DR. ROSAN MEYER (Orcid ID : 0000-0002-5710-5570)
DR. REBECCA CLAIRE KNIBB (Orcid ID : 0000-0001-5561-0904)
DR. ANNA NOWAK-WEGRZYN (Orcid ID : 0000-0002-0960-9854)

Article type : EAACI Position Paper

Diagnosis and Management of Non-IgE gastrointestinal Allergies in Breastfed Infants – an EAACI Position Paper

Short title: Non-IgE mediated allergies in Breastfed Children

Rosan Meyer, Department Paediatrics, Imperial College London, UK

Adriana Chebar Lozinsky, Department of Allergy and Immune Disorders, Murdoch Children's Research Institute, Australia.

David M. Fleischer, University of Colorado Denver School of Medicine, Children's Hospital Colorado, USA.

Mario C. Vieira, Department of Paediatrics - Pontifical Catholic University of Paraná and Center for Pediatric Gastroenterology - Hospital Pequeno Príncipe, Curitiba, Brazil

George Du Toit, Department of Pediatric Allergy, Division of Asthma, Allergy and Lung Biology, King's College London and Guy's and St. Thomas' National Health Service Foundation Trust, London, UK.

Yvan Vandenplas, KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium.

Christophe Dupont, Department of Paediatric Gastroenterology, Necker University Children Hospital, Paris, France.

Rebecca Knibb, Department of Psychology, Aston University, Birmingham, B4 7ET, UK.

Pıınar Uysal, Department of Allergy and Clinical Immunology, Adnan Menderes University, Aydin, Turkey.

Ozlem Cavkaytar, Department of Pediatric Allergy and Immunology, Istanbul Medeniyet University, Medical Faculty, Goztepe Training and Research Hospital, Istanbul, Turkey

Anna Nowak-Wegrzyn, Icahn School of Medicine at Mount Sinai, Jaffe Food Allergy Institute.

Neil Shah, Department Gastroenterology, Great Ormond Street Hospital London, UK

Carina Venter, University of Colorado Denver School of Medicine Children's Hospital Colorado, USA.

Corresponding Author: Rosan Meyer, Department Paediatrics, Imperial College London, UK, r.meyer@imperial.ac.uk. +44 7801962558, fax +44 207 904 5782

Abstract:

It is well-established that food proteins, such as egg, soya, cow's milk, and wheat, are detectable in breast milk 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 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.

Key Words: breastfed children, diagnosis of non-IgE mediated allergy, food allergy, maternal elimination, non-IgE mediated allergy.

Abbreviations:

AAF	- Amino Acid Formula
ENIGMA	- Exploring non-IgE mediated Allergy
EAACI	- European Academy of Allergy and Clinical Immunology
ESPGHAN Hepatology and Nutrition	- European Society for Paediatric Gastroenterology
FA	- Food Allergy
GORD	- Gastro-oesophageal reflux disease
HCP	- Healthcare Professional
hpf	- high power field
FPIES	- Food protein-induced enterocolitis syndrome
FPE	- Food protein-induced enteropathy
FPIAP	- Food protein-induced allergic proctocolitis
EHF	- Extensively Hydrolysed Formula
EoE	- Eosinophilic Oesophagitis
EGID	- Eosinophilic gastrointestinal disorders
FAP	- Functional abdominal pain
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
SIGN	- Scottish Intercollegiate Guidelines Network
RCT	- Randomised Controlled Trial
SIGN	- Scottish Intercollegiate Guideline Network

Definitions:
Dietary elimination: is the strict elimination of food allergens from the breast-feeding mother and in an infant that has commenced on complementary foods
Oral food challenge (OFC): physician supervised introduction of allergens
Home re-introduction: is unsupervised exposure to allergens.

Three 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.

1. Introduction

Food allergy describes adverse reactions to food with an immunological mechanism and encompasses both immunoglogulin E (IgE) and non-IgE mediated allergies.(8) 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 repeat 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).(9)

Table 1: Possible gastrointestinal symptom/signs for non-IgE mediated Allergies and consequences progression over time

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

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%).(10, 11) However, concerns have been expressed about selection bias with EuroPrevall study, as referral into that study would depend on level of awareness of clinical signs of gastrointestinal food allergy.(12) However, the true prevalence of non-IgE mediated allergy is thought to be higher, (12) as it is frequently misdiagnosed/not recognised as these symptoms commonly occur during early infancy and in breastfed infants.(13-15) Food proteins, such as cow's milk, egg, soya, and wheat, are detectable in breast milk for many hours or days after ingestion and, whilst tolerated by most infants, may sometimes elicit non-IgE mediated allergic symptoms.(16-22) 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.(23) Limited data exist outside of CMA as studies were retrospective and/or observational. (13, 24) A primary objective of the European Academy for Allergy and Clinical Immunology (25) 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 Organisation Guidelines and also avoid the negative psychological effects of an elimination diets.(6) 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, answer the most commonly asked clinical questions (Table 2), 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.

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

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 (2) reactions occur whilst 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?

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:

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

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 (2) 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

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

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 +

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, Food Protein Induced Allergic Enteropathy 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). (9, 26) 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. (27) Clinicians who adopt a single organ approach may therefore risk missing the possibility of a unifying cause such as non-IgE mediated food allergies.(28) 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.(29, 30) Although IgG and IgG4 measurement has 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.(31) Where a cessation or reduction in symptoms is noted,(15) then reintroduction or supervised oral food challenge (OFC) of the allergen is required to secure the correct diagnosis and need for ongoing exclusion.(6) The length of a diagnostic elimination diet in non-IgE mediated food allergies varies according to guidelines, but is usually between 2 to 4 weeks. Lozinsky et al.(32) found that the majority of children with non-IgE mediated allergy had improvement of symptoms within 4 weeks; however, data were mainly based on non-breastfed children.

Table 5: Characteristic non-IgE mediated food allergy disease presenting amongst breastfed infants.(26)

Non-IgE mediated Food Allergy	**Cardinal symptom**	**Additional symptoms**	**Common food allergen triggers (most common first)**	**Differential diagnoses**
FPIES	Acute FPIES: Vomiting 1-4 hours after ingestion Chronic FPIES: intermittent but progressive vomiting and diarrhoea	Acute FPIES: pallor, lethargy, hypovolemia, 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, necrotising 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 malabsorbtion, 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 most commonly recognised causative food for non-IgE mediated allergies with gastrointestinal presentation is cow's milk, which can transfer through breast milk in the form of β-lactoglobulin (levels range from 0.9 -150 ug/L),(33) a protein that is unique to cow's milk.(9, 32). However, other allergens are capable of inducing non-IgE mediated food allergies through breast milk, such as soya, wheat and egg,(19, 34) and should be considered within the history-taking and diagnostic work-up.(20)

Biomarkers have performed poorly across the spectrum of non-IgE mediated allergies. The use of atopy patch testing has been proposed to determine 'delayed sensitisation', (35) however, the latter test has yielded conflicting results.(36) 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%.(37) Lucareli et al.(7) found that atopy patch tests were positive for cow's milk in 50%, soy 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.(38, 39) Consequently, international guidelines do not recommend patch testing as a routine test for the diagnosis of non-IgE mediated allergies.(6, 40)

Similarly IgG and IgG4 testing have little established clinical validity and their use should be considered only in research studies,(41) alongside tests of gastrointestinal permeability and mucosal inflammatory markers.(42, 43) Although not specific, low albumin may support a diagnosis of enteropathy or chronic FPIES (see definition in section 7),(1) 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.(42, 43) Faecal occult blood test is also a non-specific marker and unreliable in both the diagnosis and resolution of symptoms in non-IgE mediated allergies. (44)

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 co-morbidities associated with IgE sensitisation (i.e. atopic dermatitis).(9, 45) This has been reported in FPIES, EoE and other recognised non-IgE mediated conditions (i.e. FPE, food protein-induced GORD, FPIAP), with sensitisation in publications ranging between 10% to 30% based on specific IgE and skin prick testing.(9, 32) There is, however, paucity of data on IgE sensitisation 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,(9, 45) 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.(46) Recto-sigmoidoscopy has been used to evaluate the diagnosis of FPIAP amongst 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 re-introduction.(47-49) 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 (i.e. vomiting and/or diarrhoea).(50)

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 are present when reintroduction would not occur [see International Consensus Guidelines (1)]. *(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, soy and wheat can also be transferred through breast milk 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)*
- Recto-sigmoidoscopy 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, co-morbid 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)*

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 (e.g., 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.(51) 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.(62, 63)

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 to hard and infrequent stools, painful defecation and soiling (standard definition).(64) There are very limited data in regards to food protein-induced constipation in childhood, and no publications were found pertaining 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.(65, 66) In these cases, the constipation is usually associated with presence of soft stools, excessively and prolonged straining and a soft distended abdomen.(65) 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.(67) Therefore, the release of mast cells mediators and cytokines during a food allergy reaction affect the enteric nervous system and may cause motility dysfunction.(68, 69) In the case of food protein-induced constipation, anal sphincter dysfunction and faecal retention may occur.(65, 70)

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 suggests 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 > three weeks), has been replaced by the recent Rome IV consensus (Table 6), and differs for clinical and research purposes.(71, 72) In about 5 % of these crying and distressed infants, an underlying organic disease may be present.(73)

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.(74) A 2-4 week maternal elimination diet or switching to a hypoallergenic formula has been recommended for the confirmation of possible aetiologies of prolonged crying.(75)

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 months 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 3 or more hours per day during 3 or more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician 2.Total 24-hour crying plus fussing in the selected group of infants is confirmed to be 3 hours or more when measured by at least one prospectively kept, 24-hour behaviour diary

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. (76) In crying breastfed babies, two trials were performed, with both a positive and negative effect of dietary elimination of cow's milk from a mother's diet having been reported.(77, 78) In the study by Evans et al.(78) where no effect was seen, cow's milk was replaced by soy (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 day 8 and 9 in the low-allergen group (74% vs. 37%), an absolute risk reduction of 37% (95% confidence interval: 18-56%).(77) The latter study also found that crying/fussing duration per 48 hours was reduced by a substantially greater amount in the low-allergen group.(77) 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 2-4-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 section 11 and 12 for further specific guidance on the elimination diet)

Practice Point – Grade C Recommendation

- There is insufficient evidence from 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 of cow's milk elimination and other causes have been ruled out, then the elimination of soya, egg, 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 to 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 (e.g., 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 1 population study,(2) 6 retrospective studies, (79-85) 4 review publications,(86-89) 1 international guideline publication (1) and 4 case studies/case series. (4, 5, 90, 91)

A recent population-based survey study by Mehr et al.(2) that included 240 children with acute FPIES showed that 5% (n=11) of the infants had symptoms of acute FPIES whilst being exclusively breastfed (i.e. through the maternal diet). Of this cohort, 8/10 had cow's milk as their reported trigger, 2 to grains and 1 to chicken. In the distinctly different phenotype of FPIES, Japanese researchers (81) found that up to 10% of infants reacted to the trigger food during exclusive breastfeeding. This report stated that 3 children with FPIES who were exclusively breastfed showed reaction to cow's milk as well as breast milk, even after their mothers were advised to remove cow's milk from their diets (81).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 (82, 83). In the study by Yilmaz et al.(82), infants were exclusively breastfed, and mothers were advised to remove the trigger food from their diets, leading to symptom improvement. Sicherer et al.(83) provided no additional information about the maternal diet or exclusivity of breastfeeding. In addition, Sopo et al.(84) 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.(5) 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 while exclusively breastfeeding.(90) 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 while breastfeeding, which resulted in symptom resolution(4). In addition to these two cases, one retrospective study found 3 children had symptoms of chronic FPIES triggered by maternal cow's milk intake whilst being exclusively breastfed.(80)

The four review papers give no extra guidance on maternal intake whilst breastfeeding. (86-89) However, the international guidelines do not recommend maternal avoidance of the food allergen if the infant is asymptomatic and growing well.(1)

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 non-specific gastrointestinal symptoms. A number of reports consider breast milk to be protective against the development of FPIES.(2, 80, 87, 92) Maternal avoidance of the allergens triggering FPIES is also not common (1), as to date only single cases were reported. (4, 5, 90, 91)

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.(2) 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.(1) *(100% Agreement)*
- During breastfeeding, the amount of allergen intake may have an impact on acute FPIES.(3-5) (*90.91% Agreement)*
- Maternal avoidance is not required if breast-fed 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).(40, 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 breast milk 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.(48, 98-100) In the prospective cohort, Hill and Milla reviewed children with the diagnosis of FPIAP during infancy after 5 to 10 years. Cow's milk was successful reintroduced in children's diet between the ages of 18 months to 8 years of life. The same occurred with other proteins (e.g., 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 recto-sigmoidoscopy 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 recto-sigmoidoscoppy. In this cohort, 8 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.(48), among 95 exclusively breastfed infants with FPIAP, cow's milk was implicated as a trigger in 90/95. In the only randomised controlled study by Arvola et al.(49), 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.

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 to no maternal elimination diet and ongoing bleeding has been shown to lead to mild anaemia in infants with FPIAP.(48, 49) Blood in the stool is not a normal physiological occurrence in infants and the presence can cause great distress for parents. Sopo et al.(7) has 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.(7) (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)*

Table 7. Studies on infants with FPIAP that were exclusively breastfed

Reference	Paper	Numbers	Intervention and Outcomes
Anveden-Hertzberg et al. 1996(101)	Case series	N= 9 exclusively breastfed infants	Mean age of onset: 5 weeks. Rectal biopsy findings: performed in 8 with 6/8 > 50 eosinophils/HPF in the lamina propria. Dietary elimination as treatment: 5 infants: mothers commenced cow's milk free diet and continued to exclusively breastfeed. 1 infant: mixed feed – hypoallergenic formula + breastfeeding (mother on cow's milk free diet). 1 infant: no diet change for mother and breastfeeding was continued. 1 infant: breastfeeding was stopped and hypoallergenic formula commenced. 1 infant: lost to follow up 6 infants from mothers on an elimination diet were reviewed in a follow-up visit – all recovered in 4 weeks. The infant that no diet change also recovered but no time to recover specified.
Arvola et al. 2006 (49)	RCT	N=40 (27 exclusively breasted) infants	Randomised 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. 2011(103)	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 A. 2000(48)	Case series	N=95 exclusively breastfed infants	Biopsy found eosinophilia prominent in the lamina propria in all subjects. Dietary treatment: breastfeeding stopped for 72 hours to ensure breast milk is cow's milk free and extensively hydrolysed formula (104) given during this time. After 72hs breastfeeding was resumed. In 11/95 rectal bleeding persisted, of that 7 required extensively hydrolysed formula (104) and 4 AAF for symptoms improvement.
Lozinsky AC. 2014 (105)	Literature review (systematic review).	N= 314 49%(153) were exclusively breastfed.	44% had eosinophilia; SPT were positive in only 10% with 14% specific IgE to cow's milk. 71.6% underwent lower endoscopy with eosinophil infiltration (between 5-25hpf). 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. 2011 (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. 2000 (14)	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. 2001 (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 day 3-4 days resolution occurred in 10/11 patients. By 1 year of age 8 infants were tolerating CM.
Sorea et al. 2003 (99)	Case series	N=6 exclusively breastfed infants	All infants underwent a recto-sigmoidoscopy 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.
Wilson et al. 1990 (47)	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 K. 1990 (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. 2006 (106)	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.

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 (107). It usually manifests in infancy starting between 2 and 9 months of age with a resolution in the majority of the cases between 1 to 3 years of age (108). 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 4 case reports (24, 109-113) and 2 review papers (114, 115). In the majority of cases, enteropathy was presumed

and not confirmed through endoscopy. Higuchi et al.(109) 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 (110). 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 was published in 1990 (111). Breast milk 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 1 case having the diagnosis confirmed through biopsy. Although, it is well known that food proteins are transferred through breast milk, 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).(116, 117) However, in some of the reported cases the enteropathy was associated with IgE positivity to a specific food protein.(109, 110, 112) In these cases the food-induced reaction may be a result of eosinophilic gastroenteropathy, in which food specific IgE may be detected. (118) 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.(109) 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.(112)

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 re-introduction as described by section 3. *(100% Agreement)*
- Although limited data points 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).(119) The main foods known to contribute to symptoms in EoE are milk, egg, wheat and soya.(120) There is paucity of data in regards to allergens transferred via breast milk and its impact on EoE. Only one case study reports a child, symptomatic with EoE, while 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.(121) 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 breast fed.

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 breast milk 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 approximately 99% of patients on such a formula.(122)

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 (123); 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.(124) 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.(125) recruited 8 breastfeeding mothers of allergic children to avoid milk, egg, soya, wheat, fish and nuts under dietetic supervision and compared their nutritional status to 9 breastfeeding mothers who did not require a maternal elimination diet and

8 matched non-breastfeeding 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 turn-over; 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 individualised dietary

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.(6, 40) Outside of FPIES, almost no data exist on the reintroduction/challenge for confirmation of non-IgE mediated allergies, as well as re-introduction 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.(1) If a convincing history of FPIES or severe associated symptom are 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 12-18 months of diagnosis. When a medically-supervised OFCs for FPIES is considered, a food dose of 0.06 to 0.6 g of food protein per kilogram of body weight (typically 0.3 g/kg) in 3 equal doses over 30 minutes is suggested.(1) 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 to 6 hours. As FPIES in breastfed infants is rare,(1) 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 breast-fed infant and a challenge via breast milk 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,(126) 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.(127) The latter recommendation was made, based on data from Järvinen et al.(16) 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, ß-lactoglobulin was not detected in breast milk, 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 (i.e. egg, soya, wheat) do transfer through breast milk,(18, 19) 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 re-introduction is based on individual clinical practice.

For breastfed infants with non IgE-mediated allergies, who are already on solids, there is a paucity of data. The iMAP guidelines provide a consensus-based milk ladder, which has been constructed on the existing data that heating and fermentation reduces the allergenicity of cow's milk.(128-130) This step-wise reintroduction approach has gained popularity, (131) and although there is no evidence of its efficacy, a recent systematic review (132) suggested that there may be a benefit to quality of life (133) using this approach, although no current quality of life studies exist 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 regards 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 (1) 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 breast-fed infant and a challenge via breast milk is deemed necessary, medically supervised OFC should be undertaken. *(100% Agreement)*
- For other non-IgE mediated conditions, where appropriate (i.e. presence of IgE type symptoms) IgE-mediated allergy should be excluded prior to undertaking a home-based re-introduction (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.(6) *(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 (133) 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 Organisation 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.(133) 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.(134)

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. 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.(135) 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.(136) 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.(135) 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.(137) 13 of which related to QoL, reported a significant impact of EoE on QoL. Only one study, by Klinnert et al.,(138) 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.(138) None of these studies assessed the quality of life of mothers on elimination diets for breast fed babies.

Although preliminary research has shown that dietary restrictions and maintaining an elimination diet for children with non-IgE mediated food allergies is 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)*

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.

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 encompasses a variety of different diagnoses that affect the gastrointestinal tract. Outside of FPIAP in breastfed infants, there is limited data on the occurrence and presentation of EoE, FPE, GORD, food allergy related constipation and colic in breastfed infants, which poses 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 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 breast fed 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

Contributions of authors

RM – literature review, writing of sections in article, Delphi consensus, merging of article sections and final submission.

ACL – literature review, writing of sections in article, Delphi consensus and critical review of publication.

CD - writing of sections in article, Delphi consensus and critical review of publication.

ANW- writing of sections in article, Delphi consensus and critical review of publication.

DF – writing of sections in article, Delphi consensus and critical review of publication.

MCV- writing of sections in article, Delphi consensus and critical review of publication.

RK – writing of sections in article, Delphi consensus and critical review of publication.

GdT – writing of sections in article, Delphi consensus and critical review of publication.

YV - writing of sections in article, Delphi consensus and critical review of publication.

OC - writing of sections in article, Delphi consensus and critical review of publication.

PU – writing of sections in article, Delphi consensus and critical review of publication.

NS - writing of sections in article, Delphi consensus and critical review of publication.

CV - literature review, writing of sections in article, Delphi consensus and critical review of publication.

Conflict of interest

RM – academic lectures for Mead Johnson, Danone and Nestle and academic research grant holder of Danone

ACL – No conflict of Interest

ANW- research grants: NIH ITN, DBV Technologies, Astellas Pharma, Nutricia, Nestle, Thermofisher Scientific; Advisory Board: Merck, Gerber; Lectures: Nestle, Nutricia; Royalties; UpToDate

CD - Nestlé Scientific advisory board, Danone-Nutricia Scientific advisory board, Novalac paid academic lectures, DBV Technologies stock ownership

DF – academic lectures for Abbott, Nestle and Nutricia. research funding from DBV Technologies and Aimmune Therapeutics; Advisory Board: consultant for DBV Technologies, Aimmune Therapeutics, Kaleo Pharmaceutical, INSYS Therapeutics, Aquestive, AllerGenis; Royalties; UpToDate

MCV- has participated as a consultant and/or speaker for Danone, Nestlé Nutrition Institute and Aché Laboratories

RK – research grants from Allergy UK, Midlands Asthma and Allergy Research Association, consultant for AImmune, academic lecture for Nutricia

GdT – academic lectures on Kings College London Allergy Academy which is supported by Nutrica, Abbott and Mead Johnson. Speaker travel support to FABlogCon 2018 received from Abbott

YV - 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.

OC - No Conflict of Interest

PU – No Conflict of Interest

NS - academic lectures for Mead Johnson, Danone and Nestle, consultancy in the past for Abvvie

CV - academic lectures for Mead Johnson, Abbot, Danone/Nutricia and Nestle. Research support from Thermofisher

References

1. Nowak-Wegrzyn A, Chehade M, Groetch M, Spergel JM, Wood RA, Allen K, et al. International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome: Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma, and Immunology. J Allergy Clin Immunol. 2017;139:1111-26.
2. Mehr S, Frith K, Barnes EH, Campbell DE, Group FS. Food protein-induced enterocolitis syndrome in Australia: A population-based study, 2012-2014. J Allergy Clin Immunol. 2017;140(5):1323-30.
3. Miceli SS, Greco M, Monaco S, Tripodi S, Calvani M. Food protein-induced enterocolitis syndrome, from practice to theory. Expert Rev Clin Immunol. 2013;9(8):707-15.
4. Miceli Sopo S, Monaco S, Greco M, Scala G. Chronic food protein-induced enterocolitis syndrome caused by cow's milk proteins passed through breast milk. Int Arch Allergy Immunol. 2014;164(3):207-9.
5. Tan J, Campbell D, Mehr S. Food protein-induced enterocolitis syndrome in an exclusively breast-fed infant-an uncommon entity. J Allergy Clin Immunol. 2012;129(3):873, author-4.
6. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008-25.
7. Miceli Sopo S, Monaco S, Bersani G, Romano A, Fantacci C. Proposal for management of the infant with suspected food protein-induced allergic proctocolitis. Pediatr Allergy Immunol. 2018;29(2):215-8.
8. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832-6.
9. Meyer R, Fleming C, Dominguez-Ortega G, Lindley K, Michaelis L, Thapar N, et al. Manifestations of food protein induced gastrointestinal allergies presenting to a single tertiary paediatric gastroenterology unit. World Allergy Organ J. 2013;6(1):13.

10. Schoemaker AA, Sprikkelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children--EuroPrevall birth cohort. Allergy. 2015;70(8):963-72.
11. Grimshaw KE, Bryant T, Oliver EM, Martin J, Maskell J, Kemp T, et al. Incidence and risk factors for food hypersensitivity in UK infants: results from a birth cohort study. ClinTranslAllergy. 2015;6:1.
12. Koletzko S, Heine RG, Grimshaw KE, Beyer K, Grabenhenrich L, Keil T, et al. Non-IgE mediated cow's milk allergy in Euro Prevall. Allergy. 2015;70(12):1679-80.
13. Hill DJ, Cameron DJ, Francis DE, Gonzalez-Andaya AM, Hosking CS. Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance. J Allergy ClinImmunol. 1995;96(3):386-94.
14. Hill DJ, Hosking CS. The cow milk allergy complex: overlapping disease profiles in infancy. EurJ Clin Nutr. 1995;49 Suppl 1:S1-12.
15. Petrus NC, Schoemaker AF, van Hoek MW, Jansen L, Jansen-van der Weide MC, van Aalderen WM, et al. Remaining symptoms in half the children treated for milk allergy. Eur J Pediatr. 2015;174(6):759-65.
16. Jarvinen KM, Makinen-Kiljunen S, Suomalainen H. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. J Pediatr. 1999;135(4):506-12.
17. Restani P, Gaiaschi A, Plebani A, Beretta B, Velona T, Cavagni G, et al. Evaluation of the presence of bovine proteins in human milk as a possible cause of allergic symptoms in breast-fed children. Ann Allergy Asthma Immunol. 2000;84(3):353-60.
18. Palmer DJ, Gold MS, Makrides M. Effect of cooked and raw egg consumption on ovalbumin content of human milk: a randomized, double-blind, cross-over trial. Clin Exp Allergy. 2005;35(2):173-8.
19. Franke AA, Halm BM, Custer LJ, Tatsumura Y, Hebshi S. Isoflavones in breastfed infants after mothers consume soy. Am J Clin Nutr. 2006;84(2):406-13.
20. Martin-Munoz MF, Pineda F, Garcia Parrado G, Guillen D, Rivero D, Belver T, et al. Food allergy in breastfeeding babies. Hidden allergens in human milk. Eur Ann Allergy Clin Immunol. 2016;48(4):123-8.
21. Matangkasombut P, Padungpak S, Thaloengsok S, Kamchaisatian W, Sasisakulporn C, Jotikasthira W, et al. Detection of beta-lactoglobulin in human breast-milk 7 days after cow milk ingestion. Paediatr Int Child Health. 2017;37(3):199-203.
22. Vadas P, Wei H, Burks AW, Perelman B. Detection of Peanut Allergens in Breast Milk of Lactating Women. JAMA. 2001;285:1746-8.
23. Host A, Husby S, Osterballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. Incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. Acta Paediatr Scand. 1988;77(5):663-70.
24. Latcham F, Merino F, Lang A, Garvey J, Thomson MA, Walker-Smith JA, et al. A consistent pattern of minor immunodeficiency and subtle enteropathy in children with multiple food allergy. J Pediatr. 2003;143(1):39-47.
25. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69(8):992-1007.
26. Nowak-Wegrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. J Allergy ClinImmunol. 2015;135(5):1114-24.
27. Iacono G, Merolla R, D'Amico D, Bonci E, Cavataio F, Di PL, et al. Gastrointestinal symptoms in infancy: a population-based prospective study. Dig Liver Dis. 2005;37(6):432-8.
28. Heine RG. Gastrointestinal food allergies. ChemImmunol Allergy. 2015;101:171-80.

29. Mehl A, Rolinck-Werninghaus C, Staden U, Verstege A, Wahn U, Beyer K, et al. The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. J Allergy Clin Immunol. 2006;118(4):923-9.
30. Turjanmaa K, Darsow U, Niggemann B, Rance F, Vanto T, Werfel T. EAACI/GA2LEN position paper: present status of the atopy patch test. Allergy. 2006;61(12):1377-84.
31. Skypala IJ, Venter C, Meyer R, deJong NW, Fox AT, Groetch M, et al. The development of a standardised diet history tool to support the diagnosis of food allergy. ClinTranslAllergy. 2015;5:7.
32. Chebar Lozinsky A, Meyer R, De KC, Dziubak R, Godwin H, Reeve K, et al. Time to symptom improvement using elimination diets in non-IgE mediated gastrointestinal food allergies. Pediatr Allergy Immunol. 2015;2(3):317-29.
33. Host A, Halken S. Hypoallergenic formulas--when, to whom and how long: after more than 15 years we know the right indication! Allergy. 2004;59 Suppl 78:45-52.
34. Cant A, Marsden RA, Kilshaw PJ. Egg and cows' milk hypersensitivity in exclusively breast fed infants with eczema, and detection of egg protein in breast milk. Br Med J (Clin Res Ed). 1985;291(6500):932-5.
35. Cudowska B, Kaczmarski M. Atopy patch test in the diagnosis of food allergy in children with gastrointestinal symptoms. AdvMed Sci. 2010;55(2):153-60.
36. Niggemann B, Reibel S, Roehr CC, Felger D, Ziegert M, Sommerfeld C, et al. Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. J Allergy Clin Immunol. 2001;108(6):1053-8.
37. Jarvinen KM, Caubet JC, Sickles L, Ford LS, Sampson HA, Nowak-Wegrzyn A. Poor utility of atopy patch test in predicting tolerance development in food protein-induced enterocolitis syndrome. AnnAllergy Asthma Immunol. 2012;109(3):221-2.
38. Gonzaga TA, Alves FA, Cheik MFA, de Barros CP, Rezende E, Segundo GRS. Low efficacy of atopy patch test in predicting tolerance development in non-IgE-mediated cow's milk allergy. Allergol Immunopathol (Madr). 2017.
39. Nocerino R, Granata V, Di Costanzo M, Pezzella V, Leone L, Passariello A, et al. Atopy patch tests are useful to predict oral tolerance in children with gastrointestinal symptoms related to non-IgE-mediated cow's milk allergy. Allergy. 2013;68(2):246-8.
40. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-58.
41. Bock SA. AAAAI support of the EAACI Position Paper on IgG4. J Allergy Clin Immunol. 2010;125(6):1410.
42. Campeotto F, Butel MJ, Kalach N, Derrieux S, Aubert-Jacquin C, Barbot L, et al. High faecal calprotectin concentrations in newborn infants. Arch Dis Child Fetal Neonatal Ed. 2004;89(4):F353-5.
43. Poullis A, Foster R, Northfield TC, Mendall MA. Review article: faecal markers in the assessment of activity in inflammatory bowel disease. Aliment Pharmacol Ther. 2002;16(4):675-81.
44. Feuille E, Nowak-Wegrzyn A. Definition, etiology, and diagnosis of food protein-induced enterocolitis syndrome. Curr OpinAllergy ClinImmunol. 2014;14(3):222-8.
45. Bardana EJ, Jr. Immunoglobulin E- (IgE) and non-IgE-mediated reactions in the pathogenesis of atopic eczema/dermatitis syndrome (AEDS). Allergy. 2004;59 Suppl 78:25-9.
46. Yan BM, Shaffer EA. Primary eosinophilic disorders of the gastrointestinal tract. Gut. 2009;58(5):721-32.

47. Wilson NW, Self TW, Hamburger RN. Severe cow's milk induced colitis in an exclusively breast-fed neonate. Case report and clinical review of cow's milk allergy. Clin Pediatr (Phila). 1990;29(2):77-80.
48. Lake AM. Food-induced eosinophilic proctocolitis. J Pediatr GastroenterolNutr. 2000;30 Suppl:S58-S60.
49. Arvola T, Ruuska T, Keranen J, Hyoty H, Salminen S, Isolauri E. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. Pediatrics. 2006;117(4):e760-e8.
50. Shah N, Foong RM, Borrelli O, Volonaki E, Dziubak R, Meyer R, et al. Histological findings in infants with Gastrointestinal food allergy are associated with specific gastrointestinal symptoms; retrospective review from a tertiary centre. BMC Clin Pathol. 2015;15:12.
51. Rosen R, Vandenplas Y, Di Lorenzo C, Staianono A, Thapar N, Tabbers M, et al. NASPGHAN-ESPGHAN Guidelines for Evaluation and Treatment of Gastro-Esophageal Reflux in Infants and Children. J Pediatr Gastroenterol Nutr. 2018;Accepted.
52. Vandenplas Y, Abkari A, Bellaiche M, Benninga M, Chouraqui JP, Cokura F, et al. Prevalence and Health Outcomes of Functional Gastrointestinal Symptoms in Infants From Birth to 12 Months of Age. J Pediatr Gastroenterol Nutr. 2015;61(5):531-7.
53. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al. Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines. J Pediatr Gastroenterol Nutr. 2012;55(2):221-9.
54. Salvatore S, Vandenplas Y. Gastroesophageal reflux and cow milk allergy: is there a link? Pediatrics. 2002;110(5):972-84.
55. Borrelli O, Mancini V, Thapar N, Giorgio V, Elawad M, Hill S, et al. Cow's milk challenge increases weakly acidic reflux in children with cow's milk allergy and gastroesophageal reflux disease. J Pediatr. 2012;161(3):476-81.
56. Semeniuk J, Kaczmarski M. Acid gastroesophageal reflux and intensity of symptoms in children with gastroesophageal reflux disease. Comparison of primary gastroesophageal reflux and gastroesophageal reflux secondary to food allergy. Adv Med Sci. 2008;53(2):293-9.
57. Iacono G, Carroccio A, Cavataio F, Montalto G, Kazmierska I, Lorello D, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol. 1996;97(3):822-7.
58. Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Campagna P, et al. Gastroesophageal reflux associated with cow's milk allergy in infants: which diagnostic examinations are useful? Am J Gastroenterol. 1996;91(6):1215-20.
59. McLain BI, Cameron DJ, Barnes GL. Is cow's milk protein intolerance a cause of gastro-oesophageal reflux in infancy? J Paediatr Child Health. 1994;30(4):316-8.
60. Billeaud C, Guillet J, Sandler B. Gastric emptying in infants with or without gastro-oesophageal reflux according to the type of milk. Eur J Clin Nutr. 1990;44(8):577-83.
61. Chen PL, Soto-Ramirez N, Zhang H, Karmaus W. Association Between Infant Feeding Modes and Gastroesophageal Reflux: A Repeated Measurement Analysis of the Infant Feeding Practices Study II. J Hum Lact. 2017;33(2):267-77.
62. Rommel N, De Meyer A, Feenstra L, Veereman-Wauters G. The Complexity of Feeding Problems in 700 Infants and Young Children Presenting to a Tertiary Care Institution. JPGN. 2003;37:75-84.
63. Mehta P, Furuta GT, Brennan T, Henry ML, Maune NC, Sundaram SS, et al. Nutritional State and Feeding Behaviors of Children With Eosinophilic Esophagitis and Gastroesophageal Reflux Disease. J Pediatr Gastroenterol Nutr. 2017.
64. Loening-Baucke V. Prevalence, symptoms and outcome of constipation in infants and toddlers. J Pediatr. 2005;146(3):359-63.

65. Heine RG. Allergic gastrointestinal motility disorders in infancy and early childhood. PediatrAllergy Immunol. 2008;19(5):383-91.
66. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014;58(2):258-74.
67. Ito A, Hagiyama M, Oonuma J, Murakami Y, Yokozaki H, Takaki M. Involvement of the SgIGSF/Necl-2 adhesion molecule in degranulation of mesenteric mast cells. J Neuroimmunol. 2007;184(1-2):209-13.
68. Wood JD. Histamine, mast cells, and the enteric nervous system in the irritable bowel syndrome, enteritis, and food allergies. Gut. 2006;55(4):445-7.
69. Rothenberg ME, Cohen MB. An eosinophil hypothesis for functional dyspepsia. Clin Gastroenterol Hepatol. 2007;5(10):1147-8.
70. Borrelli O, Barbara G, Di NG, Cremon C, Lucarelli S, Frediani T, et al. Neuroimmune interaction and anorectal motility in children with food allergy-related chronic constipation. Am J Gastroenterol. 2009;104(2):454-63.
71. Wessel MA, Cobb JC, Jackson EB, Harris GS, Jr., Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. Pediatrics. 1954;14(5):421-35.
72. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. Gastroenterology. 2016.
73. Freedman SB, Al-Harthy N, Thull-Freedman J. The crying infant: diagnostic testing and frequency of serious underlying disease. Pediatrics. 2009;123(3):841-8.
74. Jarvinen KM, Suomalainen H. Development of cow's milk allergy in breast-fed infants. Clin Exp Allergy. 2001;31(7):978-87.
75. Heine RG. Gastroesophageal reflux disease, colic and constipation in infants with food allergy. Curr Opin Allergy Clin Immunol. 2006;6(3):220-5.
76. Nocerino R, Pezzella V, Cosenza L, Amoroso A, Di Scala C, Amato F, et al. The controversial role of food allergy in infantile colic: evidence and clinical management. Nutrients. 2015;7(3):2015-25.
77. Hill DJ, Roy N, Heine RG, Hosking CS, Francis DE, Brown J, et al. Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. Pediatrics. 2005;116(5):e709-15.
78. Evans RW, Fergusson DM, Allardyce RA, Taylor B. Maternal diet and infantile colic in breast-fed infants. Lancet. 1981;1(8234):1340-2.
79. Ludman S, Harmon M, Whiting D, Du TG. Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom. AnnAllergy Asthma Immunol. 2014.
80. Caubet JC, Ford LS, Sickles L, Jarvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy ClinImmunol. 2014.
81. Nomura I, Morita H, Ohya Y, Saito H, Matsumoto K. Non-IgE-mediated gastrointestinal food allergies: distinct differences in clinical phenotype between Western countries and Japan. Curr Allergy Asthma Rep. 2012;12(4):297-303.
82. Arik Yilmaz E, Soyer O, Cavkaytar O, Karaatmaca B, Buyuktiryaki B, Sahiner UM, et al. Characteristics of children with food protein-induced enterocolitis and allergic proctocolitis. Allergy Asthma Proc. 2017;38(1):54-62.
83. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. J Pediatr. 1998;133(2):214-9.
84. Sopo SM, Giorgio V, Dello II, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. Clin Exp Allergy. 2012;42(8):1257-65.

85. Wang KY, Lee J, Cianferoni A, Ruffner MA, Dean A, Molleston JM, et al. Food Protein-Induced Enterocolitis Syndrome Food Challenges: Experience from a Large Referral Center. J Allergy Clin Immunol Pract. 2018.
86. Venter C, Groetch M. Nutritional management of food protein-induced enterocolitis syndrome. Curr OpinAllergy ClinImmunol. 2014.
87. Leonard SA, Nowak-Wegrzyn A. Food Protein-Induced Enterocolitis Syndrome. Pediatr Clin North Am. 2015;62(6):1463-77.
88. Wang J, Fiocchi A. Unmet needs in food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2014;14(3):206-7.
89. Gryboski JD. Gastrointestinal milk allergy in infants. Pediatrics. 1967;40(3):354-62.
90. Mane SK, Hollister ME, Bahna SL. Food protein-induced enterocolitis syndrome to trivial oral mucosal contact. Eur J Pediatr. 2014;173(12):1545-7.
91. Monti G, Castagno E, Liguori SA, Lupica MM, Tarasco V, Viola S, et al. Food protein-induced enterocolitis syndrome by cow's milk proteins passed through breast milk. J Allergy ClinImmunol. 2011;127(3):679-80.
92. Leonard SA, Nowak-Wegrzyn A. Clinical diagnosis and management of food protein-induced enterocolitis syndrome. Curr OpinPediatr. 2012;24(6):739-45.
93. Academy of Breastfeeding. ABM Clinical Protocol 24: Allergic Proctocolitis in the Exclusively Breastfed Infant. Breastfeed Med. 2011;6(6):435-40.
94. Odze RD, Bines J, Leichtner AM, Goldman H, Antonioli DA. Allergic proctocolitis in infants: a prospective clinicopathologic biopsy study. Hum Pathol. 1993;24(6):668-74.
95. Tsabouri S, Nicolaou N, Douros K, Papadopoulou A, Priftis KN. Food Protein Induced Proctocolitis: A Benign Condition with an Obscure Immunologic Mechanism. Endocr Metab Immune Disord Drug Targets. 2017;17(1):32-7.
96. Atanaskovic-Markovic M. Refractory proctocolitis in the exclusively breast-fed infants. EndocrMetab ImmuneDisordDrug Targets. 2014;14(1):63-6.
97. Lucarelli S, Di NG, Lastrucci G, D'Alfonso Y, Marcheggiano A, Federici T, et al. Allergic proctocolitis refractory to maternal hypoallergenic diet in exclusively breast-fed infants: a clinical observation. BMC Gastroenterol. 2011;11:82.
98. Pumberger W, Pomberger G, Geissler W. Proctocolitis in breast fed infants: a contribution to differential diagnosis of haematochezia in early childhood. Postgrad Med J. 2001;77(906):252-4.
99. Sorea S, Dabadie A, Bridoux-Henno L, Balancon-Morival M, Jouan H, Le Gall E. Hemorrhagic colitis in exclusively breast-fed infants. Arch Pediatr. 2003;10(9):772-5.
100. Pittschieler K. Cow's milk protein-induced colitis in the breast-fed infant. J Pediatr Gastroenterol Nutr. 1990;10(4):548-9.
101. Anveden-Hertzberg L, Finkel Y, Sandstedt B, Karpe B. Proctocolitis in exclusively breast-fed infants. Eur J Pediatr. 1996;155(6):464-7.
102. Molnar K, Pinter P, Gyorffy H, Cseh A, Muller KE, Arato A, et al. Characteristics of allergic colitis in breast-fed infants in the absence of cow's milk allergy. World J Gastroenterol. 2013;19(24):3824-30.
103. Fretzayas A, Moustaki M, Priftis KN, Attilakos A, Lapa E, Nicolaidou P. Thrombocytosis as an overt sign of cow's milk allergic proctocolitis. Allergol Immunopathol (Madr). 2011;39(6):381-3.
104. Asai Y, Yanishevsky Y, Clarke A, La VS, Delaney JS, Alizadehfar R, et al. Rate, triggers, severity and management of anaphylaxis in adults treated in a Canadian emergency department. Int Arch Allergy Immunol. 2014;164(3):246-52.
105. Lozinsky AC, Morais MB. Eosinophilic colitis in infants. J Pediatr (Rio J). 2014;90(1):16-21.
106. Sierra Salinas C, Blasco Alonso J, Olivares Sanchez L, Barco Galvez A, del Rio Mapelli L. [Allergic colitis in exclusively breast-fed infants]. An Pediatr (Barc). 2006;64(2):158-61.

107. Nagata S, Yamashiro Y, Ohtsuka Y, Shioya T, Oguchi S, Shimizu T, et al. Quantitative analysis and immunohistochemical studies on small intestinal mucosa of food-sensitive enteropathy. J Pediatr Gastroenterol Nutr. 1995;20(1):44-8.
108. Bierme P, Nowak-Wegrzyn A, Caubet JC. Non-IgE-mediated gastrointestinal food allergies. Curr Opin Pediatr. 2017;29(6):697-703.
109. Higuchi R, Booka M, Suzuki H, Tsuno H. Protein-losing enteropathy and erythema caused by egg allergy in a breast-fed infant. Pediatr Int. 2016;58(5):422-4.
110. Kondo M, Fukao T, Omoya K, Kawamoto N, Aoki M, Teramoto T, et al. Protein-losing enteropathy associated with egg allergy in a 5-month-old boy. J Investig Allergol Clin Immunol. 2008;18(1):63-6.
111. Vandenplas Y, Quenon M, Renders F, Dab I, Loeb H. Milk-sensitive eosinophilic gastroenteritis in a 10-day-old boy. Eur J Pediatr. 1990;149(4):244-5.
112. Hwang JB, Kang YN, Won KS. Protein losing enteropathy in severe atopic dermatitis in an exclusively breast-fed infant. Pediatr Dermatol. 2009;26(5):638-9.
113. Errazuriz G, Lucero Y, Ceresa S, Gonzalez M, Rossel M, Vives A. [Clinical characteristics and management of infants less than 1-year-old suspected with allergy to cow's milk protein]. Rev Chil Pediatr. 2016;87(6):449-54.
114. Salvatore S, Hauser B, Devreker T, Arrigo S, Vandenplas Y. Chronic enteropathy and feeding in children: an update. Nutrition. 2008;24(11-12):1205-16.
115. Gibbons T, Fuchs GJ. Chronic enteropathy: clinical aspects. Nestle Nutr Workshop Ser Pediatr Program. 2007;59:89-101; discussion 2-4.
116. Feuille E, Nowak-Wegrzyn A. Food Protein-Induced Enterocolitis Syndrome, Allergic Proctocolitis, and Enteropathy. Curr Allergy Asthma Rep. 2015;15(8):50.
117. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014;134(5):1016-25 e43.
118. Mehta NM, Corkins MR, Lyman B, Malone A, Goday PS, Carney LN, et al. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. JPEN J Parenter Enteral Nutr. 2013;37(4):460-81.
119. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128(1):3-20.
120. Groetch M, Venter C, Skypala I, Vlieg-Boerstra B, Grimshaw K, Durban R, et al. Dietary Therapy and Nutrition Management of Eosinophilic Esophagitis: A Work Group Report of the American Academy of Allergy, Asthma, and Immunology. J Allergy Clin Immunol Pract. 2017;5(2):312-24 e29.
121. Topal E, Egritas O, Arga M, Sari S, Poyraz A, Bakirtas A, et al. Eosinophilic esophagitis and anaphylaxis due to cow's milk in an infant. Turk J Pediatr. 2013;55(2):222-5.
122. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995;109(5):1503-12.
123. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev. 2006;3:CD000133.
124. Holmberg-Marttila D, Sievanen H, Sarkkinen E, Erkkila A, Salminen S, Isolauri E. Do combined elimination diet and prolonged breastfeeding of an atopic infant jeopardise maternal bone health? Clin Exp Allergy. 2001;31(1):88-94.
125. Adams J, Voutilainen H, Ullner PM, Jarvinen KM. The safety of maternal elimination diets in breastfeeding mothers with food-allergic infants. Breastfeed Med. 2014;9(10):555-6.
126. Venter C, Brown T, Shah N, Walsh J, Fox AT. Diagnosis and management of non-IgE-mediated cow's milk allergy in infancy - a UK primary care practical guide. ClinTranslAllergy. 2013;3(1):23.

127. Venter C, Brown T, Meyer R, Walsh J, Shah N, Nowak-Wegrzyn A, et al. Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP-an international interpretation of the MAP (Milk Allergy in Primary Care) guideline. Clin Transl Allergy. 2017;7:26.
128. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol. 2008;122(2):342-7, 7.
129. Alessandri C, Sforza S, Palazzo P, Lambertini F, Paolella S, Zennaro D, et al. Tolerability of a fully maturated cheese in cow's milk allergic children: biochemical, immunochemical, and clinical aspects. PLoS One. 2012;7(7):e40945.
130. Uncuoglu A, Yologlu N, Simsek IE, Uyan ZS, Aydogan M. Tolerance to baked and fermented cow's milk in children with IgE-mediated and non-IgE-mediated cow's milk allergy in patients under two years of age. Allergol Immunopathol (Madr). 2017;45(6):560-6.
131. Athanasopoulou P, Deligianni E, Dean T, Dewey A, Venter C. Use of baked milk challenges and milk ladders in clinical practice: a worldwide survey of healthcare professionals. Clin Exp Allergy. 2017;47(3):135-43.
132. Lambert R, Grimshaw KEC, Ellis B, Jaitly J, Roberts G. Evidence that eating baked egg or milk influences egg or milk allergy resolution: a systematic review. Clin Exp Allergy. 2017;47(6):829-37.
133. Group W. Development of the WHOQOL: Rationale and Current Status. International Journal of Mental Health. 1994;23(3):24-56.
134. Hatzmann J, Heymans HS, Ferrer-i-Carbonell A, van Praag BM, Grootenhuis MA. Hidden consequences of success in pediatrics: parental health-related quality of life--results from the Care Project. Pediatrics. 2008;122(5):e1030-8.
135. Meyer R, Godwin H, Dziubak R, Panepinto JA, Foong RM, Bryon M, et al. The impact on quality of life on families of children on an elimination diet for Non-immunoglobulin E mediated gastrointestinal food allergies. World Allergy Organ J. 2017;10(1):8.
136. Foong RX, Meyer R, Godwin H, Dziubak R, Lozinsky AC, Reeve K, et al. Parental perception of their child's quality of life in children with non-immunoglobulin-E-mediated gastrointestinal allergies. Pediatr Allergy Immunol. 2017;28(3):251-6.
137. Mukkada V, Falk GW, Eichinger CS, King D, Todorova L, Shaheen NJ. Health-Related Quality of Life and Costs Associated With Eosinophilic Esophagitis: A Systematic Review. Clin Gastroenterol Hepatol. 2018;16(4):495-503 e8.
138. Klinnert MD, Silveira L, Harris R, Moore W, Atkins D, Fleischer DM, et al. Health-related quality of life over time in children with eosinophilic esophagitis and their families. J Pediatr Gastroenterol Nutr. 2014;59(3):308-16.