Cow’s milk allergy in infants: diagnosis and management

David Campbell MD

Allergic reaction to proteins in cow’s milk is common in infants and may be as high as 1 in 20. Here, the author discusses diagnosis, the distinction between IgE- and non-IgE-mediated reactions, and recommended management.

Cow’s milk allergy is defined by the World Allergy Organization as ‘a hypersensitivity reaction against cow’s milk proteins by specific immunological mechanisms’.¹ Much of what was previously termed milk or dairy intolerance, is now considered to be true allergy. Classification of allergy into IgE mediated (or immediate) and non-IgE mediated has been accepted by professional bodies issuing guidelines on the management of cow’s milk allergy, eg NICE CG116 (2011) and Diagnosis and Rationale for Action Against Cow’s Milk Allergy (DRACMA; 2010).

Non-IgE-mediated dairy allergy is thought to operate via T-cell mediated reactions to cow’s milk proteins and in some situations through a combination of both IgE and non-IgE mediated reactions to cow’s milk proteins.² Estimates of the prevalence of IgE-mediated cow’s milk allergy vary between populations and by age within those populations, but appears to be increasing¹ and approximated to be between 2 and 7 per cent of formula-fed infants.³ Non-IgE-mediated reactions are less well studied but are far more common.

Primary lactose intolerance (homozygous deletion of 2q21) is very rare and produces catastrophic failure to thrive in a new born with severe watery diarrhoea, vomiting, acidosis and perineal rash from birth. Secondary (acquired) lactose intolerance or post-enteritis syndrome follows a well-defined acute gastroenteritis and can be treated with lactose-free formula, and differs from cow’s milk allergy by these features and those listed in Table 1.

Signs and symptoms of cow’s milk allergy
An allergy-focused history² is the cornerstone to eliciting relevant symptoms that may be overlooked. The time between symptoms and ingestion of cow’s milk protein is critical in making the diagnosis between IgE and non-IgE-mediated allergy (see Table 1 and Figure 1).

Non-IgE reactions tend to be GI predominant and most commonly present as gastroesophageal reflux or colic,⁵ but can

Figure 1. IgE-mediated allergy causes immediate symptoms such as urticaria; amino acid-based formulas are recommended for IgE or severe non-IgE milk reactions
occasionally be associated with chronic eczema (but often not) and coryza. Bloody diarrhoea in an otherwise well breast or formula fed infant is usually cow’s milk enterocolitis, but requires clear consideration of intussusception. IgE-mediated reactions tend to be within minutes of exposure and more dramatic.

Cow’s milk allergic reactions can occur in exclusively breast-fed babies, and tend to be of the non-IgE type. Either type of food allergy, IgE or non-IgE, can be associated with mucosal histological abnormalities such as eosinophilic colitis, eosinophilic oesophagitis or lymphonodular hyperplasia.

**Diagnosis of cow’s milk allergy**

Diagnosis centres on the allergy-focused history seeking to identify whether there are features to suggest either an IgE- or non-IgE-mediated reaction against milk, but occasionally it can be both or just unclear. The timing between exposure and onset of symptoms is often a major clue to which pathway is at fault.

If an IgE reaction is suspected then confirmatory tests can be very helpful. Skin prick tests using whole cow’s milk, rather than purified antigen extracts, are often confirmatory if a wheal reaction occurs (the larger the reaction the greater the chance of a true IgE-mediated allergy, but this does not correlate to the severity of the allergic reaction). One study estimated around 1 in 1000 children investigated for milk allergy by skin prick had a significant clinical reaction following the skin prick test, and as such are not recommended for use in primary care where facilities for paediatric resuscitation are not easily available.

Specific IgE tests on blood are more appropriate and can confirm a clinical history suggestive of IgE-mediated allergy. A positive skin prick test without an allergy test is unhelpful as around 40 per cent of children give a positive result for the skin prick test yet have no allergic symptoms. However, those children with true IgE-mediated allergy have a high incidence of testing positive for the skin prick test.

Non-IgE-mediated allergic reactions are suspected by a history of GI symptoms of reflux and are confirmed by a therapeutic withdrawal of cow’s milk protein from the diet (all dairy-containing foods). There is no evidence for IgG testing or hair analysis (absence of evidence to show any predictive results for non-IgE allergy) in confirming diagnosis (NICE CG116). It would be expected that a dramatic resolution of the symptoms occurs within a week of intervention.

**When to refer to a specialist?**

Non-IgE reactions do not lead to anaphylaxis and a thriving child with a single intolerance to milk can usually be managed in general practice. An extensively-hydrolysed milk (EHF; see Table 2) can be prescribed with a dairy-free diet and the diagnosis secured within two weeks. The recommended hypoallergenic milks are nutritionally complete and will not create problems with low calcium intakes if taken in similar volumes to the replaced formula. Multiple food allergies, rectal bleeding (consider intussusception) or failure to thrive should lead to a referral to a specialist.

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**Table 1. Differences between IgE- and non-IgE-mediated cow’s milk allergy**

<table>
<thead>
<tr>
<th>IgE mediated</th>
<th>Non-IgE mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate, within mins (but rarely up to 2 hours)</td>
<td>variable time from exposure</td>
</tr>
<tr>
<td>dose independent</td>
<td>dose dependent</td>
</tr>
<tr>
<td>predictable symptom response</td>
<td>variable symptom response but usually GI predominant</td>
</tr>
<tr>
<td>likely to have measurable specific IgE</td>
<td>not likely to have measurable specific IgE</td>
</tr>
<tr>
<td>acute asthma or stridor (laryngeal oedema)</td>
<td>chronic coryza and rhinorrhoea</td>
</tr>
<tr>
<td>urticaria, angioedema or erythodermic reactions</td>
<td>chronic eczema</td>
</tr>
<tr>
<td>can have acute-onset diarrhoea + vomiting</td>
<td>resistant GORD, colic, diarrhoea</td>
</tr>
<tr>
<td>no rectal bleeding anaphylaxis</td>
<td>bloody diarrhoea</td>
</tr>
</tbody>
</table>

**Table 2. Properties of EHF and amino acid-based formulas**

<table>
<thead>
<tr>
<th>EHF</th>
<th>Amino acid-based formulas</th>
</tr>
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<tbody>
<tr>
<td>milk proteins enzymatically hydrolysed to oligopeptides (&lt;2.6kDa)</td>
<td>protein free with nitrogen present as amino acids (&lt;5kDa)</td>
</tr>
<tr>
<td>vary in extent of hydrolysis (63% through to &gt;95%)</td>
<td></td>
</tr>
<tr>
<td>some may contain lactose as carbohydrate, others dextrose, glucose or sucrose</td>
<td>lactose free</td>
</tr>
</tbody>
</table>

**Examples**

- Aptamil Pepti
- Peptijunior
- Similac Alimentum
- Nutramigen
- Althera

- Neocate LCP
- Nutramigen AA

| cost and palatability vary                                           | high cost compared to EHF    |
IgE milk reactions can lead to anaphylaxis and should be referred on to a specialist.

How to manage cow’s milk allergy?
Babies with colic and reflux who are breast fed by mothers taking dairy in the diet should go on to a dairy-free diet but continue to breast feed. Supplementary calcium (1000mg per day plus 10µg of vitamin D) is advised, and milk substitutes such as oat milk and soya can be tried.

In babies with non-IgE milk reactions that have had the diagnosis confirmed by symptom resolution by going on to EHF milk, partial resolution of symptoms may be due to ongoing peptic oesophagitis. Treat vomiting babies with both EHF milk and acid suppression (ranitidine 2mg per kg twice daily), which can be discontinued after a month if the symptoms have resolved. If symptoms continue, consideration should be given to step up to an amino acid-based formula (Neocate LCP or Nutramigen AA).

Residual allergic symptoms may be due to reactions to peptides in EHF; amino acid-based formulas have no peptide fragments and are the most reliable formula for treating dairy allergy.

Amino acid formulas are recommended for IgE or severe non-IgE milk reactions as a first-line treatment (ie enterocolitis). It is recommended that involvement of a paediatric dietitian occurs to optimise nutrition.

IgE-mediated allergy should lead to advice to avoid all dairy products and carry rescue antihistamines (chlorpheniramine) to be taken if accidental exposure occurs, and referral to a specialist.

Assessment for self-administered adrenaline plus training and liaising with nurseries, childcare and school is done via paediatric allergy services. Absolute indications are anaphylaxis, poorly-controlled asthma plus food allergy or IgE reaction to minute exposure (ie air borne).

Suggested management of cow’s milk allergy is outlined in Figure 2.

Figure 2. Suggested management of cow’s milk allergy in infants

Prognosis
Resolution of IgE reactions is 50 per cent by five years of age,9 non-IgE reactions are rare after 2.5 years and the vast majority are gone by 15 months of age. For the thriving child taking a good volume of EHF (120ml per kg body and demonstration of good weight), reintroduction of dairy in to the diet can begin at one year of age. Starting with small volumes of fermented dairy products (eg yoghurt followed by soft cheese) before trying milk is often better tolerated.

Conclusion
The GP can manage the vast majority of non-IgE-mediated cow’s milk allergy presenting as reflux disease and colic through a diagnostic withdrawal of dairy from the diet, which should be continued until one year of age. Concurrently treating babies presenting with vomiting with acid suppression (ranitidine) in the early phases is also safe and effective. Immediate IgE reactions should be referred on to a specialist.

KEY POINTS
- cow’s milk allergy is very common in infants and may be as high as 1 in 20
- cow’s milk allergy can occur in breast-fed babies if mother is taking dairy in the diet
- IgE-mediated allergy causes immediate symptoms such as urticaria, angioedema, anaphylaxis and breathing problems
- non-IgE-mediated allergy commonly causes colic with reflux
- treatment is with dairy exclusion (bottles and weaning food) using an EHF or soya if a child is over 6 months
References


Declaration of interests

Dr Campbell has received payment to provide educational talks for Danone and Nutricia.

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