PULSE

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QUICK GUIDE

Managing cow's milk allergy – moving beyond extensively hydrolysed formula

Cow's milk allergy (CMA), also known as cow's milk protein allergy (CMPA), is one of the most common food allergies in infancy and is managed by excluding cow's milk from the diet.[1,2]

In formula-fed infants, this means switching to a hypoallergenic formula (box 1) – either an extensively hydrolysed formula (EHF) or, in more severe cases, an amino acid formula (AAF).[3-5]

In breastfed infants, CMA is much less common, and may mean removal of cow's milk from the mother's diet (alongside supplementation with calcium and vitamin D).[1,5-7]

This guide explains the role of hypoallergenic formulas in formula-fed infants with CMA and provides support for GPs to recognise when the use of AAF is clinically appropriate.

Figure 1 illustrates the range of available formulas and their place in CMA management. For the majority of infants, an EHF will resolve their symptoms. However, for a small subset, EHF is either not tolerated or not appropriate due to the severity of their symptoms.[1-6]

In these cases, GPs need to feel confident about when to consider prescribing an AAF or referring to a specialist.

Two main types of CMA exist as follows (in some infants, a mixture of the two may occur):[1,5-9]

- **IgE-mediated or immediate CMA:** Symptoms usually occur within minutes of ingestion and range from mild skin reactions to life-threatening anaphylaxis. Usually associated with typical allergic symptoms, such as urticaria and/or angio-oedema with vomiting and/or wheeze.

Box 1 Hypoallergenic formula

- Extensively Hydrolysed Formula (EHF) - in which the cow's milk proteins are broken down into short peptides to reduce their allergenicity.
- Amino Acid-based Formula (AAF) - where the protein is provided in the form of free synthetic amino acids (completely cow's milk free)

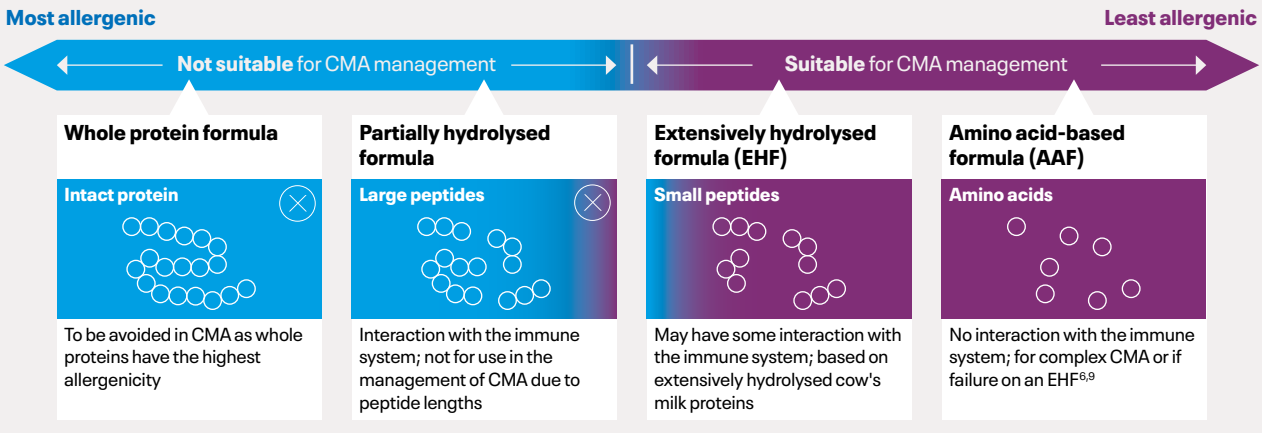
- **Non-IgE-mediated or delayed CMA:** Symptoms occur ≥2 hrs after ingestion, usually between 6-72 hours, and are typically delayed gastrointestinal (GI) or skin symptoms, again varying from mild to severe.

When to suspect CMA

Around 2-3% of infants will develop CMA in the first year of life.[1] Symptoms of CMA overlap with a number of common childhood conditions and include:[5-8]

- **Skin symptoms:** Persistent eczema, urticaria or angioedema.
- **GI symptoms:** Reflux, vomiting, diarrhoea, constipation, blood in stools or colic-like distress.
- **Respiratory symptoms:** Wheezing or chronic cough, particularly when accompanied by other allergic symptoms.

Figure 1 Types of infant formula and their role in CMA management



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● **General symptoms:** Irritability, poor feeding or failure to thrive. Immediate IgE-mediated CMA is generally easier to recognise than non-IgE-mediated, with rapid onset of allergic symptoms like facial angioedema, urticaria and, in severe cases, anaphylaxis. Non-IgE-mediated CMA tends to present with predominantly GI and skin symptoms, such as reflux or atopic eczema, that fail to respond to standard treatments.[6]

A number of UK, Irish, European and international guidelines exist for the diagnosis and management of CMA, including the international Milk Allergy in Primary Care (iMAP) Guidelines.[1,6-8] A more specific list of CMA symptoms, as described by the iMAP guidelines, is provided in Box 2.[7]

Box 2 Key symptoms of CMA[7]

IgE-mediated CMA

Mild to moderate

One or more of the following symptoms:

- Skin symptoms – acute pruritis, erythema, urticaria, angioedema, acute 'flaring' of persisting atopic eczema.
- GI symptoms – vomiting, diarrhoea, abdominal pain/colic.
- Respiratory (rarely without other allergy symptoms) – acute rhinitis and/or conjunctivitis.

Severe

- Anaphylaxis – immediate reaction with severe respiratory and/or cardiovascular signs and symptoms (rarely, severe GI symptoms), requiring emergency treatment.

Non-IgE-mediated CMA

Mild to moderate

Usually several of the following symptoms are present:

- GI symptoms, including persistent irritability (colic), vomiting (reflux), food refusal or aversion, diarrhoea-like stools, constipation (especially soft stools, with excessive straining), abdominal discomfort, painful flatus, blood and/or mucus in stools in otherwise well infant.
- Skin symptoms, in particular pruritus, erythema, non-specific rashes, moderate persistent atopic eczema.

Severe

One or more of the following symptoms that are **severe, persisting and treatment resistant:**

- GI symptoms – diarrhoea, vomiting, abdominal pain, food refusal or food aversion, significant blood and/or mucous in stools, irregular or uncomfortable stools, with or without faltering growth.
- Skin – severe atopic dermatitis, with or without faltering growth.

Diagnosis of CMA

The majority of cases of CMA are seen in formula-fed infants, with symptoms developing at the onset of formula or mixed feeding. Diagnosis is based on an allergy-focused clinical history and examination. For IgE-mediated CMA, this will be in combination with allergy testing (skin prick and/or IgE blood tests) and oral challenge.[1,5,6,8]

For non-IgE CMA, there are no reliable diagnostic tests and diagnosis requires either the mother (breastfed) or infant (formula-fed) to undergo an elimination diet for 2-4 weeks followed by reintroduction of cow's milk to confirm diagnosis.[1,6,8]

Management of CMA

Where CMA is confirmed, mothers of exclusively breastfed infants should be supported by a specialist dietitian to continue breastfeeding and exclude cow's milk from their diet, alongside supplementation with calcium and vitamin D. Formula- or mixed-fed infants will require a trial of EHF or, if symptoms are severe, a trial of AAF may be commenced. Most infants with mild-moderate non-IgE-mediated CMA can be managed in primary care (see the iMAP Guidelines).[7] However, infants with any severe presentation or IgE-mediated CMA should be referred to a specialist paediatric allergy service. Reassessment is recommended after 6 months (or at 9-12 months of age, whichever is first) to see if milk can be reintroduced.[1,6,7]

Red flags indicating an AAF required in formula-fed infants

The majority of formula-fed infants with CMA will have their symptoms managed by commencing an EHF. However, there are some situations where an AAF is more appropriate, as follows:

1. Infants reacting to an EHF

Some infants will continue to react to an EHF because it still contains fragments of milk protein.

Research suggests that around 10% of infants with uncomplicated IgE-mediated CMA will continue to react on EHF[3] and this rate increases up to 40% in infants with more complex non-IgE-mediated forms of CMA.[4]

It is generally recommended to trial an EHF for at least 2 weeks, depending on symptoms; if symptoms fail to resolve then a trial of AAF is indicated.[3,5,7] It can take time for symptoms like eczema and gut inflammation to heal, so infants with these tend to need the longer trial period.[3]

2. Faltering growth

Infants with CMA are at increased risk of faltering growth (also termed failure to thrive) – this can be low weight for age and also low height for age, or stunting, which is of particular concern.[3] Faltering growth may be due to several factors, including poor intake, persistent gastrointestinal discomfort, chronic inflammation and nutrient malabsorption.

Infants with CMA who are not gaining weight or are dropping percentiles on growth charts should be reassessed promptly and referred.[8] These infants will usually require an AAF.[6]

Clinical trials have demonstrated the benefits of AAF in overcoming faltering growth. For example, a randomised controlled trial (RCT) in 45 infants with confirmed CMA showed growth improved in the AAF group, with increased weight and length for age compared with the EHF group during the 9-month follow-up.[10] Another, multicentre RCT including 73 infants with confirmed CMA found a significant increase in height for age among those taking AAF compared with those on EHF.[11] In addition, these and other studies have shown AAF improves linear growth catch up compared with EHF, leading UK and European guidelines to advise use of AAF in infants with faltering growth.[1,2,6]

3. Severe GI symptoms

Infants with severe GI symptoms are likely to require AAF and referral to specialist care; it can be difficult to define severity but more severe GI symptoms typically involve persistent vomiting and diarrhoea, significant blood in stools, food refusal or aversion and abdominal pain (see Box 2).[3,7] Expert guidelines recommend that infants with eosinophilic oesophagitis (EoE)

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and food protein-induced enterocolitis (FPIES), conditions that are characterised by severe GI symptoms, are likely to benefit from AAF.[1,2,6]

Red flag 4: Anaphylaxis

Anaphylaxis to milk in infants is rare. However, where it occurs an EHF will be inappropriate due to the presence of residual milk proteins. Infants who have previously had anaphylaxis should be seen by a specialist allergy centre and will be prescribed an AAF.[7]

When to refer to specialist services

- **Dietitian.** All infants with CMA require dietetic support to optimise nutrition and monitor growth, especially during EHF or AAF trials and during weaning.
- **Paediatric allergy service.** Infants with suspected IgE-mediated CMA will usually require referral for allergy testing and diagnosis, as testing is not universally available in primary care.[7]

In addition, the following groups will require referral to specialist paediatric allergy services:[5,7,8]

– Severe IgE-mediated CMA (e.g. anaphylaxis, severe wheezing).
– Severe non-IgE-mediated CMA (e.g. FPIES, EoE).
– Persistent symptoms on EHF or faltering growth.
– Complex cases with mixed symptoms or diagnostic uncertainty.

Key points

- A small number of breastfed infants develop CMA and may require maternal dietary elimination.
- For most formula-fed infants with CMA, an EHF will resolve symptoms, but for some an AAF is required.
- If one or more red flags are present, GPs may consider initiating a trial of an AAF or referring to specialist services as appropriate.
- Infants reach a number of important developmental milestones at this age, so it is important to monitor growth as well as symptoms in the management of CMA.
- Early recognition of red flags, including faltering growth, helps prevent prolonged symptoms, infant distress and parental anxiety, supporting better health and developmental outcomes.

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For the dietary management of formula-fed infants with
Cow's Milk Allergy (CMA) and Multiple Food Protein Allergies

NO.1 FOR GOOD Reasons...

- Fast symptom relief in as little as 3 days[1]
- Supports growth in both IgE and non-IgE CMA infants[2-6]
- 40+ years of CMA expertise[7]

Prescribe Neocate LCP,
Ireland's No. 1 AAF[8]

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IMPORTANT NOTICE: Breastfeeding is best. Neocate LCP is a Food for Special Medical Purposes for the dietary management of Cow's Milk Allergy, Multiple Food Protein Allergies and other conditions where an amino acid-based formula is recommended. It should only be used under medical supervision, after full consideration of the feeding options available including breastfeeding. Suitable for use as the sole source of nutrition for infants under one year of age. Refer to label for details.

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AAF: Amino Acid-based Formula; CMA: Cow's Milk Allergy

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