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# Proposal for management of the infant with suspected food protein-induced allergic proctocolitis

To the Editor,

A 13-month-old girl was referred to our allergologic ambulatory because she presented hematochezia mixed with mucus in the stool when she was 2 months old; an endoscopy showed eosinophilic infiltrates in the rectal mucosa with lymphoid nodular hyperplasia. At the age of 3 months, a food protein-induced allergic proctocolitis (FPIAP) diagnosis was established. Her mother started a cow's milk (CM)-free diet and then, due to the persistence of hematochezia after a month from the beginning of the elimination diet, also an egg- and beef-free diet. Hematochezia disappeared when the child was 5 months old. Her mother continued CM-, egg-, and beef-free diet, and the girl has never eaten them. Her pediatrician believes that it is time to verify whether tolerance is reached and thinks it is necessary an expert opinion.

Is this the correct management of FPIAP, like suggested by current guidelines?

Sampson et al[1] declared "Dietary protein-induced proctitis/proctocolitis typically presents in infants who seem generally healthy but have visible specks or streaks of blood mixed with mucus in the stool. IgE to specific foods is generally absent. Milk protein is most commonly implicated, although multiple food allergens can be involved. Symptoms will resolve with dietary avoidance, which might include maternal dietary restriction in breast-fed infants. This condition typically resolves during infancy."

In 2015, Nowak-Wegrzyn[2] has extensively described the FPIAP. The author[2] describes the characteristics of FPIAP, pointing out that it is a benign disease with an excellent prognosis, and reports that elimination of offending food from the mother/child diet usually results in resolution of symptoms in the infants, typically within 48-72 hours. The author warns that the reintroduction of the guilty food within the first 6 months usually induces recurrence of bleeding. In fact, infants with FPIAP become tolerant to the offending food by one to 3 years of age and the majority achieves clinical tolerance by 1 year. In any case, Nowak-Wegrzyn[2] suggests that with negative skin prick test (SPT) and serum food-specific IgE antibody levels, food introduction typically takes place at home. Up to 20% of breastfed infants have spontaneous resolution of hematochezia without mother's elimination diet.[2]

Dello Iacono et al[3], in a paper of the Italian Society of Pediatric Allergy and Immunology (SIAIP), describing the FPIAP assert: "Because of it's typically caused by CM proteins, an extensive hydrolysate formula may be necessary. In a breast-fed child, mother's free diet of CM's proteins and derivates must be taken into account. Usually, symptoms disappear within 48-72 hours from the beginning of the free diet. Generally, at 1 year of age, the child can reassume the offending food without symptoms."

Therefore, the girl has been treated according to current guidelines. They all recommend the elimination diet for all children with FPIAP and a revaluation after the year of life, and so it was done. It is possible to think that 2 months of waiting, after the onset of the elimination diet, before hematochezia disappear are too many, and it is true of course. In this regard, Nowak-Wegrzyn[2] wrote that: "The persistence of rectal bleeding despite maternal dietary restrictions may be explained by inability to remove all sources of allergen from the diet or by an allergen that has not been identified." Perhaps, the girl's pediatrician has been using these 2 months in trying to identify all sources of allergen (cow's milk, egg, and beef) from the mother's diet.

Would it be possible to propose a different management for FPIAP? Among an informal survey performed on 117 Italian general pediatricians, 52% of these chose the elimination diet for all infants diagnosed with FPIAP, 14% chose this option only if anemia was present, 16% would not have chosen the elimination diet, and the remainder did not express a clear opinion (unpublished data). Therefore, management of FPIAP is not homogenous, probably because pediatricians believe that elimination diet is too important measure for a disease which could be considered mild. Below, we will present a new proposal for the management of the child with FPIAP, preceded by an analysis of the evidence of the literature we bring to its support.

Arvola et al[4] studied 40 infants (mean age: 2.7 months) with visible rectal bleeding. Most of the infants (68%) were fully breastfed. At enrollment, the infants were randomly allocated to receive a CM elimination diet (n = 19) or continue their previous diet (n = 21) for 1 month. The follow-up visits were scheduled 1 month later and at the age of 1 year. When evaluated in whole groups, a CM elimination diet did not affect the duration or severity of rectal bleeding during follow-up. The mean (range) number of days with rectal bleeding during follow-up was 5.6 (0-22) in infants who were randomly assigned to a CM elimination diet and 5.5 (0-20) in those randomly assigned to continue their normal diet ($P$ = .94). Also, the mean number of bloody stools per day during follow-up (2.1 in the whole population) and the time to the last occurrence of rectal bleeding (24 days in the whole population) were comparable in both groups. However, in patients who were later diagnosed to have CM allergy, random assignment to a CM elimination diet tended to shorten the duration of rectal bleeding as compared with those who were randomly assigned to continue their normal diet. CM allergy was confirmed by the reappearance of rectal bleeding and atopic eczema after reintroduction of CM to the diet of the infant in 1 case and to the lactating mother in another after a 1-month elimination period, then in 2 of 19 (10.5%) of the infants in the CM elimination diet group. Arvola et al[4] suggested that CM challenge is thus essential

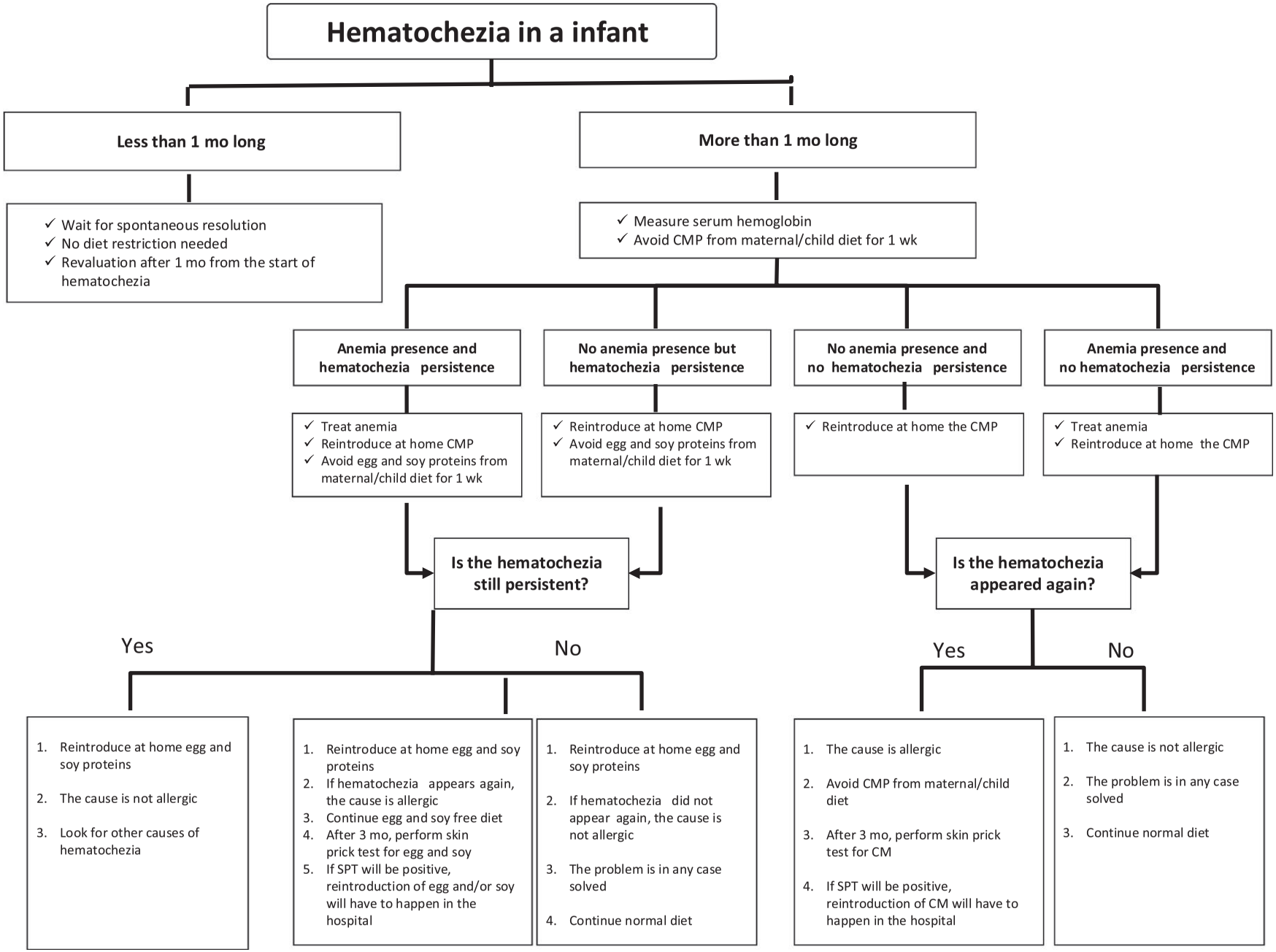


**FIGURE 1** A new proposal for the management of the infant with suspected FPIAP. FPIAP, food protein-induced allergic proctocolitis; CMP, cow's milk proteins; SPT, skin prick test

in infants who become symptom-free during a CM-free diet to reduce the number of false-positive CM allergy diagnoses.

Elizur et al[5] studied 21 otherwise healthy infants who were diagnosed as having rectal bleeding attributed to CM based on symptom presentation and response to elimination diet. Infants were evaluated at a mean age of 5.3 ± 2.1 months (2.9 ± 2.5 months following their initial presentation). Of the two infants with positive skin prick test (SPT) to CM, one had a negative oral food challenge (OFC) followed by regular consumption of CM-based formula, and the other refused OFC. Following evaluation, all families were recommended to reintroduce CM to the infants' diet along with an explanation that symptoms might recur. Fourteen of the evaluated families reintroduced CM to the infants' diet. In 11 of those who chose to reintroduce CM (78.5%), no adverse effects were noted. Three children developed symptoms upon reintroduction of CM (only 1 had rectal bleeding and other 2 had non-bloody diarrhea) and resumed their previous formulas.

We have taken note of the following remarks:

- Nowak-Wegrzyn[2] reported that up to 20% of breastfed infants with FPIAP have spontaneous resolution of bleeding without changes in the maternal diet and that the long-term prognosis of FPIAP is excellent;
- Arvola et al[4] and Elizur et al[5] reported that majority of their children with FPIAP gained tolerance in a few weeks and, furthermore, even without elimination diet[4];
- Elizur et al[5] reported that some patients show specific IgE for culprit food.[5] Nowak-Wegrzyn[2] recommends that with negative SPT and serum food-specific IgE antibody levels, food reintroduction takes place at home. Therefore, it seems appropriate to conduct a SPT with the eliminated food before its reintroduction.

For these reasons, we hypothesized a different management of child with suspected FPIAP, easier regarding the diet to follow.

The management pathway illustrated in Figure 1 is different depending on whether duration of hematochezia is less than/equal to 1 month or higher. We chose 1 month as cutoff because this is the sum of the maximum duration (21 days) of hematochezia during follow-up in children randomly assigned to continue their normal diet and the mean duration (10 days) of bloody stools before admission in the study of Arvola et al[4]

The most important points of our proposal are two:

- In case of hematochezia with duration less than or equal 1 month, we suggest waiting for the spontaneous resolution without elimination diet;
- In cases of a duration of more than 1 month, we suggest an elimination diet and, if hematochezia disappears, we suggest a challenge.

If after the challenge hematochezia reappears, then we suggest resuming the elimination diet for 3 months. In fact, Elizur et al[5] reported that after about 3 months of the beginning of the diet, the majority of children tolerated the guilty food. Before the reintroduction after a prolonged elimination diet, we suggest to perform a skin prick test. In fact, already on 2009, the Adverse Reactions to Food Committee of the American Academy of Allergy, Asthma & Immunology, in a paper on OFC,[6] suggested: "In general, if a patient has a negative skin test, undetectable serum food specific IgE level, and no history of convincing symptoms of immediate food allergy (eg, symptoms limited to behavioral changes or delayed/chronic gastrointestinal symptoms), gradual home introduction of the food in question may be attempted." And more recently, Nowak-Wegrzyn,[2] in her review on FPIAP, maintained that: "With negative skin-prick tests and serum food-specific IgE antibody levels, food introduction typically takes place at home, with gradual increase from 1 oz/day to full feedings over 2 week." Therefore, reintroduction at home is allowed only in case of negative SPT or negative food-specific serum IgE. Obviously, to verify the negativity of these tests, we must perform them. We suggest to perform it only if the diet is continued for more than 1 week, because we believe that an immune system reactivity's change is unlikely in a shortest time. So, even if the child is sensitized to the offending food, we believe unlikely that the patient may have an immediate adverse reaction to the culprit food if the reintroduction is carried out after only 1 week of elimination diet. However, this is just our opinion. This our suggestion is in line with our experience: we observed a child with FPIAP and positive prick test for CM, which, after 4 months of elimination diet, presented immediate urticaria at CM challenge (unpublished data). Making a prick by prick with, for example, fresh cow's milk in the office of pediatrician should be fairly simple. However, if it was found to be difficult to propose systematically to SPT before reintroduction of eliminated food, it could only be restricted to children with an atopic background, with increased risk of having positive specific IgE. In fact, our child with immediate urticaria (see above) had the atopic dermatitis and his father had suffered from cow's milk allergy.

Arvola et al[4] reported that only 1 patient exhibited extensive blood loss and developed anemia that required iron supplementation, yet already on admission. Moreover, blood transfusion with succeeding iron supplementation was given at the age of 8 months (6 months after admission) to 1 infant who developed iron deficiency anemia, the cause of which remained unexplained despite extensive examinations including gastroscopy and colonoscopy. All other children did not present anemia until 1 year of age, when they carried out a follow-up.

Elizur et al[5] compared 1-year hemoglobin levels in infants whose parents continued to eliminate CMP from their diet and in those who resumed CMP sooner. One-year hemoglobin levels did not differ between the 2 groups (12.26 mg/dL for those avoiding vs 12.25 mg/dL for those consuming CMP, $P = .98$).

So, risk of anemia seems to be very low. Anyway, our proposal expected performing the dosage of serum hemoglobin in case of hematochezia more than 1 month long.

In conclusion, we believe that our management proposal is easier to apply than the traditional one and is still based on scientific evidence.

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# Peanut oral immunotherapy dose variations do not result in allergic reactions

To the Editor:

Peanut allergy is the leading cause of death related to food anaphylaxis in the United States and a growing public health concern with the prevalence of peanut allergies tripling in the last 10 years, currently affecting 2% of the population.[1,2] It occurs early in life, and only 20% of children may outgrow their allergy causing a significant decline in quality of life.[3,4]

Peanut oral immunotherapy (POIT) has been demonstrated to be effective for peanut desensitization and 50% dose variations using different lots of peanut flour are tolerated in some POIT patients. POIT is administered daily with dose increments every 2 weeks. Doses are generally well tolerated with the incidence of home dose reactions at around 3.5%.[5] Symptoms range from mild-to-severe allergic reactions, with mild upper respiratory and cutaneous findings being the most common complaints.[5,6] Previously published POIT studies have demonstrated evidence of clinical desensitization and immunologic changes suggesting the development of potential long-term sustained unresponsiveness.[7,8] However, POIT is still an investigational treatment and is still not recommended for clinical practice. Adverse reactions are the primary concern during POIT treatment and occur commonly during up-dosing. Differences in potency between expired and unexpired lots of peanut flour could potentially result in allergic responses in POIT patients. The goal of this study was to demonstrate that POIT subjects could tolerate adjustments when transitioning from an expired to unexpired lot of peanut flour.

This single-center phase 1 peanut oral immunotherapy protocol was prospectively reviewed and approved by the Institutional Review Board of Baylor College of Medicine. Eleven subjects with peanut allergy from Texas Children's Hospital were enrolled. This protocol was performed similarly to prior protocols.[7] Inclusion criteria included the

**TABLE 1** Demographic and clinical data for peanut oral immunotherapy (POIT) subjects evaluated for dose variations and delta dose between the expired and unexpired peanut flour

| Variable | Peanut OIT subjects (n = 11) |
|---|---|
| Starting age, years; median (range) | 8 (5-12) |
| Male n (%) | 6 (55%) |
| Baseline peanut-specific IgE, kU/L; median (range) | 201.2 (20.4-707) |
| Baseline Ara h2 IgE, kU/L; median (range) | 165.5 (11.9-504) |
| Baseline peanut IHST, millimeters; median (range) | 20 (7-40) |
| 6-Month peanut IHST, millimeters; median (range) | 12 (3-29) |
| Threshold eliciting dose with entry food challenge, milligrams; median (range) | 75 (15-500) |
| Starting peanut OIT (POIT) dose, milligrams; median (range) | 3.6 (1.8-60) |
| Duration on POIT prior to dose change, months; median (range) | 3 (2-7.5) |
| Number of home doses administered during the lot-to-dosing analysis period | 3169 |
| Number of home doses causing an allergy reaction as a result of lot-to-lot variation; n (%) | 0 (0%) |
| Number of home doses causing mild-to-moderate reactions independent of lot-to-lot variation; n (%) | 105 (3.31%) |
| Number of home doses causing severe reactions independent of lot-to-lot variation; n (%) | 0 (0%) |
| "Delta dose" tolerated without reaction, milligrams; median (range) | 40 (14.4-450) |

POIT, Peanut oral immunotherapy.