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Diagnostic criteria for FPIES: can we do better?

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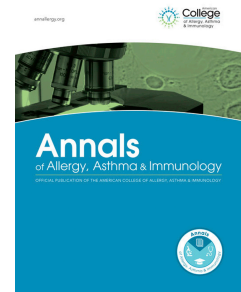
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Acute Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non IgE-mediated food allergy characterized by profuse vomiting usually 1-4 hours after ingestion. It often associates pallor, lethargy, diarrhoea, and can lead to hypotension/shock. It affects mainly infants when foods are introduced. There are no pathognomonic features or diagnostic biomarkers, partly because FPIES pathophysiology is poorly understood. Diagnosis is based on clinical history and it can be challenging, particularly for non-specialists. The clinical picture 'does not look like allergy', IgE-based tests are typically negative and some culprits are perceived as unlikely allergens. Also, FPIES differential is broad including sepsis, acute gastroenteritis, anaphylaxis, seizures, cyclic vomiting and abdominal processes ~~causes~~ such as intussusception. Therefore, misdiagnosis and diagnostic delay is common, leading to multiple reactions and significant impact on quality of life [1,2].

Awareness amongst healthcare professionals, which is poor and perceived as the top unmet need by parents [2], is key for diagnosis. A number of unvalidated diagnostic criteria sets (DCS) have been published to assist clinical diagnosis [1, 3-6]. However, DCSs have limitations and food challenges remain the gold standard. Challenges involve risks, expensive specialised resources and access is very limited. Thus, there is a need to improve our ability to accurately diagnose FPIES clinically.

Our group conducted a study assessing how published DCSs applied to a children cohort from Spain and Italy [7]. All met ~~meet~~ at least one DCS at onset and 98% (50/51) had had multiple reactions, so FPIES suspicion was high. Clear discrepancies were noted with positivity rates ranging from 92% (Lee's DCS) to 17.5% (Leonard's DCS). We assessed potential explanations for this heterogeneity.

First, whilst the high sensitivity of Lee's DCS might be positively perceived, it raises concerns about potential over-diagnosis. For instance, a child attending the emergency room with vomiting and diarrhoea would meet Lee's DCS for FPIES. Most such children will have acute gastroenteritis and not FPIES.

Interestingly, 24% (12/51) children did not meet the DCS proposed by the 2017 International Consensus on FPIES [1], the key reference for diagnosis and management. This was due to a relatively low proportion meeting some minor criteria, mainly FPIES reactions to multiple foods (18%, 9/51) and severity features such as hypotension/shock/hypothermia (6%, 3/51). Although multiple food FPIES this is reported in 35-78% in highly specialised USA centres, single food

FPIES seems the norm in other areas and less specialised centres [1,2]. Children in our cohort not meeting the 2017 Consensus DCS also presented less frequently with lethargy, diarrhoea, emergency room attendance and/or need for intravenous fluids [7]. This suggests that a proportion of children have milder presentations that, despite repeated reactions, do not meet the proposed DCS. A similar finding was observed at follow-up challenges in a recent publication by our group [8]. Other series report up to 20% of severe presentations, particularly with certain foods such as rice in Australia [1,2,3]. These heterogeneity in the severity spectrum should be acknowledged in revised DCSs, with a careful balance between sensitivity and specificity.

Reproducibility is a key feature in food allergy diagnosis, and particularly in FPIES due to the broad differential, absence of pathognomonic features and diagnostic tests. Whilst going through more than one reaction is undesirable, it is a common scenario especially in milder cases, and the key value of reproducibility towards increased specificity in DCSs should be acknowledged.

Less recent DCSs included an age limit ('below 9 months' in Powell/Sicherer's and Leonard's DCS, 'below 2 years' in Sopo's DCS). FPIES was classically considered an infants' disease, and this might have contributed to under-diagnosis in older patients. Adult-onset cases have been increasingly reported recently, highlighting that FPIES can occur at any age [9]. Also, some culprit foods may be introduced late in children's diet, such as fish, which was the culprit in 71% (36/51) in our cohort and only two thirds presented with FPIES by 9 months [7]. Thus, an age restriction in DCSs does not seem appropriate.

Most DCSs included exclusively gut symptoms or absence of IgE-mediated manifestations (skin, respiratory) as criteria. The former might be better described now as predominantly gastrointestinal with potential neurological and/or cardiovascular involvement. These features reflect the essence of FPIES reactions and should be included in DCSs. It may help prevent misdiagnosis with IgE-mediated reactions presenting with gastrointestinal symptoms. ~~This is important as the term 'atypical FPIES' i.e. IgE sensitization of unclear relevance in acute FPIES is increasingly used in clinical circles.~~ A clinical phenotype encompassing both acute FPIES plus IgE-mediated symptoms is rare both at onset and follow-up [7,8]. A minority of children, however, have so-called atypical FPIES, i.e. acute FPIES as per clinical criteria above and positive skin or serologic tests to the FPIES food trigger. Most such patients continue to manifest acute FPIES reactions but a subset might progress to more immediate-type reactions over time, which has implications for evaluation, management and prognosis [1,2].

Importantly, the absence of vomiting in acute reactions suggesting FPIES is reported in 25%-45% of recent adult series [9], and in a minority of children. Better understanding of the pathophysiology should clarify whether FPIES can occur with and without vomiting, or this relates to different entities. The possibility of FPIES without vomiting needs to be acknowledged in revised DCSs, at least for adults.

Other aspects may help in FPIES diagnosis. An increase in absolute neutrophils over $1500/\text{mm}^3$ from baseline is included as a criterion to assess food challenge outcomes but not for diagnosis at onset [1]. This was observed in virtually all children experiencing FPIES reactions at follow-up challenges in our study [8]. Whilst this may be present in common FPIES differential diagnoses such as sepsis, normalization within 24 hours in parallel with symptoms resolution may be a helpful addition to DCSs. Lastly, crampy abdominal pain is a dominant feature in 75-100% of adult series [9]. This might have been previously missed due to the focus on infants. Whether this adds in the diagnostic work-up against common differentials is unclear. Finally, particular features have been more commonly described in certain geographical areas, such as fever or blood in stools in Japanese patients [10]. A better understanding of the differences in FPIES phenotypes globally should help capture particularities that should be incorporated into DCSs.

In summary, we propose a new DCS (see table 1) that might improve diagnostic accuracy. Future studies should assess the usefulness of this proposal against the gold standard, food challenges.

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Table 1. Proposed diagnostic criteria for acute FPIES. Adapted from [1]. The major criterion and 3 points from the minor criteria are required to make a clinical diagnosis of acute FPIES.

Table 1.

Proposed diagnostic criteria for acute FPIES	
Major criterion	
Vomiting* in the 1- to 4-hour period after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms	
Minor criteria	
A second (or more) episode of repetitive vomiting* after eating the same suspect food	3 points
Repetitive vomiting* episode 1 to 4 hours after eating a different food	1 point
Extreme lethargy with any suspected reaction	1 point
Marked pallor with any suspected reaction	1 point
Need for emergency department visit with any suspected reaction	1 point
Need for intravenous fluid support with any suspected reaction	1 point
Diarrhea in 24 hours (usually 5-10 hours)	1 point
Hypotension	2 point
Hypothermia	2 point
Crampy abdominal pain	1 point
Nausea (if vomiting absent)	1 point
Increase in absolute neutrophil count > 1500/mm ³ with normalisation within 24 hours	1 point

*Vomiting may be absent in adults. In adults, 'gut symptoms, predominantly crampy abdominal pain' should replace 'vomiting' in the criteria above.

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