a non-invasive technique, as ultrasonography scan. After hydroelectrolytic resuscitation, surgical correction is considered the standard of care of pyloric stenosis.

Two reports indicate that FPIES came into the differential diagnosis with allergic proctocolitis.

### Table 1. Differential diagnosis in reported cases of acute food protein-induced enterocolitis syndrome

| Year | Ref. | Gastrointestinal | Surgical | Infectious | Allergic | Other |
|------|------|------------------|----------|------------|----------|-------|
| 1963 | [12] | Volv             |          |            |          | FPos, Munch |
| 1992 | [13] | GE               | Se       |            |          |       |
| 1996 | [14] | GE               | Se       | Ana        |          |       |
| 1998 | [15] | APC              | Se       |            |          |       |
| 2000 | [16] | GE               | Se       | Isch       |          |       |
| 2003 | [17] | GE               | Se       | NeS        |          |       |
| 2003 | [18] | GE               | I        | Se         |          |       |
| 2005 | [19] | GE, APC          | NEC, I, HD | Se        |          |       |
| 2005 | [20] | GE               | Se       |            |          |       |
| 2006 | [21] | GE               | Se       |            |          | Ep    |
| 2006 | [22] | GE               | Se       |            |          | Ep    |
| 2007 | [23] | GE               | Se       |            |          |       |
| 2007 | [6]  | GE, APC          | I        | Se         |          |       |
| 2008 | [24] | GE               | Se       |            |          |       |
| 2009 | [3]  | GE               | I        | Se         |          |       |
| 2010 | [25] | PS               | Ana      |            |          |       |
| 2010 | [26] | GE               | Se       |            |          |       |
| 2011 | [27] | APC              |          |            |          |       |
| 2011 | [28] | GE               | Se       |            |          |       |
| 2011 | [29] | GE               | I        | Se         |          |       |
| 2011 | [30] | GE               | I        | Se         |          |       |
| 2012 | [31, 32] | GE           | AA       | Se         |          |       |
| 2012 | [32] | GE               |          | Ana        |          |       |
| 2012 | [33] | GE               |          | Ana        |          |       |
| 2012 | [34] | GE               | I        | Se         |          |       |
| 2013 | [35] | GE               |          |            |          |       |
| 2013 | [36] | GE               |          |            |          |       |
| 2013 | [37] | GE               |          |            |          |       |

AA, acute abdomen; Ana, anaphylaxis; APC, allergic proctocolitis; Ep, epilepsy; FPos, food poisoning; GE, gastroenteritis; HD, Hirschsprung disease; I, intussusception; Isch, ischemia; Munch, Munchausen’s syndrome; NEC, necrotizing enterocolitis; NeS, neurologic etiologies of recurrent shock; PS, pyloric stenosis; Se, Sepsis; Volv, volvulus.
This disease of infancy usually presents by 2 months, can show thrombocytosis [42], and can occur in the early neonatal period, even in preterm infants after the first feed [43]. Infants with allergic proctocolitis may present with rectal bleeding, but are otherwise well and thriving. Their symptoms may be caused by cow’s milk, sometimes transferred via the breast milk. The typical presentation is the emission of stools containing mucus and flecks of blood rather than as frank rectal bleeding. Other systemic features (such as failure to thrive or anemia) are usually absent [44]. After some time, this condition vanishes so this is usually a temporary disorder of early childhood. The diagnosis is made on the basis of a response to the exclusion of the offending food, either from the lactating mother’s diet or by substitution by extensively hydrolyzed formula. After this, bleeding should resolve in a few days. From these considerations, it is clear that allergic proctocolitis can be easily differentiated from acute FPIES.

Not always an acute presentation of FPIES comes to the attention of an allergist. As indicated in Table 1, anaphylaxis and food allergy are not the most frequently suspected conditions. This is due to the fact that the relation among the ingestion of food and the symptoms can be unclear. The presentation of an anaphylactic reaction in the emergency room can vary widely, but the reaction usually occurs within 1–15 min of exposure to the allergen. Less frequently, reactions can begin after 30 min or even after 1 h, as in FPIES. The anaphylactic patient may feel uneasy and become agitated, with tachycardia and tachypnea. Blood pressure may fall, causing fainting. Other symptoms – including itchy and flushed skin, throbbing in the ears, coughing, sneezing, hives, and swelling (angioedema) – clearly differentiate anaphylaxis from FPIES, which never involves skin [45].

An anaphylactic reaction may progress so rapidly that it leads to collapse, cessation of breathing, seizures, and loss of consciousness within 1–2 min. The reaction may be fatal unless treatment is given immediately. At presentation in the emergency room, anaphylaxis may not be recognized if it is triggered by a novel agent, if it is an individual’s first episode, or if it occurs in an infant or young child or in an aphonic, dyspnoeic, or unconscious individual [46].

When the history links it to the ingestion of a specific food, FPIES can be misdiagnosed as IgE-mediated food allergy. To differentiate the two conditions, the main tool is the sensitization test, indicating the presence of specific IgE to foods. FPIES is by definition a non-IgE-mediated food allergy, occasionally evolving to IgE-mediated food allergy [47].

A specific IgE determination and a skin prick test with foods form the basic diagnostic procedure for food allergy, and are necessary in FPIES. An oral food challenge (OFC), an inescapable diagnostic procedure in food allergy, is also recommended for FPIES [7]. However, as for anaphylaxis, an OFC carries intrinsic risks. Thus, in the current clinical practice a clinical history of delayed vomiting with hypotensive episodes after ingestion of a particular food can be considered sufficient to diagnose FPIES [1].

### Differential diagnosis of chronic food protein-induced enterocolitis syndrome

In cases of ‘chronic’ FPIES, the differential diagnosis is even more difficult. The diagnostic boundaries, in particular with other non-IgE-mediated gastrointestinal food allergies are blurred, and it is difficult to differentiate this condition from them. This underlines the need for a precise definition. In any case, in the literature the most frequently involved conditions are gastrointestinal and food allergy (Table 2 [12–19,21,22,24,26,27,29,30,31**, 32,34,36,48,49,50*,51*]).

The symptomatic similarities of allergic eosinophilic esophagitis (EoE) with chronic FPIES are postprandial vomiting, diarrhea, occasional blood loss, iron deficiency anemia, and possible protein-losing enteropathy [52]. This allergic inflammatory condition of the esophagus is characterized also by swallowing difficulty, food impaction, refusal of food, difficulty in infant feeding, poor weight gain, and poor response to standard antireflux treatment; dietetic management is important [53]. Practically, all the clinical features of infants with allergic enteropathy are common to ‘chronic’ FPIES. Diarrhea, failure to thrive, various degrees of vomiting, and, sometimes, hypoproteinemia, and anemia can be present in children emitting stools that contain not only blood but also neutrophils [54]. Mild anemia may progress to significant anemia associated with hypoproteinemia due to protein-losing enteropathy; this is confirmed by increased fecal α-1 antitrypsin. These clinical characteristics are present with different grades both in eosinophilic enterocolitis (EoC) and in eosinophilic gastritis (EoG) and the offending foods are the same as for FPIES. In our opinion, despite the fact that EoC and EoG are listed in the differential diagnosis of FPIES, there is no clear distinction among these allergic enteropathies and chronic FPIES.

In some cases, celiac disease came into differential diagnosis with FPIES (Table 2). Common features of celiac disease may include diarrhea, abdominal distention, symptoms of malnutrition.
### Table 2. Differential diagnosis in reported cases of chronic food protein-induced enterocolitis syndrome

| Year | Ref | Gastrointestinal | Metabolic | PIDs | Allergic | Other |
|------|-----|------------------|-----------|------|----------|-------|
| 1963 | [12] | CD               |           |      | FA       |       |
| 1982 | [48] | CD               |           |      |          |       |
| 1992 | [13] | MD               |           |      | FA       | dx-1AT|
| 1996 | [14] |                  |           |      |          | FA    |
| 1998 | [15] | CD, EoEC, EoG    |           |      |          |       |
| 2000 | [16] | CD, IBD, GEF, EoG|           |      |          |       |
| 2003 | [17] | MD               |           |      | NeS      |       |
| 2003 | [18] |                   | Hy, UCD   | PID  |          |       |
| 2004 | [49] | CD, EoE, EoG     |           |      |          | FA    |
| 2005 | [19] | EoEC, EoG, MIR   |           |      |          | MD    |
| 2006 | [21] | MD               |           |      |          |       |
| 2006 | [22] |                   |           |      |          | MD    |
| 2007 | [6]  | EoG              |           |      | CoaD     |       |
| 2008 | [24] |                   |           |      |          | HFI   |
| 2009 | [3]  |                  |           |      |          | FA    |
| 2010 | [26] | EoG, EoEC        |           |      |          |       |
| 2011 | [27] | EoE, EoG, EoEC   |           |      |          |       |
| 2011 | [29] | MD               |           |      | FA       | Ht    |
| 2011 | [30] |                  |           |      |          |       |
| 2012 | [31**]| MD                |           |      |          |       |
| 2012 | [32] |                  |           |      |          | FA    |
| 2012 | [34] |                  |           |      |          | FA    |
| 2013 | [36] |                  |           |      |          |       |
| 2014 | [50*] |                 |           |      |          | FAv   |
| 2014 | [51*] |                 |           |      |          | TMAU  |

CD, celiac disease; CoaD, coagulation defect; dx-1AT, α-1 antitrypsin deficiency; EoE, eosinophilic esophagitis; EoEC, eosinophilic enterocolitis; EoG, eosinophilic gastritis; FA, food allergy; FAv, food aversion; GEF, gastroesophageal reflux; HFI, hereditary fructose intolerance; Hy, hyperammonemia; Ht, hypotension; IBD, inflammatory bowel disease; MD, metabolic disorders; NEC, necrotizing enterocolitis; PID, primary immunodeficiency; TMAU, trimethylaminuria; UCD, urea cycle defect.

### Table 3. Differential diagnosis between inborn errors of metabolism in patients presenting with acute clinical deterioration

| Parameter | FPIES | UCD | PA/MMA | HMG | KT | MSUD | β-OX | HI-HA | PDH | MITO |
|-----------|-------|-----|--------|-----|----|------|------|-------|-----|------|
| Ammonia   |       | 1   | 1      | 1   | 1  | 1    | 1    | 1     | 1   | 1    |
| Acidosis  | 1     |       | 1      | 1   | 1  | 1    | 1    | 1     | 1   | 1    |
| Glucose   | ±1    | 1   | 1      | 1   | ±1 | 1    | 1    | 1     | 1   | ±1   |
| Lactate   | 1     | 1   |       | 1   | 1  | 1    | 1    |       | 1   | 1    |
| SGOT/SGPT | 1     | 1   | 1      | 1   | 1  | 1    | 1    | 1     | 1   | 1    |
| CK        |       | 1   | 1      | 1   | 1  | 1    | 1    | 1     | 1   | 1    |
| Uric acid | 1     | 1   | 1      | 1   | 1  | 1    | 1    | 1     | 1   | 1    |
| WBC       | 1     | 1   | 1      | 1   | 1  | 1    | 1    | 1     | 1   | 1    |
| Ketonuria | 1     | 1   | 1      | 1   | 1  | 1    | 1    | 1     | 1   | 1    |

β-OX, beta oxidation defects; CK, creatine kinase; FPIES, food protein-induced enterocolitis syndrome; HI-HA, hyperinsulinism hyperammonemia syndrome; HMG, hydroxymethylglutaryl aciduria; KT, ketohiolase deficiency; MITO, mitochondrial disorders; MSUD, maple syrup urine disease; PA/MMA, propionic/methylmalonic aciduria; PDH, pyruvate dehydrogenase deficiency; SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase; UCD, urea cycle defects; WBC, white blood cell.
Table 4. Gastrointestinal manifestations in primary immunodeficiencies [58]

| Immunodeficiency                        | Evaluation with clinically significant result | Gastrointestinal manifestation                                                                 |
|----------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------------------|
| Common variable immunodeficiency       | Quantitative immunoglobulins — reduced IgG and IgA and/or IgM; antibody response (IgG) to vaccination — poor, nonprotective; lymphocyte subsets — normal or reduced B cell numbers | Diarrhea, nodular lymphoid hyperplasia, flat villous lesions, IBD-like disease, pernicious anemia |
| Selective IgA deficiency               | Quantitative immunoglobulins — serum IgA absent or near absent usually <10 mg/dl; normal IgG and IgM levels though IgG2 subclass deficiency may be present | Diarrhea, celiac sprue, nodular lymphoid hyperplasia                                            |
| Agammaglobulinemia, X-linked or autosomal recessive | Quantitative immunoglobulins — reduced serum IgA levels, antibody response (IgG) to vaccination — poor, nonprotective; lymphocyte subsets — normal numbers of pro-B cells; reduced/absent B cells | Gastrointestinal disorders rare, chronic diarrhea, malabsorption                                 |
| X-linked hyper IgM syndrome            | Quantitative immunoglobulins — normal to elevated IgM levels, low IgG and IgA; antibody response (IgG) to vaccination — poor, nonprotective; lymphocyte subsets — normal T cell numbers; B cell numbers are normal or slightly reduced | Diarrhea, progressive liver disease, sclerosing cholangitis                                    |
| Severe combined immunodeficiency       | Lymphocyte subsets — markedly diminished T cells; variable B cell and natural killer cell numbers depending on functional deficiency; in vitro assay of lymphocyte function — diminished response to mitogens PHA, ConA, PWM | Diarrhea, oral candidiasis                                                                       |
| DiGeorge syndrome                     | Quantitative immunoglobulins — immunoglobulins are usually normal though occasionally IgE is elevated and IgA may be reduced; lymphocyte subsets — variable decreases in T lymphocytes; B and natural killer cells are normal or elevated; in vitro assay of lymphocyte function — variable lymphocyte response to mitogens depending on thymic deficiency | Mucocutaneous candidiasis                                                                       |
| Immune dysregulation, polyendocrinopathy, enteropathy syndrome | Complete blood count — eosinophilia; quantitative immunoglobulins — may have increased serum IgE and IgA; lymphocyte subsets — CD4+CD25+ T cells are reduced most patients with FOXP3 mutations have markedly decreased or absent FOXP3+ Tregs; otherwise normal T cell and B cell subsets; in vitro assay of lymphocyte function — specific antigens are normal or slightly decreased | Severe enteropathy with watery often bloody diarrhea associated with eosinophilic inflammation |
| Bare lymphocyte syndrome              | Quantitative immunoglobulins — variable reductions; antibody response (IgG) to vaccination — poor, nonprotective; lymphocyte subsets — low numbers of CD4+ T cells with proportional increases in CD8+ T cells; flow cytometry-diminished expression of MHC; in vitro assay of lymphocyte function — impaired antigen specific responses | Progressive liver disease, sclerosing cholangitis                                                 |
| Chronic granulomatous disease         | Dihydrorhodamine reductase or nitroblue tetrazolium — diminished respiratory burst in neutrophils | Colitis, hepatic abscess, gastric outlet obstruction, small bowel obstruction, granulomatous stomatitis, oral ulcers, esophageal dysmotility |
| Wiskott–Aldrich syndrome               | Complete blood count — platelet numbers are reduced and small in size; quantitative immunoglobulins — variable concentrations secondary to accelerated synthesis and catabolism of IgG (usually low IgM, elevated IgA and IgE, and normal or slightly low IgG3); antibody response (IgG) to vaccination — impaired antibody response; lymphocyte subsets — moderate reductions in percentages of CD3+, CD4+ and CD8+ bearing T cells; in vitro assay of lymphocyte function — impaired lymphocyte response to mitogens | Colitis, bloody diarrhea, malabsorption                                                          |
| Hermansky–Pudlak syndrome             | Complete blood count — normal platelet count; coagulation studies — prolonged bleeding time, with abnormal platelet function assays | Granulomatous colitis                                                                            |

IBD, inflammatory bowel disease; ConA, concanavalin A; FOXP3, forkhead box P3; MHC, major histocompatibility complex; PHA, phytohaemagglutinin; PWM, pokeweed mitogen.
Adapted from [58].
such as short stature, anemia, defects in dentition, failure to thrive, or developmental delay. Some of these are common to chronic forms of FPIES; IgA antitransglutaminase is the standard of diagnosing and screening for celiac disease [55].

The inborn errors of metabolism are frequently reported in the differential diagnosis of FPIES. Urea cycle defects, organic acidemias, certain disorders of amino acid metabolism, and some inherited disorders of energy metabolism may present in infancy with general malaise and/or with sudden neurological deterioration [56]. Symptoms such as lethargy, apnea or tachypnea, and vomiting are the result of toxic effects of accumulating metabolites on the central nervous system; they represent an acute presentation of a chronic condition. In such cases, a handful of routine laboratory tests can give a rapid clinical indication:

1. Blood: Blood count, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, creatine kinase, electrolytes, uric acid, blood urea nitrogen and creatinine, glucose, phosphate, acid-base status, bicarbonate, anion gap, lactate ammonia determination;
2. Urine: Specific gravity, ketones.

If the clinician is oriented toward a metabolic condition, these few simple tests, combined with the list of metabolic diseases that may present with clinical and biochemical features resembling those of FPIES provided in Table 3, should give an indication at the onset. In case of strong suspicion, a metabolic specialist should be alerted without delay.

Recently, a specific metabolic differential diagnosis emerged. When FPIES is due to fruit, acute symptoms after fruit consumption are generally interpreted as hereditary fructose intolerance (HFI). The clinical presentation of the two conditions can be similar, so a careful evaluation of laboratory data is necessary. When atypical cases of HFI do not fulfil the ‘canonical’ diagnostic criteria, it has been suggested to involve an allergist [51].

Another metabolic disease involved in FPIES is trimethylaminuria (TMAU), an autosomal recessive disorder caused by excessive excretion into body fluids and breath of unoxidized trimethylamine (TMA) derived from the enterobacterial metabolism of dietary precursors. A case was described in which FPIES episodes (from rice, oat, and banana) produced a fish-like odor, typical of superfluous excretion of TMA [52].

In one report, FPIES in the chronic phase generated a clinical suspicion of primary immunodeficiency disease (PID) [18].

In our experience, such a differential diagnosis is not exceptional (see infra). Considering that the gastrointestinal tract is the largest lymphoid organ in the body, continuously exposed to antigen derived from food and bacteria [57], it is not surprising that many children with primary immunodeficiencies develop gastrointestinal symptoms [58]. Note the gastrointestinal manifestations may be the initial presentation of PID. Therefore, a careful history and evaluation should be carried out to exclude an underlying immunologic disorder.

A detailed list of the main gastrointestinal disorders reported in these patients is described in Table 4. From all these considerations, it appears that the possible differential diagnosis of chronic FPIES is very wide. It also includes psychosocial (Munchausen by proxy syndrome, food aversion),
neurological, and infectious (e.g. HIV, Salmonella, Yersinia) conditions. Although the clinical definition is vague, chronic FPIES is a factual entity in children not recognized for the syndrome, when they freely consume the offending food(s). In this situation, infants may incur the odyssey of FPIES.

THE ODYSSEY OF FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME CHILDREN

To exemplify the difficulties in the differential diagnosis of FPIES, we performed a retrospective evaluation of clinical records of children diagnosed with FPIES [59]. Between August 2012 and April 2013, three patients were diagnosed with FPIES from rice, apple, and fish. They had been admitted with acute symptoms including vomiting, pallor, and asthma. One had dehydration and diarrhea, none had fever. Two were admitted with a suspicion of sepsis, treated with antibiotics, steroids, and plasma. They had two, three, and four episodes, respectively, before diagnosis. After their stay in the emergency room, each child was admitted in a different ward: immunology, metabolic diseases, and general pediatrics. During their hospital stay, diagnostic evaluations included the specialists reported in Table 5. The table also includes the suspected conditions for which the specialists ordered supplemental diagnostic tests. The time lapse between the first episode and the diagnosis was 8 ± 2 months (with a median of three acute events before reaching the diagnosis). This illustrates how wide the spectrum of possible differential diagnoses can be, when a relatively simple clinical history could solve the problem. For this reason, we share the vision that educational interventions on FPIES are needed for hospital-based pediatricians to shorten the time lapse between the first episode and the diagnosis [2].

CONCLUSION

The risks of a late diagnosis are concrete for FPIES. The longer the delay, the greater the risk of unuseful diagnostic evaluations and erroneous treatments. These will entail costs and risks. FPIES is relatively easy to treat, and its diagnosis is relatively easy: knowing it is all that is needed. The effect of appropriate informative interventions has been described [60]. Thus, educational interventions on FPIES are needed for hospital-based pediatricians and general practitioners to shorten the time lapse between the first episode and the diagnosis [2].

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

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