Paediatric non-IgE mediated food allergy: guide for practitioners

Kahn Preece, Annaliesse Blincoe, Erik Grangaard, Genevieve Ostring, Diana Purvis, Jan Sinclair, Amin Sheikh, Robert Winkler and the Paediatric Allergy Special Interest Group, PSNZ

ABSTRACT

AIM: Food avoidance in children is increasingly common due to concerns about allergy. We aim to review the current literature on paediatric non-IgE mediated food allergy including what is known about pathophysiology, diagnosis, management and prognosis of common and severe presentations. Considerations regarding appropriate formula selection are also presented.

METHODS: Common non-IgE mediated conditions were searched through common medical databases. Thorough review of available literature was then synthesised and critically appraised.

RESULTS: Current understanding of immunological mechanisms of most non-IgE mediated conditions remains elusive. Most conditions are outgrown in childhood and have a good prognosis. Dietary modification for some conditions is important to ensure safety. They are not recommended in all situations due to potentially harmful consequences.

CONCLUSION: Assessment of children with concerns regarding non-IgE mediated conditions requires a thorough history and is generally not supported by reliable diagnostic tests. Caution is warranted when advising families to undertake dietary exclusions unless well supported by the evidence and ensuring benefits outweigh any potential harm.

Childhood food allergy is an increasingly common problem presenting to both primary care providers and paediatric services. IgE-mediated food allergy has been estimated to affect more than 10% of one year olds in Australia, and has recently been reviewed in this journal. Perceived adverse reactions to foods is generally much higher, affecting up to 30% in some studies. For these additional cases, non-IgE based mechanisms are often considered. Presentation is often in young, preverbal children with symptoms and signs non-specific, vague, inconsistent and subjective, making assessment and management challenging. The absence of any reliable testing further adds to diagnostic uncertainty.

A trial of elimination and re-challenge of the proposed culprit food is often considered best practice. However this can have limitations. Merras-Salmio et al recently undertook a double-blind placebo-controlled food-challenge for cow’s milk protein (CMP) associated complaints, with outcome assessed by a paediatrician. Symptoms were attributed to placebo in 46% (18/39) of challenges, and in half of these patients the parents felt reaction on placebo milk was more severe than on CMP. Furthermore, exclusion of a staple food protein in children has considerable negative effects. Growth and micronutrient deficiency have been well shown in children on exclusion diets and food avoidance can contribute to family anxiety, adversely affecting mother-baby interactions.

According to the World Allergy Organization (WAO), a reaction to food can only be referred to as an allergy if related to the immune system. In this article, we review the commonly considered non-IgE mediated food allergy presentations. This includes Food Protein-Induced Enterocolitis Syndrome (FPIES), food-protein induced proctocolitis, eosinophilic oesophagitis (EoE), eczema and gastroesophageal reflux/colic. We also look at the best practice...
## VIEWPOINT

**FPIES Eosinophilic Oesophagitis**

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>FPIES</th>
<th>Eosinophilic Oesophagitis</th>
<th>Colic / reflux</th>
<th>Proctocolitis</th>
<th>Eczema</th>
<th>Immediate Food Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetitive vomiting</td>
<td>Infants</td>
<td>• Irritable</td>
<td>Excessive crying</td>
<td>Itch and dry skin</td>
<td>Vomiting, diarrhoea</td>
<td></td>
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<tr>
<td>Lethargy</td>
<td>• Feeding difficulty/ refusal</td>
<td></td>
<td></td>
<td>Papulovesicular inflammation</td>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>• FTT</td>
<td></td>
<td>Low level blood and mucous in stools</td>
<td>Infantile eczema may clear by 2 years</td>
<td>Urticaria, pruritus</td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td>Older children</td>
<td></td>
<td>Generally well</td>
<td></td>
<td>Angioedema</td>
<td></td>
</tr>
<tr>
<td>Floppiness</td>
<td>• Food impaction</td>
<td></td>
<td>Thriving</td>
<td></td>
<td>Wheeze</td>
<td></td>
</tr>
<tr>
<td>Sepsis-like</td>
<td>• Dysphagia, chest pain</td>
<td></td>
<td></td>
<td>Cardiovascular collapse</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to reaction</th>
<th>Vomiting 2–4hs</th>
<th>Days</th>
<th>N/A</th>
<th>Hours to days</th>
<th>Hours to days</th>
<th>Minutes–2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea 5–10hs</td>
<td>6–12 weeks</td>
<td>6 weeks to 6 months</td>
<td>~70% in infancy (3–6 months)</td>
<td>Infancy–childhood</td>
<td></td>
<td></td>
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</tbody>
</table>

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<thead>
<tr>
<th>Age of onset (predominant)</th>
<th>6-12 months</th>
<th>Median 15 months (8–36)</th>
<th>Variable</th>
<th>6–12 weeks</th>
<th>6 weeks to 6 months</th>
<th>~70% in infancy (3–6 months)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Foods implicated</th>
<th>Any</th>
<th>Mill most common</th>
<th>Milk most common</th>
<th>Wheat, egg, soy frequently implicated</th>
<th>Milk</th>
<th>Occasionally soy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60% one food</td>
<td>30% two foods</td>
<td>9% three foods</td>
<td>Controversial</td>
<td></td>
<td>Controversial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controversial</td>
<td>Any</td>
<td>Likely minimal role</td>
</tr>
<tr>
<td></td>
<td>Milk most common</td>
<td></td>
<td></td>
<td></td>
<td>&gt;90% due to milk, soy, egg, wheat, peanut, tree nut, fish, shellfish</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occurrence in breast feeding</th>
<th>Case reports</th>
<th>No</th>
<th>Yes (unrelated to maternal diet)</th>
<th>Yes (most common &gt;60%)</th>
<th>Yes (unrelated to maternal diet)</th>
<th>Possible but rare</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pathology (if known)</th>
<th>Possibly T-cell mediated</th>
<th>Uncertain</th>
<th>None</th>
<th>Uncertain</th>
<th>Epidermal barrier dysfunction</th>
<th>IgE mediated mast cell degranulation</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Clinical</th>
<th>OFC usually unnecessary</th>
<th>Endoscopy</th>
<th>S1 IgE / patch testing</th>
<th>Swab for culture if evidence of infection</th>
<th>ssIgE Skin prick testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OFC usually unnecessary</td>
<td>Up to 20% have ssIgE</td>
<td>IgE / patch testing</td>
<td>Probably unhelpful</td>
<td>No role for IgE testing to manage eczema</td>
<td>IgE mediated mast cell degranulation</td>
</tr>
</tbody>
</table>

| Differential diagnosis | Septic shock | Intussusception | GORD Infectious oesophagitis (candida) | Malrotation | Urinary tract infection | Constipation (fissure) | Infectious colitis | Meckel’s diverticulum | Chronic granulomatous disease | Wide differential includes: seborrhoeic dermatitis, psoriasis, ichthyosis, scabies, tinea, immune deficiency, GVHD, nutritional and others | | Idiopathic/viral induced urticaria |

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Avoidance</th>
<th>Adrenaline NOT indicated</th>
<th>PPI trial</th>
<th>Empiric elimination diets</th>
<th>Swallowed steroid</th>
<th>Parental support (association with SBS)</th>
<th>Avoidance</th>
<th>Emollients</th>
<th>Topical steroid</th>
<th>Avoidance of triggers</th>
<th>Avoidance</th>
<th>Emergency adrenaline for anaphylaxis if indicated</th>
<th>Ongoing research into desensitisation</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Association</th>
<th>Atopy (60% atopic background)</th>
<th>Sensitisation may progress to IgE mediated food allergy</th>
<th>Male predominance</th>
<th>Atopic dermatitis</th>
<th>IgE mediated food allergy</th>
<th>Nil reproducible</th>
<th>Nil</th>
<th>IgE mediated food allergy (~30%)</th>
<th>Other atopic disease</th>
<th>Atopic dermatitis</th>
<th>Other atopic disease</th>
</tr>
</thead>
</table>

| Natural history | Resolve 3–5years | OFC at least 12 months after last reaction | Unknown and unpredictable | Generally resolves by 6 months | Benign with spontaneous resolution before 12 months | Infantile eczema may clear by 2 years | Most outgrown by teens | Adult eczema in 2–10% | Food dependant: | Many outgrown by adolescence | Milk, egg: 70–80% | Peanut: 20% | Tree nuts: 10% |
|-----------------|-----------------|---------------------------------|-----------------|-----------------------------|-----------------------------|-----------------------------|-----------------|---------------------|-------------------|------------------|-------------------|-------------------|

<table>
<thead>
<tr>
<th>Home challenge</th>
<th>No</th>
<th>Yes (unless suggestion of IgE mediated allergy)</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes (unless suggestion of IgE mediated allergy)</th>
<th>Food and history dependant</th>
</tr>
</thead>
</table>

**Table 1:** Summary of Non-IgE mediated food allergies in children.

FPIES, Food protein-induced Enterocolitis Syndrome; IgE, immunoglobulin E; ssIgE, serum specific IgE; FTT, failure to thrive; GORD, gastroesophageal reflux disease; PPI, proton pump inhibitor; OFC, observed food challenge; SBS, shaken baby syndrome
guidelines for dietary modification in infants with presumed CMP-related symptoms and information is summarised in Table 1. Finally, appropriate dietary modification is outlined including the vital role of a paediatric dietitian.

**Food Protein-Induced Enterocolitis Syndrome (FPIES)**

FPIES is a rare condition characterised by severe gastrointestinal symptoms generally presenting in young infants. First described in 1967 due to cow’s milk, a wide variety of foods have now been implicated in triggering FPIES. Pathogenesis remains uncertain however antigen specific T cells are thought to be important and other atopic conditions (atopic dermatitis, asthma) are commonly seen in affected children.

Recent large cohorts of FPIES patients in the UK, the US and Australia have helped outline the common characteristics of the condition and also variations among different populations. In all studies, the most common symptom was vomiting (81–100%). Classically, this is profuse, and begins 1–4 hours after ingestion. Hypotension is well recognised and is documented in almost 20% of patients at supervised challenge. The presentation of severe vomiting, abdominal pain and shock can lead to extensive investigation and empiric management for sepsis or intra-abdominal pathology. In general, cow’s milk is the most common trigger; however rice was more common in the Australian cohort.

The diagnosis of FPIES is made on clinical grounds and centres on a thorough history. Repeated exposure causing symptoms consistent with FPIES are required by some experts. Laboratory investigations are generally unhelpful, with a raised white cell count (peaking at 6 hours after exposure) often adding to clinical confusion. Acute inflammatory markers are generally not increased. Skin prick and patch testing are not useful in the identification of causative foods. Challenge, if required, should be done under medical supervision in hospital. Sopo et al reported fluid resuscitation was required in more than 40% of patients at food challenge.

Management requires specific food avoidance. Most patients (67–83%) react to a single food. In cases where more than one causative food is identified, data is discrepant regarding associations and subsequently, firm recommendations are difficult. As an example, different series report coincident cow’s milk and soy FPIES affecting from 0% to 35%. The prognosis for FPIES is good, with half of affected children outgrowing the condition by 3 years of age. Resolution is delayed in some children, particularly with solid food triggers.

**Eosinophilic oesophagitis**

Eosinophilic oesophagitis (EoE) is a chronic immune/antigen-mediated disease, associated with symptoms of oesophageal dysfunction. It is characterised by eosinophil predominant inflammation of the oesophageal mucosa and is generally classed as an allergic condition, as clinical and histological improvement are often seen with antigen avoidance. The incidence and prevalence of EoE range from 0.7–10/100,000 per person year and 0.2–43/100,000 respectively, and appears to be increasing. Caucasian males are most commonly affected, with a reported male to female ratio of 3:1. With increasing recognition it is also the subject of many recent reviews, and some confusion remains around pathophysiology, investigations and treatment strategies.

The clinical presentation varies, depending on the age of presentation. Infants and young children usually present with irritability, feeding difficulties, abdominal pain, vomiting and failure to thrive. Older children and adolescents present with dysphagia, abdominal or chest pain, food impaction and, rarely, symptoms similar to those of gastro-oesophageal reflux disease. A personal or family history is common and research continues into determining firm genetic or HLA associations.

Diagnosis requires endoscopy and the histological presence of ≥15 eosinophils per high powered field (eos/hpf) in at least one oesophageal mucosal biopsy, with or without the presence of other microscopic features of eosinophil inflammation. Upper gastrointestinal endoscopic findings are variable, ranging from normal oesophageal mucosa...
to longitudinal furrows, white plaques, oesophageal trachealisation, and strictures. Clinical differential diagnoses include gastro-oesophageal reflux disease (GORD), infectious oesophagitis, oesophageal achalasia, Crohn’s disease, and connective tissue disorders. This is generally resolved on endoscopy and biopsy.

Uncertainty remains about the best choice of management strategies and balancing treatment effectiveness, side effects and patient quality of life. Use of acid suppression (omeprazole for 6–8 weeks prior to endoscopy) is generally suggested to resolve any reflux associated eosinophilic infiltration/inflammation (PPI-responsive oesophageal eosinophilia).21 Topical anti-inflammatory therapy is an effective treatment option. Swallowed fluticasone or budesonide slurry (not available in New Zealand) is effective at achieving histological remission in ~80% of patients that are able to comply.22

Dietary modification is the alternative mode of therapy. Cow’s milk is thought to be the most common food trigger. Transition to exclusive amino acid formula feeding is effective at achieving remission in >90% of patients. Unfortunately, for many patients this is not sustainable and may be unnecessary. For targeted allergen elimination, possible causative foods are identified by skin prick or patch testing and removed from the diet. While CMP is the most common trigger in EoE, it is also the food allergen for which the testing is least helpful. Alternatively, empiric elimination diets have been suggested, where commonly implicated food allergens are removed. Six-food elimination diet (SFED) (milk, soy, wheat, egg, peanut/tree nuts and fish/shellfish), a four-food elimination diet (FFED) (milk, soy, wheat, egg) and milk avoidance alone have all been assessed with 74%, 72% and 62% histological disease remission, respectively.23 Multiple endoscopic procedures may be required to monitor response to treatment; however, there are no consensus guidelines to recommend timing and duration of these dietary restrictions.

Not all patients have clinical or histological remission on elemental diet suggesting that factors other than diet play a role. Environmental allergens (eg, grass pollens, house dust mites) may cause some of the fluctuations in histological disease seen on surveillance. Oral immunotherapy to environmental allergens is a well-recognised cause of EoE, with 2.7% of patients affected.24 With the variable response to current therapeutics and uncertainty about the long-term consequences of uncontrolled EoE, ‘best practice’ is still yet to be defined.

**Gastro-oesophageal reflux disease/colic**

Colic is a common presentation to both primary care and paediatricians. For research purposes, a definition of colic is paroxysms of crying for more than 3 hours a day, more than 3 days in a week, for at least 3 weeks.25 Several population questionnaires have identified normal crying patterns in infancy. In 1962, Brazelton found the median crying time in a 3-month-old infant was 3 hours a day,26 with similar results found by other groups.27,28 Above this is considered excessive crying. Importantly, excessive crying does not equate to disease.

A large population study of >76,000 one-month-old infants in the UK demonstrated that colic affected 18%.29 This study suggested that bottle feeding (standard formula) was protective (OR 0.74 (95% CI: 0.70–0.78)) when compared to sole breast feeding. Risk factors identified were higher socioeconomic status, increased maternal age and higher levels of parental education. Multiple community studies were compiled by Lucassen et al.30 The type of feed was unrelated to the diagnosis in most studies, as was parental atopy. Exposure to household smoking was an associated risk factor. The lack of any clear association to feeds in multiple, large, population-based cohorts make the type of feed an uncommon and unlikely cause of excessive crying in the first 3 months of life.

Gastro-oesophageal reflux (GOR), defined as passive regurgitation of stomach contents in to the oesophagus, is extremely common in infancy. The prevalence reaches a peak affecting ~40% of infants at 3–4 months of age, declining to <5% at 13–14 months of age.31 It is also a common cause for medical review. A large, population-based, Melbourne study found 14% of families...
had sought medical review for perceived GOR related symptoms. With such similar chronological co-association, it is common for parents and physicians to consider a causative role of reflux and gastrointestinal contents (feed) in excessive crying.

Gastro-oesophageal reflux disease (GORD) refers to the disease state, thought to be secondary to retrograde movement of stomach contents into the oesophagus. The symptoms may include crying and/or irritability, poor appetite, vomiting, wheezing, stridor, apparent life-threatening event (ALTE), abdominal and/or chest pain, chronic cough, hoarseness, and Sandifer syndrome. Many of these are interchangeable with physiological reflux in the setting of a baby with excessive crying, and can make diagnosis difficult. Failure to thrive, feed refusal or respiratory involvement should prompt further investigation or referral for review by a paediatrician. Medications are frequently prescribed for infants with suspected GOR. However, their role is controversial, as meta-analyses have failed to demonstrate benefit in symptom control and GORD is generally self-limiting.

There is no good evidence for dietary modification to treat colic, reflux or GORD. For the vast majority of infants, this is a physiological transition that requires support and understanding for families who are stressed, sleep deprived and desperate to find a ‘solution’.

Food protein-induced proctocolitis

Colitis in infancy due to cow’s milk protein ingestion has been described for more than 30 years. While other foods have been identified as precipitants, milk is by far the most common trigger. Infants usually present with low-grade rectal bleeding and mucous stools, but are otherwise healthy and thriving. Histopathology of rectal biopsies taken from affected infants reveal a high proportion of eosinophils (>60/hpf), suggesting a possible allergic inflammatory process.

Cow’s milk protein proctitis is the only food allergic condition that is frequently seen in exclusively breastfed infants. Low levels of food proteins have been demonstrated in human milk. Amounts vary considerably from person to person, with only about 50% of lactating women having food proteins detectable. Excretion can vary over time and can be independent of the amount of daily consumption.

Differential diagnoses include necrotising enterocolitis, chronic granulomatous disease, intussusception, infectious colitis, perianal fissure, bleeding Meckel diverticulum or bleeding secondary to thrombocytopenia. Children generally respond promptly (within 2 weeks) to dietary exclusion of the culprit food. This may include maternal milk avoidance if exclusively breastfed. Maternal soy avoidance can also be considered if there is no improvement with dairy avoidance. Transition to extensively hydrolysed formula may be required if formula fed or if symptoms are severe, prolonged or associated with failure to thrive. More severe features should prompt thorough investigation for other differential diagnoses. Monitoring of haemoglobin and iron may be warranted if bleeding is protracted or refractory. Home-based challenge (maternal dairy ingestion or CMP based formula) can be considered from 6 months of age and the vast majority of children will have outgrown symptoms by 12 months.

Eczema

Eczema is a common inflammatory disease of the skin that affects 15–30% of New Zealand children. Eczema is characterised by itch, chronic, relapsing skin inflammation, epidermal barrier dysfunction, and immunological changes including IgE-mediated sensitisation to food and environmental allergens. In infants, eczema typically affects the cheeks, trunk and extensor surfaces of the limbs. In older children, flexural eczema is seen, often with facial and eyelid dermatitis. Only 2–10% of adults have eczema, typically affecting the head and neck, hands and flexures.

There are two main theories of the pathogenesis of eczema. The first proposes that the primary cause is an immunological defect, resulting in IgE-mediated sensitisation and local inflammation which causes the epidermal barrier dysfunction. The second proposes that abnormalities of epidermal barrier function are the
primary cause, with immunological changes occurring as a consequence of local inflammation and abnormal antigen presentation. This second hypothesis is supported by the fact that early onset eczema is often seen in the absence of IgE-mediated sensitisation, and many individuals with eczema never develop IgE sensitisation. Interestingly, loss of function mutations in FLG (a gene that encodes filagrin, an important protein in skin barrier function) are more common in people with eczema, and are also associated with immediate hypersensitivity to peanut, independent of eczema. This suggests that skin barrier dysfunction may be a common cause underlying both conditions.36

One of the hypothesised mechanisms of food allergy development is via transdermal antigen exposure in children with atopic dermatitis.37 It is estimated that 35–45% of children with severe eczema have immediate hypersensitivity reactions to foods on double-blind, placebo-controlled food challenge.38 However, Cochrane review of the benefit of food exclusion for treating eczema found little evidence to support this as a management strategy.39 The quality of studies was generally poor. One randomised controlled study found a small, but just statistically significant, benefit (reduced body surface area affected) from egg exclusion in children with eczema and egg sensitisation.40 Numbers were small (~25 in each group) and both groups are stated as having ‘hidden’ egg in foods, such as pasta and cakes. There is no evidence to support widespread indiscriminate food exclusions for the treatment of eczema.39

Epidemiology of childhood eczema and prevention strategies have recently been reviewed.41 With regard to preventing the onset of eczema, current advice is that there is no benefit from exclusion of foods from the maternal diet during pregnancy or breastfeeding to prevent eczema. There is also no evidence for dietary supplementation during infancy. Partially or extensively hydrolysed formulas (eg, HA formulas, PeptiJr®) have also not consistently been shown to significantly reduce onset of eczema, but these remain the recommendation of the American Academy of Allergy, Asthma & Immunology42 and the European Society of Asthma, Allergy and Clinical Immunology43 in high-risk babies unable to breastfeed in the first 4–6 months of life. Application of emollients to the skin of high-risk newborns before the onset of eczema may reduce rates by up to 50% and may prove a simple and low-risk alternative to dietary manipulation, as demonstrated in two small studies.44,45

There is mounting evidence that food avoidance in high-risk atopic infants and children is associated with loss of tolerance and increased food allergy risk. These effects may be lifelong. Good skin care remains the cornerstone of eczema management.

Dietary manipulation
Firstly, it must be stated that if breastfeeding is intended by the mother, then this is the feed of choice regardless of the presenting complaints. If maternal dietary restrictions are recommended by the treating practitioner, it is important that maternal diet is assessed to ensure adequate micro- and macronutrient intake. Despite the lack of scientific evidence supporting dietary manipulation as management for many of these conditions, it is often initiated by patients/families and physicians. When prescribing a dietary restriction for a child, we must provide families with information to do this effectively while preventing unnecessary harm. Nutritional deficiency and growth impairment is well documented in patients with dietary restrictions associated with IgE mediated allergy.5,46 Enlisting the help of a dietician is highly recommended and often vital in the setting of multiple food avoidances.

If dietary restriction is being considered as treatment for non-IgE mediated allergy it is vital a plan for a clear trial period of single food elimination (most often 2 weeks, maximum 4 weeks) followed by re-introduction. This timing is sufficient to demonstrate effective change if the condition is immune mediated, with symptoms returning after re-exposure.

Cows’ ilk alternatives
A flow-diagram for alternative formula is presented in Figure 1. In New Zealand, there are strict requirements for the prescription of extensively hydrolysed and amino acid formulae for children. These are
aimed at ensuring appropriate use of these expensive formulae. Prescription of amino acid formula requires any of the following:

- Extensively hydrolysed formula has been reasonably trialled and is inappropriate due to documented severe intolerance, allergy or malabsorption;
- Cows’ milk anaphylaxis;
- Eosinophilic oesophagitis.

This means a trial of extensively hydrolysed formula is required for all clinical indications other than CMP anaphylaxis or EoE. Most clinical guidelines recommend soy milk as a cows’ milk alternative in infants over the age of 6 months where breast feeding is not possible.47,48 Soy formulas have been used for more than 100 years in the western world. Vandenplas et al conducted an extensive literature review on the use and safety of soy formula in children.49 In all, 156 studies were identified and 35 were included in their meta-analysis. This study examined markers of nutrition (growth, weight gain, bone density), neurological effects (IQ, behavioural problems, learning) and reproductive function (more than 30 outcomes assessed) with no difference demonstrated between soy and other milks (human milk, cows’ milk or alternate formula).49

**Risks**

Food avoidance in children to manage non-IgE mediated conditions has the potential to alter the natural history of IgE mediated food allergy. There is now good evidence that early exposure to food allergens in high-risk infants decreases the risk of food allergy. The LEAP study, conducted in the UK, demonstrated both primary and secondary prevention of peanut allergy by incorporating peanut into the diet of infants prior to 11 months of age.50 640 infants (4–11 month of age) with eczema or egg allergy were randomised to complete avoidance or regular consumption of peanut until 5 years of age. In skin-test negative infants, a reduction in peanut allergy from 13.7% (avoidance group) to 1.6% (consumption) was seen. In those who were already peanut skin test positive (1–4mm) on enrolment, peanut allergy was diagnosed in 35.3% (avoidance), compared to 10.6% (consumption) at 5 years. In another randomised-controlled trial focusing on egg allergy, a trend to allergy reduction was also seen with early egg introduction. However, results did not quite reach significance.51 Milk allergy reduction has been demonstrated (OR 19 (95% CI, 6–62) in a large Israeli prospective cohort, if milk is introduced before 15 days of age.52
Allergen avoidance in atopic high-risk children has been shown to allow loss of tolerance and development of severe reactions, including a fatal reaction to food that had previously been tolerated.53

Recent evidence also suggests dietary restriction of milk due to real or perceived allergy can lead to reduced growth percentiles in children and the effect was most pronounced in children younger than 2 years.46 Older children with >2 food restrictions had BMI reductions similar to children with coeliac disease46 and seems unrelated to caloric intake.5

As well as potential health costs, the costs of living have been recently shown to be increased in patients avoiding milk, egg and/or wheat. Children and adolescents with these dietary restrictions have approximately €4,000 (NZD 8,000)/year increased household expenditure compared to their peers.54

Conclusion

Non-IgE mediated food allergy is a common presenting complaint, with some conditions causing significant morbidity and family stress. Availability of specialised formulae has allowed complete avoidance for cow’s milk allergic infants, ensuring safety and facilitating adequate growth and nutrition. Dietary modification is not without harm and should be reserved for patients where it is clinically indicated and necessary. It should also be undertaken with the assistance of a dietitian wherever possible. When appropriately managed, paediatric non-IgE mediated food allergy has an excellent prognosis.

Competing interests:
Diana Purvis reports non-financial support from Galderma, and personal fees from Johnson and Johnson, outside the submitted work.

Acknowledgements:
The authors would like to thank all members of the Paediatric Special Interest Group (ASIG) who provided useful feedback that was incorporated into the final manuscript. The ASIG is a group of paediatricians and allied health professionals who are New Zealand Paediatric Society members treating children and families with food allergy around the country.

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