

# Journal Pre-proof

Diagnostic criteria for acute FPIES: what are we missing?

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**Title:**

Diagnostic criteria for acute FPIES: what are we missing?

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## Clinical implications

Acute FPIES may include different phenotypes including variable severity. Milder cases (1/4 in our Southern European cohort) might not be captured by the 2017 Consensus diagnostic criteria. This may lead to misdiagnosis and increased need for costly, potentially risky food challenges. Accurate diagnostic biomarkers need to be investigated.

To the editor,

Acute food protein-induced enterocolitis syndrome (FPIES) is a potentially severe and poorly understood non IgE-mediated food allergy. It usually presents in infancy when the culprit food is introduced. Patients experience repetitive vomiting usually 1-4 hours post-ingestion, often with lethargy, pallor, diarrhoea and potentially hypotension/shock. Although FPIES is considered a rare disease, recent data suggest a much higher prevalence than initially estimated [1]. This is probably partly explained by misdiagnosis and delayed diagnosis (only once patients have experienced multiple reactions), very common occurrences that compromise patients' safety and quality of life.

Several reasons contribute to poor diagnosis in FPIES. First, awareness amongst healthcare professionals other than allergy specialists is very limited. Symptoms 'do not look like allergy' (delayed onset, no skin or respiratory symptoms). Also, available (IgE-based) allergy tests are usually negative. Indeed, there is no accurate diagnostic biomarker for FPIES as the underlying biological mechanisms are poorly understood and only starting to be explored [2].

Therefore, diagnosis relies on clinicians' ability to suspect FPIES based on clinical history. In unclear cases, highly specialised centres may offer diagnostic oral food challenges (OFC) at onset. OFC are the gold standard for diagnosis but they involve risks, expertise and resources [2].

To guide clinical diagnosis, a number of unvalidated expert-driven Diagnostic Criteria Sets (DCS) have been used in the literature, including the most recent one from the 2017 International Consensus on FPIES - the key reference for FPIES care currently [2] . Inconsistencies across different DCS have been suggested when applied to individual patients [3]. However, the performance of different DCS have not been compared in larger cohorts. Also, series from around the world suggest geographical differences in acute FPIES phenotypes regarding type and severity of symptoms, culprit foods and prognosis [1, 4-6]. How these potential geographical particularities impact on the suitability of DCSs for FPIES diagnosis in given populations has not been explored.

Our study sought to compare how different DCSs used in the literature apply to a cohort of patients with high clinical suspicion of acute FPIES from Southern Europe, and to estimate potential limitations of available DCSs for that population.

Children aged 0-18 years with high clinical suspicion of acute FPIES were recruited from 11 tertiary allergy services from Spain and Italy as part of the multicentre BIO-FPIES study. Children were eligible if they met at least one of the following published DCSs: 1) Lee 2017 [4], 2) Nowak-Wegrzyn (International Consensus) 2017 [2], 3) Powell modified by Sicherer 1998 [7], 4) Sopo 2013 [8], 5) Leonard 2012 [9] (see Online repository text and Fig 1A for description of DCSs).

Detailed clinical history was gathered from medical records and interviews with patients/families at recruitment. Fulfilment of the above-mentioned DCSs was assessed. Positive rates for different DCSs were compared. Descriptive data, including clinical characteristics contributing to diagnosis were

analysed. Comparative analysis between the subgroups meeting vs not meeting DCS 2 were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Informed consent was obtained from parents/guardians. The study was approved by the Santiago-Lugo Research Ethics Committee, Spain (reference: BIO-FPIES, 2017/396).

Fifty-one children were included between 10/2017 and 06/2018. Clinical characteristics of the entire population and their initial acute FPIES reaction(s) -which contribute to the different DCS- are presented in Table 1. Median age at recruitment was 43 months (range: 17-144). Median age at onset: 9 months (1-72). 53% (27/51) children were male. 82% (42/51) had single food FPIES. Implicated foods were fish (70.6%, 36/51), milk (9.8%, 5/51), egg (9.8%, 5/51), shellfish (3.9%, 2/51), other (6%, 3/51). All but 1 patient (50/51, 98%) had experience multiple reactions to the culprit food. During the initial FPIES episode(s), 100% (51/51) of children experienced repetitive vomiting, 69% (35/51) pallor, 63% (32/51) lethargy and 43% (22/51) diarrhoea. 98% (50/51) had had more than one episode to the same food prior to diagnosis. Only 6% (3/51) had hypotension or hypothermia and only 27% (14/51) required iv fluids.

The proportion of children meeting the various DCS was: 1) Lee: 92.2% (47/51); 2) Nowak-Wegrzyn (International Consensus) 2017: 76.5% (39/51); 3) Powel modified by Sicherer: 64.7% (33/51); 4) Sopo: 43.1% (22/51); 5) Leonard: 17.6% (9/51). These differences were statistically significant ( $p<0.05$ ). A Venn diagram representing the number of study patients meeting the different combinations of published DCSs is presented in Fig. 1B. Individual patient data on diagnostic criteria are provided in the Online Repository Figure E1. Clinical characteristics of the subgroup meeting DCS 2 versus the subgroup not meeting DCS 2 [2], and their initial FPIES reactions are compared in Table 1. The subgroup meeting DCS 2 had higher rates of FPIES to multiple food, lethargy, diarrhoea, attendance to emergency department and need for intravenous fluids ( $p<0.05$ ) than the subgroup not meeting DCS 2.

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119 Our results show that existing expert-based unvalidated DCSs for acute FPIES provide conflicting  
120 results when applied to individual patients and cohorts. This may lead to inconsistencies in clinical  
121 practice and research in this area. Our results are partly explained by an age restriction in some DCS  
122 (e.g. age below 9 months, as 50% of our cohort first presented beyond that age) [7,9]. As FPIES is  
123 increasingly recognised as a condition that can affect any age including adults [2], such restriction has  
124 not been included in more recent DCS, which seems appropriate.

125

126 Importantly, despite meeting other DCS and having had multiple reactions to the culprit food in 98%  
127 of cases, 1 out of 4 children in our cohort did not meet the '2017 Consensus' DCS. This seems due to  
128 low rates of multiple food FPIES, hypotension, hypothermia, need for intravenous fluids and relatively  
129 low rates of lethargy and diarrhoea in our series, in line with previous observations from Southern  
130 Europe [5]. In contrast, series from the US or Australia have reported higher rates of multiple food  
131 FPIES or hypotension [4,6]. Whether this is purely due to geographical differences in FPIES  
132 phenotypes requires further investigation. Potential selection bias may play a role as historical  
133 cohorts -which have probably influenced available DCSs- seem to come from large complex referral  
134 centres..

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136 Our findings suggest that acute FPIES may include phenotypes with variable severity and milder cases  
137 might not be captured by the most recent 2017 Consensus DCS. This may lead to misdiagnosis and an  
138 increased need for diagnostic food challenges, which are costly and potentially risky. Although the  
139 balance between sensitivity and specificity of DCS is difficult -and overdiagnosis can be an issue as  
140 well-, potential variations in FPIES presentation should be further explored -including by thorough  
141 observational phenotyping at OFC- and reflected in DCS to improve their diagnostic performance. For  
142 instance, from our experience, it is unclear whether lethargy is generally extreme in FPIES reactions,  
143 as required in the 2017 Consensus DCS. In our study it was often difficult to determine whether

lethargy in previous reactions -when present- had been extreme, partly due to subjectivity in interpretation.

Our study highlights the need to validate DCS for FPIES against the gold standard, OFCs, and more importantly, to investigate the biological mechanisms underlying FPIES to develop definitive diagnostic biomarkers to avoid misdiagnosis in this poorly understood condition.

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## Tables/Figures legends

**Table 1.** Clinical characteristics of the population and their acute FPIES episode(s) at onset, including a comparison of the subgroup meeting the 2017 FPIES Consensus diagnostic criteria set (\*so-called 'DCS 2') vs the subgroup not meeting DCS 2 [2].

**Figure 1A.** Venn diagram representing the criteria included in the different Diagnostic Criteria Sets (DCS) available in the literature [2,4,7-9]. **Figure 1B.** Venn diagram representing the number of study patients meeting the different combinations of published Diagnostic Criteria Sets (DCS) [2,4,7-9]. For instance, only 3 patients met all 5 DCSs considered in the study.

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| Clinical characteristics                              | Entire sample<br>(n=51) | Groups                  |                             | p value            |
|-------------------------------------------------------|-------------------------|-------------------------|-----------------------------|--------------------|
|                                                       |                         | Subgroup meeting DCS 2* | Subgroup not meeting DCS 2* |                    |
| Study population                                      | (n=51)                  | (n=39)                  | (n=12)                      |                    |
| Gender (male, %)                                      | 53% (27/51)             | 54% (21/39)             | 50% (6/12)                  | >0.05              |
| Age at first episode in months (median, range)        | 9 (1-72)                | 9 (1-72)                | 9 (1-18)                    | >0.05              |
| Age at diagnosis in months (median, range)            | 12 (3-72)               | 12 (3-72)               | 16 (7-36)                   | >0.05              |
| Age at recruitment in months (median, range)          | 43 (17-144)             | 42 (17-131)             | 54 (20-44)                  | >0.05              |
| Age at most recent reaction in months (median, range) | 14.5 (2-108)            | 15 (4-107)              | 10 (2-108)                  | >0.05              |
| Multiple food allergies (%)                           | 35% (18/51)             | <b>43.6% (17/39)</b>    | <b>8.3% (1/12)</b>          | <b>0.027</b>       |
| Atopic dermatitis (%)                                 | 27.5% (14/51)           | 30.8% (12/39)           | 16.7% (2/12)                | >0.05              |
| Asthma (%)                                            | 11.8% (6/51)            | 12.8% (5/39)            | 8.3% (1/12)                 | >0.05              |
| Allergic rhinitis (%)                                 | 2% (1/51)               | 2.6% (1/39)             | 0% (0/12)                   | >0.05              |
| Chronic urticaria (%)                                 | 0% (0/0)                | 0% (39/39)              | 0% (0/12)                   | >0.05              |
| Atopic family background (%)                          | 56.9% (29/51)           | 53.8% (21/39)           | 66.6% (8/12)                | >0.05              |
| FPIES family background (%)                           | 0% (0/0)                | 0% (39/39)              | 0% (0/12)                   | >0.05              |
| Initial acute FPIES reaction(s)                       |                         |                         |                             |                    |
| Repetitive vomiting (%)                               | 100% (51/51)            | 100% (39/39)            | 100% (12/12)                | >0.05              |
| More than 1 episode to culprit food (%)               | 98% (50/51)             | 97% (38/39)             | 100% (12/12)                | >0.05              |
| No. reactions to culprit food (median, range)         | 3 (1-8)                 | 3 (1-7)                 | 4 (2-8)                     | >0.05              |
| FPIES to more than 1 food (%)                         | 18% (9/51)              | <b>23% (9/39)</b>       | <b>0% (0/12)</b>            | <b>0.07</b>        |
| Lethargy (%)                                          | 63% (32/51)             | <b>82% (32/39)</b>      | <b>0% (0/12)</b>            | <b>&lt; 0.0001</b> |
| Marked pallor (%)                                     | 69% (35/51)             | 74% (29/39)             | 50% (6/12)                  | >0.05              |
| Diarrhoea (%)                                         | 43% (22/51)             | <b>54% (21/39)</b>      | <b>8.3% (1/12)</b>          | <b>0.0057</b>      |
| Hypotension (%)                                       | 6% (3/51)               | 8% (3/39)               | 0% (0/12)                   | >0.05              |
| Hypothermia (%)                                       | 6% (3/51)               | 8% (3/39)               | 0% (0/12)                   | >0.05              |
| Younger than 9 months at onset (%)                    | 65% (33/51)             | 61.5% (24/39)           | 75% (9/12)                  | >0.05              |
| Younger than 2 years at onset (%)                     | 100% (51/51)            | 100% (39/39)            | 100% (12/12)                | >0.05              |
| Exclusively gut symptoms (%)                          | 100% (51/51)            | 100% (39/39)            | 100% (12/12)                | >0.05              |
| Absence of IgE-mediated symptoms (%)                  | 100% (51/51)            | 100% (39/39)            | 100% (12/12)                | >0.05              |
| Absence of symptoms on avoidance                      | 100% (51/51)            | 100% (39/39)            | 100% (12/12)                | >0.05              |

|                                        |             |                      |                    |               |
|----------------------------------------|-------------|----------------------|--------------------|---------------|
| Attendance to emergency department (%) | 55% (28/51) | <b>69% (27/39)</b>   | <b>8.3% (1/12)</b> | <b>0.0003</b> |
| Need for intravenous fluids (%)        | 27% (14/51) | <b>35.9% (14/39)</b> | <b>0% (0/12)</b>   | <b>0.0158</b> |

**Table 1.** Clinical characteristics of the population and their acute FPIES episode(s) at onset, including a comparison of the subgroup meeting the 2017 FPIES Consensus diagnostic criteria set (\*so-called 'DCS 2') vs the subgroup not meeting DCS 2 [2].

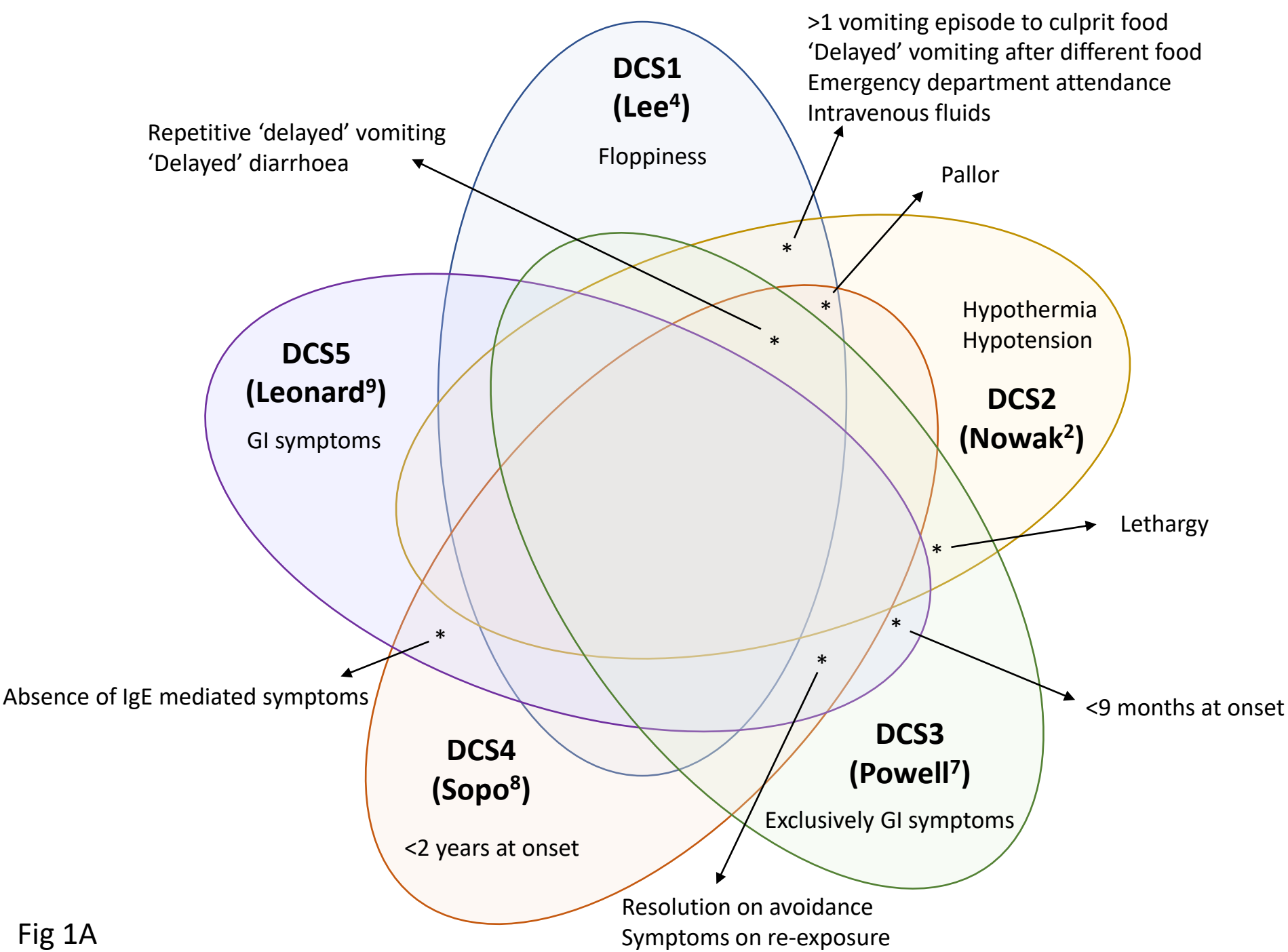


Fig 1A

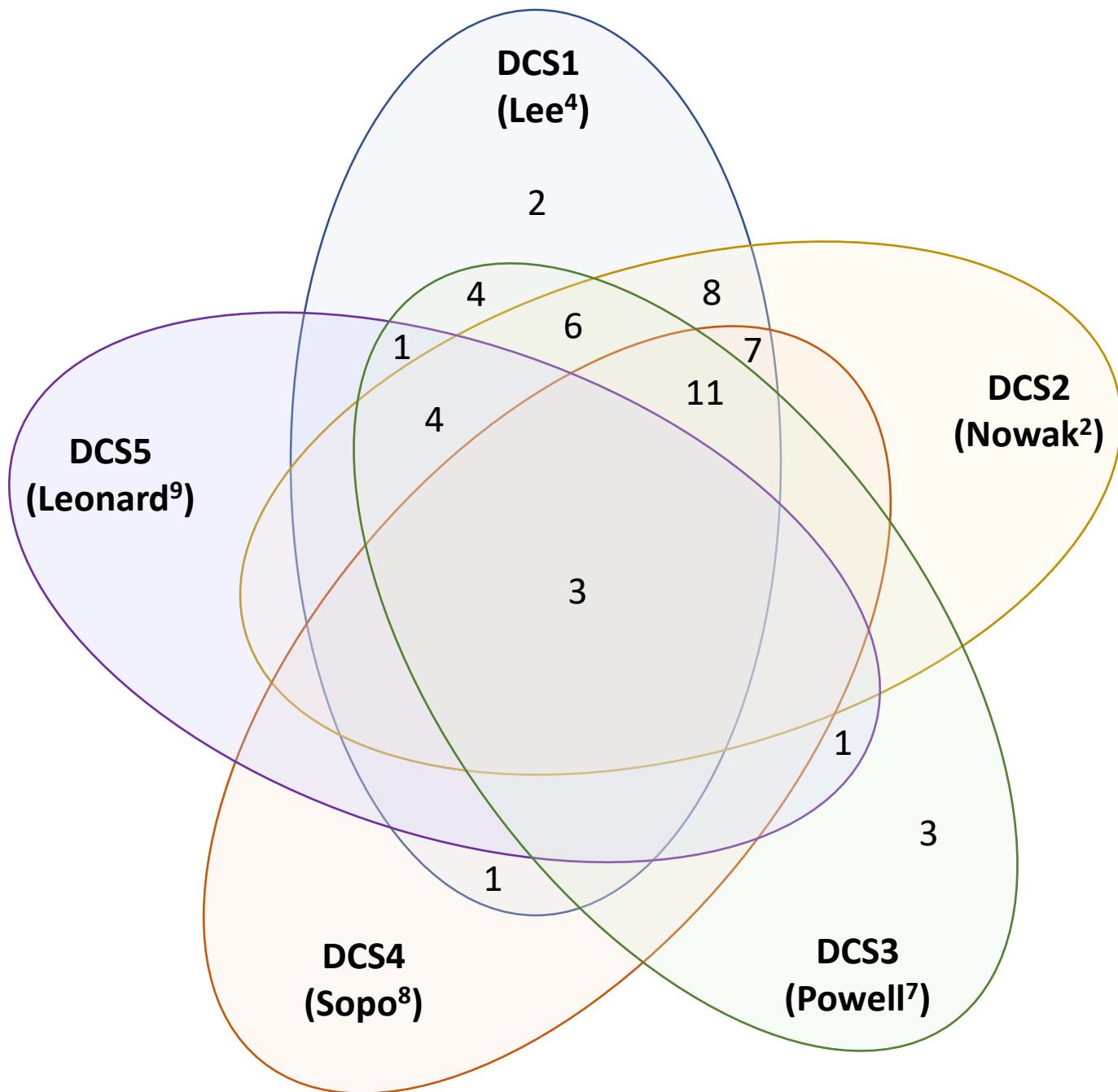


Fig 1B

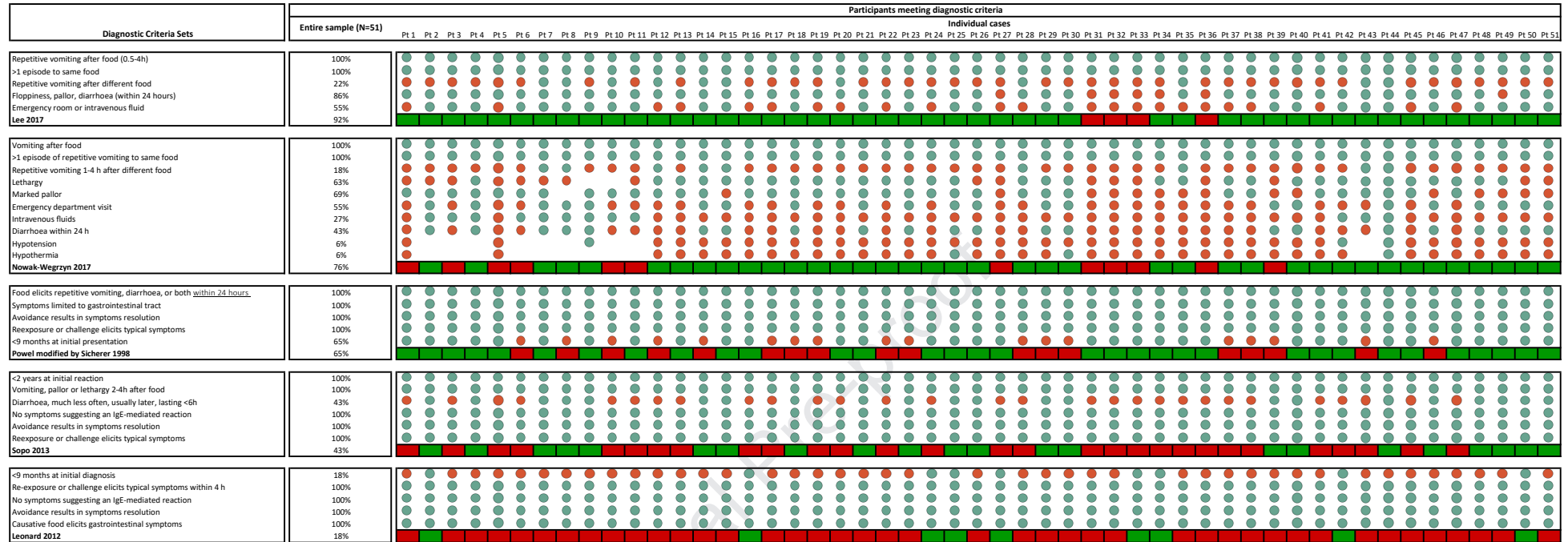


Figure 1.

Online repository text. Description of Diagnostic criteria sets for acute FPIES from the literature used for this study [2,4,7-9].

#### **DCS 1: LEE 2017 [4]**

This requires children to meet in their presenting episodes:

- Major criterion: repetitive vomiting (0.5-4 hours) after eating a suspect food(s) AND
- At least 2 of the following minor criteria:
  - A second (or more) episode of repetitive vomiting (0.5-4 hours) after eating the same suspect food
  - Repetitive vomiting episode (0.5-4 hours) after eating a different food
  - Associated floppiness, pallor, and/or diarrhoea (within 24 hours) during at least one episode
  - Need for an emergency room visit and/or intravenous fluid therapy during at least one reaction

#### **DCS 2: Nowak-Wegrzyn (International Consensus) 2017 [2]**

This requires children to meet in their presenting episodes:

- Major criterion: Vomiting in the 1- to 4-h period after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms AND
- At least 2 of the following minor criteria:
  - A second (or more) episode of repetitive vomiting after eating the same suspect food
  - Repetitive vomiting episode 1-4 h after eating a different food
  - Extreme lethargy with any suspected reaction
  - Marked pallor with any suspected reaction
  - Need for emergency department visit with any suspected reaction
  - Need for intravenous fluid support with any suspected reaction
  - Diarrhoea in 24 h (usually 5-10 h)
  - Hypotension
  - Hypothermia

#### **DCS 3: POWEL criteria modified by SICHERER 1998 [7]**

This requires children to meet all the following criteria in their presenting episodes:

- Less than 9 months of age at initial presentation
- exposure to the incriminated food elicits repetitive vomiting, diarrhoea, or both within 4 hours without any other cause
- symptoms are limited to the gastrointestinal tract
- avoidance of the offending protein results in symptoms resolution AND

- a standardized oral food challenge or isolated re-exposure elicits typical symptoms

#### DCS 4: SOPO 2013 [8]

This requires children to meet in their presenting episodes:

- Less than 2 years of age at first presentation
- Exposure to the incriminated food elicits repetitive and important vomiting, pallor, hypo-reactivity and lethargy within 2-4 hours
- Absence of symptoms that may suggest an IgE-mediated reaction
- Avoidance of the offending protein from the diet results in resolution of symptoms
- Re-exposure or oral food challenge elicits typical symptoms within 2-4 h. Two typical episodes are needed to deliver the definitive diagnosis
- Diarrhoea may be present, much less frequently and later. The symptoms last a few hours, usually fewer than 6 hours

#### DCS 5: Leonard 2012 [9]

This requires children to meet in their presenting episodes:

- Less than 9 months of age at initial diagnosis
- Repeated exposure to causative food elicits gastrointestinal symptoms without alternative cause
- Absence of symptoms that may suggest an IgE-mediated reaction
- Removal of causative food results in resolution of symptoms
- Re-exposure or oral food challenge elicits typical symptoms within 4 hours

#### Legend Figure E1

Diagnostic criteria sets (DCS) and individual criterion met by the entire sample and by individual participants (green dot means 'criterion met', red dot means 'criterion not met', green cell means 'DCS met', red cell means 'DCS not met', blank space means 'missing data') [2,4,7-9].