

A REVIEW ON THE DIAGNOSIS AND MANAGEMENT OF FOOD-INDUCED GASTROINTESTINAL ALLERGIES

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ABSTRACT

The prevalence of food allergy in children between 0 and 3 years of age ranges between 2.1% and 4.2%. Food allergies are caused by cow's milk, hen's egg, soya bean, wheat, peanut, tree nuts, fish and shellfish in 90% of cases. Food-induced gastrointestinal allergies according to current classifications are either non-immunoglobulin E (IgE)-mediated or mixed IgE and non-IgE-mediated. Because of the continually evolving knowledge on the pathophysiology of gastrointestinal food allergies, this condition continues to pose significant diagnostic and management dilemmas, as there are no specific diagnostic tests and there is paucity of data on diagnostic elimination diets. The most common involved allergens in food-induced gastrointestinal allergies include cow's milk, soya, egg and wheat. However, in some cases other allergens including beef, rice, chicken and nuts have been implicated. In the absence of breast milk and maternal dietary exclusion, the correct choice of hypoallergenic formula is an integral part of optimal dietary management and should be considered carefully. However, dietary elimination in many cases does not lead to complete symptom resolution and may require the targeted introduction of medication. Further research is required to allow for a more targeted dietary exclusion, as well as guiding the medical management.

The prevalence of food allergy in children between 0 and 3 years of age ranges between 2.1% and 4.2%. In 90% of cases, it is caused by 8 foods, namely cow's milk, hen's egg, soya bean, wheat, peanut, tree nuts, fish and shellfish.¹⁻³ Typically, food allergy symptoms involve the skin, respiratory system and gastrointestinal tract and can occur immediately after ingestion of an allergen or develop over several hours/days.⁴

Although our general understanding of food allergies has improved significantly over the last decade, food-induced gastrointestinal allergies continue to pose significant diagnostic and management dilemmas, related to the still-evolving understanding of these conditions and a lack in diagnostic tests.⁵ This publication therefore aims to review current clinical evidence related to both diagnosis and management of food-induced gastrointestinal allergies, and to translate this evidence into practical advice.

CLASSIFICATION

The classification of food-induced gastrointestinal allergies remains challenging despite up to 60% of children with all types of food allergies presenting with varying severity of gastrointestinal symptoms. In 2004 the World Allergy Organization (WAO) published its no-

menclature for food hypersensitivity. According to this classification a food allergy is an immune-mediated adverse food reaction and can be either immunoglobulin E (IgE)-mediated or non-IgE-mediated.⁶ More recently the National Institute of Allergy and Infectious Disease (NIAID) published an updated version of the classification of food hypersensitivity and have added mixed IgE- and non-IgE-mediated reactions (Fig. 1).⁷ Food-induced gastrointestinal allergies according to this classification are either non-IgE-mediated or mixed IgE- and non-IgE-mediated (Table I).⁷⁻¹⁰

Unlike the well-described pathophysiology of IgE-mediated reactions,¹¹ non-IgE-mediated gastrointestinal reactions are poorly defined. Several factors are thought to be involved in the pathophysiology of this type of food allergy: failure to develop oral tolerance to exposed allergens, altered intestinal bacterial flora, intestinal mucosal barrier dysfunction, transepithelial transport of antigens, eosinophil recruitment and the impact of food antigens on intestinal motility.⁵ Table II^{5,12} describes the presumed impact of each of these factors on the development of this type of allergy. In essence these disorders are predominantly mediated by cells such as eosinophils and lymphocytes, recruited by T-helper 2 (Th2) cytokines.

DIAGNOSIS

Slower-developing gastrointestinal food allergic reactions are difficult to diagnose, compounded by a lack of diagnostic tests to confirm a suspected diagnosis.⁵

Table I. Classification of food-induced gastrointestinal food allergy and typical symptoms⁷⁻¹⁰

Mixed IgE and cell-mediated (immediate to delayed-onset reactions)

Allergic eosinophilic oesophagitis (EOE)

Non-IgE-mediated (delayed onset)

Food protein-induced enterocolitis

Food protein-induced proctocolitis

Food protein-induced enterocolitis syndrome (FPIES)

Eosinophilic gastritis

Eosinophilic enteritis

Eosinophilic colitis

Eosinophilic gastroenteritis

Common reported symptoms

Vomiting

Diarrhoea

Constipation

Blood/mucus in stools

Gastro-oesophageal reflux

Perianal redness

Infantile colic

Food refusal/aversion with swallowing difficulties (i.e. gagging on solids, regurgitation of textured foods)

Colicky abdominal pain

Faltering growth and one or more of the gastrointestinal symptoms above (with or without serious atopic eczema)

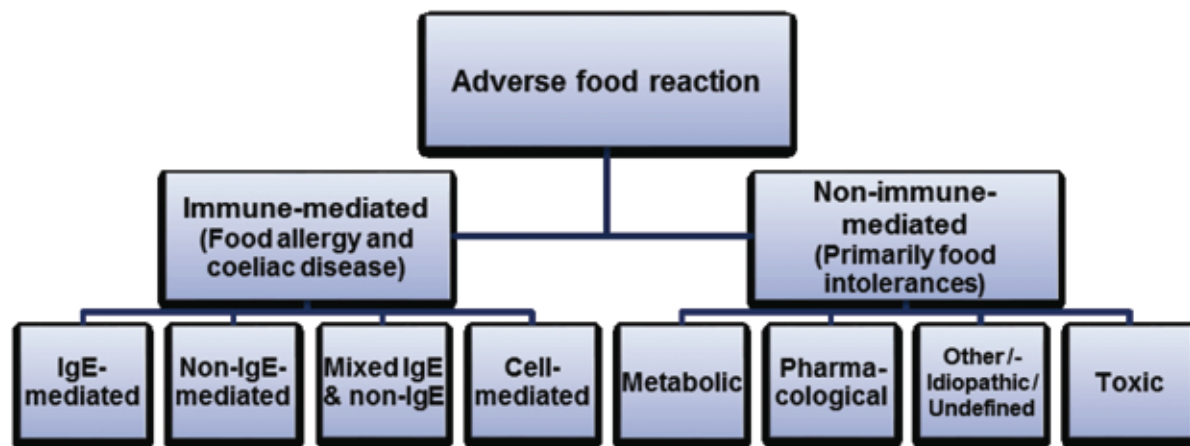


Fig. 1. Classification of food hypersensitivity according to the NIAID (amended from publication by Boyce et al. ⁷).

Most patients with gastrointestinal food allergic disorders have no evidence of systemic IgE sensitisation, hence food-specific IgE antibodies and skin-prick tests (SPTs) are often negative.^{13,14} Atopy patch testing has been used with varying success and reproducibility in aiding the diagnosis, in particular for eosinophilic oesophagitis (EOE).^{15,16} Varying levels of sensitivity and specificity, depending on the individual food and whether commercial extracts or fresh foods are used, have been found in studies of atopy patch tests.¹⁷ Spergel *et al.*¹⁸ suggest that patch testing may add another dimension to our ability to diagnose gastrointestinal food allergy, but if performed, should be used in conjunction with diagnostic elimination diets, food challenges and, if indicated, SPTs and specific IgE.

Recently there has also been a trend in using IgG4 antibody tests to establish gastrointestinal food allergies. Both the European Academy for Allergy and Clinical Immunology (EAACI) and the American Academy for Allergy, Asthma and Immunology (AAAAI) are clear in their guidance regarding this test.^{19,20} Food-specific IgG4 does not indicate food allergy or intolerance, but rather a physiological response of the immune system after exposure to food components. Therefore, testing for IgG4 to foods is considered as irrelevant for the laboratory work-up of food allergy or intolerance and should not be performed in case of food-related complaints.²⁰ Recently guidelines have been published by Liacouras *et al.*²¹ clarifying the diagnostic criteria for EOE. The

diagnosis is a clinicopathological one with the histological gold standard being 15 or greater eosinophils in the oesophageal biopsy on any one high-power microscopic field (x40 magnification). This is a minimum requirement and a diagnosis should include careful and precise consideration of all clinical and pathological information. Neither of these parameters should be interpreted in isolation and for optimal evaluation, multiple biopsy specimens from the proximal and distal oesophagus should be obtained and evaluated for a variety of pathological features.²¹

Gastrointestinal biopsies also play an important role in determining eosinophilic inflammation and/or villous atrophy of the lower gastrointestinal tract in food-induced gastrointestinal allergies and can be very useful in determining a diagnosis.^{5,22}

The cornerstone for diagnosing non-IgE-mediated gastrointestinal food allergies remains an allergy-focused history (Tables I and III),^{5,23-27} followed by a targeted elimination diet with resolution of symptoms, and recurrence of symptoms on re-introduction of foods. There is paucity of data on the length of a diagnostic elimination diet; some recommend 2-4 weeks and others 4-6 weeks.^{16,28,29} From a practical perspective, taking into account that such an elimination diet is new and complex for patients/parents and may require at least 1 week for proper implementation, it seems advisable to recommend 4 weeks' exclusion instead of 2.

Table II. Proposed pathophysiological mechanisms of food-induced gastrointestinal allergies^{5,12}

Factors	Proposed pathophysiology
Oral tolerance	Oral tolerance requires transforming growth factor- β (TGF- β). Several studies found low TGF- β levels in gastrointestinal food allergic children. Th3 lymphocytes are involved in regulating oral tolerance development in response to stimulation by microbial antigens. Failure to generate Th3 cells, as a result of insufficient stimulation of innate immune responses by commensal intestinal microbes, may be a factor contributing to impaired development of oral tolerance.
Bacterial flora	Differences between atopic and non-atopic children have been found in bacterial flora. These bacteria interact with the gut-associated immune system via toll-like receptors. It is thought that microbial stimulation of the infant's immune system modulates early adaptive immune responses from a Th2 to a Th1-type cytokine profile.
Intestinal barrier function	Increased gut permeability has been described in food allergic children. Tumour necrosis factor- α , secreted by activated T lymphocytes, may increase intestinal permeability, whereas TGF- β improves mucosal barrier function (see oral tolerance).
Transepithelial transport of antigens	A disrupted mucosal intestinal barrier increases direct exposure of luminal antigens to mast cells in the lamina propria.
Eosinophilic recruitment	IL-5, one of the Th-2 cytokines, is important for the trafficking of eosinophils, in addition to eotaxin-1, a small cytokine which selectively recruits eosinophils by inducing their chemotaxis.
Intestinal motility	Electrophysiological studies have demonstrated gastric dysrhythmias in infants with food allergies. The exact mechanisms are unclear, but it may be related to the release of mast cell and eosinophil mediators, which impact on the mucosal plexus networks or may stimulate the release of motility-active gut hormones, such as motilin or vasoactive intestinal peptide.

Table III. Taking an allergy-focused history in children with suspected gastrointestinal food allergies

Questions should aim to establish the following:	Significance
What is the food allergen causing the reported reaction?	The most commonly reported allergens causing gastrointestinal food allergies include: cow's milk, soya, hen's egg and wheat. ⁵
What is the timing of the reaction post exposure?	Reactions are typically delayed in nature (>2 hours up until 2-3 days post exposure), except for FPIES which may occur rapidly after ingestion of an allergen. ⁵
What are the allergic symptoms?	While symptoms are usually typical (Table I), food-induced gastrointestinal reactions may not always be obvious, e.g. the young infant with silent reflux may refuse to breastfeed/drink a formula. In addition to the major symptoms described in Table I, extra-intestinal manifestations have been described in these children including: nocturia, joint pain, headaches and night-time sweating. ⁹
When do symptoms occur?	Time of occurrence of symptoms may indicate the region of the affected gastrointestinal tract.
Is there a prior history of tolerance to the offending food?	It is rare to have a history of ongoing tolerance to food allergens (i.e. cow's milk and soy) and then to develop an allergy. Most infants with food-induced gastrointestinal allergies present during infancy (<1 year) following the introduction of one of the major allergens.
Concomitant disease, and in particular, allergic disease?	About 40% of children with gastrointestinal food allergies have concomitant atopic dermatitis in early infancy and many will develop asthma in later childhood. ^{9,26,27}
Growth and feeding history in relation to introduction of major allergens?	Growth faltering often occurs in children with food-induced gastrointestinal allergies, because of malabsorption of major nutrients and reduced intake. ^{23,24} Aversive feeding is in particular a common symptom in children with food-induced eosinophilic gastrointestinal disorders. ²⁵

DESCRIPTION OF FOOD-INDUCED GASTRO-INTESTINAL ALLERGIES

Allergic eosinophilic gastroenteropathies

First described by Kaijser in 1937, this heterogeneous group of conditions is characterised by eosinophilic inflammation in the gut.³⁰ These enteropathies are classified according to the site of the inflammation and it is the depth and severity of the inflammation which influences the presenting symptoms. The spectrum of pathologies (often with overlapping symptoms) includes EOE, the most common of these conditions, eosinophilic gastroenteritis and eosinophilic gastroenterocolitis. While EOE is clearly associated with the atopic phenotype, the underlying mechanism remains uncertain. The local production of eotaxin, a potent eosinophil chemo-attractant, appears to be pivotal. Inhalant allergens may also be implicated in older children and adolescents with EOE. Although dietary exclusions are essential, they are often not sufficient to control symptoms and pharmacological management is required (see below).

Food protein-induced proctocolitis

This is a disease of infancy, usually presenting by 2 months of age and represents the benign end of the spectrum of non-IgE-mediated allergy to cow's milk protein (CMP).³¹ Infants usually present with colic-like symptoms and visible fresh blood mixed with mucus in the stool, but are otherwise thriving.³² It is surprisingly more common in, but not exclusive to, breastfed babies whose mothers are ingesting cow's milk or soy protein.¹⁴ Important differential diagnoses include intestinal infection and anal fissures. The diagnosis is usually made on the basis of a response to the exclusion of cow's milk and soy from the lactating mother's diet and/or by substitution of breast milk with a hypo-allergenic formula. Bleeding usually resolves within 72 hours, although persistent bleeding may only respond to an amino acid-based formula (AAF). The underlying

mechanism is unclear.³³ SPTs and specific IgE to allergens are also typically negative.

Food protein-induced enteropathy

Unlike proctocolitis, infants with enteropathy usually have protracted diarrhoea, occasionally with vomiting.³² This may result in malabsorption and faltering growth; a firm diagnosis is therefore very important. Diagnosis is usually made on a combination of clinical response to food exclusion and, if needed, small-bowel biopsy. Histological findings include mucosal inflammation and distortion of the villous architecture with a 'patchy' distribution, features that may be difficult to distinguish from untreated coeliac disease.³⁴

Food protein-induced enterocolitis syndrome

Despite being described as far back as 1967, food protein-induced enterocolitis syndrome (FPIES),³⁵ remains an underdiagnosed condition for which there are many food triggers including cow's milk and soy (most common triggers), but also cereal grains (rice, oat and barley), fish, poultry, and vegetables.³⁶ While conditions described above may all present with overlapping clinical features,³⁷ FPIES represents the severe end of gastrointestinal food allergies.³⁸ FPIES is an acute cell-mediated, gastrointestinal food hypersensitivity characterised by severe protracted diarrhoea and vomiting, pallor and hypotonia,^{12,39,40} and symptoms can appear between 1 and 3 hours after ingestion. Progression can occur to a state of dehydration; hypovolaemic shock is described in 20% of cases.^{41,42} The combination of vomiting, lethargy and resulting acidosis in the infant may lead to a false diagnosis of sepsis; however, symptoms typically recur upon reintroduction of the food. A leucocytosis with raised neutrophils is common in FPIES.¹² Failure to recognise the link with a dietary allergen may lead to multiple admissions.⁴² The presence of the above findings in association with bloody diarrhoea may also lead to a clinical suspicion of infective diarrhoea, coagulation defects or intussusception.⁴³ However fever is uncommon.

mon, suggesting a non-infective cause. The presence of eosinophilic debris in the stools, and negative stool cultures can also help differentiate FPIES from alternative diagnoses. Symptoms rapidly resolve on a diet free of the offending allergen. Patients with FPIES classically have no raised specific IgE and are negative on skin-prick testing. Endoscopy is often unhelpful as infants may remain well between challenges.⁴⁴ Atypical cases have been described with detectable IgE to the causal protein and with a more prolonged course of allergy.⁴⁰

Allergic dysmotility

Essentially, all clinical gastrointestinal presentations in non-IgE-mediated allergies represent a dysmotile event, including vomiting, gastro-oesophageal reflux (GOR), constipation, intestinal colic and diarrhoea. Allergic gastrointestinal motility disorders are common in infancy and early childhood.^{45,46} The exact mechanisms of delayed-onset allergic gastrointestinal dysmotility are slowly being unravelled with a focus on interaction of inflammatory cells such as mast cells and eosinophils within the enteric nervous system, known as a 'neuro-immune' interaction.⁴⁵⁻⁴⁷ Human gastric biopsy studies have demonstrated that mast cells can degranulate in a matter of minutes post exposure to the food allergen, with associated disruption of normal gastric peristalsis. Food allergens may also trigger transient lower oesophageal sphincter relaxations resulting in GOR episodes.⁴⁸

Food allergens, in particular CMP, have been suggested as the underlying cause in up to 40% of diagnosed GOR in infants and young children.⁴⁹ It may be clinically difficult to distinguish food protein-induced reflux episodes from other causes of reflux. In GOR disorder (GORD) secondary to CMP allergy (CMPA), symptoms usually but not always resolve within 2 weeks of commencing a suitable hypoallergenic formula. Therefore a longer period of exclusion may be required in addition to extending the number of foods to be eliminated. Similar to other food-induced gastrointestinal allergies, food-allergy-mediated GORD may require further pharmacological management as outlined below.

Clinical features associated with food protein-induced GOR include feeding difficulties, colic-like symptoms, and abnormal posturing such as back arching known as Sandifer's syndrome. Non-specific symptoms such as persistent crying are often reported as a sign of gastrointestinal allergy in children and one of the most common reasons for parents to request specialist input. These non-specific symptoms should be taken into account as part of an allergen-focused history. Children with food-induced GOR often have had little or no response to a multitude of anti-reflux medications. Significant aversive feeding, including feed refusal and gagging on solids is often associated with food-allergy-related GORD.^{25,50,51} CMP influences the ability of the stomach to distend (known as poor compliance) and rhythmically contract. This manifests as an inability to consume large volumes of feeds, vomiting on liquids more than solids and delayed gastric passage such as vomiting of curdled milk.

The differential diagnosis of food-protein-induced GORD includes EOE, mechanical obstruction (which usually presents with bilious vomits), chronic low-grade infections such as urinary tract infections and space-occupying brain lesions.

Food protein, in particular CMP, has also been implicated as a cause of constipation.^{52,53} The neural-inflammatory response in the lower gastrointestinal tract may cause insensitivity of the external anal sphincter, so an infant may strain excessively to defecate but pass normal consistency stools.⁵⁴ Food allergens should be consid-

ered as a possible cause of intractable constipation in young infants who develop hard and infrequent stools or have difficulty in passing normal consistency stools corresponding to the dietary introduction of cow's milk and occasionally wheat.⁵⁵ This clinical presentation may mimic Hirschsprung's disease. Increased numbers of mucosal eosinophils on rectal biopsy suggest an allergic aetiology, while the presence of submucosal ganglia excludes Hirschsprung's disease.⁵⁶ Empirical treatment relies on a suitable hypoallergenic formula and elimination diet for at least 4 weeks. In responders, reintroduction of the offending allergen (i.e. CMP) may be attempted after 3-6 months.

DIETARY MANAGEMENT

General

The mainstay of treatment for gastrointestinal food allergies in children is the complete avoidance of all offending allergens. The most commonly reported causative foods eliciting gastrointestinal symptoms include cow's milk, soy, egg and wheat,⁵⁷ however, one has to take into account that in conditions like FPIES and EOE, other foods including rice, chicken, beef, corn, peanut, potato and on rare occasions vegetables/fruit have been indicated.^{42,58} There is a lack of consensus whether to initiate dietary elimination in gastrointestinal disorders using the 'top-down approach', which avoids a wide variety of foods or even uses an elemental diet and then reintroduces foods singly to establish an allergic reaction, versus the 'bottom-up approach' where a small number of foods are avoided and the elimination diet is expanded according to continuing symptoms. This choice should be based on an allergen-focused history, assessing the severity of symptoms, and growth parameters. It is well known that unnecessary food avoidance may lead to nutritional deficiencies, particularly in children with increased requirements or losses leading to macro- and micronutrient deficiencies.^{23,59} It is therefore important to consider the impact of such an elimination diet on the child's health and involve a qualified dietitian for specialised dietary advice. Table IV provides guidance on how to avoid common gastrointestinal allergens in addition to the nutrients involved with each allergen.⁵⁷

Hypoallergenic formula

Breast milk remains, also for the young child with gastrointestinal food allergies, the 'gold standard' source of nutrition. Although cow's milk β -lactoglobulin, soy isoflavone and egg ovalbumin can be detected in the breast milk of lactating women, the amount is insignificant to many of the infants with food-induced gastrointestinal allergies and strict maternal elimination is not always necessary.⁶⁰⁻⁶² However, if symptoms persist in the breastfed infant, a strict maternal exclusion diet may be required. With such a dietary intervention, it is important to consider the adequacy of the lactating mother's dietary intake, specifically calcium and protein requirements.

Most children with food-induced gastrointestinal allergies who are not breastfed, will require a hypoallergenic formula; therefore, it is important to understand the indications for each different formula. Hypoallergenic formulas can be defined using clinical criteria or through analysis of constituent proteins. The clinical definitions state that a hypoallergenic formula should be tolerated by 90% of cow's-milk-allergic infants (with a 95% confidence interval).⁶³ Formulas are also classified according to the degree of protein hydrolysis; extensively hydrolysed formulas (EHF) contain peptides with molecular weights less than 3 000 Da, whereas partially hydrolysed formulas (PHF) contain peptides with molecular

Table IV. Common food allergens, nutrients and alternatives (amended from Venter & Meyer)⁵⁷

Sources	Other terms	Nutrients involved	Alternatives
Milk	Butter/most fat spreads, cheese, cow/sheep/goat milk, evaporated/-condensed milk, cream, ghee, yoghurt, ice creams, custard, dairy desserts and manufactured foods using milk or butter in their ingredients	Casein, caseinates, curd, lactoglobulin, lactose, milk solids, whey, buttermilk, milk sugar, whey, sugar whey syrup sweetener	Vitamin A, vitamin D, riboflavin, pantothenic acid, cyanocobalamin, calcium, magnesium, phosphate
Egg	Egg white and yolk, cakes, biscuits, speciality breads, mayonnaise, glazing, batter	Albumin, dried egg, egg powder, egg protein, frozen egg, globulin, lecithin (E322), livetin, ovalbumin, ovomucin, ovovitellin, pasteurised egg, vitellin	Riboflavin, biotin, protein, vitamin A, cyanocobalamin, vitamin D, vitamin E, pantothenic acid, selenium, iodine, folate
Wheat	Bread, breakfast cereals, pasta, cakes, biscuits, crackers, cold cooked meat, pies, batter, flour, semolina, couscous, bottled sauces and gravies	Bran, cereal filler, farina, starch, wheat, durum wheat, semolina, spelt, kamut, wheat bran, wheat gluten, wheat starch, wheat germ oil, hydrolysed wheat protein, triticale, bulgar wheat	Fibre, thiamine, riboflavin, niacin, calcium, iron, folate if fortified
Soya	Soya sauce, soya products, meat substitutes, breads, vegetarian/vegan foods, processed meat, e.g. hot dogs, foods labelled as 'diet' and 'high-protein'	Soya beans, soya flour, soya protein/gum/starch, texturised (or hydrolysed) vegetable protein, soya flavouring, soya lecithin (E322)	Thiamin, riboflavin, pyridoxine, folate, calcium, phosphorus, magnesium, iron, zinc, protein, fibre.

Under 6 months:
EHF, AA
Above 6 months- 2 years:
EHF, AAF, soy formula
Over 2 years:
Rice milk, soya milk, oat milk, potato milk, almond milk, coconut milk, pea milk
Other foods:
Milk-free versions of spreading fats, cheese, yoghurts, ice cream and cream

Egg replacers
Adjust recipes with extra liquid or fruit purées.
Variety of egg-free products such as mayonnaise, cakes, muffins, puddings, and omelette mix

Corn, rice, potato, cassava, yam, quinoa, millet, gram (chick pea), sago, tapioca, amaranth, buckwheat.
Wheat and/or gluten free foods. Barley, rye and oats may be tolerated by some individuals with wheat allergy or intolerance. Oats may be tolerated by some individuals with celiac disease

Cow's milk (if not cow's milk allergic), rice milk, soya milk, oat milk, potato milk, almond milk, coconut milk, pea milk, meat, fish, poultry or other non-soya vegetarian alternatives

weights ranging from 3 000 to 10 000 Da.^{29,60} PHF do not meet the clinical criteria of hypoallergenicity and should not be used for infants with cow's milk allergy.

It is thought that 2-10% of infants with IgE-mediated disease continue to react to EHF and will require an AAF.^{64,65} This is related to the residual CMP β -lactoglobulin (0.84-14.5 μ g/l) detected in EHF.⁶⁰ However, Latcham *et al.*²⁶ found that 29.7% of the children in their retrospective study with non-IgE-mediated gastrointestinal allergies were intolerant to EHF. A systematic review by Hill *et al.*⁶⁶ found that EHF are efficacious at relieving CMPA symptoms in the majority of infants. However, infants with non-IgE-mediated food-induced gastroenterocolitis and proctitis syndromes with faltering growth, severe atopic eczema, or symptomatic during exclusive breastfeeding, were more likely overall to benefit from AAF.⁶⁶ Figure 2 provides a proposed algorithm,⁶⁷ based on current evidence, on the choice of hypoallergenic formula.

Concomitant soya allergy in non-IgE-mediated cow's milk allergy is thought to be as high as 50%, especially in enterocolitis/enteropathy syndromes.^{29,68,69} This is in contrast to the significantly lower levels of soya allergy (7-14%) in cow's-milk-allergic infants with IgE-mediated disease.⁷⁰ In addition, higher rates of adverse reactions to soya are reported in infants below 6 months of age in both IgE- and non-IgE-mediated allergies.⁶⁹ The WAO²⁹ has therefore published guidelines recommending that

soya formulas should not be used below 6 months of age and that EHF or AAF should be the preferred feed. For children with gastrointestinal food allergies >6 months of age, in particular EHF and AAF should be used in preference.

PHARMACOLOGICAL MANAGEMENT

Dietary exclusions in some cases do not lead to full symptom resolution and the condition requires additional pharmacological management, especially in children presenting to tertiary specialist services. In patients with EOE the consensus guidelines from Liacouras *et al.*²¹ provide some guidance on the use of pharmacological agents. According to these guidelines proton pump inhibitors (PPI) are useful to help eliminate GORD as a cause of oesophageal eosinophilia with a recommended dose of omeprazole of 2.6 mg/kg/day, for 8-12 weeks in children. In addition topical corticosteroid therapy should be considered in all children given a diagnosis of EOE for both initial and maintenance therapy (i.e. fluticasone 88-440 μ g 2-4/day, budesonide slurry under 10 years 1 mg/daily and older children 2 mg daily). For severe cases of EOE with reported weight loss, small-calibre oesophagus and hospitalisation, systemic corticosteroids can also be used (i.e. 1-2 mg/kg per day).²¹

The pharmacological management of other food-induced gastrointestinal allergies are less well defined

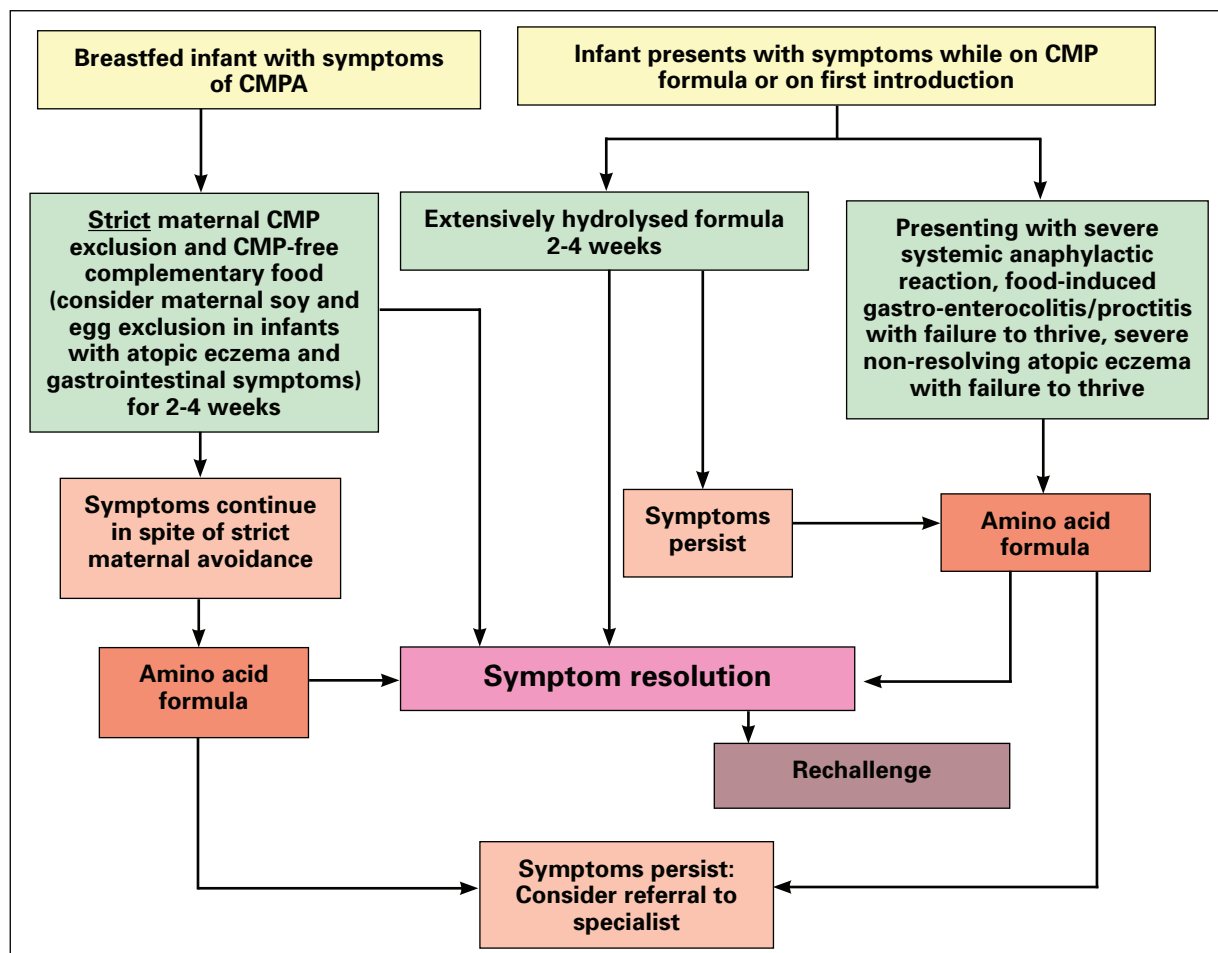


Fig. 2. Suggested algorithm for the choice of hypoallergenic formula.⁶⁷

than EOE, as most information available comes from case reports based on a small number of patients.⁷¹ Therefore, insufficient evidence is available to guarantee clinical effectiveness. However, the most common other pharmacological agents include the mast cell stabiliser sodium cromoglycate with varying success, in particular in eosinophilic gastroenteritis.⁷² Ketotifen and H1-antihistamines have also been used with varying success in addition to the leukotriene antagonist montelukast.^{73,74}

NATURAL HISTORY OF GASTROINTESTINAL FOOD ALLERGIES

Unlike the well-described natural progression of IgE-mediated food allergies, which is constantly updated by new data on the development of tolerance,^{75,76} there are limited data on the progression of disease in the delayed-type food-induced gastrointestinal allergies. Whereas it was previously believed that many of these conditions, including food protein-induced proctocolitis and enteropathy have a good prognosis,^{8,31,33} recent studies have hinted towards the development of tolerance much later than previously thought, as well as progression of food-induced gastrointestinal allergies into functional gastrointestinal disorders in later life. Saps *et al.*⁷⁷ found that 44.2% of 8-year-old children, who had cow's milk allergy below 1 year of age, had functional gastrointestinal disorders including constipation, diarrhoea and significant abdominal pain. The persistence of cow's milk allergy was not ruled out in the children studied. Similarly Kokkonen *et al.*⁷⁸ evaluated 10-year-olds who presented with CMPA below 1 year of age and found that 45% had residual gastrointestinal symptoms to CMP at this age. It is therefore important to

monitor these patients routinely and challenge children with the offending food allergens at regular intervals using validated challenge protocols. Many children may tolerate baked milk and egg at an earlier stage, prior to developing full tolerance.^{79,80}

CONCLUSION

Food-induced gastrointestinal allergies fall mainly under non-IgE-mediated, delayed-type food hypersensitivities. The diagnosis of this food allergy remains a challenge despite the evolving understanding on the pathophysiology. The mainstay of management remains targeted dietary exclusion, which requires the input of a qualified dietitian, to ensure nutritional adequacy. However, a significant number of children will only have partial resolution on dietary elimination, which will require further input from a gastroenterologist. Further research is required to allow for a more targeted dietary exclusion as well as guiding the medical management.

Declaration of conflict of interest

None of the authors has any association/affiliation with any commercial companies. Authors are employed by the National Health Service within the UK and declare no conflict of interest.

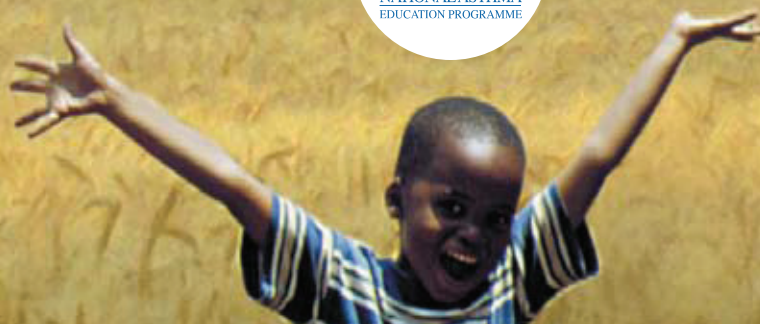
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