

Differentiating Acute Food Protein–Induced Enterocolitis Syndrome From Its Mimics: A Comparison of Clinical Features and Routine Laboratory Biomarkers



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What is already known about this topic? Misdiagnosis and delayed diagnosis are common in food protein–induced enterocolitis syndrome (FPIES) presentations due to a poor understanding of the underlying pathophysiology and lack of available point-of-care tests.

What does this article add to our knowledge? Clinical features obtained from a thorough history and physical examination remain vital in the diagnosis of acute FPIES. Elevated C-reactive protein, a marker of inflammation, is not a key feature of FPIES presentations.

How does this study impact current management guidelines? This study strengthens the evidence behind recently published international consensus guidelines for the diagnosis and management of FPIES.

BACKGROUND: Food protein–induced enterocolitis syndrome (FPIES) is frequently misdiagnosed and subject to diagnostic delay. Profuse vomiting, the cardinal feature of acute FPIES, may occur in more common pediatric disorders such as gastroenteritis and sepsis.

OBJECTIVES: We sought to determine differentiating features at acute presentation between FPIES, gastroenteritis, and sepsis in young children presenting to an emergency department (ED) with profuse vomiting.

METHODS: We conducted a retrospective case-control study of children aged 6 months to 4 years with a diagnosis of acute FPIES who had presented to ED and compared the clinical features, vital signs, and routine laboratory studies of this cohort to similarly aged children presenting to ED with vomiting diagnosed with bacterial/viral gastroenteritis or bacterial sepsis.

RESULTS: A total of 181 acute FPIES ED presentations were compared with 55 gastroenteritis and 36 bacterial sepsis ED presentations. Children with FPIES were more likely to present with lethargy, floppiness, and pallor. Compared with children with FPIES, children with sepsis were likely to present with fever, tachycardia, tachypnea, and diarrhea, whereas those with gastroenteritis were likely to present with fever, diarrhea, and blood in stools. Normal C-reactive protein (CRP), leucocytosis, lymphocytosis, thrombocytosis, low MPV, and an elevated albumin/globulin ratio were more commonly seen in FPIES than in sepsis or gastroenteritis. No other clinical or laboratory markers examined reliably distinguished between the 3 disease groups.

CONCLUSIONS: In the young vomiting child, lethargy, floppiness, pallor without fever, and normal CRP should alert clinicians to a possible diagnosis of FPIES. In contrast, a highly elevated CRP is not a feature of FPIES, and in such cases an alternative diagnosis must be considered.

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Key words: FPIES; Diagnosis; Bacterial sepsis; Gastroenteritis; Clinical features; Laboratory investigations; Full blood cell count; C-Reactive protein

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INTRODUCTION

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy that predominantly affects infants and young children. The clinical phenotype and incidence have significant regional variation, with 1 in 6400 Australian infants per year¹ estimated to have suffered from acute FPIES

Abbreviations used

BS- Bacterial sepsis
 CHW- the Children's Hospital at Westmead
 CRP- C-reactive protein
 ED- Emergency department
 FPIES- Food protein–induced enterocolitis syndrome
 GE- Gastroenteritis
 GGT- Gamma glutamyl transferase
 IQR- Interquartile range
 LFT- Liver function test
 MPV- Mean platelet volume
 NSW- New South Wales
 OR- Odds ratio

(although this likely underestimates true disease burden). Diagnosis is based on a characteristic constellation of symptoms, with profuse vomiting 1 to 4 hours after ingestion of the trigger food as the hallmark symptom. This may occur in conjunction with pallor, floppiness, lethargy, hypotension, and/or diarrhea.^{2,3} Almost all food groups have been described as causative triggers, with the most common triggers being cow milk, soy, and grains (especially rice).⁴

Diagnosing FPIES is often challenging due to the large number of disorders that present with vomiting. Furthermore, a lack of comprehensive understanding of the immune mechanisms driving FPIES reactions has impeded the development of useful point-of-care diagnostic tests. Although FPIES has historically been considered a T-cell–mediated response, recent studies suggest that the innate immune response may play a larger role in its pathophysiology.^{5,6}

The time delay between food ingestion and clinical reaction complicates accurate diagnosis. Infants often present numerous times to emergency departments (EDs) or health care providers before a correct diagnosis of FPIES is finally made.^{1,7} Abnormalities reported to date in routine blood biomarkers during acute FPIES are nonspecific. These include reports of leucocytosis, predominantly with neutrophilia, thrombocytosis, and in some chronic FPIES cases, methemoglobinemia and metabolic acidosis.^{2,8,9} Mild elevation in C-reactive protein (CRP) (0.88–13.4 mg/dL) accompanied by fever has been reported in 2 studies to date.^{6,10} Published international consensus guidelines do not recommend any routine investigations for the diagnosis of FPIES but suggest they may be helpful to exclude other differential diagnoses.²

Considering this, we sought to compare characteristics of clinical presentations and routine laboratory investigations from similarly aged infants and children attending the ED with vomiting as a key presenting symptom as a consequence of an acute FPIES reaction, bacterial sepsis (BS), or acute infectious viral/bacterial gastroenteritis (GE). We sought to identify potential characteristics and laboratory parameters that would assist in distinguishing these common disorders from acute FPIES.

METHODS**FPIES case identification**

Children aged 6 months to 4 years and with a diagnosis of FPIES were initially identified using the database of the Allergy Department, the Children's Hospital at Westmead (CHW), New South

Wales (NSW), Australia, between 1997 and 2017. Cases were then screened for inclusion criteria and included if (a) they had previously presented on at least 1 occasion to a NSW ED for a suspected episode of FPIES and (b) such presentations satisfied the diagnostic criteria from the recent international consensus guidelines with modifications⁵ (Table 1).

To identify and obtain medical records for all FPIES-related ED presentations, parental questionnaire and follow-up phone calls were conducted to determine whether children with a diagnosis of FPIES attending the outpatient allergy department at CHW had ever presented to a NSW ED. Medical records and pathology results from these FPIES episodes were obtained from each NSW hospital.

Sepsis and acute infective GE case identification

Children aged 6 months to 4 years who presented to the ED at CHW between 2012 and 2015 with vomiting as a major clinical feature, who were subsequently diagnosed with microbiologically confirmed BS and GE, were identified by using the CHW microbiology laboratory database. The inclusion criteria for sepsis and GE presentations are presented in Table 1. Patients were further randomly selected using RAND (random number generator function in Microsoft Excel) from the CHW Department of Microbiology database of all positive blood cultures, stool viral culture, or immunofluorescence and stool bacterial cultures reported from CHW ED presentations within the specified period. These cases were then screened for vomiting as a major clinical feature at presentation by review of emergency notes and clinical coding. Data for these episodes were also collected from CHW electronic and paper medical records.

Data collected

Prespecified data fields for all data collection were established. All data for analysis for all 3 patient groups were obtained from retrospective review of the medical records repository, including admission and discharge summaries, triage documentation, and pathology results. We sought information specifically on features at presentation; vital signs upon triage; blood tests including full blood cell count, electrolytes, urea, and creatinine, calcium, magnesium, and phosphate (CMP), liver function tests (LFTs), blood gas, CRP, and erythrocyte sedimentation rate, where available. Where appropriate, vital signs and blood tests were qualified with age-adjusted reference ranges adapted from CHW pathology department (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Statistical analysis

Nonparametric (χ^2 and Mann-Whitney tests) and logistic regression analysis with odds ratio (OR) estimates and 95% CI were used to compare FPIES with BS and FPIES with GE using SAS version 9.4 (SAS Institute Inc., Cary, NC) and GraphPad Prism 7 (GraphPad Software, La Jolla, Calif). A *P* value of .01 or less was considered significant. Each ED presentation of FPIES was considered a discrete episode of FPIES for statistical purposes. Not all children identified had a complete set of laboratory investigations at presentation to the ED. No imputation for missing data was performed. Ethics approval was granted by the Sydney Children's Hospitals Network Human Research Ethics Committee (LNR/15/SCHN/15).

RESULTS**Case identification**

A total of 109 children with FPIES who had presented to an ED with an acute FPIES episode over the study period were

TABLE I. Modified diagnostic criteria for acute FPIES,⁵ sepsis,¹¹ and GE¹²

FPIES	BS	GE
Major criteria		
• Vomiting within 0.5- 4 h of eating suspect food(s) without classic IgE-mediated allergic skin and respiratory symptoms	• Vomiting	• Vomiting
	• Positive blood culture (excluding <i>Staphylococcus epidermidis</i> or coagulase-negative staphylococci)	• Negative blood culture
	• Age = 0.5 mo-4 y	• Positive stool viral culture/immunofluorescence and/or bacterial culture
		• Age = 0.5 mo-4 y
Minor criteria		
• A second (or more) episode of vomiting to the same suspect food(s)	• Temperature <36°C or >38°C	
• Vomiting within 0.5- 4 h of eating a different food, without classic IgE-mediated allergic skin and respiratory symptoms	• Tachycardia	
• Extreme lethargy with any suspected reaction	• Tachypnea	
• Marked pallor with any suspected reaction	• Elevated or reduced WCC	
• Floppiness with any suspected reaction		
• Need for ED visit with any suspected reaction		
• Need for intravenous fluid resuscitation with any suspected reaction		
• Diarrhea within the subsequent 24 h of a suspected reaction		

A diagnosis of acute FPIES must satisfy the major criterion and ≥ 3 minor criteria. A diagnosis of BS must satisfy the major criteria and ≥ 1 minor criteria. A diagnosis of GE must satisfy the major criteria.

TABLE II. Frequency of demographic features in our cohort of patients with FPIES who presented to the ED

Demographic features	No. (%) of patients (N = 109)
Male	55 (50)
Asthma	13 (12)
Eczema	47 (43)
IgE food allergy	20 (18)
Anaphylaxis	7 (6)
Family history of FPIES	5 (5)
Family history of atopy	48 (44)
Multiple food triggers	41 (38)
Food triggers	
Rice	52 (29)
Cow's milk	33 (18)
Fish	22 (12)
Soy	15 (8)
Chicken	15 (8)
Eggs	13 (7)

identified. These 109 children had a total of 181 separate emergency visits. In 94 instances, the child was brought to the ED upon first known reaction to the trigger food. The diagnosis was unknown in 124 presentations (69%; n = 181), with 82 of these in patients with their first presentation (75%; n = 109). The median age of children at emergency presentation was 6 months (interquartile range [IQR], 5-10 months).

A total of 91 children who presented to the ED with vomiting and had a subsequent diagnosis of BS (n = 36) and GE (n = 55) were included. The median age of presentation of patients with BS and patients with GE was more compared with that of patients with FPIES, at 16 months for both disease groups (IQR,

10-29 months and 9.5-33 months, respectively). The median length of stay in hospital for FPIES, sepsis, and GE were less than 1 day, 8.5 days, and 1 day, respectively.

Features of patients with FPIES presenting to ED

Of the 109 children who presented to hospital with FPIES, there was a median time delay to diagnosis of 3 months (IQR, 1-6 months); 47 (43%) children had 2 or more presentations to the ED. The demographic features of our cohort of patients with FPIES are presented in Table II. There was no sex predominance. Eczema was the most common comorbid atopic condition (43%). Eighteen percent had coexistent clinical history of an IgE-mediated food allergy (with positive skin test result to the food trigger) and 12% had asthma. There was a family history of atopy in 44% of patients, and history of FPIES in siblings in 5%. Most children had a single FPIES food trigger (62%).

Clinical features of acute FPIES presentations

Rice (29%), cow's milk (18%), fish (12%), soy (8%), chicken (8%), and eggs (7%) were the 6 most common food triggers resulting in an ED presentation for FPIES (Table II). Clinical features and abnormalities in vital signs observed in children presenting to emergency with vomiting in acute FPIES, BS, and GE are presented in Table III.

Of the 181 FPIES emergency presentations, 75% involved lethargy, 77% floppiness, and 77% pallor. A total of 112 (62%) presentations involved all 4 symptoms of vomiting, lethargy, floppiness, and pallor and were considered severe; 24% had diarrhea in the subsequent 24 hours of presentation; and 42% of presentations required intravenous fluid resuscitation.

Abnormal vital signs (age-adjusted) recorded at emergency triage for FPIES presentations included hypothermia (41%), hyperglycemia (38%), bradypnea (21%), tachypnea (13%),

TABLE III. Clinical features and abnormal vital signs (age-adjusted)

Clinical features	FPIES (N = 181)	Sepsis (N = 36)	GE (N = 55)
Diarrhea	43 (24)	14 (39)	51 (93)
Blood in stools	2 (1)	1 (3)	13 (24)
Lethargy	135 (75)	17 (47)	27 (49)
Floppiness	140 (77)	1 (3)	1 (2)
Pallor	139 (77)	2 (6)	5 (9)
Intravenous fluids given (where known)	61 of 143 (42)	12 (33)	17 (31)
Vital signs			
Weight	(N = 72)	(N = 28)	(N = 52)
<−2 SD for age	8 (11)	5 (18)	3 (6)
>+2 SD for age	6 (8)	0 (0)	5 (10)
Heart rate	(N = 114)	(N = 36)	(N = 55)
Bradycardia	6 (5)	0 (0)	0 (0)
Tachycardia	12 (11)	14 (39)	7 (13)
Respiratory rate	(N = 109)	(N = 36)	(N = 55)
Bradypnea	23 (21)	1 (3)	7 (13)
Tachypnea	14 (13)	13 (36)	9 (16)
Systolic blood pressure	(N = 27)	(N = 9)	(N = 6)
Hypotension	1 (4)	1 (11)	0 (0)
Hypertension	15 (56)	8 (89)	6 (100)
Oxygen saturation	(N = 77)	(N = 15)	(N = 12)
<95%	4 (5)	5 (33)	0 (0)
Temperature (°C)	(N = 109)	(N = 36)	(N = 54)
Median	36.60	38.20	37.35
IQR	36.00-37.00	37.35-38.95	36.80-38.50
Bedside blood sugar (mmol/L)	(N = 37)	(N = 7)	(N = 29)
Median	6.80	6.60	4.60
IQR	5.20-7.80	6.40-7.60	3.60-6.20

tachycardia (11%), and bradycardia (5%). Patients were underweight (Table E1) in 11% of presentations.

Clinical features and vital signs—All disease groups

Children with FPIES were more likely to present with lethargy, floppiness, and pallor than children with BS or GE (Figure 1). Children presenting with diarrhea (OR, 41; 95% CI, 14-120) or bloody stools (OR, 28; 95% CI, 6-127) were less likely to have a subsequent diagnosis of FPIES than GE, but these characteristics did not differentiate between FPIES and BS.

Differences in vital signs between FPIES and BS and between FPIES and GE are shown in Figure 1. Tachycardia was more common in BS than in FPIES (OR, 5; 95% CI, 2-13). Fever was less likely to occur in FPIES compared with both BS (OR, 5; 95% CI, 3-9) and GE (OR, 4; 95% CI, 2-6). There was no evidence of association between weight, respiratory rate, systolic blood pressure, and blood sugar levels between FPIES and BS or GE presentations. A blood pressure was recorded only in 15%, 25%, and 11% of FPIES, BS, and GE presentations, respectively.

Routine laboratory investigations

There was no association between the severity of FPIES reaction and whether any blood tests were performed, where a severe reaction was considered to be one that included all 4 major symptoms of vomiting, lethargy, floppiness, and pallor (40%

with bloods performed) versus all other FPIES presentations with 3 or fewer symptoms (30% with bloods performed).

Full blood cell count

Laboratory blood investigations of the 3 disease groups are presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org. Ninety percent of children presenting with FPIES had normal hemoglobin, 71% had normal mean cell volume. Thirty-four percent of FPIES presentations involved leucocytosis, 22% thrombocytosis, 46% neutrophilia, and 27% monocytosis. Fifty-four percent presented with mean platelet volume within the lower limit of normal range. Eosinophilia and basophilia were observed in 2% and 6% of presentations, respectively. Erythrocyte sedimentation rate was performed in only 2 presentations, both being within normal limits.

There were only minor differences observed in white cell count, neutrophil count, and platelet count between the 3 groups (Figure 2). Normal or elevated MPV was more likely to be observed in BS than in FPIES (OR, 4; 95% CI, 2-8). High red cell distribution width was more likely to occur in BS (OR, 2; 95% CI, 1-3) and GE (OR, 1.5; 95% CI, 1-2) than in FPIES. Presentations involving eosinophilia were more likely to be diagnosed with FPIES compared with GE (OR, 0.01; 95% CI, 0-0.2); however, there was overall a low proportion of children presenting with FPIES where eosinophilia was observed. No

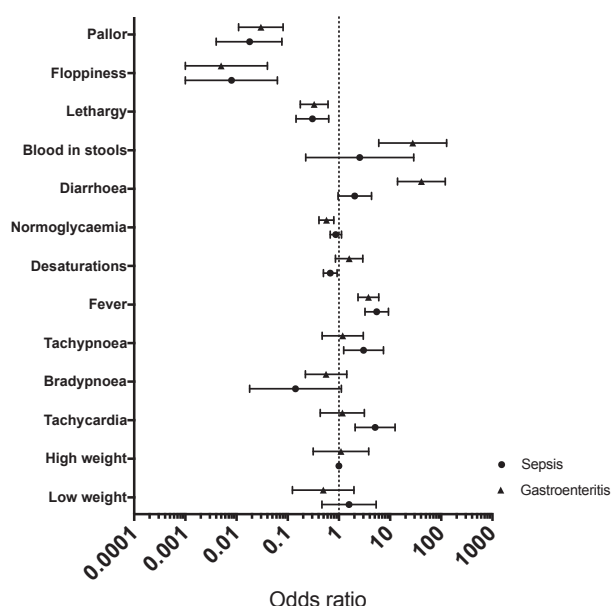


FIGURE 1. Logistic regression analysis of vital signs and clinical features of FPIES vs sepsis and GE. ORs and 95% CI are shown. Clinical features where the OR is less than 1 are more likely to be predictors of a diagnosis of FPIES.

differences were noted in other parameters of full blood cell count.

Electrolytes, minerals, LFTs, acid-base, and CRP

Low bicarbonate levels were observed in 62% of presentations. Serum electrolytes and LFTs were within normal limits in most FPIES presentations. This included sodium (96%), potassium (96%), chloride (92%), total protein (82%), creatinine (82%), urea (86%), calcium (88%), magnesium (83%), and phosphate (92%). CRP was measured in only 24 FPIES presentations, and of these, 29% had minor elevation in CRP (median, 1.5 mg/L; IQR, 0.3-6.5 mg/L). No FPIES presentation had a CRP value of greater than 20 mg/dL. Despite these minor elevations in CRP, a high CRP was associated with BS (OR, 1.2; 95% CI, 1.1-1.4; median, 69.95 mg/L) or GE (OR, 1.21; 95% CI, 1.1-1.3; median, 30.5 mg/L) (Figure 3).

Relatively high albumin (OR, 0.8; 95% CI, 0.7-0.9) and albumin/globulin ratio (OR, 0.001; 95% CI, 0-0.04) were associated with FPIES compared with BS, with a conversely high globulin more likely to be present in BS (OR, 1.43; 95% CI, 1.16-1.75). No evidence of other differences in LFT was observed between FPIES and either BS or GE presentations.

Normal sodium levels were observed in most presentations in all 3 disease groups; however, higher values were associated with FPIES compared with BS (OR, 0.8; 95% CI, 0.7-0.9) and GE (OR, 0.9; 95% CI, 0.8-1.0) (Figure 4). Low chloride levels were associated with sepsis presentations compared with FPIES (OR, 0.8; 95% CI, 0.7-0.9). There were no differences among the other electrolyte parameters between groups. Calcium was elevated (though within normal limits) in FPIES compared with BS (OR, <.001; 95% CI, 0-0.13) and GE (OR, <.001; 95% CI, 0-0.019). No differences in magnesium and phosphate levels between groups were identified.

Twenty-one children with FPIES had a venous blood gas performed, whereas 4 had an arterial blood gas performed. Forty-nine venous blood gases and 7 arterial blood gases were performed in children with sepsis and GE. Most children with FPIES in whom testing was performed had normal pH (81%), bicarbonate (81%), and base excess (85%). Ionized calcium and lactate were high in 50% and 38% of FPIES presentations, respectively. Low methemoglobin was noted in 21% of presentations. No other differences were observed between FPIES and either sepsis or GE presentations in blood gas analysis.

DISCUSSION

We sought to further characterize the common clinical characteristics, vital signs, and changes in routine laboratory investigations that accompany acute FPIES presentations. Although past cohorts have reported on isolated laboratory abnormalities, there have been no other reports that have compared all available routine tests and vital signs of children presenting with acute FPIES and other common causes of acute vomiting, such as BS and viral/bacterial GE. Here, we identified several key differences that may help in distinguishing acute FPIES from its mimics and our findings give further weight to the sensitivity of the symptoms required for the diagnosis of FPIES in the emergency setting according to recently revised international consensus criteria.^{2,13}

The diagnosis of FPIES remains difficult. We found that only 25% of FPIES cases were diagnosed on first presentation, with an ongoing delay to diagnosis of 3 months. Although this delay is lower than that in other reported cohorts, for example, a median delay of 8 months in a European cohort reported by Fiocchi et al,⁷ there remains the need for educational interventions and increased awareness of FPIES in the acute care setting.¹⁴ Clinical features remain key in diagnosing acute FPIES. Aside from vomiting (which occurred in 100% of cases based on case definition), we confirm that the presence of lethargy, floppiness, and pallor is associated with FPIES compared with BS and viral/bacterial GE.^{1,15,16} Diarrhea was less associated with FPIES when compared with its mimics. Although observed in 24% of presentations in our cohort, and up to 55% in published cohorts,¹⁶⁻¹⁸ diarrhea alone is a poor differentiating feature for acute FPIES.

Fever was a strong predictor for sepsis and GE, with only a small minority of FPIES presentations involving fever. One case report by Andrews et al¹⁹ describes fever of 38.8°C in a 6-month-old male presenting in acute shock with soy FPIES. Fever, along with elevations in IL-2, IL-5, and IL-8 in peripheral blood, was a prominent feature of a small cohort of patients with FPIES in Kimura et al's study.^{6,10} Instead our findings suggest that fever is not common in FPIES presentations, consistent with the understanding of FPIES lacking an overt systemic infective or inflammatory response, and cautions against the presumptive diagnosis of FPIES in a child presenting with vomiting with fever. Relatively rapid response to treatment is also associated with a diagnosis of FPIES, as measured by length of duration of stay; however, this is not a parameter that can be appreciated until after initial assessment and fluid rehydration.

Of the routine laboratory investigations, a normal CRP, normal electrolytes, thrombocytosis, and lower MPV and elevated albumin/globulin ratio were more likely to occur with FPIES compared with BS or bacterial/viral GE. CRP levels were at least 3 times more likely to be markedly elevated in sepsis and

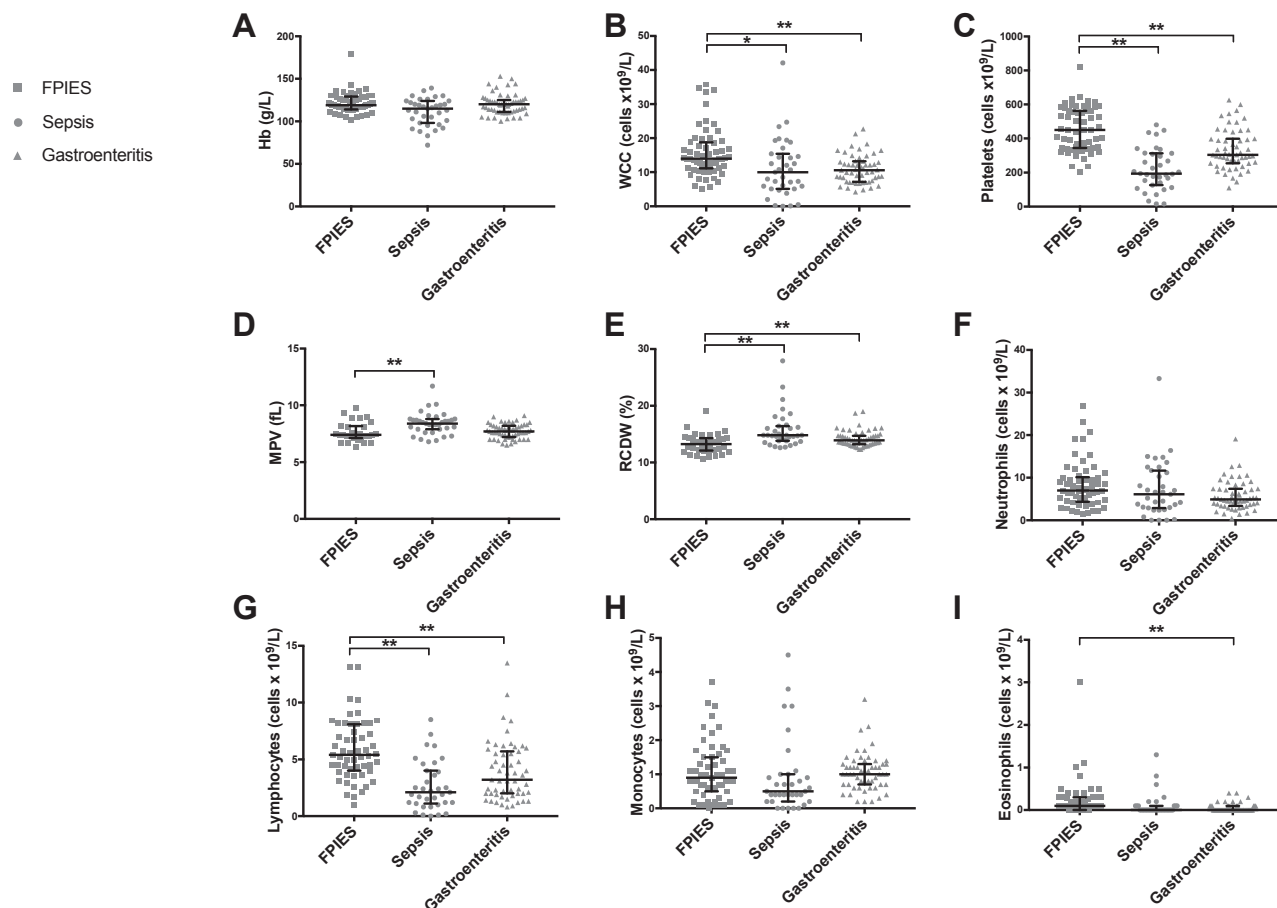


FIGURE 2. Full blood cell count parameters at each FPIES, sepsis, and GE presentation. Median and IQR are shown. Values for (A) hemoglobin, (B) white cell count, (C) platelets, (D) MPV, (E) red cell distribution width, (F) neutrophils, (G) lymphocytes, (H) monocytes, and (I) eosinophils are shown. *RCDW*, Red cell density width; *WCC*, white cell count. * $P < .01$, ** $P < .001$.

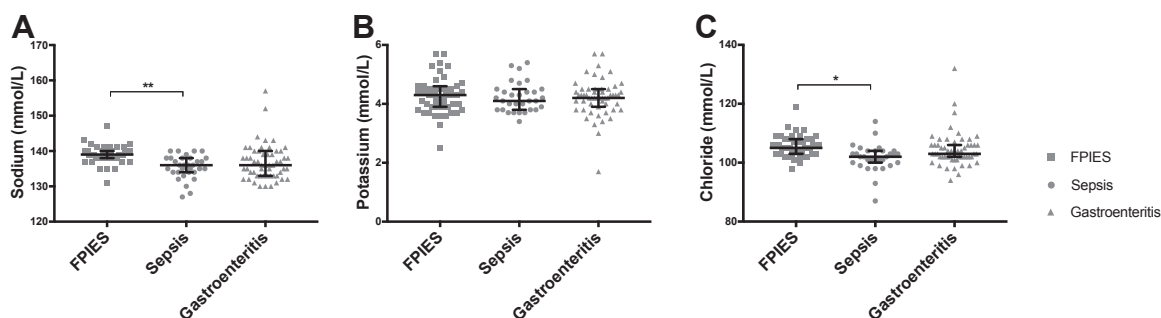


FIGURE 3. (A) Sodium, (B) potassium, and (C) chloride levels at each FPIES, sepsis, and GE presentation. Median and IQR are shown. * $P < .01$, ** $P < .001$.

GE compared with FPIES, with median CRP for sepsis and GE 27 and 14 times higher than in FPIES, respectively. There are studies describing both normal and mildly elevated CRP in acute FPIES presentations^{4,6,10,20}; however, our study demonstrates that acute FPIES is more likely to present with normal CRP compared with its mimics of sepsis and GE. It is possible that elevation in CRP may occur in the subsequent days following an acute FPIES episode.²¹ Regardless, our findings suggest normal

CRP at presentation to ED to be a strong predictor for a diagnosis of FPIES in this context.

We identified a relative leucocytosis and lymphocytosis in acute FPIES when compared with sepsis and GE. However, the median values of both leucocyte and lymphocyte count in all 3 disease groups were within normal ranges. The mechanisms behind this observation are uncertain, although we and others have shown systemic activation of innate immunity in acute

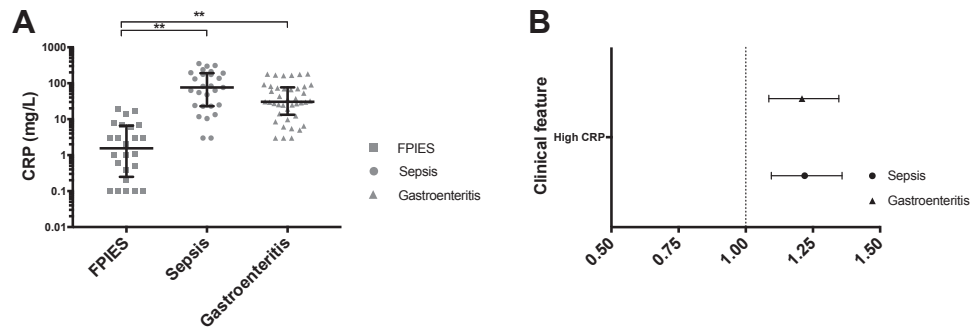


FIGURE 4. **A**, CRP values at each FPIES, sepsis, and GE presentation. Median and IQR are shown. The y-axis is demonstrated as log10 scale. **B**, Logistics regression analysis of CRP of disease cohorts compared with FPIES presentations. OR and 95% CI are shown. An OR of less than 1 indicates a feature being a likely predictor of a diagnosis of FPIES. ** $P < .001$.

FPIES reactions, which could trigger recruitment of lymphocytes into the circulating pool, but not sufficient or of a different type to that which induces fever.^{5,6} Thrombocytosis and a low MPV did not occur together in most FPIES reactions and likewise, the median values were within normal reference ranges. Although neutrophilia is a reportedly common finding in acute FPIES,^{15,22} it did not help to differentiate because similar trends were noted in the non-FPIES presentations. High methemoglobinemia has been described predominantly in chronic FPIES (and in 1 unique case, a neonate presenting with failure to thrive and metabolic acidosis), but we did not observe this in our cohort. Instead, a proportion of FPIES cases presented with low methemoglobin levels, though there was no difference observed relative to sepsis and GE. When compared with BS and GE, our findings indicate that leucocytosis was associated with acute FPIES in this age group. Certainly, an elevated white cell count should not reduce the suspicion of FPIES over a diagnosis of BS.

Despite the presence of profuse vomiting, most patients with FPIES had normal blood sodium, potassium, and chloride. Hyponatremia was less likely to occur in acute FPIES, relative to sepsis and GE, which correlates with the pathology and severity of hypovolemic hyponatremia in a more protracted duration of vomiting such as in sepsis or GE.²³ A subtle elevation in calcium levels compared with both BS and GE was observed in FPIES, though the mechanism behind this is unclear, and given that patients still presented with calcium levels within normal limits, no further investigations for hypercalcemia were undertaken. Bicarbonate levels at the lower limit of normal were detected in more than half of FPIES presentations despite a normal pH found on blood gas. This may suggest the presence of a potentially mild but compensated metabolic acidosis in acute FPIES, comparable to similar metabolic derangements observed in chronic FPIES.²⁴ However, when compared with sepsis and GE, no differences were observed in bicarbonate levels.

LFTs were not generally useful in discriminating between disease states. We did however observe a mild transaminitis in acute FPIES. A relatively high albumin and low globulin and elevated albumin/globulin ratio were observed in FPIES when compared with sepsis. The mechanism behind this is unclear, but the magnitude of the difference between groups in this parameter deserves exploration with further prospective studies.

There are a number of limitations of our study, primarily due to the retrospective design and retrospective collection of data for analysis. A lack of comprehensive information and variability in

practices among EDs may have led to a reporting bias. In some cases, parents may have alerted the ED to the possibility of an FPIES diagnosis, which may have biased the triage and medical case notes reporting of typical features such as lethargy and floppiness. However, most FPIES presentations to the ED occurred before the diagnosis, and most emergency staff in Australia are largely unaware of the disease entity FPIES. In addition, investigations performed were not standardized and data were reliant on accurate clinical documentation of historical features on presentation, and subject to consistency when triaging, and assessing patients, features that also contribute to the difficulty in diagnosing FPIES. Furthermore, not all children had all investigations performed, and this was particularly so for blood gas analysis and a lesser extent LFTs in infants presenting with FPIES. Although we did not observe that infants with more severe presentations (based on the presence of the combination of lethargy, pallor, and floppiness) were more likely to have more extensive investigations, this possibility cannot be completely ruled out. Caution should be taken in overinterpretation of the findings where only a small subcohort of the overall disease group had results from those particular investigations. Findings such as the albumin/globulin ratio need to be confirmed in larger prospective FPIES cohorts.

The capacity to make a more certain diagnosis in the acute ED setting can improve timely administration and selection of appropriate treatment. In the case of FPIES, early use of ondansetron would be recommended where the likelihood of sepsis and/or GE is lower and FPIES more probable. In the absence of a disease-specific biomarker, the implementation of multicenter prospective studies in acute clinical settings is needed to better elucidate the utility of standard laboratory markers as effective diagnostic tools to assist in distinguishing acute FPIES from other common diseases of early childhood that present with vomiting as a predominant clinical feature. Meanwhile the combination of the typical clinical features of FPIES (many of which form the minor criteria in the current consensus criteria) such as lethargy, floppiness, and pallor, a normal CRP, and the absence of fever should alert the physician to the possibility of FPIES in an acute presentation of the vomiting infant or young child.

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TABLE E1. CHW Pediatric age-related references ranges for normal vital signs*

Vital sign	Age (y)			
	<1	1-2	2-5	5-12
Respiratory rate (breaths/min)	30-40	25-35	25-30	20-25
Heart rate (beats/min)	110-160	100-150	95-140	80-120
Systolic blood pressure (mm Hg)	70-90	80-95	80-100	90-110
Temperature (°C)	36.5-37.5			
Oxygen saturations (%)	95-100			
Blood sugar level (mmol/L)	5.0-7.0			
Weight (Z score)	SD between -2 and +2 *			

*Based on the World Health Organization sex-specific weight-for-age child growth standard charts.

TABLE E2. A comparison of laboratory investigations in the 3 disease groups (median, IQR, *P* value for BS and GE compared with FPIES)

Parameter	FPIES (N = 181)	BS (N = 36)	GE (N = 55)	Normal values*
FBC (n)	59	36	55	
Hemoglobin (g/L)	119 (114-129)	115 (100-124) <i>P</i> = .002	120 (111-125) <i>P</i> = .667	95-138
White cell count ($\times 10^9$ cells/L)	14.0 (11.2-18.8)	10.4 (5.5-15.0) <i>P</i> = .005	10.6 (7.2-13.2) <i>P</i> < .001	5.0-13.6
Platelets ($\times 10^9$ cells/L)	450 (344-563)	199 (133-314) <i>P</i> < .001	304 (255-399) <i>P</i> < .001	150-600
MPV (fL)	7.4 (7.1-8.1)	8.5 (7.9-8.8) <i>P</i> < .001	7.7 (7.2-8.2) <i>P</i> = .182	6.7-9.7
Hematocrit (%)	35 (34-38)	35 (31-38) <i>P</i> = .059	36 (33-38) <i>P</i> = .827	27-41
MCV (fL)	79 (76-83)	78 (74-83) <i>P</i> = .270	78 (76-81) <i>P</i> = .089	70-89
RCDW (%)	13.3 (12.1-14.3)	14.8 (13.8-16.3) <i>P</i> < .001	13.9 (13.2-14.7) <i>P</i> = .009	12.3-14.1
Neutrophils ($\times 10^9$ cells/L)	7.0 (4.6-10.0)	6.4 (3.0-11.5) <i>P</i> = .467	4.9 (3.4-7.4) <i>P</i> = .012	0.8-8.0
Lymphocytes ($\times 10^9$ cells/L)	5.4 (4.0-8.1)	2.0 (1.1-4.0) <i>P</i> < .001	3.2 (2.0-5.7) <i>P</i> = .001	2.0-10.8
Monocytes ($\times 10^9$ cells/L)	0.9 (0.5-1.5)	0.5 (0.3-1.0) <i>P</i> = .248	1.0 (0.7-1.3) <i>P</i> = .884	0.0-1.2
Eosinophils ($\times 10^9$ cells/L)	0.1 (0.0-0.3)	0.0 (0.0-0.1) <i>P</i> = .104	0.0 (0.0-0.1) <i>P</i> = .002	0.0-0.9
Basophils ($\times 10^9$ cells/L)	0.0 (0.0-0.1)	0.0 (0.0-0.1) <i>P</i> = .271	0.0 (0.0-0.0) <i>P</i> = .048	0.0-0.2
EUC (n)	49	32	55	
Sodium (mmol/L)	139 (138-140)	136 (134-138) <i>P</i> < .001	136 (133-140) <i>P</i> = .014	135-145
Potassium (mmol/L)	4.3 (3.9-4.6)	4.2 (3.8-4.5) <i>P</i> = .826	4.2 (3.9-4.5) <i>P</i> = .589	3.5-5.5
Chloride (mmol/L)	105 (103-108)	102 (100-104) <i>P</i> = .002	103 (102-106) <i>P</i> = .276	95-110
Bicarbonate (mmol/L)	20 (18-23)	21 (18-23) <i>P</i> = .235	19 (17-21) <i>P</i> = .444	18-30
Total protein (g/L)	66 (62-69)	69 (65-72) <i>P</i> = .060	68 (66-71) <i>P</i> = .030	52-81
Urea (mmol/L)	3.3 (2.6-4.8)	3.5 (2.6-4.5) <i>P</i> = .963	3.2 (2.1-4.3) <i>P</i> = .622	1.0-6.0
Creatinine (μ mol/L)	26 (21-32)	24 (21-29) <i>P</i> = .570	28 (24-32) <i>P</i> = .471	13-41
CMP (n)	24	15	22	
Calcium (mmol/L)	2.50 (2.40-2.61)	2.30 (2.25-2.39) <i>P</i> = .001	2.36 (2.18-2.45) <i>P</i> = .001	2.10-2.65
Magnesium (mmol/L)	0.88 (0.82-0.96)	0.88 (0.80-0.96) <i>P</i> = .426	0.84 (0.80-0.87) <i>P</i> = .220	0.65-1.00
Phosphate (mmol/L)	1.8 (1.6-2.0)	1.5 (1.2-1.6) <i>P</i> = .034	1.5 (1.4-1.8) <i>P</i> = .227	1.1-1.9
Inflammatory markers (n)	24	28	41	
CRP (mg/dL)	2 (0-7)	70 (23-184) <i>P</i> < .001	31 (14-74) <i>P</i> < .001	<5
LFTs (n)	29	23	35	
Albumin (g/L)	42 (40-44)	36 (32-41) <i>P</i> = .002	40 (38-43) <i>P</i> = .556	31-48
Globulin (g/L)	24 (22-27)	32 (26-35) <i>P</i> < .001	28 (26-31) <i>P</i> = .014	10-37
Total bilirubin (μ mol/L)	6 (4-9)	10 (6-14) <i>P</i> = .980	6 (3-8) <i>P</i> = .122	<10

(continued)

TABLE E2. (Continued)

Parameter	FPIES (N = 181)	BS (N = 36)	GE (N = 55)	Normal values*
Conjugated bilirubin (μmol/L)	3 (1-9)	4 (2-9) <i>P</i> = .303	4 (2-6) <i>P</i> = .937	<10
AST (U/L)	52 (43-61)	52 (38-78) <i>P</i> = .635	46 (35-56) <i>P</i> = .814	10-90
ALT (U/L)	37 (30-48)	42 (27-65) <i>P</i> = .158	33 (26-48) <i>P</i> = .785	<45
GGT (U/L)	14 (11-23)	27 (15-92) <i>P</i> = .062	11 (10-13) <i>P</i> = .575	<150
ALP (U/L)	247 (186-281)	187 (135-240) <i>P</i> = .458	158 (138-192) <i>P</i> = .094	80-320
Blood gas (n)	25	22	34	
pH	7.40 (7.36-7.41)	7.42 (7.38-7.45) <i>P</i> = .367	7.43 (7.38-7.44) <i>P</i> = .756	7.35-7.45
pCO ₂ (mm Hg)	35 (32-39)	36 (33-41) <i>P</i> = .633	33 (30-35) <i>P</i> = .119	32-45
Base excess (mmol/L)	−3 (−3 to −1)	−1 (−6 to 1) <i>P</i> = .372	−3 (−5 to −1) <i>P</i> = .362	−4 to +3
Actual bicarbonate (mmol/L)	22 (20-22)	22 (20-26) <i>P</i> = .503	21 (18-23) <i>P</i> = .158	18-25
Ionized calcium (mmol/L)	1.30 (1.27-1.35)	1.23 (1.19-1.26) <i>P</i> < .001	1.28 (1.22-1.31) <i>P</i> = .042	1.12-1.30
Lactate (mmol/L)	1.8 (1.3-2.2)	1.8 (1.3-2.2) <i>P</i> = .334	1.6 (1.5-2.3) <i>P</i> = .624	<2.0
Carboxyhemoglobin (%)	0.7 (0.3-0.9)	0.5 (0.3-1.0) <i>P</i> = .649	0.3 (0.3-0.6) <i>P</i> = .108	<1.5
Methemoglobin (%)	0.6 (0.4-0.7)	0.3 (0.2-0.5) <i>P</i> = .180	0.4 (0.2-0.5) <i>P</i> = .033	<2.0

ALP, Alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CMP, calcium, magnesium, and phosphate; EUC, electrolytes, urea, and creatinine; FBC, full blood cell count; GGT, gamma glutamyl transferase; MCV, mean cell volume; RCDW, red cell density width.

*As per local CHW pathology and biochemistry laboratory values—age-adjusted.