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REVIEW

Pathophysiology of Non-IgE-Mediated Food Allergy

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Abstract: Non-IgE-mediated food allergies are a group of disorders characterized by subacute or chronic inflammatory processes in the gut. Unlike IgE mediated food allergies that may result in multi-organ system anaphylaxis, the non-IgE mediated food allergies primarily affect the gastrointestinal tract. This review outlines the clinical manifestations, epidemiology, pathophysiology, and management of non-IgE-mediated food allergies. An updated literature search of selected non-IgE-mediated food allergies was conducted for this review using PubMed database to the current year (2021). Reviewed disorders include food protein-induced enterocolitis syndrome (FPIES), food-protein enteropathy (FPE), food protein-induced allergic proctocolitis (FPIAP), and eosinophilic gastrointestinal disorders (EGIDs) such as eosinophilic esophagitis (EoE). While extensive gains have been made in understanding FPIES, FPIAP, FPE, and EoE, more information is needed on the pathophysiology of these food allergies. Similarities among them include involvement of innate immunity, T-lymphocyte processes, alteration of the intestinal lumen at the cellular level with the appearance of inflammatory cells and associated histologic changes, and specific cytokine profiles suggesting food-specific, T-cell, and immune-mediated responses. While FPIES and FPIAP typically resolve in early childhood, EGIDs typically do not. Emerging new therapies for EoE offer promise of additional treatment options. Further studies identifying the immunopathogenesis, associated biomarkers, and mechanisms of tolerance are needed to inform prevention, diagnosis and management.

Keywords: food protein-induced enterocolitis syndrome, FPIES, food protein-induced enteropathy, FPE, food protein-induced allergic proctocolitis, FPIAP, eosinophilic gastrointestinal disorders, EGIDs, eosinophilic esophagitis, EoE, pathophysiology

Introduction

Food allergies can be categorized by pathophysiology into IgE-mediated, non-IgE-mediated, or mixed IgE and non-IgE-mediated conditions. Non-IgE-mediated food allergies are characterized by subacute or chronic symptoms, whereas IgE-mediated food allergies are characterized by the rapid onset of symptoms following ingestion (eg, anaphylaxis). Symptoms of non-IgE-mediated food allergies are primarily localized to the gut but may also affect the skin or lungs.[1,2] Mixed IgE and non-IgE-mediated food allergies include eosinophilic gastrointestinal disorders (EGIDs) such as eosinophilic esophagitis (EoE), and dermatologic conditions such as atopic dermatitis. In this review, we will discuss the clinical manifestations, epidemiology, pathophysiology, and management of non-IgE-mediated food allergies including food protein-induced enterocolitis syndrome (FPIES), food-protein enteropathy (FPE), and food protein-induced allergic proctocolitis (FPIAP). We will also briefly review non-IgE-mediated food allergies of eosinophilic origin, including eosinophilic esophagitis (EoE).

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Food Protein-Induced Enterocolitis (FPIES)

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food hypersensitivity that affects the entire gastrointestinal tract.[1] In 1967, one of the first case descriptions of FPIES by Gryboski described 21 hospitalized patients diagnosed with gastrointestinal milk allergy that presented with symptoms of chronic diarrhea and hematochezia.[3] Eight of these children underwent sigmoidoscopy and rectal biopsy which revealed colitis that normalized after milk elimination. Respiratory and cutaneous symptoms were absent, unlike in IgE-mediated food allergy, and milk-induced colitis was identified as a distinct entity.[3] Nearly a decade later, Powell described additional findings of increased peripheral leukocytosis, and neutrophilia, as well as increased presence of inflammatory cells in stool, among infants following a positive response to milk and/or soy challenge.[4,5] The term, food protein-induced enterocolitis, was coined by McDonald et al in 1982.[6] Further recognition of the constellation of symptoms and laboratory features seen in cases led to a refined understanding of the disease as a clinical syndrome by Sicherer et al in 1998.[7]

Clinical Manifestations

FPIES typically presents in infancy as either an acute or chronic phenotype.[8] Acute FPIES is characterized by repetitive, profuse, and protracted vomiting starting approximately 2 hours following ingestion of the culprit food and may include later onset of watery diarrhea. The reaction may lead to dehydration, pallor, lethargy, and/or hypovolemic shock. Laboratory abnormalities include an elevated white blood cell count with neutrophilia and bandemia, and possibly acidemia and methemoglobinemia. Symptoms usually resolve within 24 hours as long as the culprit food is not re-introduced. Chronic FPIES is characterized by intermittent, yet progressive vomiting, and watery diarrhea, leading to weight loss, failure to thrive (FTT), lethargy, dehydration and/or metabolic derangements.[8] Chronic FPIES symptoms are insidious and triggered by repeated ingestion of a culprit food, often cow milk or soy-based formula, over several days to weeks.[8] Diagnosis is clinical and based on history and symptom resolution following elimination of the suspected triggering food(s).[8] Table 1 compares features of acute and chronic FPIES based on international guidelines.[8]

Epidemiology

FPIES awareness is increasing worldwide, and prevalence rates vary geographically.[8,9] The cumulative worldwide incidence of FPIES is estimated at 0.015% to 0.7%, and the prevalence of FPIES is estimated to be 0.51% in US infants.[10] In a retrospective Korean study of 142 infants admitted for vomiting and/or diarrhea, 11.3% of infants were

Table 1 Acute vs Chronic FPIES

	Acute FPIES	**Chronic FPIES**
Age of onset	2–7 months of age	2–7 months of age
Symptom onset	Follows intermittent food exposures and includes emesis (within 1–4 hours), diarrhea (within 24 hours), lethargy, and pallor	Follows daily food ingestion and includes emesis (within 1–4 hours), diarrhea (within 24 hours, usually 5–10 hours, and may be chronic), poor weight gain/FTT
Clinical features	Vomiting, pallor, lethargy without skin or respiratory symptoms. May also include watery or bloody diarrhea, hypotension, abdominal distention, hypothermia	Intermittent but progressive vomiting and diarrhea, dehydration, metabolic acidosis, poor weight gain, FTT
Laboratory findings	Leukocytosis, neutrophilia, thrombocytosis, metabolic acidosis, methemoglobinemia	Leukocytosis, neutrophilia, thrombocytosis, metabolic acidosis, methemoglobinemia
Symptom resolution	Resolves within 24 hours after food elimination	Resolves within 3–10 days of food elimination and switching to hypoallergenic formula
Average age of resolution based on triggering food	Soy: 12 months (range 6 months to >22 years) Grains: 35 months Milk: 3 years Other solids: 42 months	

diagnosed with cow's milk protein-induced enterocolitis.[11] In an Israeli prospective birth cohort, Katz et al noted an incidence of 3 per 1000 newborns (0.34%) with cases attributed to cow's milk.[12] In Australia, an estimated incidence of 15.4 per 100,000 has been reported.[13] Chronic FPIES is less prevalent but appears more frequently in Japan and Korea.[11,14] In an international survey of caregiver-reported FPIES in 441 children, most affected children were female (50.7%), white (86.2%), and atopic (54.8%) suggesting that various demographic and atopic risk factors may exist.[15] In the United States, grains (oat, rice), cow's milk (CM) and soy are most often implicated.[15] Avocado is the most commonly avoided fruit and associated with increased likelihood of banana avoidance.[15] In Mediterranean countries, such as Spain and Italy, fish is a common trigger, whereas in Australia, rice was the most common trigger observed.[13,16,17] Geographic differences in FPIES prevalence and trigger foods may exist due to differences in feeding behaviors (eg, breastfeeding vs cow milk/soy formula use rates), timing of solid food introduction, intestinal microbiome, and genetics, but more studies are needed to ascertain the reasons for these regional variations.[18]

The typical ages for FPIES presentation may also vary by food trigger. For CM/soy FPIES, existing international studies report a range of 0.28–7 months for symptom onset.[3,4,7,8,12,14,17,19–26] Conversely, in solid-food FPIES, an older age of presentation is more common with a reported range of 4.5–12.1 months.[7,8,17,19,23–26] In adult-onset FPIES, seafood is the most common trigger.[27]

Pathophysiology

The pathogenesis of FPIES is poorly understood, but thought to be a combination of intestinal, innate, and cell-mediated pathways.[8] FPIES appears to largely be a combination of innate and cellular immunity processes involving antigen-specific T cells and cytokines, leading to gut inflammation in the colon and ileum.[3,28–34] This inflammation is believed to cause increased intestinal permeability and fluid shifts into the gastrointestinal lumen.[35] In early studies, Chung et al demonstrated increased TNF-α expression coupled with diminished TGF-β1 receptors in the intestinal epithelium by gut immunohistochemistry in FPIES patients, supporting initial thoughts that this cascade of inflammatory factors weakens the integrity of the intestinal epithelial barrier and allows antigen in to propagate an inflammatory response.[22] Studies in subsequent years have highlighted the complexity of potential pathways underlying the inflammatory cascade of FPIES. A Japanese study elucidating serum cytokine participants in FPIES pathophysiology demonstrated interleukin (IL)-2, IL-5, and IL-8 were increased in all four positive FPIES oral challenges obtained from 6 studied patients with FPIES.[36] IL-8 was again noted to be elevated in patients with cow's milk induced FPIES reactions, along with tryptase, supporting roles for neutrophils and mast cells, respectively, in FPIES reactions.[37]

Innate immune activation in FPIES reactions has been implicated in the pathogenesis of FPIES. Broad activation of the innate immune system was confirmed via CyTOF analysis of whole blood of 14 patients with FPIES by Goswami et al.[38] This study demonstrated dominant activation of monocytes in addition to neutrophils, eosinophils, and natural killer cells after positive challenges with trigger foods.[38] Mehr et al used transcriptional profiling of 36 children with FPIES to identify several genes associated with granulocytes and innate signaling (IL-10, TREM1).[39] In this study, matrix metalloproteinase 9, IL-B, and STAT3 were identified as key factors in positive FPIES challenge responses.[39] A number of additional innate cytokines (TNF-alpha, oncostatin M, leukemia inhibitory factor, IL-10, and IL-6) were identified as elevated in serum during and after FPIES reactions.[40]

Many studies have supported the involvement of T lymphocytes mediating FPIES reactions.[41,42] Global activation of T lymphocytes and their extravasation from the peripheral blood after positive FPIES challenges are demonstrated through significant loss of circulating T lymphocytes and associated CD69 upregulation of remaining lymphocytes.[38] However, evidence for pathways for T cell specific immune responses and the subtype of effector cells and cytokine profiles mediating this activation have conflicted. An early, double-blind, placebo-controlled food challenge to rice in Italy revealed Th2 activation in the form of immediate increase in IL-4 expression during a positive rice FPIES challenge.[41] Broad investigation of antigen-specific lymphoproliferation and cytokine production profiles in patients with non-IgE-mediated gastrointestinal food allergies and patients with IgE-mediated allergy also found Th2 cytokines, such as IL-3, IL-5, and IL-13, were significantly produced in vitro by milk protein-stimulated, peripheral blood mononuclear cells from patients with non-IgE gastrointestinal food allergies.[42] IgE or Th1 cytokines such as IFN-Y or IL-17 were not found to be significantly expressed in these same populations.[42] Conversely, Adel-Patient et al found very weak expression of inflammatory Th2 and Th17 cytokines after stimulation of peripheral blood mononuclear cells with cow's milk protein in subjects with cow's milk FPIES.[43] Other studies also demonstrated weak Th2 responses that were not significantly different from control populations.[44]

A recent prospective study of children with FPIES undergoing supervised oral food challenges offers new insights to an IL-17 signaling pathway in acute FPIES reactions. Berin et al used proteomic and flow cytometric analysis to examine peripheral blood samples from children (11 reactors and 12 outgrown) at baseline, symptom onset, and 4 hours after symptom onset in children undergoing FPIES food challenges.[45] Specifically, acute FPIES reactions were associated with activated IL-17 pathway signaling, demonstrating significant elevations in chemokine CCL20 and TH-17-related cytokines (IL-17A, IL-22, IL-17C, and CCL20).[45] Sources of IL-17 in peripheral cells were confirmed as primarily CD4+ TH17 cells.[45] In this study, the IL-17 pathway was identified as a key feature of acute FPIES from symptom onset until resolution, which was not previously described.[45]

Achievement of immune tolerance may also be, in part, mediated by T lymphocytes. Mori et al observed increased serum IL-10 expression in a follow-up negative rice challenge, in an 8-month-old who reacted to rice 6 months prior, suggesting that IL-10 was associated with achieving tolerance.[41] In addition, IL-10 serum levels have been demonstrated to increase in subjects after cow's milk FPIES had resolved, further suggesting a role for IL-10 in food tolerance.[37] Tregs have also been noted to be elevated during the course and or resolution of FPIES, suggesting roles for these cells in tolerance.[41] T-lymphocyte processes overall appear central in our understanding of FPIES. Table 2 summarizes findings of cytokine profiles seen in FPIES.

Additional branches of the immune process have been speculated to be included in FPIES pathophysiology such as humoral immunity. The presence of specific IgE towards trigger foods is associated with persistent FPIES[23] and up to 30% of individuals with FPIES also have low positive specific IgE levels.[7,14,42] Atypical FPIES can also present with some degree of serum IgE positivity and IgE-mediated cutaneous reactions.[10] Though associations between FPIES symptomatology and IgE presence are suggested, there have been no studies successfully describing a food-specific IgE-mediated response in FPIES. For instance, Adel-Patient et al did not detect IgE reactivity to 8 separate milk allergens or digested cow's milk when comparing milk FPIES with IgE-mediated milk or peanut allergy.[43]

Studies suggesting involvement of other immunoglobulin isotypes are conflicting.[10] Plasma cells producing IgA and IgG were noted in the intestinal mucosa in the earliest studies of subjects with cow's milk malabsorption syndromes, along with increased IgA and IgM content of the stool and serum post-challenge with cow's milk.[46] Additionally, egg and soy induced FPIES reactions also demonstrated elevations in specific IgA and IgG post-challenge when compared to control subjects in a small study by McDonald et al.[20] However, larger studies indicate no evidence for food-triggered antibody recognition.[40] A comparison of individuals with challenge-

Table 2 Inflammatory Responses Implicated in FPIES

Study	Year	Country	Population	Elevated Cytokines
Berin C, Lozano-Ojalvo D, Agashe C et al[45]	2021	United States	23 children with history of FPIES (11 reactors, 12 outgrown) undergoing supervised FPIES OFCs	Increased IL-17 family cytokines (IL-17A, IL-22, IL-17C, and CCL20) in symptomatic OFCs. Increased IL-2 and increased inflammatory markers (IL-8, oncostatin M, leukemia inhibitory factor, TNF-α, IL-10, and IL-6). Increased mucosal damage marker regenerating family member 1 alpha (REG1A).
Kimura M, Ito Y, Shimomura M et al[36]	2017	Japan	6 OFCS in 4 patients with FPIES	IL-2, IL-5, and IL-8 were elevated in all 4 positive OFCs.
Morita H, Nomura I, Orihara K et al[42]	2013	Japan	65 patients with GI food allergies, 12 with IgE-mediated cow's milk allergy (CMA) with non-gastrointestinal symptoms with milk ingestion, and 12 asymptomatic controls	Increased IL-3, IL-5, and IL-13 in peripheral blood mononuclear cells from those with GI food allergies
Mori F, Barni S, Cianferoni A et al[41]	2009	Italy	Double-blind placebo-controlled OFC to rice in an 8-month-old boy during an acute FPIES reaction and after FPIES resolution	Increased IL-4 (positive OFC) Increased IL-10 (negative OFC done 6 months after initial positive OFC)

proven milk FPIES and individuals with history of milk FPIES that had since resolved did not reveal significant differences in milk-specific IgG1, IgG, IgM, and IgA levels.[44,47] There has even been suggestion of suppression of immunoglobulin responses, specifically IgG4 and IgA, when subjects with FPIES were challenged with their food triggers thus highlighting the lack of understanding of the role of humoral immunity in FPIES.[47,48]

Neuroimmune mechanisms are also suggested in the pathogenesis given the symptomatic improvement of vomiting, abdominal pain, and lethargy with ondansetron use in acute episodes of FPIES.[49] However, this is also poorly understood. Rapid recovery of acute FPIES reactions in a case series of 5 consecutive patients undergoing oral food challenges at a pediatric allergy clinic was observed with ondansetron treatment, a selective serotonin 5-HT3 receptor antagonist.[49]

Existing imaging and biopsy studies have revealed additional insight to the gross pathology of FPIES. Initial rectal biopsies of children who underwent sigmoidoscopy with suspected FPIES identified colitis that normalized after a milk elimination diet.[3] A review of 53 cases of children with allergic disorders of the GI tract, including 15 with allergic proctitis and 38 with allergic gastroenteritis, confirmed diffuse eosinophils in the lamina propria with focal infiltration of the epithelium by eosinophils on rectal mucosal biopsy.[28] Proctosigmoidoscopy in four infants with suspected soy protein intolerance after soy formula challenge showed mucosal friability and loss of vascular pattern. Their rectal biopsies showed acute colitis with crypt abscesses, mucus depletion of rectal glands, and polymorphonuclear leukocytes within the lamina propria.[29] Intestinal biopsies of 31 infants with cow's milk protein intolerance confirmed mucosal damage with partial villous atrophy and blunting seen most often.[30]

Management

In acute management of FPIES reactions, the severity of presenting symptoms should be considered.[8] For mild symptoms, oral rehydration, ondansetron (for ages 6 months and older), and close monitoring for 4–6 hours from onset of symptoms at home is suggested.[8] For moderate or severe symptoms with greater than 3 episodes of emesis or lethargy, emergency care and/or hospitalization may be required.[8] Aggressive fluid resuscitation in an emergency setting, a single dose of intravenous methylprednisolone, and ondansetron may be considered.[8] In severe cases, close attention to electrolyte abnormalities such as acidemia, correction of methemoglobinemia, and intensive cardiorespiratory support may be indicated.[8] Management of acute and chronic FPIES is also based on an elimination diet of the triggering food.[8] Due to high milk and soy co-reactivity, transition to soy formula is not recommended in cases of FPIES to cow's milk.[8] Use of extensively hydrolyzed or amino-based formula may be considered in addition to breastfeeding.[8] Guided introduction of low risk solids is recommended for long-term management, beginning with less allergenic foods (eg, berries, carrot, quinoa, lamb, and apple).[8]

Prognosis is favorable for FPIES. Most children outgrow FPIES by age 1–5 years, but timing varies by triggering food and patient. For example, CM-triggered FPIES tends to resolve by age 3–5 years, whereas rice FPIES typically resolves by age 5 in 50% of cases.[1,8]

Food Protein-Induced Allergic Proctocolitis (FPIAP)

Clinical Manifestations

Food protein-induced allergic proctocolitis (FPIAP) is a non-IgE-mediated, self-limited, food allergy of the rectum and colon. Lake et al first described FPIAP in 1982 in six exclusively breastfed infants who developed inflammatory changes in the rectum in the first month of life.[50] FPIAP typically starts in the first 6 months of life with blood-streaked and/or mucus-containing stools.[1] Breastfed infants are often older at initial presentation and with less severe histologic findings. Infants appear well but may have colicky behavior with increased bowel movements. FTT is absent, which is a key difference from other non-IgE-mediated food allergies. Anemia secondary to stool blood loss may rarely occur, requiring iron supplementation.[1]

Epidemiology

Estimates of prevalence in infants with rectal bleeding range widely from 18% to 64%.[51,52] A recent prospective study of newborn infants identified a cumulative incidence of 17% (n = 153) for FPIAP when diagnosed clinically by community pediatricians without confirmatory oral challenge.[53] This study likely over-represented the prevalence by including infants with occult or chronic blood in the stool without confirming food as a trigger. Varying practices in screening and diagnosis of FPIAP may account for different rates. Risk factors for FPIAP include atopy, such as having a first-degree relative with food allergy), eczema, or household pets at birth.[53] Infants fed both breast milk and formula during the first 4 months of life in this recent prospective study were 56% less likely than exclusively formula-fed infants, and 38% less

likely than exclusively breastfed infants to develop FPIAP.[53] IgE-mediated allergy is also strongly associated with FPIAP, with Martin et al observing that infants with FPIAP were almost twice as likely to develop IgE mediated allergy.[54]

Pathophysiology

FPIAP pathology is mostly limited to the rectosigmoid colon for unknown reasons, and like other non-IgE-mediated food allergies, is poorly understood. Similar to FPIES, inflammatory cytokine TNF-α is overexpressed, whereas TGF-β1 receptor activity and TGF-β ligand expression are decreased in tissue and allergen-restimulated peripheral blood mononuclear cells in subjects with FPIAP.[42,55] The hypothesized role for abnormal expression of TNF-α and TGF-β is to weaken the epithelial barrier of intestinal mucosa and promote fluid shifts resulting in diarrhea and hematochezia.

Endoscopy and biopsy are rarely undertaken because FPIAP is a clinical diagnosis. When biopsied, gross findings of focal erythema with lymphoid nodular hyperplasia are present.[56] Signature findings on biopsy include marked eosinophilic infiltration and degranulation of the rectosigmoid colon in close proximity to the lymphoid nodules.[28,51,57] A prospective study of 35 infants with rectal bleeding and allergic colitis revealed 31 infants with marked eosinophilic infiltrate (with >20 eosinophils per high-power field) on histopathology.[57] No correlation between tissue and peripheral eosinophilia has been noted in FPIAP.[56]

There are currently no reported biomarkers identified to support FPIAP diagnosis.[53] Children with an FPIAP diagnosis had a two-fold risk of developing IgE-mediated food allergy, even when accounting for atopic dermatitis as a risk.[54] A shared pathophysiology may explain this, or the possibility that dietary elimination was a risk factor, which underscores the need for more studies in this area and consideration to rechallenge to the presumed trigger after symptom resolution to confirm the diagnosis.

Management

A maternal elimination diet of the triggering food in exclusively breastfed infants, or a trial of extensively hydrolyzed or amino acid-based cow's milk formula in either breastfed or formula-fed infants, may be considered for the management of cow's milk induced FPIAP.[1] To establish a dietary trigger, a re-trial of the suspected food a few weeks after resolution of rectal bleeding is advised.[58] Regarding maternal dietary restriction, some suggest waiting a month before starting dietary elimination, since bleeding may self-resolve, but individual approaches may vary.[58,59]

Prognosis is favorable, and cases usually resolve by 12 months of age.[1] In fact, a recent US prospective study of FPIAP showed the median age of symptom resolution was potentially earlier, at 123 days.[53] Infants are otherwise well-appearing without significant morbidity resulting from this self-limited condition.

Food Protein-Induced Enteropathy (FPE)

Food protein-induced enteropathy (FPE) is a non-IgE-mediated food allergy affecting the small bowel. The diagnosis is rarely made nowadays. FPE was first described by Kuitunen et al in 1975 among 54 infants with malabsorption syndrome and cow's milk intolerance from 1962 to 1971 in Finland. Infants presented with diarrhea, FTT, vomiting and 20% had eczema and recurrent respiratory infections that resolved around age 1. Labs showed malabsorption, raised serum IgA and CM precipitants, while biopsies revealed damaged jejunal mucosa.[60] Unlike FPIES or FPIAP, histological confirmation of FPE requires biopsy.[1]

Clinical Manifestations

FPE presents with protracted, non-bloody, diarrhea in the first 9 months of life. Symptoms typically present within the first 2 months, and usually within weeks of CM introduction.[1,2,8,31,32,60] Other food triggers include soy, wheat, and egg.[2] Up to half of affected infants have FTT, abdominal distention, and/or malabsorption.[1] Additional features include protein-losing enteropathy, hypoalbuminemia, and FTT.[1] FPE is characterized by abnormal small intestinal mucosa, improved after dietary avoidance.[2]

Epidemiology

FPE is a rare condition. An overall decline in FPE has been noted over the last few decades.[61] Peak incidence was noted in the 1960s in Finland, followed by a gradual disappearance of cases of severe jejunal damage caused by CM in the following three decades.[1,61] Personal history of atopy is estimated to be 22% in FPE, whereas family history of atopy is unknown.[1]

Pathophysiology

Distinguishing features of biopsies in patients with FPE include specific damage to villous architecture of the small intestine mucosa, unlike the other non-IgE mediated gastrointestinal allergies mentioned in this review.[62,63] Specific

histological findings include villous atrophy, lymphonodular hyperplasia of the duodenum and colon, increased intraepithelial lymphocytes (>25/100 epithelial cells) and marked eosinophil infiltration and degranulation in the mucosa.[1,34,61,64–66] Suggested cellular etiologies for the inflammation induced structural damage include the presence of food (milk) specific T lymphocytes in duodenal tissue which express Th2 cytokines upon stimulation with milk.[67] Increased intestinal intraepithelial CD8+ T cells that are food-allergen specific are noted in FPE, similar to celiac's disease, and thus likely also contribute to the malabsorption.[1,61,68,69] Expression of IFN-Y and IL-4 cytokines have also been identified in jejunal biopsy specimens.[1,70] Overall, pathophysiology of FPE involves eosinophils, cow-milk specific T lymphocytes, and specific cytokine profiles.[2,34,37,67]

Management

Avoidance of the triggering food is recommended. Introduction of non triggering foods can occur without restriction, unlike FPIES which requires a more gradual approach of slow introduction of foods related to the trigger.[44] Further management, including food introduction, has been discussed at length.[8] Prognosis is favorable with resolution of symptoms usually reported by age 24–36 months.[1]

Eosinophilic Gastrointestinal Disorders (EGIDs)

The eosinophilic gastrointestinal disorders (EGIDs) include eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), eosinophilic enteritis, and eosinophilic colitis (EC). These disorders are characterized by chronic eosinophilic inflammation and although IgE mediated allergy is not necessarily identified, they are typically categorized as "mixed" IgE and non-IgE mediated because allergic sensitization is often observed. EoE, the most well-studied, will be primarily discussed here. Eosinophilic esophagitis (EoE) is a chronic, immune-mediated esophageal disease characterized by symptoms related to esophageal dysfunction and eosinophil-predominant inflammation on histology.[71]

Clinical Manifestations

Symptoms include abdominal pain, dysphagia, nausea, emesis, esophageal food impaction, gastroesophageal reflux symptoms, diarrhea, chest pain, and bloody stools.[72] Symptoms vary by age, with nonspecific gastrointestinal symptoms and FTT more common in childhood, and esophageal symptoms like heartburn, chest pain, and dysphagia more prevalent in older children and adults.[72] Other immunological disorders, like celiac disease, and psychosocial comorbidities, such as depression and anxiety, are also associated with EoE.[72] Eosinophilic gastritis/gastroenteritis (EG/EGE) are inflammatory disorders characterized by with eosinophilic infiltration within in the GI tract beyond the esophagus. In EGE, symptoms of abdominal pain are more common.[73] Diagnosis of EoE is based on marked eosinophilic infiltrates on esophageal biopsy with ≥15 eosinophils per high-power field (hpf).[74] Eosinophilia is localized to specific tissues in the GI tract in EGIDs, and is typically independent of peripheral blood eosinophilia.[73]

Epidemiology

The prevalence of EoE is increasing in the United States and is estimated at 0.5–1 case/1000 persons.[75] There is limited data on the prevalence of other EGIDs such as EG/EGE due to their rarity, however EGE in the United States is estimated to be 22–28 per 100,000.[76] Conflicting reports suggest lower prevalences of 6.3/100,000 for EG, 8.4/100,000 for EGE, and 3.3/100,000 for eosinophilic colitis.[77] Most existing studies of EoE take place in North America, and more information is needed on worldwide prevalence rates and diagnostic screening recommendations. A large multicenter US EoE study revealed a predominantly male (68.2%) and white (87.9%) EoE phenotype.[72] The median age of EoE symptom onset was 5 years (range 1–12 years) and the median age of EoE diagnosis was 8 years (range 3–15 years).[72] Food allergy (67.0%), allergic rhinitis (60.3%), atopic dermatitis (46.4%), and asthma (45.4%) were common comorbidities.[72]

Pathophysiology

The pathogenesis of EGIDs, as with other non-IgE-mediated food allergies discussed, is not fully understood. The pathogenesis of EoE, the EGID most often evaluated by allergists, is multifactorial, involving a combination of genetic, host, and environmental factors.[78,79] EoE is characterized by the endoscopic findings of eosinophilic infiltration of the esophagus.[71] Additional endoscopic findings may include fixed and transient esophageal rings, whitish exudates, longitudinal furrows, edema, esophageal narrowing, and esophageal lacerations.[71]

The impaired epithelial barrier of the esophagus is central to EoE pathogenesis.[78] There are several genes that are specific to the esophageal epithelium in which perturbations in expression are associated with EoE disease.[78,80] Increased

EoE susceptibility has been associated with pathogenic variants at gene loci of the esophageal-derived genes thymic stromal lymphopoietin (TSLP) encoded at gene locus 5q22, and calpain 14 protease (CAPN14) encoded at gene locus 2p23.[74,78,81,82] Genes encoding for IL-1 family genes, serine peptidase inhibitors (SERPINs), serine protease inhibitors, Kazal-type-related inhibitors (SPINKs), and the calpain protease, CAPN14 part of the EoE transcriptome, serve as a collection of genes that are highly expressed in the esophagus, and when dysregulated, increase EoE risk.[78,81,82] In particular, loss of SPINK7 function induces an epithelial barrier defect, proteolytic activity, and a proinflammatory Th2 cytokine response by epithelial cells of the esophagus, in individuals with EoE.[78,83]

Localized Th2 inflammation in the esophagus is also key in EoE, which includes the proinflammatory cytokine responses of IL-5 and IL-13. IL-5 traffics eosinophils to the esophagus, as identified in early mouse models, and in part promotes remodeling of the esophagus as noted by increased basal layer thickness and collagen accumulation in mice overexpressing IL-5.[84,85] IL-13 is overexpressed in subjects with EoE and may serve as a downstream mediator of esophageal inflammation.[74] T cell-mediated responses involving cytokines IL-5 and IL-13 are hypothesized to induce eotaxin 3, which then recruits eosinophils from the periphery into the tissue.[86,87] Major degranulation of eosinophilic granules in the esophageal epithelia occurs upon arrival as evidenced by findings of increased major basic protein, eosinophil peroxidase, and cationic protein deposited in the tissue.[78] Previous studies have also shown increased levels of IL-5, IL-13, IL-15, and plasma basic fibroblast growth factor in EoE.[71,88–90]

IL-13, in particular, also exacerbates the barrier disruption of the esophagus. IL-13 induces calpain 14, which as mentioned previously, is found specifically in the upper GI tract/esophageal epithelium.[91,92] Calpain 14 acts as a proteolytic enzyme whose overexpression has been associated with decreased in vitro expression of desmoglein 1 and filaggrin proteins, and an associated impaired epithelial barrier in the esophagus.[91–94] Filaggrin and desmoglein 1 were confirmed to be downregulated in expression in vivo in EoE, with the ability of IL-13 overexpression to independently decrease filaggrin.[72]

Tissue remodeling is seen in chronic EoE.[95] Epithelial desquamation, basal zone hyperplasia, subepithelial fibrosis, angiogenesis, and/or smooth muscle hypertrophy have been reported in EoE.[95] In a immunohistochemical analysis of esophageal biopsy specimens of children with and without EoE, biopsies from pediatric cases of EoE demonstrated increased subepithelial fibrosis and TGFβ expression compared to controls.[96] There was also increased vascularity seen with increased vascular cell adhesion molecule 1 expression.[96] Chehade et al found that esophageal subepithelial fibrosis was also common (57%) among a sample of 21 children with EoE undergoing distal esophageal biopsy, of which 42% had dysphagia.[97] Fibrosis was correlated with esophageal eosinophil degranulation and activation.[97] Aceves et al found that a rigid substrate matrix induces changes in esophageal smooth muscle cells leading to increased contraction and cellular hypertrophy.[98] Clinically, tissue remodeling results in esophageal narrowing, strictures, dysmotility, and food impactions over time.[95]

The pathogenesis of other EGIDs is even less understood, although an allergic component has been suggested in some instances. An adult study of allergic EGE noted increased allergen-specific, IL-5-producing Th2 cells present in EGE as compared to increased non-IL-5-producing Th2 cells in IgE-mediated peanut allergy, which has yet to be further explored.[99] Gastric biopsy samples in patients with EGE also showed increased Th2 cytokines (IL-4, IL-5, IL-13) and eosinophil-related chemokine eotaxin-3 upregulation.[100] A Japanese case series of EGE revealed small intestinal villi flattening in 4 of 6 patients on endoscopy.[101] A comparison of EGE patients with controls showed increased IL-3, GM-CSF, and IL-5 in 9 of 10 EGE patients, which was not observed in controls.[102] While eosinophils are normally found to varying degrees in the lower gastrointestinal tract, uncertainty exists when assessing the origin of lower GI tract eosinophilia, since other non-EGID disorders may contribute such as parasitic infection, food or drug allergy, inflammatory bowel disease, or hypereosinophilic syndrome.[103] Endoscopic and histopathologic features of non-esophageal EGIDs are being investigated, and there is an ongoing need for consensus of diagnostic criteria for these EGIDs.[104] Table 3 summarizes the clinical features and pathophysiology of EGIDs.

Management

Management options for EoE are diverse. The 2020 Joint Task Force (JTF) of the American Gastroenterological Association (AGA), American Academy of Allergy, Asthma, and Immunology (AAAAI), and American College of Allergy, Asthma, and Immunology (ACAAI) recently provided an updated practice parameter guideline for management of EoE.[105] Swallowed topical steroids are considered first-line therapy for EoE, and the only therapy to receive a strong recommendation by the 2020 Joint Task Force.[105,106]

Elimination diets have been used with varying success rates for EGIDs, with most success reported in EoE.[105–107]

Table 3 Summary of EGIDs

Disorder	EoE[71,72,86–90,92,94,104]	EG[73,100,104]	EGE[73,101,102,104,125]
Clinical features	Abdominal pain, dysphagia, nausea, emesis, esophageal food impaction, heartburn, diarrhea, chest pain, bloody stools, failure to thrive	Abdominal pain, vomiting, diarrhea, bloody stools, iron-deficiency anemia, malabsorption, protein losing enteropathy, and failure to thrive (mucosal form); GI obstructive symptoms (muscularis form)	Abdominal pain, vomiting, diarrhea, bloody stools, iron-deficiency anemia, malabsorption, protein losing enteropathy, and failure to thrive (mucosal form); GI obstructive symptoms (muscularis form)
Endoscopic findings	Furrows, white plaques, loss of vascular pattern, rings, stricture, shearing	Micronodules (and/or polyposis) often with aggregates of lymphocytes and eosinophils	Flattening of small intestinal villi
Histologic findings	Eosinophils on biopsy	Eosinophils on biopsy	Eosinophils on biopsy
Associated inflammatory cytokine	IL-5, IL-13, IL-15, plasma basic fibroblast growth factor	IL-4, IL-5, IL-13	IL-3, GM-CSF, and IL-5

A six food empiric elimination diet (milk, egg, wheat, soy, peanut, tree nuts) has been effective in children and adults, with studies citing rates as high as 74% remission of disease.[108] Less restrictive empiric eliminations diets, such as four food (milk, egg, wheat, soy) and two food (milk, wheat) eliminations diets, provide less conservative alternatives that can be stepped up or down and monitored for symptom response with endoscopy.[107] Allergy test directed elimination diets are not recommended as skin prick testing, patch testing, and serum IgE have poor positive and negative predictive values for identifying food triggers.[107] The use of elemental formula and food restriction is another less popular approach, given the significant restrictions it places on the individual. Elemental formula can be expensive, have limited insurance approval, and may be difficult to introduce due to unpleasant tastes associated with this formula type.[109] Overall, elimination diets are only conditionally recommended with low to very low quality evidence to support its use.[105] A comprehensive nutritional assessment is suggested with the use of any elimination diet to ensure adequate nutrition.[110] Similarly, proton pump inhibitors and periodic esophageal dilation are additional therapies with conditional recommendations.[105]

Biologic treatment therapies are the new frontier of EoE management and are actively being explored. Lirentelimab, an anti–siglec-8 antibody that depletes eosinophils and acts as a mast cell inhibitor, has been shown to reduce gastrointestinal eosinophils in patients with eosinophilic gastritis or duodenitis in Phase 2 trials.[111] The average percentage change in GI eosinophilia was −86% in the treatment group compared to 9% in the placebo group ($P<0.001$), which was the study's primary endpoint.[111] Targeted biologic therapies also being evaluated include dupilumab which targets anti-IL-4 and anti-IL-13.[105,112,113] A phase 2 clinical trial of adults with active EoE undergoing dupilumab treatment assessed for a change from baseline to week 10 in Straumann Dysphagia Instrument patient-reported outcome score as its primary outcome.[113] Phase 3 trials for dupilumab are ongoing, and has been suggested as a potential add-on or monotherapy for EoE patients refractory to standard interventions for the future.[114] A reduction of mean value of 3.0 at week 10 compared with a mean reduction of 1.3 in the placebo group in patient-reported scores of dysphagia was seen with dupilumab use ($P = 0.0304$).[113] Biologics with anti-IL-5 activity are also under investigation including benralizumab, mepolizumab, and reslizumab.[115] Anti-IL-13 targeted biologics studied in adult EoE patients has demonstrated significant decrease in cellular markers of epithelial mesenchymal transition which mediates the complication of fibrostenosis in patients.[116–118] Hirano et al's study of a monoclonal antibody against IL-13 showed a dose-dependent reduction in mean esophageal eosinophil count per hpf at 16 weeks of 94.8 ± 67.3 compared to placebo.[117] Additional therapeutic targets include TNF-α and chemoattractant receptors on Th2 cells (CRTH2).[119–121] Investigations into omalizumab as treatment for EoE have not been fruitful, further supporting EoE being an non-IgE mediated process, despite its utilization of Th2 pathway.[114,122,123] Table 4 provides a summary of biologics under consideration for EoE.[89,105,111–122]

Table 4 Biologics Under Consideration for EoE

Biologic	Therapeutic Target	Mechanism of Action	Findings
Dupilumab	Anti-IL-4 and anti-IL-13	Human monoclonal antibody targeting alpha subunit of IL-4 receptor (IL-4Rα), modulates IL-4 and IL-13 signaling	Decrease in esophageal eosinophilia, endoscopic activity, and patient-reported symptoms[113]
Lirentelimab	Anti–siglec-8	Anti–siglec-8 antibody that depletes eosinophils and acts as a mast cell inhibitor	Decrease in tissue eosinophilia and symptoms in EG and eosinophilic duodenitis[111,115]
Benralizumab	Anti-IL-5	Humanized monoclonal antibody against IL-5 receptor alpha-chain on eosinophils	Decrease in absolute eosinophil count in hypereosinophilic syndrome[115,126]
Mepolizumab	Anti-IL-5	Humanized monoclonal antibody against IL-5 preventing receptor binding	Decrease in tissue eosinophilia Minor symptomatic improvement[115,127–129]
Reslizumab	Anti-IL-5	Humanized monoclonal antibody against IL-5 preventing receptor binding	Decrease in tissue eosinophilia[115,130–132]
QAX576	Anti-IL-13	Humanized monoclonal antibody against IL-13 that inhibits T cell secreted IL-13	Decrease in tissue eosinophilia No significant effect on clinical activity.[116]
RPC4046	Anti-IL-13	Humanized monoclonal antibody against IL-13 that prevents binding to receptor subunits IL13RA1 and IL13RA2	Decrease in tissue eosinophilia and endoscopic activity. Trend of reduction in dysphagia noted.[117,133]
Omalizumab	Anti-IgE	Humanized monoclonal antibody against IgE	Not helpful in EoE[114,122,123]
Infliximab	Anti-TNF-α	Chimeric IgG1 monoclonal antibody and TNF-α inhibitor	Does not induce resolution of tissue eosinophilia or significant reduction of symptoms[120]
OC000459	Anti-CRTH2	Antagonist of chemoattractant receptors on Th2 cells (CRTH2) that interferes with prostaglandin pathway including prostaglandin D2	Decrease in tissue eosinophilia and symptoms[121]
Vedolizumab	Anti-α4β7	Humanized monoclonal antibody against α4β7	Clinical and histologic improvement of EoE[134–136]
Tofacitinib	Janus kinase inhibitor (JAK1 and JAK 3)	JAK1 and JAK3 inhibitor	Clinical and histologic improvement of EoE[137]

Table 5 Comparison of FPIES, FPIAP, and FPE

Disorder	FPIES	FPIAP	FPE
Clinical features	Acute: repetitive, protracted vomiting, watery diarrhea, pallor lethargy, hypovolemic shock Chronic: intermittent yet progressive vomiting, watery diarrhea, weight loss, failure to thrive, lethargy, dehydration, metabolic derangements	Blood-streaked and/or mucus-containing stools, colicky behavior, increased bowel movements, anemia in severe cases	Protracted, non-bloody, diarrhea in the first 9 months of life, failure to thrive, vomiting, eczema, recurrent respiratory infections, abdominal distention, malabsorption
Endoscopic findings	Colitis, mucosal friability, and loss of vascular pattern	Focal erythema with lymphoid nodular hyperplasia	Lymphonodular hyperplasia of the duodenum and colon, villous atrophy
Histologic findings	Eosinophils in the lamina propria, focal eosinophilic infiltration of the epithelium on rectal mucosal biopsy; colitis with crypt abscesses, mucus depletion of rectal glands, and polymorphonuclear leukocytes within the lamina propria; partial villous atrophy and blunting	Eosinophilic infiltration and degranulation of the rectosigmoid colon in close proximity to the lymphoid nodules	Damage to villous architecture of the intestine: villous atrophy, lymphonodular hyperplasia of the duodenum and colon, increased intraepithelial lymphocytes (>25/100 epithelial cells) and marked eosinophil infiltration and degranulation in the mucosa; increased intestinal intraepithelial CD8+ T cells that are food-allergen specific
Inflammatory mediators of pathogenesis	Interleukin (IL)-1B, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17 family cytokines (IL-17A, IL-22, IL-17C, and CCL20), oncostatin M, leukemia inhibitory factor, TNF-α, and REG1A Evidence suggests broad innate immune cell activation and T lymphocyte (non Th2) mechanism	Increased TNF-α; decreased TGF-β1 receptor activity and TGF-β ligand expression Evidence suggests predominantly eosinophil mediated response	IFN-Y and IL-4 cytokines have been identified in jejunal biopsy specimens Evidence suggests T lymphocyte (Th2 and CD8 effector cells) predominant mechanisms
Diagnosis	Based on clinical history	Based on clinical history	Requires biopsy for histological confirmation, clinical history
Management	Removal of triggering food, supportive care with fluid rehydration (PO or IV), consider steroids and/or ondansetron for severe cases, guidance for further food introduction	Maternal elimination diet in breastfed infants, trial of extensively hydrolyzed or amino acid-based formula in either breastfed or formula-fed infants	Avoidance of triggering food, dietary support
Prognosis	Resolution of symptoms by age 1–5 years	Resolution of symptoms by age 12 months	Resolution of symptoms by age 24–36 months

Discussion and Conclusions

In this review, we summarize the clinical manifestations, epidemiology, and current understanding of the pathophysiology of FPIES, FPIAP, FPE, and EGIDs, including mainly EoE. With regard to epidemiology, overlapping features of common pediatric conditions in infancy (ie, reflux, colic, rash) and variations in infant dietary practices (ie, breastfeeding versus formula use) may affect existing prevalence rates. While gains have been made in understanding these disorders, more information is needed on the exact pathophysiology of these less well understood food allergies. Among the non-IgE-mediated food allergies, there are a variety of immunologic pathways that may underlie their pathophysiology. While FPIES is likely driven by innate immunity, EGIDs appear to be predominantly driven by Th2 processes (Table 5). At the tissue level, the morphology of the intestinal lumen integrity is altered in each disorder leading to findings which can be confirmed histologically. A significant eosinophilic presence is also seen among these non-IgE mediated disorders and in EGIDs to sustain inflammation and possible tissue remodeling.

Several gaps, however, remain in our understanding of non-IgE-mediated food allergy. For example, reasons for why these disorders localize to certain areas of the gut are unknown. Studies identifying why the rectosigmoid colon may be more affected in FPIAP versus the more extensive small and large intestinal involvement seen in FPIES and/or FPE small intestinal involvement are needed. Additional limitations include gaps in understanding the exact pathways involved in how these disorders develop. While activation of certain immune cell subtypes and cytokines have been identified these disorders, the mechanistic steps in which these cells may perceive food antigen, recruit cytokines to specific locations, and propagate inflammatory effects to their respective tissues are largely unknown.

For instance, in FPIES, the phenotype and mechanism of a pathogenic food-specific T cell response in the intestinal mucosa of affected individuals has not yet been demonstrated, which could likely offer many insights.[124] Barriers, as previously noted, include the fact that the inflammatory cascade may be in part localized to the gastrointestinal tract, thus activated T cells cannot be easily accessed in the peripheral circulation for study.[38] There is simultaneously a lack of access to gastrointestinal tissue of affected patients, since endoscopy and biopsy are not part of the routine clinical care of FPIES—thus limiting the ability for further studies.[40] We thus rely on non-invasive means of identifying food-specific cells in the gastrointestinal tract during acute reactions.[40]

While FPIES, FPIAP, EGIDS and FPE have different timelines for symptom resolution (Table 5), it remains unclear exactly how tolerance develops, and how this may vary by disorder. Future studies aimed at understanding the exact immunological mechanisms of disease, in the hopes of identifying additional diagnostic markers and even therapeutic targets for intervention, are recommended. Future studies that distinguish between infants with varying feeding practices, such as those that are mostly breastfed versus formula fed, are also recommended in order to understand how small amounts of protein found in breast milk may still cause symptomatology among infants. For now, given the self-limited nature of many of these conditions, the mainstay of management is diagnosis based on clinical symptoms and food trigger avoidance.

Abbreviations

FPIES, food protein-induced enterocolitis; FPE, food-protein enteropathy; FPIAP, food protein-induced allergic proctocolitis; EGIDs, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; EG, eosinophilic gastritis; EGE, eosinophilic gastroenteritis; EC, eosinophilic colitis; CM, cow's milk; FTT, failure to thrive; OFC, oral food challenge.

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