Cow’s milk allergy
Frequently asked questions

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1. What is the difference between food allergy and food intolerance?

Food allergy is an adverse reaction to certain foodstuffs that is mediated by the immune system. By contrast, food intolerance is a non immune-mediated adverse reaction. Both allergy and intolerance are encompassed within the umbrella term of ‘food hypersensitivity’. These conditions differ from toxic food reactions, which derive from the general toxicity to humans of some substances in foods, such as poison in non-edible mushrooms (Figure 1).

![Figure 1. Classification of adverse reactions to food.](image)

Adverse reactions to food are common in infants. Cow’s milk allergy (CMA) is one of the most common causes, and occurs in 2–6% of infants.1 CMA is an immune reaction to one or more cow’s milk proteins. However, it may be confused with lactose intolerance, which is caused by an enzyme deficiency, not an immune response. Although primary lactose intolerance is frequently seen in adolescence and adulthood, it is extremely rare in infants under 1 year (although secondary intolerance may occur in infants as a result of damage to the gut, typically following gastroenteritis).

2. What impact does food allergy have on patients and the people around them?

Food allergy can have a profound impact on quality of life for patients and their families, and the effects should not be underestimated. This impact arises both from the distress caused by the symptoms of food allergy and the need for constant vigilance to avoid allergens.

For the parent, grocery shopping for a child with food allergy has been shown to take on average 39% longer and incur 11% greater expense than for a non-allergic child.2 For the child, the allergy may result in a considerable burden of disease, anxiety about eating and fear of adverse reactions.1 Compounded, these effects can seriously impair the everyday functioning of the families and children affected by allergy. Perhaps the most stark illustration of the personal burden of food allergy is the finding that quality of life in children with peanut allergy is more impaired than in children with insulin-dependent diabetes.4

At a broader level, the impact of food allergy may vary between communities. Food allergy has a genetic component,5 and there is evidence that some ethnic groups in the UK may be more affected than others. One study indicated that, compared with Caucasians, non-Caucasian children have greater numbers of food allergies per child, and earlier average age of presentation.6

In addition to its impact on patients and families, food allergy has a substantial burden on society, and this is felt, in large part, through the cost of medical treatment and management. There is a strong perception, particularly among parents, that the prevalence of allergy is increasing, implying that the overall impact is also rising. Certainly with peanut allergy, for instance, there is clear evidence to suggest that the prevalence has significantly increased in recent years.7 In contrast, however, a study examining the total prevalence of food hypersensitivity in children born on the Isle of Wight found little evidence of an increase in the last 20 years, with the prevalence remaining at around 5%.8 Although conclusive evidence for an increase is lacking, the high prevalence of food allergy nevertheless presents a significant cost to society.

3. What is the difference between IgE- and non-IgE-mediated cow’s milk allergy?

Although it is often thought of as a single condition, cow’s milk allergy (CMA) can in fact be driven by two distinct immune pathologies, referred to as IgE-mediated allergy and non-IgE-mediated allergy.

IgE-mediated allergy is often referred to as an ‘immediate onset reaction’, as symptoms appear rapidly after exposure to an allergen (Table 1). Symptoms typically affect one or more of the GI, skin and respiratory systems.
Severe IgE-mediated reactions with cardiorespiratory features are referred to as anaphylaxis, and are potentially life threatening. IgE-mediated reactions are relatively easily diagnosed, using a combination of clinical history and validated tests to measure levels of circulating milk protein-specific IgE \textit{in vivo} (skin prick test) or \textit{in vitro} (specific IgE test). The higher the level of specific IgE, the more likely the patient is to have a clinical allergy to that protein.

By contrast, a significant proportion of infants with CMA do not have detectable circulating milk protein-specific IgE. These non-IgE-mediated reactions often manifest in GI or cutaneous symptoms, and tend to be delayed for hours or even days after ingestion of milk (Table 1). Hence, they are often referred to as 'delayed-onset reactions'. The delayed onset of symptoms and lack of simple diagnostic tests can make diagnosis of non-IgE-mediated allergy challenging. Despite the simple classification of CMA into IgE- and non-IgE-mediated pathologies, in practice patients with CMA present a spectrum of overlapping symptoms, making differentiation and diagnosis difficult.

4. What approach should be used to identify patients with cow’s milk allergy?

Unfortunately, the simple classification of cow’s milk allergy (CMA) as either IgE- or non-IgE-mediated reaction (Table 1) does not correlate closely with the clinical reality. What we actually see in practice is a whole spectrum of reactions to cow’s milk. While some classic cases of immediate-onset CMA may indeed be easily spotted, many cases of delayed-onset CMA are obscured by reactions that lag by many hours or even days, and may involve only subtle exacerbations of symptoms.

Table 1. Comparison of IgE-mediated and non-IgE-mediated cow’s milk allergy in infants.

<table>
<thead>
<tr>
<th></th>
<th>IgE-mediated</th>
<th>Non-IgE-mediated</th>
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</thead>
<tbody>
<tr>
<td>Allergen</td>
<td>Milk proteins</td>
<td>Milk proteins</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Well-defined: IgE antibody-mediated</td>
<td>Unclear: cell-mediated (possibly additional unknown mechanisms)</td>
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<tr>
<td>Common symptoms</td>
<td>Urticaria</td>
<td>Gastro-oesophageal reflux</td>
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<tr>
<td></td>
<td>Angiooedema</td>
<td>Diarrhoea</td>
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<td></td>
<td>Runny nose and eyes</td>
<td>Abdominal pain</td>
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<td></td>
<td>Nausea</td>
<td>Constipation</td>
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<tr>
<td></td>
<td>Vomiting</td>
<td>Atopic eczema</td>
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<tr>
<td></td>
<td>Diarrhoea</td>
<td>Colic</td>
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<tr>
<td></td>
<td>Wheezing</td>
<td>Food aversion</td>
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<tr>
<td></td>
<td>Anaphylaxis</td>
<td>Blood and/or mucus in the stools</td>
</tr>
<tr>
<td>Time of onset post ingestion</td>
<td>&lt;2 hours</td>
<td>Between 1 hour and several days</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>Skin prick test</td>
<td>Elimination diet followed by oral challenge</td>
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<tr>
<td>Gold standard test</td>
<td>Double-blind, placebo-controlled food challenge</td>
<td>Elimination diet followed by oral challenge</td>
</tr>
<tr>
<td>Management</td>
<td>Avoid cow’s milk protein</td>
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The key to identifying these more difficult cases of CMA is to recognise the patterns and overlap among the symptoms. To this end it is crucial to obtain a complete personal and familial history for the patient, as well as conducting a thorough physical examination.

Certain historical features increase the likelihood that a patient’s symptoms are caused by an underlying allergy. These include a personal or family history of atopy, most likely manifested as eczema or possibly immediate-onset allergy to other foods. Timing is also important; the appearance of symptoms around the same time as a change in diet, such as the introduction of cow’s milk-based formula as a top-up to breast-feeding, is cause to suspect CMA.

Another pattern to look out for involves colic. Fussy but otherwise asymptomatic infants cry episodically for prolonged periods, typically in the evenings, but may be distracted from crying by external stimuli. This behaviour alone is not cause to suspect CMA. If however, the infant is crying constantly, and is truly inconsolable and undistractable, there is reason to suspect an underlying pathology. In combination with symptoms such as poor feeding, reflux or loose stools, this kind of crying may be related to CMA.

Similarly, persistent gastro-oesophageal reflux (GOR) that is resistant to anti-reflux treatment may be symptomatic of CMA, especially when presenting in combination with eczema, other GI symptoms and a history of atopy.

5. How is eczema linked to food allergy?

Food allergy and eczema both fall within the atopic spectrum, a family of hypersensitivity disorders with a strong genetic component. The prevalence of food allergy is high among infants with eczema, and it increases with the severity of eczema. Indeed, the prevalence of IgE-mediated food allergy may be as high as 70% among infants with severe infantile eczema. Studies have also shown that the earlier the onset of eczema, and the more severe it is, the more likely it is that the infant will also have food allergies.

In recent years, it has become increasingly recognised that eczematous reactions to allergens have both an immediate and a delayed component, and that changes in diet may ameliorate skin conditions. Accordingly, current NICE guidance on treatment of children with atopic eczema recommends that bottle-fed babies with moderate to severe atopic eczema who are suspected of having a food allergy should be offered a 6–8 week trial of an extensively hydrolysed formula or an amino acid-based formula.

Although 85–90% of infants with cow’s milk allergy naturally acquire tolerance to cow’s milk by the age of 3 years, there remains a strong trend for these infants to retain or develop atopic disorders such as asthma or hay fever in later life. This tendency has become known as the ‘atopic march’ or ‘allergic march’.

6. How can a diagnosis of cow’s milk allergy be confirmed?

The diagnosis of cow’s milk allergy (CMA) in primary and community care is guided by the NICE clinical guidelines on food allergy in children. Diagnosis begins with obtaining the patient’s complete personal and familial history, which should provide an indication of whether the allergy is IgE-mediated or non-IgE-mediated (see Questions 3 & 4 and Table 1).

This is followed by a physical examination and one or more tests, as determined by the suspected underlying mechanism of allergy.

**Suspected IgE-mediated allergy**

For suspected IgE-mediated allergy, a clear clinical history together with a positive specific IgE test or skin prick test is sufficient to confirm the diagnosis. However, positive results for specific IgE tests or skin prick tests can occur in people without symptoms, and conversely, false negative results may also occur.

Where the history is less clear, the allergy tests should be interpreted with caution, and where there is diagnostic doubt an oral milk challenge may be performed. This involves incremental exposure of the child to milk under careful supervision in a hospital environment. If an age-appropriate quantity of milk (for example, 120–200 ml, depending on age) is tolerated without symptoms throughout a 2-hour period of observation then IgE-mediated allergy can be effectively excluded.

**Suspected non-IgE-mediated allergy**

Where non-IgE-mediated milk allergy is suspected, specific IgE tests and skin prick tests are generally unhelpful. Furthermore, it remains unclear whether there is a role for
atopy patch testing in non-IgE-mediated allergy. This involves prolonged contact of the allergenic food to the skin, and may be useful for the workup in infants with eczema. However this technique has not been widely adopted in the UK and is considered to be of little value in primary care. The only reliable test for non-IgE-mediated allergy is food elimination (to see if symptoms resolve) followed by reintroduction (to see if they return). This procedure is considered the gold standard test, and is outlined in detail below.

**Food elimination followed by oral challenge**

The procedure for an elimination diet followed by oral challenge is outlined in Figure 2. For diagnosis of non-IgE-mediated CMA, the food challenge begins with complete avoidance of milk protein for 2–6 weeks. It is important to seek advice from a dietitian about adequate nutrition during the trial, reintroduction and subsequent follow-up. If the patient shows no improvement during the elimination diet, it is unlikely that CMA is causing the symptoms.

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**Figure 2. Procedure for elimination diet followed by oral challenge.**

- **Elimination diet using an extensively hydrolysed formula (2–6 weeks)**
  - **Improvement**
    - Reintroduction of milk*
  - **No improvement**
    - No allergic symptoms
      - Reintroduce milk in normal diet and monitor for delayed symptoms
      - Allergic symptoms
        - Diagnosis of CMA is confirmed
          - Continue elimination diet
            - Repeat challenge in 6 months time or at age 9–12 months, whichever occurs first
        - No allergic symptoms
          - CMA unlikely
            - Try using an amino acid formula and/or refer to paediatric specialist
  - Allergic symptoms
    - No allergic symptoms

*Where there is suspicion of IgE-mediated allergy or severe non-IgE-mediated reactions, a challenge must be performed under medical supervision.
If the symptoms substantially improve or disappear on the elimination diet, reintroduction of a formula based on whole milk protein should be performed. For suspected non-IgE-mediated allergy, this challenge may be safely performed at home, but only in the absence of evidence of severe reactions or IgE-mediated milk allergy.19

If no reaction occurs, the child should receive cow’s milk formula as part of a normal diet for the next week, and the parents should be told to observe the child for any symptoms. For those challenges that are positive, in that symptoms return on the reintroduction of cow’s milk, the diagnosis of CMA is confirmed and the infant should be maintained on an elimination diet. The patient should be rechallenged after 6 months, or at the age of 9–12 months, whichever occurs first.15

7. Are there guidelines for the dietary management of cow’s milk allergy?

A number of international and UK bodies have published guidelines to support effective, evidence-based management of cow’s milk allergy (CMA).11,13–21 Importantly, NICE has published guidelines on the diagnosis and assessment of food allergy in children in primary and community care settings.13 Management of CMA is further supported by a food allergy care pathway from the Royal College of Paediatrics and Child Health (RCPCH), DRACMA guidelines from the World Allergy Organization and European consensus guidelines.14,15,21 Key recommendations for dietary management of CMA are summarised in Box 1.

8. What are the differences between available hypoallergenic formulas?

Current treatment guidelines recommend that bottle-fed infants with cow’s milk allergy (CMA) should be given hypoallergenic formulas, defined as those formulas which are tolerated by at least 90% of infants with documented CMA.17 Several hypoallergenic formulas are available, and these fall into two classes: extensively hydrolysed formulas (eHFs) and amino acid-based formulas (AAFs). Formulas based on unmodified proteins (including soya milk, goat’s milk and sheep’s milk), or partially hydrolysed protein, are not considered hypoallergenic, and therefore are not recommended for management of CMA.

Box 1: Summary of UK and international guidelines on dietary management of CMA.

- Diagnosis and assessment of CMA are guided by recommendations from NICE and the RCPCH.13,21
- For management of CMA in exclusively breast-fed infants, a strict elimination of the causal protein from the diet of the lactating mother should be tried.14,15,19,20
- Infants with CMA who are not exclusively breast fed should receive a hypoallergenic formula based on extensively hydrolysed protein as first-line.15,19
- In cases where extensively hydrolysed formula is ineffective, or where the infant has severe/multiple food allergy, or if the infant is sensitive to cow’s milk in maternal breast milk, an amino acid-based formula should be used.15,19
- In cases of moderate to severe atopic eczema, bottle-fed babies who are suspected of having a food allergy should be offered a 6–8 week trial of an extensively hydrolysed formula or an amino acid-based formula.11
- Formulas based on unmodified proteins of other species’ milk (for example, goat’s or sheep’s milk), or partially hydrolysed protein, are not hypoallergenic and should not be used for the management of CMA.15,19,20
- Soya-based formulas contain high phytate, aluminium, and phytoestrogen concentrations, the long-term effects of which are unknown. These formulas should not be used in infants with CMA during the first 6 months of life, and should not be the first choice thereafter.16,18
The protein in eHFs has been extensively hydrolysed (broken down) into small peptides and amino acids. These small fragments are not as readily recognised by the immune system, and are therefore less likely to trigger an allergic reaction than whole milk proteins. AAFs are based on free amino acids and do not contain the proteins that can trigger allergic reactions in people with CMA. However, AAFs are substantially more expensive than eHFs; in some cases, by more than 2½ times. Current treatment guidelines recommend that eHFs are used as the first-line option for managing CMA, while AAFs are reserved for infants who do not tolerate eHFs, have severe CMA or suffer from multiple allergies. AAFs are also suitable for infants who have reacted to the cow’s milk content of maternal breast milk. Currently available eHFs differ in the degree of protein hydrolysation, which may influence the incidence of allergic manifestations. In addition, comparative studies of such formulas suggest that casein hydrolysates have the least residual allergenic activity.

Nutrient content is an important consideration when choosing between different brands of eHF or AAF. One notable difference is the content of DHA and ARA, which are long-chain polyunsaturated fatty acids (LCPs). An evidence review by the European Food Standards Agency (EFSA) concluded that DHA in formula, present at ≥0.3% of total fatty acids, contributes to the visual development of infants. Lactose content also varies between formulas. Infants with GI symptoms may have gut damage, which can cause secondary lactose intolerance. Therefore a lactose-free formula might be useful for managing CMA in these infants until the gut recovers.

In addition, each brand may offer a range of formulations, with varying nutritional content optimised for different age groups. For instance, formulas staged from 6 months have a higher calcium and iron content to complement the weaning process.

9. How do the NICE guidelines on diagnosis of food allergy in children affect clinical practice?

The NICE guidelines aim to address variation in the diagnosis and assessment of children and young people with food allergy in primary and community settings, encouraging patient-centred care and well-structured links with secondary care.

The guidelines emphasise that a number of core skills and competencies are key to the delivery of high quality care for children with food allergy. At the same time, several clinical and governmental bodies have highlighted the pressing need for allergy training in primary and community care. Accordingly, NICE highlights that most GPs may benefit from allergy training, as either first-time training or a refresher course. Such training can be incorporated into continuing professional development, and specialists in allergy can support training at a local level, helping to avoid additional costs.

Under these guidelines, NICE predicted increases in the number of diagnoses made in primary care, and the number of early diagnoses. Conversely, reductions in misdiagnosis were expected. Taken together, these factors may result in a reduction in the number of GP visits, with potential for local-level cost savings.

The NICE guidelines outline a careful and methodical approach to diagnosis of food allergy. Combined with a thorough understanding of the underlying pathology, the guidelines represent an important clinical tool, supporting front-line practitioners in the diagnosis and care of children with food allergy in primary and community settings.
Improving the care of infants with cow’s milk allergy


**ALLE CN** is an educational programme supporting healthcare professionals in the care of infants with cow’s milk allergy. The programme publishes a comprehensive range of learning resources, from allergy education for healthcare professionals, to leaflets on weaning and milk-free recipes for parents. Allerni also hosts a programme of seminars around the country, linking front-line practitioners with local allergy experts and leading researchers. For further information please contact Mead Johnson.

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