Management of food protein-induced allergic proctocolitis in Italy: A nationwide survey by SIGENP

**LETTER**

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To the Editor,

The elevated prevalence of food protein-induced allergic proctocolitis (FPIAP) in both healthy subjects and patients with rectal bleeding contrasts with a lack of consensus on applied management protocols.

Food protein-induced allergic proctocolitis is recognized as a clinical entity, and its diagnosis relies on medical history and physical examination, as there is no precise diagnostic investigation available.

Confirmation of the diagnosis often involves observing the dis-appearance of symptoms upon the removal of a suspected food allergen and their recurrence upon reintroduction.

In rare instances, invasive procedures such as endoscopy with biopsy may be necessary[1], revealing focal or diffuse colitis marked by edema and erosions.

Food protein-induced allergic proctocolitis poses a common challenge for pediatric gastroenterologists, marked by a lack of standardized guidelines, and only management protocol suggestions. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) has produced a document with recommendations relating to milk protein allergy, within which it has issued a statement also dedicated to FPIAP[2].

Addressing this gap, we, on behalf of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP), conducted a nationwide electronic survey from January to September 2022 to provide the first analysis of allergic proctocolitis management in Italy.

The survey had a participation of 97 of 262 SIGENP members, representing 16 of 20 regions. The interviewed sample could there-fore be considered representative of the national context. However, broader participation could further improve geographical representativeness. Eighty- eight participants were pediatric specialists, and nine were residents, all specializing in the field of pediatric gastroenterology.

Notably, 94 of 97 respondents reported having encountered at least one case of FPIAP. We therefore considered the subsequent responses only from the 94 respondents with previous clinical experience of FPIAP.

Although consensus on the definition of this condition remains elusive, 88.7% of respondents classified it as a non-IgE-mediated food allergy, and 96.9% emphasized its onset in the first year of life, even among breastfed infants.

These data appear in line with what is suggested by the position paper of the European Academy of Allergy & Clinical Immunology (EAACI), in which FPIAP is described as a pathology that occurs pre-dominantly in the first 3 months of life[3].

Most respondents (78.4%) reported treating 1–10 FPIAP cases per year. The most frequently observed symptom in FPIAP patients was the presence of visible blood in the stool (99%), followed by mucus in the stool (56.3%) and diarrhea (41.7%). Approximately 50% of cases also had anemia at the time of diagnosis.

Regarding the suspicion of FPIAP, our results show that 64.9% of the respondents do not recommend in- depth examinations in the initial phase. Alternatively, 18.6% of physicians recommend stool culture, while 8.2% recommend abdominal ultrasound.

It is interesting to note that a retrospective analysis of 13 infants diagnosed with allergic proctocolitis in the United States found that 12 of them (92.3%) had abnormal ultrasound results. Notable ultrasound findings suggestive of colitis included increased vascularity and thickened bowel walls, particularly in the descending colon and sigmoid colon. These ultrasound findings were confirmed by colonoscopy and histopathologic examinations and confirmed the diagnosis of FPIAP in these infants[4]. In our survey, it was found that 69.8% of physicians do not typically perform allergy testing, while 30.2% recognized the potential value of such testing in the diagnostic process. Limited research has been conducted to evaluate the role of skin prick testing, patch testing, and serum IgE assessment specifically in the context of FPIAP[5].

Milk emerged as the most reported trigger, highlighted by 99% of survey participants. The literature extensively associates cow's milk proteins with FPIAP, though other food allergens may play a role[6]. For breastfeeding infants, recognizing the benefits of breast-feeding while eliminating cow's milk proteins from the mother's diet is crucial. Typically, clinical bleeding resolves within 1–2 weeks after complete removal of the offending protein, with improvement often observed within 72–96 h. If symptoms persist after 2 weeks, assessing maternal compliance is recommended, followed by potential elimination of soy and then egg from the maternal diet[7].

The use of atopy patch testing as a means of studying delayed sensitization has been proposed. However, it is important to note that international guidelines do not currently recommend patch testing as a routine diagnostic tool for non-IgE-mediated allergies[8]. In our survey, it was observed that 45.4% of respondents tend to change the order of food introduction during the weaning process, which often delays the introduction of certain food categories.

These data appear alarming if one considers that it has been widely demonstrated that the delayed introduction of major allergenic foods is related to a higher risk of IgE-mediated food allergy, which supports the updated guidelines for allergy prevention[9].

Regarding the healing times during diet therapy, different re-actions were reported: 51.5% reported resolution within 48–72 h, 44.3% within about a week, and 4.1% within 24 h.

In cases where the nutritional approach fails, endoscopy may be considered as a diagnostic resource (Figure 1).

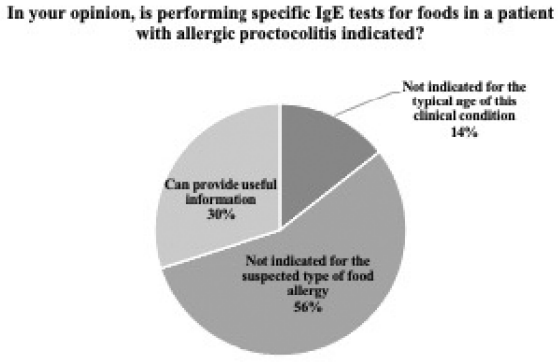
However, it is worth remembering that carrying out the endoscopic examination may be necessary even after the first evaluation in the presence of alarm signals (severe perianal disease, abdominal distension, growth failure, anemia, and poor general conditions) to rule out gastrointestinal infections, fissures Infantile polyp, necrotizing enterocolitis, Meckel's diverticulum, intussusception, and infantile inflammatory bowel disease[10]. The diagnosis of FPIAP in the literature is mainly based on clinical features, exclusion of trigger with an allergen-free diet, and the recurrence of symptoms

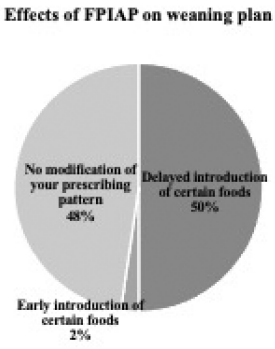
during an allergy challenge test. It is worth noting that the clinical features can sometimes be non-specific, and the etiology of rectal bleeding in children can have various causes. Therefore, it is important to rule out other possible causes of rectal bleeding in the pediatric age group, such as: bacterial infections, anal fissures, intestinal intussusception and, in infants, necrotizing enterocolitis and early- onset inflammatory bowel disease (IBD)[11].

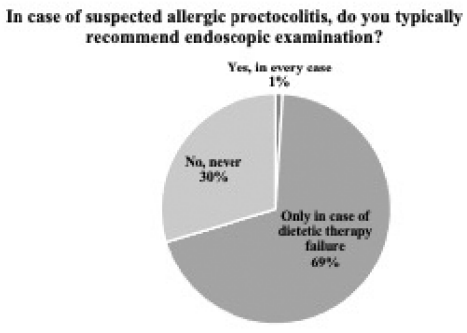
Hurrel et al. to provide practical diagnostic information for eosinophilic esophagitis and gastrointestinal diseases through histopathological findings. Looking specifically at allergic proctocolitis in infancy, they first found that the density of eosinophils in the colon varies between different segments (from 10 to 70 eosinophils per high- power field [HPF] in the cecum to 1–30 in the rectum). They also suggest that the mucosal architecture remains histologically in-tact in FPIAP, and the eosinophilic infiltration is typically localized in the rectum. They propose that greater than 60 eosinophils per 10 HPFs in the lamina propria along with eosinophilic infiltration in the epithelium or muscularis mucosae indicates FPIAP[12].

It is important to emphasize that rectal bleeding is not uncommon in otherwise healthy breastfed infants[13]. Approximately 12% of reported FPIAP cases in the literature occur in infants exclusively breastfed. However, identifying specific trigger foods is often challenging due to fluctuations in maternal food intake, and continued breastfeeding can lead to intermittent persistent bleeding.14

The optimal treatment for this group of infants is not yet clear and should be addressed on a case-by- case basis. According to 14.6% of survey respondents, there is a higher likelihood of developing functional gastrointestinal diseases (FGIDs) in patients with FPIAP.

Previous studies have identified FPIAP as a risk factor for FGIDs, lending support to the concept of “post-inflammatory” FGIDs[15].

It is important to underline that 43.8% of respondents believe that patients with FPIAP are more likely to develop another allergic disease later. In this context, pediatric gastroenterologists would need the assistance of an allergist when treating a case of FPIAP.

Survey participants underscored the imperative for further studies on FPIAP, emphasizing the need for elucidating its pathogenesis, immunological mechanisms, nutritional aspects, and potential biomarkers. Their collective stance highlighted a consensus on the necessity for specific guidelines to manage this condition. The sur-vey results emphasize the role of SIGENP in standardizing pediatric FPIAP management through key actions. Prioritizing the development of national consensus guidelines is crucial, providing a consistent framework for diagnosis and management. Additionally, establishing specialized pediatric training programs for practitioners is essential to enhance their proficiency in handling FPIAP cases. Exploring global data on pediatric FPIAP diagnosis and treatment is suggested to evaluate current practices and stimulate the development of harmonized protocols for consistent clinical approaches worldwide.

Our survey conducted represents a crucial step in understanding the clinical landscape of FPIAP in Italy. This methodology has allowed us to gain close knowledge of the current management of this condition and the needs highlighted by specialists for future improvement. It therefore appeared effective for the purpose set by SIGENP.

It is possible to report some other experiences worldwide. Suzuki H. et al. conducted a nationwide cross- sectional survey of on IgE-mediated gastrointestinal food allergies in Japan. From the analysis of their data, they recognize that FPIAP is a clinical reality of the first weeks of life and that the absence of specific guidelines may have underestimated the number of diagnoses[16].

In 2022, Granot M. et al. distributed a computerized questionnaire between pediatric gastroenterologists and immunologists. They identified significant practice variations in diagnosis and management of FPIAP between pediatric gastroenterologists and immunologists, with lack of adherence to society guidelines. The authors reiterated that joint task forces of primary care pediatricians, gastroenterologists, and immunologists should provide uniform guidelines to standardize care[17]. In summary, based on the survey results, it is recommended that SIGENP take responsibility for standardizing pediatric management of FPIAP. Furthermore, fostering collaborations with pediatric allergists and gathering global data would greatly enhance the assessment and refinement of protocols aimed at promoting uniformity in clinical practices for FPIAP.

## AUTHOR CONTRIBUTIONS

Maurizio Mennini: Conceptualization; investigation; writing – original draft. Elena Lionetti: Conceptualization; methodology; investigation. Monica Malamisura: Formal analysis; investigation. Giovanni Di Nardo: Conceptualization; validation; methodology. Renata Auricchio: Formal analysis; investigation. Paolo Lionetti: Validation; visualization. Claudio Romano: Validation; visualization; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

None to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.14109.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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