

Dietetic management of non-IgE mediated allergies in children

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Introduction

The World Allergy Organisation defines any adverse reaction to food as Food Hypersensitivity. This can be divided into immune-mediated reactions (Food Allergy) and non-immune mediated reactions (Food Intolerance). Food allergic reactions include both Immunoglobulin E (IgE) (immediate-onset) and non IgE-mediated (delayed-onset >2 hs) reactions. Non-IgE mediated reactions typically affect the gastrointestinal tract and skin, with the latter (i.e. eczema) often being classified as a mixed IgE and non-IgE mediated condition. Children usually present with a combination of symptoms that are summarised in [Table 1](#).

Prevalence

Worldwide, the prevalence of non-IgE mediated allergies is not well established, due to the absence of reliable tests and the length of time it takes for symptoms to develop. Double blind food challenges, the gold standard for prevalence studies, are difficult and require significant resources to admit children for several days of observation, following a challenge. Data from the United Kingdom (UK) has indicated that around 60% of children “with food allergy” present with gastrointestinal and skin symptoms.

The recent Europrevall study provides the most accurate prevalence data for non-IgE mediated cow’s milk protein allergy (CMPA). The overall prevalence in Europe was below 1% but from that cohort, the UK had one of the highest incidence rates at 1.28%. However, the Europrevall study design may have not adequately identified all children with delayed allergy. Moreover, non-IgE mediated allergies occur to other common allergens, therefore it is very likely that the prevalence matches (or is even higher) than IgE mediated allergies.

Diagnosis of non-IgE mediated allergies

The diagnosis of most non-IgE mediated allergies is reliant on an elimination diet and reintroduction. (The exception to this generalisation is the eosinophilic disorders which can be confirmed by endoscopy and biopsy.) If symptom improvement occurs following the elimination diet, then confirmation of a non-IgE mediated allergy requires the reintroduction of the allergen(s) to coincide with reoccurrence of symptoms. There is great variation in current guidelines to the time required for a diagnostic elimination diet, which may range from 2 to 12 weeks, depending on the guideline and the type of suspected non-IgE mediated

diagnosis. However, in the vast majority of patients a strict 4 week elimination diet is sufficient to establish symptom resolution. Children with eosinophilic gastrointestinal disorders may require longer periods of exclusion to establish remission.

Dietary management

a) Guidelines

Many guidelines have been published on the management of food allergies; in particular for the UK the National Institute for Health and Care Excellence (NICE) Guidelines contain some information on dietary management of non-IgE mediated allergies. There has been significantly more focus on the dietary management for non-IgE mediated CMPA, the most common allergen. Guidelines in the UK include Milk Allergy guidelines for Primary care (MAP), which have now been updated with the iMAP (international) guidelines, the British Society for Allergy and Clinical Immunology (BSACI) guidelines for secondary and tertiary care and the NICE Clinical Knowledge Series on CMPA.

b) General

The mainstay of treatment for non-IgE mediated food allergies in children is the complete avoidance of all offending allergens. The most common causative foods eliciting delayed symptoms include cows’ milk, soy, egg and wheat, however, in conditions like FPIES and EOE other foods may be responsible. The common patterns seen in different types of non-IgE mediated food allergies are summarised in [Table 2](#). Whilst cow’s milk is the most common food allergen in around 50% of patients with a delayed CMPA, soya allergy is also present. This needs to be taken into account when considering how best to undertake an elimination diet.

As many of the allergenic foods contribute significantly to the nutritional status, particularly of younger children, it is 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 3](#) provides a summary of common gastrointestinal allergens in addition to the nutrients associated with each allergen.

Hypoallergenic Formulas for non-IgE mediated Allergies

Breast milk remains the “gold standard” source of nutrition in young infants. Although cow’s milk β -lactoglobulin, soy isoflavone and egg ovalbumin can all be detected in the breast milk of lactating women, the amount is very low. Many children therefore only develop symptoms following direct ingestion of the allergen. In these cases, strict maternal elimination diets are not necessary. However, if symptoms are present whilst breastfeeding a maternal elimination diet will need to be considered.

If breast milk is not available, a hypoallergenic formula will be required for children <2 years of age. A hypoallergenic formula should be tolerated by 90% cow’s milk allergic infants (with a 95% confidence interval). These formulas are also divided into amino acid formulas (AAF), which do not contain any cow’s milk protein, and extensively hydrolysed formulas (EHF) which contain peptides with molecular weights less than 3000 Da.

Although it is thought that only around 10% of infants with IgE-mediated allergy continue to react to an EHF and will require an AAF, the failure rate in non-IgE mediated allergies seems to be

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Summary of non-IgE mediated conditions and common symptoms

Commoner non-IgE mediated conditions

Atopic Eczema (note that this is often a mixed IgE and non-IgE mediated condition)

Food protein-induced enterocolitis

Food protein-induced proctocolitis

Food protein-induced enteropathy

Food protein-induced enterocolitis syndrome (FPIES)

Eosinophilic gastrointestinal Disorders: Eosinophilic Oesophagitis (EoE), Eosinophilic gastritis, Eosinophilic enteritis, Eosinophilic colitis, Eosinophilic gastroenteritis

Common non-IgE mediated symptoms

Vomiting

Diarrhoea

Constipation

Blood/mucus in stools

Gastro-oesophageal Reflux (GORD)

Perianal redness

Food refusal/Aversion

Colicky abdominal pain

Faltering growth

Eczema

Table 1

higher. A study from the UK, has found that 29.7% of the children with non-IgE mediated gastrointestinal allergies were intolerant to an EHF. In addition a recent review found that in children with EoE and complex gastrointestinal symptoms in particular with associated faltering growth an AAF may be indicated as first choice.

Table 4 summarises current guidelines. In general, most patients will improve on an EHF, but if they have severe non-IgE mediated allergies, including EoE, FPIES and severe gastrointestinal and skin symptoms in association with faltering growth an AAF should be considered.

Concomitant soya allergy in non-IgE-mediated cow's milk allergy occurs in about half of children, especially in those with enterocolitis/enteropathy syndromes. None of the UK (and European) guidelines recommend the use of soya formulas below 6 months and above this age an EHF or AAF is the preferred feed.

However, if these are refused >6 months of age, these can be trialled, knowing that a high proportion of patients, with this delayed allergy, may also react to this formula.

Vitamin and mineral supplementation

Children with food allergies are at an increased risk for vitamin and mineral deficiencies due to their dietary elimination. In non-IgE mediated allergies this risk is increased due to ongoing gastrointestinal inflammation, increased losses through both diarrhoea and vomiting. It is therefore important to ensure that their intake meets current requirements. In particular vitamin D, calcium, iron, zinc and iodine should be monitored in children with non-IgE mediated allergies. In the UK, current government recommendations for vitamin D should be followed (<1 year 8.5–10 ug, >1 year of age 10 ug) and children should have an individualised assessment for other vitamin and minerals. For complex non-IgE mediated allergic children on long term AAF and minimal oral foods, annual nutritional bloods are recommended, in particular if proton pump inhibitors are used, which are known to impact on the bioavailability of some of the micronutrients.

For lactating mothers on an elimination diet, as a minimum calcium and vitamin D supplementation will need to be considered, however they may require further supplementation depending on their pregnancy nutritional status (i.e. iron deficiency), the extent of elimination and nutritional beliefs (i.e. vegetarian).

Reintroduction of food allergens

The prognosis of most non-IgE mediated food allergies is good, but the age of tolerance of allergens depends on the type of non-IgE mediated allergy (i.e. EoE versus proctocolitis) and the severity of symptoms. In the absence of IgE-mediated allergy, home reintroductions of allergens can usually occur. The exception to this is FPIES, in which reintroductions should occur under medical supervision.

The use of milk ladders for non-IgE mediated CMPA is common, but to date no evidence of their superiority for tolerance induction exists. However, a recent systematic review has acknowledged the fact that there may be a benefit to quality of life. The recent iMAP guidelines have published a new milk ladder with recipes that are useful for clinical practice.

Common allergens in children with non-IgE mediated allergies^a

	Milk	Soya	Hens egg	Wheat	Rice	Oat	Sweet potato	Beef	Chicken/turkey	Other
EoE	X	X	X	X				X	X	X
FPIES	X	X	X	X	X	X	X		X	X
Proctocolitis	X	X								
Enteropathy	X	X	X	X						
GORD	X	X								

^a It is important to note, that children can have non-IgE mediated allergies to many other foods, this table only contains the most commonly reported offending allergens.

Table 2

Sources, nutrients and alternatives of common non-IgE mediated allergens

	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.	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	<i>Breast milk and/or hypoallergenic formula (see below)</i> <i>Over 2years:</i> Calcium enriched oat milk, hemp milk, almond milk, coconut milk, pea milk, rice milk (> 4.5 years of age) <i>Other foods:</i> Milk free versions of spreading fats, cheese, yoghurts, ice cream and cream
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	Egg replacers Adjust recipes with extra liquid or fruit purees. Variety of egg-free products such as mayonnaise, cakes, muffins, puddings, and omelette mix
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	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 delayed wheat allergy.
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.	Cow's milk (if not cow's milk allergic), rice milk (> 4.5 years), soya milk, oat milk, potato milk, almond milk, coconut milk, pea milk, meat, fish, poultry or other nonsoya vegetarian alternatives

Table 3

Hypoallergenic formulas recommended by current guidelines

Clinical presentation	iMAP guidelines — mild to moderate non-IgE mediated allergies	BSACI guidelines
Atopic eczema/dermatitis	EHF	If breastfed AAF otherwise EHF
EoE	Classified as severe presentation and not covered in iMAP	AAF
Gastroesophageal reflux disease	EHF	EHF
Cow's milk protein-induced enteropathy	EHF	EHF unless severe in which case AAF
Food protein induced enterocolitis syndrome	Classified as severe presentation and not covered in iMAP	AAF
Proctocolitis	EHF	EHF

Table 4

Conclusion

Currently no diagnostic tests are available to aid the diagnosis for the majority of non-IgE mediated allergies. As such, an elimination diet of suspected allergens is required to aid the diagnosis of this allergy. When the diagnosis has been established a strict elimination diet is required and children should be monitored for growth retardation, vitamin and mineral deficiencies. In the

absence of breast milk, a hypoallergenic formula with proven efficacy should be used, knowing that children on the more severe spectrum of non-IgE mediated allergies, in particular with growth faltering, an AAF may be required. Prognosis for this type of allergy is good and reintroduction in the absence of specific IgE and FPIES can occur at home using the published milk ladder and local introduction protocols for other foods. ◆

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