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The Management of Non-IgE-Mediated Allergies in Human Milk-Fed Infants

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To the Dean of the Graduate School:

We are submitting a thesis written by Sarah Kelly Rowe entitled The Management of Non-IgE-Mediated Allergies in Human Milk Fed Infants. We recommend acceptance in partial fulfillment of the requirements for the degree of Master of Science in Human Nutrition.

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THE MANAGEMENT OF NON-IgE-MEDIATED ALLERGIES IN HUMAN MILK-FED INFANTS

A Thesis

Presented to the Faculty

Of the

College of Arts and Sciences

In Partial Fulfillment

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By

Sarah Kelly Rowe

Abstract

Background: Non-IgE (immunoglobulin E)-mediated food allergies (FA) present diagnostic and management challenges despite guidelines due to knowledge gaps amongst clinicians. Given that 60% of food protein-induced allergic proctocolitis (FPIAP) cases occur in breast-fed infants, maternal elimination diets are routinely prescribed to manage allergy symptoms. The implications of maternal dietary eliminations extend beyond maternal nutrition to consideration of infant nutrition and feeding skill acquisition.

Methods: A survey-based retrospective, cross-sectional study sought to identify dietary triggers and symptom management techniques practiced by (n=59) lactating mothers of infants with confirmed and suspected cases of non-IgE FA in the United States. Statistical significance was set at $p < 0.05$ and correlations were performed using SPSS statistical software version 29.0.

Results: Cow's milk followed by soy represented the most common dietary antigens at 96.6% and 22.0% respectively of all those surveyed. Of these, 88% reported maternal elimination of cow's milk and 35.6% reported elimination of milk and soy. Only 14.3% of respondents received a referral to a dietitian. Among infants with confirmed or suspected non-IgE FA (n=59), 72.9% (n=43) continued breastfeeding during maternal elimination, 13.5% (n=8) transitioned to a hypoallergenic formula, and the other 5.1% (n=3) were fed a combination of breast milk and formula. The predominant symptoms reported were abdominal pain (59.3%), feeding difficulties (59.3%), and colic (50.8%).

Conclusion: Based on the number of lactating mothers practicing cow's milk avoidance, there are nutritional concerns for mothers and infants experiencing non-IgE FA. Dietitians can play a crucial role in supporting the breastfeeding mother through dietary eliminations for the management of non-IgE FA in their infant.

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Table 1 *Common abbreviations utilized in the manuscript*

IgE: Immunoglobulin E

FA: Food allergy

FDA: Food and Drug Administration

TH2: T helper 2 cell

FOBT: Fecal occult blood tests

CMA: Cow's milk allergy

CM: Cow's milk

FPIES: Food protein-induced enterocolitis syndrome

FPIAP: Food protein-induced allergic proctocolitis

FPE: Food protein-induced enteropathy

HS: Heiner's syndrome

CD: Celiac disease

CMF: Cow's milk formula

OFC: Oral food challenge

eHF: Extensively hydrolyzed formulas

AAF: Amino acid-based formulas

EGID: Eosinophilic gastrointestinal disorders

FTT: Failure to thrive

TBF-B: Transforming growth factor B

TNF: Tumor necrosis factor

EmA: Anti-endomysium antibodies

DPG: Deaminated gliadin peptide

FGID: Functional gastrointestinal disorders

NEC: Necrotizing enterocolitis

GERD: Gastroesophageal reflux disease

GER: Gastroesophageal reflux

IBD: Inflammatory bowel disease

MAP: Milk allergy in primary care guideline

iMAP: International milk allergy in primary care guideline

CMPI: Cow's milk protein intolerance

RDN: Registered Dietitian Nutritionist

Chapter 1: Literature Review

Introduction

Infants depend on parents and caregivers for all their basic needs until they reach an age when they can learn to care for and feed themselves. In the first few months of life, infants communicate their feelings through facial expressions, vocalizations, and body language.[1] They will generally use vocalizations until their needs have been met.[2] Symptoms of a larger problem become apparent when an infant's basic needs are met, but they are still showing signs of emotional and physical distress.[2,3] When an infant is experiencing constipation, sleep disturbance, colic, diarrhea, emesis, anaphylaxis, or hematochezia (bloody stools), parents often seek tertiary care [3,4] Although these symptoms can present in a variety of conditions, dietary triggers are a significant culprit of digestive distress in infants and should not be overlooked.[5,6] This can complicate a situation when a mother-child dyad is trying to exclusively breastfeed for the first six months, as recommended by public health guidelines.[7]

Problem

The incidence and prevalence of food allergies (FA) have steadily increased throughout history.[8] An estimated 5-10% of the population in the developed world and over 26 million Americans have been diagnosed with FA as of 2019. [9–11] The increased prevalence of FA in recent decades has prompted scientists and physicians to suspect the involvement of one or more

environmental factors including nutrition, the intrauterine environment, and lifestyle factors that shape gene expression and epigenetic modifications, apart from a genetic predisposition.[12,13]

A food allergy is defined as a reproducible adverse immune-mediated response to specific dietary proteins.[5,14] Food intolerance, on the other hand, lacks an immune component and routinely presents as a response to an enzyme deficiency, a pharmacologic ingredient, or toxic contaminants.[5,14] Food intolerances often do not require the strict elimination of offending foods and are outside of the scope of this literature review. In the case of FA, the body perceives benign food proteins as an external threat. A reaction to a food protein can occur immediately or present as a delayed response.[5,15,16]

Immunoglobulin E or IgE-mediated FA is characterized by an immune-mediated response to a dietary protein. The top nine food allergens recognized by the Food and Drug Administration (FDA) in the United States include cow's milk, eggs, fish, shellfish, tree nuts, wheat, peanuts, soybeans, and sesame. These allergens account for most FA.

When an individual is first exposed to a dietary allergen, T helper 2 (T_H2) cells stimulate the proliferation of B cells which activate IgE antibodies.[17] The antigen-specific IgE antibodies are transferred to resting mast cells.[17] Subsequent exposure to dietary antigens results in the cross-linkage of FcERI receptors between IgE antibodies.[17] The linked IgE antibodies fuse with the mast cell membrane which signals mast cell degranulation and results in the

immediate release of inflammatory mediators including histamine, proteases, and heparin.[17]

Contrastingly, non-IgE-mediated FA does not involve the action of IgE antibodies and the release of histamine by mast cells.[17,18] Rather, the allergic response characteristic of a non-IgE-mediated FA involves cellular mechanisms that produce an inflammatory response specific to the condition. Generally, during non-IgE-mediated FA reactions, antigen-presenting cells deliver the dietary antigen to t-cells which form antigen-specific t-cells and cytokines.[19,20] Together antigen-specific t-cells and cytokines promote gut inflammation which increases intestinal permeability.[19,20] Gut microbial dysbiosis may occur as a result of increased intestinal permeability and inflammation.[19,20] Pro-inflammatory

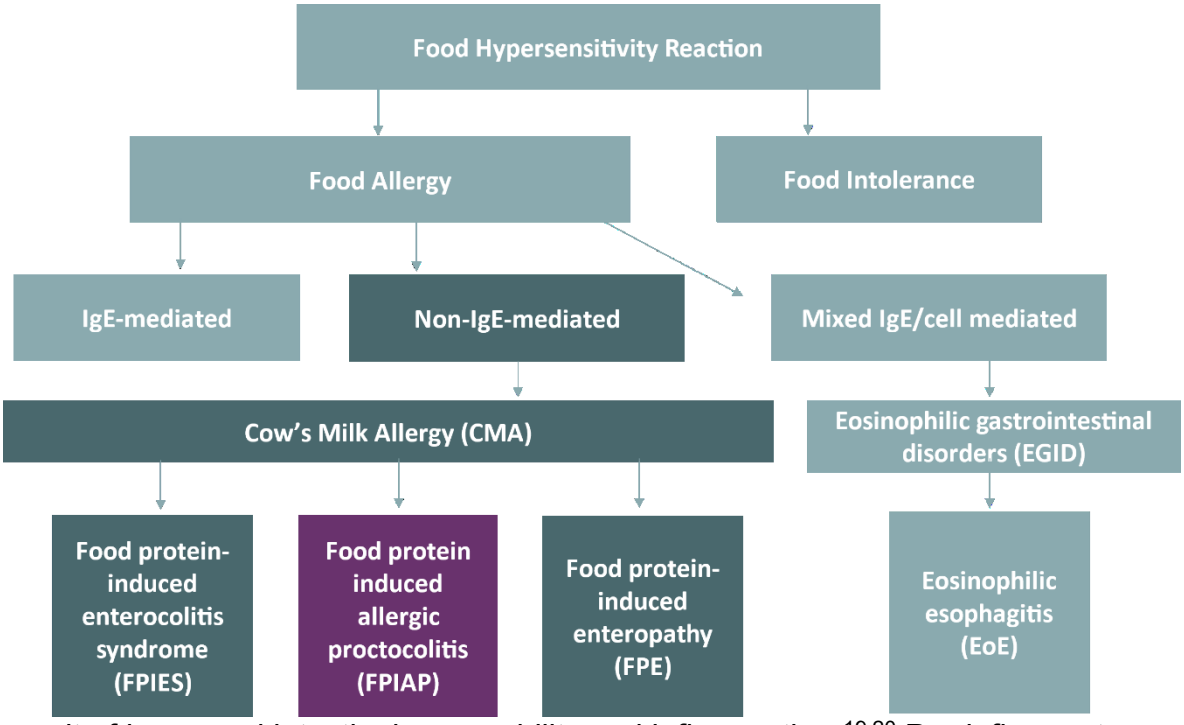

Figure 1 *Non-IgE-mediated food allergies, especially food-induced allergic proctocolitis (FPIAP) are more common in human milk-fed infants. Cow's milk allergy is a broad term encompassing many IgE and non-IgE conditions. Mixed forms include eosinophilic gastrointestinal disorders such as Eosinophilic esophagitis.*

markers such as interleukin-5 and alpha tumor necrosis factor are often noted to be elevated in individuals with non-IgE-mediated FA.[19,20]

Infants with non-IgE-mediated FA present with delayed gastrointestinal symptoms which can arise within hours after the ingestion of a dietary antigen.[21] The delayed nature of non-IgE-mediated FA can confound a diagnosis.[5,6] Cow's milk, soy, and grains are the three most common FA that present with gastrointestinal symptoms.[6] In 2015, it was estimated that non-IgE-mediated FA accounted for 40 percent of cow's milk allergies (CMA) in infants and young children.[18] Most non-IgE-mediated FA diagnosed during infancy have favorable prognoses and normally resolve by the time the child reaches school age.[5]

Pathophysiology

Food allergies can arise in infancy for many reasons and there are several well-supported hypotheses in the literature today. Atopic family history of FA and eczema remain the predominant risk factors for an infant to experience an allergic reaction to one or more foods.[9,22] Male children, certain ethnicities, and atopic dermatitis have also been credited with an increased prevalence of FA in infants.[12] Nevertheless, given the dramatic rise in FA, non-genetic, environmental factors are assumed to play a major role in the development of allergies.[12]

Of the many epidemiological hypotheses for food allergies, the hygiene hypothesis is the leading theory for FA.[12] First described by London researcher David Strachan in 1989 during his research on hay fever,[23] the hygiene hypothesis is based on the idea that modern obsession with germ reduction has

resulted in a lack of exposure to infectious agents during infancy and childhood.[12,23] The disruption of early exposure to various environmental and oral antigens has been shown to interrupt the natural development of the immune system and predispose infants to a wide array of allergic conditions.[12] Contrastingly, frequent oral exposure to environmental microbes has been shown to reduce allergy and asthma cases in infants and children.[24] Strachan also noted that cohabitation with domestic animals, creatures, and older siblings sufficiency boosts infant immune systems leaving them less susceptible to allergic conditions.[23,24]

The vitamin D hypothesis is based on the idea that a deficiency in serum vitamin D status increases rates of FA.[25] Vitamin D might play a role in the regulation of immunologic mechanisms that influence oral tolerance of foods including the suppression of mast cell activation, the synthesis of IgE antibodies in B cells, and the proliferation of regulatory T (T_{reg}) cells.[12,25] The recommendation for vitamin D supplementation in exclusively breastfed infants is 400 IU per day.[26] Hollis et al.[27] found that high maternal supplementation of vitamin D equivalent to 6400 IU per day safely and effectively provided adequate vitamin D to infants through breastmilk.[27,28] It is hypothesized that failure to ingest adequate vitamin D during infancy could increase the chances of infants developing FA, although the correlation has not been confirmed in clinical trials.[12,25]

The dual allergen exposure hypothesis presents the idea that cutaneous exposure to allergens is positively associated with the development of FA,

whereas early oral exposure to food protein induces tolerance.[9,29,30] Infants with atopic dermatitis or other inflammatory skin conditions such as eczema are at greater risk of transcutaneous exposure, although some data suggests that respiratory exposure to allergens can also result in sensitivity.[9,12] The dual allergen exposure hypothesis, while a leading pathophysiology hypothesis, is more relevant to IgE-mediated FA than non-IgE-mediated FA. Nevertheless, immunotolerance remains an important component of infant development and may play a role in FA.[9] A visual representation of the three leading FA hypothesis can be found in Du Toit et al.[12]

The pathophysiology of immunotolerance is tightly regulated by the body. Higher levels of regulatory T_{reg} cells correlate with the prevention of FA.[9] The gut microbiome impacts T_{reg} cell function and homeostasis. Researchers have observed differences in the gut microbiotas of infants with non-IgE-mediated FA casting speculation that gut microbial dysbiosis (imbalanced bacteria in the gut) predisposes infants to CMA and FPIAP due to a disruption in the T_{reg} cell response.[31] Fewer T_{reg} cells result in overactive CD4 and CD8 cell populations which are heightened during an allergic response.[31] CD4+ Th cells may generate oral immune tolerance to dietary protein antigens through the production of cytokines that interact with B cells.[9,32] Additionally, the intestinal epithelial barrier plays a role in the regulation of FA, especially in non-IgE-mediated FA.[9,33] Infants with a healthy intestinal epithelial barrier, defined by low levels of gut inflammation biomarkers, are less prone to developing allergic reactions to dietary proteins.[9,19,20,33]

Studies such as the LEAP study conducted in the United Kingdom in 2015 support the early introduction of peanuts for the prevention of atopic (IgE-mediated) peanut allergies. This groundbreaking study demonstrated a potential window of opportunity for early introduction of highly allergenic foods during the rapid development of the infant immune system. Peanuts and eggs are the allergens where early oral exposure has demonstrated the strongest success in preventing IgE-mediated FA among small cohorts of at-risk infants.[34,35] Presently, there is evidence to support the early oral introduction of allergens for the prevention of FA.[36]

Research has not revealed a strong correlation between in-utero factors and FA and there is little data to suggest that altering the maternal diet during pregnancy prevents FA.[12,37] Observational studies show that healthy, well-balanced maternal diets correlate with reduced disease outcomes in offspring including FA.[37,38] New research findings show that Vitamin D and omega-3 fatty acid supplementation during pregnancy may play a role in preventing food allergies of offspring.[39] Prolonged breastfeeding delays the onset of allergies; however, there is insufficient evidence to conclude that breastfeeding or the use of hydrolyzed formulas prevents allergy development.[12,40,41] Since the pathophysiology and prevention of FA in infants remain muddled, management should include a multi-disciplinary approach.[5]

Non-IgE Mediated Food Allergies

Non-IgE-mediated FA is more common in breastfed infants than IgE-mediated or mixed forms.[28] Due to a lack of evidence-based testing methods, non-IgE-mediated FA can be challenging to diagnose. Diagnostic tests such as fecal occult blood tests (FOBT) and small bowel biopsies aid in the diagnosis of some forms of non-IgE-mediated FA.[16,42] *(See Diagnosis sections for FPIAP and FPE)* Colonoscopies and endoscopies are routinely used to perform biopsies to rule out mixed forms of IgE and non-IgE-mediated FA affecting the gastrointestinal tract.[42]

Oral food challenges (OFC) are the gold standard for identifying FA.[43,44] Oral food challenges are used to diagnose both IgE and non-IgE-mediated FA and to reintroduce foods after a diagnosis-specific time frame to evaluate tolerance.[6,45] Oral food challenges vary based on physician preference and diagnosis and work by gradually re-introducing offending foods that have been eliminated from the diet for a period of time.

The remainder of this literature review will concentrate on defining the types of non-IgE-mediated FA, identifying signs and symptoms, recognizing diagnostic challenges, and analyzing the current evidence on the management and outcomes of non-IgE-mediated FA in human milk-fed infants. After the review of non-IgE conditions, future directions in the field of FA will be discussed, and existing research gaps highlighted.

Cow's milk allergy (CMA)

Cow's milk (CM) remains the predominant food antigen for non-IgE-mediated FA.[46] Cow's milk allergy is a broad category of allergic reactions to cow's milk that includes IgE-mediated, non-IgE, and mixed reaction forms.[40,45] **Figure 1** shows the different conditions associated with CMA in IgE, non-IgE, and mixed (IgE and non-IgE) mediated FA.[40] Adverse reaction to CM proteins can occur from direct feeding or through the passing of proteins via breast milk. CMA often resolves by adolscense.[47]

Signs and Symptoms

Symptoms of non-IgE-mediated CMA typically present within 2 - 72 hours of ingestion of cow's milk.[40] Symptoms include gastrointestinal distress, skin barrier dysfunction, and growth concerns if left unmanaged.[36]

Diagnosis

Infants with CMA may exhibit signs of malnutrition which can alert a practitioner to make a CMA diagnosis.[40] Steps for diagnosing CMA are outlined in the international milk allergy in primary care (iMAP) guidelines and the recently updated Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines.[48–50] *(See Future Directions in the Field of Food Allergies).*

Management & Outcomes

Treatment of CMA involves the removal of cow's milk proteins from the diet. If breastfed, maternal avoidance of cow's milk may also be recommended for managing non-IgE forms of CMA in exclusively breastfed infants.[46] *(See Maternal Elimination Diet section)*

Standard infant formulas are manufactured with CM as the source of protein and carbohydrates, therefore formula-fed infants with non-IgE-mediated

FA may require hypoallergenic formulas. Extensively hydrolyzed formulas (eHF) have hydrolyzed proteins that are broken down to less than 1,500 daltons and free amino acids reducing their allergenicity and increasing their likelihood of tolerance in 80-90% of infants with CMA.[42,51] For infants with non-IgE-mediated CMA, hematochezia typically resolves in 48-72 after initiation of hypoallergenic formula.[45] Soy-based formulas may be more cost-effective than hypoallergenic options but are not recommended in CMA under 6 months of age.[52]

In the 10-20% of CMA infants that do not tolerate eHF, Amino acid-based formulas (AAF) may be required.[42] They are hydrolyzed to amino acids and contain fully hydrolyzed carbohydrate and fat sources. Due to their cost burden and high likelihood of eHf tolerance, AAFs should not be the first line of treatment for infants with a CMA.[52] Amino acid-based formulas should be reserved for severe cases when an infant is experiencing anaphylaxis to cow's milk protein or when hematochezia has not resolved, and after less expensive formulas have been unsuccessful.[40]

Food Protein Induced Enterocolitis Syndrome (FPIES)

Signs and Symptoms

The most severe type of non-IgE-mediated FA is food protein-induced enterocolitis syndrome (FPIES) which can manifest as an acute or chronic condition.[44] Diagnostic criteria for acute FPIES include profuse/repetitive vomiting 1 to 4 hours after ingestion of the food antigen, with diarrhea often following 5-10 hours later leading to dehydration, metabolic acidosis, and symptoms of lethargy.[5,43,44,53,54] Chronic FPIES is uncommon and occurs in infants less than 4 months

of age who are consuming CM or soy-based formulas.[44] Signs and symptoms of chronic FPIES occur at regular intervals upon digestion of formula and include intermittent emesis, watery diarrhea, and failure to thrive (FTT).[5,18,43,44,54] Hypoalbuminemia combined with weight loss can also predict severe chronic cases of CM-induced FPIES.[44] Additionally, FPIES may be combined with atopic conditions such as eczema or IgE-mediated FA.[44]

Diagnosis

FPIES is diagnosed based on a clinical history of signs and symptoms.[44] More than 95% of infants diagnosed with either form of FPIES will display profuse and repetitive emesis.[5] Cow's milk and soy are the most common liquid dietary antigens for FPIES and approximately 25-50% of infants with FPIES will react to both CM and soy proteins.[44] Adverse reactions to CM or soy-based formulas typically manifest as FPIES symptoms between 2-7 months of age.[19,44]

Infants with incomplete clinical histories of symptoms may require supervised OFCs to diagnose FPIES.[44] *(See Non-IgE Mediated Food Allergies section).* An OFC for FPIES is considered a high-risk procedure and should be conducted in a clinical setting with access to intravenous hydration to correct hypotension should the infant experience a severe reaction to the dietary antigen.[44,54] The OFC protocol includes administering a pre-determined dose of the suspected dietary allergen over a facility-specified time frame to infants who can tolerate solid foods followed by a 4-hour observation period.[54] Repetitive emesis, which may be accompanied by paleness, lethargy, and/or diarrhea,

signifies a severe FPIES reaction.[54] Lower doses of the dietary allergen are typically given to infants who have a history of severe reactions.[44]

Management & Outcomes

Switching infants with FPIES to a hypoallergenic formula effectively manages symptoms.[44] Acute FPIES resolves within 24 hours of removing the dietary antigen, whereas, infants with chronic FPIES typically respond positively to eHF and return to their normal health within 3 to 10 days.[18,19] Research indicates that 10-20% of infants with FPIES will require AAF.[44,55,56] Breastfeeding can also help manage FPIES symptoms.

Eosinophilic Gastrointestinal Disorders (EGIDs)

Eosinophilic gastrointestinal disorders (EGIDs) are another umbrella category of FA characterized by chronic eosinophilic inflammation in the gastrointestinal tract.[19] They are often defined as a mix of IgE and non-IgE-mediated FA reactions and symptoms can be confused with non-IgE-mediated conditions.[19,46] Eosinophilic esophagitis (EoE) is the most well-studied EGID that affects both children and adults.[19,57]

Signs and Symptoms

Symptoms of EoE are gastrointestinal and may include abdominal pain, dysphagia, nausea, emesis, esophageal food impaction, gastroesophageal reflux symptoms, diarrhea, chest pain, and hematochezia.[19] Failure to thrive may also be noted in children.[19]

Diagnosis

Upper endoscopy with biopsy remains the gold standard for diagnosing and monitoring EoE.[57] Symptoms are less reliable for diagnosing the condition; however, there is a push to validate non-invasive biomarkers of disease.[57]

Management & Outcomes

As recommended by the 2020 Joint Task Force, swallowed topical steroids are the first line of treatment for EoE.[19] Historically, six-food elimination diets have also been successful in achieving disease remission in children and adults with EoE.[19,58] Nevertheless, a ground-breaking research article comparing one-food versus six-food elimination diets for the management of EoE found minimal variations in disease outcomes between the two groups.[59] Researchers concluded that the exclusion of cow's milk is an acceptable initial diet therapy for EoE.[59]

Food Protein-Induced Allergic Proctocolitis (FPIAP)

Food protein-induced allergic proctocolitis (FPIAP) is another common non-IgE-mediated FA. Unlike FPIES, 60% of FPIAP cases occur in breastfed infants.[18,28,42,60] Additionally, the pathogenesis of FPIAP is largely unknown. Researchers speculate the underdevelopment of transforming growth factor B (TBF-B) is a likely cause of FPIAP in infants. [42,61,62] TBF-B produces regulatory cells which impair the development of Th3 resulting in reduced oral tolerance to dietary proteins.[42,61,62] Other speculations include the action of a tumor necrosis factor (TNF)-alpha cytokine, which is associated with chronic inflammation and the alteration of tight junctions in the gastrointestinal tract.[42] Elevated levels of

eosinophils in the large intestinal epithelium are common in individuals with non-IgE conditions.[42]

Signs and Symptoms

Most cases of FPIAP manifest with gastrointestinal symptoms in the first few days of life when the infant has indirect exposure to dietary protein through breast milk.[5,18,42,63] Although, FPIAP may develop in infants as old as six months.[45] FPIAP primarily impacts the large intestine.[5] Symptoms include gastrointestinal disturbances such as altered bowel habits, hematochezia presenting as hematochezia, constipation, and diarrhea.[40]

Concerning the dietary allergens which account for symptoms, 80% of infants with FPIAP will react to cow's milk only, and 40% are sensitive to cow's milk and soy.[18,28,42] A 2017 study conducted with (n=77) infants with FPIAP ages 0-36 months discovered that 78% of the infants in their study reacted to cow's milk, 13% to cow's milk and egg, and 5% to egg only.[64] Another study conducted in the same year concluded that out of the 37 infants in their study, 100% reacted to cow's milk protein; however, 5 infants had adverse reactions to egg whites and 8 reacted to other foods.[65] Yet another study identified that 100% of infants with FPIAP reacted to cow's milk protein and it was the sole trigger of symptoms in 83% of the cohort.[66]

Diagnosis

FPIAP is routinely diagnosed with a history of hematochezia that develops in the first six months of life and subsequent resolution of bleeding after the initiation of an elimination diet.[18,42,67] While there are many causes for hematochezia in infants, FPIAP accounts for 16-64% of cases and persists as

the strongest indicator of the condition.[5,42,45,60,68] Hematochezia in FPIAP is thought to occur from localized inflammation in the distal colon and perirectal fissures.[5,18] Occasionally, blood in the stool exists in microscopic amounts that are not visible to the naked eye. Nevertheless, fecal occult blood tests are unreliable for diagnosing or verifying the resolution of FPIAP.[46]

Laboratory biomarkers are non-existent for non-IgE mediated FA including FPIAP. The lack of histamine release in non-IgE mediated FA also nullifies the use of IgE skin prick testing as a diagnostic procedure. Subsequently, measuring IgG antibody levels in specific foods is also not recommended as a diagnostic test for any type of food allergy.[42,46,69] Biopsies prove useful as a histologic confirmation of severe cases of FPIAP when an infant is not responding to dietary treatment, but it is not routine.[45] The main challenge with diagnosing FPIAP is that infants appear healthy, other than hematochezia, and typically do not present with weight loss.[42]

Management & Outcomes

FPIAP is generally considered a benign condition, yet infants could develop anemia from profuse hematochezia.[18,42,45] Nevertheless, the risk of anemia in infants with FPIAP remains relatively low.[18] Maternal elimination diets are the predominant method for treating FPIAP and clinical hematochezia should resolve within 72 to 96 hours after maternal elimination of offending dietary proteins.[5,18] *(See Maternal Elimination Diet section)* However, 20% of infants will see a spontaneous resolution of hematochezia within a few months without maternal dietary alterations which suggest that strict elimination diets may not be

necessary.[16,18,42,70] Therefore, FPIAP can be classified as a transitionary disease that resolves by age one.[42]

OFCs and elimination diets are especially useful for identifying which foods trigger symptoms and verifying the clinical resolution of FPIAP in infants. For FPIAP, failed OFCs do not pose a significant risk to infant health. Thus, parents and caregivers may attempt to reintroduce allergen foods to their child(ren) with FPIAP safely at home following the proposed guidelines.[45] *(See Non-IgE Mediated Food Allergies section)*

The duration of elimination diets remains highly debated in the literature. One study recommends the reintroduction of dietary allergens after 4-8 weeks of elimination.[45] A separate article recommends the initiation of re-introductory OFCs for FPIAP infants following six months without ingestion of the offending dietary protein or at 12 months of age.[42] Standard reintroduction takes place when an infant reaches one year of age when FPIAP cases are expected to resolve.[42]

Food Protein-Induced Enteropathy (FPE)

Signs and Symptoms

Food protein-induced enteropathy (FPE) is a rarely diagnosed non-IgE-mediated FA. It impacts the small intestine and causes malabsorption complications.[5,19] Like other types of non-IgE conditions, symptoms of FPE occur after the introduction of offending food antigens to an infant's diet. FPE causes malabsorption with can lead to steatorrhea, FTT, emesis, and non-bloody diarrhea.[5,19]

Diagnosis

FPE is typically diagnosed during infancy anytime from birth to two years but most cases occur before nine months of age.[16,45] Cow's milk formulas are the most common dietary trigger in those with FPE followed by soy, wheat, and egg.[5,45] Diagnosis practices resemble those for FPIAP and there are no standard diagnostic tests for FPE.[16] However, small bowel biopsies are used to confirm cases of FPE more than other forms of non-IgE mediated FA.[16,19]

Management & Outcomes

Upon elimination of the offending dietary protein(s) symptoms of FPE will clear within 1 to 3 weeks.[45] Reintroduction of the offending allergens is conducted at home to determine if the infant has symptom resolution after a 4–8-week elimination period.[16,45] FPE usually completely resolves by 24 -36 months of age.[19]

Food Allergy Diagnosis Challenges

There are standardized testing methods for IgE-mediated FA, and although non-IgE-mediated FA lack testing methods, there are accepted diagnostic criteria. Diagnosing non-IgE-mediated FA in infants is a challenging process and many receive delayed or misdiagnoses before clinicians arrive at the correct diagnosis.[16,46,71] The overlap of non-IgE-mediated FA symptoms and functional gastrointestinal disorders (FGID) in infants increases the likelihood of diagnosis confusion.[6,46] Additionally, the lack of standardized diagnostic criteria for diagnosis such as FPIAP and CMA makes a practitioner's methodology less clear and misdiagnoses more prevalent.[46] Occasionally, the offending dietary

protein may not be discovered if the infant experiences symptom resolution from growth and development.[16] The latter scenario is more common in non-IgE-mediated FA as conditions like FPIAP are more likely than IgE-mediated FA to resolve spontaneously.

Given the absence of standard diagnostic testing for non-IgE-mediated FA, healthcare workers who are largely unfamiliar with FPIES, FPE, and FPIAP conditions account in part for the high rate of misdiagnoses.[5,72,73] A study conducted in 2016 discovered that at least one-third of healthcare practitioners surveyed were not competent in their understanding of FPIES which is the most severe non-IgE-mediated FA diagnosis.[73] Healthcare practitioners could benefit from additional education on non-IgE-mediated FA conditions. Unfortunately, with undefined diagnostic criteria for many non-IgE allergies, standardized training remains an anomaly.

Overlapping symptoms remain a barrier to non-IgE diagnoses which often results in misdiagnoses. For example, the variety of reasons for hematochezia in infants creates confusion that can delay the accurate diagnosis of FPIAP. In a study with 300 neonatal patients by Lin et al.[74], hematochezia was found to be caused by CMA (53%), swallowed blood syndrome (10%), viral enteritis (9.7%), necrotizing enterocolitis (NEC) stage II (8.3%), non-specific enteritis (7.3%) and anal fissures (5%) of the time.[74] Alternative diagnoses that are routinely offered to explain an infant's CMA symptoms include colic, lactose intolerance, allergies to other food, anatomical abnormalities, pyloric stenosis, constipation, chronic gastrointestinal conditions, and gastroesophageal reflux disease (GERD).[40,46] For

all non-IgE mediated FA, misdiagnoses include infections, GERD, idiopathic pyloric hypertrophy, volvulus, malrotation, ileus, inflammatory bowel disease (IBD), primary immunodeficiency disorders, autoimmune enteropathy, celiac disease, and coagulation disorders.[45]

Management of Maternal Elimination Diets in Cases of Suspected non-IgE Allergies

Maternal elimination diets are commonly prescribed by healthcare practitioners for symptom management in young infants with non-IgE-mediated FA.[45] Starting an elimination diet will require the mother to eliminate all forms of cow's milk protein from her diet which includes, but is not limited to, milk, yogurt, and cheese.[42] Sometimes, practitioners will recommend avoidance of multiple foods, and the mother may eliminate soy and egg protein food products.[42,46] Despite the need to remove offending dietary proteins from their diets, mothers should not discontinue breastfeeding.[42] For infants with FPIAP, the risk of adverse outcomes is not life-threatening and thus human milk remains their optimal nutrition. Some evidence suggests that breastfeeding may help mitigate symptoms in infants with FPIES.[45] Other studies noted that exclusive breastfeeding in infants with FPIES and FPE achieves symptom resolution.[45]

Sometimes a maternal elimination diet is insufficient for symptom resolution when multiple allergens are at play.[42] After checking maternal adherence to a cow's milk elimination, soy followed by egg may be eliminated.[42] If symptoms persist, the infant may be switched to a hydrolyzed or elemental

formula.[42] Although, mothers may still choose to breastfeed without adherence to elimination diets as up to 20% of infants with FPIAP will experience spontaneous resolution of bleeding without maternal diet alterations.[16,18,42]

Following an elimination diet requires that specific attention be paid to the mother's and infant's nutrient profiles.[28] Eliminating one or more foods from the maternal diet can introduce nutrient complications that if left unchecked could be detrimental to the health of the mother and/or the infant.[28] Thus, maternal elimination diets should be exercised with caution.[28]

Healthcare practitioners should weigh the benefits and risks of starting someone on a maternal elimination diet to avoid unnecessary elimination and minimize adverse effects.[28,46] Elimination diets are not designed as permanent dietary modifications since removing food groups creates gaps in one's nutrient intake. Rather, maternal elimination diets are intended to be used as a short-term tool to manage gastrointestinal symptoms in infants with FA. The goal of going on an elimination diet is to understand dietary triggers, achieve symptom resolution, and conclude the diet so that mothers and infants can return to a varied nutrient intake.

Mothers should be provided with support from healthcare practitioners when adhering to maternal elimination diets to reduce nutrient deficiencies.[46] Dietitians can work with mothers to address specific nutrient needs and suggest foods that will complement their typical intake. Dietitians or other healthcare practitioners will need to recommend alternative dietary sources or supplements for calcium intake as well as monitor thiamin, riboflavin, and vitamin B6, vitamin

B12, choline, vitamin A, and vitamin D in mothers adhering to an elimination diet.[28] For example, the avoidance of cow's milk significantly reduces the availability of calcium, vitamin D, riboflavin, and phosphorus in the diet.[28] Plant-based beverages fortified with calcium and tofu offer ideal replacements for cow's milk when soy is tolerated.[28]

For breast-fed infants receiving their nutrition indirectly through the maternal diet, care must be taken to ensure the availability of adequate nutrition for growth and development during maternal elimination diets. Calcium, iron, zinc, copper, and folate are not highly dependent on the maternal diet, however, certain nutrients such as Omega 3 fatty acids pass easily through human milk and support growth, and cognitive and motor development.[28] Breastfed infants typically require supplementation with vitamin D given the difficulty of obtaining vitamin D in large quantities through the maternal diet.[28] Children with FA are at an increased risk of poor growth so reducing nutrient gaps in maternal and infant diets should be prioritized.[28]

Infants enjoying complementary feeding will need to avoid offending dietary proteins for the management of their non-IgE conditions. Complementary feeding eliminations increase the risk of nutrient deficiencies for infants and often they will have lower weight status than infants fed a normal diet.[52]Infants with CMA who are avoiding cow's milk after one year of age will have lower intakes of calcium and may require supplementation.[52] Nevertheless, one study found that infants eliminating food groups during complementary feeding had higher nutritional intakes overall.[52] The contradicting phenomenon could be explained

by the extra attention given to the nutrient needs of infants with allergies. While many parents of children with CMA may be searching for an alternative to cow's milk to increase calcium intake, rice milk is not advised. Rice milk has naturally occurring arsenic and should not be given to children under five years of age.[40]

Future Directions in Food Allergies

The long-term management of non-IgE-mediated FA includes avoiding offending foods. However, since most infants with non-IgE-mediated FA experience resolution at an early age, reintroducing allergens into the child's diet helps determine tolerance. The Milk Allergy in Primary Care guideline (MAP) developed by UK clinicians, was published in the Journal of Clinical and Transitional Allergy in 2013.[49] MAP provided an algorithm that healthcare practitioners could follow for the correct diagnosis of a non-IgE-mediated CMA. In 2017, the allergy-focused clinical history guidelines were expanded for global utilization and dubbed the International Milk Allergy in Primary Care Guideline (iMAP).[49,75]

Designed in an easy-to-read figure format, iMAP provides clinicians with a course of action when assessing infants with mild to severe symptoms indicative of CMA *(see **Figure 2**)*. Maternal elimination diets and hydrolyzed formulas are included as management strategies for CMA in the iMAP guideline. Mothers following iMAP are instructed to gradually increase their intake of cow's milk over one week.[75] Considering the overlap of symptoms in infants with CMA and those of healthy infants, critics of the algorithm argue that iMAP is partly responsible for the increased prescription of hydrolyzed formulas and unnecessary maternal elimination diets.[49]

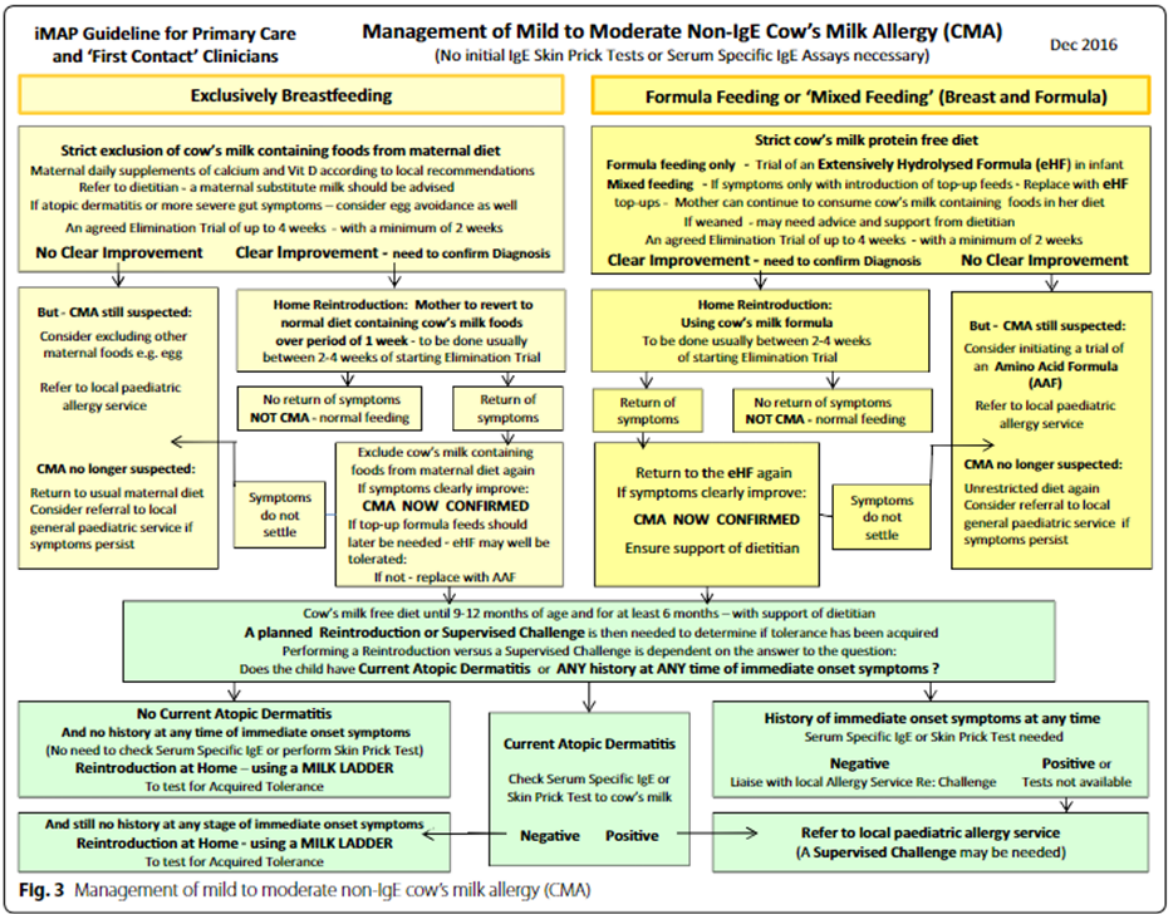

***Figure 2** The International Milk Allergy in Primary Care Guideline (iMAP) provides an algorithm for physicians to diagnose and manage cow's milk allergies (CMA). Taken from Venter et al.*

The increasing rates of infant FA have prompted the development of alternative management strategies through oral immunotherapy.[9] Providing allergenic foods to infants and children with confirmed allergy diagnoses in the form of an OFC has been previously discussed as a form of diagnosing and assessing the clinical resolution of FA. Oral immunotherapy, on the other hand, depicts a method for overcoming childhood allergies and liberating the diet. Oral immunotherapy calls for the incorporation of allergenic foods into the child's diet by increasing the dose of a dietary protein to achieve full oral tolerance. Oral immunotherapy has been utilized for many different allergens, but the milk ladder challenge is the most researched method that exists to achieve full tolerance to dairy products.[76]

The milk ladder challenge is based on the standard that individuals with CMA are better able to tolerate baked milk over fresh pasteurized cow's milk.[76] Recent data suggesting that a majority of CMA cases present with mild to moderate symptoms has increased the popularity of oral immunotherapy for achieving infant tolerance to dairy products.[77] Nevertheless, severe allergic reactions to cow's milk can occur when dairy products are reintroduced to infants with CMA, especially those with the IgE form of CMA. The possibility of serious reactions has some healthcare practitioners concerned about the safety of home-based introductions. However, severe reactions such as anaphylaxis are more likely to occur in cases of IgE-mediated CMA rather than non-IgE-mediated CMA.[77]

One researcher attempted to clarify the safety and efficacy of milk ladder challenges by suggesting that they only be used for infants and children who experience mild-to-moderate symptoms when ingesting cow's milk.[75] Yet another trial, identified that a majority of CMA cases present with mild to moderate symptoms and claimed that home-based cow's milk reintroductions were generally safe.[76] In an international survey of healthcare practitioners, 62% of those surveyed agreed that it is safe to perform baked milk challenges and milk ladder challenges in a home setting for infants with non-IgE-mediated FA.[77] Furthermore, hospital-based reintroductions may be impractical and could result in an unwarranted delay of oral challenge initiation.[76] FPIES is the only non-IgE-mediated FA that has the potential to result in severe reactions and exemplifies a time when clinical supervision is warranted.[77]

A 2019 study monitored by dietitians and clinicians tested the efficacy of at-home milk ladder challenges with 82 infants to see if it could induce dairy tolerance before they reached 3 years of age.[76] The infants previously diagnosed with IgE-mediated CMA were monitored for the appearance of symptoms throughout the 4 stages of the milk ladder challenge. In stage 1, the infants were given malted milk biscuits every day at home with increasing doses over 5 weeks. Parents were briefed on how to complete a milk ladder challenge and how to detect adverse reactions. Although mild to moderate symptoms were noted in 81 of the infants, eventually, 62 progressed to the next stage of the challenge.

Stage 2 called for the introduction of baked milk products into the infants' diets.[76] The foods in stage 2 were required to contain flour and dairy and be baked in the oven. After the successful completion of stage 1, each subsequent stage lasted approximately 4-6 months. The extra time accounted for the oral immunotherapy component of the challenge which aimed to achieve complete dairy tolerance in the cohort. Infants who progressed to stage 3 of the challenge were given foods made with cheese or whole heated cow's milk such as pizza, custard, white sauce, or cream soups. Finally, in stage 4, uncooked cheese, dairy desserts, and fresh cow's milk were given in small but increasing doses. Upon completion of the study, only 8 participants did not achieve full dairy tolerance.

It is estimated that 75% of infants with cow's milk allergies can become tolerant of dairy products through oral immunotherapy challenges that use baked milk.[77] Often, these individuals will experience symptom resolution after several months without adverse effects. Considering the success of milk ladder challenges for infants with IgE CMA, the method provides a potential solution for infants with non-IgE mediated CMA. Milk ladder challenges combined with multiplexed allergen assays detecting which allergens pass through human breastmilk could help eliminate unnecessary elimination diets and liberate dietary intakes for mothers and infants.[28]

Research Gap

After reviewing the current literature on the topic of non-IgE-mediated FA in human milk-fed infants, several important concepts remain understudied. For one, the prevalence and pathophysiology of non-IgE allergies are largely undefined, which, creates a challenge for healthcare practitioners and families attempting to arrive at a diagnosis for their infant. More research is needed to generate standard diagnostic criteria for conditions such as FPIAP and CMA. Unfortunately, the symptoms related to FPIAP and CMA are generic and represent a wide variety of conditions that sometimes appear in healthy, full-term infants. Nonetheless, the consequences of prolonged maternal elimination diets and complementary food restrictions cannot be overlooked. Removing cow's milk products and other food groups from the diet can result in nutrient deficiencies that pose consequences for lactating mothers and their infants. Therefore, our study will seek to understand the current management techniques practiced by parents of infants with non-IgE-mediated FA.

Chapter 2: Manuscript

Background

Non-IgE-mediated FA include food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis, (FPIAP), and food protein enteropathy (FPE). Non-IgE-mediated FA differs from IgE-mediated FA in that infants present with a delayed, often gastrointestinal, inflammatory response to dietary proteins.[21] Since cow's milk is the predominant dietary trigger, many non-IgE-mediated FA fall under the umbrella of a cow's milk allergy(CMA).[40,45] Overlapping symptoms between conditions and knowledge gaps amongst clinicians creates diagnostic and management challenges which result in a high rate of misdiagnoses and unstandardized care.[16,46,71,73]

Lactating mothers of infants with non-IgE-mediated FA are routinely prescribed maternal elimination diets to achieve symptom resolution.[28,45] This process includes eliminating cow's milk protein from the maternal diet followed by soy or eggs if needed to allow for the continuation of breastfeeding.[45,46] The suggested length of maternal elimination diets varies between non-IgE conditions; however, guidelines recommend 2 – 4 weeks to minimize nutrient gaps.[46] Oral food challenges (OFC), where the mother reintroduces the eliminated food back into the diet, can confirm diagnoses and help reach a clinical resolution of non-IgE-mediated FA in the infant while maintaining as liberal of a diet as possible in the mother.[6,43,45]

Most infants will outgrow their non-IgE-mediated FA by early childhood.[19] However, the implications of managing non-IgE-mediated FA with maternal

elimination diets include nutritional concerns for mothers and nutritional and growth and development concerns for infants.[28,46] Dietitians can recommend alternative sources for calcium intake as well as monitor thiamin, riboflavin, vitamin B6, vitamin B12, choline, vitamin A, and vitamin D in mothers adhering to an elimination diet.[28] In breastfed infants calcium, iron, zinc, copper, and folate are not highly dependent on the maternal diet, however, certain nutrients such as Omega 3 fatty acids pass easily through human milk and support growth, and cognitive and motor development.[28] Breastfed infants typically require supplementation with vitamin D given the difficulty of obtaining vitamin D in large quantities through the maternal diet.[28] Infants with FA are at an increased risk of poor growth and development so reducing nutrient gaps in maternal and infant diets should be prioritized.[28]

Research Objective

The primary goal of our study was to explore the application of maternal elimination diets for the management of non-IgE-mediated FA in breast-fed infants. Secondary goals included identifying dietary triggers, symptoms, and feeding practices of infants with confirmed non-IgE-mediated FA. Given the overlapping symptoms associated with CMA and the knowledge gap amongst practitioners, we hypothesized that misdiagnoses would complicate the management of non-IgE-mediated FA leading to unnecessary elimination diets. We also hypothesized that few mothers following elimination diets would reintroduce offending foods after noticing symptom improvement in their infants.

Additionally, we suspected that mothers would express feeling unsupported when undergoing elimination diets despite clinician instruction.

Methods

Research Design

A retrospective, cross-sectional study design was used to explore the experiences of breastfeeding mothers in the clinical management of their child's non-IgE-mediated FA. Participants were recruited to complete a 45-question survey that was estimated to take approximately 10 minutes to complete. A copy of the survey can be found in **Appendix A**. The study was considered exempt by the Winthrop University IRB and administered via Qualtrics survey software between April 25, 2022, and December 6, 2022. Participants provided informed consent before beginning the survey in the form of a yes/no question, and there were no incentives for participation. Recruitment for the study included advertising on social media (Instagram and Facebook), posting flyers in pediatrician and allergy specialist offices in Mount Pleasant and Rock Hill, South Carolina, and through word of mouth.

Research Participants

The inclusion criteria for the study comprised lactating mothers of children with a suspected or diagnosed non-IgE-mediated FA. Survey respondents who provided dietary triggers and symptoms for their infant with or without maternal elimination diets (represented by a 40% completion rate) were included in the results. Exclusion criteria consisted of those withholding consents to participate

in the survey, those who had never breastfed/expressed human milk, mothers of children without a suspected or diagnosed non-IgE-mediated FA, and those who had never been pregnant. Responses were determined incomplete if less than 40% of the questions were answered and were excluded from the study.

The survey collected retrospective data about mothers' experiences managing their infants' non-IgE conditions. Questions were categorized into six survey sections: inclusion/exclusion, demographics, reproductive history, child allergy information, family allergy history, and elimination diet information. Information obtained from the survey included but was not limited to the age of onset of allergy symptoms, dietary triggers of symptoms, clinical symptoms, misdiagnoses, diagnostic testing procedures, foods eliminated from maternal diets, observation of symptom improvement, and an open response asking the extent to which mothers felt supported during their elimination diets.

Data Analysis

Survey data were analyzed using Excel and SPSS statistical software, version 29.0 for Windows (IBM Corp., Armonk, New York). Statistical significance was set at $p < 0.05$. Frequency charts and bar graphs, tables, and pie charts were designed to display preliminary results. Data analysis is set to continue in the coming weeks to include a comprehensive representation of the results.

Results

Sample Demographics

Out of the 93 recruited participants who were eligible to take the survey, 63.4% (n=59) qualified and were included in the data analysis. Fifty-eight percent of respondents (n=54) reached the end of the survey providing information on maternal elimination diets. An additional 5 respondents completed 40% or more of the survey and were also included in the results. Nearly all participants were female, of Caucasian ethnicity, and had completed a bachelor's level education. Participant demographics are summarized in **Table 2**. While nearly half of the respondents were of normal childbearing age, 45.8% of respondents were 35 years or older (see **Table 2**).

Table 2 *Participant demographics show a high percentage of Caucasian females with varying education levels.*

Sample Demographics	
Characteristic (*n = 59*)	*n* (%)
Gender	
Female	58 (98.3)
Male	1 (0.02)
Participant Age in Years	
18-24	5 (8.5)
25-34	27 (45.8)
35-40	19 (32.2)
>40	8 (13.6)
Ethnic Origin	
Black or African American	1 (1.7)
Hispanic, Latino, or Spanish	1 (1.7)
White, Caucasian	52 (88.1)
Multiethnic	5 (8.5)
Highest Level of Education Obtained	
High School	0 (0)
Some College	4 (6.8)
Associate's Level Degree	4 (6.8)
Bachelor's Level Degree	28 (47.5)
Master's Level Degree	17 (28.8)
Doctoral Level Degree	4 (6.8)

Trade School	2 (3.4)

Non-IgE-Mediated Food Allergies

Cow's milk protein intolerance was diagnosed in 59.32% (n=35) of infants and was suspected in an additional 27.11% (n=16) of infants. Fifteen percent (n=9) were diagnosed with FPIAP followed by a few cases of FPIES and CD. **Figure 3** shows a breakdown of the confirmed diagnoses. Misdiagnoses were reported in 42.1% (n=24) of infants. The most common misdiagnoses were GERD (45.8%), infantile colic (41.7%), and lactose intolerance (25%).

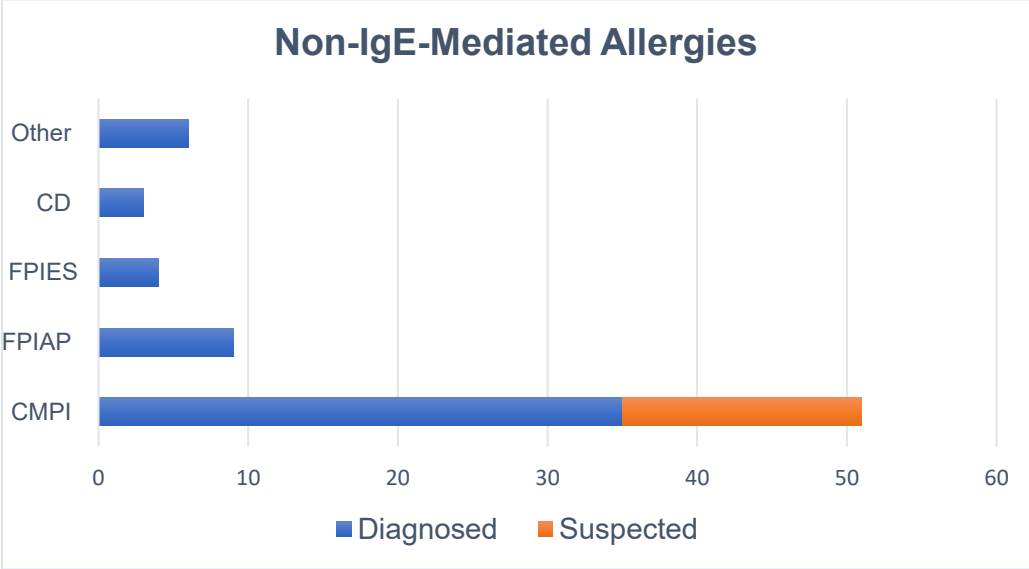

Figure 3 *Cow's milk protein intolerance accounted for nearly all non-IgE-mediated food allergies in breastfed infants.*

Dietary Allergens

Cow's milk protein represented the most common dietary allergen in 96.5% (n=55) of all non-IgE cases followed by soy at 22.8% (n=13). **Table 3** displays the frequency of dietary allergens across all conditions. **Figure 4** and **Figure 5** visually represent the ratio of dietary allergens in FPIAP and CMPI, respectively.

Table 3 *Cow's milk was the most common dietary protein allergen followed by soy. The leading symptoms reported include feeding difficulties, abdominal pain, and gastroesophageal reflux disease.*

Non-IgE Presentation	
Characteristic (*n*)	*n* (%)
Dietary Protein Allergens (*n* = 57)	
Cow's Milk	55 (96.5)
Egg	3 (0.05)
Soy	13 (22.8)
Wheat	2 (0.03)
Tree Nuts	3 (0.2)
Sesame	1 (0.02)
Peanut	1 (0.02)
Oats	2 (0.03)
Other	2 (0.03)
Symptoms (*n* = 59)	
Growth Failure	27 (45.8)
Blood in Stool	19 (32.2)
Abdominal Pain	40 (67.8)
GER	35 (59.3)
Nausea	12 (20.3)
Feeding Difficulties	35 (59.3)
Diarrhea	29 (49.2)
Constipation	26 (44.1)
Colic	30 (50.8)
Anemia	7 (11.9)
Fatty Stool	12 (20.3)
Vomiting	21 (35.6)

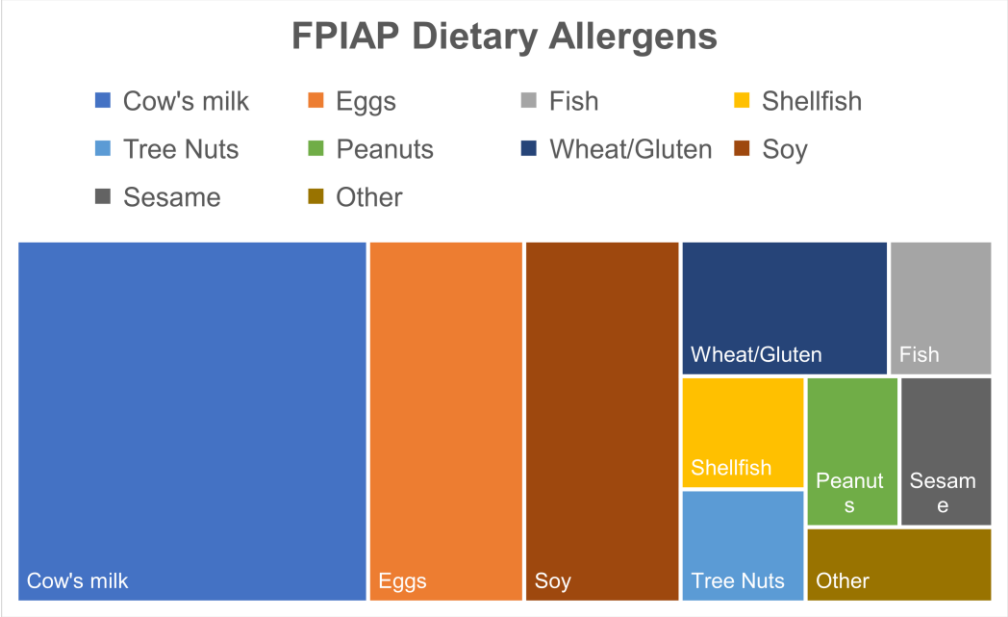

Figure 4 *Cow's milk was the leading dietary allergen among infants with food protein-induced allergic proctocolitis (FPIAP), followed by eggs and soy.*

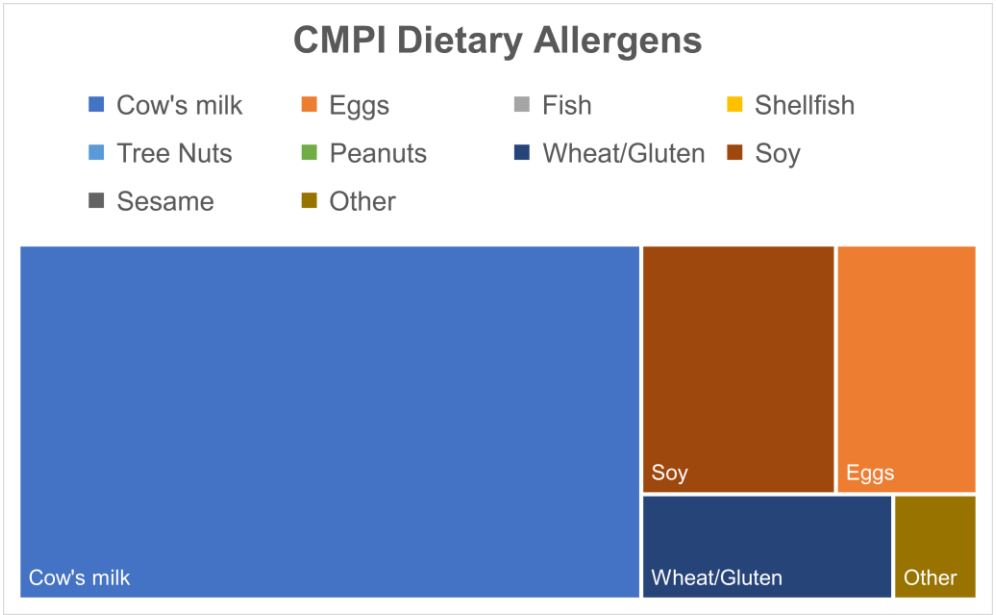

Figure 5 *Cow's milk was the primary dietary allergen among infants with cow's milk protein intolerance. Some infants had multiple food allergies.*

Symptoms

Abdominal pain was the predominant symptom (67.8%) in infants with non-IgE-mediated FA (see **Table 3**). Feeding difficulties, gastroesophageal reflux (GER), and colic were also reported in over half of the infants (see **Table 3**). **Figures 6** and **Figure 7** depict the most common symptoms associated with CMPI and FPIAP.

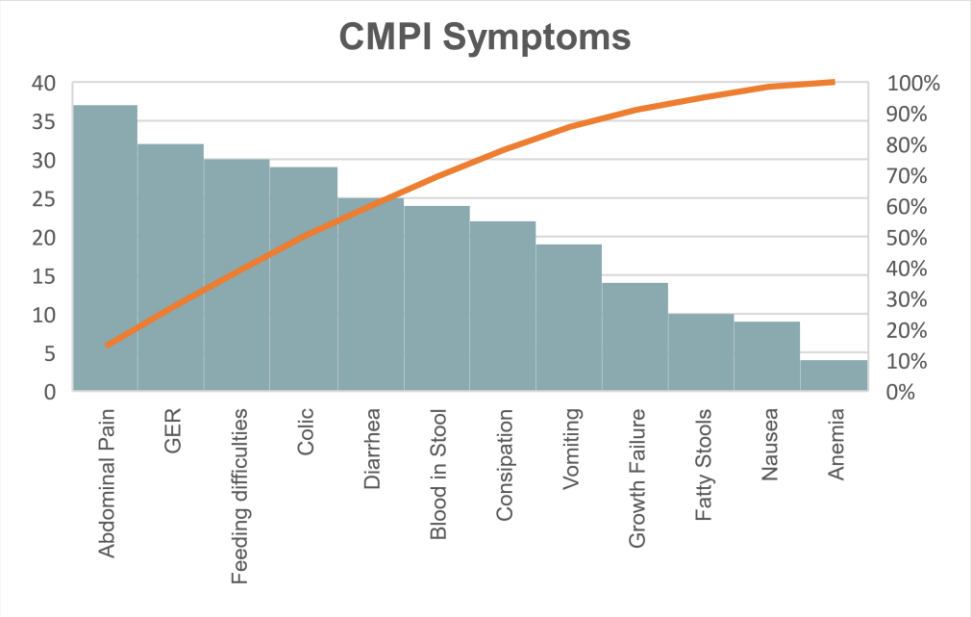

Figure 6 *Abdominal pain, gastrointestinal reflux, and feeding difficulties were the most common symptoms reported among infants with diagnosed or suspected cow's milk protein intolerance.*

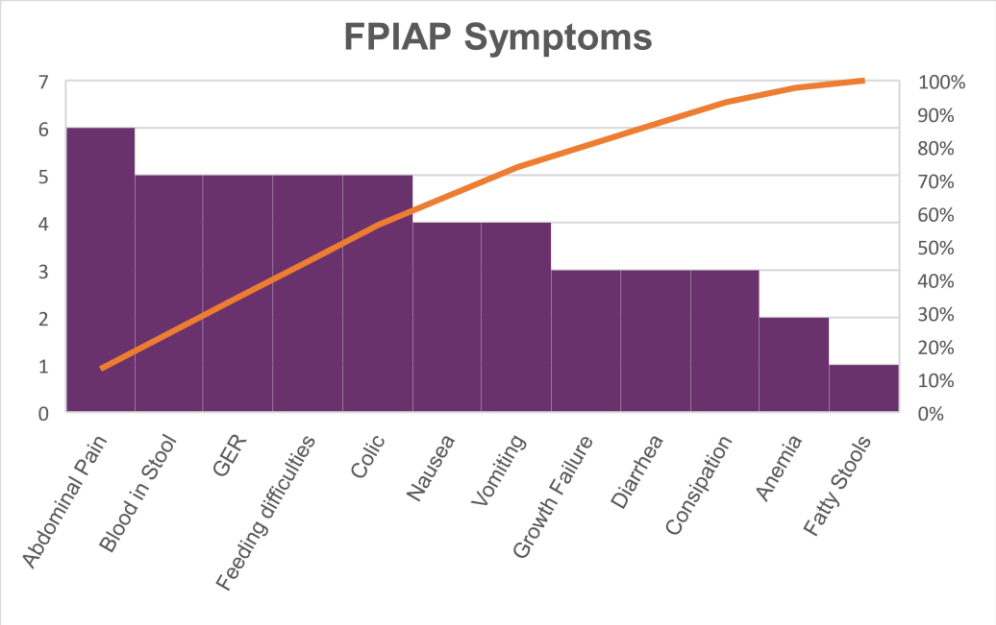

Figure 7 *Abdominal pain, blood in the stool, gastroesophageal reflux disease, feeding difficulties, and colic was the highest reported symptoms among infants diagnosed with food protein-induced allergic proctocolitis (FPIAP).*

Infant Feeding and Maternal Elimination

Among those with confirmed or suspected non-IgE-mediated FA, 72.9% (n=43) of mothers continued breastfeeding their infants, 22.0% (n=13) switched to

formula, and the remaining 5.1% (n=3) practiced mixed feeding. **Figure 8** shows the feeding practices for infants with CMPI and FPIAP.

Eighty-nine percent (n=53) of mothers completed a maternal elimination diet for the management of their infants' symptoms. Nearly all mothers, 88.1% (n=52) eliminated cow's milk protein from their diets and 35.6% (n=21) also eliminated soy protein. Wheat protein 23.7% (n=14) and egg protein 35.6% (n=21) were additionally eliminated in some cases. Mothers followed an elimination diet for one to six months, and 55.9% (n=33) reported reintroducing

foods back into their diets after the elimination period. Only 14.3% (n=8) of mothers were referred to a dietitian for the nutritional management of their elimination diet.

Figure 8 *More than three-quarters of mothers continued breastfeeding their infants after receiving a non-IgE-mediated food allergy diagnosis. The rates of switching to formula or mixed feeding were higher among the cow's milk protein intolerance (CMPI) group.*

Challenges of Maternal Elimination Diets

Several common themes emerged in the open-response survey question which asked participants to share any challenges they experienced during their elimination diets. Out of the 15 respondents who answered the question, six expressed that their infants' pediatrician displayed a lack of knowledge of non-IgE-mediated FA and minimized their infants' symptoms. A few parents recorded that gastroenterologists were unhelpful at best and harmful at worst in that they urged one mother to eliminate all allergen food groups or switch to feeding their infant formula. Most respondents identified barriers that hindered them from following elimination diets. Few elimination-diet-friendly restaurants, an inability to fully engage in social activities, and confusion surrounding nutrition label

reading and feeding their infants were common sentiments. Two participants also attributed unsupportive families and stress as challenges contributing to a poor elimination diet experience.

Discussion

Major findings from the study indicate that breast-fed infants with non-IgE-mediated FA had a high prevalence of cow's milk protein dietary allergens, CMPI, and misdiagnoses. The rate of confirmed and suspected cases of CMPI suggests that clinicians are increasingly attributing infant gastrointestinal symptoms to cow's milk protein. The finding that 42.1% of infants received a misdiagnosis before arriving at their current diagnosis supports the probability that unwarranted maternal elimination diets may have been prescribed for the management of infant gastrointestinal symptoms. This finding is consistent with diagnosis inconsistencies represented in the literature.[46,78] However, the significant percentage of cow's milk as the predominant dietary allergen observed in this study with soy being the runner-up, is also consistent with the literature, albeit slightly high.[18,28,42]

While abdominal pain was a commonly reported symptom in both CMPI and FPIAP, the inconsistencies between symptoms reported in the literature and symptoms reported in this study hint at the subjective nature of parent perceptions and the indirect communication practices between parents, infants, and clinicians. On the other hand, the literature claims that hematochezia is a clear indicator of FPIAP.[18] However, our study revealed that hematochezia was

the second most prevalent symptom among infants with FPIAP. Even with the loss of blood through stool (sometimes in microscopic amounts), our results show a low rate of iron deficiency anemia in breastfed infants with FPIAP. The few FPIAP cases represented in our sample population could account for the atypical order of prevalent symptoms and may not reflect the characteristics of a larger population.

Since 78% (including mixed feeding) of mothers continued breastfeeding after their infants received a confirmed or suspected non-IgE-mediated FA diagnosis, many attempted maternal elimination diets in hopes of improving their infants' symptoms. The actual rate of those who tried elimination diets (89%) is higher than those who continued breastfeeding (78%). The inflated rates of elimination diets suggest that 11% of mothers switched their infant to formula feeding after attempting an elimination diet. Nevertheless, it is difficult to ascertain the efficacy of maternal elimination diets given the variability in duration and reintroduction of eliminated foods. Moreover, the open response results show that many mothers were dealing with unsupportive clinicians and family members when undergoing elimination diets which manifested as a lack of education about elimination-friendly food options, and unnecessary stress. More than three-quarters of mothers reported following an elimination diet longer than the recommended duration of one month which indicates a high probability of nutritional inadequacies.[46]

The findings of the study point to the demand for clinician education on non-IgE-mediated FA and the necessity of registered dietitians (RDNs) to be

involved in the maternal elimination diet process. Although evaluating the nutritional status of mothers and infants undergoing elimination diets was outside of the scope of the descriptive, retrospective study design, research indicates that eliminating food groups from a mother's diet such as cow's milk protein creates nutritional gaps in the diets of mothers and infants.[28,46] Dietitians can work with mothers of infants with non-IgE-mediated FA to provide label reading and restaurant menu education, minimize nutrient gaps, support the reintroduction of eliminated foods, and ultimately limit the duration of maternal elimination diets.

Limitations

Limitations of the study include the modest sample size, mixed ages of mothers, lack of ethnic diversity, and the misinterpretation of some survey questions. We originally aimed for 100 survey responses and received 93 of which only 59 were eligible for data analysis. Given that 13.6% of the respondents were over the age of 40, it may have been several years since those mothers had managed their child's non-IgE-mediated FA which could have influenced their accuracy when taking the survey. Since most of the participants identified as Caucasians, our results cannot be generalized for a multi-ethnic population such as is the case in the United States. Lastly, a few of the participants reported being confused by the wording of some of the survey questions, which may limit the accuracy of responses.

As far as we know, this is the first study to evaluate the use of maternal elimination diets for the management of a variety of non-IgE-mediated FA in

breast-fed infants. A similar study conducted by Wangberg et. al [79] with 133 mothers of breastfed infants with IgE-mediated FA sought to determine how mothers were being advised by clinicians to manage their infants' symptoms. Results of the study showed that 47.4% of respondents were advised by a clinician to continue breastfeeding their infant with an IgE-mediated FA without dietary restriction, 17.3% were told to avoid foods their infants were allergic to, and the remaining 28.6% were not advised either way.[79]

Future Research

Future research could explore clinician perspectives on the management of non-IgE-mediated FA. Surveying pediatricians and pediatric gastroenterologists about their experiences working with infants who present with gastrointestinal symptoms would provide insight into the clinical diagnostic methods and management of non-IgE-mediated FA conditions. Additionally, it would provide a more complete picture of the prevalence of individual non-IgE-mediated FA and clinician knowledge in that area of practice. Future research could also assess the nutritional status of mothers undergoing elimination diets to justify the need for more clinical guidance on the management of non-IgE-mediated FA in breastfed infants.

Conclusion

The results of this study indicate that many infant gastrointestinal symptoms were attributed to an inability to comfortably digest cow’s milk protein. Cow’s milk protein intolerance proved to be the single most suspected and

confirmed diagnosis of non-IgE-mediated FA among breastfed infants in this study. Even though non-IgE conditions such as FPIAP, FPIES, and FPE primarily manifest as allergies to cow's milk protein, this study found few confirmed cases of these non-IgE conditions. The feeding difficulties and colicky symptoms observed in infants allude to the challenges of managing non-IgE-mediated FA in breastfed infants and the deficits in clinician knowledge. Additionally, many mothers expressed frustration with maternal elimination diets and individual practices varied widely. The breakdown in clinical support led many mothers to switch to feeding their infant formula which contradicts the recommendation to exclusively breastfeed infants for the first six months of life. Moreover, the nutritional concerns of maternal elimination diets constitute the crucial need for the involvement of dietitians in the administration of these diets. Therefore, while most cases of non-IgE-mediated FA prove benign apart from FPIES, the current management techniques for these conditions have the potential to introduce a host of nutritional and growth and developmental concerns for lactating mothers and their infants. Additional research is warranted to determine the appropriate length and reintroduction practices of maternal elimination diets for the effective management of specific non-IgE-mediated FA in breast-fed infants.

Appendix A: Qualtrics Survey

Management of Non-IgE Mediated Allergies in Human Milk-Fed Infants

Start of Block: Inclusion / Exclusion

Q1 You are invited to take part in a research study whose purpose is analyze the management of non-IgE mediated allergies in human milk-fed infants. This study is open to adults over the age of 18. Your decision to take part in this study is voluntary. You are free to choose whether or not you will take part in the study. Even if you decide to participate now, you may change your mind and stop at any time. You may choose not to answer an individual question, or you may skip any section of the survey. Simply click "Next" at the bottom of the survey page to move to the next question. Your participation will last approximately **10 minutes** and you will be completing an anonymous online survey. This project is deemed as no more than minimal risk. The research team does not foresee or anticipate any risk greater than that encountered in your routine daily activities. While you may not receive any direct benefit for participating, we hope that this study will help us understand the effectiveness of maternal elimination diets for infants with food protein-induced allergies (FPIAP). If you are interested in learning the results of the study, you may contact the researchers after 5/1/2023. Your cost to participate in the study is the time that you will dedicate to this activity. Researchers will make no attempt to link your survey responses to you. We may publish the results of this study but will not include any information that would identify you. If you have questions about this research study, you may contact Sarah Kelly Rowe, via email at rowes3@winthrop.edu. You may also contact my faculty advisor Dr. Hope Lima at limah@winthrop.edu or 803-323-4540. You may also contact: Grants and Sponsored Research Development Winthrop University Rock Hill, SC 29733

Do you consent to participate in this survey?

- ☐ Yes (1)
- ☐ No (2)

Skip To: End of Survey If You are invited to take part in a research study whose purpose is analyze the management of non-I... = No

Q2 Have you ever breast/chest fed or expressed human milk?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If Have you ever breast/chest fed or expressed human milk? = No

Q3 Have any of your children ever been **diagnosed** with a non-IgE-mediated food allergy? Non-IgE food allergies include food protein-induced allergic proctocolitis (FPIAP), celiac disease, food protein-induced enterocolitis syndrome (FPIES), eosinophilic esophagitis, Heiner syndrome (pulmonary hemosiderosis), cow's milk protein intolerance, among others).

- ○ Yes (1)
- ○ No (2)

Skip To: End of Block If Have any of your children ever been diagnosed with a non-IgE-mediated food allergy? Non-IgE food... = Yes

Q4 Have any of your children been **suspected** of having a non-IgE-mediated food allergy? Non-IgE food allergies include food protein-induced allergic proctocolitis (FPIAP), celiac disease, food protein-induced enterocolitis syndrome (FPIES), eosinophilic esophagitis, Heiner syndrome (pulmonary hemosiderosis), cow's milk protein intolerance, among others).

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If Have any of your children been suspected of having a non-IgE-mediated food allergy? Non-IgE food... = No

End of Block: Inclusion / Exclusion

Start of Block: Demographics

Q5 Please indicate your gender

- ○ Male (1)
- ○ Female (2)
- ○ Non-binary / third gender (3)
- ○ Prefer not to say (4)

Q6 Please indicate your age in years

- ○ 18-24 (1)
- ○ 25-34 (2)
- ○ 34-40 (3)
- ○ >40 (4)

Q7 Please indicate your ethnic origin

- [ ] American Indian or Alaska Native (1)
- [ ] Asian (2)
- [ ] Black or African American (3)
- [ ] Hispanic, Latino or Spanish Origin (4)
- [ ] Middle Eastern or North African (5)
- [ ] Native Hawaiian or Other Pacific Islander (6)
- [ ] White, Caucasian (7)
- [ ] Multiethnic (8)
- [ ] Prefer not to disclose (9)
- [ ] Other (10)

Q8 What is the highest degree or level of education you have completed?

- ○ Some high school (1)
- ○ High School (2)
- ○ Some college (3)
- ○ Associate degree (4)
- ○ Bachelor's degree (5)
- ○ Master's degree (6)
- ○ Doctoral degree (7)
- ○ Trade school (8)
- ○ Prefer not to disclose (9)
- ○ Other (10)

End of Block: Demographics

Start of Block: Reproductive History

Q9 Have you ever been pregnant?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If Have you ever been pregnant? = No

Q10 How many pregnancies have you had?

_____

Q11 How many children have you given birth to?

_____

Q12 How many children that you have given birth to are living?

_____

End of Block: Reproductive History

Start of Block: Child Allergy Information

Q13 Which non-IgE mediated food allergy was **your oldest child with non-IgE food allergies** diagnosed with or suspected of having? (Select all that apply)

- ☐ Food protein-induced allergic proctocolitis (FPIAP) (1)
- ☐ Celiac disease (must avoid gluten) (2)
- ☐ Food protein-induced enteropathy (FPE) (3)
- ☐ Heiner syndrome (pulmonary hemosiderosis) (4)
- ☐ Food protein-induced enterocolitis syndrome (FPIES) (5)
- ☐ Cow's milk (CM) protein intolerance (6)
- ☐ Other (please specify): (7) _____

Q14 How old was your **oldest child with non-IgE** mediated food allergies when they first had symptoms related to their allergy? If you cannot remember, please put your best estimate.

- ○ 0-3 months (1)
- ○ 4-6 months (2)
- ○ 7-12 months (3)
- ○ > 1 year (4)

Q15 Which allergen(s) trigger(s) symptoms in your **oldest child with non-IgE mediated food allergies?** (Select all that apply)

- ☐ Cow's milk (1)
- ☐ Eggs (2)
- ☐ Fish (3)
- ☐ Shellfish (4)
- ☐ Tree nuts (5)
- ☐ Peanuts (6)
- ☐ Wheat / Gluten (7)
- ☐ Soy (8)
- ☐ Sesame (9)
- ☐ Other: please specify (10) _____

Q16 Complete the chart depending on how often you see the following symptoms in your **oldest child with a diagnosed or suspected non-IgE-mediated food allergy:**

Growth Failure (1)	▼Never (1) ... Always (5)
Blood in the stool (2)	▼Never (1) ... Always (5)
Abdominal pain (3)	▼Never (1) ... Always (5)
Gastroesophageal reflux (4)	▼Never (1) ... Always (5)
Nausea (5)	▼Never (1) ... Always (5)
Feeding difficulties (6)	▼Never (1) ... Always (5)
Diarrhea (7)	▼Never (1) ... Always (5)
Constipation (8)	▼Never (1) ... Always (5)
Colic (9)	▼Never (1) ... Always (5)
Anemia (iron deficiency) (10)	▼Never (1) ... Always (5)
Fatty stools (11)	▼Never (1) ... Always (5)
Vomiting (12)	▼Never (1) ... Always (5)

Q17 After breast/chest feeding, how long does/did it take to see food allergy symptoms occur in your **oldest child with suspected or diagnosed non-IgE-mediated food allergies**?

- ○ < 1 hour (1)
- ○ 2-12 hours (2)
- ○ 12-24 hours (3)
- ○ 1-2 days (4)
- ○ > 2 days (5)

Q18 Was your **oldest child with non-IgE food allergies** misdiagnosed or suspected of having a different diagnosis prior to receiving their official diagnosis of non-IgE food allergy?

- ○ Yes (1)
- ○ No (2)

Skip To: Q20 If Was your oldest child with non-IgE food allergies misdiagnosed or suspected of having a different... = No

Q19 Which if any of the following diseases was your **oldest child with non-IgE mediated food allergy** misdiagnosed with or suspected of having prior to receiving a diagnosis for a non-IgE-mediated food allergy? (Select all that apply)

- ☐ Infantile Colic (1)
- ☐ Gastroesophageal Reflux (GERD) (2)
- ☐ Pyloric stenosis (3)
- ☐ Gastroenteritis (4)
- ☐ Gastrointestinal infections (5)
- ☐ Infantile Inflammatory Bowel Disease (6)
- ☐ Food Poisoning (7)
- ☐ Lactose Intolerance (8)
- ☐ Autoimmune Enteropathies (9)
- ☐ Other (please specify): (10)

_____

Q20 Who did you receive information from about non-IgE-meditated allergy symptoms in your **oldest child diagnosed with non-IgE food allergy**? (Select all that apply)

- ☐ Doula (1)
- ☐ Family member (2)
- ☐ Family physician (3)
- ☐ Friend (4)
- ☐ Lactation consultant (5)
- ☐ Midwife (6)
- ☐ OB/GYN (7)
- ☐ Pediatrician (8)
- ☐ Allergists (9)
- ☐ Other: please specify (10) _____
- ☐ N/A, I was never given information about non-IgE mediated allergy symptoms in my child (11)

Q21 Were you referred to a dietitian or an allergist to help manage your oldest child's symptoms with a suspected or diagnosed non-IgE-mediated food allergy?

- ○ Yes, dietitian (1)
- ○ Yes, allergist (2)
- ○ Other: please specify (3) _____
- ○ No referral was made for management of my child's food allergy (4)

Q22 Which of the following diagnostic test(s) have been performed on your oldest child with non-IgE mediated food allergy? (Select all that apply)

- [ ] Oral food challenge (1)
- [ ] Skin prick test (2)
- [ ] Patch testing (3)
- [ ] Serum IgE measurement (4)
- [ ] Elimination diet without subsequent oral food challenge (5)
- [ ] Elimination diet with subsequent oral food challenge (6)
- [ ] Fecal Inflammatory marker tests (7)
- [ ] Endoscopy (8)
- [ ] Observation (9)
- [ ] Blood Test (10)
- [ ] Other: please specify (11) _____
- [ ] N/A, my child has not undergone any diagnostic testing (12)

Q23 Were you instructed to continue breast/chest feeding your **oldest child with non-IgE mediated food allergies** after identification of their non-IgE mediated food allergies?

- ○ Yes (1)
- ○ No (2)
- ○ N/A I was not advised to stop or continue breast/chest feeding my child (3)

Q24 Did you ever need to supplement your **oldest child with a non-IgE mediated food allergy** with infant formula or donor human milk?

- ○ Yes (1)
- ○ No (2)

Skip To: Q28 If Did you ever need to supplement your oldest child with a non-IgE mediated food allergy with infan... = No

Q25 How old was your **oldest child with non-IgE mediated food allergy** when you first had to supplement?

- ○ 0-3 months (1)
- ○ 4-6 months (2)
- ○ 7-12 months (3)
- ○ >1 year (4)

Q26 What did you supplement your **oldest child with a non-IgE mediated food allergy** with?

- ☐ Donor human milk from a milk bank (1)
- ☐ Donor human milk from an individual that I knew (2)
- ☐ Donor human milk from an individual that I did not know (3)
- ☐ Infant formula (4)
- ☐ Other (please specify): (5) _____

Q27 In cases where it was recommended that you refrain from breast/chest feeding or breast/chestfeeding was not an option, which of the following supplements was recommended for your **oldest child with suspected or diagnosed non-IgE-mediated allergies**? (Select all that apply)

- ☐ Extensively Hydrolyzed Formula (EHF) (1)
- ☐ Amino Acid Based Formula (AAF) (2)
- ☐ Elemental formula (3)
- ☐ Soy-based formula (4)
- ☐ Hypoallergenic formula (5)
- ☐ N/A (6)
- ☐ Other (7)

Q28 Do you have more than one child that has been suspected of or diagnosed with a non-IgE mediated food allergy?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Block If Do you have more than one child that has been suspected of or diagnosed with a non-IgE mediated f... = No

Q29 Which allergen(s) trigger(s) symptoms in your other child(ren) with non-IgE mediated food allergies? (Select all that apply)

- ☐ Cow's milk (1)
- ☐ Eggs (2)
- ☐ Fish (3)
- ☐ Shellfish (4)
- ☐ Tree nuts (5)
- ☐ Peanuts (6)
- ☐ Wheat / Gluten (7)
- ☐ Soy (8)
- ☐ Sesame (9)
- ☐ Other: please specify (10) _____

End of Block: Child Allergy Information

Start of Block: Family Allergy History

Q30 Does anyone in your family other than your child have a food allergy (IgE or non-IgE mediated)?

- ○ Yes (1)
- ○ No (2)

Q31 Which food allergies are present in your family (select all that apply):

- ☐ Cow's milk (1)
- ☐ Eggs (2)
- ☐ Fish (3)
- ☐ Shellfish (4)
- ☐ Tree Nuts (5)
- ☐ Peanuts (6)
- ☐ Wheat / Gluten (7)
- ☐ Soy (8)
- ☐ Sesame (9)
- ☐ Other (please specify): (10)

_____

End of Block: Family Allergy History

Start of Block: Elimination Diet Information

Q32 Did you ever follow an elimination diet to help resolve your child's symptoms with suspected or diagnosed non-IgE mediated food allergies while breast/chest feeding?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Block If Did you ever follow an elimination diet to help resolve your child's symptoms with suspected or d... = No

Q33 Who recommended or provided you with information about following an elimination diet? (Select all that apply)

- ☐ Doula (1)
- ☐ Family Member (2)
- ☐ Family practice physician (3)
- ☐ Friend (4)
- ☐ Lactation consultant (5)
- ☐ Midwife (6)
- ☐ OB/GYN (7)
- ☐ Pediatrician (8)
- ☐ Allergist (9)
- ☐ Other (please specify): (10) _____
- ☐ N/A (11)

Q34 Did your primary care provider know that you were following an elimination diet?

- ○ Yes (1)
- ○ No (2)

Q35 Before starting an elimination diet, did you restrict any of the following in your diet? (Select all that apply)

- ☐ Meat (vegetarian) (1)
- ☐ Milk (2)
- ☐ Wheat / Gluten (3)
- ☐ Peanuts (4)
- ☐ Soy (5)
- ☐ Fish (6)
- ☐ Shellfish (7)
- ☐ Tree nuts (8)
- ☐ Sesame (9)
- ☐ Other (please specify): (10) _____
- ☐ N/A (11)

Q36 What type of elimination diet did you follow for your child's suspected or diagnosed non-IgE-mediated food allergy?

- ○ 1-food (1)
- ○ 2-food (2)
- ○ 4-food (3)
- ○ 6-food (4)
- ○ Total elimination with formula supplementation (5)
- ○ Other (please specify): (6) _____

Q37 Which food(s) did you remove from your diet while following an elimination diet? (Select all that apply)

- [ ] Milk (1)
- [ ] Eggs (2)
- [ ] Wheat / Gluten (3)
- [ ] Peanuts (4)
- [ ] Soy (5)
- [ ] Fish (6)
- [ ] Shellfish (7)
- [ ] Tree Nuts (8)
- [ ] Sesame (9)
- [ ] Other (please specify): (10)

_____

Q38 After the elimination period, were you instructed, or did you reintroduce any foods back into your diet to confirm the diagnosis of your child with a non-IgE mediated food allergy?

- ○ Yes (1)
- ○ No (2)

Skip To: Q41 If After the elimination period, were you instructed, or did you reintroduce any foods back into you... = No

Q39 On average, how long **were you told to follow** an elimination diet before performing an oral food challenge to test for remission?

- 2-4 weeks (1)
- 1-2 months (2)
- 3-6 months (3)
- 6-12 months (4)
- >12 months (5)

Q40 On average, how long **did you follow** an elimination diet before performing an oral food challenge to test for remission?

- 2-4 weeks (1)
- 1-2 months (2)
- 3-6 months (3)
- 6-12 months (4)
- >12 months (5)

Q41 Did you continue to breast/chest feed your child while following the elimination diet?

- Yes (1)
- No (2)

Q42 If breast/chest feeding, did your child's symptoms improve while you were on the elimination diet?

- Yes (1)
- No (2)

Skip To: Q44 If If breast/chest feeding, did your child's symptoms improve while you were on the elimination diet? = No

Q43 How long did it take for you to notice symptom changes in your child after adhering to an elimination diet

- 1 week (1)
- 2 weeks (2)
- 3 weeks (3)
- 1 months or longer (4)
- I did not see symptom improvement (5)

Q44 Did you feel that you were well supported while on your elimination diet?

- Yes, I felt supported (1)
- No, I did not feel supported (2)

Display This Question:

If Did you feel that you were well supported while on your elimination diet? = No, I did not feel supported

Q45 Please share any challenges that made it difficult to follow your elimination diet.

_____

End of Block: Elimination Diet Information

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