Received: 19 March 2019 | Revised: 16 April 2019 | Accepted: 20 April 2019

DOI: 10.1111/all.13947

EAACI POSITION PAPER

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

Diagnosis and management of Non-IgE gastrointestinal allergies in breastfed infants—An EAACI Position Paper

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Abstract

It is well-established that food proteins, such as egg, soya, cow's milk and wheat, are detectable in breastmilk for many hours or days after ingestion. Exposure to these proteins is important to the process of developing tolerance but can also sometimes elicit IgE-mediated and non–IgE-mediated allergic symptoms in breastfed infants. Non–IgE-mediated allergy, outside of food protein-induced allergic proctocolitis and eosinophilic oesophagitis, is not well understood, leading to variations in the diagnosis and management thereof. A primary objective of the European Academy for Allergy and Clinical Immunology is to support breastfeeding in all infants, including those with food allergies. A Task Force was established, to explore the clinical spectrum of non–IgE-mediated allergies, and part of its objectives was to establish diagnosis and management of non–IgE-mediated allergies in breastfed infants. Eight questions were formulated using the Patient, Intervention, Comparison, Outcome (PICO) system and Scottish Intercollegiate

Abbreviations: AAF, amino acid formula; EAACI, European Academy of Allergy and Clinical Immunology; EGID, eosinophilic gastrointestinal disorders; EHF, extensively hydrolysed formula; ENIGMA, exploring non–IgE-mediated allergy; EoE, eosinophilic oesophagitis; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; FA, food allergy; FAP, functional abdominal pain; FPE, food protein-induced enteropathy; FPIAP, food protein-induced allergic proctocolitis; FPIES, food protein-induced enterocolitis syndrome; GORD, gastro-oesophageal reflux disease; HCP, healthcare professional; Hpf, high power field; HRQL, health-related quality of life; ICTP, I C-terminal propeptide; IgE, immunoglobulin E; NASPGHAN, North American Society for Paediatric Gastroenterology Hepatology and Nutrition; OFC, oral food challenge; PICO, Patient, Intervention, Comparison, Outcome; QoL, QoL; RCT, randomized controlled trial; SIGN, Scottish Intercollegiate Guideline Network; SIGN, Scottish Intercollegiate Guidelines Network.

Guideline Network (SIGN) criteria for data inclusion, and consensus was achieved on practice points through the Delphi method. This publication aims to provide a comprehensive overview on this topic with practice points for healthcare professionals.

KEYWORDS

breastfed children, diagnosis of non–IgE-mediated allergy, food allergy, maternal elimination, non–IgE-mediated allergy

1 | INTRODUCTION

Food allergy describes adverse reactions to food with an immunological mechanism and encompasses both immunoglobulin E (IgE) and non–IgE-mediated allergies.[1] Signs of IgE-mediated allergies typically develop soon after exposure and are usually evident within one to two hours after consumption of the allergen. In contrast, signs of non–IgE-mediated food allergies typically occur several hours later and even up to several days after exposure. Although atopic dermatitis can present as delayed immune response to food, this review will only focus on the gastrointestinal manifestations of non–IgE-mediated allergies that are experienced by breastfed children. Non-IgE gastrointestinal symptoms are typically chronic and occur as a result of repeated exposure to the food allergen, examples include gastro-oesophageal reflux and vomiting, abdominal pain, altered stool habit (with and without blood) and with faltering growth (Table 1).[2]

The prevalence of challenge-proven non–IgE-mediated allergies to cow's milk protein, according to the EuroPrevall study, was low at around 1%. In the UK birth cohort of this study, the cumulative incidence to all allergens was 2.4% (cow's milk 1.7%).[3,4] However, concerns have been expressed about selection bias with EuroPrevall study, as referral into that study would depend on the level of awareness of clinical signs of gastrointestinal food allergy.[5] However, the true prevalence of non–IgE-mediated allergy is thought to be higher, [5] as it is frequently misdiagnosed/not recognized as these symptoms commonly occur during early infancy and in breastfed infants.[6-8] Food proteins, such as cow's milk, egg, soya and wheat, are detectable in breastmilk for many hours or days after ingestion and, whilst tolerated by most infants, may sometimes elicit non–IgE-mediated allergic symptoms.[9-15] In a prospectively recruited cohort of breastfed children from 1988, 0.5% of the 2.2% children diagnosed with an IgE-mediated cow's milk allergy (CMA) presented whilst being exclusively breastfed.[16] Limited data exist outside of CMA as studies were retrospective and/or observational. [6,17] A primary objective of the European Academy for Allergy and Clinical Immunology[18] is to support breastfeeding in all infants, including those with food allergies and to ensure that healthcare professionals reinforce the importance of breastfeeding, in line with the World Health Organization Guidelines and also avoid the negative psychological effects of an elimination diets.[19] As no specific guidance for breastfed infants with non–IgE-mediated allergies and the mother on an elimination diet exists, this Task Force aimed to establish the prevalence and clinical presentation, to answer the most commonly asked clinical questions (Table 2), to highlight the impact on quality of life for the mother and family and to provide practical consensus-based management suggestions centred on the limited published data.

2 | METHODOLOGY

The Task Force on non–IgE-mediated allergy (ENIGMA = **e**xploring **n**on–IgE-**m**ediated **a**llergy) consists of EAACI experts in paediatric gastroenterology, allergy, dietetics and psychology from Europe, United States of America, Turkey and Brazil.

Definitions

Dietary elimination: it is the strict elimination of food allergens from the breastfeeding mother and in an infant that has commenced on complementary foods.

Oral food challenge (OFC): it is the physician-supervised introduction of allergens.

Home re-introduction: it is the medically unsupervised exposure to allergens.

Highlights

1. Breastmilk is the best source of nutrition for infants with non–IgE-mediated gastrointestinal food allergies and should be supported by healthcare professionals.
2. The cornerstone for the diagnosis of non–IgE-mediated food allergies in the breastfed infant remains the elimination of foods from the maternal diet for 2-4 weeks with symptom improvement/resolution, followed by reintroduction with symptom deterioration.
3. Unnecessary elimination of food allergens may adversely impact the nutritional status of the breastfeeding mother.
4. Healthcare professionals should be aware of the added burden and impact on quality of life of adhering to an elimination diet for mother.

TABLE 1 Possible gastrointestinal symptom/signs for non–IgE–mediated allergies and consequences progression over time

<Day 1	Days 1-3	>Day 3
Acute vomiting	Intermittent vomiting	Faltering growth
Acute abdominal discomfort which may present with persistent crying and unsettled behaviour	Diarrhoea	Ongoing abdominal discomfort
	Abdominal discomfort	Ongoing abdominal bloating
	Blood in stool	Ongoing diarrhoea
	Abdominal bloating	Constipation
		Hypoalbuminaemia
		Iron deficiency anaemia
		Blood in stool

At the first meeting in June 2016, the PICO (Patient, Intervention, Comparison/Intervention and Outcome) system was used to generate questions in regard to the topic, to enable focus on outstanding clinical question pertaining to non–IgE-mediated allergies in breastfed infants. These questions were debated/amended and approved following this meeting and are summarized in Table 2.

2.1 | Literature review, grading of the evidence and strategy

Two members of the Task Force independently performed a systematic literature search using PubMed, Cochrane and EMBASE databases using the inclusion criteria below and search terms outlined in Table 3. The two literature searches were compared, duplicates eliminated, and articles were assessed for suitability. In addition, the Snowball method was used to obtain further relevant publications from articles already sourced through the search.

Inclusion criteria were as follows:

TABLE 2 PICO questions related to non–IgE-mediated allergies in breastfed infants

1. How do you diagnose non–IgE-mediated food allergies in breastfed infants?
2. Does allergic GORD improve with dietary elimination in breastfed infants?
3. Does constipation improve with dietary elimination in breastfed infants?
4. Does colic improve with dietary elimination in breastfed infants?
5. Can food protein-induced enterocolitis syndrome[75] reactions occur whilst the infant is being breastfed and is dietary elimination required?
6. Does allergic proctocolitis improve with dietary elimination in breastfed infants?
7. Does allergic enteropathy improve with dietary elimination in breastfed infants?
8. Does EoE/EGID improve on an elimination diet in breastfed infants?
9. What is the nutritional status of mothers on an elimination diet of a breastfed child with non–IgE-mediated allergies?
10. How to reintroduce/challenge food allergens in breastfed children with non–IgE-mediated allergies?
11. What is the quality of life of mothers on an elimination diet for breastfed infants with non–IgE-mediated allergies?

1. Published between 1990 and May 2018.
2. Study population consisting of breastfed children with the diagnosis of non-IgE gastrointestinal food allergies.
3. Full-text articles in English.
4. Population studies and case reports.

The levels and quality of evidence of the included articles were assessed using the Scottish Intercollegiate Guidelines Network (SIGN) grading system (Table 4). Grades of recommendation for each section were based on the SIGN grading system of the literature, and the Delphi method was used for reaching consensus on practical recommendations where insufficient data were available to provide guidance. We aimed to reach at least 80% agreement among task force

TABLE 3 Search Terms

Non-IgE mediated allergy/Food Hypersensitivity/Allergy/Delayed AND gastrointestinal tract AND children AND breast milk/feeding
Breastfeeding/breast milk AND non-IgE mediated allergy/Food Allergy/Food Hypersensitivity AND children
Proctocolitis AND breastfeeding/breast milk AND allergy/non-IgE mediated allergies/Food Hypersensitivity
Enteropathy AND breastfeeding/breast milk AND allergy/non-IgE mediated allergies/Food Hypersensitivity
Dysmotility AND allergy/non-IgE mediated allergies/Food Hypersensitivity
AND breast feeding/milk
Colic AND allergy/non-IgE mediated allergies/Food Hypersensitivity
AND breast feeding/milk
Eosinophilic oesophagitis (EoE) AND allergy/non-IgE mediated allergies/Food Hypersensitivity
Reflux/Gastro-oesophageal reflux disease (GORD) AND allergy/non-IgE mediated allergies/Food Hypersensitivity
AND breastfeeding/breast milk
Food protein-induced enterocolitis syndrome (FPIES)[75] AND breastfeeding/breast milk AND allergy/non-IgE mediated allergies/Food Hypersensitivity
Maternal elimination AND allergy/non-IgE mediated allergies/Food Hypersensitivity
AND breast feeding/breast milk
Nutritional status AND non-IgE mediated allergies AND elimination diet AND breastfeeding/breast milk
Quality of Life AND allergy/non-IgE mediated allergies/Food Hypersensitivity AND breastfeeding/breast milk

TABLE 4 Grades of Recommendation

Grades	Description
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+

members on the practice points, and where this was not achieved, the practice point was amended until this level of agreement was achieved.

3 | HOW TO DIAGNOSE NON-IGE FOOD ALLERGY IN BREASTFED INFANTS?

There are many diseases that fall under the umbrella term of non–IgE-mediated gastrointestinal food allergies, including FPIES, EoE, food protein-induced allergic proctocolitis (FPIAP), food protein-induced allergic enteropathy (FPE) and food protein-induced dysmotility disorders (GORD and constipation). The diagnosis of non–IgE-mediated gastrointestinal disease is a clinical challenge. Whilst each disease has unique symptoms and signs, these may overlap and vary in severity. It is also not uncommon for more than one organ system to be involved (Table 5).[2,20] Non–IgE-mediated food protein-related gastrointestinal conditions usually present at a young age and often whilst the infant is breastfed. Further complicating the diagnosis of non–IgE-mediated food allergy is that symptoms such as altered bowel habit, reflux, constipation and colic may occur in more than half of otherwise healthy infants.[21] Clinicians who adopt a single organ approach may therefore risk missing the possibility of a unifying cause such as non–IgE-mediated food allergies.[22] Table 5 lists the many other pathologies that need to be considered in the differential diagnosis of non–IgE-mediated food allergy.

A limited series of studies have assessed the role of skin prick testing, patch testing, serum IgE measurement and faecal inflammatory marker tests for the diagnosis of non–IgE-mediated food allergy.[23,24] Although IgG and IgG4 measurements have been trialled in mainly adult studies, there is no robust evidence that this or any other biomarker shows clinical validity for the diagnosis of non–IgE-mediated food allergy in childhood. Consensus documents guiding clinical practice have consistently highlighted the need for taking an allergy-focused history and use this to guide the elimination diet.[25] Where a cessation or reduction in symptoms is noted,[8] then reintroduction or supervised oral food challenge (OFC) of the allergen is required to secure the correct diagnosis and need for ongoing exclusion.[19] The length of a diagnostic elimination diet in non–IgE-mediated food allergies varies according to guidelines, but is usually between 2 and 4 weeks. Chebar Lozinsky et al[26] found that the majority of children with non–IgE-mediated allergy had improvement of symptoms within 4 weeks; however, data were mainly based on nonbreastfed children.

The most commonly recognized causative food for non–IgE-mediated allergies with the gastrointestinal presentation is cow's milk. The only easily detected dietary cow's milk protein in human breastmilk is β-lactoglobulin (levels range from 0.9 to 150 μg/L).[27] Beta-lactoglobulin is absent in human breastmilk; therefore, detection of β-lactoglobulin indicates a dietary origin through maternal ingestion of cow's, goat and/ or sheep's milk.[2,26] However, other allergens are capable of inducing non–IgE-mediated food allergies through breastmilk, such as soya, wheat and egg,[12,28] and should be considered within the history-taking and diagnostic work-up.[13]

Biomarkers have performed poorly across the spectrum of non–IgE-mediated allergies. The use of atopy patch testing has been proposed to determine 'delayed sensitization'[29]; however, the latter test has yielded conflicting results.[30] A trial on 25 patients with FPIES determined a sensitivity of only 11.8% and specificity 85.7%, yielding a positive predictive value of 40% and negative predictive value of 54.5%.[31] Lucareli et al[32] found that atopy patch tests were positive for cow's milk in 50%, soya in 28%, egg in 21%, rice in 14% and wheat in 7% for FPIES breastfed infants. The atopy patch test has also shown inconsistency in predicting when tolerance has been achieved in non-IgE CMA.[33,34] Consequently, international guidelines do not recommend patch testing as a routine test for the diagnosis of non–IgE-mediated allergies.[19,35]

Similarly, IgG and IgG4 testing have little established clinical validity and their use should be considered only in research studies,[36] alongside tests of gastrointestinal permeability and mucosal inflammatory markers.[37,38] Although not specific, low albumin may support a diagnosis of enteropathy or chronic FPIES (see definition in Section 7),[39] and in some cases, faecal calprotectin may be considered to rule out very early-onset inflammatory bowel disease. However, values need to be carefully interpreted as healthy young babies have higher calprotectin levels than older children.[37,38] Faecal occult blood test is also a nonspecific marker and unreliable in both the diagnosis and resolution of symptoms in non–IgE-mediated allergies.[40]

TABLE 5 Characteristic non–IgE-mediated food allergy disease presenting among breastfed infants[20]

Non–IgE-mediated food allergy	Cardinal symptom	Additional symptoms	Common food allergen triggers (most common first)	Differential diagnoses
FPIES	Acute FPIES: Vomiting 1-4 h after ingestion Chronic FPIES: intermittent but progressive vomiting and diarrhoea	Acute FPIES: pallor, lethargy, hypovolaemia, hypotension, diarrhoea Chronic FPIES: faltering growth.	Cow's milk, soya, rice, oat, wheat, meat, fish	Gastro-oesophageal reflux disease, sepsis, inborn errors of metabolism, pyloric stenosis, malrotation, intussusception, gastroenteritis with vomiting.
Food protein-induced allergic proctocolitis (FPIAP)	Blood in stool	Occasional loose stools, mucous in the stools, painful flatus, anal excoriation	Cow's milk and soya	Gastrointestinal infections, fissures Infantile polyp, necrotizing enterocolitis, Meckel's diverticulum, intussusception, infantile inflammatory bowel disease (rare)
Eosinophilic Oesophagitis (EoE)	Intermitted vomiting, abdominal discomfort, feeding difficulties	Faltering growth	Cow's milk, soya, egg, wheat	Gastro-oesophageal reflux of infancy, infantile inflammatory bowel disease
Food protein-induced constipation	Straining with soft stools	Faecal impaction, bloating, abdominal pain	Cow's milk and soya	Normal straining associated with infancy, idiopathic constipation, Hirschsprung's Disease
Food protein-induced GORD	Intermitted painful vomiting/regurgitation	Faltering growth, feeding difficulties back-arching with pain	Cow's milk and soya	Gastro-oesophageal reflux of infancy, acute gastroenteritis, food poisoning.
Food protein-induced enteropathy (FPE)	Failure to thrive, diarrhoea	Mucus and bloating, abdominal pain, faltering growth, hypoalbunaemia	Cow's milk, soya, egg and wheat	Sepsis, congenital disaccharide malabsorption, metabolic disorders, chronic kidney disease, neglect, secondary lactose intolerance, chronic FPIES, autoimmune enteropathies, epithelial dysplasia syndromes, cystic fibrosis, immunodeficiencies and/or chronic infection, coeliac disease.

The absence of specific IgE is an expected characteristic feature of non–IgE-mediated food allergies; however, some children may present with overlapping disease and allergic comorbidities associated with IgE sensitization (ie atopic dermatitis).[2,41] This has been reported in FPIES, EoE and other recognized non–IgE-mediated conditions (ie FPE, food protein-induced GORD, FPIAP), with sensitization in publications ranging between 10% and 30% based on specific IgE and skin prick testing.[2,26] There is, however, paucity of data on IgE sensitization specifically in the non–IgE-mediated breastfed cohort. Therefore, the decision to perform targeted IgE/SPT should be based on an allergy-focused history, and the presence of immediate-onset allergic symptoms,[2,41] but the interpretation of results requires careful consideration and may require OFCs.

Outside of EoE, endoscopy is commonly reported in research related to the diagnoses of various non–IgE-mediated allergic conditions. However, this procedure can be technically difficult at such a young age, requires full anaesthesia, and outside of EoE, the interpretation of results can be challenging.[42] Rectosigmoidoscopy has been used to evaluate the diagnosis of FPIAP among breastfed infants with suspected non–IgE-mediated CMA, with eosinophilic infiltration supporting the diagnosis; however, this procedure is unlikely to change the current practice of elimination followed by reintroduction.[43-45] In clinical practice, endoscopy should therefore only be performed when there is a strong suspicion of an alternative diagnosis (autoimmune enteropathy, tufting enteropathy, microvillus inclusion disease, congenital disaccharides deficiencies) or unremitting symptoms (ie vomiting and/or diarrhoea).[46]

4 | DOES ALLERGIC GORD IMPROVE WITH DIETARY ELIMINATION IN BREASTFED INFANTS?

The following definitions are used in the new North American and European Societies of Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN/ESPGHAN)[47]:

(a) GOR: the passage of gastric contents into the oesophagus with or without regurgitation and vomiting; (b) GORD: when GOR leads to troublesome symptoms that affect daily functioning and/or complications; (c) refractory GORD: GORD, not responding to optimal treatment after eight weeks. For a non–IgE-mediated allergy in a breastfed child to be considered as the cause of GORD (not GOR), the infant should have symptom resolution following a maternal elimination diet with re-occurrence on reintroduction. However, it can be challenging to distinguish between GORD and GOR, as 'troublesome symptoms' remains a definition open for interpretation, particularly in breastfed infants; what is troublesome for one parent or caregiver might be considered normal for another.

There is very limited evidence on the incidence and severity of GORD in breastfed infants, and it is estimated that about 25% of infants (both breastfed and bottle-fed) suffer from troublesome regurgitation.[48] The association between GORD and food allergy in both breastfed and bottle-fed infants is poorly studied and therefore remains difficult to establish.[49] However, some data point towards CMA being more common in formula-fed infants who present with GORD.[50-55] The literature search

Practice Points—Grade C Recommendation

- Non–IgE-mediated food allergies are diagnosed according to an allergy-focused history and symptom recognition as there is a conspicuous lack of validated biomarkers. *(91.67% Agreement)*
- The absence of specific IgE is an expected characteristic feature of non–IgE-mediated food allergies in children, and random IgE testing to foods in those with no reported immediate-onset symptoms and/or atopic dermatitis is not recommended. *(81.82% Agreement)*
- The cornerstone for diagnosis remains a maternal elimination diet for 2-4 weeks with symptom improvement/resolution of the presenting symptoms, followed by reintroduction with symptom deterioration, unless convincing history of FPIES or severe associated symptom is present when reintroduction would not occur [see International Consensus Guidelines[39]]. *(91.67% Agreement)*
- The diagnostic elimination diet should ideally be implemented with the support of a registered dietitian/nutritionist or suitably qualified HCP. *(83.33% Agreement)*
- When reintroduction of suspect foods into the maternal diet gives ambiguous results, reintroduction into the child's diet is recommended when complementary feeding has started. *(91.67% Agreement)*
- Cow's milk is the most common allergen, but evidence shows that other allergenic food proteins including egg, soya and wheat can also be transferred through breastmilk and should therefore also be considered as possible allergens. *(91.67% Agreement)*
- Endoscopy with biopsies is of limited routine use and should be restricted to cases that do not resolve with dietary elimination and when differential diagnoses are considered. *(100% Agreement)*
- Rectosigmoidoscopy is easier to perform and well tolerated by infants without sedation but may not change the dietary management. *(83.33% Agreement)*
- IgE testing may be considered in breastfed infants with symptoms associated with IgE-mediated allergies, comorbid presentations such as atopic dermatitis and after a long period (at discretion of physician) of avoidance before home reintroduction. *(90.91% Agreement)*
- Consider specific IgE testing of children with FPIES to their trigger food because comorbid IgE-mediated sensitisation to triggers, such as cow's milk, can infer a greater chance of persistent disease. *(100% Agreement)*

TABLE 6 Rome IV criteria for infantile colic

Diagnostic criteria for infantile colic
For clinical purposes, must include all of the following:
1. An infant who is <5 mo of age when the symptoms start and stop
2. Recurrent and prolonged periods of infant crying, fussing or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers
3. No evidence of infant failure to thrive, fever or illness
For clinical research purposes, a diagnosis of infant colic must meet the preceding diagnostic criteria and also include both of the following:
1. Caregiver reports infant has cried or fussed for three or more hours per day during three or more days in 7 d in a telephone or face-to-face screening interview with a researcher or clinician
2. Total 24-h crying plus fussing in the selected group of infants is confirmed to be 3 h or more when measured by at least one prospectively kept, 24-h behaviour diary

has not yielded any data on food protein-induced GORD in breastfed infants. [56,57] Although this Task Force recognizes that no randomized, controlled, prospective trial has been performed to establish whether dietary manipulation alone may improve GORD in exclusively breastfed infants, it is known that cow's milk protein and other food allergens transfer through breastmilk. Therefore, non–IgE-mediated food allergy should be considered in the diagnosis of infants presenting with persistent reflux and irritability, in particular if associated with other atopic presentations (eg atopic eczema). It is important to follow conventional treatment guidelines by ESPGHAN/NASPGHAN for GORD and only consider food allergy if symptoms do not improve.[47] If there is clinical improvement after antigen elimination and subsequent relapse upon reintroduction, the diagnosis of food-induced GORD is established (if EoE is suspected an endoscopy is recommended—discussed further under Section 10). Early recognition and adequate management are crucial to prevent nutritional sequelae and/or feeding difficulties.[58,59]

Practice Points—Grade D Recommendation

- No data are available on GORD as a single manifestation of food allergy in exclusively breastfed infants. *(91.1% Agreement)*
- Follow current guidelines for standard treatment of GORD and consider food allergy if conventional treatment does not yield symptom improvement. *(81.82% Agreement)*
- A diagnosis of food protein-induced GORD can only be made following the clinical improvement/resolution of presenting GORD symptoms on a maternal elimination diet followed by a relapse of symptoms after reintroduction as described in section 3. *(100% Agreement)*
- Cow's milk is the primary allergenic food most commonly associated with the causation of GORD, but other allergenic foods, such as soya, egg and wheat, may also provoke symptoms. *(100% Agreement)*

5 | DOES CONSTIPATION IMPROVE WITH DIETARY ELIMINATION IN BREASTFED INFANTS?

Constipation is one of the most common disorders in infancy and childhood, with the majority of cases being classified as functional disease, associated with hard and infrequent stools, painful defecation and soiling (standard definition).[60] There are very limited data in regard to food protein-induced constipation in childhood, and no publications were found pertaining to the role of food allergy in breastfed infants. However, consensus-based constipation guidelines do recommend considering food allergy (mainly CMA) as a possible cause for constipation in infants.[61,62] In these cases, the constipation is usually associated with the presence of soft stools, excessively and prolonged straining and a soft distended abdomen.[61] Due to limited evidence, the pathophysiology of food protein-induced constipation is poorly understood, but it is known that the gastrointestinal motility is controlled by a neuronal complex, the enteric nervous system. Research has shown an interaction between mast cells (and possibly eosinophils and lymphocytes) with the gastrointestinal nerve fibres.[63] Therefore, the release of mast cell mediators and cytokines during a food allergy reaction affects the enteric nervous system and may cause motility dysfunction.[64,65] In the case of food protein-induced constipation, anal sphincter dysfunction and faecal retention may occur.[61,66]

Characteristics and differential diagnoses are summarized in Table 5. Therefore, if food protein-induced constipation is suspected in a breastfed infant, the recommended treatment is to commence a maternal elimination diet. Any testing, including blood/skin prick test, endoscopy and biopsy, should only be performed as per recommendations in Section 3, and Hirschsprung's disease, as well as other diagnoses, needs to be considered.

Practice Points—Insufficient data for Grade recommendation

- No data are available on constipation as single manifestation of food allergy in exclusively breastfed infants. *(90.91% Agreement)*
- Data from formula-fed infants and older children suggest that cow's milk is the most commonly associated allergen in food protein-induced constipation. *(100% Agreement)*
- Current consensus guidelines for constipation consider food allergy as a possible differential diagnosis if conventional treatment does not lead to symptom improvement. *(90.91% Agreement)*
- A diagnosis of food protein-induced constipation in breastfed infants is based on the clinical improvement of the constipation during maternal elimination diet followed by the recurrence of symptoms after reintroduction of the culprit food (see Section 3; *100% Agreement*)

6 | DOES COLIC IMPROVE WITH DIETARY ELIMINATION IN BREASTFED INFANTS?

Over the years, the definition of infantile colic has changed. The Wessel criteria, which required the rule of 'three' for a diagnosis (crying for more than three hours/day, during more than three days/week over >3 weeks), have been replaced by the recent Rome IV consensus (Table 6) and differ for clinical and research purposes.[67,68] In about 5% of these crying and distressed infants, an underlying organic disease may be present.[69]

Infantile colic, in combination with atopic dermatitis, abnormal stool patterns, colitis with rectal bleeding, GORD, wheezing and coughing are reported as symptoms of CMA in exclusively breastfed infants.[70] A 2- to 4-week maternal elimination diet or switching to a hypoallergenic formula has been recommended for the confirmation of possible aetiologies of prolonged crying.[71]

Elimination of cow's milk from the mother's diet in relation to food protein-induced colic remains controversial; because of differences in study design, poor characterization of atopy and different approaches to dietary elimination, no firm conclusions can be drawn. [72] In crying breastfed babies, two trials were performed, with both a positive effect and a negative effect of dietary elimination of cow's milk from a mother's diet having been reported.[73,74] In the study by Evans et al[74] where no effect was seen, cow's milk was replaced by soya (a possible allergen), and interestingly, the frequency of colic was significantly higher on days on which mothers reported eating chocolate or fruit. In a publication from 2010, cow's milk, eggs, peanuts, tree nuts, wheat, soya and fish were excluded from the maternal diet from infants presenting with colic within the first 6 weeks of life. This resulted in a significant improvement by days 8 and 9 in the low-allergen group (74% vs 37%), an absolute risk reduction of 37% (95% confidence interval: 18%-56%).[73] The latter study also found that crying/fussing duration per 48 hours was reduced by a substantially greater amount in the low-allergen group.[73] However, mothers' subjective assessments of the responses to diet indicated little difference between the groups. Many other studies have been performed on the efficacy of hypoallergenic formulas in colic, which were outside of the scope of this review focusing on breastfed infants.

Therefore, in the vast majority of breastfed infants with colic, food allergy is unlikely to be causative; however, in those with other atopic symptoms, a 2- to 4-week maternal cow's milk elimination may be considered followed by reintroduction. If clinicians agree that objective symptoms persist despite milk avoidance and other causes have been ruled out, then further elimination of allergens (soya, wheat, eggs, peanuts, tree nuts, fish) may be considered, but should occur under the supervision of a doctor, registered dietitian/nutritionist. (see Sections 11 and 12 for further specific guidance on the elimination diet).

Practice Point—Grade C Recommendation

- There is insufficient evidence from the literature to recommend routine elimination of cow's milk from the mother's diet in an exclusively breastfed baby with infantile colic as single manifestation. *(90.91% Agreement)*
- In breastfed infants with colic symptoms, atopic comorbidities and other gastrointestinal symptoms, a cow's milk elimination diet may be warranted. *(100% Agreement)*
- The elimination of allergens from the maternal diet with observed symptom improvement should always be followed by a reintroduction to confirm the allergy (as per Section 3; *100% Agreement)*
- If objective symptoms persist despite cow's milk elimination and other causes have been ruled out, then the elimination of soya, egg and wheat may be considered under the supervision of a doctor or registered dietitian/nutritionist or suitably qualified HCP. *(90.91% Agreement)*

7 | CAN FPIES REACTIONS OCCUR IN BREASTFED INFANTS, AND IS MATERNAL DIETARY ELIMINATION REQUIRED?

Acute FPIES is defined as a non–IgE-mediated food allergy that typically presents in infancy, with repetitive protracted vomiting that occurs 1-4 hours after food ingestion. Vomiting is often accompanied by lethargy and pallor and can be followed by diarrhoea. On the other hand, chronic FPIES is defined as symptoms occurring with daily ingestion of the food (eg feeding with cow's milk or soy-based formula); symptoms include intermittent vomiting, chronic diarrhoea, poor weight gain or faltering growth. The latter diagnosis remains highly controversial, as the symptoms overlap with other non–IgE-mediated allergies, and the diagnostic criteria are being debated by a separate EAACI Task Force. Limited data exist on the presence of FPIES in breastfed infants, and conclusions about the need for maternal avoidance of FPIES trigger foods have to be drawn from one population study,[75] six retrospective studies,[76-82] four review publications,[83-86] one international guideline publication[39] and four case studies/case series. [87-90]

A recent population-based survey study by Mehr et al[75] that included 240 children with acute FPIES showed that 5% (n = 11) of the infants had symptoms of acute FPIES whilst being exclusively breastfed (ie through the maternal diet). Of this cohort, 8/10 had cow's milk as their reported trigger, two to grains and one to chicken. In the distinctly different phenotype of FPIES, Japanese researchers[78] found that up to 10% of infants reacted to the trigger food during exclusive breastfeeding. This report stated that three children with FPIES who were exclusively breastfed showed reaction to cow's milk as well as breastmilk, even after their mothers were advised to remove cow's milk from their diets.[78] These patients also developed symptoms when orally challenged with rice and/or soya, but there was no information provided about elimination to rice and/or soya.

In two of the retrospective studies, 6/64 (9.3%) and 8/16 (50%) presented with their first FPIES reaction whilst breastfed.[79,80] In the study by Yilmaz et al,[79] infants were exclusively breastfed, and mothers were advised to remove the trigger food from their diets, leading to symptom improvement. Sicherer et al[80] provided no additional information about the maternal diet or exclusivity of breastfeeding. In addition, Sopo et al[81] indicated that 63/66 (95%) of children with FPIES were breastfed, but it is unclear if the infants were exclusively breastfed when symptoms occurred.

Tan et al[88] reported one case in an infant that was exclusively breastfed who developed acute FPIES following maternal ingestion of a large amount of soya ice cream. The same study group found a further 21 breastfed infants with acute FPIES that presented whilst breastfeeding, but it was unclear if they were exclusively breastfed. Another case was triggered by infant exposure to rice and sweet potato, but due to the small amount of rice triggering severe reactions, maternal avoidance of rice and sweet potato was recommended whilst exclusively breastfeeding.[89] Two cases of chronic FPIES (in one report) associated with maternal cow's milk intake whilst exclusively breastfed were reported, and in both cases, mothers discontinued cow's milk intake whilst breastfeeding, which resulted in symptom resolution.[87] In addition to these two cases, one retrospective study found three children had symptoms of chronic FPIES triggered by maternal cow's milk intake whilst being exclusively breastfed.[77]

The four review papers give no extra guidance on maternal intake whilst breastfeeding.[83-86] However, the international guidelines do not recommend maternal avoidance of the food allergen if the infant is asymptomatic and growing well.[39]

It is important to realize that symptoms of chronic FPIES can overlap with a continuum of other non–IgE-mediated food-allergic conditions with a variety of nonspecific gastrointestinal symptoms. A number of reports consider breastmilk to be protective against the development of FPIES.[75,77,84,91] Maternal avoidance of the allergens triggering FPIES is also not common,[39] as to date only single cases were reported. [87-90]

Practice Points: Grade C Recommendations

- In Western countries, the paediatric population prevalence of diagnosed FPIES to cow's milk is 0.34%, but only 5% of this population may present with symptoms whilst exclusively breastfed.[75] It is therefore extremely uncommon to see FPIES in exclusively breastfed infants in clinical practice. *(90.91% Agreement)*
- International FPIES guidelines do not recommend routine allergen avoidance in breastfeeding mothers unless a child presents with symptoms whilst breastfeeding, in which case it may be required.[39] *(100% Agreement)*
- During breastfeeding, the amount of allergen intake may have an impact on acute FPIES.[87,88,92] *(90.91% Agreement)*
- Maternal avoidance is not required if breastfed infants only react to a food introduced during complementary feeding. *(100% Agreement)*

8 | DOES FPIAP IMPROVE WITH AN ELIMINATION DIET IN BREASTFED CHILDREN?

The exact prevalence of FPIAP in exclusively breastfed infants is unknown.[93] FPIAP is a cell-mediated inflammation of the distal sigmoid colon and rectum characterized by oedema and erosions of the mucosa; histological examination shows eosinophilic infiltration of the epithelium and lamina propria.[94] Symptoms typically present in the first three months of life, but can occur later in infancy, with the main clinical manifestation of the disease being the presence of blood in the stool (haematochezia), which may appear as grossly visible blood in the stool or may be microscopic (Table 5).[35,93,94] It is believed that the main risk factors for the disease are an immature innate and adaptive immune system seen in early infancy, altered intestinal permeability, and underlying genetic cause in combination with sensitizing foods.[95]

Although cow's milk is the most common causative food protein involved, as with other non–IgE-mediated food allergies, soya, egg and wheat may also be involved (Table 5).[96] The transfer of these allergens through breastmilk is thought to be responsible for inducing the inflammatory response and subsequent symptoms associated with this non–IgE-mediated food allergy.[97] The strict elimination of the offending food protein(s), most commonly cow's milk, from the mother's diet results in resolution of the symptoms in the majority of the cases, and tolerance to the allergenic food usually occurs by one year.[44,98-100] In the prospective cohort, Hill and Milla reviewed children with the diagnosis of FPIAP during infancy after 5-10 years. Cow's milk was successfully reintroduced in children's diet between the ages of 18 months to 8 years of life. The same occurred with other proteins (eg egg).

The majority of the previously published studies on FPIAP in breastfed infants are case series or case reports.[101] Rectal biopsy with or without rectosigmoidoscopy was performed in almost all studies (and in the majority of patients) to confirm the diagnosis of FPIAP. All studies adopted histological diagnosis based on inflammation and eosinophilic infiltration in the lamina propria [ranging from 5 to >50/high power field (hpf)] (Table 7). In the majority of studies, maternal exclusion diet was initiated with improvement of symptoms—up to 4 weeks. However, in some cases breastfeeding was stopped and a hypoallergenic formula was used. In 2013, Molnar et al [102] described a cohort of 30 children who all had their FPIAP confirmed by rectosigmoidoscopy. In this cohort, eight improved on maternal elimination diet but 22/30 did not, and an amino acid formula led to full improvement of rectal bleeding. Over half of the patients (57%) had a positive family history for atopy.[102]

In another study by Lake et al,[44] among 95 exclusively breastfed infants with FPIAP, cow's milk was implicated as a trigger in 90/95. In the only randomized controlled study by Arvola et al,[45] 40 infants (27 exclusively breastfed) with blood in the stools were randomly assigned to treatment with cow's milk elimination diet (mother and/or infant) or no treatment. From this cohort, 7/40 (18%) were diagnosed following an OFC to cow's milk as having FPIAP.

TABLE 7 Studies on infants with FPIAP that were exclusively breastfed

Reference	Paper	Numbers	Intervention and outcomes
Anveden-Hertzberg et al[101]	Case series	N = 9 exclusively breastfed infants	Mean age of onset: 5 wk Rectal biopsy findings: performed in 8 with 6/8 >50 eosinophils/HPF in the lamina propria Dietary elimination as treatment: Five infants: mothers commenced cow's milk-free diet and continued to exclusively breastfeed. One infant: mixed feed—hypoallergenic formula + breastfeeding (mother on cow's milk-free diet) One infant: no diet change for mother and breastfeeding was continued. One infant: breastfeeding was stopped and hypoallergenic formula commenced One infant: lost to follow-up Six infants from mothers on an elimination diet were reviewed in a follow-up visit—all recovered in 4 wk. The infant that no diet change also recovered but no time to recover specified
Arvola et al[45]	RCT	N = 40 (27 exclusively breasted) infants	Randomized to cow's milk-free diet (mother and infant) or normal diet. Cow's milk-free diet shortened the duration of rectal bleeding compared with normal diet only in patients diagnosed with CMA.
Fretzayas et al[135]	Case series	N = 3 exclusively breastfed infants	2 infants—Maternal elimination off cow's milk with partial improvement of symptoms and then complete improvement on amino acid formula (AAF). The third infant's symptoms resolved completely on immediate switch to AAF
Lake[44]	Case series	N = 95 exclusively breastfed infants	Biopsy found eosinophilia prominent in the lamina propria in all subjects. Dietary treatment: breastfeeding stopped for 72 h to ensure breastmilk is cow's milk free and extensively hydrolysed formula[136] given during this time. After 72hs, breastfeeding was resumed. In 11/95 rectal bleeding persisted, of that seven required extensively hydrolysed formula[136] and four AAF for symptom improvement
Lozinsky[137]	Literature review (systematic review).	N = 314 49% (153) were exclusively breastfed.	44% had eosinophilia; SPT was positive in only 10% with 14% specific IgE to cow's milk. 71.6% underwent lower endoscopy with eosinophil infiltration (between 5 and 25 hpf). Cow's milk was removed from the diet of the mother in most cases. The majority of patients were tolerant to milk by the age of 1
Lucarelli et al [97]	Case series	N = 14 exclusively breastfed infants	Diagnosis confirmed in all subjects through endoscopy and APT which was positive in all cases for cow's milk. SPT was negative in all of infants. In all 14 infants, blood in the stools persisted in spite of maternal allergen avoidance. In all, breastfeeding was stopped and an AAF commenced. Clinical and endoscopic remission was confirmed in all infants
Patenaude et al[7]	Case report	N = 1 exclusively breastfed infant	Rectal biopsy showed up to 25 eosinophils/hpf Treatment: Mixed feeding with hypoallergenic formula and maternal exclusion diet of cow's milk with improvement of symptoms
Pumberger et al[98]	Case series	N = 11 exclusively breastfed infants	5 out of 11 infants underwent endoscopy with biopsy. Eosinophilic infiltration was found in all Dietary treatment: Maternal cow's milk elimination diets commenced in all and by 3-4 d of resolution occurred in 10/11 patients By 1 y of age 8, infants were tolerating CM
Sorea et al[99]	Case series	N = 6 exclusively breastfed infants	All infants underwent a rectosigmoidoscopy with biopsy. Eosinophilic infiltrates found in 100% of the patients Mothers were started on cow's milk elimination diet, and breastfeeding was continued. All infants recovered between 6 and 23 months of age

(Continues)

TABLE 7 (Continued)

Reference	Paper	Numbers	Intervention and outcomes
Wilson et al[43]	Case report	N = 1 exclusively breastfed	Case report infant with allergic proctocolitis confirmed by rectal biopsy showing eosinophilic infiltration. Breastfeeding was stopped and EHF was commenced, with resolution of symptoms
Pittschieler[100]	Case report	N = 1 exclusively breastfed infant	Case of an infant with blood in the stools that underwent a colonoscopy and biopsy. Marked eosinophilic infiltration was found Treatment: breastfeeding was stopped, and infant was started on EHF with improvement
Sierra Salinas et al[138]	Case series	N = 13 exclusively breastfed infants	12 out of 13 infants had mucus and blood in the stools. The rectal biopsies showed acute inflammation, neutrophil infiltration and increased eosinophils in the lamina propria Maternal elimination diet was commenced—3/13 infants improved after maternal cow's milk elimination diet. The other 10 infants required AAF as treatment

As infants with FPIAP are generally healthy with only the symptom of haematochezia, it has often been argued that a dietary elimination may not be required. However, a maternal cow's milk elimination diet has been shown to shorten the duration of rectal bleeding in comparison with no maternal elimination diet and ongoing bleeding has been shown to lead to mild anaemia in infants with FPIAP.[44,45] Blood in the stool is not a normal physiological occurrence in infants, and the presence can cause great distress for parents. Sopo et al[32] have recently suggested a 'watch and wait' for 1 month before an elimination diet is commenced, to see whether spontaneous resolution occurs. This may be contemplated, but clinicians must consider also other atopic symptoms and also the distress caused to parents.

Practice Points (Grade C recommendation)

- FPIAP is one of the most common manifestations of food protein-induced non–IgE-mediated food allergies in exclusively breastfed infants. *(100% Agreement)*
- The main presenting symptom is the presence of blood in the stools, but diarrhoea and mucous may also be present. *(100% Agreement)*
- Diagnosis needs to occur as described in Section 3 through a maternal elimination diet followed by reintroduction of the allergen. *(100% Agreement)*
- It is important to rule out other causes of blood in the stools in infancy. *(100% Agreement)*
- A one-month 'watch and wait' approach may be considered in some patients depending on other atopic manifestations and the distress caused to parents.[32] (90.19% Agreement)
- Treatment, if required, is based on strict maternal exclusion of the culprit food, usually cow's milk, but other dietary antigens may also need to be eliminated—see Section 3. *(90.91% Agreement)*
- Tolerance of cow's milk (or other food triggers) is usually achieved by one year of age. *(90.91% Agreement)*

9 | DOES ALLERGIC ENTEROPATHY (FPE) IMPROVE WITH AN ELIMINATION DIET IN BREASTFED CHILDREN?

Allergic enteropathy or FPE is a type of non–IgE-mediated food allergy that affects the small intestine. It is thought to be mostly mediated by T-cell mechanisms and may present with a patchy distribution, moderate crypt hyperplasia and mild-to-moderate increase in intraepithelial lymphocytes.[103] It usually manifests in infancy starting between 2 and 9 months of age with a resolution in the majority of the cases between 1 and 3 years of age.[104] The characteristic symptoms are persistent diarrhoea and failure to thrive, and the differential diagnoses are summarized in Table 5.

There is paucity of data regarding the presence and management of FPE in breastfed infants, and information has been drawn from four case reports [17,105-109] and two review papers.[110,111] In the majority of cases, enteropathy was presumed and not confirmed through endoscopy. Higuchi et al[105] reports a case who developed protein-losing enteropathy whilst being exclusively breastfed with symptoms of poor weight gain, loose stools with mucous and peripheral oedema. Specific IgE antigens to egg yolk and white were detected, and the elimination of egg from the mother's diet and afterwards from the infant's diet during the weaning period resulted in resolution of the symptoms. Symptoms recurred upon challenge with the introduction of egg in the infant's diet; however, enteropathy was not confirmed with biopsy. In another case report, an infant presented with severe atopic dermatitis and protein-losing enteropathy that commenced during exclusively breastfeeding period. Specific IgE antigens to egg white, cow's milk, wheat and peanut were detected in serum. Elimination of the allergic food proteins from infant's diet resulted in resolution of the symptoms. As with the previous case, enteropathy was assumed, as no biopsy results were documented. A similar case was reported with presumed enteropathy (no biopsy performed), also to egg in a child that was exclusively breastfed.[106] Positive specific IgE to egg protein was detected, and the elimination of egg from mother's diet revealed resolution of the symptoms, whereas reintroduction

resulted in reappearance of the symptoms. Lastly, a case report of an exclusively breastfed 10-day-old infant with symptoms of enteropathy and marked mucosal infiltration by eosinophils in the antral, duodenal, jejunal, colonic and rectal biopsies but no abnormalities in villous length of the jejunal biopsies were published in 1990.[107] Breastmilk was stopped, and the child received an extensively hydrolysed formula and was symptom-free at 1 month of age when he was discharged. A re-challenge was not reported for this patient but he was doing well on elimination diet at 4 months of age, and by 2 months, eosinophils had disappeared from the gastrointestinal mucosa.

The occurrence of FPE in breastfed infants remains controversial, as only case studies have been published, with only one case having the diagnosis confirmed through biopsy. Although it is well known that food proteins are transferred through breastmilk, convincing evidence of this being causative of a protein-induced enteropathy is lacking. In addition, the absence of specific IgE is an expected characteristic feature of FPE and is therefore not routinely recommended (see Section 3).[112,113] However, in some of the reported cases the enteropathy was associated with IgE positivity to a specific food protein.[105,106,108] In these cases, the food-induced reaction may be a result of eosinophilic gastroenteropathy, in which food-specific IgE may be detected.[114] Additionally, one of these cases also had cutaneous erythema as an immediate reaction after the ingestion of egg white during food challenge possibly due to an IgE-mediated reaction.[105] The other case showed severe atopic dermatitis before the onset of FPE, which may be a consequence of specific IgE positivity to certain food allergens.[108]

Practice Points—Grade D Recommendation

- There is paucity of data on the existence of FPE in breastfed infants. *(100% Agreement)*
- The role of maternal dietary elimination in breastfed infants with food protein-induced enteropathy remains unclear due to limited data. *(100% Agreement)*
- When food protein is suspected, a maternal elimination diet should be implemented followed by reintroduction as described in Section 3; *100% Agreement)*
- Although limited data point towards cow's milk being the primary allergen involved, other common allergens (Section 3), including egg, have been implicated. *(100% Agreement)*
- In breastfed infants with symptoms of FPE, if there are associated symptoms of atopic dermatitis or IgE-mediated food allergy, performing SPT/specific IgE may be considered. *(100% Agreement)*

10 | DOES EOE IMPROVE ON AN ELIMINATION DIET IN BREASTFED CHILDREN?

EoE is a chronic, immune-mediated, antigen driven, inflammatory disorder defined by both clinical and histological features (Table 4).[115] The main foods known to contribute to symptoms in EoE are milk, egg, wheat and soya.[116] There is paucity of data in regard to allergens transferred via breastmilk and its impact on EoE. Only one case study reports a child, symptomatic with EoE, whilst breastfed and mother consuming cow's milk products. The child improved on a cow's milk-free diet and amino acid formula after breastfeeding was discontinued.[117] It is, therefore, unclear if the child's EoE would have improved if the mother adhered to strict cow's milk avoidance from her diet and it is unclear if the symptoms of EoE presented whilst being exclusively breastfed.

Due to a lack of data, the management of EoE in breastfed infants remains a challenge. Whilst EoE could exist in breastfeeding infants, it may not be diagnosed until later in childhood, at which time breastfeeding more commonly has stopped (see Section 3 on indications for endoscopy). It is unclear from published literature if children with EoE are able to tolerate ß–lactoglobulin present in breastmilk of cow's milk-consuming mothers. In line with this, it is, therefore, unclear if mothers of breastfeeding infants with EoE should be advised to avoid the main allergens from the maternal diet. If a hypoallergenic formula is required, an AAF is recommended based on the data on resolution of eosinophilic inflammation in ~99% of patients on such a formula.[118]

Practice Points—Insufficient data for grade recommendations

- Due to lack of evidence, advice about maternal avoidance diet, dietary elimination should be given on a case by case basis and in consultation with the overseeing physician, and preferably in conjunction with registered dietitian/nutritionist support (see Section 3). *(90.91% Agreement)*

11 | WHAT IS THE NUTRITIONAL STATUS OF MOTHERS ON AN ELIMINATION DIET OF A BREASTFED CHILD WITH NON–IGE-MEDIATED ALLERGIES?

There are no specific studies assessing the nutritional status of breastfeeding mothers on an elimination diet specifically for infants with non–IgE-mediated allergy. However, as the maternal dietary elimination advice is the same for IgE-mediated allergies, these studies were deemed appropriate for this section. A Cochrane review on maternal elimination during pregnancy and breastfeeding highlighted the negative impact of maternal elimination on nutritional status [119]; however, this was based on only one study of pregnant mothers of infants at high risk of atopic disease on an elimination diet who had significantly lower gestational weight compared to the mothers on a standard diet. On the contrary, Holmberg-Martilla et al[120] found that there was no difference in weight of breastfeeding mothers on an elimination diet (various combinations of milk, egg, wheat, fish and nuts) of atopic infants when compared to controls. There was, however, a

substantially lower intake of calcium in the elimination group and therefore a significant reduction in bone mineral density of 4%-6% at the spine and femoral neck. This study also found lower levels of omega-6 fatty acids in the elimination cohort, which was attributed to fish elimination.

To date, there is just one publication studying the impact of maternal elimination whilst breastfeeding in a cohort of infants with existing food allergies. Adams et al[121] recruited eight breastfeeding mothers of allergic children to avoid milk, egg, soya, wheat, fish and nuts under dietetic supervision and compared their nutritional status to nine breastfeeding mothers who did not require a maternal elimination diet and eight matched nonbreastfeeding women. The results indicated that the anthropometric and bone density measurements, as well as the indices of iron, protein and lipid metabolism, and trace elements were comparable and within the normal range between the two groups. However, in spite of 1000 mg calcium supplementation, bone turnover was increased as indicated by collagen type I C-terminal propeptide (ICTP), collagen type III N-terminal propeptide and osteocalcin that were significantly higher in lactating mothers with dietary restrictions compared with those without dietary restrictions. The level of the bone resorption marker, ICTP, was significantly elevated in the two groups of lactating mothers compared with controls. It does remain a concern that in spite of calcium supplementation mothers had increased bone turnover; the role of vitamin D and phosphate was not discussed in that publication.

Practice Points—Grade D recommendation

- Maternal elimination for all non–IgE-mediated food allergies should ideally be guided by a registered dietitian/nutritionist or suitably qualified HCP, as this may prevent any negative nutritional impact of the elimination diet. *(100% Agreement)*
- HCPs need to be aware that bone turnover in breastfeeding mothers may still increase in spite of calcium supplementation. Both vitamin D and phosphate need to be considered as well. *(90.91% Agreement)*
- Unnecessary elimination of food allergens may be harmful for the breastfeeding mother. *(100% Agreement)*
- Country-specific guidelines for healthy eating and vitamin D supplementation during breastfeeding should be followed in addition to individualized dietary advice. *(100% Agreement)*

12 | HOW TO REINTRODUCE/CHALLENGE FOOD ALLERGENS IN BREASTFED CHILDREN WITH NON–IGE-MEDIATED GI ALLERGIES?

The requirement to reintroduce or challenge for the confirmation and also assessment of tolerance is recommended by all current guidelines on non–IgE-mediated food allergy.[19,35] Outside of FPIES, almost no data exist on the reintroduction/challenge for confirmation of non–IgE-mediated allergies, as well as reintroduction when it is thought that tolerance may have developed. In the breastfed infant with non–IgE-mediated allergies, an additional question is raised: whether reintroduction should occur through the mother's diet or as a complementary food in the infant's diet? As there is absence of data comparing challenge/reintroduction through the maternal diet versus directly via the child, this decision should primarily be driven whether the child is still exclusively breastfed or whether complementary food/formula feed has been introduced.

The international FPIES consensus guidelines discuss both challenge for diagnosis and tolerance.[39] If a convincing history of FPIES or severe associated symptom is present, then an OFC does not need to be performed for diagnosis. For assessing tolerance, the ideal timing to perform an OFC for FPIES has not been systematically studied and varies between countries. Most data, however, suggested that an OFC may occur between 12 and 18 months of diagnosis. When a medically supervised OFCs for FPIES is considered, a food dose of 0.06-0.6 g of food protein per kilogram of body weight (typically 0.3 g/kg) in three equal doses over 30 minutes is suggested.[39] The guidelines also suggest not to exceed a total of 3 g of protein or 10 g of total food (100 mL of liquid) protein for an initial feed (which aims to approximate an age appropriate portion) and observe the patient for 4-6 hours. As FPIES in breastfed infants is rare,[39] these guidelines do not discuss the reintroduction in the breastfed child with this non–IgE-mediated allergy. However, if severe FPIES is suspected in an exclusively breastfed infant and a challenge via breastmilk is deemed necessary for identification of the food trigger, medically supervised OFC should be done.

In 2013, diagnosis and management guidelines were published in the United Kingdom on non–IgE-mediated CMA,[122] which for the first time outlined consensus on home reintroduction of cow's milk for the purposes of diagnosis (after 2-4 weeks of elimination) or to establish if the patient has achieved tolerance (6 months after diagnosis or at around 1 year of age). These guidelines (known as iMAP guidelines) were recently updated with an international expert panel and recommend in exclusively breastfed children that cow's milk products should be reintroduced in the mother's diet in previously consumed amounts and over a 1-week period.[123] The latter recommendation was made, based on data from Järvinen et al[9] in a challenge-proven non–IgE-mediated cow's milk-allergic breastfed cohort. In this cohort, 16/17 infants reacted within a mean time of 21 hours (2-80 hours) after the reintroduction of cow's milk in the lactating mother's diet. Interestingly, although symptoms reoccurred, in 7/15 children, β-lactoglobulin was not detected in breastmilk, even after the reintroduction of cow's milk. This might be explained by reactions to the other fractions of milk proteins such as casein or alpha-lactalbumin. Although it is well-known that other allergens (ie egg, soya, wheat) do transfer through breastmilk,[11,12] similar data on re-occurrence of reactions following a maternal elimination diet of egg, soya and wheat do not exist for non–IgE-mediated allergies, and therefore, reintroduction is based on individual clinical practice.

For breastfed infants with non–IgE-mediated allergies, who are already on solids, there is paucity of data. The iMAP guidelines

provide a consensus-based milk ladder, which has been constructed on the existing data that heating and fermentation reduce the allergenicity of cow's milk.[124-126] This step-wise reintroduction approach has gained popularity,[127] and although there is no evidence of its efficacy, a recent systematic review[128] suggested that there may be a benefit to quality of life[129] using this approach, although no current quality of life studies exists to support this statement. From what is known, the use of the milk ladder in a non–IgE-mediated patient is safe as long as IgE-mediated disease is ruled out first. No data are currently available in regard to the reintroduction of other allergens (egg, soya and wheat) in breastfed infants already on solids in any form, including a ladder approach.

Practice Points—Insufficient data to grade recommendations

- For FPIES, the consensus guidelines[39] on supervised OFCs (usually 12-18 months after most recent reaction), that include recommended dosages, should be used for infant eating complementary foods. It is also recommended to measure IgE to cow's milk prior to OFC, given the risk of conversion to IgE mediated CMA in FPIES. IgE-testing to other allergens may also be considered in FPIES. *(100% Agreement)*
- There are no guidelines on a "breast milk" challenge for FPIES, as it is not recommended to routinely avoid the other food allergens when breastfeeding in the majority of cases. However, if severe FPIES is suspected in an exclusively breastfed infant and a challenge via breastmilk is deemed necessary, medically supervised OFC should be undertaken. *(100% Agreement)*
- For other non–IgE–mediated conditions, where appropriate (ie presence of IgE type symptoms) IgE-mediated allergy should be excluded prior to undertaking a home-based reintroduction (see Section 3; *100% Agreement)*
- Based on the limited data and consensus guidelines, the confirmation or resolution of food allergies in exclusively breastfed infants with non–IgE-mediated food allergy other than FPIES can safely occur through the reintroduction cow's milk (6 months after diagnosis/ 1 year of age) or allergens in normally consumed amounts in the maternal diet over 1 week. *(90.91% Agreement)*
- In the non–IgE-mediated cow's milk-allergic breastfed infant that is on solids, a milk ladder may be used (not including FPIES), but HCP need to be aware that there are no data on its efficacy. *(100% Agreement)*
- There is currently no consensus on the reintroduction of other allergens in the breastfed child with a non–IgE-mediated allergy that has already been weaned onto solids. In the absence of this, the EAACI guidelines should be followed, which state that an individual approach based on the past reaction and risk profile should be followed for reintroduction.[19] *(100% Agreement)*

13 | WHAT IS THE QUALITY OF LIFE OF MOTHERS ON AN ELIMINATION DIET FOR A BREASTFED BABY WITH NON–IGE-MEDIATED ALLERGIES?

QoL[129] is a broad-ranging, multi-dimensional concept, which determined by both objective and subjective factors. These include a person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment. The World Health Organization states that QoL should be viewed in the context of the culture and value systems of the individual, in relation to their goals, expectations, standards and concerns.[129] Health-related quality of life (HRQOL) is the functional effect of a medical condition and/or its consequent therapy upon a patient. HRQOL is also subjective and multidimensional, encompassing physical and occupational function, psychological state, social interaction and somatic sensation.

Measuring HRQOL is extremely important in order to understand and document experiences of an illness over time and measure the impact of healthcare interventions on patients' lives. Where patients are too young to report on their own HRQOL, proxy measures can be taken, which are usually reported by the parent or caregiver. It is often important to also measure the QoL of the caregiver themselves, as research has found that parents of children with long-term conditions have poorer QoL than parents of healthy children.[130]

There is a large body of research examining the impact of IgE-mediated food allergies on QoL life; however, research that has looked at the impact of non–IgE-mediated food allergies is limited, particularly in relation to the breastfed infant. The gastrointestinal symptoms are common in non–IgE-mediated food allergy, and these, together with the burden of elimination diets, may have an impact on the QoL of the patient and family and should be taken into account when assessing the outcome of the elimination diet. In one of the only studies to explore non–IgE-mediated allergies, Meyer et al (2014) measured QoL in families of children on elimination diets for non-IgE food protein-induced gastrointestinal allergies.[131] Parents of 122 children completed the Family Impact module of the Paediatric Quality of Life Questionnaire (PedsQL) to measure quality of life. They found that the number of foods excluded, symptom severity, young age and nasal congestion significantly predicted QoL. However, these data were produced in a cohort of hypoallergenic formula-fed infants.

More recently, Foong et al[132] compared QoL in children with non–IgE-mediated gastrointestinal food allergy, children with IgE-mediated food allergy and children with functional abdominal pain. Parents completed the PedsQL and the Family Impact module. The cohort with non–IgE-mediated allergies had poorer physical QoL than the IgE cohort and lower emotional functioning scores than the functional abdominal pain (FAP) cohort. Similar to results reported by Meyer et al,[131] number of foods and nasal congestion significantly predicted QoL scores in the non–IgE-mediated cohort, as reported by the parents. The authors concluded that the QoL of children with non–IgE-mediated food allergies is affected in a different way to that

of FAP or IgE-mediated food allergy, which needs to be considered when treating these patients.

Research has also explored the impact of EoE on QoL. A systematic review of 22 studies by Mukkada et al,[133] 13 of which related to QoL, reported a significant impact of EoE on QoL. Only one study, by Klinnert et al,[134] measured the impact on QoL of caregivers. They conducted a longitudinal study following 96 families with children diagnosed with EoE and measured QoL using the Family Impact Questionnaire. They reported poorer QoL associated with more severe symptoms and a greater impact on the family where children were on dietary restrictions.[134] None of these studies assessed the quality of life of mothers on elimination diets for breastfed babies.

Although preliminary research has shown that dietary restrictions and maintaining an elimination diet for children with non–IgE-mediated food allergies are associated with poorer parent-reported QoL, to date no research exists examining the QoL of the mother on an elimination diet whilst breastfeeding a baby with non–IgE-mediated allergies.

Practice Points—Insufficient data to grade recommendations

- There are no published data establishing the QoL of breastfeeding mothers on an elimination diet for non-IgE mediated allergy. *(100% Agreement)*
- Healthcare professionals should be aware of the added burden and impact on QoL of adhering to an elimination diet for mother and patient. *(100% Agreement)*
- Healthcare professionals should ensure nutritional support is provided to families needing to eliminate foods from their diet during this critical developmental period. *(100% Agreement)*
- Parents managing children with non–IgE-mediated allergies on elimination diets may be especially worried or anxious; they should be reassured that such feelings are normal and encouraged to discuss their concerns with healthcare professionals. *(100% Agreement)*

14 | LIMITATIONS OF THIS TASK FORCE REPORT

This EAACI Task Force aimed to address the complex and often controversial topic of non–IgE-mediated allergies affecting the gastrointestinal tract in breastfed children. This report has many limitations, including having to limit the number of clinical questions that could be addressed through such a manuscript. The ENIGMA Task Force is, however, committed to continue to review further clinical questions in this area of non–IgE-mediated allergies using published evidence and where required reach consensus. Furthermore, it is clear from the literature published in this area that studies are either observational, retrospective or based on single cases and most studies did not specify whether infants were exclusively breastfed, which is a major limitation. As such, the Delphi method was used to achieve consensus to establish practice points and recommendations. The authors acknowledge that this does not replace well designed studies in this area, but allows for practice recommendations, whilst further studies in this area are awaited.

15 | CONCLUSIONS

Breastfeeding is the best source of nutrition for all infants and should be supported, also in infants with suspected non–IgE-mediated food allergies. Non–IgE-mediated food allergies encompass a variety of different diagnoses that affect the gastrointestinal tract. Outside of FPIAP in breastfed infants, there are limited data on the occurrence and presentation of EoE, FPE, GORD, food allergy-related constipation and colic in breastfed infants, which pose a challenge in both diagnosis and management. The ENIGMA Task Force from EAACI has used a systematic approach to generate clinical questions, search data and reach consensus on practice points pertaining to this topic, so that HCP can apply diagnostic and management recommendations in practice. The review of this topic has highlighted the requirement for further research on all areas of non–IgE-mediated food allergy in breastfed infants, including the prevalence, diagnostic criteria for the spectrum of non–IgE-mediated food-allergic diseases and most importantly the dietary management, including challenges/reintroduction.

CONFLICTS OF INTEREST

RM gives academic lectures for Mead Johnson, Danone and Nestle and academic research grant holder of Danone. ACL, OC and PU declare no conflict of interest. ANW received research grants from NIH ITN, DBV Technologies, Astellas Pharma, Nutricia, Nestle, Thermo Fisher Scientific; member of Advisory Board in Merck, Gerber; gives lectures in Nestle, Nutricia; Royalties; UpToDate. CD member of Nestlé Scientific advisory board, Danone-Nutricia Scientific advisory board, Novalac paid academic lectures, DBV Technologies stock ownership. DF gives academic lectures for Abbott, Nestle and Nutricia; received research funding from DBV Technologies and Aimmune Therapeutics; member of Advisory Board: consultant for DBV Technologies, Aimmune Therapeutics, Kaleo Pharmaceutical, INSYS Therapeutics, Aquestive, AllerGenis; received royalties; UpToDate. MCV has participated as a consultant and/or speaker for Danone, Nestlé Nutrition Institute and Aché Laboratories. RK received research grants from Allergy UK, Midlands Asthma and Allergy Research Association, consultant for Aimmune, academic lecture for Nutricia. GdT gives academic lectures on Kings College London Allergy Academy which is supported by Nutricia, Abbott and Mead Johnson. Speaker travel support to FABlogCon 2018 received from Abbott. YV is a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Biocodex, Danone, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson, United Pharmaceuticals, Wyeth. NS gives academic lectures for Mead Johnson, Danone and Nestle,

consultancy in the past for AbbVie. CV gives academic lectures for Mead Johnson, Abbot, Danone/Nutricia and Nestle; and received research support from Thermo Fisher.

AUTHOR CONTRIBUTIONS

RM involved in the literature review, writing of sections in article, Delphi consensus, merging of article sections and final submission. ACL involved in the literature review, writing of sections in article, Delphi consensus and critical review of publication. CD, RK, ANW, GdT, DF, YV, MCV, OC, PU and NS involved in writing of sections in article, Delphi consensus and critical review of publication. CV involved in the literature review, writing of sections in article, Delphi consensus and critical review of publication.

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How to cite this article: Meyer R, Chebar Lozinsky A, Fleischer DM, et al. Diagnosis and management of Non-IgE gastrointestinal allergies in breastfed infants—An EAACI Position Paper. *Allergy*. 2020;75:14–32. https://doi.org/10.1111/all.13947