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POSITION PAPER

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Diagnosis and management of food allergy-associated gastroesophageal reflux disease in young children—EAACI position paper

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Abstract

Gastro-oesophageal reflux (GOR) and food allergy (FA) are common conditions, especially during the first 12 months of life. When GOR leads to troublesome symptoms, that affect the daily functioning of the infant and family, it is referred to as GOR disease (GORD). The role of food allergens as a cause of GORD remains controversial. This European Academy of Allergy and Clinical Immunology (EAACI) position paper aims to review the evidence for FA-associated GORD in young children and translate this into clinical practice that guides healthcare professionals through the diagnosis of suspected FA-associated GORD and medical and dietary management. The task force (TF) on non-IgE mediated allergy consists of EAACI experts in paediatric

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Abbreviations: AAF, amino acid formula; CMA, cow's milk allergy; CMP, cow's milk protein; EAACI, European Academy for Allergy and Clinical Immunology; EHF, extensively hydrolyse formula; EoE, eosinophilic oesophagitis; ESPGHAN, European Society for Paediatric Gastroenterology Heptalogy and Nutrition; FA, food allergy; GI, gastrointestinal; GOR, gastro-oesophageal reflux; GORD, gastro-oesophageal reflux disease; H2RA, histamine 2-receptor antagonists; LOS, lower oesophageal sphincter; NASPGHAN, North American Society for Paediatric Gastroenterology Hepatology and Nutrition; NICE, National Institute for Health and Care Excellence; PPI, proton-pump inhibitor; TF, task force.

gastroenterology, allergy, dietetics and psychology from Europe, United Kingdom, United States, Turkey and Brazil. Six clinical questions were formulated, amended and approved by the TF to guide this publication. A systematic literature search using PubMed, Cochrane and EMBASE databases (until June 2021) using predefined inclusion criteria based on the 6 questions was used. The TF also gained access to the database from the European Society of Paediatric Gastroenterology and Hepatology working group, who published guidelines on GORD and ensured that all publications used within that position paper were included. For each of the 6 questions, practice points were formulated, followed by a modified Delphi method consisting of anonymous web-based voting that was repeated with modified practice points where required, until at least 80% consensus for each practice point was achieved. This TF position paper shares the process, the discussion and consensus on all practice points on FA-associated GORD.

KEYWORDS
amino acid formula, cow milk allergy, extensively hydrolysed formula, gastroesophageal reflux, infants, non-IgE mediated food allergy

1 | INTRODUCTION

Gastro-oesophageal reflux (GOR) and food allergy (FA) are common conditions, especially during the first 12 months of life.[1,2] GOR is defined as the passage of any gastric contents into the oesophagus with or without regurgitation and/or vomiting. However, when GOR leads to troublesome symptoms, that affect the daily functioning of the infant and family, with or without complications, it is referred to as GOR disease (GORD).[2,3] The role of food allergens as a cause of GORD remains controversial.[4]

GORD is currently classified by the European Academy for Allergy and Clinical Immunology and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)[5] as a "possibly non-immunoglobulin (IgE)-mediated food allergic disorder."[6] The joint ESPGHAN-North American Society for Paediatric Gastroenterology Hepatology and Nutrition[7] guidelines on GORD from 2009 already recognised the possible role of cow's milk allergy (CMA)[8] and has further increased in prominence in the treatment pathway in the updated guidelines from 2018, with the consideration of a cow's milk elimination diet prior to the use of medication in infants <1 year of age.[2] Whilst one study from 20 years ago suggested that CMA could play a role in up to 40% of infants with GORD,[3] even less data exists on its association with other common food allergens, such as egg, soy and wheat. Studies have also highlighted the difficulties in distinguishing between FA and non-FA-associated GORD. This is related to the heterogeneous nature of extra-oesophageal symptoms, patient selection and the assessment of clinical improvement of these symptoms, which may have a multitude of heterogeneous causes.[2,8] This EAACI position paper therefore aims to review the evidence for FA-associated GORD in young children and translate this into clinical practice that guides healthcare professionals through the diagnosis of suspected FA-associated GORD and the medical and dietary management.

2 | METHODOLOGY

The task force (TF) on non-IgE mediated allergy (ENIGMA = Exploring Non-IgE Mediated Allergy) consists of EAACI experts in paediatric gastroenterology, allergy, dietetics and psychology from Europe, United Kingdom, United States, Turkey and Brazil. After the TF meeting in June 2019, priority topics in non-IgE mediated allergy were deliberated. Following on from the 2018 updated guidelines by ESPGHAN/NASPGHAN on FA-associated GORD and the ongoing confusion in regard to the role of FA in this common childhood disorder, the group considered this a priority topic to support the clinical practice of healthcare professionals working in food allergy. During the meeting, clinical questions were formulated and circulated to the group to guide the literature review. Those questions were further amended and approved by the ENIGMA TF and are summarised in Table 1.

TABLE 1 Clinical questions related to FA-associated GORD in early childhood

1. What is the pathophysiology of FA-associated GORD?
2. What are the symptoms related to FA-associated GORD?
3. How should FA-associated GORD be diagnosed?
4. What is the dietary management of FA-associated GORD?
5. What is the medical management of FA-associated GORD?
6. What is the prevalence and management of FA-associated in GORD?
7. What is the impact on the quality of life of FA-associated GORD?

2.1 | Literature review, grading of the evidence and strategy

Two members of the TF independently performed a systematic literature search using PubMed, Cochrane and EMBASE databases (until November 2021) using the inclusion criteria below and search terms outlined in Table 2. The two literature searches were compared, duplicates eliminated and articles were assessed for suitability. We also gained access to the database from the ESPGHAN/NASPGHAN working group on this topic and ensured that all publications used within that position paper,[2] were also considered for this position statement. The Snowball method was used to obtain further relevant publications from articles already sourced through the search.

Inclusion criteria:

1. Study population consisted of infants and children with a diagnosis of non-IgE gastrointestinal (GI) food allergies and GORD.
2. Full-text articles in English
3. Randomised controlled studies, observational studies, case-control studies and retrospective studies.
4. Studies published until February 2021.

Following the literature review, evidence-based clinical practice points were formulated for each of the questions the TF set out to answer and publications were distributed and reviewed by TF members working on each question. A modified Delphi method consisting of anonymous web-based voting was used for reaching a consensus on practical recommendations. We aimed to reach at least 80% agreement among the TF members on the practice points and where this was not achieved the practice point was amended, and the anonymous voting was repeated, until this level of agreement was achieved.

3 | FA-ASSOCIATED GORD

3.1 | Pathophysiology

GOR is a physiological phenomenon that occurs in early childhood and may lead to regurgitation and intermittent vomiting. Regurgitation is a functional GI disorder, defined as at least 2 episodes per day over 3 weeks in an otherwise healthy infant.[9] Conversely, GORD is overt GOR that is associated with complications, such as distress and irritability (see further information in section b).[10] The mechanisms of GORD are multiple, but the predominant mechanism is attributed to transient lower oesophageal sphincter (LOS) relaxation. Both IgE-mediated, non-IgE-mediated or mixed IgE/non-IgE-mediated FA have been implied in the pathophysiology of GORD.[11] Whilst the relationship between FA and GORD is likely to be bidirectional, with GORD inducing changes in mucosal immunity that may in turn increase the risk of FA, the pathophysiology is still poorly understood.[12] FA-related symptoms are manifestations of digestive motility dysfunction that may be due to food allergen-induced mediators.[13] A direct interaction between the enteric neurons and inflammatory cells (mast cells and eosinophils) and pro-inflammatory cytokines secretion has been suggested.[13] Stimulation of afferent nerve circuits via the brainstem during allergic reaction may cause dysregulation of sphincter tone and elicit GI symptoms.[14] A recent study by Omari et al,[15] found that the elimination of cow's milk proteins (CMP) significantly improved GORD symptoms in infants with non-IgE-mediated CMA when compared with controls. That study also showed improved oesophageal peristaltic function and mucosal integrity, increased acid clearance and oesophageal mucosal impedance.[15] Whilst this publication focused on the association between non-IgE mediated FA and GORD, the TF also found one study by Yukselen et al[16] on children with persistent vomiting and refractory GORD unresponsive to standard treatment who were challenged with cow's milk and egg after an elimination period and 40% had symptoms of urticaria, eczema, vomiting, wheezing, diarrhoea, rhinitis and anaphylactic shock. In the group that had a positive challenge nearly half of them exhibited positive specific IgE or skin prick test to the culprit food.[16]

TABLE 2 Search terms

Food hypersensitivity AND reflux/gastroesophageal reflux disease
Food allergy AND reflux/gastroesophageal reflux disease
Non-IgE mediated allergies AND reflux/gastroesophageal reflux disease
Non-IgE mediated allergies AND reflux/gastroesophageal reflux disease AND aversive feeding/feeding difficulties
Non-IgE mediated allergies AND reflux/gastroesophageal reflux disease AND quality of life

3.2 | Symptoms

FA-associated GORD has primarily been described in young children, with the majority presenting within the first 6 months of life.[17,18] However, there is variation in documented onset (4–102 months), with GORD also presenting in later childhood.[17,19] The typical GI symptoms attributed to GORD are recurrent regurgitation and vomiting in infants, together with or without excessive crying, distress/discomfort/irritability, dystonic neck posturing, feeding difficulties/food refusal, faltering growth, oesophagitis, pulmonary diseases or rarely occurring apparent life-threatening events, now described as brief resolved unexplained events.[9] In older children, symptoms can also include heartburn/chest pain, epigastric pain and dysphagia/odynophagia. From the published studies, non-IgE mediated FA may be more relevant in infants with severe and persistent GORD with associated food aversion and faltering growth, other GI symptoms commonly associated with non-IgE mediated allergies, but also atopic manifestations including atopic dermatitis and/or urticaria and rhinitis.[20,21]

4 | DIAGNOSIS OF FA-ASSOCIATED GORD

Practice points

- FA-associated GORD symptoms are difficult to distinguish from non-FA-associated GORD and a clinical and allergy-focused history (i.e. dietary intake in relation to symptoms, atopic comorbidities) forms the cornerstone for an accurate diagnosis. *(100% agreement)*
- The presence of other GI symptoms typically associated with non-IgE mediated and/or eczema may increase the likelihood of the GORD being FA associated. *(100% agreement)*
- For infants unresponsive to currently recommended standard GOR treatment including thickening of feeds and avoidance of overfeeding, FA needs to be considered. *(100% agreement)*
- A 2–6 week targeted diagnostic elimination of cow's milk (and/or other culprit food implicated through the food allergy history) needs to be followed by the reintroduction of the offending allergen, to confirm the diagnosis. *(80% agreement)*
- Whilst there may be parental reluctance to reintroduce foods, in particular following symptom improvement, it is important for healthcare professionals to highlight this as part of the diagnostic process when a FA is suspected and provide families with support to enable timely reintroductions. *(100% agreement)*
- Specific IgE or skin prick test are not indicated unless symptoms of an IgE-mediated allergy are presented and/or atopic eczema. *(100% agreement)*
- MII-pH metry is desirable in cases with alarm signs, not responding to either GORD or FA-associated GORD management and if MII-pH is not available, then pH-metry alone can still be useful. *(90% agreement)*
- Endoscopy should be performed if EoE is suspected, in cases that have not responded or insufficiently responded to GORD treatment (elimination diet and/or medications), as infants with EoE often present with similar symptoms as infants with GORD. *(90% agreement)*

Studies have suggested that pH-metry or multiple intraluminal impedance-pH (MII-pH)[22] recording could be helpful tools to distinguish between GORD and FA-related GORD, but results are conflicting.[23] MII-pH testing differs from pH-metry as it does not only measure episodes of acid reflux (pH <4) but also non-acid acid reflux.[9] Semeniuk et al[24] studied the intensity of symptoms and the acid GOR index in children diagnosed with primary GORD and GORD secondary to CMA/FA [confirmed by oral food challenge (OFC)]. The patients with GORD secondary to CMA had longer reflux episodes with a pH lower than 4.0 compared to the ones with primary GORD. However, conflicting results were obtained with pH-metry in other studies showing a comparable degree of reflux indexes in those with/without FA-associated GORD.[24,25] Nevertheless, the former studies showed that the postprandial decline in the oesophageal pH below 4.0 was especially noted for patients with CMA. Borrelli et al[21] studied 17 children with OFC-proven CMA and suspected GORD. They underwent 48 h MII-pH, with patients receiving amino acid formula (AAF) for the first 24 hrs and a cow's milk challenge in the subsequent 24 hrs. They found that although the total number of acid and weakly alkaline episodes did not differ, the number of weakly acidic episodes and episodes of gastric dysrhythmia increased during the CMP challenge compared to the period of AAF ingestion in patients with confirmed CMA.[21] On the other hand, Semeniuk et al studied the LOS pressure measured by manometry in primary GORD and GORD secondary to FA and found no difference between the two groups.[26]

In the absence of alarm signs indicating complicated GORD, invasive diagnostic procedures are not recommended, but whenever a child treated for GORD does not or insufficiently responds to treatment, eosinophilic oesophagitis (EoE) needs to be considered.[27] Symptoms are very similar between EoE and GORD, and early onset of EoE < 24 months was found in 17% of children in a retrospective chart review in Cincinnati Children's Hospital.[28,29] Vomiting, feeding difficulties (failure to progress with food introduction) and weight loss were more prominent symptoms in early onset EoE, where dysphagia, food refusal and food impaction were more common in older children. It is therefore not possible, to make this distinction based on symptoms only, and endoscopy and oesophageal biopsy should be performed if EoE is suspected.[30] Classic GORD is typically characterised by eosinophils below 15/hpf,[31] whilst the diagnosis of EoE requires ≥15 eosinophils/hpf with other distinctive features. Proton-pump inhibitor (PPI) responsiveness is no longer accepted as an exclusion criterion of EoE as it effectively down-regulates allergic Th2 in PPI-responsive patients, similarly to topical steroid therapy.[30] Children with EoE, who respond to PPI, are therefore seen as part of the EoE continuum, rather than a separate entity. Caution should therefore be applied when interpreting oesophageal biopsies in children on PPI.[30]

To date, there are no objective markers, including gastric emptying dynamics, small intestine permeability measures or faecal calprotectin that can reliably differentiate between FA related/unrelated GORD.[15] A limited number of studies have assessed the role of skin prick testing, serum IgE measurements and patch testing to aid the diagnosis of FA-related GORD.[32,33] Whilst Yukselen et al[16] found that in a subset of patients these tests are positive, it is important to understand their limitations in FA-associated GORD, which is thought to be a non-IgE mediated FA. When approaching a child with symptoms of possible FA-associated GORD, the first step is a detailed clinical history to establish presenting symptoms (Table 3), assess growth, feeding history (including any dietary changes associated with worsening of symptoms) and whether other atopic features are present (Figure 1). The latter should also guide the need for any allergy testing. Positive family history of atopy and early onset eczema in the infant may suggest a greater risk for allergic disease, but may also be the consequence of coincidence as atopic conditions can occur in at least 20% of all infants.[34-36] If no other atopic features are present and/or feeding history indicates worsening of

TABLE 3 Summary of symptoms, atopic co-morbidities, differential diagnosis and alarm signs that need to be considered across the age spectrum of GORD

General symptoms	Atopic comorbidities	Differential diagnosis	Alarm signs suggesting other gastrointestinal disorders and warrant further investigations
General symptoms Discomfort and pain Faltering growth Feeding difficulties Gastrointestinal symptoms Vomiting with discomfort Regurgitation without vomiting § Back arching during feed Epigastric pain § Dysphagia Respiratory Symptoms Wheezing Stridor Cough Horseness Other Apnoea episodes	Existing IgE-mediated allergies Other non-IgE mediated allergies (i.e. rectal bleeding and diarrhea) Atopic dermatitis Recurrent wheezing Asthma Rhinitis	Other gastrointestinal disorders (i.e. non-allergic GORD EoE and achalasia) Gastrointestinal obstruction disorders (i.e. pyloric stenosis, intussusception, and malrotation) Metabolic/endocrine (i.e. galactosaemia and metabolic acidocis) Neurologic or metabolic disorders (i.e. hydrocephalus and intracranial mass) Infectious (i.e. urinary tract infection, sepsis, and gastroenteritis) Toxic (i.e. lead poisoning) Cardiac (i.e. heart failure) Other (i.e. cyclical vomiting)	Persistent vomiting Haematemesis Nocturnal vomiting Bilious vomiting

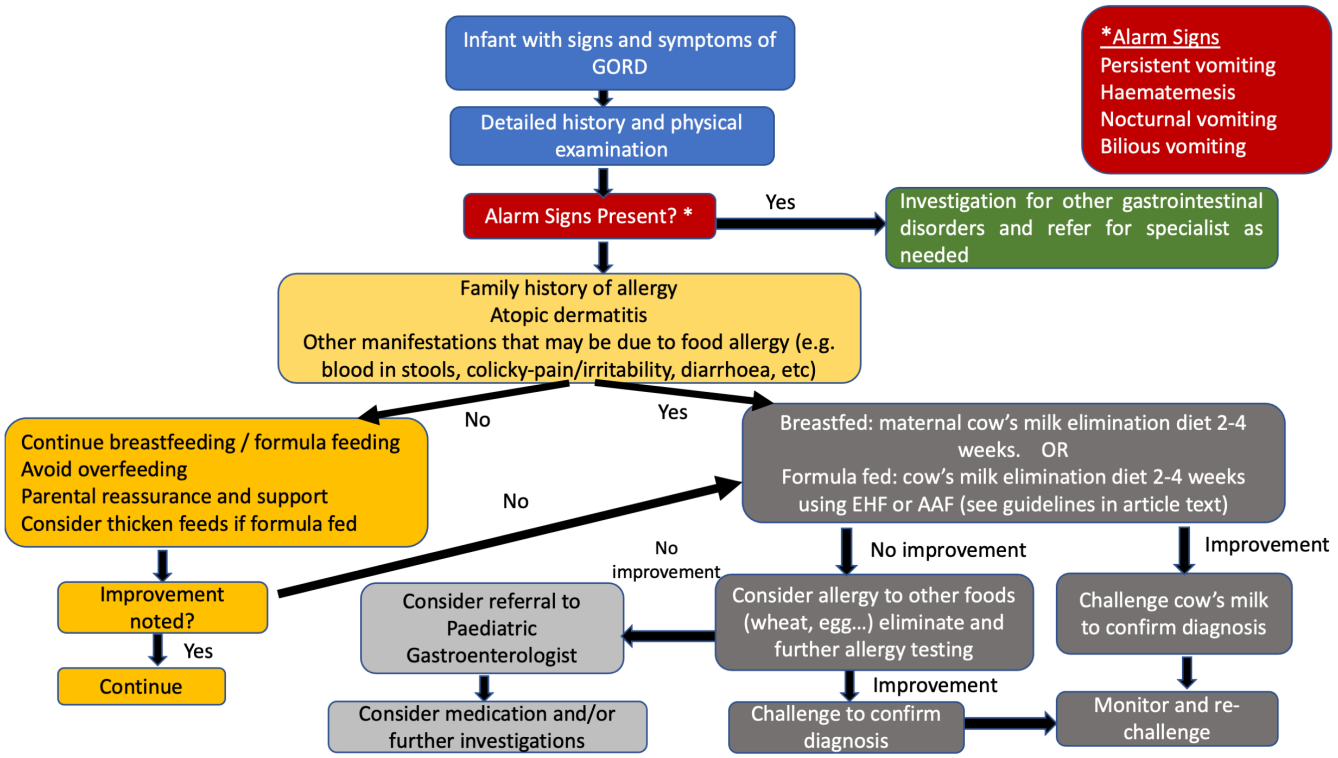

FIGURE 1 Proposed pathway in the assessment and diagnosis of FA-associated GORD

GORD with the introduction of food allergen, conventional first-line GORD therapy, as outlined by ESPGHAN-NASPGHAN in 2009 and 2018 should be followed (i.e. avoiding overfeeding and thickening of feed) and only if this does not yield a positive clinical response, the involvement of FA in GORD needs to be explored.

The confirmation of FA-associated GORD is based on the elimination diet followed by reintroduction. An elimination diet of the cow's milk (or other suspected food allergens) should be implemented for at least 2 weeks but may need to be extended until 6 weeks to see full symptom(s) resolution and should be followed with the subsequent reintroduction of the suspected food allergens.[37] Involvement of a registered dietitian is desirable, especially in severe/multiple cases of FA and when feeding difficulties and/or faltering growth are present.[38] In most cases, reintroduction of food can be performed safely at home, but this requires sufficient time for symptoms to develop, guidance on how to reintroduce and most importantly how parents should assess reactions.[39] In the presence of a positive (or suggestive) history of IgE-mediated FA, with or without a positive skin prick test and/or specific serum IgE, it is recommended to perform the OFC under medical supervision in a hospital setting.[6]

5 | MEDICATION MANAGEMENT

Practice points

- In infants (<1 year of age) pharmacological GORD treatment should only be considered after an elimination diet has been trialled and with proven GORD through MII-pH-recording, or pH-metry and/or endoscopy. *(100% agreement)*
- In toddlers and school-aged children, pharmacological treatment may be considered before an elimination diet when oesophagitis is diagnosed on endoscopy. *(100% agreement)*
- Young children with GORD symptoms, where the elimination diet has not been successful, should ideally be seen by a paediatric gastroenterologist or allergist for further investigations. *(100% agreement)*
- There is inconsistent evidence around the impact on symptom relief of alginates in infants with GORD and its use should be decided on an individual basis. *(100% agreement)*
- H2RAs do not reduce crying/distress and visible regurgitation/vomiting in children with GORD and ranitidine, which has most research in infants and children is no longer in use in most countries. *(100% agreement)*
- In children with EoE, all recommended therapeutic options, including PPI's elimination diet and swallowed steroids should be considered on an individual basis, recognising the pro's and con's of each treatment modality. *(100% agreement)*
- There is insufficient evidence to recommend routine use of PPI for infants (<1 year of age) with FA-associated GORD. *(100% agreement)*
- PPIs have been shown to have a significant impact on selected micronutrient availability, the microbiome, the risk of developing food allergy and protein breakdown and require special attention to counteract these effects. *(100% agreement)*

GORD in infants is non-specific and the differentiation between GOR and GORD is difficult in regard to medication management. Pharmacological treatment with gastric acid inhibitors (i.e. PPI, H2 blockers and antiacids) and prokinetics are widely used without objective investigations to guide treatment.[40] The algorithm proposed by NASPGHAN and ESPGHAN recommends reassurance and dietary intervention as the first options in the management of GOR and GORD in infants, in the absence of alarm symptom/s (Table 3).[2,41] If FA-associated GORD is suspected in infants, the first treatment option should be the elimination of the offending allergen (*See section Diagnosis of FA-associated GORD*). However, when symptoms do not improve or partially improve, medication may need to be considered and can be used complementary to dietary management. Pharmacological management can be divided into four categories: prokinetics, antiacids and alginates, H2 receptor antagonists and PPIs.

5.1 | Prokinetic agents

From the pathophysiological point of view, prokinetics would be the most logical therapeutic approach to treat non-erosive GORD in infants, since acid reflux is of minor relevance in this age group. Prokinetic agents (metoclopramide and domperidone) have been widely employed in paediatric patients.[42] The use of these compounds is based on their alleged ability to enhance LOS tone, improve oesophageal clearance and increase gastric motility thus increasing the emptying of gastric contents. However, none of these medications have been shown to be effective in decreasing the frequency of transient relaxation of the LOS.[43] Furthermore, the use of these agents is associated with undesirable side effects such as extra-pyramidal syndrome and cardiac dysrhythmias.[2,42] Therefore since 2014, the use of domperidone in newborns, infants, children under 12 years and adolescents weighing less than 35 kg is no longer approved at the European level.[44] Currently, no guideline recommends the use of domperidone or metoclopramide to treat GORD in infants.[2] Erythromycin was mostly studied in infants with feeding problems, and has been very poorly studied in GORD.[42,45,46] Erythromycin was shown to not reduce GOR in preterm infants,[45] and consequently, it is not recommended as first-line approach in GORD.[2]

5.2 | Alginates and anti-acid medication

Alginates are used to treat acid-related disorders such as heartburn or dyspepsia by neutralising acid exposure to the oesophagus. There are opposing views on the use of these in GORD. The National Institute for Health and Care Excellence guidelines recommend alginates as an alternative treatment to feed thickening agents in breastfed infants or as a trial in infants in whom symptoms persist despite conservative measures as short-term use has no significant side effects.[47] Similarly, the Cochrane guidelines from 2014 suggest a 2-week trial of alginates in GORD.[48] However, the NASPGHAN-ESPGHAN guidelines found insufficient evidence to recommend a trial with alginate.[2] Some of the differences in treatment guidelines can be explained by the variation in product formulation (i.e. liquid vs powder), which differ between countries and therefore instructions of use may also vary. Care should be taken with liquid aluminum-containing antacids, which may lead to increased aluminum plasma concentrations in infants.[49] These should only be used for short-term relief of symptoms in older children and adolescents and should be avoided in infants.[2]

5.3 | Histamine 2-receptor antagonists (H2RAs)

H2RAs (i.e. ranitidine, cimetidine hydrochloride, nizatidine and famotidine) selectively block the histamine-2 receptor of the gastric parietal cell (activated by histamine or gastrin), resulting in a decreased production of pepsin and gastric acid. Gastric pH begins to increase within 30 minutes of administration and the effect lasts for 6 h. Whilst H2RAs are less effective than PPIs in reducing mucosal healing, they have a rapid onset of action and can, therefore, provide immediate symptomatic relief.[50] Tachyphylaxis or tolerance to oral H2RAs is

well recognised (8) and is a drawback to chronic use.[51] In some infants, therapy with H2RAs can cause side effects including irritability, head banging, headache and somnolence, which may be interpreted as persistent symptoms of GORD.[52] One systematic review has been published on the efficacy and safety of H2RAs in paediatric GORD, including 8 studies with a total of 276 children (1 month −15 years of age).[53] This study concluded that the evidence to support the efficacy and safety of H2RAs in infants and children are limited and of poor quality.[53] Furthermore, H2RAs do not reduce crying/distress and visible regurgitation/vomiting in children with GORD compared with placebo. However, it is important to note, that none of these studies, systematically ruled out CMA as a differential diagnosis.

Ranitidine was the only studied H2RA in infants and children, and thus the most commonly used compound for GORD, but has been taken off the market because of the presence of nitrosamines, a carcinogen.[54] Moreover, the liquid presentation did contain a clinically relevant amount of alcohol.

5.4 | Proton-pump inhibitors

PPIs inhibit acid secretion by binding to the H+/K+ATPase complex ("proton pump") of gastric parietal cells and preventing the reuptake of extracellular potassium in exchange with intracellular hydrogen.[55] The currently available PPIs are omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole and dexlansoprazole.[2] Their use in infants has been extrapolated from various studies in adults, where PPIs were demonstrated to be superior in healing erosive oesophagitis and providing symptom relief in comparison with H2RAs, which are more effective than placebo.[2] PPIs have been found to maintain intragastric pH >4 for prolonged periods and to inhibit meal-induced acid secretion. Nevertheless, it has not been demonstrated that PPIs are effective in reducing infant GORD symptoms related to distress when compared with placebo.[56-58] However, when it comes to acid reflux, one study enrolling infants with endoscopically confirmed GORD (i.e. eosophagitis), found that omeprazole significantly reduced the reflux index (percentage of total duration pH <4) in these infants compared with placebo, but irritability improved regardless of treatment.[57,59] In the study by Winter et al,[58] with esomeprazole in infants <12 months old, the discontinuation rates owing to symptom worsening were 48.8% for placebo-treated vs 38.5% for esomeprazole-treated patients (hazard ratio 0.69; $p = .28$).[58]A review for the Food and Drug Administration of 4 clinical trials evaluating the use of PPIs in this age group (1 month to <12 months) has failed to show any benefit.[60]

Significant concerns have been raised in regards to PPI use in infants, not only related to acute side effects, including headaches, diarrhoea, constipation and nausea but also the long-term impact on the bioavailability of iron, calcium, phosphate, the effect on the microbiome due to pH change, the risk for developing, impact on protein breakdown and allergic reactions.[61-68]

In food allergic disorders, PPI are primarily used, in a subgroup of patients with EoE, which is a chronic immune-mediated disorder of the oesophagus associated with eosinophilic infiltrates as well as eotaxin-3 and Th2 cytokine overexpression.[30] The mechanism of effectiveness, may in part be explained by the anti-inflammatory effects of PPIs unrelated to acid suppression, with inhibition of Th2 cytokines and eotaxin-3 production as demonstrated in previous studies, but the precise mechanism of such effects remains elusive.

6 | DIETARY MANAGEMENT

Practice points

- The most common allergen reported in FA-associated GORD is cow's milk, however, some studies do report other allergens (i.e. soy, hen's egg and wheat) being culprit foods. *(100% agreement)*
- Breastfeeding should be supported in infants with GORD and a maternal elimination of targeted foods should only be considered if a child presents with symptoms whilst breastfeeding. *(100% agreement)*
- A minimum of 2 weeks elimination diet is required to start seeing symptoms improvement, but symptom improvement may take up to 6 weeks in some cases, which should be followed by the reintroduction of an age-appropriate portion and frequency of the offending allergen for 2 weeks. *(100% agreement)*
- If breastmilk is not available or insufficient an EHF is recommended as first-line treatment, unless faltering growth, multi-system involvement and multiple FAs are suspected, in which case an AAF needs to be considered. *(100% agreement)*
- Thickened EHF or AAF, where available, may give an additional benefit in infants with ongoing GI symptoms. *(100% agreement)*
- If symptoms do improve insufficiently and there are other ongoing lower GI symptoms possibly related to non-IgE mediated FA and/or atopic dermatitis the further elimination of other allergens may need to be considered (i.e. soya, egg and wheat). *(100% agreement)*
- After 6–12 months of elimination (in confirmed FA-related GORD) a trial of reintroduction of the offending allergen should occur. *(87.5% agreement)*
- Reintroduction can be conducted at home when the patient has no food-specific IgE and/or IgE-mediated FA history. *(100% agreement)*
- In the absence of data on challenge/reintroduction dosage for food allergens, it makes sense to aim for a "normal portion" of expected intake of that allergen for age. *(100% agreement)*
- Whilst there is limited evidence specifically in FA-associated GORD, in a subset of children tolerance to baked/heated milk may develop before they tolerate a whole protein formula/pasteurised whole milk. *(100% agreement)*

6.1 | Elimination diet

For children with GOR dietary elimination is not required, but parental reassurance, an adaptation of volume and frequency of feeding and considering thickened feeds is important, as symptoms often improve from the age of 6 months onwards and resolve by the age of 12-15 months.[69]

The elimination diet should only be considered for children with GORD, who have failed standard treatment and/or have atopic co-morbidities.

6.2 | Duration of the elimination diet

The pool of evidence on dietary elimination in relation to FA-associated GORD is very limited. Seven original studies discuss the use of cow's milk elimination diets in diagnosing CMA in infants/children with GORD. These studies used an elimination period ranging from 24 hours to 4 months (Table 5).[70] Three review publications[70-72] recommend a 2–6 weeks avoidance period of cow's milk and two guideline papers[39] recommend a 2–4 week period of cow's milk avoidance in GORD. Although the publication by Lozinsky et al[37] was not specifically aimed at infants with GORD, it collected data on a cohort with non-IgE mediated allergies, including food protein-induced GORD and found that 98% had symptom improvement after a 4-week elimination diet, although complete resolution of symptoms may require a longer and full resolution of symptoms may not occur in all infants. This implies, that a minimum of 2 weeks is required to start seeing symptom improvement, but symptom resolution may up to 6 weeks.

6.3 | Food allergens associated with GORD

Only two original studies[19,73] mention the possibility of hen's egg, wheat and soy allergy alongside CMA in FA-associated GORD. Whilst three review publications[70-72] and two guideline papers[39] discuss avoidance of cow's milk only, there is no guidance on the further elimination of other allergens (Table 4). Undoubtedly, the elimination of CMP has been most studied, consensus publications, based on limited data, indicate, that if GORD symptoms are accompanied by manifestations from the lower GI tract and/or are accompanied by atopic dermatitis and elimination of CMP alone was insufficient to improve the symptoms in all cases. Therefore, additional food allergens might be considered as potential triggers of GORD, similar to other forms of non-IgE mediated food allergic disorders, for example, food protein-induced enteropathy, food protein-induced allergic proctocolitis or food protein-induced enterocolitis syndrome.[74,75]

7 | BREASTMILK IN THE MANAGEMENT OF GORD

Breastfeeding is strongly supported by EAACI for all young children with FA. In 2019, the EAACI position statement outlining the management and diagnosis of non-IgE mediated allergies in breastfed infants was published.[78] A full literature review for that publication revealed the paucity of data on the prevalence of GORD related to FA in breastfed infants, thereby implying limited data also on dietary management. A subsequent literature search for this publication did not yield any new research on this topic, however, there is agreement amongst TF members that cow's/goats and/or sheep milk protein can transfer through human milk in the form of β-lactoglobulin (levels range from 0.9 to 150 μg/L) and may therefore have the potential to elicit symptoms of CMA-associated GORD.[79] It is however also important to consider other allergens, including soy, wheat and hen's egg which are also capable of transferring through breastmilk.[80,81] Whilst Host et al[79] reported CMA in breastfed infants, it should be noted that this was not GORD specific and data on the presence of other food allergies in breastfed infants with GORD is extremely limited.[82]

This position paper supports the ESPGHAN-NASPGHAN GORD guidelines, to consider FA only when standard management (i.e. thickening of feed and avoiding overfeeding) of symptoms is not successful and/or where other atopic manifestations are present. Whilst a 2–4 week maternal elimination diet of cow's milk, and if required other allergens, may be sufficient for most children, it should be noted that in some it can take longer (up to 6–8 weeks).[37] As per current guidelines,[78] the elimination diet should always be followed by a reintroduction of cow's milk (and/or any other foods that are being eliminated) either through the breastfeeding mother's diet or directly into the baby if complementary foods have been introduced. Breastfeeding mothers should receive support to maintain breastfeeding and their dietary adequacy needs to be considered at all times, which may include, calcium, vitamin D and other micronutrient supplementation.

8 | FORMULAS FOR CMA IN THE MANAGEMENT OF GORD

Several guidelines on the diagnosis and management of CMA, include suggested formulas suitable for the management of CMA, when breastmilk is insufficient or not available.[6,83,84,85] There is consensus that these formulas need to be tested and conform with current guidelines on hypoallergenicity and growth.[86,87] Whilst most guidelines suggest an extensively hydrolysed formula as first-line treatment for CMA-associated GORD, the impact of growth faltering and formula choice is acknowledged in some of the guidelines [i.e. evidence of better catch up with the amino acid formula (AAF)] and the involvement of multiple organ systems and multiple food allergies may also require the consideration of the AAF as first line formula (Table 5).[88] However, none of the current guidelines on CMA, cover hypoallergenic formulas that have specifically been designed for GORD. There are now thickened casein-based EHF and AAF with proven hypoallergenicity suitable for these patients available in some countries.[89-92] The studies by Dupont et al[91,93] and Vandenplas et al[90] also assessed regurgitation episodes, crying

TABLE 4 Summary of publications discussing elimination diets in GORD

	Food avoided	Duration	Diagnostic CM challenge Procedure to confirm the diagnosis of CMA	Reintroduction/tolerance
Original papers				
Hill[73]	Milk, egg and soy	2 months	4 weeks DBPCFC	NA
Borrelli[21]	Milk avoided and substituted with AAF formula	At least 2 months	48-hour multichannel intraluminal impedance-pH monitoring. First 24 hours on AA and subsequent 24 hours receiving cow's milk	NA
Cavataio[76]	Milk avoided and substituted with AAF/EHF	6–8 weeks	3 hours DBPCFC	NA
Farahmand[17]	Milk free	4 weeks	NA	NA
Nielsen[19]	Milk free (SPT to soy, egg and wheat)	3–4 months	DBPCFC	NA
Omari[77]	Milk avoided and substituted with AAF or maternal exclusion	10-14 days	7 Day DBPCFC	NA
Yukselen[16]	Milk free	2 weeks	1 day up to 1 month	NA
Review				
Dupont[70]	Milk free	2 weeks	gradual reintroduction at home: at least 200 ml/day for at least 2 weeks	To determine cow's milk tolerance in clinical practice, tolerance development may be indicated by a child tolerating milk in small quantities, baked or probably also in some fermented forms
Heine[71]	Milk avoided and substituted with hypoallergenic formula or maternal exclusion	4-6 weeks	Formal food challenges	NA
Vandenplas[72]	CMP free diet	2 weeks	>24 hours	NA
Guidelines				
Rosen 23	CMP free diet EHF and use protein hydrolysate or AAF or, in breastfed infants, elimination of cow's milk in maternal diet	2–4 weeks	NA	NA
Fox[39]	CMP free diet and use EHF or maternal cow's milk avoidance if breast fed	2–4 weeks	1 week	After 6 months or around 1 year of age Milk ladder

TABLE 5 Overview of recommended formula for GORD by different guidelines[5,83,84,85,100]

DRACMA (2010)	ESPGHAN(2012)	Australian Guidelines (2009)	BSACI (2014)	iMAP (2017
EHF (hydrolysed rice formula when available)	No specific mention for GORD but EHF is recommended as 1st line formula for the most presentation of CMA	EHF if <6 months Soy if >6 months EHF if >6 months if also presenting with faltering growth	EHF (unless faltering growth then AAF)	EHF

and sleeping time. In children that had challenge positive CMA, both thickened and un-thickened extensive hydrolysates were equally tolerated and for those that were challenge positive, a thickened hydrolysate had a significantly better impact than a non-thickened hydrolysate. However, symptoms also improved (to a lesser degree) with a casein-based EHF in the challenge-negative children. This may be related to a placebo effect or to the increased gastric emptying in comparison with intact protein.

The position of soy formula needs to also be considered, in particular in resource-poor countries. Whilst some data indicates that up to 50% have a concomitant allergy to soy in non-IgE mediated CMA,[94,95] this is not confirmed by all published data and limited data exist on soy as a primary allergen in FA-induced GORD.[96,97] This is already acknowledged in the Australian and South African guidelines.[98,99]

9 | REINTRODUCTION OF ALLERGENS

9.1 | Initial reintroduction to confirm CMA

Six original studies[16,17,19,21,73,76,77] suggest that cow's milk should be introduced after a period of avoidance (diagnostic elimination diet). The reintroduction duration from these studies varies between 1 day up to 1 month and may be conducted as either open food challenges or double blind placebo controlled food challenges, although blinded challenges are difficult to implement outside research, in particular in non-IgE mediated FAs. The reintroductions are usually conducted at home when there is no suspicion or history of IgE-mediated FA, but some clinical settings start the food challenge in the hospital and in the absence of symptoms, continue at home.[73] Three review papers[70-72] confirm the information from the clinical studies: cow's milk should be introduced after a period of avoidance, gradually and over a period of time lasting from 1 day to 2 weeks. Only one guideline paper suggests reintroduction over a period of 1 week.[39] Challenge/reintroduction procedures varied widely in terms of dose and timing and to date no standardised procedure outside of FPIES exists for any other non-IgE mediated food allergy conditions, including GORD. In the absence of clear guidance, it would make sense to aim for a "normal portion" of the allergen according to the child's age and gradually increase the dose over the period of a week. For cow's milk, a normal portion is considered 120–240 ml of infant formula or cow's milk for toddlers.[101] The challenge/reintroduction may start with 30 ml of formula/milk and increase by 30 ml per day with the aim of reaching 210–240 ml by the end of the first week. It is recommended to continue with this dose for at least 2 weeks.

9.2 | Reintroduction to determine the possible acquisition of immune tolerance

The World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines,[83]

ESPGHAN[5] and International guidelines for Cow's milk allergy in Primary Care (iMAP) guidelines[39] suggest that after a period of avoidance, usually between 6 and 12 months, periodic reintroductions to determine if immune tolerance has developed. The iMAP guidelines suggest that milk can be reintroduced after a period of avoidance of 6 months or around 1 year of age in the form of the milk ladder.[100] The recommendation to follow the milk ladder is based on an expert consensus as there are no studies that evaluated the milk ladder in infants with FA-associated GORD. The milk ladder concept is well-accepted by the majority of caregivers because it introduces milk proteins in a very gradual manner, starting from lower doses of less allergenic forms of milk, such as baked goods and advances slowly, as tolerated. Whilst the efficacy has yet to be established, it is currently being used by many healthcare professionals and the potential for improvement in quality of life using this method of reintroduction has been recognised.[99,102,103]

10 | FEEDING DIFFICULTIES AS A SYMPTOM OF NON-IGE MEDIATED ALLERGIES

Practice points

- Whilst feeding difficulties are commonly reported in GORD, limited published data exists on this as a symptom of non-IgE FA-associated GORD. *(100% agreement)*
- Healthcare professions need to be aware that children with FA-associated GORD can present with feeding difficulties and include questions about feeding difficulties in their consultation. *(100% agreement)*
- To date, no validated questionnaire exists on establishing feeding difficulties in non-IgE mediated FAs and further work is required to develop a tool specific for FA. *(100% agreement)*
- Clinicians need to take into account that feeding difficulties present differently depending on age. *(100% agreement)*

Feeding difficulties are not listed in all international guidelines as part of the clinical presentation for non-IgE mediated FA-associated GORD. ESPGHAN includes food refusal in their clinical presentation of CMA and symptoms of GORD in children. Similarly, feeding difficulties are also included in International Milk allergy in Primary Care (iMAP) guidelines as a presenting symptom for mild to moderate non-IgE mediated FA,[5,100] and feeding difficulties are highlighted as a primary clinical presentation, in EoE in the international guidelines.[27]

Whilst it is recognised that feeding difficulties are often present in GORD,[104] limited data exists on its co-existence with FA-associated GORD. To date only one retrospective study has been published on feeding difficulties, covering the whole spectrum of non-IgE mediated FA diagnoses, including GORD.[105] In that study, 30% of children had feeding difficulties, as noted by clinicians in the medical notes, with the most commonly reported being texture hypersensitivity (i.e. gagging on textured foods). Notably more data exists in EoE where publications have found that up to 90% of children have maladaptive feeding behaviour.[106,107] Mehta et al[106] found that the Behavioral Pediatric Feeding Assessment Scale as a marker of feeding dysfunction for both children with GORD and EoE were significantly raised when compared to healthy controls.

True prevalence data as well as an accurate description of the type of feeding difficulties have been made difficult by the diagnosis itself (i.e. food allergy-related GORD or general GORD) and varying presentations of food refusal in infancy vs later childhood (Table 6). In a study published by Rommel et al[108] who assessed the underlying diagnosis of 700 children with feeding difficulties, 60% presented with GORD as an underlying diagnosis.

To date, no standardised questionnaire exists for establishing feeding difficulties in GORD and therefore studies have used a variety of different questionnaires, summarised in Table 7, which may be useful for healthcare professionals. Singendonk et al[109] published in 2019 a list of core outcomes for infants with GORD and suggested that feeding difficulties should form part of this core list of questions for clinicians. Whilst the majority of children with FA-associated GORD with reflux may present with mild to moderate feeding difficulties, healthcare professionals need to be aware of avoidant restrictive food intake disorder that can present in older children (usually after 2 years of age) and has been reported in EoE and FPIES.[110-112] The latter is an eating disorder with specific criteria described in DSM-V.[113,114]

11 | QUALITY OF LIFE (QOL) IMPACT OF GORD

Practice points

- FA-associated GORD can have a significant impact on the QoL of families. *(100% agreement)*
- Healthcare professionals need to recognise the distress that this disorder can cause and medical, dietary and psychological management should aim to improve the QoL of the child and the family. *(100% agreement)*

FA-associated GORD may present with a wide spectrum of symptoms that can have a significant impact on the QoL of the child and the parents. There is the paucity of data specifically related to GORD but a recent paper by Salvatore et al[59] looked at the relationship between infant distress and GOR. Symptoms of reflux occurred significantly more often before an episode of distress compared to simultaneously or after distress episodes and were similarly associated with acid and non-acid reflux. Work specifically on QoL has

TABLE 6 Feeding difficulties commonly developed in infancy vs later childhood[105,108]

Feeding difficulties reported in infancy (<1 year of age)	Feeding difficulties reported in older children (>1 year of age)
Breastfeed or bottle refusal/aversion	Tactile defensiveness (do not want to touch messy foods, play with pain, feel certain textures on their hands and body)
Gagging on textured foods	Color and texture specificity
Sealing of mouth and pushing the spoon away	Extended mealtimes
Crying when seeing the spoon	Gagging/choking/vomiting of foods with specific texture characteristics
Extended mealtimes	

TABLE 7 Feeding questionnaires that can be used in children with feeding difficulties

Questionnaire	Target population	Description/criteria
Children's Eating Behaviour Questionnaire[115]	2–7-year-olds	Multi-dimensional questionnaire to assess eating style in children, based on parents' reports of their child's behaviour.
Mealtime Behaviour Questionnaire[116,117]	9 months–13 years	Parent-reported frequency of child mealtime behaviours and frequency of parent feelings and strategies for dealing with eating problems using a 5-point Likert scale from "never" to "always."
Montreal's Children Hospital for Identification of feeding difficulties[118]	6 months–6 years of age	14-item parent report tool designed to identify feeding problems.
Behavioural Paediatrics Feeding Assessment Scale[119]	20–85 months	This is is a 35-item scale, divided into 25 questions about child behaviour, and 10 questions about parent attitudes and behaviour. Parents rate the frequency of specific behaviours on a 5-point Likert scale, and provide a dichotomous answer about whether that behaviour is considered to be a problem

been conducted with children with non-IgE mediated FA compared to other conditions. Meyer et al[120] found that children with non-IgE mediated FA had a significantly worse Family Impact Score for all domains of functioning when compared to sickle cell anaemia and intestinal failure. In particular, number of foods eliminated and the severity of symptoms negatively impacted the QoL. When this cohort of children with non-IgE mediated FA, were compared to children with IgE-mediated FA, the total QoL score was not significantly different, but the family impact score was significantly lower in non-IgE mediated FA in the physical, emotional and psychosocial domains.[121] The authors of the latter study, hypothesised that children existing growth concerns, which may explain the outcome of the study. Vandenplas et al[122] have found that functional GI disorders in infancy, including regurgitation, have a significant impact on the QoL of families. Although more data are required specific to FA-associated GORD, there is consensus that GORD negatively impacts the QoL of both the child and the parents. Ther ESPGHAN-NASPGHAN guidelines from 2018 recommended parental education and support as part of the treatment of GORD, which is also recognised by this TF as a critical factor in the management of FA-related GORD.

12 | CONCLUSION

This position paper set out to explore the role of FA in the GORD. Due to limited data on many of the areas related to this topic, a Delphi approach has been used to reach consensus and therefore provide healthcare professionals with practical advice on the management of FA-associated GORD. An extensive literature search has found that whilst food proteins, in particular CMP, can be a contributing factor to FA-associated GORD, it is difficult to distinguish between FA and non-FA-associated GORD. An elimination diet should always be followed by the reintroduction of the offending allergen and QoL should be considered within the diagnosis and treatment pathway. Breastfeeding should be supported in FA-associated GORD and dietary advice should take the potential nutritional impact on the breastfeeding mother into account. When breastmilk is not available or insufficient and EHF or AAF will need to be considered together with dietary advice to counteract any nutrient deficiencies in the child. Whilst there is some clarity on when medication may be considered for GORD, this TF does recognise that these are often inappropriately used, with potentially detrimental results, in particular in infants.

This TF has also identified a need for further, better-designed research on FA-associated GORD to better inform clinical practice.

CONFLICT OF INTEREST

RM – academic lectures for Mead Johnson, Abbott Laboratories, Nestle and Nutricia/Danone and consultancy to Else Nutrition, Abbott and Nestle Healthcare. Dr. CV reports grants from Reckitt Benckiser, grants from Food Allergy Research and Education, grants from the National Peanut Board, during the conduct of the study; personal fees from Reckitt Benckiser, personal fees from Nestle Nutrition Institute, personal fees from Danone, personal fees from Abbott Nutrition, personal fees from Else Nutrition and personal fees from Before Brands, outside the submitted work. RBC – research grants from Humana, Mead Johnson Nutrition, Nestlè, Novalac and Nutricia/Danone. MCV – academic lectures for Danone Nutricia, Nestle, Mead Johnson and Aché Laboratories

PEER REVIEW

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