

Managing cows' milk allergy in children

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Cows' milk allergy mainly affects young children and because it is often outgrown is less commonly seen in older children and adults. It is one of the most common childhood food allergies in the developed world, second to egg allergy,¹ affecting 2-7.5% of children under 1 year of age.² The mainstay of treatment is to remove cows' milk protein from the diet while ensuring the nutritional adequacy of any alternative.

Cows' milk allergy can often be recognised and managed in primary care. Patients warranting a referral to specialist care include those with severe reactions, faltering growth, atopic comorbidities, multiple food allergies, complex symptoms, diagnostic uncertainty, and incomplete resolution after cows' milk protein has been excluded.

Although there are non-immune reactions to cows' milk, such as primary lactose intolerance (when malabsorption

SOURCES AND SELECTION CRITERIA

Our search included PubMed, the Cochrane Collaboration using the search terms "Cow's milk allergy," "milk allergy," "natural history," "management," and "treatment." When possible, evidence from randomised controlled trials and systematic reviews were used, although case series and observational studies were also included. We referenced expert review articles and used expert clinical opinion.

of sugar can cause bloating and diarrhoea), these are extremely rare in very young children. Except after a gastrointestinal infection, infants with gastrointestinal symptoms on exposure to cows' milk are more likely to have cows' milk allergy than lactose intolerance. This article focuses on immune mediated reactions to cows' milk in children and reviews the evidence on how to diagnose and manage the condition.

What is cows' milk allergy?

Cows' milk allergy is an immune mediated reaction to proteins within milk.³ Milk contains casein and whey fractions, each of which have five protein components. Patients can be sensitised to one or more components within either group.

Cows' milk allergies are classified according to the underlying mechanism, which affects the presentation, diagnosis, treatment, and prognosis. IgE mediated allergy is an immediate type (type 1) hypersensitivity reaction that occurs rapidly after exposure, usually within 20 minutes. One of the main causes of symptoms is histamine release, and the symptoms are highlighted in table 1.

Non-IgE mediated allergy is a delayed type (type 4) hypersensitivity reaction that seems to be equally common but less well described than IgE mediated cows' milk allergy. Non-IgE mediated milk allergy can occasionally cause a severe form of allergic reaction with acute gastrointestinal symptoms that can mimic sepsis (food protein induced enterocolitis syndrome). However, the T cell mediated reactions are usually more delayed and are often chronic because of continued milk exposure during infancy. Typical symptoms are largely gastrointestinal or cutaneous (table 1).⁴ The high frequency of such symptoms in infants without cows' milk allergy, combined with the lack of an immediate temporal relation with milk exposure or any clinical tests, can make non-IgE mediated allergy difficult to diagnose.

How does it present?

IgE mediated allergy usually manifests within minutes but no longer than two hours after ingestion of cows' milk protein. Symptoms include angio-oedema of the oropharynx, oral pruritus, urticaria, and rhinorrhoea. Although most reactions are mild, around 15% may be more severe with features of anaphylaxis such as stridor or wheeze.⁵

Non-IgE mediated allergy presents with more non-specific symptoms that are often chronic because of regular consumption. The most common presentations are treatment

Table 1 | Symptoms and signs of IgE and non-IgE mediated cows' milk allergy⁴

IgE mediated	Non-IgE mediated
Skin	
Pruritus	Pruritus
Erythema	Erythema
Acute urticaria—localised or generalised	Atopic eczema
Acute angioedema—most commonly lips, face, and around eyes	
Gastrointestinal system	
Angioedema of the lips, tongue, and palate	Gastro-oesophageal reflux disease
Oral pruritus	Loose or frequent stools
Nausea	Blood or mucus in stools
Colicky abdominal pain	Abdominal pain
Vomiting	Infantile colic
Diarrhoea	Food refusal or aversion
	Constipation
	Perianal redness
	Pallor or tiredness
	Faltering growth in conjunction with at least one of above gastrointestinal symptoms (with or without atopic eczema)
Respiratory system (usually in combination with one or more of above symptoms and signs)	
Upper respiratory tract symptoms (nasal itching, sneezing, rhinorrhoea, stridor, or congestion ± conjunctivitis)	Lower respiratory tract symptoms (cough, chest tightness, wheezing, or shortness of breath)
Lower respiratory tract symptoms (cough, chest tightness, wheezing, or shortness of breath)	
Other	
Signs or symptoms of anaphylaxis or other systemic allergic reactions	

SUMMARY POINTS

Cows' milk allergy is common, occurring in up to 7% of children and usually presents in infancy. Allergy may be IgE mediated with rapid onset of symptoms such as urticaria or angioedema or non-IgE mediated, producing more delayed symptoms such as eczema, gastro-oesophageal reflux, or diarrhoea.

Management is by exclusion of cows' milk protein from the diet (including from the diet of a breastfeeding mother) under dietetic supervision.

Most children with milk allergy outgrow it (average age 5 years for IgE mediated and majority by age 3 years for uncomplicated non-IgE mediated allergy).

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- ▶ Frontotemporal dementia (BMJ 2013;347:f4827)

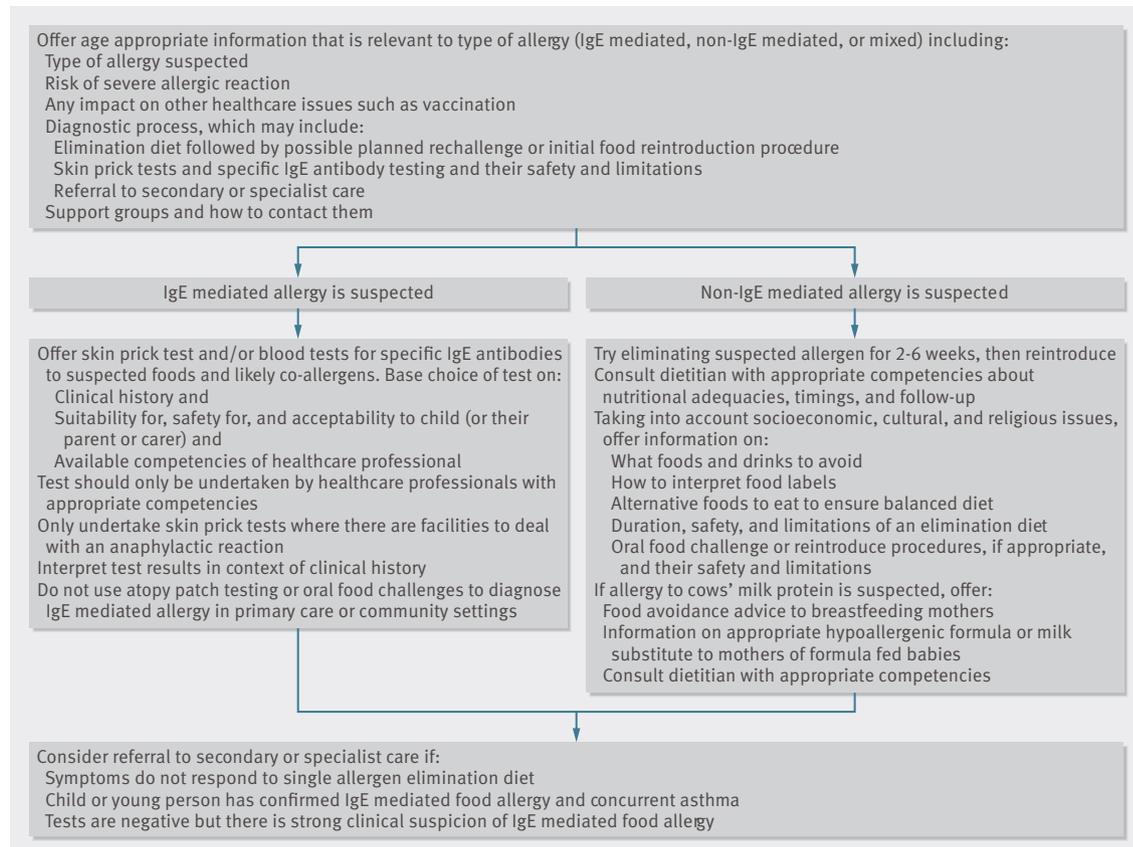


Fig 1 | National Institute for Health and Care Excellence recommendations for diagnosis and management of cows' milk allergy⁴

resistant gastro-oesophageal reflux, eczema, colic or persistent crying, diarrhoea (sometimes with mucous or blood), food aversion, and, less commonly, constipation. Gastrointestinal symptoms are thought to be due to gastrointestinal inflammation and associated dysmotility.

Who is affected?

Cows' milk allergy affects all ages but is most prevalent in infancy, affecting 2-7% of formula fed infants.² It can present in the first month of life and is one of the most common food allergies. Exclusively breast fed babies can also develop cows' milk allergy as a result of protein in the maternal diet transferring through breast milk.⁶

Predicting which children will develop a food allergy is difficult, but the presence of atopic dermatitis is a risk factor for developing sensitisation to common food allergens. The earlier the atopic dermatitis starts and the more severe it is, the higher the risk of food allergy. Hence there should be the highest index of suspicion of IgE mediated allergy in infants with moderate to severe atopic dermatitis that starts in the first six months of life.⁷⁻⁹

A family history of atopy is a risk factor for developing food allergies, although only an allergic predisposition is inherited not specific allergies.¹⁰ Associated atopic comorbidities, especially asthma, are a risk factor for more severe reactions to milk.⁵ The frequency of severe reactions is higher in asthmatic children, especially those with poorly controlled asthma, than in those without asthma.⁵ The underlying mechanisms that cause initial sensitisation to milk remain unclear.

What are the symptoms?

An allergy focused history is vital in establishing whether cows' milk allergy is a potential diagnosis in patients presenting with suggestive symptoms. The investigations depend on whether the clinician suspects an IgE or non-IgE mediated allergy. The history should elicit the symptoms and how quickly they occur after ingestion of cows' milk protein, how long they last, their severity, and which treatments were implemented and their effects.

It is important to distinguish children with non-IgE mediated cows' milk allergy from those who have gastro-oesophageal reflux or eczema with other causes. Clinical clues lie in the severity of the symptoms and treatment resistance, both of which make underlying milk allergy more likely. A dose dependent relation to any change in milk protein consumption—for example, when moving from breast to bottle feeding—may also provide useful insight. The presence of symptoms in more than one system also suggests a possible unifying underlying cause—for example, gastro-oesophageal reflux or diarrhoea in infants with atopic dermatitis.¹¹

As well as exploring the symptoms in table 1,⁴ doctors should ask about other symptoms of atopy such as atopic dermatitis or seasonal allergic rhinitis (hay fever) and asthma in older children. Any family history of atopy should also be documented, as well as the foods that the parents have already removed from the child's diet, and the effect of exclusions and subsequent food challenges.

How is cows' milk allergy investigated?

Once clinical suspicion has guided the clinician towards a diagnosis, appropriate investigation can be undertaken (fig 1). If IgE mediated allergy is suspected, then confirmation is by either a skin prick test or measurement of specific immunoglobulin E in the blood (spIgE, previously known as RAST). Skin prick testing is ideally done using fresh milk as commercial extracts can be less sensitive.^{w1} It should be carried out only where there are the facilities and expertise to manage anaphylactic reactions as 0.12% of patients having skin prick tests develop systemic allergic reactions.^{w2} Specific immunoglobulin E testing is therefore usually more suitable in primary care.

Although a larger wheal diameter on skin prick test or a higher IgE concentration gives a higher probability of clinical allergy, an appropriate clinical history on exposure to the allergen is required for diagnosis. An observational study showed that 5.6% of infants had a positive skin prick test response to milk but only 2.7% had clinical cows' milk allergy, showing that a positive test result in isolation is not enough for a conclusive diagnosis.¹² The size of the response to testing does not relate to the severity of the clinical response to exposure.

When the allergy tests fail to confirm the history, the gold standard for investigating cows' milk allergy is a double blind placebo controlled food challenge. These can be expensive and time consuming so an open oral food challenge can be used to elicit reproducible, objective symptoms. Like skin prick tests, food challenges must be carried out in a safe environment with resuscitation facilities and experience, such as an allergy clinic or hospital day case unit.

Skin prick tests and specific IgE measurement are of little use if non-IgE mediated cows' milk allergy is suspected. The only reliable diagnostic test is a strict elimination diet.¹³ If symptoms do not improve within two to eight weeks, cows' milk allergy is unlikely and milk should be reintroduced. Improvement of symptoms on milk exclusion coupled with recurrence of symptoms on reintroduction is strongly indicative of non-IgE mediated allergy. In a breast fed baby, the cows' milk protein can be removed from the mother's diet under dietetic advice.

No evidence supports the use of investigations such as serum IgG testing, Vega testing, kinesiology, or hair analysis.⁴

How do we manage cows' milk allergy?

IgE mediated cows' milk allergy is managed by exclusion of cows' milk protein from the diet. For non-IgE mediated allergy both cows' milk protein and soya (if applicable) should be removed from the diet in the first instance because of the risk of cross reactivity.¹³ For exclusively breast fed babies, the mother should be put on an exclusion diet under supervision to ensure she maintains adequate nutrition. Mothers should be given a supplement of 1000 mg of calcium and 10 µg of vitamin D every day.¹⁴ In formula fed infants, cows' milk based formula can be replaced by hypoallergenic infant formulas such as extensively hydrolysed (tolerated by 90% of children with cows' milk allergy) or amino acid formulas.

Most symptoms will usually resolve within two to four weeks of a cows' milk elimination diet. Once it has been instituted and shown to help, milk must be reintroduced into the diet to prove it is the causal agent. Once the diagnosis is confirmed, the child should remain on the elimina-

tion diet for at least five months or until 1 year of age, when reintroduction can be tried, usually at home.

The input of a dietitian is highly recommended to maintain optimal nutrition and guide choice of milk substitute. Observational and cohort data show malnutrition in children on exclusion diets as well as those with newly diagnosed food allergies.^{15 w4 w5} These patients require dietetic input to ensure that this is managed or averted. Obesity can also be present in children on exclusion diets.^{w6} If access to a dietitian is not possible in primary care, the child's height and weight should be measured regularly to assess growth and nutrition and appropriate calcium supplements should be initiated. The child should be referred to a hospital dietitian or allergy clinic if concerns arise.

Once cows' milk protein is excluded from the diet, the family must be counselled on how to both avoid and manage accidental exposures to milk. This requires education on reading and understanding food labels. Management of IgE mediated reactions may require the use of antihistamines, or in rare cases of anaphylaxis, an adrenaline autoinjector. Autoinjectors are indicated for patients who meet the criteria in the European Academy of Allergy and Clinical Immunology management of anaphylaxis guideline (box 1, see bmj.com).^{w7}

Any children who also have asthma should be identified and well controlled because of the increased risk of severe reactions. For IgE mediated allergy, a written emergency management plan should be provided for the families' reference and for nursery or school. Examples of these can be found on the British Society for Allergy and Clinical Immunology website (www.bsaci.org).

Which milk should be recommended?

In most cases, first line treatment would be with an extensively hydrolysed formula—these are based on cows' milk but are extensively broken down into smaller peptides that are less well recognised by the immune system. If symptoms do not fully resolve after two to eight weeks, infants should be changed to an amino acid formula,¹⁶ which contains no peptides to be bound by IgE.

Amino acid formula should be the first choice in infants with severe reactions such as anaphylaxis or severe delayed gut (unresponsive bleeding per rectum leading to a haematological disturbance) or skin symptoms as well as those with faltering growth. Children who exhibited symptoms when exclusively breast fed should also have an amino acid formula in the first instance.

Soya based formula milks should be avoided in children aged under 6 months because they contain isoflavins, which have a weak oestrogen effect.¹⁷ Further advice is available in the milk allergy in primary care guideline (see supplementary material on bmj.com).¹⁸

Other mammalian milks, such as goat, mare, or sheep, are not recommended because of the high species cross reactivity.^{18 19} Children over 6 months can be tried on a soy formula if this is more palatable,¹³ but clinicians also need to consider the cross reactivity between cows' milk and soya; up to 60% of patients with non-IgE mediated cows' milk allergy and up to 14% with IgE mediated allergy also react to soya.^{w3} In older children there are a range of supplemental milks such as oat, or in the over 5 year olds, rice milk. These

AREAS FOR FUTURE RESEARCH

- What is the initial event causing sensitisation to cows' milk protein?
- What intervention could prevent the acquisition of cows' milk protein allergy in children?
- Can a biomarker be developed to diagnose non-IgE mediated cows' milk allergy?
- Is there a role for oral tolerance induction?

ADDITIONAL EDUCATIONAL RESOURCES

Resources for health professionals

NICE guideline 116: Assessment and diagnosis of food allergy in young children and young people in a community setting. (www.nice.org.uk/nicemedia/live/13348/53214/53214.pdf)

Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Paediatr Gastrointest Nutr* 2012;55:221-9

Consortium of Food Allergy Group online milk allergy calculator (www.cofargroup.org)—Tool to help predict likely age of milk tolerance development in IgE mediated allergy based on clinical features and allergy test results

Venter C, Brown T, Walsh J, Shah N, Fox AT. Diagnosis and management of non-IgE mediated cow's milk allergy in infancy—a UK primary care practical guide. *Clin Translational Allergy* 2013;3:23. A practical primary care focused guideline

Resources for patients and carers

Allergy UK (www.allergyuk.org)—Day to day tips and support

NHS Choices (www.nhs.uk/conditions/food-allergy/pages/intro1.aspx)—Clear guidance on symptoms and how to access help

Food Allergy Research and Education (www.foodallergy.org)—US resource for people with food allergies

Food Standards Agency allergy alerts (http://food.gov.uk/policy-advice/allergyintol/alerts/#.UbYDf_lIHc)—Provides text message alerts of incorrect food labelling

TIPS FOR NON-SPECIALISTS

- Most formula fed infants can be started on an extensively hydrolysed formula, but if symptoms persist, an amino acid formula may be required
- Infants with severe reactions, faltering growth, or who developed symptoms when exclusively breast fed should be started on an amino acid formula
- Soya milk is not suitable for children under 6 months old
- Other mammalian milks (goat, sheep, etc) should not be substituted for cows' milk because of the risk of allergic cross reactivity
- In older children milk substitutes such as soya, oat, and in children over 5 years, rice milk may be used. These should be fortified with calcium
- Ensure parents are aware of all the terms in ingredients lists that can be substituted for milk and provide dietetic support to ensure nutritional adequacy
- Patients should be referred to specialist care if they have multiple food allergies, severe allergic reactions, faltering growth, or complex symptoms or if they fail to respond to an exclusion diet

should be calcium fortified, but it is important to note that organic milks under governmental legislation cannot be fortified with calcium. Children should be eating three portions of calcium rich foods per day to obtain adequate calcium; this should be titrated to the recommended daily allowances for particular age groups (table 2, see bmj.com).^{w8}

When to refer on to specialist care

Uncomplicated cows' milk allergy can be managed in primary or secondary care as long as dietetic support is available. Referral to a paediatric allergy specialist is indicated if cows' milk is:

- Not the only allergen suspected of causing a reaction (other than cross reaction to soya in non-IgE mediated allergies)
- Thought to be causing gastrointestinal symptoms or faltering growth
- Thought to have caused severe IgE or non-IgE mediated reactions (box 2, see bmj.com)⁴

In addition, review by a paediatric allergist is prudent in children with IgE mediated allergies and asthma because of the risk of more severe reaction.^{w9}

A prospective parental survey has shown that children attending specialist allergy clinics are more likely to be able to manage a reaction as well as being less likely to have one.^{w9} However, provision of specialist allergy services is relatively limited. The British Society for Allergy and Clinical Immunology website has a tool to identify the nearest allergy clinic in the UK (www.bsaci.org).

What is the prognosis?

Recent prospective longitudinal studies²⁰⁻²¹ following children with IgE mediated cows' milk allergy found that 53-57% outgrow their milk allergy by 5 years of age. Tolerance is assessed by intermittent allergy tests to detect a fall in either specific IgE level or skin prick wheal diameter with a hospital based oral food challenge when tolerance is suspected. The Consortium of Food Allergy Research website has a tool to help predict when tolerance will develop (www.cofargroup.org). Observational and cohort studies have shown that IgE mediated cows'

milk allergy is more likely to persist in children with asthma or allergic rhinitis, those who have more severe reactions, and those with larger allergy test results at diagnosis.^{3 21-24}

The natural course of non-IgE mediated cows' milk allergy is less well defined, but one large prospective population based study and a large retrospective study suggest that most children will be milk tolerant by 2.5 years of age.²²⁻²⁵ The development of tolerance can be assessed by a carefully planned home challenge, which can be undertaken every six months from the age of 1 year. If a child has a history of severe non-IgE mediated reactions (such as food protein induced enterocolitis syndrome), the challenges should be supervised in hospital.

A recent well designed prospective study of 100 children has established that up to 70% of children with IgE mediated milk allergy are able to tolerate baked milk.²⁶ In these children, the IgE binds predominantly to milk proteins that alter when milk is extensively heated, making them unrecognisable to the patients' immune system. Such children tend to have milder reactions, smaller allergy test responses, and outgrow their allergy earlier.^{w10-w12} Introducing baked milk to the diet may also speed up the acquisition of tolerance to unheated milk.²⁷ However, testing to identify children who are tolerant to baked milk is limited and requires challenge testing best directed by a paediatric allergist.

What new therapies are on the horizon?

Much research interest exists in the use of oral immunotherapy to induce tolerance in patients with cows' milk allergy. Oral immunotherapy is the controlled introduction of small but increasing volumes of cows' milk to allergic patients. A recent Cochrane review of four randomised controlled trials and five observational studies in children with IgE mediated allergy concluded that the chances of achieving full tolerance (>150 ml of milk a day) was 10 times higher in the oral immunotherapy treatment group than the control group.²⁸ However, the authors commented on the possibility of bias in these small trials and also the safety as 90% of patients experienced adverse reactions. This approach is not currently advocated in any national or international guidelines.

Another area of interest is the addition of prebiotics and probiotics to hypoallergenic milk formulas as a means to speed up the development of tolerance.^{w13} Also under investigation is the possibility that the type of formula milk chosen for treatment could affect outcome.^{w14}

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ANSWERS TO ENDGAMES, p 38 For long answers go to the Education channel on [bmj.com](http://www.bmj.com)

CASE REPORT Acute epiglottitis

- 1 Acute epiglottitis can be caused by bacteria (such as *Haemophilus influenzae* type B), viruses (such as herpes simplex), fungi (such as *Candida albicans*), and non-infectious insults (such as physical trauma, chemicals, and heat). Clinical features include stridor, dyspnoea, and drooling.
- 2 Owing to the physics of flow, in a partially obstructed airway, heliox should reduce the work of breathing and result in larger tidal volumes and improved gas exchange.
- 3 Actual or impending airway obstruction requires an immediate definitive airway, which needs to be carefully planned. The procedure should occur in a safe place, such as the operating theatre, with the appropriate senior staff, equipment, and skill sets. In less severe cases, patients may be managed conservatively.

ANATOMY QUIZ

A diagnostic intravenous urogram

- A: Calyx
 B: Right kidney
 C: Left renal pelvis
 D: Infundibulum
 E: Right ureter
 F: Bladder

STATISTICAL QUESTION

Allocation concealment versus blinding in randomised controlled trials

Statements a and b are true, whereas c and d are false.