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REVIEW

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Diagnosis and management of food allergy-induced constipation in young children—An EAACI position paper

Rosan Meyer[1,2] | Yvan Vandenplas[3] | Adriana Chebar Lozinsky[4] | Mario C. Vieira[5] | Roberto Berni Canani[6] | George du Toit[7,8] | Christophe Dupont[9] | Mattia Giovannini[10,11] | Pinar Uysal[12] | Ozlem Cavkaytar[13] | Rebecca Knibb[14] | David M. Fleischer[15] | Anna Nowak-Wegrzyn[16] | Carina Venter[15]

Correspondence
Rosan Meyer, Department Paediatrics, Imperial College, London, UK and Department Nutrition, University of Winchester, Winchester, UK.
Email: rosan.meyer@gmail.com

Funding information
European Academy of Allergy and Clinical Immunology

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Abstract

The recognition of constipation as a possible non-Immunoglobulin E (IgE)-mediated allergic condition is challenging because functional constipation (unrelated to food allergies) is a common health problem with a reported worldwide prevalence rate of up to 32.2% in children. However, many studies in children report challenge proven cow's milk allergy and constipation as a primary symptom and have found that between 28% and 78% of children improve on a cow's milk elimination diet. Due to the paucity of data and a focus on IgE-mediated allergy, not all food allergy guidelines list constipation as a symptom of food allergy. Yet, it is included in all cow's milk allergy guidelines available in English language. The Exploring Non-IgE-Mediated Allergy (ENIGMA) Task Force (TF) of the European Academy for Allergy and Clinical Immunology (EAACI) considers in this paper constipation in the context of failure of standard treatment and discuss the role of food allergens as culprit in constipation in children. This position paper used the Delphi approach in reaching consensus on both diagnosis and management, as currently published data are insufficient to support a systematic review.

KEYWORDS
constipation, cow's milk allergy, food allergy induced constipation, food protein induced constipation, non-IgE-mediated allergy

1 | INTRODUCTION

Non-Immunoglobulin E (IgE)-mediated food allergy has been defined as a delayed reaction, which usually manifests 1–48 h after the ingestion of an allergen, but symptoms may take up to 1 week or longer in some cases.[1,2] Symptoms typically impact either or both the skin and the gastrointestinal tract. While eczema is considered a possible non-IgE-mediated food allergic condition in children,[3,4] there is significant variation in the gastrointestinal symptoms listed in general food allergy and cow's milk-specific guidelines. This is in particular evident with food protein-induced motility disorders (FPIMD), which include gastro-esophageal reflux disease (GORD).[5–7]

The recognition of constipation as a possible symptom of non-IgE-mediated food allergy is acknowledged by this EAACI TF as being challenging because functional constipation, a disorder of gut brain interaction, previously known as functional gastrointestinal

For affiliations refer to page 10.

disorders, is a common health problem with a reported worldwide prevalence rate of up to 32.2% in children and accounts for 3% of pediatrician visits and 25% of referrals to pediatric gastroenterologists.[8,9] The majority of children with constipation respond to oral laxative treatment. In children with withholding behavior, the approach also focuses on behavioral aspects with initial therapeutic steps involving toilet training.[10,11] When conventional treatments fail, children and adults are considered to have intractable functional constipation, a troublesome and distressing condition.[10] Analyzing every aspect of constipation physiopathology is thus a very important approach, prior to considering food allergens as a possible cause.

The ENIGMA TF of the EAACI[12] has published two position papers on complex and controversial topics in non-IgE-mediated allergy, including the management of non-IgE-mediated food allergies in breastfed infants and food protein-associated GORD.[13,14] In this paper, we consider constipation in the context of failure of standard treatment and discuss the role of food allergens as culprit in constipation in children. A literature review by Miceli Sopo et al.[15] in 2014 identified 10 clinical trials (2 were randomized controlled studies) in children with challenge-proven cow's milk allergy[16] and found that the success of a cow's milk elimination diet in improving constipation ranged between 28% and 78%. Since then, there have been no further randomized controlled trials conducted but some case reports and retrospective studies have been published.[17,18]

Due to the paucity of data and a focus on IgE-mediated allergy, not all food allergy guidelines list constipation as a symptom of food allergy. Yet, it is included in most cow's milk allergy guidelines available in English language. Table 1 summarizes the inclusion of this symptom within current guidelines.

This EAACI position paper therefore aims to review the evidence for food allergy induced (FAIC) constipation in young children and translate this into clinical practice that guides healthcare professionals through the diagnosis of suspected FAIC and the medical and dietary management.

Key message

This position paper used the Delphi approach in reaching consensus on the diagnosis and management of food allergy-induced constipation (FAIC) and provides healthcare professionals with practical guidance on this controversial food allergy-induced dysmotility disorder.

2 | METHODOLOGY

The ENIGMA TF consists of EAACI experts in pediatric gastroenterology, allergy, dietetics/nutrition, and psychology from Europe, the United States, Turkey, and Brazil.

A virtual meeting of members occurred in 2022 to formulate the clinical questions, which were then circulated to the group for amendment and approval. These clinical questions were used to guide the literature search and as outline for this publication (Table 2).

2.1 | Literature review

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. Study population consisting of infants and children with diagnosis of non-IgE-mediated gastrointestinal food allergies and constipation.
2. Full-text articles in English.
3. Randomized controlled studies, observational studies, case control studies, and retrospective studies.
4. Studies published up to July 2023.

The modified Delphi method was used for reaching consensus on practical recommendations for healthcare professionals. Voting occurred anonymously using the JotForm online system (www.jotform.com). We aimed to reach at least 80% agreement among the 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.

3 | PATHOPHYSIOLOGY OF FA-ASSOCIATED CONSTIPATION

The pathophysiology of FAIC is still largely undefined, with alteration of the enteric nervous system, which controls gastrointestinal motility, suggested as being involved.[29] Gastrointestinal motility and the enteric nervous system are regulated by multiple immune and non-immune mechanisms, including the activity of the mast cells, which play a pivotal role in the allergic inflammation.[30,31]

A potential role of mast cells in regulating the gastrointestinal motility in children with FA-associated constipation versus functional constipation children have been suggested.[32] From the published research, it is thought that mast cells can be activated by diverse non-IgE stimuli, which include IgG, complement components, TLR ligands, neuropeptides, cytokines, chemokines, and other inflammatory products.[33] Mast cells are in close proximity to the enteric neurons and can influence nerve function with a variety of mediators and mast cell degranulation results in activation of neural reflexes leading to changes in gut motility. Increase in rectal mast cell density close to the submucosal rectal nerve endings and spatial interactions between mast cells and gastrointestinal nerve fibers

TABLE 1 Summary of guidelines with/without constipation as a possible symptom of non-IgE mediated food allergies.

General allergy guidelines	Presence of constipation as symptom	Cow's milk allergy specific guidelines	Presence of constipation as symptom
EAACI 2014 Food Allergy and Anaphylaxis Guidelines[4]	No	ESPGHAN guidelines[1]	Yes
South African Food Allergy Consensus Document[19]	No	Chinese guidelines[20]	Yes
NIAID diagnosis and management of food allergy[21]	No	DRACMA guidelines[22]	No
Japanese guidelines for food allergy[23]	No	Australian guidelines[24]	Yes
Managing Food Allergy – GALEN Guideline 2022[25]	No	iMAP guidelines[26]	Yes
		Middle East Consensus guidelines[27]	Yes
		Hongkong guidelines[28]	Yes

have been described in children with chronic constipation by Borrelli et al.[32] These alterations were correlated with abnormalities in anorectal motility (anal resting pressure, percentage of relaxation, and residual pressure of anal canal during rectal distension). In this study, 18/30 children responded to an elimination of cow's milk, egg, and soya, and the dietary elimination was successful in reducing mast cells mucosal infiltration, normalizing mast cells—nerve interactions, and improving motor abnormalities in these patients.

Once activated through a food protein, gastrointestinal mast cells act both as effector and conductor cells, with recruitment of eosinophils, lymphocytes, and neutrophils, which may in turn contribute to release bioactive mediators and to perpetuate allergic inflammation.[34] Mast cells release mediators, such as cytokines and chemokines, vasoactive, and nociceptive substances, which may affect the enteric nerve function and muscle contractility, establishing a bidirectional interaction and defining the concept of "neuro-immune crosstalk."[35]

FAIC may be also associated with proctitis, and a high number of intra-epithelial lymphocytes and eosinophils in the rectal mucosa. More specifically, Carroccio et al.[36] have described a significant reduction in rectal epithelium mucous layer thickness in patients with FAIC.

In conclusion, emerging data are supporting the pivotal role of gastrointestinal mast cells and its mediators in the pathogenesis of FAIC, but further research is needed.

Practice points (achieving 100% agreement)

1. The pathophysiology of FAIC is largely undefined.

4 | DIAGNOSING FA-ASSOCIATED CONSTIPATION

4.1 | Differential diagnosis

Constipation is well-documented as a disorder of gut–brain interaction in early infancy and may also be a presenting symptom in many other pediatric conditions.[37] It is therefore crucial that a detailed clinical assessment is performed, accompanied with suitable tests where appropriate, to establish a correct diagnosis, which has an impact on the treatment.

A recent electronic survey collected information obtained from 2199 respondents from Russia, Indonesia, Malaysia, KSA, Mexico, Turkey, Hong Kong, and Singapore.[38] The highest reported prevalence of constipation was less than 5% in infants, which is slightly below the median of 7.8% according to a review of the literature prior to 2015.[39,40] The most widely used definition of constipation are the Rome IV criteria, who differ for non-toilet-trained and toilet-trained children.[41] While the majority of breastfed infants defecate several times a day, some breastfed infants produce stools (with a normal consistency) only once a week, which is not considered as constipation.[42] Constipation is often associated with changes in dietary habits, such as switching from breast to formula feeding or the introduction of solids, which should be taken into account in the differential diagnosis.

Constipation is a prominent symptom in children who have other underlying medical conditions such as prematurity, developmental delay, or other organic diseases, with the latter being responsible for less than 5% of children with constipation.[43] In the full-term new-born infant, the first bowel movement usually occurs within 36 h of birth but may happen later in infants who are born prematurely. Ninety percent of normal new-borns pass meconium within the first 24 h of life, and 95% within the first 48 h. Delayed emission of meconium may be a feature of Hirschsprung's disease.[44] Pediatric intestinal pseudo-obstruction is seldom a cause of constipation. It is, however, estimated that 80%–90% of infants with a meconium plug syndrome suffer from cystic fibrosis.[45]

"Infant Dyschezia" is quite frequently erroneously confused with constipation because these infants are irritable when they defecate.[41] Parents describe infants with dyschezia as straining for extended periods, crying, and grimacing with effort, until soft or liquid stools (usually daily) are passed.[41] The symptoms begin in the first months of life and resolve spontaneously after a few weeks.

While fulfilling Rome criteria is important for clinical research, infants not fulfilling all Rome IV criteria can suffer constipation as

well. Other, less stringent, definitions have been proposed such as "difficulty with defecation for at least 2 weeks, which causes significant distress to the patient."[46]

The neurologic evaluation of infants with chronic constipation should focus on symptoms and signs suggesting spinal cord and/or autonomic nervous system dysfunction, such as sensory loss or motor weakness, a patulous anus, an absent cremasteric reflex, associated bladder dysfunction, abnormal muscle tone, and/or deep tendon reflexes. Patients with truncal hypotonia (e.g., those with Down syndrome) may develop constipation because they do not efficiently generate abdominal pressure for defecation; this is a form of dyssynergic defecation.[47,48] Patients with generalized lower motor neuron dysfunction, suggested by hyporeflexia and hypotonia, develop constipation because of slow intestinal transit. In patients with upper motor neuron dysfunction, suggested by hypertonia and hyperreflexia, constipation is caused by overactive pelvic muscle contraction and inability to voluntarily relax the external anal sphincter. Abnormal deep tendon reflexes (delayed relaxation) are also seen in hypothyroidism, a rare cause of constipation in children. The perineum should be inspected for abnormalities of anorectal development, which represent a spectrum from high imperforate anus to anteriorly displaced anus. When the communication is abnormally close to the fourchette or scrotum, the anus is considered "anteriorly displaced" or "ectopic."[49]

Coeliac disease is well-known possible etiology of constipation.[50] If central hypothyroidism is suspected, the screen should include measurement of free thyroxine (T4) as well as TSH.

There is currently no specific definition for constipation in children with a non-IgE-mediated food allergy. While the Rome IV criteria for functional constipation has not been developed specifically with food allergy in mind, the ENIGMA TF, does consider this definition to be also applicable to constipation in food allergy. In addition, the TF have also added constipation symptoms listed in guidelines/publications specifically associated with food allergy to support clinicians in their allergy focused history (Table 4).[1,22,26,41]

4.2 | The role of food allergy test in FAIC

4.2.1 | Specific IgE, skin prick, and patch testing

FAIC, is thought to be a non-IgE-mediated condition, where previous studies have shown minimal use for skin prick testing and specific IgE-measurements.[54] However, Iacono et al.[52] assessed cow's milk-specific IgE (using the Phadebas RAST kit) and skin prick test for whole cow's milk, lactalbumin, casein, and b-lactalbumin in a population of 44 children (11–72 months) with a double-blind challenge-proven cow's milk-associated constipation. In this study, 11 and 20 children showed reactivity to cow's milk on skin prick and specific IgE, respectively. Following this study, Daher et al.[55] responded in a letter to the editor that they had similar findings with seven children improving on a cow's milk elimination diet and 5/7 the constipation re-occurred on an open challenge. From this cohort of 7, 5 had raised IgE levels to cow's milk and 2 had positive skin prick test (SPT). There was concern raised by Eigenmann et al.[56] about the cutoffs being used for the specific IgE for the study by Iacono et al.[52] and possible overinterpreted of SPT as many children in that study had allergic comorbidities, including eczema. The role of specific IgE to β-lactoglobulin in the gastrointestinal phenotype of CMA was studied by Poza-Guedes in 2016.[57] In that study 39/336 seen over a 12-month period with challenge-proven CMA had exclusively gastrointestinal symptoms and 12% presented with constipation. Children with confirmed extra-intestinal-cutaneous, ocular, respiratory, and/or cardiovascular-symptoms were excluded of the study group. SPT with commercial extracts (Stallergenes, Spain) of cow's milk protein were performed and measurement of the total concentration of IgE in each serum was obtained by Immuno-CAP (Phadia AB, Uppsala, Sweden). Specific IgE (sIgE) against whole cow's milk, casein, a-lactalbumin and beta-lactoglobulin were measured with a detection limit of 0.1 kIU/L. Commercial SPT test were positive in only 40% of these patients and while overall average of specific IgE levels were low to (whole milk 0.74, casein 1.74, α-lactabumin 0.83) researchers have found an average β-lactoglobulin of 4.4 (range 0.1–33.4). The authors of this study suggested that in these patients values over 0.1 kIU/L should be considered instead of 0.35 kIU/L.

The use of atopy patch testing (APT) has also been proposed to determine "delayed sensitisation"[58]; however, the latter test has yielded conflicting results in non-IgE-mediated food allergies.[59] The usefulness of patch testing was assessed by Syrigou et al.[60] on 54 children aged 6 months-14 years with chronic constipation non-responsive to 3 months of laxative therapy. All participants had a SPT, specific IgE, and APT cow's milk, egg, wheat, rice, corn, potato, chicken, beef, and soy performed. Thirty-two children had positive APT: 15 were mono-sensitized (8 to wheat, 5 to egg and 2 to rice), 6 were positive to 2 food allergens, and the remaining 11 were sensitive to three or more foods. Wheat was found to be the most common allergen testing positive in 21/32 APTs, followed by egg that was positive in 16/32, while cow's milk was positive in only three cases and sIgE and/or SPT were positive in 29/54 children. Concomitant atopy was reported in 25 children, but the study did not provide further details to whether this was eczema, rhinitis, or asthma. A dietary elimination diet was suggested, based on the APT and after 8 weeks of following this diet, 28/32 had improved symptoms, as assessed by the Rome criteria for constipation. An open food challenge followed the 8-week elimination, out of which 22 were positive (constipation returned).

The sensitivity and specificity of APT was assessed in 30 children with challenge confirmed food allergy-associated gastrointestinal symptoms. In this study, APT using lyophilized allergen extracts yielded high sensitivity (80%) and high positive predictive value (85.7%). However, APT using commercial allergen extracts yielded low sensitivity (30%) but high specificity (90%). The negative predictive value of APT using lyophilized and commercial allergen extracts was 53.8% and 32.2%, respectively. All cases with positive APT using lyophilized allergen extracts together with positive SPT also had positive OFC.[61] A meta-analysis of 41 studies

in 2019 found that in FA-related gastrointestinal symptoms in children, the pooled sensitivity and specificity were 57.40% (95% CI: 52.10–62.50) and 91.50% (95% CI: 88.30–94.10), respectively, concluding that APT is specific but not sensitive for diagnosing FA in children, especially in children with FA-related gastrointestinal symptoms.[62] More recently, a systematic review and meta-analysis of 17 studies showed that APT had a high specificity of 94% (95% CI: 0.88–0.97) in children affected by food protein induced motility disorders (including constipation). This study also showed a high pooled specificity of 96% (95% CI: 0.89–0.98) with the highest accuracy of this test in patients affected by cow's milk allergy.[63] That systematic review did not set out to establish a mechanism of non-IgE-mediated allergies in motility disorders. However, a recent study using a mouse model by Wang et al.[64] found that there is cross talk between the skin and the gastrointestinal tract, facilitated by succinate and mitochondrial DNA. While this study did not focus on the accuracy of patch test in non-IgE-mediated allergies, it may provide a possible explanation to the high pooled specificity specifically for food protein-induced motility disorders.

TABLE 2 Clinical questions related to FAIC.

1. What is the definition of constipation and FAIC?
2. What is the prevalence and natural history of FAIC?
3. What is the pathophysiology of FAIC?
4. How should FAIC be diagnosed and what are the main differential diagnosis of PAIC?
5. What is the dietary management of FAIC?
6. What is the impact of the FAIC in the quality of life of patients and their families?

4.2.2 | Other diagnostic tests

Anorectal manometry

Anorectal manometry is performed using a catheter which is inserted into the rectum in order to assess the neuromuscular function

TABLE 3 Search terms and number of publications (this excludes the publications found through snowballing of review particles).

Search term	Number of publications	Full text of publications reviewed	Number of publications included
Constipation AND Food Hypersensitivity /Allergy AND children	3022	50	17
Dysmotility AND Food Hypersensitivity/ Allergy AND children	664	22	3
Allergic constipation/ Dysmotility AND children	5086	37	6
FAIC AND children	7764	29	2
Cow's milk induced constipation AND Children	5057	3	3
Allergy focused history AND dysmotility/ constipation AND Children	1864	21	5
Constipation AND breastmilk AND Children	329	5	1
Constipation AND hypoallergenic formula	236	9	6
Constipation AND allergy AND quality of life	5612	22	2

TABLE 4 Differential diagnosis of constipation.

Cardinal symptom, taken from Rome IV Criteria	Additional symptoms	Differential diagnoses
Must include 1 month of at least 2 of the following in infants/children up to 4 years of age: • 2 or fewer defecations per week • History of excessive stool retention • History of painful or hard bowel movements • History of large-diameter stools • Presence of a large fecal mass in the rectum In toilet-trained children, the following additional criteria may be used: • At least 1 episode/week of incontinence after the acquisition of toileting skills • History of large-diameter stools that may obstruct the toilet	• Failure on standard treatment for constipation • Excessive, painful straining followed by soft stools • Perianal rash (perianal erythema)[51,52] • Anal fissures[7,53]	Dyschezia, idiopathic constipation, Hirschsprung's Disease, coeliac disease, neurological conditions, hypothyroidism

of the anus and rectum.[65] In children with CMA, anorectal manometry may demonstrate elevated anal sphincter resting pressure and impaired relaxation mimicking Hirschsprung's disease,[36,66,67] but these abnormalities are reversible with elimination diet.[68–70] If symptoms do not respond to diet and the recto-anal inhibitory reflex is absent, rectal suction biopsy may be recommended for exclusion of Hirschsprung's disease.

Endoscopy

Outside EoE, endoscopy is commonly reported in research related to the diagnoses of various non-IgE-mediated allergic conditions. Recto-sigmoidoscopy has been used to evaluate the diagnosis of food-protein induced allergic proctocolitis (FPIAP)[71] among breastfed infants with suspected non-IgE mediated CMA, with eosinophilic infiltration supporting the diagnosis; however, this procedure is unlikely to change the current practice of elimination followed by re-introduction.[72–74] 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 diarrhea).[75]

4.2.3 | Diagnostic dietary elimination

All guidelines for non-IgE-mediated allergy recommend that food elimination of common food allergens, followed by reintroduction, is the most reliable method to diagnose a non-IgE-mediated food allergy and therefore also for FAIC.[4,13] The approach to a diagnostic diet may differ between breast- and formula-fed infants, as discussed below. Constipation may be revealed when the child starts an elimination diet: parents then notice that rarity of the stools was not a constitutive trait of the child, but rather a consequence of CMA. Also, constipation may appear when reintroduction of milk starts, something frequently mentioned by the parents.

Breastfed infants

The only easily detected cow's milk protein in human breastmilk is β-lactoglobulin (levels range from 0.9 to 150 μg/L).[76] Beta-lactoglobulin is not naturally present in human breastmilk, and the presence of β-lactoglobulin indicates maternal ingestion of cow's, goat, and/ or sheep's milk.[77,78] There are, however, other allergens that are capable of inducing non-IgE-mediated food allergies through breastmilk, such as soya, wheat, and egg,[79,80] and these should be questioned during history-taking and diagnostic work-up.[81] The length of a diagnostic elimination diet varies in the literature for FA-associated constipation from 2 to 8 weeks.[2,53,82] Usually, a period between 2 and 4 weeks of maternal avoidance of the offending allergen is sufficient, while ensuring that both infant and breastfeeding mother's diet are optimized for macro- and micronutrients associated with the elimination diet.[13,26] Carroccio et al.[54] found that the majority of children with non-IgE-mediated allergy had improvement of symptoms within 4 weeks.

If symptoms resolve or a reduction in symptoms is noted,[83] then reintroduction of the allergen is required to confirm the diagnosis, to justify ongoing exclusion.[4] Mothers should reintroduce age-appropriate normal servings for cow's milk containing foods for at least 2 weeks to determine whether symptoms recur.

Formula-fed infants

Vandenplas et al.[84] published consensus-based algorithms for the diagnosis of CMA in formula-fed infants presenting with constipation. The authors suggest changing the cow's milk formula (CMF) to a partially hydrolysed formula (PHF) or extensively hydrolysed formula (EHF) to identify the role of CMA, but no elimination period was suggested for the duration of the exclusion diet. The international Milk Allergy in Primary care guidelines (iMAP), lists constipation, in combination with other symptoms, as a possible presentation of CMA, and suggested an exclusion of cow's milk formula for 2–4 weeks, using an EHF. If symptoms improve, reintroduction of cow's milk formula is suggested to confirm/refute the diagnosis. The process of home-reintroduction involves gradually replacing the EHF with standard cow's milk formula in one bottle per day over the course of 1 week and then changing all formula to cow's milk. If no symptoms occur within 1 week of the child having more than 200 mL (almost 7 fl. oz.) of cow's milk formula per day, CMA is ruled out. If symptoms recur, CMA is confirmed.[26]

Infants' formula and breastfed infants

In case of infants fed formula and breastmilk, a similar process for the diagnosis of CMA is suggested by replacing the CMF with EHF,

while the mother continues milk in her diet. Most often symptoms of CMA only occurs after the CMF was introduced.[85]

Practice points (achieving 100% agreement)

1. FAIC may be considered once organic causes and functional constipation has been ruled out and the child has failed standard treatment or when constipation relapses each time the treatment is interrupted.
2. FAIC is diagnosed according to an allergy-focused history and symptom recognition as there is a conspicuous lack of validated biomarkers.
3. The diagnostic elimination diet should ideally be implemented with the support of a registered dietitian/nutritionist or suitably qualified HCP.
4. Cow's milk is the most common allergen, but evidence shows that other allergenic food proteins including egg, soya, and wheat can also be transferred through breastmilk and should therefore also be considered as possible allergens in breastfed infants. Unwarranted elimination of multiple allergens is not advised.
5. Routine IgE testing is not recommended for establishing possible culprit foods in FPIC. Of note we also find no evidence to support the use of IgG testing to establish possible culprit foods in FPIC.
6. APT has shown high specificity, in particular in children with food protein- induced motility disorders like constipation. This test should ideally be performed under the guidance of a clinician with experience in the interpretation of this test and confirmation should occur through elimination followed by reintroduction.
7. Blood specific IgE testing may be considered if the child presents with symptoms associated with IgE-mediated allergies or comorbid presentations such as atopic dermatitis and after a long period of avoidance before home reintroduction (at discretion of physician).
8. The diagnosis of FAIC requires a 2–4-week elimination of the likely offending allergens followed by reintroduction to confirm the diagnosis.
9. Continuing with the usual dietary and medical approach for functional constipation may be required during a diagnostic elimination diet.

5 | DIETARY MANAGEMENT IN CHILDREN WITH FA-ASSOCIATED CONSTIPATION

5.1 | General

While this document is particularly focused on FAIC, healthcare professionals should also consider other dietary factors, that may be associated with the development of constipation, when taking an allergy-focused history. For infants that are on complementary foods, this includes the assessment of total fluid consumption, volume of cow's milk consumption, fiber intake, including fruit and vegetable consumption.[86,87] For infants on an infant formula only, it is important to note that calcium and fatty acid soaps were the dominant factors related to the difference in stool hardness between formula and breastfed infants.[88] In human milk, 70%–85% of palmitic acid is positioned at the sn-2 position of the triacylglycerol molecule, whereas in standard infant formulas, 88%–94% of palmitic acid is found at the sn-1 and sn-3 position. Lipolysis of triacylglycerol by pancreatic lipase occurs predominantly at the sn-1 and sn-3 positions, yielding free fatty acids and a 2-monoacylglycerol.[89] Subsequently, free palmitic acid may form insoluble calcium fatty acid soaps which are excreted via the feces, resulting in firmer stools. It is therefore important to also be aware of ingredients in standard infant formula to assess the type of palmitic acid. Tryptophan metabolites have also been shown to play a role in gut motility. Tryptophan is an essential amino acid that is found naturally in breastmilk, milk (formula milk is fortified), tuna, turkey, oats, cheese, nuts, and seeds, of which many are known allergens in pediatrics. While there is paucity of data in relation to tryptophan metabolites and non-IgE-mediated driven constipation, this may also be considered in children presenting with constipation.[90]

5.2 | Breastfeeding

Breastfeeding is strongly supported by EAACI for all children with FA. In 2020, the EAACI position statement outlining the management and diagnosis of non-IgE-mediated allergies in breastfed infants was published.[13] The literature search from that position statement was updated for the current FPIC position paper and no studies have been published assessing constipation as specific symptom for food allergies (or CMA) in breastfed infants. The paucity of data is likely to be related to three factors: constipation is difficult to diagnose in breastfed infants, the ethical consideration of performing randomized controlled studies where dietary manipulation is required in breastfed infants and the varying levels of allergens detectable in breastmilk.[42,91–93]

The detection of β-lactoglobulin, a protein unique to mammalian milks and marker of maternal consumption of cow's milk, in breastmilk has been documented, similarly for egg albumin and soya protein.[92,93] 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 presented while being exclusively breastfed.[94]

Based on the limited evidence from other non-IgE-mediated conditions in breastfed infants, following the diagnostic elimination diet (see section on diagnosis of FA-associated constipation), the maternal elimination of the offending allergens needs to be carefully monitored to avoid unnecessary food avoidance and provide micronutrient supplementation that in particular may include, vitamin D and calcium and a review or iodine, iron, and zinc intake.[13]

5.3 | Formulas suitable for FA-associated constipation

According to the published data, FAIC can occur at all pediatric ages; however, infants are most likely to be affected.[18,52,55,66,67,95–99] For

infants with FAIC when breastmilk is insufficient or not available, an infant formula suitable for cow's milk allergy is recommended. These include, EHF,[100] soy formulas (SF), hydrolysed rice formula (HRF), and amino-acid formulas (AAF).[1,4,101] By definition, a formula suitable for the dietary management of cow's milk allergy has to be tolerated by 90% of infants with a challenge proven cow's milk allergy with a 95% CI.[102] In the majority of cases an EHF or where available, a HRF is suitable as first line formula. However, in cases of constipation where there is also a history of anaphylaxis, multiple food allergy, faltering growth with multiple comorbidities (e.g., gastrointestinal manifestations and eczema), eosinophilic oesophagitis and patients that are still symptomatic on EHF, AAF should be preferred.[103]

EHF, HRF, and AAF have been investigated in a number of trials, but only a small number of studies have included constipation/or stool consistency as symptom.[18,78,104–107] While Niggemann et al.[108] included constipation as a symptom in their study investigating the tolerance of a whey-based EHF with lactose, none of the children within that study presented with this as a symptom. This is similar to the study by Burks et al.[109] assessing an AAF with new long chain fatty acid mixture, where none of the children included in the study presented with constipation. Sekkidou et al.[18] reported in a study on five children (2/3 challenge proven) the resolution in CMA-induced constipation in 3/5 on an EHF, while the rest of the patients responded to AAF. Two studies have been performed in challenge proven cow's milk-allergic infants using a casein-based EHF that was thickened, and stool consistency was assessed. In both studies, stool consistency (type I/II Bristol stool chart) improved during the assessment period. The tolerance of HRF has also been investigated in patients with non-IgE-mediated food allergy. Vandenplas et al.[104] studied 40 infants with frequent vomiting, blood in stool, diarrhea and constipation, eczema, and respiratory symptoms due in infants with challenge proven CMA. Stool consistency was improved in 50% of the participants at the end of 1 month on an HRF.

Pre, pro, and synbiotics have been assessed in children with functional constipation with varying result,[110] but limited data exists in FAFIC. Berni Canani et al.[111] has found that gut microbiota dysbiosis in non-IgE-mediated CMA, was driven by an enrichment of *Bacteroides* and *Alistipes*. It is therefore important to also assess the impact of pre/pro and symbiotic supplementation in feeds. Several studies have been performed assessing constipation in EHF and AAF supplemented with pre/probiotics or synbiotics. Vandenplas et al.[112] compared a whey-based EHF supplemented with *Bifidobacterium lactis* to a casein-based EHF supplemented with *Lactobacillus GG* in children with mild–moderate CMA confirmed by an open food challenge. For both formulas, stool consistency (including diarrhea and constipation) improved based on the Bristol stool chart. Nocerino et al.[113] reported that the incidence rate ratio of later functional gastrointestinal disorders (including constipation) development was decreased at a ratio of 40% using a casein-based EHF supplemented with *Lactobacillus GG* receiving CMA patients with gastrointestinal symptoms. The addition of a synbiotic blend using *Bifidobacterium breve*, oligofructose, and inulin has been assessed and while there was an improvement in stool frequency and consistency (for both diarrhea and soft stool constipation) this did not reach statistical significance.[114,115] Due to the varying results in studies, no current guidelines on CMA and/or CM-induced constipation make any specific recommendation about the use of pre/probiotics or synbiotics in food allergy.

While studies have found mixed results in outcome in infant formulas suitable for CMA with pre-, pro-, and synbiotics, the question on whether these should be added as a supplement, has also been asked. Previous studies have demonstrated that food allergy is associated with dysbiosis early in life.[116] These modifications may be predictive of disease persistence or tolerance acquisition. Studies have demonstrated differences in the gut microbiota composition in infants with or without food allergies develop food allergies before the development of any clinical manifestations of atopy.[117,118] There is limited evidence that *Lactobacillus reuteri* DSM 17938 may help infants with constipation. Tabbers and Benninga performed a systematic review in 2015, finding no harm in the supplementation of various strains of probiotics for constipation, but variable success in improvement of symptoms.[119]

Infant formula based on soy protein is commonly used as a cost-effective formula option for infants with a CMA. However, most guidelines for the management of CMA do not recommend this formula to be used below 6 months and not as first option above 6 months of age. While some data indicates that up to 50% have a concomitant allergy to soy in non-IgE-mediated CMA,[77,120] this is not confirmed by all published data and limited data exist on soy as a primary allergen in FAIC.[121,122] This is already acknowledged in the Australian and South African guidelines.[24,123]

5.4 | Solid food elimination

A limited number of studies have been published investigating food elimination as treatment modality in constipation. Borrelli et al.[32] assessed the elimination of cow's milk, egg, and soya in children with constipation and challenged the responders to these foods after 8 weeks of elimination. The food challenge showed recurrence of constipation in all 18 patients that improved on this diet within 2 weeks after the beginning the challenge. In that study, 10 relapsed on cow's milk, two on cow's milk and soya, four on egg, and two on egg, soya, and cow's milk. A study by Carroccio et al.[53] assessed an oligo-antigenic diet including cow's milk and its derivatives, wheat, egg, tomato, and chocolates in adults with chronic anal fissures and found that 69% of the subjects on the elimination diet improved compared to 45% in the placebo diet. Thirteen of the 60 patients had anal fissure recurrence during the 2-week cow's milk double-blind challenge and seven patients had recurrence on wheat challenge. This study found that six patients were reactive to egg, two to tomato, and two to chocolate on double-blind challenge. Other studies focused primarily on cow's milk elimination, with one study reporting that 35/69 children with an average age of 5 years with chronic constipation responded to a cow's milk elimination diet and 27/69 relapsed during a food challenge or allergen reintroduction.[98]

Similarly, 25/35 children aged between 4 and 14 years, responded to a cow's milk elimination diet, however this study did not challenge the children after the elimination diet.[124]

Practice points (achieving 100% agreement)

1. Food FAIC is rare in breastfed infants.
2. Carers should be advised on general healthy eating with sufficient fiber and fluid before embarking on an elimination diet.
3. Only food allergens proven to cause constipation through elimination and reintroduction should be avoided in the maternal elimination diet.
4. Breastfeeding mothers should ideally receive advice from a registered dietitian/nutritionist when a dietary elimination diet is commenced.
5. Micronutrient intake including vitamin D, calcium, iodine, iron, and zinc needs to be assessed in breastfeeding mothers on an elimination diet.
6. EHF is the first choice of infants' formulas in patients with FA-induced constipation when breast-feeding is not available or sufficient for a healthy growth rate.
7. Some studies with pre, pro, and synbiotics have investigated the impact on stool frequency. Data are inconsistent to make a firm recommendation in relation to FA-induced constipation.
8. While there is no harm in the addition of pre- and probiotic supplements for constipation, no recommendation for routine use can be made based on current published studies.
9. In more severe cases such as in the case of multiple food allergy, faltering growth with multiple comorbidities (e.g., gastrointestinal manifestations and eczema), and in patients when symptoms did not fully resolved on EHF, AAF should be the preferred choice of infant formula.
10. Cow's milk is the most common culprit food allergen reported in FA-associated constipation, but other allergens, including wheat, soya, and egg have also been shown to be involved based on food challenges. Unwarranted elimination of multiple allergens is not advised.
11. It is important to consider vitamin and mineral supplementations appropriate for the elimination diet, even during the diagnostic process.

6 | FOOD-ALLERGY RELATED CONSTIPATION AND QUALITY OF LIFE

Constipation has been shown to have an impact on quality of life[125] in adults and children, using both generic and constipation-specific measures. In a systematic review of 13 studies using generic scales to measure QoL in those with constipation, mental and physical QoL of children and adults was significantly impacted. This was particularly so for those seen in secondary care.[126] Similar results were seen in a review of studies using constipation-specific scales, where physical, social, and emotional QoL was affected in children and adults.[127] In some cases, QoL scores were worse than those from cardiac and rheumatological pediatric patients. The impact on QoL appears to be present even when controlling for demographic factors. In pediatric patients with functional constipation, an additional 47% of variance in generic health-related QoL was explained by the condition, after controlling for age, gender, and race/ethnicity.[128] The authors noted that stomach pain and diarrhea in particular were significant predictors of QoL.

There are no studies looking at QoL associated with FAIC. One study has looked at feeding difficulties associated with constipation in those on a cow's milk elimination diet for cow's milk protein allergy.[129] They found that picking eating, avoidant eating and feeding problems were all associated with constipation in this group. There are also no data on the effectiveness of treatments for children with constipation in improving QoL, and there is evidence to suggest that poor health-related QoL can predict greater healthcare use.[127]

Further research is needed in this area, to measure the impact of food-allergy-related constipation on QoL and the effectiveness of treatments to improve QoL. There are no validated scales to measure food-allergy-related QoL; however, generic scales such as SF36, the PedsQL or the Child Health Questionnaire-Parent Form (CHQ-PF50) have been used to measure generic QoL in those with constipation. These are very useful when measuring and comparing QoL across different conditions. For measuring constipation-specific QoL, the PedsQL has a gastro-intestinal symptoms module, which can be used by patients with constipation, with versions for children (aged 5–18 years) and a parent proxies (for 2–4 years and 5–18 years).[130] Other scales such as Defecation Disorder List (valid for aged 7-15 years) are also available.[127] These specific scales are able to measure health-related QoL that is more sensitive to issues related to constipation, but it should be noted that they may still not measure all aspects of QoL that are important in food-allergy-related constipation.

Practice points (achieving 100% agreement)

1. Constipation can have a significant impact on the QoL of children.
2. Further research is needed to understand the specific impact of food allergy-related constipation.
3. No validated food allergy-related constipation QoL scales exist and so care should be taken when deciding on how to measure QoL in this patient group.

7 | CONCLUSION

FPIC may be considered when organic causes have been ruled out and standard treatment has been failed. The cornerstone of the diagnosis remains an allergy focused history followed by a targeted elimination diet and then reintroduction of the culprit food (s) to avoid the unnecessary elimination of allergens. The most commonly reported food allergy in the context of constipation is cow's milk, but other allergens have also been implied in the research assessed. This TF acknowledges the paucity of research in this area

of non-IgE-mediated allergies and supports future randomized controlled trials in this area of food allergy.

AUTHOR CONTRIBUTIONS

Rosan Meyer: Conceptualization; writing – original draft; methodology; project administration; supervision; resources; writing – review and editing; funding acquisition. **Yvan Vandenplas:** Conceptualization; writing – review and editing; methodology. **Adriana Chebar Lozinsky:** Conceptualization; writing – review and editing; methodology; validation. **Mario C. Vieira:** Conceptualization; writing – review and editing; validation. **Roberto Berni Canani:** Writing – review and editing; validation; conceptualization. **George du Toit:** Conceptualization; writing – review and editing; validation. **Christophe Dupont:** Conceptualization; writing – review and editing; validation. **Mattia Giovannini:** Conceptualization; validation; writing – review and editing. **Pinar Uysal:** Conceptualization; writing – review and editing; validation. **Ozlem Cavkaytar:** Conceptualization; validation; writing – review and editing. **Rebecca Knibb:** Conceptualization; writing – review and editing; validation. **David M. Fleischer:** Conceptualization; writing – review and editing; validation. **Anna Nowak-Wegrzyn:** Conceptualization; writing – review and editing; validation. **Carina Venter:** Conceptualization; writing – review and editing; validation; methodology.

AFFILIATIONS

[1]Department of Nutrition and Dietetics, University of Winchester, Winchester, UK
[2]Department of Medicine, KU Leuven, Leuven, Belgium
[3]KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussel, Belgium
[4]Department of Allergy and Immune Disorders, Murdoch Children's Research Institute, Parkville, Victoria, Australia
[5]Center for Pediatric Gastroenterology – Hospital Pequeno Príncipe, Curitiba, Brazil
[6]Department of Translational Medical Science and ImmunoNutritionLab at CEINGE – Advanced Biotechnologies Research Center, University of Naples "Federico II", Naples, Italy
[7]Department of Women and Children's Health (Paediatric Allergy), School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK
[8]Children's Allergy Service, Evelina London Children's Hospital, Guy's and St Thomas' Hospital, London, UK
[9]Department of Paediatric Gastroenterology, Necker University Children Hospital, Paris, France
[10]Allergy Unit, Meyer Children's Hospital IRCCS, Florence, Italy
[11]Department of Health Sciences, University of Florence, Florence, Italy
[12]Department of Allergy and Clinical Immunology, Adnan Menderes University, Aydin, Turkey
[13]Department of Pediatric Allergy and Immunology, Istanbul Medeniyet University, Faculty of Medicine, Goztepe Prof Suleyman Yalcin City Hospital, Istanbul, Turkey
[14]School of Psychology, Aston University, Birmingham, UK
[15]University of Colorado Denver School of Medicine, Children's Hospital Colorado, Aurora, Colorado, USA
[16]Icahn School of Medicine at Mount Sinai, Jaffe Food Allergy Institute, New York, New York, USA

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ORCID

Rosan Meyer https://orcid.org/0000-0002-5710-5570
Yvan Vandenplas https://orcid.org/0000-0002-1862-8651
Christophe Dupont https://orcid.org/0000-0002-4943-6329
Mattia Giovannini https://orcid.org/0000-0001-9568-6882
Pinar Uysal https://orcid.org/0000-0003-0288-608X
Ozlem Cavkaytar https://orcid.org/0000-0002-5747-7032
Rebecca Knibb https://orcid.org/0000-0001-5561-0904
Carina Venter https://orcid.org/0000-0002-7473-5355

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