

Diagnosis and Management of Food Protein-Induced Allergic Proctocolitis in the pediatric age: A position paper from the Italian Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Italian Society for Pediatric Allergy and Immunology

Serena Coppola^{1,2,3,4}  | Laura Carucci^{1,2,3,4} | Caterina Anania⁵ | Renata Auricchio^{1,3} | Mariella Baldassarre⁶ | Mauro Calvani⁷ | Gaetano Cecere¹ | Enza D'Auria^{8,9}  | Fabio Decimo¹⁰ | Monica Malamisura¹¹ | Stefania Arasi¹²  | Osvaldo Borrelli¹³ | Francesco Paolo Brunese¹⁴ | Barbara Cuomo¹⁵ | Valentina Giorgio¹⁶ | Cristiana Indolfi¹⁰ | Massimo Martinelli¹ | Licia Pensabene¹⁷  | Silvia Salvatore¹⁸ | Renato Tambucci¹¹ | Angela Klain¹⁰  | Giovanni Marasco^{19,20} | Michele Miraglia del Giudice¹⁰ | Claudio Romano²¹ | Roberto Berni Canani^{1,2,3,4}

Correspondence

Roberto Berni Canani, Pediatric Allergy Program at the Department of Translational Medical Science, University of Naples "Federico II", Via Sergio Pansini 5, 80131 Naples, Italy.
Email: berni@unina.it

Abstract

Background: Food protein-induced allergic proctocolitis (FPIAP) is one of the most common phenotypes of food allergy in the first years of life. Several clinical aspects of FPIAP remain largely undefined, with a negative impact on its management. To bridge these gaps, a dedicated joint working group (WG) from the Italian Society for Pediatric Gastroenterology, Hepatology, and Nutrition (SIGENP) and the Italian Society for Pediatric Allergy and Immunology (SIAIP) was launched to provide practical evidence-based suggestions for the best diagnostic approach and management of this condition in pediatric age.

Methods: This position paper was developed by a multidisciplinary panel of experts in the pediatric food allergy field from SIGENP and SIAIP. A structured literature review was conducted, and consensus was achieved through the Delphi process. Key topics include anamnestic factors, clinical presentation, diagnostic criteria, differential diagnosis, the role of laboratory and endoscopic investigations, dietary management, reintroduction strategies, and long-term outcomes.

Results: The panel proposes a structured diagnostic approach emphasizing the role of a focused clinical history, response to the elimination diet, and recurrence of

Serena Coppola and Laura Carucci are contributed equally to this work.

For affiliations refer to page 11.

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symptoms during the oral food challenge. Best strategies for the elimination diet in different clinical settings and for the appropriate use of diagnostic tools were also addressed. The paper underscores the importance of avoiding overdiagnosis and unnecessary diagnostic procedures and dietary restrictions, which can impact management, nutritional status, and quality of life.

Conclusion: This position paper provides practical, evidence-based recommendations for the diagnosis and management of FPIAP in infants. The guidance aims to reduce diagnostic errors and delays and to promote appropriate, non-invasive, and family-centered care.

KEYWORDS

breastfeeding, calprotectin, elimination diet, endoscopy, food allergy, formula feeding, histology, occult blood test, oral food challenge, rectal bleeding

1 | INTRODUCTION

Food protein-induced allergic proctocolitis (FPIAP) is one of the most common non-IgE mediated food allergy (FA) phenotypes in early life worldwide.¹⁻³

Although position papers and guidelines are available for this condition, several clinical aspects of FPIAP, including the main anamnestic risk factors, the quantity or frequency of bloody/mucus stools to raise the FPIAP suspicion, the type and duration of elimination diet, remain largely undefined with a negative impact on its management.^{1,4-10} These issues further contribute to increasing the nutritional, psychosocial, and socioeconomic burden of the disease, including nutritional risk, heightened parental anxiety, and rising healthcare costs.⁴⁻¹⁰

To address these gaps, a dedicated joint working group (WG) from the Italian Society for Pediatric Gastroenterology, Hepatology, and Nutrition (SIGENP) and the Italian Society for Pediatric Allergy and Immunology (SIAIP) has been launched to provide practical evidence-based recommendations for the best diagnostic approach and management of this condition in the pediatric age, with the aim of standardizing clinical practice, avoiding overdiagnosis, and unnecessary dietary restrictions.

2 | METHODS

During the 2024 Annual Meetings of the SIGENP and the SIAIP, RBC proposed to the Presidents of both Societies the foundation of a SIGENP/SIAIP joint WG to promote collaboration and innovation in pediatric FA clinical practice and research. Thus, a Steering Committee composed of seven members, including the Chair (RBC), the Presidents of both Societies (MMdG, CR), the heads of Food Allergies WGs of both Societies (MC, RA), and junior members (LC, SC) of both Societies (SIGENP/SIAIP) was established. The Committee selected other WG affiliate experts in pediatric FA and representing diverse viewpoints, including family pediatricians,

Key message

FPIAP is a frequent and often mismanaged condition in early infancy. This work provides consensus-based recommendations from the SIGENP/SIAIP WG to support a standardized approach for diagnosis and management. This position paper aims to improve clinical practice, reduce misdiagnosis, and lessen the socio-economic burden on families and healthcare systems.

pediatric allergists and gastroenterologists, a dietitian, and a methodologist.

At the end, the SIGENP/SIAIP joint WG consisted of 25 representatives, members of both Societies coming from 16 Italian Centers (5 from the North, 5 from the Center, 6 from the South), and 1 UK Center (*see affiliations section*).

2.1 | Patient, intervention, comparison/intervention, and outcome (PICO) identification, literature review, and grading of the evidence

All the WG panel members participated in the Delphi process aimed at developing consensus statements for the diagnostic approach and management of FPIAP in the pediatric age.¹¹

All the WG panel members during the first meeting (May 2024) submitted a conflict-of-interest statement and identified 13 questions to answer the Patient, Intervention, Comparison/Intervention, and Outcome (PICO). The questions were debated/amended and approved at the end of the meeting.

Three members of the WG (RBC, LC, SC) performed a literature search to answer the PICOs, and then they provided references included in an online shared folder accessible to all members.

The literature search was performed on PubMed, Cochrane, Web of Science, and EMBASE databases. A summary table including

inclusion/exclusion criteria and databases consulted is outlined in [Appendix S1](#) together with the list of search terms used.

WG members drafted statements with a summary of the evidence to address the PICO questions. Each statement produced reported the quality of available evidence and the strength of the recommendation according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.¹² To evaluate the level of evidence (LoE), the following definitions were used: high (further research is unlikely to change confidence in the estimate), moderate (further research is likely to change confidence in the estimate), low (further research is very likely to change confidence in the estimate), very low (the estimate of the effect is very uncertain), or unable to assess using GRADE methodology. The LoE could be downgraded or upgraded according to different factors such as limitations or implementation in the study design, imprecision of estimates, variability in the results, indirectness of the evidence, publication bias, large magnitude of effects, dose-response gradient, or if all the plausible biases would reduce an apparent treatment effect. In addition, the recommendations also considered other factors such as alternative management strategies, variability in values and preferences, and the costs.

The strength of recommendation (GR) was assessed using the GRADE methodology, and the recommendations for the different clinical scenarios were classified into three categories: strong (desirable effects outweigh undesirable effects), weak (trade-offs are less certain), or consensus (the expert opinion supports the guideline recommendation even though the available scientific evidence did not present consistent results or controlled trials were lacking).

The finalized list of statements with the summary of evidence was edited and discussed in a 3-day telematics session. Thereafter, all participants were asked to provide the vote in a first blinded round in January 2025 to vote on their agreement with the statements using a 6-point Likert scale ([Table 1](#)) and to provide feedback on their clarity. When 80% of the Consensus Group agreed with a statement (A+ or A), this was defined as consensus. The agreement on all statements was reached after the first voting round except for PICO 7, which was revised and then approved after the second voting round. All the WG panel members participated and voted in both rounds.

Finally, the manuscript was drafted and reviewed by WG members for final approval.

TABLE 1 Six-point Likert scale.

Point	Description
A+	Agree strongly
A	Agree with minor reservation
A-	Agree with major reservation
D-	Disagree with major reservation
D	Disagree with minor reservation
D+	Disagree strongly

3 | RESULTS

3.1 | Summary of included studies

The systematic search identified 510 unique records. A total of 113 studies were included after the application of our predefined eligibility criteria. [Figure 1](#) illustrates the PRISMA flowchart for the studies screening and selection process.

3.2 | PICO 1: Which are the main anamnestic factors raising the suspicion of FPIAP in pediatric patients?

Statement: We suggest raising the suspicion of FPIAP in breastfed subjects, born by cesarean delivery, aged <6 months, with a positive family allergy risk, and concomitant presence of other atopic comorbidities, especially atopic dermatitis presenting the typical symptoms of FPIAP. GRADE: consensus. LoE: unable to assess using GRADE methodology. Agreement 100%.

A total of 70 articles, 31 observational studies,¹³⁻⁴³ 1 randomized controlled trial (RCT),⁴⁴ 8 case report/series,⁴⁵⁻⁵² 28 reviews,^{2-4,53-77} and 2 position papers^{5,78} reported data on anamnestic features of FPIAP pediatric patients. Among the case reports, only 1 confirmed the FPIAP diagnosis by oral food challenge (OFC),⁴⁵ whereas 23 observational studies analyzed OFC-confirmed FPIAP pediatric patients.^{21-42,44} The anamnestic features reported in these papers were age at symptom onset, sex, mode of delivery, gestational age, type of feeding, presence of family allergy risk, and other concomitant allergic manifestations.

Despite a causative association between anamnestic factors and FPIAP occurrence not being defined, literature analysis revealed that the main anamnestic features of FPIAP pediatric patients were having an age <6 months at symptom onset,^{21-42,44} being born at term,^{25,39,40,42,44} by cesarean section ranging from 55% to 85.7%,^{24-26,33,39-41,44} and being breastfed.^{22,23,25,27,28,31-33,35-38,40,42} No differences regarding sex have been reported.^{21,23,25,26,29-33,36-40} Other anamnestic features were a positive family allergy that was reported in 20%–60% of patients^{23,25,27,29,32,33,35,36,38,39,41,42,44} and the presence of concomitant allergic manifestations, which were reported in up to 78% of FPIAP patients.^{21,22,25,27-29,32,33,35,36,38-40,42,44} The most prevalent allergic manifestation was atopic dermatitis, which was reported in 7.6%–78% of OFC-confirmed FPIAP pediatric patients^{21,22,25,27-29,32,33,35,36,38-40,42,44} followed by wheezing, which was reported in 2.7%–26.3% of FPIAP patients.^{21,22,27,32,36,38}

Collectively, the main anamnestic features reported in FPIAP pediatric patients were age at symptoms onset <6 months, cesarean delivery, breastfeeding, presence of a positive family history for allergies and of other atopic comorbidities, mainly atopic dermatitis.^{5,78-80}

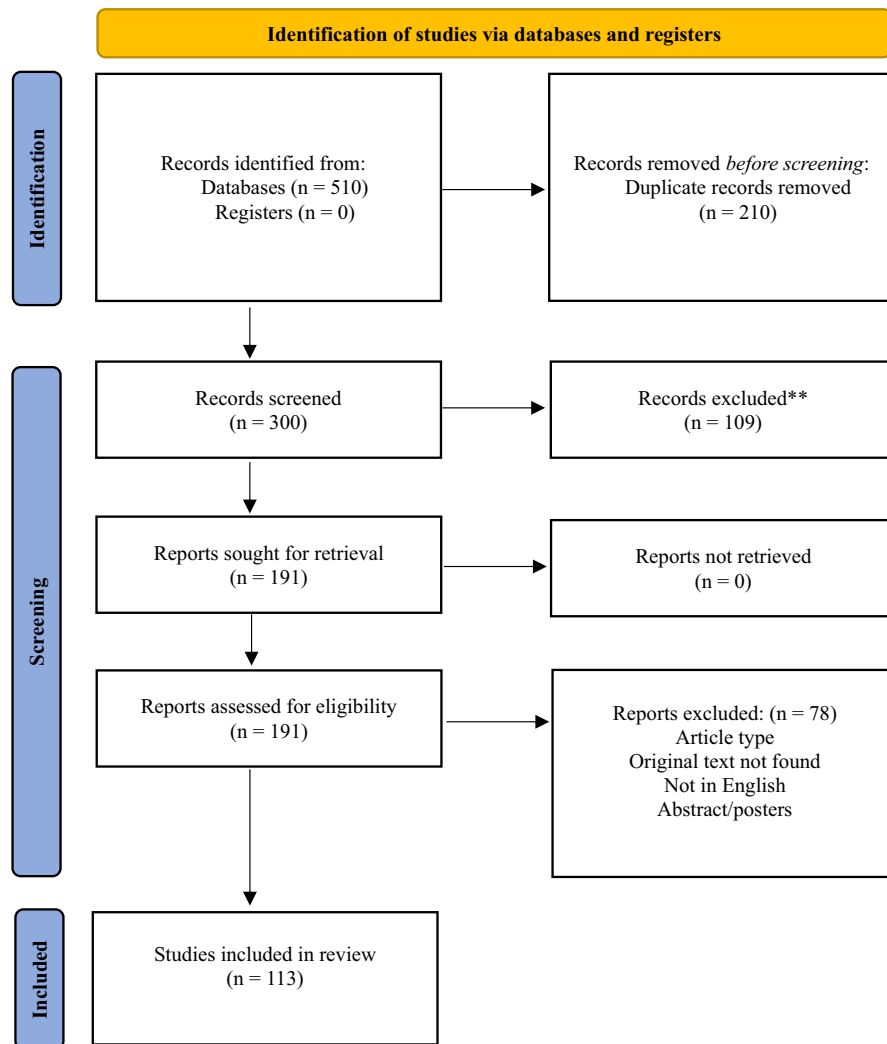


FIGURE 1 PRISMA flow-diagram. **No automatization tools were used.

3.3 | PICO 2: Which are the typical symptoms of FPIAP in pediatric patients?

Statement: We suggest the presence of macroscopic blood and/or mucus in the stools, in apparently healthy and thriving infants, as typical symptoms of pediatric FPIAP. GRADE: strong. LoE: low. Agreement 91.7%.

A total of 87 articles evaluated the typical symptoms of FPIAP, 7 case report/series,^{45,47-52} 33 observational studies,^{14-25,27-43,81-84} 1 RCT,⁴⁴ 43 review papers,^{2-4,10,53-64,67-73,75,76,79,80,85-100} 2 position papers,^{5,78} and 1 guideline paper.¹ Among these, only 1 case report,⁴⁵ 24 observational studies,^{21-25,27-43,81,83} and 1 RCT⁴⁴ analyzed OFC-confirmed FPIAP.

The main clinical features of FPIAP were the presence of macroscopic blood^{21-25,27-41,43-45,81} and/or mucus in the stools,^{22,25,27-29,31-33,35,37-42,44,81} in apparently healthy and thriving infants.^{21,23,27,33,37,43,81}

However, other symptoms reported in these studies were colicky behavior 0%–91%,^{25,28,32,35,40,44,81} diarrhea

0%–60%,^{25,28,32,38,42,44,81} feeding refusal 0%–53%,^{28,32,40} vomiting/regurgitation 0%–49%,^{25,28,32,35,36,38,40,41,44} constipation 0%–20%,^{25,40,44,45} and in up to 32% poor weight gain has been reported.^{32,35,38,81} The panel members considered that the presence of these symptoms could be due to possible overlaps with other non-IgE-mediated FA phenotypes and/or anemia deriving from diagnostic delay.^{32,35,38,81}

Perianal dermatitis and/or fissures were reported in up to 32% of FPIAP pediatric patients. In this case, the panel members suggest considering that the presence of hard and formed stools could be the cause of rectal bleeding and anal fissures themselves.^{28,35,38,39,45} Whereas the anal fissures related to FPIAP present more frequently with blood mixed in frothy and mucous stools.⁷³

The transient presence of macroscopic blood in the stools could be recognized in up to 34% of healthy infants.¹⁰¹ Despite the fact that the quantity/frequency of bloody and mucus stools in FPIAP patients has not been defined, the WG panel suggests raising the suspicion of FPIAP in the presence of persistent macroscopic blood and/or mucus in the stools for at least 7 consecutive or non-consecutive days in the last 4 weeks, especially in breastfed infants, born by cesarean section, aged <6 months, with a positive family allergy risk,

and concomitant presence of other atopic comorbidities, especially atopic dermatitis.

The presence of other additional symptoms like fever, severe intestinal bleeding, and persistent anemia despite adherence to the elimination diet is not typical of FPIAP, and they impose additional diagnostic work up to exclude other gastrointestinal diseases that could mimic FPIAP, such as anal fissure, intussusception, infections, transient idiopathic colitis, necrotizing enterocolitis, very early onset inflammatory bowel disease, Meckel's diverticulum, vitamin K deficiency, immunodeficiencies, ingestion of maternal blood during lactation through nipple fissures, vascular malformations, polyps, lymph node hyperplasia.^{1,36}

3.4 | PICO 3: How to perform the diagnostic elimination diet in breastfed infants with suspected FPIAP?

Statement: We suggest a period of 2–4 weeks of a diagnostic maternal elimination diet of cow's milk proteins in breastfed infants with suspected FPIAP. In case of symptom persistence, the elimination from the maternal diet of other allergens including soy, hen's egg, and wheat should be considered and based anamnesis, clinical history, and dietary habits of the mother. GRADE: strong. LOE: low. Agreement 83.4%.

A total of 76 papers evaluated the diagnostic maternal elimination diet, 3 case report/series,^{45,51,52} 3 position papers/guidelines,^{1,5,78} 1 RCT,⁴⁴ 31 observational studies,^{15,16,18,19,21,22,25,27–30,32–43,81,83,84,101–105} 38 review papers.^{2–4,7,8,10,53,55–59,61,62,64,65,67,69,70,72–77,79,80,85,90,92,93,96–98,100,106–108} Among these, only 1 case report,⁴⁵ 1 RCT,⁴⁴ and 17 observational studies^{21,22,25,27,28,30,32–38,42,43,81,83} reported data from OFC-confirmed FPIAP patients.

In the breastfed infants with suspected FPIAP, with at least 7 consecutive or not consecutive days of hematochezia in the last 4 weeks, a maternal elimination diet, followed by a diagnostic OFC, should be considered.¹ Only a few studies assessed the timing of symptoms resolution during the elimination diet period, reporting that blood in the stools disappeared in most cases within 3–4 days,^{28,32,38,83} even if in a small portion of patients bloody stools can last for 2 weeks.³² The timing of mucus disappearance is reported to be longer, up to 30 days.^{28,38} For this reason, a period of 2–4 weeks of diagnostic maternal elimination diet has been suggested by several observational studies, followed by a diagnostic OFC to confirm the FPIAP diagnosis.^{21,27,28,30,32,33,38,42,44,81}

Cow's milk (CM) resulted in the most common culprit food in FPIAP infants, but other allergens such as soy, hen's egg, and wheat have also been reported.^{15,16,18,19,21,22,25,27–30,32–43,81,83,84,101–105} Thus, a period of at least 2 weeks of maternal CM elimination diet resulted in the first step of the diagnostic process of infants with suspected FPIAP. In case of symptoms persistence, the elimination of other foods, for an additional 2 weeks, should be based on the

clinical history and dietary habits of the mother. The most commonly reported foods other than CM were soy, hen's eggs, wheat, and more rarely beef, corn, pear, nuts, rice, lentils, sesame, and grape.^{22,25,27,30,32,34,35,38,42,44,45,81} The persistence of macroscopic blood and/or mucus in the stools beyond this period should suggest the necessity of an extensive work-up to rule out the presence of other conditions in differential diagnosis.

3.5 | PICO 4: Which are the first and second choices for the diagnostic elimination diet and their duration in formula fed infants with suspected FPIAP?

Statement: We suggest for formula-fed infants with a suspicion of FPIAP a diagnostic elimination diet with extensively hydrolysed formula for 2–4 weeks. In neonates, in severe forms or in case of symptoms persistence for ≥ 2 weeks, the use of amino-acid-based formula should be considered. GRADE: consensus. LoE: very low. Agreement 91.7%.

A total of 30 papers, 10 observational studies,^{18,19,34,37,39,41–43,83,101} 2 case report/series,^{45,47} 17 reviews,^{2,4,53,57,58,60,62,64,65,67,69,72–74,93,94,107} and one guideline⁷ evaluated the dietary management of formula-fed FPIAP pediatric patients. Among these, only 8 observational studies,^{34,37,39,41–43,83,101} and 1 case report⁴⁵ reported data from OFC-confirmed FPIAP pediatric patients.

The use of an extensively hydrolyzed formula for 2–4 weeks resulted effective in symptoms remission in most of the formula-fed FPIAP pediatric patients; thus, it has been suggested as the first choice for the diagnostic elimination diet in formula-fed infants with suspected FPIAP.^{34,37,39,42,43,83,101} The use of amino acid-based formula (AAF) could be considered as the first choice in neonates, in preterm babies or as a second choice in case of symptoms persistence for ≥ 2 weeks. A diagnostic OFC after this period is needed to confirm the FPIAP diagnosis.^{4,5,34,37,39,41–43,83,101}

3.6 | PICO 5: How the diagnostic elimination diet in weaned pediatric patients with suspected FPIAP should be performed?

Statement: We suggest the elimination of suspected food antigens for 2–4 weeks in weaned pediatric subjects with suspicion of FPIAP. GRADE: consensus. LoE: very low. Agreement 100%.

A total of 21 studies evaluated the elimination diet in weaned pediatric subjects: 9 observational studies,^{15,18–20,32,33,38,39,81} 6 reviews,^{4,60,76,106,108,109} 4 case reports/series,^{46,49,51,52} 1 RCT,⁴⁴ and 1 guideline.⁷⁸ Only 5 observational studies^{32,33,38,39,81} and 1 RCT⁴⁴ provided data from subjects with OFC-confirmed FPIAP.

Data about diagnostic elimination diet in weaned pediatric subjects with suspected FPIAP is scarce. CM has been reported as the most frequent culprit food, although other foods have been reported, mostly soy, egg, wheat, and fish in weaned children.^{32,33,38,39,81} It has been reported that up to 42% of patients with FPIAP could be affected by multiple FAs.³⁸ In different FPIAP cohorts, nuts, corn, and beef have also been reported.^{32,33,38,81} In summary, despite the fact that CM is the most common culprit food responsible for FPIAP, the role of other foods and/or the presence of multiple FAs could be considered, and a 2–4 weeks' elimination diet should be designed according to anamnestic and clinical data, followed by the OFC to confirm the diagnosis.

3.7 | PICO 6: What is the usefulness of skin prick tests in identifying the culprit food in pediatric subjects with suspected FPIAP?

Statement: We suggest against the routinary use of skin prick tests in identifying the culprit food in pediatric subjects with suspected FPIAP. GRADE: strong. LoE: low. Agreement 100%.

A total of 33 articles evaluated the skin prick tests (SPT) in identifying the culprit food in pediatric subjects with FPIAP: 2 case reports/series,^{46,49} 1 guideline,¹ 13 observational studies,^{15,17,25,28,29,32,35,36,39,43,81,84,102} 1 RCT,⁴⁴ and 16 reviews.^{4,53,55,57,58,60,64,65,69,70,74,76,85,88,89,95} Among these, only 1 RCT⁴⁴ and 9 observational studies^{25,28,29,32,35,36,39,43,81} reported data from OFC-confirmed FPIAP pediatric patients. In subjects with FPIAP, SPT usually resulted negative.^{4,39,65,73} Several studies investigating SPT in FPIAP patients^{25,28,29,32,35,36,39,43,44,81} reported SPT positivity in up to 35% of patients.^{25,28,29,32,35,44,81} The presence of positive SPT was most common among patients with multiple FA, IgE-associated symptoms, and atopic dermatitis.^{32,35,36} Unfortunately, most of these studies did not correlate the SPT positivity to the allergen responsible for FPIAP.^{25,29,32,44,81} Only two OFC-confirmed studies showed that in a minority of FPIAP patients SPT identified the culprit food.^{28,35} In conclusion, the routine use of SPT for identifying the culprit foods in FPIAP patients is not recommended, but in selected cases, when an IgE-mediated mechanism is suspected and/or in the presence of atopic dermatitis or multiple FA, the use of SPT could be considered.

3.8 | PICO 7: What is the usefulness of atopy patch tests in identifying the culprit food in pediatric subjects with suspected FPIAP?

Statement: There is insufficient evidence to suggest for or against the use of atopy patch tests to identify the trigger food in pediatric subjects with suspected

FPIAP. GRADE: consensus. LoE: very low. Agreement 100%.

A total of 15 articles evaluated the role of atopy patch tests (APT) in identifying the culprit food in FPIAP patients, 1 RCT,⁴⁴ 3 observational studies,^{84,110,111} 11 reviews.^{4,64,65,67,69,70,76,85,88,89,112} Of note, in only 3 studies, the FPIAP diagnosis was confirmed by the OFC result.^{44,110,111}

The role of APT in identifying the culprit food in infants with FPIAP is widely debated. A recent systematic review evaluated the diagnostic accuracy of APT in children with OFC-confirmed non-IgE-mediated FAs.¹¹² Among the OFC-confirmed FPIAP patients, only two studies were found and reported different results.^{110,111} Arshi et al. reported a positive predictive value of 52.17% for all tested foods,¹¹⁰ whereas Alves et al. showed a 100% specificity with a negative predictive value (NPV) of 80.7%. Due to the lack of controversial data, current international guidelines do not recommend the routine use of APT.^{1,68} In conclusion, there is insufficient evidence to suggest for or against the use of APT to identify the trigger food in children with suspected FPIAP.

3.9 | PICO 8: What is the usefulness of serum food-specific IgE testing in identifying the culprit food in pediatric subjects with suspected FPIAP?

Statement: We suggest against the routinary use of specific food-specific serum IgE level measurement for identifying the culprit food in infants with suspected FPIAP. GRADE: consensus. LoE: very low. Agreement 100%.

A total of 29 articles evaluated the role of specific food-specific IgE serum levels in patients with FPIAP, 1 guideline,¹ 13 observational studies,^{15–18,25,28,29,32,36,37,39,41,113} 1 RCT,⁴⁴ and 14 reviews.^{4,53,55,60,69,70,73–77,85,89,90} Among these, 1 RCT⁴⁴ and 9 observational studies^{16,25,28,29,32,36,37,39,41} reported data from patients with OFC-confirmed FPIAP diagnosis.

Usually, FPIAP pediatric patients showed undetectable food-specific IgE serum levels.^{37,39,69,70,89,90} Some studies investigating serum food-specific IgE in FPIAP patients reported a positivity in up to 30% of patients, in particular in subjects with the concomitant presence of atopic dermatitis and in patients with multiple FAs.^{16,25,28,29,32,36,37,39,41,44} Unfortunately, most of them did not correlate the serum food-specific IgE positivity to the allergen responsible for FPIAP.^{16,25,29,32,36,37,39} A positive correlation between positive serum food-specific IgE levels and the food responsible for FPIAP was reported in a minority of patients in three studies.^{28,41,44} In conclusion, the routinary measurement of serum food-specific IgE levels for identifying the culprit foods in FPIAP patients is not recommended, but in selected cases, when an IgE-mediated mechanism is suspected and/or in the presence of atopic dermatitis or multiple FAs, their use could be considered.

3.10 | PICO 9: What is the usefulness of fecal occult blood and/or fecal calprotectin test in the diagnosis of pediatric subjects with suspected FPIAP?

Statement: We suggest against the use of fecal occult blood test and fecal calprotectin test in the diagnostic approach to pediatric subjects with suspected FPIAP.
GRADE: strong. LoE: moderate. Agreement 100%.

A total of 12 articles evaluated the role of fecal occult blood and/or fecal calprotectin in the diagnosis of FPIAP: 1 case report,⁴⁵ 5 observational studies,^{18,30,42,43,101} 6 review papers.^{4,60,65,70,85,109} Among these, only 1 case report paper⁴⁵ and 4 observational studies^{30,42,43,101} evaluated the role of these biomarkers in patients with OFC-confirmed FPIAP diagnosis. Fecal occult blood test (FOBT) has been proposed as a potential screening tool for the diagnosis of FPIAP in a few observational studies, mainly not OFC confirmed.^{18,42,43,101} In a prospective case-control study, Concha et al.¹⁰¹ evaluated the diagnostic accuracy of FOBT in a population of OFC-confirmed FPIAP versus healthy control infants. The FOBT resulted positive in 34% of healthy infants, suggesting that although the FOBT has adequate sensitivity to diagnose FPIAP in infants with rectal bleeding, this test had abnormal results in more than a third of healthy infants; therefore, the routine use of FOBT is not recommended for the diagnosis of FPIAP, because it can lead to FPIAP overdiagnosis. Accordingly, the FOBT test is not mentioned in any of the international guidelines.^{1,5,7}

Fecal calprotectin (FC) is a calcium- and zinc-binding protein primarily derived from neutrophils.⁴² Over the last 20 years, the role of FC in intestinal inflammation has been widely evaluated, particularly in diagnosing and monitoring inflammatory bowel diseases, but its role in FA is still widely debated. Zhang et al. conducted a systematic review to evaluate the value of FC in the diagnosis and monitoring of cow's milk protein allergy (CMPA); twelve studies including 310 patients and 217 controls were available for the meta-analysis. Of these studies, only 6 enrolled non-IgE-mediated FA patients, without distinguishing FPIAP from the other non-IgE-mediated FA phenotypes. The authors concluded that FC could act as a reliable and straightforward biomarker for diagnosing non-IgE-mediated CMPA infants and that it could be a helpful marker for predicting therapy response in children with CMPA.¹⁰⁶ On the other hand, Xiong et al., in a scoping review performed on thirteen studies with different study designs embracing 1,238 children affected by non-IgE-mediated FA, concluded that there is no sufficient evidence to confirm the use of FC both in diagnosis and monitoring of CMPA and predicting allergic diseases.¹¹³ The same conclusion has been reiterated in a wide review on non-IgE- or mixed IgE/non-IgE-mediated gastrointestinal food allergies by Calvani et al.^{5,7,85,96} In a recent prospective study evaluating OFC-confirmed FPIAP and healthy controls, although FC resulted higher in FPIAP patients, a high variability of FC levels was observed in both study groups.⁴²

Collectively, these data show that neither FOBT nor FC is useful in the diagnostic approach to pediatric patients with suspected FPIAP.

3.11 | PICO 10: What is the usefulness of invasive (i.e., endoscopy, histology) tests in the diagnosis of pediatric subjects with suspected FPIAP?

Statement: We suggest against the use of gastrointestinal endoscopy and histology in the diagnosis of pediatric subjects with suspected FPIAP, except in the case of presenting alarm symptoms. GRADE: strong. LoE: low. Agreement 100%.

A total of 28 articles evaluated the role of endoscopy and histology in the diagnosis of FPIAP, 1 case report,⁴⁵ 11 observational studies,^{16,18,31,32,35-38,43,83,84} 14 reviews,^{3,4,8,58,65-67,69,70,72,74,77,91,106} and 2 guidelines.^{1,114} Among these, only 1 case report⁴⁵ and 9 observational studies^{16,31,32,35-38,43,83} evaluated the role of these procedures in pediatric patients with an OFC-confirmed diagnosis of FPIAP.

The diagnosis of FPIAP is based on the presence of typical symptoms that resolve within a few days of elimination diet and reappear after the reintroduction of the culprit food. However, in some studies, due to the presence of bloody stools, lower gastrointestinal endoscopy was performed in patients with suspected FPIAP. The main endoscopic features were focal erythema, friable mucosa, and increased nodule formation, suggestive of nodular hyperplasia, that is not pathognomic for FPIAP.^{36,38,45,83} Histologically, FPIAP patients may present focal infiltrates of eosinophils in all mucosal compartments, particularly the presence of large numbers of eosinophils in the lamina propria (>60 eosinophils per 10 high-power fields)^{16,35-38,43,83} but also in this case, these aspects are not specific to FPIAP but can also be shared by idiopathic neonatal transient colitis (INTC) patients.⁸³

In the study of Jang et al., they examined 16 unaffected newborns with small and fresh rectal bleeding without diarrhea, fever, and bloating. Sigmoidoscopy was performed in all 16 patients: ten patients met the suggested histological criteria for FPIAP diagnosis, but only two cases were confirmed as FPIAP by a positive OFC. Most cases were INTC, which has similar clinical symptoms and histopathological findings as FPIAP but resolve spontaneously within the first week of life without dietary avoidance or medical treatment. Based on these results, the authors emphasized that INTC is often misdiagnosed as FPIAP despite biopsy without OFC testing,⁸³ highlighting that OFC is the gold standard for FPIAP diagnosis.

In conclusion, these data showed how the endoscopic and histological features of FPIAP patients are not pathognomic, and that these procedures are not useful to get the diagnosis of FPIAP. Otherwise, in case of atypical or alarm signs including constipation or diarrhea with mucous stools without blood, fever, weight loss,

severe intestinal bleeding, persistent anemia despite adherence to an elimination diet, or lack of clinical improvement after initiation of a maternal elimination diet in breast-fed infants or after the introduction of an AAF in bottle-fed infants, endoscopy with histological examination should be performed to exclude other gastrointestinal diseases that may mimic FPIAP, such as anal fissure, intussusception, infections, transient idiopathic colitis, necrotizing enterocolitis, very early onset inflammatory bowel disease, Meckel's diverticulum, vitamin K deficiency, immunodeficiencies, ingestion of maternal blood during lactation through nipple fissures, vascular malformations, polyps, lymph node hyperplasia.^{1,36}

3.12 | PICO 11: How to perform the diagnostic oral food challenge in pediatric subjects with FPIAP?

Statement: We suggest the open OFC in pediatric patients with suspected FPIAP, with a gradual re-introduction of the allergen and at least 2 weeks of observation period. IgE-mediated protocol should be adopted in the case of positive food-specific IgE and/or signs and symptoms of IgE-mediated FA. GRADE: strong. LoE: low. Agreement 100%.

A total of 26 articles evaluated how to perform the diagnostic OFC for the diagnosis of FPIAP: 13 observational studies,^{15,18,24,26,28-30,33,36,37,42,43,83} 1 RCT,⁴⁴ 11 reviews,^{53,57,58,64,65,67,69,70,73,85,90} and 1 guideline.¹ Among these, only 1 RCT⁴⁴ and 11 observational studies^{24,26,28-30,33,36,37,42,43,83} evaluated this aspect in pediatric patients with OFC-confirmed FPIAP diagnosis.

The OFC is the gold standard for FPIAP diagnosis and should be performed after a 2–4 weeks elimination diet.^{1,65} We aimed at defining the methods and the protocol of OFC in FPIAP infants. The double-blind placebo-controlled food challenge (DBPCFC) is widely reported as the gold standard and most specific diagnostic test, especially when subjective symptoms are expected.¹ However, due to the time-consuming, costly, and demanding nature of its implementation, clinical practice often adopts open OFC, especially in the case of objective and delayed reactions for FPIAP.^{64,69,85} There is a lack of consensus regarding the dose and timing of challenge procedures as no standardized method has been established.^{24,26,28-30,33,36,37,42-44,83} One of the main issues is determining whether to provide the suspected culprit food through the maternal diet or directly to the child in a breastfed infant. Because of the lack of data comparing the two strategies, the decision should primarily be driven by whether the patient is still on exclusive breastfeeding or has already begun complementary feeding or formula intake.¹ The reintroduction of culprit food ranges from 1 day to 2 weeks in different studies by using different time and dosing protocols.^{24,29,30,33,42,44} In line with what is suggested by the EAACI and Imap guidelines, we suggest reintroducing CMP into the mother's

diet in an amount previously consumed over a 1-week period, if the baby is exclusively breastfed. If the baby receives formula, the OFC should be performed starting from 30 mL of regular CM in one bottle on the first day, by proceeding with a daily increase of 30 mL, until the age-appropriate portion has been reached by the end of 7 days. If no symptoms occur during this period, CM formula should be replaced in all bottles; then, a daily amount of the age-appropriate portion for an additional 2 weeks is needed to complete the OFC.^{1,115}

In children affected by atypical forms of FPIAP (serum specific IgE or SPT positivity), OFC must be carried out in the same way as the IgE-mediated forms. This protocol involves the administration of seven incremental doses of feed with increasing semi logarithmic protein: 0.003 g, 0.01 g, 0.03 g, 0.1 g, 0.3 g, 1.0 g, 3.0 g, interspersed with a small interval of time (20–30 min).^{29,42}

3.13 | PICO 12: Which is the most appropriate setting to perform the OFC in pediatric subjects with FPIAP?

Statement: We suggest a home OFC in pediatric subjects with FPIAP, except in cases of severe forms of FPIAP or in the presence of IgE type symptoms and/or IgE-test positivity. GRADE: strong. LoE: low. Agreement 100%.

A total of 31 articles evaluated the most appropriate setting to perform OFC for the diagnosis of FPIAP: 14 observational studies,^{15,18,25,28-30,33-36,38,42,101,116} 1 RCT,⁴⁴ 14 reviews,^{1,53,57-59,62,64,67,69,70,73,74,85,90} and 2 guidelines.^{1,115}

FPIAP is characterized by a low severity and delayed onset of symptoms; for this reason, the most recent guidelines suggest performing OFC at home.^{1,115} Analyzing observational studies, some of them performed the OFC at the hospital, with no immediate allergic reactions occurring.^{15,18,25,28-30,33-36,38,42,44,101,116} Whereas other studies did the OFC at home, especially in the case of lactating mothers in which the culprit food was reintroduced into the mothers' diet.^{28,33,38,39} Also, in these studies, no severe reactions were observed. Based on the available data, a home reintroduction could be the preferred strategy for FPIAP pediatric patients.^{1,101,115,116} The hospital setting should be considered in case of severe forms of FPIAP, defined as bleeding more than the form of spots, with mild to moderate anemia, in cases of IgE sensitization, IgE symptoms, and parental anxiety.^{28,29,33,44} Additionally, up to 10% of cases can develop IgE-mediated symptoms during the follow-up, with a negative impact on the disease course.^{25,29} For this reason, some authors suggest performing SPT or food-specific IgE before the reintroduction of the offending food at home.^{1,29} Based on this evidence, we suggest using this approach to perform a safe home reintroduction of the culprit food in FPIAP patients, and in cases of IgE symptoms, and/or SPT or food-specific IgE positive, we suggest performing the OFC in a hospital setting.

TABLE 2 Practice points and statements.

PICO	Statement	Level of evidence	GRADE	Agreement
1. Which are the main anamnestic factors raising the suspicion of FPIAP in children?	<i>We suggest rising the suspicion of FPIAP in breastfed subjects, born by cesarean delivery, aged <6 months, with a positive family allergy risk, and concomitant presence of other atopic comorbidities especially atopic dermatitis presenting the typical symptoms of FPIAP</i>	NA	Consensus	100%
2. Which are the typical symptoms of FPIAP in children?	<i>We suggest for the presence of macroscopic blood and/or mucus in the stools, in apparently healthy and thriving infants, as typical symptoms of pediatric FPIAP</i>	Low	Strong	91.7%
3. How to perform the diagnostic elimination diet in breastfed infants with FPIAP?	<i>We suggest for a period of 2–4 weeks of diagnostic maternal elimination diet of cow's milk protein in breastfed infants with suspected FPIAP. In case of symptoms persistence, the elimination from the maternal diet of other allergens including soy, eggs, wheat, fish, beef, corn should be considered and based on the anamnesis</i>	Low	Strong	83.4%
4. Which are the first and second choices for the diagnostic elimination diet and their duration in formula fed infants with suspected FPIAP?	<i>We suggest for formula fed infants with a suspicion of FPIAP a diagnostic elimination diet with extensively hydrolysed formula for 2–4 weeks, followed by an oral food challenge to confirm the diagnosis. In neonates, in severe forms or in case of symptoms persistence for ≥2 weeks, the use of amino-acid-based formula should be considered</i>	Very low	Consensus	91.7%
5. How the diagnostic elimination diet in weaned children with suspected FPIAP should be performed?	<i>We suggest for the elimination of suspected food antigens for 2–4 weeks in weaned pediatric subjects with suspicion of FPIAP</i>	Very low	Consensus	100%
6. What is the usefulness of skin prick tests in identifying the culprit food in infants with suspected FPIAP?	<i>We suggest against the routinary use of skin prick test in identifying the culprit food in pediatric subjects with suspected FPIAP</i>	Low	Strong	100%
7. What is the usefulness of atopy patch tests in identifying the culprit food in infants with suspected FPIAP?	<i>There is insufficient evidence to suggest for or against the use of atopy patch tests to identify the trigger food in pediatric subjects with suspected FPIAP</i>	Very low	Consensus	100%
8. What is the usefulness of food-specific IgE test in identifying the culprit food in infants with suspected FPIAP?	<i>We suggest against the routinary use of serum food-specific IgE test in identifying the culprit food in infants with suspected FPIAP</i>	Very low	Consensus	100%
9. What is the usefulness of fecal occult blood and/or fecal calprotectin test in the diagnosis of infants with suspected FPIAP?	<i>We suggest against the use of fecal occult blood test and fecal calprotectin test in the diagnosis of pediatric subjects with suspected FPIAP</i>	Moderate	Strong	100%
10. What is the usefulness of invasive (i.e., endoscopy, histology) tests in the diagnosis of infants with suspected FPIAP?	<i>We suggest against the use of lower gastrointestinal endoscopy and histology in the diagnosis of pediatric subjects with suspected FPIAP, except in the case of presenting alarm symptoms</i>	Low	Strong	100%
11. How to perform the diagnostic oral food challenge in infants with FPIAP?	<i>We suggest for an open OFC in pediatric patients with FPIAP, with a gradual reintroduction of the allergen and up to 2 weeks' observation period. IgE-mediated protocol should be adopted in the case of positive food-specific IgE and/or signs and symptoms of IgE-mediated FA</i>	Low	Strong	100%

(Continues)

TABLE 2 (Continued)

PICO	Statement	Level of evidence	GRADE	Agreement
12. Which is the most appropriate setting to perform the OFC in infants with FPIAP?	<i>We suggest for a home OFC in pediatric subjects with FPIAP, except in case of severe form of FPIAP or in the presence of IgE type symptoms and/or IgE-test positivity</i>	Low	Strong	100%
13. When is suggested to assess the acquisition of immune tolerance through the OFC in infants with FPIAP?	<i>We suggest for performing OFC to assess the acquisition of immune tolerance in FPIAP pediatric patients after at least 6 months of elimination diet. In case of FPIAP persistence, immune tolerance should be assessed every 6 months</i>	Moderate	Strong	100%

3.14 | PICO 13: When is suggested to assess the acquisition of immune tolerance through the OFC in infants with FPIAP?

Statement: We suggest performing OFC to assess the acquisition of immune tolerance in FPIAP pediatric patients after at least 6 months of elimination diet. In case of FPIAP persistence, immune tolerance should be assessed every 6 months. GRADE: strong. LoE: moderate. Agreement 100%.

A total of 30 papers reported data on the timing of assessment of the acquisition of immune tolerance through the OFC in pediatric patients with FPIAP: 13 observational studies,^{15,16,21,25,32-37,39,71,116} 1 case series,⁴⁹ 14 reviews,^{2,4,58,59,61,65,67,69,70,72-74,77,106} 1 RCT,⁴⁴ and 1 guideline.¹ Among these, only 1 RCT⁴⁴ and 11 observational studies^{16,21,25,32-37,39,116} evaluated this aspect in OFC-confirmed FPIAP pediatric patients.

When to perform OFC to assess immune tolerance is a debated point in FPIAP.¹ Based on the rate of immune tolerance acquisition among different observational studies, at 9–12 months of age up to 50% of patients acquired immune tolerance; the rest of the patients became tolerant at the age of 1–2 years (up to 30%); 2–3 years (10–15%); and at the age of >3 years about the last 5%.^{21,25,32,34,35} In different observational studies, in the case of positive OFC, the immune tolerance acquisition was assessed every 6 months.³³⁻³⁶ Based on this evidence, we suggest performing the OFC to explore the immune tolerance acquisition in FPIAP infants after 6 months of elimination diet, and in the case of FPIAP persistence, immune tolerance should be assessed every 6 months.

4 | DISCUSSION

Food Protein-Induced Allergic Proctocolitis is one of the most common non-IgE mediated FA phenotypes in early infancy, and usually has a favorable outcome. It occurs typically within the first 6 months of life. It is commonly associated with the presence of atopic dermatitis and a positive family history for allergies. It is possible that the FPIAP prevalence has increased over the last decade, but definitive data on this

trend are lacking. The actual prevalence ranges from 0.16% to 17% in the first 3 years of life, related to differences in the study populations, study design, diagnostic criteria, confirmation with OFC versus clinical diagnosis only.^{4,52} Due to these criticisms, the risk of overdiagnosis and mismanagement, including unnecessary dietary restrictions with the risk of nutritional deficiencies, impaired growth, and increased parental anxiety, is common in clinical practice.^{10,13,26,117} The joint SIGENP/SIAIP WG has used a systematic approach to generate clinical questions, search data, and reach consensus on recommendations for relevant aspects related to the diagnosis and the management of FPIAP in pediatric clinical practice (Table 2). A standardized approach for this condition could have a significant impact on clinical practice. By promoting evidence-based recommendations, it could reduce the current variability in the diagnosis and the management observed in clinical practice across different Centers. This shared approach may allow infants with suspected FPIAP to receive an early and accurate diagnosis, avoiding unnecessary dietary restrictions and prolonged elimination diets. Moreover, by adopting an evidence-based strategy, it would likely enhance cost-effectiveness by reducing redundant investigations and follow-up visits, and the socio-economic burden for both families and National Health Systems. Lastly, shared recommendations could facilitate communication and collaboration among healthcare professionals, supporting the development of structured care pathways and standardized follow-up protocols that improve long-term outcomes for affected infants.

AUTHOR CONTRIBUTIONS

Serena Coppola: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; writing – review and editing; formal analysis; project administration; data curation; supervision; resources. **Laura Carucci:** Conceptualization; investigation; writing – original draft; methodology; validation; writing – review and editing; formal analysis; project administration; data curation; supervision; resources. **Caterina Anania:** Investigation; writing – review and editing; writing – original draft; methodology. **Renata Auricchio:** Investigation; writing – original draft; methodology; writing – review and editing. **Mariella Baldassarre:** Investigation; writing – original draft; methodology; writing – review and editing. **Mauro Calvani:** Investigation; writing – original draft; methodology; writing – review and editing. **Gaetano Cecere:** Investigation;

writing – original draft; methodology; writing – review and editing. **Enza D'Auria**: Investigation; writing – original draft; methodology; writing – review and editing. **Fabio Decimo**: Investigation; writing – original draft; methodology; writing – review and editing. **Monica Malamisura**: Investigation; writing – original draft; methodology; writing – review and editing. **Stefania Arasi**: Investigation; writing – original draft; methodology; writing – review and editing. **Oswaldo Borrelli**: Investigation; writing – original draft; methodology; writing – review and editing. **Francesco Paolo Brunese**: Investigation; writing – original draft; methodology; writing – review and editing. **Barbara Cuomo**: Investigation; writing – original draft; methodology; writing – review and editing. **Valentina Giorgio**: Investigation; writing – original draft; methodology; writing – review and editing. **Cristiana Indolfi**: Investigation; writing – original draft; methodology; writing – review and editing. **Massimo Martinelli**: Investigation; writing – original draft; methodology; writing – review and editing. **Licia Pensabene**: Investigation; writing – original draft; methodology; writing – review and editing. **Silvia Salvatore**: Investigation; writing – original draft; methodology; writing – review and editing. **Renato Tambucci**: Investigation; writing – original draft; methodology; writing – review and editing. **Angela Klain**: Investigation; writing – original draft; methodology; writing – review and editing. **Giovanni Marasco**: Formal analysis; methodology. **Michele Miraglia del Giudice**: Conceptualization; investigation; methodology; writing – review and editing. **Claudio Romano**: Conceptualization; investigation; methodology; writing – review and editing. **Roberto Berni Canani**: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; writing – review and editing; formal analysis; project administration; data curation; supervision; resources.

AFFILIATIONS

- ¹Pediatric Allergy Program at the Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy
- ²NutriTechLab at CEINGE Advanced Biotechnologies, University of Naples "Federico II", Naples, Italy
- ³European Laboratory for the Investigation of Food-Induced Diseases, University of Naples "Federico II", Naples, Italy
- ⁴Task Force for Microbiome Studies, University of Naples "Federico II", Naples, Italy
- ⁵Department of Maternal, Infantile and Urological Science, Sapienza University of Rome, Rome, Italy
- ⁶Department of Interdisciplinary Medicine, Neonatology and NICU Section, University of Bari, Bari, Italy
- ⁷Operative Unit of Pediatrics, S. Camillo-Forlanini Hospital, Rome, Italy
- ⁸Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy
- ⁹Allergy Unit-Department of Pediatrics, Buzzi Children's Hospital, Milan, Italy
- ¹⁰Department of Woman, Child and of General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy
- ¹¹Gastroenterology and Nutrition Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
- ¹²Allergy Unit – Area of Translational Research in Pediatric Specialties, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
- ¹³Division of Neurogastroenterology and Motility, Department of Pediatric Gastroenterology, University College London (UCL) Institute of Child Health and Great Ormond Street Hospital, London, UK
- ¹⁴Primary Care Pediatrics, ASL Caserta, Caserta, Italy

- ¹⁵Central Operative Unit of Pediatrics and Allergy Center for Children and Adults, Santa Rosa Hospital, Viterbo, Italy
- ¹⁶UOSD Spina Bifida e Altre Branche Specialistiche, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
- ¹⁷Pediatric Unit, Department of Medical and Surgical Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy
- ¹⁸Department of Pediatrics Department of Medicine and Technical Innovation, "F. Del Ponte" Hospital, University of Insubria, Varese, Italy
- ¹⁹Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
- ²⁰IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
- ²¹Pediatric Gastroenterology and Cystic Fibrosis Unit, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy

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ORCID

Serena Coppola  <https://orcid.org/0000-0003-0421-7904>
 Enza D'Auria  <https://orcid.org/0000-0003-2750-5810>
 Stefania Arasi  <https://orcid.org/0000-0002-8135-0568>
 Licia Pensabene  <https://orcid.org/0000-0003-2043-5530>
 Angela Klain  <https://orcid.org/0000-0001-7823-2125>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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