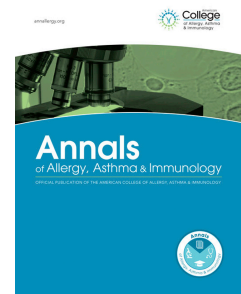


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PII: S1081-1206(21)00102-2

DOI: <https://doi.org/10.1016/j.anai.2021.02.004>

Reference: ANAI 3496

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 30 November 2020

Revised Date: 22 January 2021

Accepted Date: 5 February 2021

Please cite this article as: Hoffmann NV, Ahmed A, Fortunato JE, Food protein-induced enterocolitis syndrome (FPIES): Dynamic Relationship among Gastrointestinal Symptoms, Immune Response and the Autonomic Nervous System, *Annals of Allergy, Asthma and Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.02.004>.

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Food protein-induced enterocolitis syndrome (FPIES): Dynamic Relationship among
Gastrointestinal Symptoms, Immune Response and the Autonomic Nervous System

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Conflicts of Interest: None

Funding Source: None

National Clinical Trial Registration: Not applicable

Key words: Food protein-induced enterocolitis syndrome, FPIES, food allergy, intestinal mucosal barrier, autonomic nervous system, neuroimmune

Abbreviations/Acronyms: Food protein-induced enterocolitis syndrome (FPIES), gastrointestinal (GI), autonomic nervous system (ANS), serum IgE (sIgE), patient-reported outcomes (PRO), Patient-Reported Outcomes Measurement Information System (PROMIS), tumor necrosis factor

alpha (TNF α), transforming growth factor beta (TGF β), C-reactive protein (CRP), Inflammatory Bowel Disease (IBD)

Word Count: 3432

Figures: 3

Tables: 1

20-12-0777R1

Objective: To explore the relationship between gastrointestinal (GI) symptoms, immune response, and autonomic nervous system (ANS) in food protein-induced enterocolitis syndrome (FPIES) in relation to current understanding of disease phenotype and pathogenesis.

Data sources: Relevant studies related to FPIES, GI symptomatology, and ANS were reviewed. Literature search was performed using PubMed, with keyword combinations including but not limited to FPIES, allergic GI disorders, ANS, autonomic dysfunction, dysautonomia, GI, diarrhea, vomiting, neuroimmune, clinical phenotyping tools.

Study selections: Peer-reviewed case-control studies, observational studies, reviews and guidelines, and systematic reviews related to FPIES and the ANS were selected for review.

Results: There is limited research directly relating GI symptoms and FPIES to the ANS and immunologic response. To support proposed mechanisms of action related to patient symptoms, studies relevant to co-existing GI-autonomic processes and FPIES immunologic triggers were examined. These related disease processes were extrapolated to FPIES based on current knowledge of FPIES phenotype and pathogenesis.

Conclusion: The etiology of FPIES and the underlying mechanisms triggering symptoms is not well understood. Based on the exaggerated GI symptoms and hemodynamic response observed, the ANS likely plays an important role in FPIES possibly as a compensatory response. The trigger for this cascade of symptoms may be related to disruption of immunologic homeostasis that typically contributes to immune tolerance. To more accurately assess FPIES pathophysiology necessitates understanding the diverse spectrum of presenting symptoms. A consistent and comprehensive symptom assessment tool may improve our understanding of this dynamic relationship.

1 Introduction

FPIES is a non-IgE-mediated allergic disorder in which an apparent food antigen triggers an inflammatory cascade. This can result in profound gastrointestinal (GI) symptoms and hemodynamic instability.^{1,2} Its etiology is not well understood, and the mechanisms precipitating symptoms are not defined. Cumulative incidence in infants ranges from 0.015% to 0.7%, while prevalence in US infants is estimated at 0.51%.³⁻⁵ While the age of presentation varies, FPIES typically manifests in previously healthy infants.² Practitioners must therefore be attentive towards recognizing early symptoms after ingestion along with a high index of suspicion for a food trigger. Diagnosis requires a thorough history including recognition of key characteristic clinical symptoms.² Further, recognition of a wide and diverse spectrum of presentations has led to the now well-described entity of FPIES in older children and adults.⁶ To better understand potential associations among the multiple symptoms in FPIES necessitates a consistent and comprehensive method of defining symptoms and identifying potential underlying co-morbidities.

GI symptoms in FPIES can progress rapidly to include cardiovascular decompensation and mental status changes. The inciting event is breakdown of immunologic tolerance to a food antigen.^{1,2,7} While it is difficult to predict the timing of symptom development, FPIES has been associated with history of atopy, FPIES to another food, and family history of allergic disease.^{8,9} Laboratory abnormalities during an acute episode may include leukocytosis with neutrophilia, thrombocytosis, metabolic acidosis, and methemoglobinemia.² Although supportive of FPIES, laboratory markers remain non-diagnostic. Radiological studies and histologic analysis of endoscopic biopsies have similarly proven non-specific,² resulting in an absence of effective diagnostic biomarkers. FPIES thus remains a clinical diagnosis. Despite this, prognosis is

excellent, as most children develop immune tolerance to their specific food antigen trigger by three years of age.²

The inflammatory cascade from the presumptive food exposure can be accompanied by systemic symptoms of vomiting, diarrhea, hypotension, lethargy, and pallor. These symptoms can be associated with autonomic dysregulation¹⁰ and raise the question of a role of the autonomic nervous system (ANS) in FPIES. The symptom profile of FPIES, specifically the hemodynamic response, may be driven in part by the ANS. This may be related to the need to maintain homeostasis in the face of an immune response to a food antigen trigger. In this review, we aim to discuss GI symptoms in FPIES as they relate to the immune response and ANS. We will explore how inflammatory triggers mechanistically impact the GI tract and ANS resulting in the cascade of symptoms described in FPIES. Towards this end, we will emphasize the need for a comprehensive clinical assessment tool in FPIES demonstrating the value of transdiagnostic questionnaires used for other difficult to define clinical conditions.

Role of Clinical Assessment of Symptoms

FPIES is considered a heterogeneous disorder with a spectrum of clinical phenotypes. Diagnosis is based on a thorough history including recognition of key characteristic clinical symptoms, as defined by international consensus guidelines.² Laboratory tests, imaging, and histologic findings on endoscopic biopsy are suggestive but non-specific, and are therefore not recommended for diagnostic purposes. The gold standard to confirm FPIES diagnosis is provocative testing with an oral food challenge. International consensus guidelines suggest oral food challenge only be considered in the initial diagnostic work up if the clinical history or time course are atypical, if the food trigger is unable to be identified, or if symptoms persist despite elimination of the suspected trigger food from the diet.²

Current FPIES clinical phenotypes are based on the following: (1) timing and duration of symptoms along with clinical signs of hemodynamic compromise, (2) age of presentation, and (3) IgE positivity.² This has led to a classification system that includes acute, chronic, adult, and atypical FPIES (Table 1, Figure 1). Acute FPIES is the most widely described and has specific criteria for diagnosis.² Typically, acute FPIES occurs with intermittent ingestion of the food antigen trigger. It is characterized by onset of profound GI symptoms 1-4 hours after ingestion followed by acute hemodynamic compromise. Chronic FPIES occurs with recurrent ingestion of the food antigen trigger. Symptoms are insidious in onset with days to weeks of watery diarrhea, worsening emesis, and failure to thrive. Both acute and chronic FPIES can progress to hypovolemic shock. Re-exposure to the food trigger of chronic FPIES after a period of avoidance elicits an acute FPIES reaction, suggesting analogous mechanisms along a phenotypic spectrum.

Less well defined FPIES subtypes include adult FPIES and atypical FPIES. Adult FPIES is an entity of FPIES-like symptoms described in older children and adults.⁶ Atypical FPIES is characterized by the development of food-specific serum IgE antibodies (sIgE) to the identified FPIES trigger.² It has been associated with a protracted course with symptom resolution at a later age.^{8,9} Twenty-five percent of patients with atypical FPIES will evolve to develop IgE-mediated food allergic reactions, suggesting that both processes may evoke closely related immunologic mechanisms.^{9,11}

While the advent of acute FPIES guidelines has streamlined diagnostic and research cohorts of acute FPIES, there remains considerable work to be done to more accurately classify clinical FPIES phenotypes. Delineation of distinct disease subtypes, especially in relation to associated symptoms outside of the GI tract, may advance our understanding of disease

pathogenesis and targeted management strategies. Clinical phenotyping instruments are useful in disorders that are clinically and genetically heterogeneous, especially those with involvement of multiple organ systems and without a clear diagnostic biomarker.

In conditions with symptoms suggestive of autonomic nervous system dysregulation, there is demonstrated value in the use of multidimensional symptom intake instruments. As an illustrative example, there is a high burden of autonomic dysregulation in children with functional nausea. Up to 80% of patients with functional nausea have concomitant orthostatic intolerance as measured by head upright tilt table testing.^{12, 13} Tilt table testing provides information about the ANS response to orthostatic challenge, and is used as a proxy measure of an appropriately regulated ANS.¹⁴ Wagoner et al utilized the Nausea Profile Questionnaire¹⁵ to better understand the relationship between symptoms of nausea with orthostatic intolerance in comparison to hemodynamic findings demonstrated on tilt table testing.¹⁶ Unlike standard GI symptom questionnaires, the Nausea Profile Questionnaire evaluates characteristics of nausea in 3 domains—GI, somatic, and emotional distress. The presence of higher somatic Nausea Profile Questionnaire scores helped identify patients at higher risk for autonomic dysregulation as supported by subsequent tilt testing. Once patient phenotypes were better defined, investigators were able to identify neurohormonal profiles for specific patient groups towards better understanding potential underlying mechanisms.¹⁷ While functional nausea and FPIES represent two distinct conditions, similarities including disabling GI symptoms and hemodynamic compromise may support a similar model of investigation in FPIES.

Overall, the use of comprehensive symptom intake and patient-reported outcomes (PRO) measures improve providers' and researchers' understanding of the patient illness experience in a structured format. The National Institutes of Health Patient-Reported Outcomes Measurement

Information System (PROMIS) offers a framework to measure patient-reported or proxy-reported symptoms with validated instruments to comprehensively assess a patient's state of health and disease.¹⁸ PROMIS instruments have been used in both adults and children across a multitude of chronic diseases to provide measures of global, physical, mental, and social health across several domains.¹⁸ As a further example related to functional nausea, the combination of the Composite Autonomic Symptom Score 31 (COMPASS 31)¹⁹ and PROMIS instruments helped identify high rates of concomitant cardiovascular, psychological, neurologic, and constitutional symptoms in this patient population.¹³

As in FPIES, when laboratory markers or radiologic findings are unable to comprehensively capture the patient symptom profile and illness experience, PRO measures offer the potential to discriminate between different clinical meaningful subgroups. Better definition of the clinical characteristics of FPIES is necessary to thoroughly understand the multifactorial nature of FPIES as it relates to underlying GI, immunologic, and autonomic mechanisms. Comprehensive characterization of clinical phenotype, including further investigation of serum neurohormones that are associated with both autonomic dysregulation and GI symptoms,^{16, 20} may be of great benefit to further define FPIES phenotypes.

FPIES and the ANS

The exaggerated cardiovascular response with associated GI symptoms observed in FPIES suggests potential involvement of the ANS. Whether ANS dysregulation is a cause or consequence of the cascade of events in FPIES is not clear. The ANS functions to maintain homeostasis and coordinate adaptive responses to external or internal stimuli.²¹ As an involuntary motor/effector system, outflow occurs either independently or via integration within a central autonomic network.²² The ANS is composed of three divisions: the sympathetic,

parasympathetic, and enteric nervous system. The sympathetic and parasympathetic divisions have a central and peripheral component, while the enteric nervous system is housed within the walls of the gut and functions relatively autonomously.¹⁰ Central autonomic areas, located throughout the cerebral cortex, diencephalon, and brainstem, receive visceral afferent inputs and integrate signals to initiate autonomic reflexes. Coordinated responses include the maintenance of appropriate blood pressure, heart rate, respiration, GI motility, thermoregulation, osmoregulation, energy metabolism, pain modulation, and emotional and social behavior.²¹ The nucleus of the solitary tract and hypothalamus are two areas that play essential roles in coordinating integrated responses from visceral sensory neurons via the vagus nerve.²²

With any perturbation in the body's internal or external environment, the ANS regulates compensatory mechanisms to maintain organ perfusion and function.²³ Interactions between the ANS and the immune system via reciprocal signaling and widespread connections across organ systems are crucial to maintaining homeostasis.²⁴ When the compensatory mechanisms of the ANS are overwhelmed or dysregulated, autonomic dysfunction ensues.¹⁰ This can result in suppressed or excessive activity of the ANS. It can lead to a variety of clinical symptoms due to the widespread integration of ANS regulation across organ systems.^{10, 22} For instance, the cardiovascular system has robust autonomic connections to regulate cardiac output and cerebral perfusion. Dysregulation or overstimulation of the cardiovascular autonomic response can result in symptoms of hypotension, arrhythmias, dizziness, headache, or syncope/loss of consciousness. The GI system additionally houses extensive autonomic connections to maintain bowel motility and digestive function. When this orchestrated regulation of digestion fails, symptoms of diarrhea or constipation, abdominal pain, nausea, or vomiting can result.

While several symptoms of autonomic dysfunction are found in FPIES reactions, the ANS response during an FPIES reaction has never been explored. It remains unknown whether the ANS response to an FPIES reaction is secondary to GI symptoms, a direct result of the immune response via neuroimmune interactions, or a combination of both processes. Profound GI losses and hypovolemia may overwhelm compensatory mechanisms of the ANS, resulting in hypotension and lethargy. On the other hand, inflammatory mediators may act systemically to directly contribute to symptoms of autonomic dysregulation. Given the pervasiveness of autonomic connections throughout the body, and specifically the dense innervation of the GI tract, the autonomic response in FPIES may encompass both appropriate compensatory mechanisms, as well as influence from neuroimmune interactions (Figure 2).

Immune Response

It is well established that the immune system and ANS are tightly integrated and function to maintain physiologic homeostasis when challenged by a foreign antigen. Coordinated responses and cross-talk between immune cells and neurons occur via inflammatory mediators, neurotransmitters, and neuropeptides.²⁵ The GI tract specifically is an immunologically and neurologically rich barrier to the external environment. Downstream effects of the immune response in FPIES, specifically the ANS response, may significantly impact the unique clinical phenotype of this disorder.

In the last decade, our understanding of the immune mechanisms underlying FPIES has expanded. Though several important questions remain, a growing body of literature is now helping build a framework to identify key immune mechanisms related to this disease process. An improved understanding of the mechanistic drivers of FPIES, specifically in relation to

clinical phenotype and multisystem involvement, is the next step towards target therapeutics and preventative strategy. Several aspects of immune activation have been identified:

Innate Immunity

Recent studies have helped formulate a model for innate immune activation in the setting of acute FPIES. Mehr et al performed systemic transcriptional profiling of peripheral blood following positive FPIES challenges.²⁶ Their study identified clusters of genes associated with immune pathways regulating granulocyte adhesion and diapedesis as well as other genes related to innate immune activation.²⁶ This finding can potentially explain the neutrophilia that is detected in acute FPIES reactions. In addition, Goswami et al used mass cytometry or CyTOF (Cytometry by Time-of-Flight) analysis to demonstrate broad innate immune activation of monocytes, neutrophils, eosinophils and CD56dimNK cells in the setting of positive FPIES challenge.²⁷ Marked increase in tissue mast cells have also been found in patients with acute FPIES as well as elevated baseline tryptase levels suggesting a role for localized mast cell activation in this disease.^{28, 29} Numerous studies have identified increased neutrophil and eosinophils in the lamina propria as well as fecal mucus following a positive FPIES challenge.^{28, 30} Higher concentration of eosinophil-derived neurotoxin has been seen in fecal extracts suggesting eosinophils are not only present, but degranulating.³¹ Their exact role remains to be further elucidated, but as recent studies have shown, innate immune pathways are activated during acute FPIES.

Humoral Immunity

Humoral immune responses in FPIES remain unclear, but are not completely absent. Circulating food specific sIgE is typically absent in FPIES, but is detected in atypical FPIES. Patients with atypical FPIES have a protracted disease course and may develop subsequent IgE

mediated reactions which suggests that there may be a role for IgE production in disease pathogenesis.^{7, 32} The production of localized IgE responses has been hypothesized though not consistently demonstrated.^{7, 32, 33} Increased numbers of IgA and IgM producing plasma cells were found on jejunal biopsies of patients with FPIES, though that has not translated into consistent detectable increase in antibody production.^{7, 34} In contrast, many studies demonstrated decreased levels of IgG, IgA and IgG4 antibodies, specifically in response to casein.^{29, 33, 35} The data regarding humoral responses in acute FPIES remains conflicting and the seemingly small role of humoral immunity in acute FPIES may be explained by lack of adequate B and T lymphocyte interaction, altered antigen processing or B cell anergy.²⁹

Cellular immunity

Cell mediated immunity is thought to be the predominant immune mechanism contributing to this disease, though many crucial details remain unclear. T cells have long been implicated in the pathogenesis of FPIES because earlier studies demonstrated that challenge with the protein component of an implicated food (for example, casein) resulted in symptoms. In addition, increased number of lymphocytes have been noted on jejunal biopsies³⁴ and preliminary studies show that these intestinal lymphocytes may be activated T cells.³³ Recently, activation and redistribution of lymphocytes from peripheral circulation during acute FPIES has been demonstrated,²⁷ suggesting lymphocytes may home to the GI tract in response to antigenic stimuli. These studies highlight central role adaptive immunity, specifically T cell responses have in disease pathogenesis. However, the mechanism for T-cell activation remains to be characterized. Antigen specific T-cell responses have been very difficult to identify, despite utilizing various experimental techniques.^{7, 27, 29, 33} This may be due to a few reasons: the activated lymphocytes could be localized to the gastric mucosa or require longer time for

activation, factors which have been limitations of prior studies. Alternatively, it has been postulated that the trigger antigen may undergo enzymatic modification, similar to gliadin.^{27, 33}

Specific T cell populations have been observed in patients with FPIES. There are high rates of co-atopy (up to 40%), which can be explained by Th2 cytokine profile (IL 4, 5, 9, 13) in this patient population.^{29, 36-39} Th1 and Th17 activation in acute FPIES is evidenced by interferon gamma and IL-22 expression in patients during acute FPIES reactions.³³ Increased regulatory T cells and IL-10 are also noted in patients who gain tolerance.^{29, 37}

Cytokines

A series of studies have now helped develop a specific cytokine signature found in patients with active FPIES versus those that have acquired tolerance, suggesting a disrupted homeostasis between pro and anti-inflammatory cytokines. The source of these cytokines is unclear though many are thought to be secreted by T cells. Decreased IL-10 and increased IL-9 levels have been noted in patients with active FPIES²⁹ along with increased tumor necrosis factor alpha (TNF α) and decreased transforming growth factor beta (TGF β).^{29, 35, 36, 39, 40} Interestingly, the TGF β receptors correlate with degree of villous atrophy.⁴⁰ Increase in other pro-inflammatory cytokines such as IL-6 has also been noted. The altered immune homeostasis and skewing towards pro-inflammatory conditions likely leads to innate and adaptive immune responses noted in acute FPIES. This is further elucidated in particular in immune dysregulatory conditions such as Down's Syndrome which have specific pro-inflammatory cytokine profile (decreased IL-10, increased TNF α) and has now been associated with protracted FPIES disease course.⁴¹

Proposed Mechanism

The immunologic milieu that typically contributes to immune tolerance and homeostasis is disrupted in FPIES (Figure 3). Activation of the innate immune system by improper recognition of food antigen launches a unique inflammatory cascade.⁴² This may lead to a pro-inflammatory milieu due to cytokine production, neutrophil migration, eosinophil degranulation and mast cell activation. Resultant lymphocytic infiltration and inflammation may follow, with significant disruption in mucosal barrier permeability. With this breakdown in mucosal immunity, there can be increased antigen uptake, and continued innate immune activation, initiating development and amplification of disease.^{26, 36} This model has demonstrated direct effect of increased TNF α on barrier disruption and lymphocyte activation.⁴³

Elevated C-reactive protein (CRP) and platelets during positive oral food challenges provides evidence for an acute inflammatory process.^{36, 42} Interestingly, CRP level was associated with disease prognosis, with increased level associated with delayed acquisition of tolerance.³⁸ This further supports the hypothesis that pro-inflammatory cytokines play a role in this disease. Conversely, there was a negative correlation of eosinophilia and tolerance acquisition, which questions whether eosinophilia may actually be a protective mechanism in FPIES.³⁸ Decreased regulatory T cells can contribute towards Th1 and Th2 skewing.⁴⁴ The association of FPIES and atopy is supported both by Th2 cytokine signature and elevated thymus and activation-regulated chemokine (TARC), both of which are implicated in other atopic conditions.⁴⁵

Neuroimmune Interactions in FPIES

The ANS plays a role in modulating immune function in response to inflammation.⁴⁶ All three divisions of the ANS—sympathetic, parasympathetic, and enteric nervous systems—receive input from immune cells and release neurotransmitters that regulate the immune

response.²⁴ The intestinal neuroimmune barrier consists of constant interactions among immune cells, enteric neurons, enteric glia, enteroendocrine cells, and microbiota. Inflammatory signals reach the central nervous system via humoral signaling, vagal sensory afferents, and dorsal root ganglion neurons. The ANS modulates immune function via sympathetic nervous system activation of lymphoid organs, including gut-associated lymphoid tissue, producing a pro-inflammatory response.²⁴ The neuroimmune response may play a central role in the unique symptom profile of FPIES.

The use of ondansetron during acute FPIES reactions supports the possibility of neuroimmune-mediated symptoms.⁷ Ondansetron is a selective serotonin or 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist that acts on both central and peripheral nerves to attenuate symptoms of nausea and vomiting.⁴⁷ It acts centrally by inhibiting 5-HT₃ receptors in chemoreceptor trigger zones of the brain, and peripherally by acting on 5-HT₃ receptors on vagal afferents, thus dampening the nociceptive response from stimuli within the GI tract.⁴⁷ Data supporting the use of serotonin-antagonist ondansetron in FPIES is promising but limited. Three case series have demonstrated resolution of vomiting during oral food challenge with intravenous, intramuscular, or oral ondansetron.⁴⁸⁻⁵⁰ A larger retrospective review showed significant reduction in vomiting, pallor, and lethargy with parenteral ondansetron compared to corticosteroids and fluids.⁵¹ There have been no prospective, randomized studies on the use of ondansetron in acute FPIES reactions to definitively validate its effectiveness, although management guidelines suggest its use in appropriate patients.²

Further investigation into the role of serotonin in intestinal inflammation may provide insight into the neuroimmune response in FPIES. Although a neurohormone, serotonin is primarily synthesized by enterochromaffin cells in the intestinal mucosa.⁵² In the GI tract

serotonin mediates intestinal motility, secretion, vasodilation, and perception of pain and nausea.⁵³ Studies have demonstrated that serotonin signaling is altered in intestinal inflammatory conditions, including inflammatory bowel disease (IBD), celiac disease, infectious enteritis, and irritable bowel syndrome (IBS).⁵³ Immune cells, including T cells, macrophages, dendritic cells, and mast cells, express machinery to synthesize and/or process serotonin.⁵² Furthermore, mucosal serotonin has been implicated in activation of proinflammatory mediators, and generation of innate and adaptive immune responses.⁵⁴ Other than the use of ondansetron, there are no published investigations of the role of serotonin in FPIES.

There are a few disease models that highlight the importance of the neuroimmune response in modulating intestinal homeostasis and function. These models suggest possible mechanisms through which the inflammatory cascade initiated in acute FPIES may contribute to a dysregulated ANS response. For example, patients with IBS have increased tryptase on colonic biopsies as well as increased numbers of mast cells^{55, 56} which are known to activate myenteric and submucosal neurons. Perhaps a similar mechanism may account for the abnormal neuronal activation in FPIES. Additionally, patients with IBD have altered sympathetic innervation.⁵⁷ The constant state of inflammation results in sprouting of sensory neurons and is thought to contribute to visceral hypersensitivity in IBD.^{57, 58} One can surmise that the inflammatory milieu that results from disrupted immune homeostasis in FPIES could also promote a hyperresponsive ANS response. Though many mechanisms have been proposed, the dysregulated cytokine profile found in FPIES is likely an important contributor in the neuroimmune-intestinal response and disease pathogenesis. Cytokine signaling in the brain contributes to fever, fatigue, confusion, and activation of the neuroendocrine response.⁵⁹ Dysregulated or hyperresponsive interactions can result in neuronal tissue damage and neuroinflammatory conditions. Other disease processes

such as stress-induced depression, West Nile encephalitis, and cognitive decline have all been linked to abnormal neuronal synapse resulting from inflammatory cytokine production.⁶⁰

Conclusion

FPIES is a disorder of immune intolerance to specific food antigens, primarily affecting infants but shown to occur across all ages. It is characterized by immune dysregulation leading to profound GI symptoms and an exaggerated hemodynamic response that is not seen in other allergic GI disorders. The ANS functions to regulate compensatory mechanisms to maintain organ perfusion and function and may play a critical role in the symptomatology of FPIES. Whether there is a dysregulated ANS response in FPIES requires more detailed clinical phenotyping from symptom onset throughout the disease process. Comprehensive clinical assessment of the FPIES phenotype would enhance understanding of the dynamic relationship of the immune system, GI tract, and ANS in FPIES. Investigation into neuroimmune interactions and neurohumoral profiles of FPIES patients may provide further insight into the relationship between the immune response and the ANS. There are several unmet needs in the field of FPIES research including mechanistic understanding, predictive biomarkers, and targeted therapeutic interventions. To optimally address these needs requires a multidisciplinary team approach that recognizes the constant interplay between the immune system, GI tract, and ANS.

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Acknowledgement:

The authors would like to recognize Ms. Elizabeth Ramirez for her efforts and attention to detail in assisting with graphical design of figures for this manuscript.

Table 1. Diagnostic criteria and defining features of FPIES subtypes based on international consensus guidelines for the diagnosis and management of FPIES.^{2, 6}

Acute FPIES	
Diagnostic Criteria	Requires major criterion and 3 or more minor criteria: Major Criterion: 1. Vomiting 1-4 hours after ingestion without symptoms of IgE-mediated allergic reaction Minor Criteria: 1. Prior episodes of repeated vomiting after exposure to food 2. Repetitive vomiting 1-4 hours after eating another food 3. Lethargy 4. Pallor 5. Need for emergency department care 6. Need for intravenous fluids 7. Diarrhea within 24 hours of ingestion 8. Hypotension 9. Hypothermia
Additional Features	• Intermittent exposure to offending food trigger • Asymptomatic unless exposed to food trigger • Normal growth and development • Optional lab findings: leukocytosis with neutrophilia, thrombocytosis; electrolyte derangements, metabolic acidosis, methemoglobinemia; stool with leukocytes, eosinophils, reducing substances
Chronic FPIES	
Defining Features	• Days to weeks of progressive vomiting +/- watery diarrhea (can be bloody) with poor weight gain or failure to thrive • Typically presents in infants <4 months of age • Daily, repeated exposure to offending food • Common triggers: cow's milk or soy-based formula • Dehydration, metabolic acidosis, hypotension, and hypovolemic shock can occur
Adult FPIES	
Defining Features	• Older age of onset: adolescents and adults • Symptoms of vomiting, diarrhea, severe abdominal pain develop 1-4 hours after food ingestion • Common triggers: shellfish, dairy, wheat, egg • Hypothermia, lethargy, pallor, weakness, dizziness, blurred vision, and loss of consciousness have been reported at presentation and during oral food challenge
Atypical FPIES	
Defining Features	• Development of food-specific IgE to identified FPIES trigger • Protracted course with symptom resolution at an older age • IgE-mediated allergic reactions to FPIES food trigger can develop

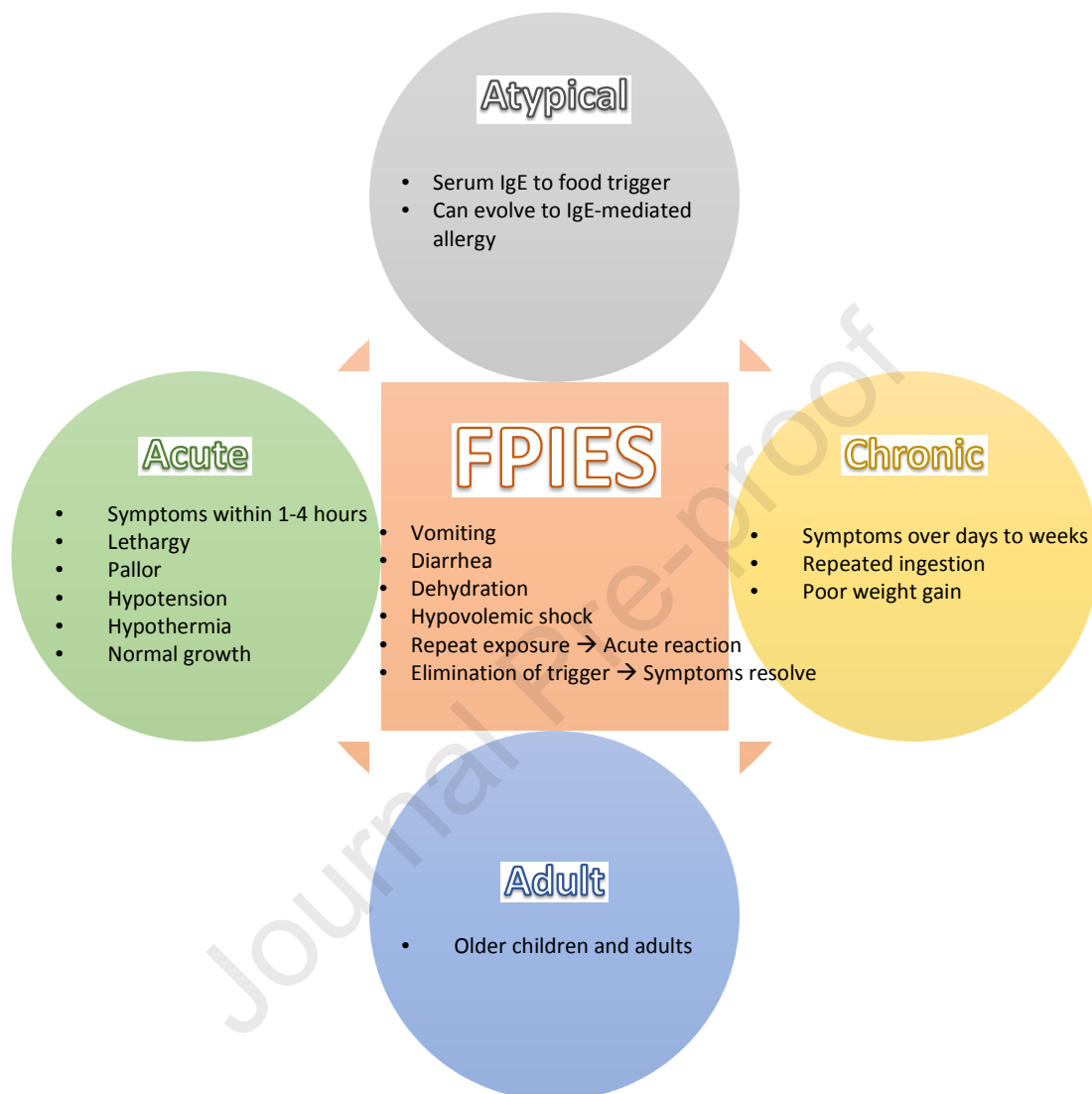
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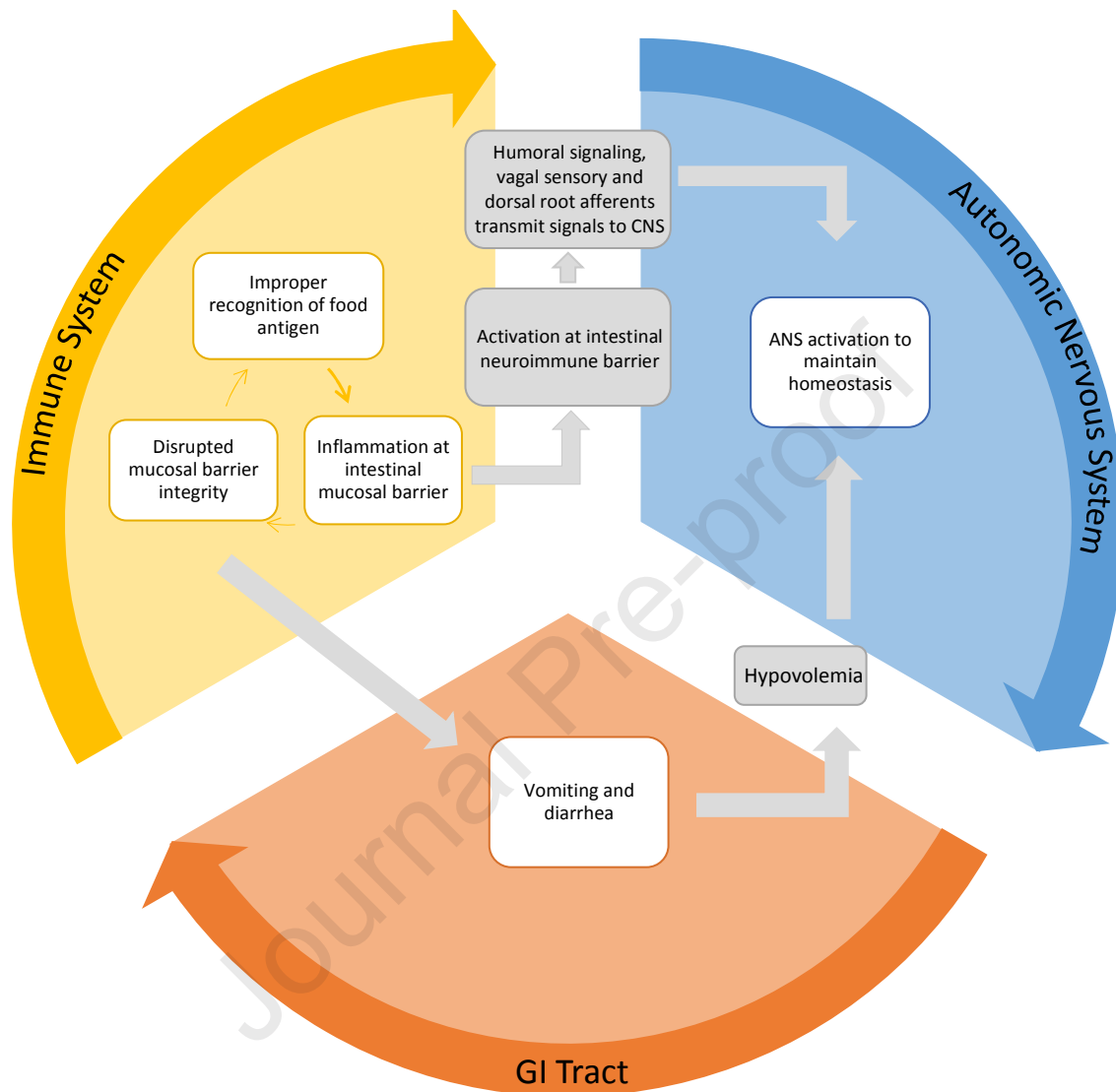
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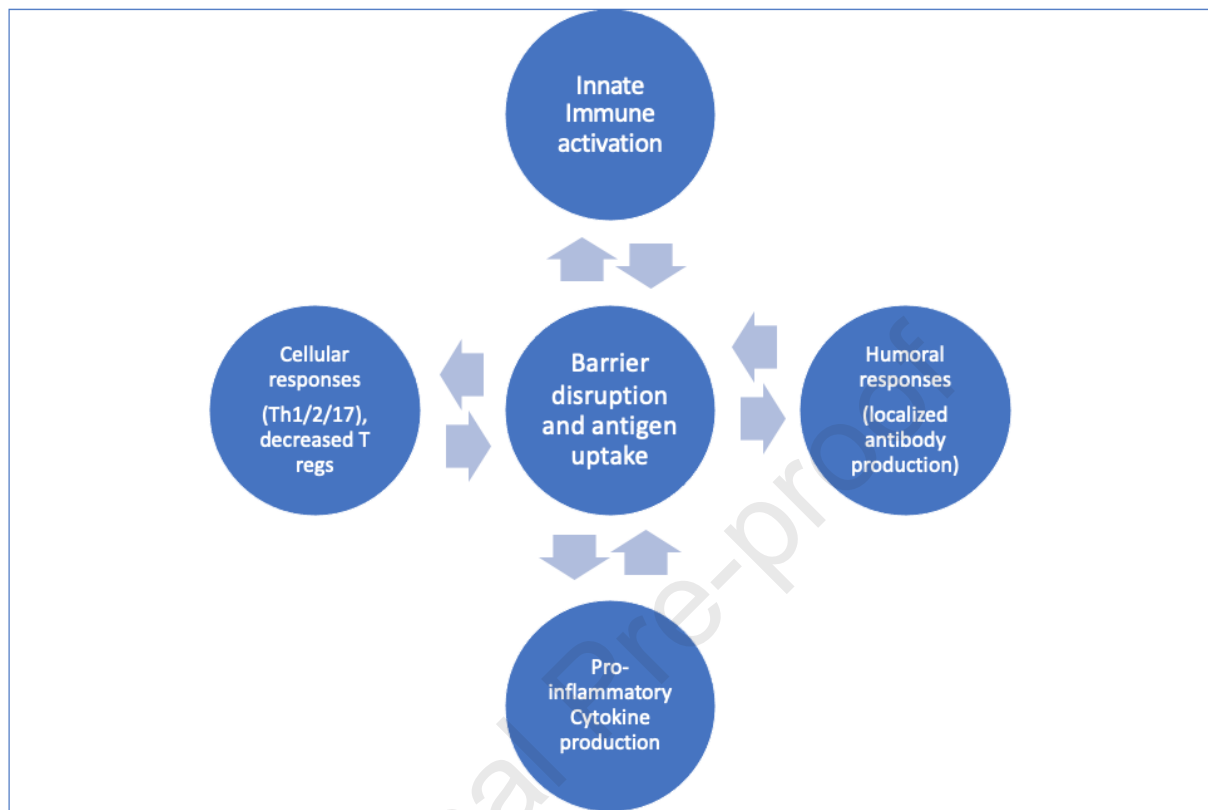
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Figure Legend

Figure 1. Relationship among clinical subtypes of FPIES. Current characterization may be incomplete to capture the dynamic interactions of the immune, gastrointestinal, and autonomic nervous system response.

Figure 2. Proposed fluid relationship between the immune, gastrointestinal, and autonomic nervous system (ANS) response in FPIES. (CNS, central nervous system)

Figure 3. Proposed immune mechanisms for acute FPIES. Activation of innate, cellular and humoral immune pathways with resultant pro-inflammatory cytokine production leads to gastrointestinal barrier disruption and increased permeability. (Tregs, T regulatory cells)

Key Messages:

- Food protein-induced enterocolitis syndrome (FPIES) is characterized by immune dysregulation incited by a food antigen trigger leading to profound gastrointestinal (GI) symptoms and an exaggerated hemodynamic response.
- The autonomic nervous system (ANS) functions to regulate compensatory mechanisms to maintain organ perfusion and function, and may play a critical role in the symptomatology of FPIES.
- Comprehensive clinical assessment of FPIES phenotype may enhance understanding of the dynamic relationship of the immune system, GI tract, and ANS.
- Investigation into neuroimmune interactions and neurohumoral profiles of FPIES patients may provide further insight into the relationship between the immune response and the ANS.

References

1. Nowak-Wegrzyn A, Berin MC, Mehr S. Food Protein-Induced Enterocolitis Syndrome. *J Allergy Clin Immunol Pract.* 2020;8:24-35.
2. Nowak-Wegrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol.* 2017;139:1111-1126 e1114.
3. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *J Allergy Clin Immunol.* 2011;127:647-653 e641-643.
4. Nowak-Wegrzyn A, Warren CM, Brown-Whitehorn T, Cianferoni A, Schultz-Matney F, Gupta RS. Food protein-induced enterocolitis syndrome in the US population-based study. *J Allergy Clin Immunol.* 2019;144:1128-1130.
5. Alonso SB, Ezquiaga JG, Berzal PT, et al. Food protein-induced enterocolitis syndrome: Increased prevalence of this great unknown-results of the PREVALE study. *J Allergy Clin Immunol.* 2019;143:430-433.
6. Du YJ, Nowak-Wegrzyn A, Vadas P. FPIES in adults. *Ann Allergy Asthma Immunol.* 2018;121:736-738.
7. Berin MC. Immunopathophysiology of food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol.* 2015;135:1108-1113.

8. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol Pract.* 2013;1:343-349.
9. Caubet JC, Ford LS, Sickles L, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol.* 2014;134:382-389.
10. Novak P. Autonomic Disorders. *Am J Med.* 2019;132:420-436.
11. Kessel A, Dalal I. The pendulum between food protein-induced enterocolitis syndrome and IgE-mediated milk allergy. *Acta Paediatr.* 2011;100:e183-185.
12. Tarbell SE, Shaltout HA, Wagoner AL, Diz DI, Fortunato JE. Relationship among nausea, anxiety, and orthostatic symptoms in pediatric patients with chronic unexplained nausea. *Exp Brain Res.* 2014;232:2645-2650.
13. Tarbell SE, Sullivan EC, Meegan C, Fortunato JE. Children with Functional Nausea-Comorbidities outside the Gastrointestinal Tract. *J Pediatr.* 2020;225:103-108 e101.
14. Cheshire WP, Jr., Goldstein DS. Autonomic uprising: the tilt table test in autonomic medicine. *Clin Auton Res.* 2019;29:215-230.
15. Muth ER, Stern RM, Thayer JF, Koch KL. Assessment of the multiple dimensions of nausea: the Nausea Profile (NP). *J Psychosom Res.* 1996;40:511-520.
16. Wagoner AL, Tarbell SE, Shaltout HA, Diz DI, Weese-Mayer DE, Fortunato JE. Chronic nausea and orthostatic intolerance: Diagnostic utility of orthostatic challenge duration, Nausea Profile Questionnaire, and neurohumoral measures. *Neurogastroenterol Motil.* 2018;30:e13433.

17. Wagoner AL, Shaltout HA, Fortunato JE, Diz DI. Distinct neurohumoral biomarker profiles in children with hemodynamically defined orthostatic intolerance may predict treatment options. *Am J Physiol Heart Circ Physiol*. 2016;310:H416-425.
18. Cook KF, Jensen SE, Schalet BD, et al. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. *J Clin Epidemiol*. 2016;73:89-102.
19. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. *Mayo Clin Proc*. 2012;87:1196-1201.
20. Koch KL. A noxious trio: nausea, gastric dysrhythmias and vasopressin. *Neurogastroenterol Motil*. 1997;9:141-142.
21. Idiaquez J, Benarroch E, Nogues M. Anatomy, Physiology, and Pharmacology of the Autonomic Nervous System (ANS). In: Idiaquez J, Benarroch E, Nogues M, eds. *Evaluation and Management of Autonomic Disorders*. Cham, Switzerland: Springer International Publishing; 2018:3-18.
22. Axelrod FB, Chelimsky GG, Weese-Mayer DE. Pediatric autonomic disorders. *Pediatrics*. 2006;118:309-321.
23. Wehrwein EA, Orer HS, Barman SM. Overview of the Anatomy, Physiology, and Pharmacology of the Autonomic Nervous System. *Compr Physiol*. 2016;6:1239-1278.
24. Benarroch EE. Autonomic nervous system and neuroimmune interactions: New insights and clinical implications. *Neurology*. 2019;92:377-385.
25. Voisin T, Bouvier A, Chiu IM. Neuro-immune interactions in allergic diseases: novel targets for therapeutics. *Int Immunol*. 2017;29:247-261.

26. Mehr S, Lee E, Hsu P, et al. Innate immune activation occurs in acute food protein-induced enterocolitis syndrome reactions. *J Allergy Clin Immunol*. 2019;144:600-602 e602.
27. Goswami R, Blazquez AB, Kosoy R, Rahman A, Nowak-Wegrzyn A, Berin MC. Systemic innate immune activation in food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol*. 2017;139:1885-1896 e1889.
28. Ishige T, Yagi H, Tatsuki M, et al. Endoscopic findings in the acute phase of food protein-induced enterocolitis syndromae. *Pediatr Allergy Immunol*. 2015;26:90-91.
29. Caubet JC, Bencharitiwong R, Ross A, Sampson HA, Berin MC, Nowak-Wegrzyn A. Humoral and cellular responses to casein in patients with food protein-induced enterocolitis to cow's milk. *J Allergy Clin Immunol*. 2017;139:572-583.
30. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. *J Pediatr*. 1978;93:553-560.
31. Kalach N, Kapel N, Waligora-Dupriet AJ, et al. Intestinal permeability and fecal eosinophil-derived neurotoxin are the best diagnosis tools for digestive non-IgE-mediated cow's milk allergy in toddlers. *Clin Chem Lab Med*. 2013;51:351-361.
32. Caubet JC, Nowak-Wegrzyn A. Current understanding of the immune mechanisms of food protein-induced enterocolitis syndrome. *Expert Rev Clin Immunol*. 2011;7:317-327.
33. Adel-Patient K, Lezmi G, Castelli FA, et al. Deep analysis of immune response and metabolic signature in children with food protein induced enterocolitis to cow's milk. *Clin Transl Allergy*. 2018;8:38.
34. Fontaine JL, Navarro J. Small intestinal biopsy in cows milk protein allergy in infancy. *Arch Dis Child*. 1975;50:357-362.

35. Konstantinou GN, Bencharitiwong R, Grishin A, et al. The role of casein-specific IgA and TGF-beta in children with food protein-induced enterocolitis syndrome to milk. *Pediatr Allergy Immunol.* 2014;25:651-656.
36. Labrosse R, Graham F, Caubet JC. Non-IgE-Mediated Gastrointestinal Food Allergies in Children: An Update. *Nutrients.* 2020;12.
37. Mori F, Barni S, Cianferoni A, Pucci N, de Martino M, Novembre E. Cytokine expression in CD3+ cells in an infant with food protein-induced enterocolitis syndrome (FPIES): case report. *Clin Dev Immunol.* 2009;2009:679381.
38. Kimura M, Shimomura M, Morishita H, Meguro T. Prognosis of infantile food protein-induced enterocolitis syndrome in Japan. *Pediatr Int.* 2017;59:855-860.
39. Morita H, Nomura I, Orihara K, et al. Antigen-specific T-cell responses in patients with non-IgE-mediated gastrointestinal food allergy are predominantly skewed to T(H)2. *J Allergy Clin Immunol.* 2013;131:590-592 e591-596.
40. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor beta1, transforming growth factor type I and II receptors, and TNF-alpha in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol.* 2002;109:150-154.
41. Wakiguchi H, Hasegawa S, Kaneyasu H, et al. Long-lasting non-IgE-mediated gastrointestinal cow's milk allergy in infants with Down syndrome. *Pediatr Allergy Immunol.* 2015;26:821-823.
42. Pecora V, Prencipe G, Valluzzi R, et al. Inflammatory events during food protein-induced enterocolitis syndrome reactions. *Pediatr Allergy Immunol.* 2017;28:464-470.

43. Heyman M, Darmon N, Dupont C, et al. Mononuclear cells from infants allergic to cow's milk secrete tumor necrosis factor alpha, altering intestinal function. *Gastroenterology*. 1994;106:1514-1523.
44. Stanisavljevic S, Dedovic N, Vujicic M, et al. Strain-specific helper T cell profile in the gut-associated lymphoid tissue. *Immunol Lett*. 2017;190:282-288.
45. Hamano S, Yamamoto A, Fukuhara D, Yan K. Serum thymus and activation-regulated chemokine level as a potential biomarker for food protein-induced enterocolitis syndrome. *Pediatr Allergy Immunol*. 2019;30:387-389.
46. Marvar PJ, Harrison DG. Inflammation, Immunity and the Autonomic Nervous System. In: Robertson D, Biaggioni I, Burnstock G, Low PA, Paton JFR, eds. *Primer on the Autonomic Nervous System*. Third ed. London, UK: Academic Press; 2012:325-329.
47. Ye JH, Ponnudurai R, Schaefer R. Ondansetron: a selective 5-HT(3) receptor antagonist and its applications in CNS-related disorders. *CNS Drug Rev*. 2001;7:199-213.
48. Holbrook T, Keet CA, Frischmeyer-Guerrero PA, Wood RA. Use of ondansetron for food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol*. 2013;132:1219-1220.
49. Miceli Sopo S, Battista A, Greco M, Monaco S. Ondansetron for food protein-induced enterocolitis syndrome. *Int Arch Allergy Immunol*. 2014;164:137-139.
50. Le S, de Boissieu D, Garcelon N, et al. Efficacy of oral ondansetron in acute FPIES: A case series of 6 patients. *Allergy*. 2020;75:2949-2951.
51. Miceli Sopo S, Bersani G, Monaco S, et al. Ondansetron in acute food protein-induced enterocolitis syndrome, a retrospective case-control study. *Allergy*. 2017;72:545-551.

52. Wu H, Denna TH, Storkersen JN, Gerriets VA. Beyond a neurotransmitter: The role of serotonin in inflammation and immunity. *Pharmacol Res.* 2019;140:100-114.
53. Mawe GM, Hoffman JM. Serotonin signalling in the gut--functions, dysfunctions and therapeutic targets. *Nat Rev Gastroenterol Hepatol.* 2013;10:473-486.
54. Khan WI, Ghia JE. Gut hormones: emerging role in immune activation and inflammation. *Clin Exp Immunol.* 2010;161:19-27.
55. Barbara G, Wang B, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology.* 2007;132:26-37.
56. Buhner S, Li Q, Vignali S, et al. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. *Gastroenterology.* 2009;137:1425-1434.
57. Belai A, Boulos PB, Robson T, Burnstock G. Neurochemical coding in the small intestine of patients with Crohn's disease. *Gut.* 1997;40:767-774.
58. Shea-Donohue T, Urban JF, Jr. Neuroimmune Modulation of Gut Function. *Handb Exp Pharmacol.* 2017;239:247-267.
59. Prieto GA, Cotman CW. Cytokines and cytokine networks target neurons to modulate long-term potentiation. *Cytokine Growth Factor Rev.* 2017;34:27-33.
60. Huh JR, Veiga-Fernandes H. Neuroimmune circuits in inter-organ communication. *Nat Rev Immunol.* 2020;20:217-228.