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SEPTEMBER 2017
**SUPPLEMENT**


# COW'S MILK ALLERGY

## CONTENTS



1 CPD CREDIT

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## 7 Red Flag Indicators for when to use an AAF

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## can make a difference
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## to provide fast and effective resolution of Cow's Milk Allergy symptoms[6,7]

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**References: 1.** Koletzko S, Niggemann B, Arato A, et al. J Pediatr Gastroenterol Nutr 2012; 55(2):221-229. **2.** Venter C, Brown T, Shah N, et al. Clinical and Translational Allergy 2013; 3(1):23. **3.** Ludman S, Shah N, Fox A. BMJ 2013; 347-355. **4.** Fiocchi A, Brozek J, Schünemann H, et al. WAO J 2010; 3:57-161. **5.** Hill DJ, Murch SH, Rafferty K et al. Clin Exp Allergy 2007; 37(6):808-822. **6.** De Boissieu D, Matarazzo P, Dupont C. J Pediatr 1997; 131(5):744-747. **7.** Vanderhoof JA, Murray MD, Kaufman S et al. J Pediatr 1997; 131 (5):741-744.

**Neocate is a Food for Special Medical Purposes for use under medical supervision, after consideration of all feeding options including breastfeeding.**

**eHF=Extensively Hydrolysed Formula; AAF=Amino Acid-Based Formula; GI= Gastro Intestinal**

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## Introduction

Cow's milk allergy (CMA) may be defined as a reproducible adverse reaction to one or more milk proteins (usually caseins or whey beta-lactoglobulin) mediated by one or more immune mechanisms.[1] Non-allergic cow's milk hypersensitivity (lactose intolerance) does not involve the immune system.[2]

CMA is one of the most common childhood allergies in the developed world.[3] It presents in the first year of life when milk forms the greatest proportion of an infant's food intake. The UK prevalence is estimated between 2% and 3%. Most affected children present with symptoms by six months of age and onset is rare after 12 months. The condition can affect both breastfed and formula-fed infants, although it is less common in breastfed infants. Most infants grow out of CMA around the age of one to three years.[1]

CMA can present:[2]

- Following exposure to cow's milk in the maternal diet in breastfed infants
- When formula-fed infants are exposed through standard infant formula
- When cow's milk is introduced to the diet for the first time during weaning.

Factors associated with an increased risk of CMA include:[4]

- Associated atopic comorbidities (such as asthma and eczema)
- Family history of atopy.

## Symptoms

CMA has a wide variety of different symptoms and many of these can also overlap with those of a number of other conditions commonly experienced in early childhood, for example reflux, colic, eczema. Symptoms can be unpleasant and painful, which can cause distress for infants and their families.

There are two types of CMA:[4]

- Immunoglobulin E (IgE)-mediated where symptoms start acutely, usually within two hours of ingesting food
- Non-IgE-mediated where symptoms have a delayed onset and may not present for 48 hours or even up to seven days after milk ingestion.

©ISTOCK

CMA symptoms can be unpleasant and painful causing distress for infants and their families

## TABLE 1
**Symptoms and signs of cow's milk allergy[4]**

| | IgE-mediated | Non-IgE-mediated |
|---|---|---|
| **Skin reactions** | Pruritus | Pruritus |
| | Erythema | Erythema |
| | Urticaria | Atopic eczema |
| | Angioedema of lips, face, eye | |
| **Gastrointestinal** | Angioedema of lips, tongue, palate | Gastro-oesophageal reflux |
| | Oral pruritus | Loose stools or constipation |
| | Nausea | Blood/mucus in stools |
| | Abdominal pain | Abdominal pain |
| | Vomiting | Perianal redness |
| | Diarrhoea | Pallor and tiredness |
| | | Faltering growth in conjunction with at least one or more gastrointestinal symptoms above (with or without significant atopic eczema) |
| **Respiratory** (usually in combination with one or more of the above symptoms and signs) | Upper respiratory tract symptoms (nasal itching, sneezing, rhinorrhoea or congestion [with or without conjunctivitis]) | |
| | Lower respiratory tract symptoms (cough, chest tightness, wheezing or shortness of breath) | |
| **Other** | Signs or symptoms of anaphylaxis or other systemic allergic reactions | |

The diagnosis and management of these two clinical expressions of CMA differs significantly.

## Diagnosis[4]
A thorough history must be taken which includes:
- Family history of atopic disease in parents or siblings
- Personal history of early atopic disease
- Infant's feeding history
- Presenting symptoms and signs and speed of onset
- Age of onset of symptoms
- Reproducibility of symptoms on repeated exposure
- Details of previous management, including any medication and the perceived response to any management
- Any attempts to change the diet and the outcome.

A full physical examination along with weight and height and the presence of comorbidities such as eczema should be carried out.

IgE-mediated CMA is an immediate allergic reaction (type 1 hypersensitivity) which involves the release of

histamine and other mediators. Reactions usually involve rapid onset skin signs, for example urticaria and angioedema. More severe reactions can potentially lead to anaphylaxis.

IgE-mediated CMA is diagnosed via skin prick testing (SPT) or specific IgE antibody testing. However, a positive SPT or specific serum IgE test merely indicates sensitisation and does not confirm clinical allergy. A positive test coupled with a clear history of a reaction should usually be sufficient to confirm a diagnosis.

Non-IgE-mediated CMA (type 4 hypersensitivity) is thought to be caused by T-cells. The reactions are non-acute with delayed symptoms following milk ingestion occurring within hours or days after ingestion. Symptoms tend to be gastrointestinal or cutaneous and the respiratory system can sometimes be involved.

There are no validated tests for the diagnosis of non-IgE-mediated CMA. It is diagnosed via a clinical history followed by a successful dietary elimination trial.

Differential diagnoses of CMA include:[4]

- Food intolerance, for example lactose intolerance
- Allergic reactions to other food allergens, for example eggs, soya, wheat
- Anatomical abnormalities, such as Meckel's diverticulum
- Chronic gastrointestinal conditions, for example gastro-oesophageal reflux disease, Crohn's disease, coeliac disease, constipation, gastroenteritis, ulcerative colitis
- Pancreatic insufficiency (such as in cystic fibrosis).
- Infections, for example urinary tract infections.

## Management[4,5]

IgE-mediated CMA is usually managed in the secondary care setting, while non-IgE-mediated CMA can be managed in primary care with dietetic input.

More than half of children with IgE-mediated CMA outgrow their milk allergy by five years of age. Most children with non-IgE-mediated CMA will be milk-tolerant by three years of age.

### Non-IgE-mediated CMA

Management of non-IgE-mediated CMA involves totally excluding cow's milk from the infant's diet (or mother's diet if the child is breastfed) for a period of two to six weeks, followed by reintroduction of cow's milk to prove that it is the cause of symptoms. Dietitians can support the family with these changes and ensure the child (or mother in the case of breastfed babies) consumes a balanced diet. Formula-fed babies should be switched to appropriate alternatives, usually in the form of extensively hydrolysed formulas which are whey- or casein-based.

The infant remains on a cow's-milk-free diet until 9–12 months of age and for at least six months. The reintroduction of milk after this extended period of avoidance is usually done at home as a 'milk ladder' which is limited by the individual's tolerance.

The milk ladder (see page 6) takes into account factors that influence the allergic potential of cow's milk foodstuffs: the volume or quantity, effect of heating (including duration and degree of heating) and the wheat matrix effect (which increases tolerance):[1]

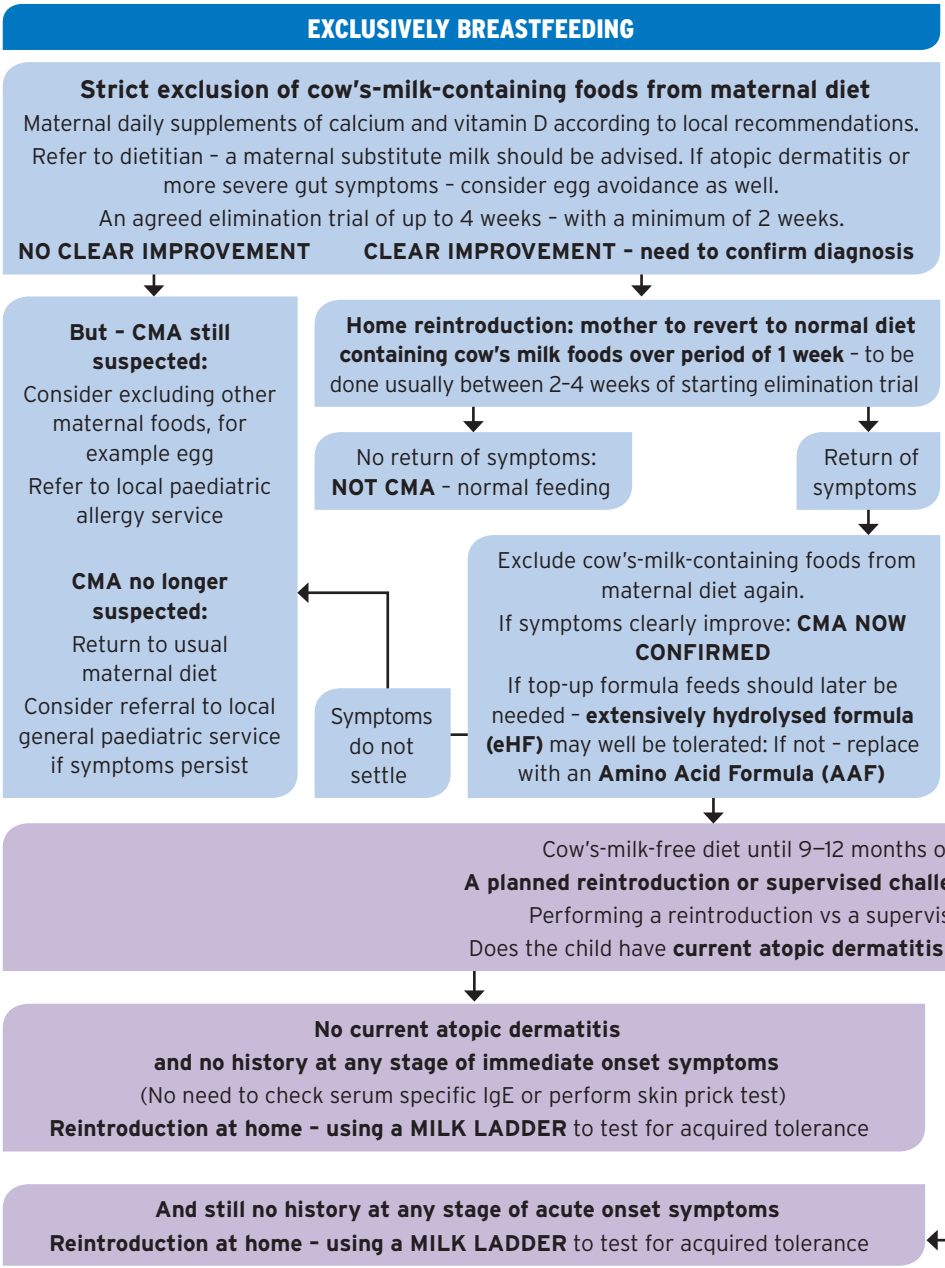
**Stage 1:** Small quantity, baked and matrix

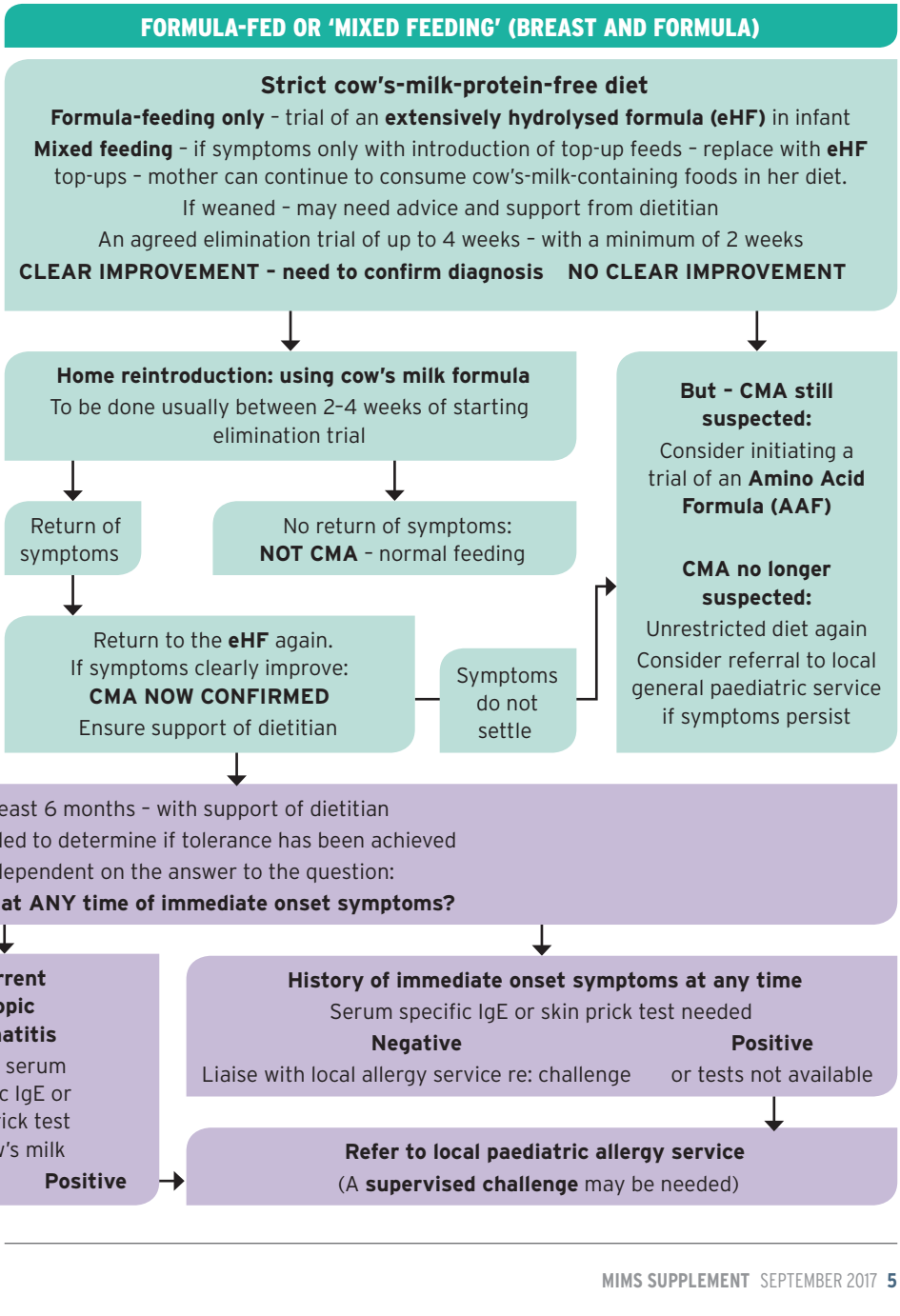
**Stage 2:** Larger quantity, baked and matrix OR traces without matrix or with minimal heating

**Stage 3:** Larger quantity, less heating, and less matrix OR all with some degree of protein change with heating or manufacturing

**Stage 4:** Fresh milk products.

**FIGURE 1** iMAP guideline: Management of mild to moderate non-IgE CMA[5]

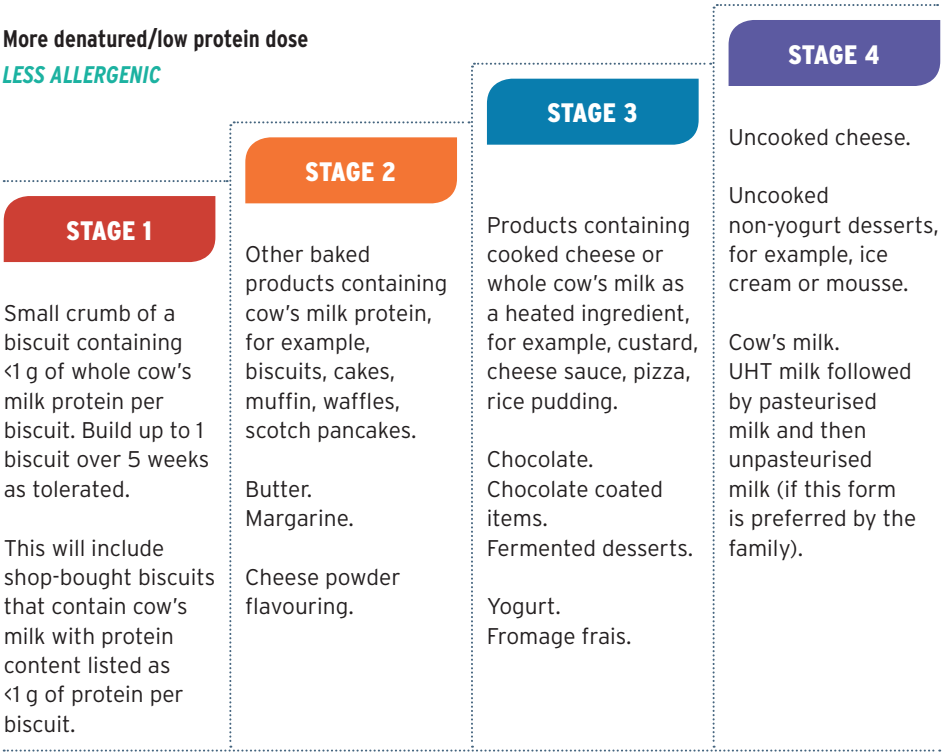



FORMULA-FED OR 'MIXED FEEDING' (BREAST AND FORMULA)
Strict cow's-milk-protein-free diet
Formula-feeding only – trial of an extensively hydrolysed formula (eHF) in infant
Mixed feeding – if symptoms only with introduction of top-up feeds – replace with eHF top-ups – mother can continue to consume cow's-milk-containing foods in her diet.
If weaned – may need advice and support from dietitian
An agreed elimination trial of up to 4 weeks – with a minimum of 2 weeks
CLEAR IMPROVEMENT – need to confirm diagnosis
NO CLEAR IMPROVEMENT
Home reintroduction: using cow's milk formula
To be done usually between 2–4 weeks of starting elimination trial
Return of symptoms
No return of symptoms: NOT CMA – normal feeding
Return to the eHF again.
If symptoms clearly improve:
CMA NOW CONFIRMED
Ensure support of dietitian
Symptoms do not settle
But – CMA still suspected:
Consider initiating a trial of an Amino Acid Formula (AAF)
CMA no longer suspected:
Unrestricted diet again
Consider referral to local general paediatric service if symptoms persist
d for at least 6 months – with support of dietitian
nen needed to determine if tolerance has been achieved
enge is dependent on the answer to the question:
history at ANY time of immediate onset symptoms?
Current atopic dermatitis
Check serum specific IgE or skin prick test to cow's milk
ative
Positive
History of immediate onset symptoms at any time
Serum specific IgE or skin prick test needed
Negative
Liaise with local allergy service re: challenge
Positive
or tests not available
Refer to local paediatric allergy service
(A supervised challenge may be needed)

## FIGURE 2
**Example of milk ladder**[1]

**More denatured/low protein dose**
*LESS ALLERGENIC*

**Less denatured/high protein dose**
*MORE ALLERGENIC*




### Referral to secondary care[4]
For suspected IgE and non-IgE-mediated CMA, referral to secondary care should be considered if there is:
- Faltering growth in combination with one or more gastrointestinal symptoms
- One or more acute systemic reactions
- One or more severe delayed reactions
- Significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parent or carer
- Persisting parental suspicion of food allergy (especially in children with difficult or perplexing symptoms) despite a lack of supporting history.

### Complications of CMA[4]
CMA may result in poor nutritional intake or malabsorption, leading to possible:
- Chronic iron deficiency anaemia
- Faltering growth, with the associated consequences in a growing child.

Rare cases of anaphylactic shock leading to death have been reported following cow's milk ingestion in sensitised children.

Heiner's syndrome, a milk-induced pulmonary disease, is a rare complication of CMA in children.

## CMA in the UK

Early recognition and diagnosis, appropriate management and dietary advice are all very important in effectively managing CMA. CMA imposes a substantial burden on the NHS, as many children with CMA go through months of treatment and often unnecessary investigations before the cause of their symptoms is finally recognised.

It is estimated that 18,350 infants will present to GPs with CMA each year in the UK. The cost of managing these infants over the first 12 months following initial presentation has been estimated to be £25.6 million.[8]

In 2013, a survey undertaken in 201 GPs, found that 92% of GPs would like a clearer

**CASE STUDY**

## Five-month-old baby with suspected CMA

Mrs H and her five-month-old baby daughter attended the surgery. Baby S was born by normal vaginal delivery at 40 weeks and is exclusively breastfed. For the past three to four weeks she has been having an increasing number of loose and foul-smelling stools.

A week ago Mrs H noticed some fresh blood present in her nappies. Baby S has shown a steady weight gain along the 75th centile. A detailed history revealed an older sibling who is asthmatic and that Mrs H suffers from eczema.

Examination of baby S was normal.

Differential diagnosis includes: Gastro-oesophageal reflux disease, colic, lactose intolerance.

### Discussion

Exclusively breastfed babies can also develop CMA due to protein in the maternal diet transferring through breast milk. However, the incidence is much lower than for formula- or mixed-fed infants with only about 0.5% of exclusively breastfed infants showing reproducible clinical reactions to cow's milk protein, and these are mostly mild to moderate in intensity.[7]

As the examination was normal and Baby S has had a steady weight gain, the history points to a possible diagnosis of CMA. As there does not appear to be a direct correlation with feeds, and there are no skin symptoms, it is most likely to be a non-IgE-mediated reaction.

Diagnosis would be made by strict cow's milk exclusion from Mrs H's diet for two to six weeks. A challenge test could then be carried out to confirm the diagnosis. Specialist dietitian advice should be sought to help the parents through the weaning process, allowing gradual reintroduction of cow's milk after a six-month period. Mrs H was prescribed calcium and vitamin D supplements while she continues to breastfeed.

Dietitians play an important role in the diagnosis and management of CMA. Their tasks include: choice of formula, monitoring nutritional status, suggesting nutritional supplements, dietary advice for breastfeeding mothers and infants, providing appropriate weaning advice, advice on level of cow's milk allergen avoidance that is required and organising or designing food challenges to diagnose CMA and determine development of tolerance.[4,6]

explanation of the options for diagnosis of CMA, and 91% would like to increase their understanding of management options for CMA.[6,8]

## MAP guideline[6]

The Milk Allergy in Primary Care (MAP group) was established by a group of experts who recognised the unmet needs in primary care in the diagnosis and management of CMA in the UK.

They have developed the MAP Guideline for the diagnosis and management of CMA presenting in infancy, for use in UK primary care.

The guideline is in the form of algorithms which show the steps needed to diagnose and manage the condition. The guideline covers:

- How to recognise the differing presentations of CMA in infancy (IgE-mediated and non-IgE-mediated)
- How to distinguish between severe and mild to moderate clinical expressions of CMA
- When to refer patients onwards
- Practical guidance on the initial management of mild to moderate non-IgE-mediated CMA in primary care
- Practical guidance on the ongoing primary care management of such infants.

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# The importance of palatability in an extensively hydrolysed formula for the management of cows' milk allergy

## Clinical guidelines† now recognise that palatability is an important factor in formula choice, particularly in older infants, when managing cows' milk allergy (CMA)[1–3]

### Palatability is important because by the time infants are prescribed EHF their taste preferences have already developed

An audit of GP data shows the first prescription of specialised formula is generally over 5 months of age[4] by which time the "window of acceptance", from birth until 3.5-4 months, has already closed. After this window they are less likely to accept bitter tastes and the chances of rejection are high.[5,6] The more palatable the formula the more likely it is to be accepted by the infant.

### Extensively hydrolysed formulas can be bitter

Extensively hydrolysed formulas (EHF) are the first-line choice for most formula-fed infants with CMA.[1,7]

The protein in EHF is broken down by hydrolysis to produce a mixture of short peptides and free amino acids, which are less likely to trigger an allergic reaction.[8] Unfortunately, the resulting formula can taste bitter which can be a problem as infants over four months of age are likely to strongly reject newly introduced bitter tastes.[2]

### An adequate intake of EHF is important for growth

Parents commonly report that their child refuses EHF because of its unpleasant taste,[9] which may make it hard to achieve recommended intakes.

Optimal growth is particularly important in the early years when CMA occurs.[10] Cows' milk is a rich nutrient source and avoidance, plus increased requirements due to allergic symptoms, can cause poorer growth and nutritional status in infants with CMA.[11–14] Adequate consumption of a hypoallergenic formula, like EHF, is recommended to achieve nutrient requirements,[12,13] and should continue up to two years of age where CMA persists.[1,2,8]

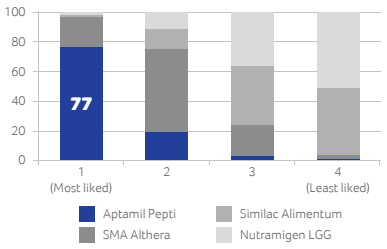
### Aptamil Pepti is the UK's most palatable EHF[15*]

Healthcare professionals believe that a palatable EHF could increase acceptance, reduce wastage and costs for the NHS.[15*]

In a recent independent taste panel of 100 dietitians and GPs, Aptamil Pepti was ranked the most liked EHF formula (figure 1).[15*]

Aptamil Pepti is whey-based and contains lactose, GOS/FOS oligosaccharides, LCPs and nucleotides.

*Figure 1 – Aptamil Pepti is the UK's most palatable EHF[15*]*
*(% participants placing each sample in each rank position)*




### KEY POINTS

- GP data shows that EHFs are commonly introduced after 5 months[4]
- EHFs are first-line formulas in most infants with CMA[1–7]
- Bitter EHFs are often strongly rejected after 4 months of age[2]
- Poor palatability can lead to rejection, which could impact growth[9,10]
- Clinical guidelines† recognise palatability as a key factor in EHF choice[1–3]
- Aptamil Pepti is the UK's most palatable EHF[15*]

# REASSURE with **Aptamil Pepti**

**The UK's most palatable extensively hydrolysed formula[15*]**

NOW PROVEN[15]

* A home usage test assessment was carried out between 16/11/16 and 9/12/16 on the 4 products indicated for cows' milk allergy from birth and included 100 UK healthcare professionals.
† BSACI Milk Allergy guidelines and the Milk Allergy in Primary Care (MAP) guidelines.

**References: 1.** Venter C, *et al.* Clin Transl Allergy 2013;3(1):23. **2.** Luyt D, *et al.* Clin Exp Allergy 2014;44(5):642-72. **3.** Walsh J, *et al.* Br J Gen Pract 2014;64(618):48-49. **4.** Sladkevicius E, *et al.* J Med Econ 2010;13(1):119-28. **5.** Mennella JA, *et al.* Am J Clin Nutr 2011;93(5):1019-24. **6.** Mennella JA, Castor SM. Clin Nutr 2012;31(6):1022-5. **7.** Muraro A, *et al.* Allergy 2014;69(8):1008-25. **8.** Fiocchi A, *et al.* World Allergy Organ J 2010;3(4):57-161. **9.** Vandenplas Y, *et al.* Eur J Pediatr 2014;173(9):1209-16. **10.** Meyer R, *et al.* Clin Transl Allergy 2014;4(1):31. **11.** Christie L, *et al.* J Am Diet Assoc 2002;102(11):1648-51. **12.** Maslin K, *et al.* Clin Transl Allergy 2016;6:20. **13.** Flammarion S, *et al.* Pediatr Allergy Immunol 2011;22(2):161-5. **14.** Meyer R, *et al.* J Hum Nutr Diet 2014;27(3):227-35. **15.** Campden BRI conducted a blind taste test using a home usage design with 100 Dieticians and General Practitioners. The results from ranking ordering showed that Danone Aptamil Pepti was liked significantly more than all the other three samples tested.



17-059 / June 2017

# Aptamil Pepti

## for the effective management of cows' milk allergy

# RELIEVE

cows' milk allergy symptoms[1]
with **97% efficacy**[2]

# REDUCE

incidence of atopic dermatitis
up to five years[3]




NOW PROVEN[4*]

# REASSURE

with the **UK's most palatable** extensively hydrolysed formula[4*]

For further information contact our Healthcare Professional Helpline on **0800 996 1234** or visit **www.eln.nutricia.co.uk/cma**

**References: 1.** Verwimp JJ *et al.* Eur J Clin Nutr. 1995;49 (Suppl1):S39-S48. **2.** Giampietro PG *et al.* Pediatr Allergy Immunol. 2001;12:83-86. **3.** Arslanoglu S *et al.* J Biol Regul Homeost Agents. 2012;26:49-59. **4.** Campden BRI conducted a blind taste test using a home usage design with a sample of 100 Dieticians and General Practitioners from 16.11.2016 to 09.12.16. Participants rank ordered the extensively hydrolysed formula (EHF) milk samples (Danone Aptamil Pepti, Abbott Similac Alimentum, Nestle SMA Althera and Mead Johnson Nutramigen LGG) in term of overall liking and answered a series of attitudinal questions in relation to the impact of EHF's palatability on infants with CMA and their families. The results from the ranking showed that the Danone Aptamil Pepti sample was liked significantly more than all the other three samples tested.

* A home usage test assessment was carried out between 16/11/16 and 9/12/16 on the 4 products indicated for cows' milk allergy from birth and included 100 UK healthcare professionals.

IMPORTANT NOTICE: Aptamil Pepti 1 & 2 are foods for special medical purposes for the dietary management of cows' milk allergy. They should only be used under medical supervision, after full consideration of the feeding options available including breastfeeding. Aptamil Pepti 1 is suitable for use as the sole source of nutrition for infants from birth, and/or as part of a balanced diet from 6-12 months. Aptamil Pepti 2 is suitable for babies over 6 months as part of a mixed diet.

17-026 / June 2017

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