

A Practical Interpretation of the iMAP Guideline for Dietitians in the UK



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Cows' milk allergy (CMA) is one of the most common presentations of food allergy seen in early childhood (2-3% of 1 to 3-year-olds in the UK¹) and is one of the most complex, implicated in both IgE (rapid onset following ingestion) and non-IgE mediated CMA (delayed symptoms occur usually 2 hours up to days after ingestion). Non-IgE mediated CMA is associated with a diverse range of symptoms often difficult to discriminate from other common symptoms observed in infancy, such as gastro-oesophageal reflux, infantile colic, abnormal bowel frequency and consistency.² As a result, diagnosis of non-IgE mediated CMA is often delayed or missed altogether. Concerns regarding the early and timely diagnosis of CMA and suboptimal management, including choosing the most appropriate initial alternative formula when breast milk is not available, have been highlighted³ and, in response, a number of national and international guidelines have been published.⁴⁻⁹

In 2010, a review of 1000 infants with CMA randomly chosen from a UK primary care database showed that 86% children were first diagnosed in primary care and that the majority remained there for their care.³ As a result, the Milk Allergy in Primary Care (MAP) Guideline was published in 2013,¹⁰ based on the National Institute for Health and Care Excellence (NICE) food allergy guidelines,⁶ with the aim of supporting early recognition, diagnosis and management of mild to moderate non-IgE mediated CMA in children in primary care in the UK. The following year, the British Society of Allergy and Clinical Immunology (BSACI) cows' milk allergy guidelines were also published,⁸ with a greater focus on secondary and tertiary care and support for children with IgE as well as non-IgE mediated CMA.

In spite of these guidelines, Lozinsky and colleagues¹¹ found in a UK survey of GPs and parents in 2015, that there

remained significant delay in diagnosis, lack of knowledge and perception of symptoms. They highlighted that better communication between the GP and parents, alongside a range of practical diagnostic tools, algorithms, education and supporting materials could improve the diagnostic process and outcome for both parties.¹¹

Based on international uptake and local feedback of the MAP Guideline, it became clear that this practical guidance needed to be interpreted for an international audience. Hence, the MAP guideline has been adapted and updated in light of further publications^{12, 13} and feedback.¹¹ Therefore, the aim of this paper is to present the revised international version of the MAP Guideline (iMAP)¹⁴ from a practical dietetic perspective, to support dietitians with its implementation in primary care in the UK.

Nomenclature

There is common confusion between the terms food intolerance and food allergy, with many referring to non-IgE mediated CMA as lactose intolerance or cows' milk intolerance.¹⁵ Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.⁵ Food intolerance does not involve an immune response, as seen in lactose intolerance, which is associated with a deficiency in the enzyme lactase.¹⁶ Despite these clear differences in nomenclature, similar gastrointestinal symptoms of loose, watery stools, abdominal distension and pain may present in the two conditions, contributing to the confusion (Figure 1).¹⁶

Sladkevicius *et al*³ showed that 59% of infants with CMA in the UK presented with a combination of gastrointestinal symptoms and eczema,³ most of which could be categorised as mild to moderate in severity (severe symptoms are usually considered to be persistent and severe

versions of those seen in mild and moderate CMA and often accompanied by faltering growth).¹⁴

Diagnosis of CMA

Diagnosis of non-IgE mediated CMA involves a 3-staged process (Table One).

The iMAP Guideline contains a number of algorithms and additional fact sheets to

support the diagnostic process, which are available to download from the Allergy UK iMAP webpage and will be referred to throughout this paper (Figure 2).

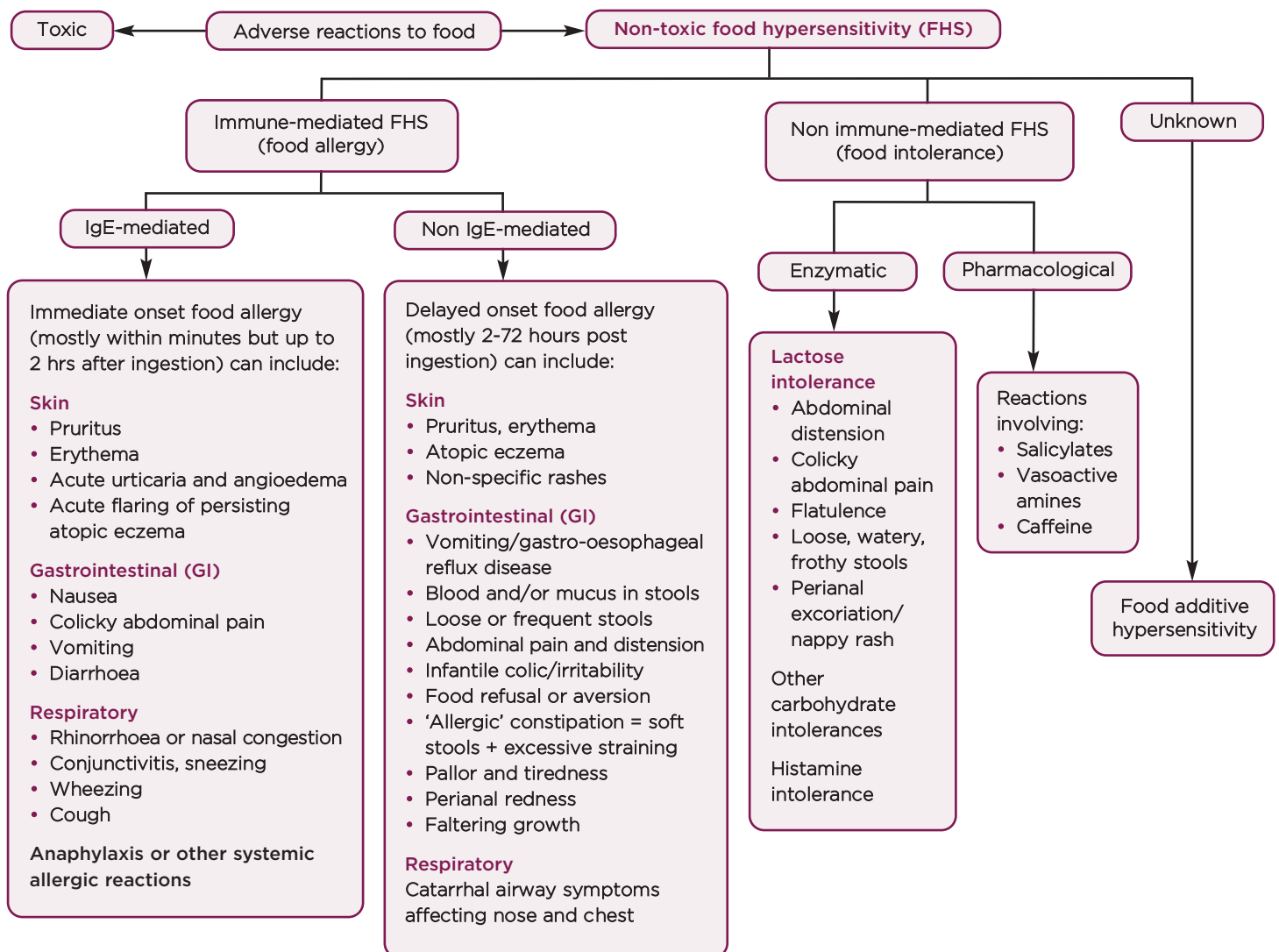
Step 1: Allergy focused clinical history (AFCH)

The AFCH is the cornerstone of the diagnosis^{13,17} and the new iMAP Guideline provides key questions to ask (Figure 3).

Table One: Steps Involved in Diagnosis of CMA

Diagnosis of cows' milk allergy		
Step	Non- IgE mediated	IgE mediated
1	Allergy focused clinical history (AFCH)	Allergy focused clinical history (AFCH)
2	If positive AFCH, 2-4 weeks of complete cows' milk exclusion	If positive AFCH, exclude cows' milk and allergy test (skin prick test and/or specific IgE to cows' milk). Positive result confirms diagnosis. Negative indicates either non-IgE mediated or alternative diagnoses
3	Reintroduction of cows' milk to establish if it is the cause (or not)	Do not re-challenge at home. Continue on exclusion diet

Figure 1: Nomenclature and Symptom Chart



Allergy trained health visitors, community dietitians and pharmacists are ideally placed to obtain this information in a timely manner and support GPs within their limited resources. In some areas, clinical history templates for use in patient electronic records and scoring tools for health professionals (CoMISS)[®] have been developed. Tools to support parents to gather this information themselves are also in development in the form of apps and online assessments.

The case study shown in **Figure 4** illustrates the benefits of undertaking a detailed allergy focused clinical history to determine the likely diagnosis.

The following information should therefore be sought to attempt to identify red flags strongly suggestive of CMA (**Figure 5**), determine whether they are suspected to be IgE (immediate) or non-IgE (delayed) mediated reactions (**Figure 1**) and assess the severity (mild to moderate or severe reactions) (see **Figure 2** to access iMAP presentation and symptom algorithm).

Figure 2: Allergy UK iMAP Tools

The following tools are available for download from the Allergy UK iMAP webpage: www.allergyuk.org/health-professionals/mapguideline:

- Full iMAP guideline paper
- Presentation/symptom algorithm
- Diagnosis and management algorithm
- Allergy focused clinical history questions
- Patient fact sheet on CMA and how to establish a diagnosis
- Home reintroduction guide to confirm/exclude diagnosis
- Milk Ladder for non-IgE mediated CMA
- Recipes to support the Milk Ladder

Figure 3: Allergy Focused Clinical History Core Information

- Any family history of atopy (conditions associated with raised levels of IgE, i.e. atopic eczema, allergic rhinitis, hay fever, food allergy) in parents or siblings
- Any personal history of atopic disease as an infant/young child (usually eczema is first observed and especially relevant if noted in first 3 months of life)
- The infant's feeding history and growth. Use as the timeline to document changes in feeding patterns and associations with symptom development and resolution
- Presenting symptoms and signs, focusing on those relating to the gut, skin and respiratory systems
- Details of previous management, including medications and documenting perceived response to any treatment or dietary change

Figure 4: Case Study

Baby P was bottle-fed from birth and at around 3-4 weeks of age she started vomiting effortlessly either during, or up to half an hour after a bottle. She was an extremely unsettled baby who would cry incessantly and keep waking in the night. She seemed to want a bottle every few hours, but only drank 1-2 floz each time; was restless and seemed to choke on her feeds. She was more comfortable when upright, although was never really settled. The GP prescribed Gaviscon Infant without effect, but baby P continued to gain weight satisfactorily. Mum was very anxious and kept returning to the surgery, but the GP reassured her that Baby P was growing acceptably and that things should improve once solids were introduced. Mum therefore started weaning at 17 weeks of age, but by 21 weeks of age when you saw the child for the first time, there had been no improvement; still vomiting, very distressed and poor sleeping so you undertook an allergy focused clinical history

Allergy focused clinical history	Symptoms suggestive of	
	GORD	CMA
Family history of atopy: Mum had IBS and feeding issues as a baby	✗	✓
Personal history of atopy: None	✗	✗
Feeding history: Poor feeding – small, frequent feeds, feed refusal, choking on feeds. Minor differences noted with different formulas but symptoms continued	✓	✓
Growth: no concerns (adequate growth does not rule out either condition)	-	-
Gut symptoms:		
• Vomiting related to feeds, sometimes projectile	✓	✓
• Loose, frequent stools x 4-6 daily	✗	✓
• Mucus in stools regularly	✗	✓
• Abdominal distension and excessive flatulence	✗	✓
Skin and respiratory symptoms: none	✗	✗
Distress:		
• Infantile colic – constant crying for hours	✓	✓
• Poor sleeping	✓	✓
• More settled when upright	✓	✗
Response to medications/treatment: Gaviscon Infant – little difference	✗	✓

Likely diagnosis

Non-IgE mediated CMA alongside gastro-oesophageal reflux disease (GORD), but until a cows' milk exclusion trial has been undertaken, you will not know whether her symptoms are all attributable to CMA or whether she is suffering from primary GORD in addition.^{19,20}

While growth/poor weight gain is not a common symptom of CMA or GORD, it can occur as a result of either and therefore growth measurements (weight, length, head circumference) should be taken and monitored at intervals in children suffering from these conditions.

Step 2a: Cows' milk exclusion trial for non-IgE mediated CMA

Diagnosis of mild to moderate non-IgE mediated CMA can be made if symptoms clearly improve after 2-4 weeks on a cows' milk exclusion diet; although, for some children with more severe symptoms a longer exclusion may be needed. A firm diagnosis can only be made if reoccurrence of symptoms has been demonstrated following a cows' milk reintroduction and it is important to outline this to families at the outset (see **Figure 2** to access iMAP patient fact sheet on CMA and how to establish a diagnosis).

Exclusively breastfed

If the infant is reacting to traces of cows' milk protein in mother's breast milk when breast fed exclusively, the mother should adopt a strict cows' milk-free diet. In light of the high risk of an infant with a non-IgE mediated CMA developing an allergy to soya too (up to 60%²¹), the use of non-soya based cows' milk substitutes is generally recommended while breastfeeding, as reactions to soya would complicate the diagnostic process. If the reactions are clearly IgE mediated, as indicated by urticaria/angioedema, then the chance of reacting to soya is significantly less (around 10%) and soya substitutes are therefore a more viable option while breastfeeding.²²

Close attention needs to be paid to a mother's energy, protein, calcium, iodine and vitamin D status in particular, and both mother and baby should be in receipt of vitamin D supplements.^{23, 24}

Vitamins should be available to both babies and mothers in receipt of income support, otherwise they can be purchased from chemists and supermarkets. Care should be taken to choose ones that supply sufficient vitamin D (around 8.5-10 mcg for babies and 10 mcg for mothers and children over 1 year of age) without providing excessive vitamin A (ideally no more than 400 mcg daily), which can be harmful to health.²⁵ Attempts should be made to replace the energy and protein usually obtained from cows' milk-based products with 'free from' alternatives, rather than just excluding all types of meals and products which are generally dairy predominant.

It can be particularly difficult to achieve the higher intakes of calcium and iodine while breastfeeding on a milk-free

diet, as milk and dairy products are key sources of these minerals^{26, 27} (**Table Two**). Additional calcium supplements are therefore usually required. Most calcium preparations provide 400-500 mg elemental calcium per tablet, and therefore two tablets are often recommended. A number of these can be prescribed in forms with or without vitamin D. Iodine supplements are not readily available on prescription or for purchase, although many micronutrient preparations aimed at pregnant and breastfeeding women include iodine at the recommended dose of 150 mcg daily. If not taking a supplement, attempts should be made to consume iodine rich foods, such as white fish and shellfish, regularly and iodised salt could be used in place of regular table salt.²⁷

Figure 5: Red Flags Suggestive of CMA

Red flags suggestive of non-IgE mediated cows' milk allergy

- Itching skin, non-specific rashes, skin flushing, persistent atopic eczema
- Gastro-oesophageal reflux unresponsive to first line medications alongside other red flags
- Loose or frequent stools, abdominal distension and pain, mucus/blood in stools
- Constipation (especially straining to pass even a soft stool) and in those unresponsive to first line laxatives
- Refusing or disliking being fed, poor sleeping, irritability and excessive crying (colic)
- Gut and/or skin or respiratory symptoms plus a family history of atopic disease

Table Two: Recommended Nutrient Intakes for Specific Micronutrients in Infants and Lactating Mothers

	Recommended nutrient intake		
	Vitamin D (mcg/d)	Calcium (mg/d)	Iodine (mcg/d)
Lactating mother	10	1250	250
Adult	10	700	150
Infant (0-12 months)	8.5 (safe intake)	525	-
Children 1-3 yrs	10	350	-

Table Three: Hypoallergenic Formulas in the UK

Formula name	Targeted age	Company	Tin size (g)	Casein (C)/ whey-based, lactose containing EHF (W) or amino acid (AAF)
Nutramigen 1 with LGG	0-6 months	Mead Johnson Nutrition	400	C
Nutramigen 2 with LGG	6 months plus	Mead Johnson Nutrition	400	C
Similac Alimentum	Birth onwards	Abbott Nutrition	400	C
SMA Althera	Birth onwards	Nestlé Health Science	450	W
Aptamil Pepti 1	0-6 months	Danone Nutricia ELN	400 or 800	W
Aptamil Pepti 2	6 months plus	Danone Nutricia ELN	400 or 800	W
Neocate LCP	Birth onwards	Danone Nutricia AMN	400	AAF
Neocate Junior	1 year onwards	Danone Nutricia AMN	400	AAF
SMA Alfamino	Birth onwards	Nestlé Health Science	400	AAF
Nutramigen Puramino	Birth onwards	Mead Johnson Nutrition	400	AAF

Exclusively/partially bottle fed

More commonly, infants develop symptoms following ingestion of cows' milk-based formula and therefore treatment requires provision of a hypoallergenic formula. These formulas are categorised into two main types:

1. Extensively hydrolysed formulas (EHF):

These are cows' milk protein-based formulas where the protein is hydrolysed into varying short peptide lengths (described by their Dalton size, predominantly below 1-1.5 kDa) and should comply with guidance that at least 90% of children with proven CMA tolerate the feed with a 95% confidence interval.^{28, 29}

2. Amino acid formulas (AAF): These products are comprised of individual amino acids and seen as truly hypoallergenic as they contain no cows' milk protein. However, they are costly and should be reserved for the more severe form of CMA.

The original MAP Guideline summarises which type of hypoallergenic formula should be considered for various clinical presentations of CMA,¹⁰ and it is recommended that an EHF is the first type of formula that should be prescribed for the majority of infants presenting with suspected mild to moderate CMA. **Table Three** provides an updated list of the hypoallergenic formulas currently available for treatment of CMA in the UK.

In around 75% of mothers taking a normal cows' milk containing diet, breast milk was found to provide similar levels of the cows' milk protein residue β -lactoglobulin as that found in EHF.³⁰ Therefore, if an infant is reacting to cows' milk proteins in breast milk, an AAF is more likely to be required, although this may not be the case for everyone. The iMAP Guideline¹⁴ recommends an EHF even in infants who react to cows' milk protein via breast milk, which differs from the original MAP Guideline,¹⁰ to reflect international practices and clinical experience. However, there may be some infants who require AAF as first line but these are likely to present with more severe symptoms of CMA. Individualised assessment of predominantly breastfed infants is essential as they are potentially at nutritional risk, particularly if the mother has to exclude more than one food allergen; a scenario which also complicates the diagnostic process.

If an infant fails to settle on an EHF, then an AAF is required. In accordance with the iMAP Guideline,¹⁴ infants who have been

commenced on an AAF should be referred for specialist input.

Soya infant formulas are not considered to be hypoallergenic as they are based on an allergenic protein, although clearly devoid of cows' milk protein. These formulas are not recommended for children <6 months of age and older children with non-IgE mediated CMA, but may be useful for those children >6 months of age who have a negative specific IgE to soya and will not accept or tolerate standard hypoallergenic formulas.²² They are not recommended in infants under 6 months of age due to concerns about their possible effects on reproductive health.³¹

Step 2b: Allergy test to cows' milk protein for IgE mediated CMA

If the clinical history suggests IgE mediated CMA, then either a skin prick test or blood test for specific IgE to cows' milk should be undertaken, with a positive result confirming diagnosis¹⁵ (see **Figure 2** to access iMAP diagnosis and management algorithm). If the results are negative, it doesn't necessarily rule out CMA as the infant may be suffering from non-IgE mediated CMA; a common misunderstanding in primary care.

Step 3: Reintroduction of cows' milk to confirm diagnosis of non-IgE mediated cows' milk allergy

The iMAP Guideline includes a fact sheet detailing the process for reintroduction of normal infant formula over a seven-day period to confirm or exclude the diagnosis of CMA (see **Figure 2** to access iMAP patient fact sheet on 'home reintroduction guide to confirm the diagnosis of CMA'). If the infant is exclusively breastfed, then mother should return to her normal cows' milk containing diet; there is no need to gradually increase the amount of cows' milk and products in her diet.

If at any stage the infant reacts following reintroduction, cows' milk should be discontinued and the diagnosis of non-IgE mediated CMA is confirmed. If there has been no reaction during the re-challenge period, it can be assumed that the infant is not suffering from CMA and should remain on a normal infant formula and a cows' milk containing diet if weaning. Reintroduction should not be conducted with children who are thought to have acute, IgE mediated allergy (see **Figure 2** to access iMAP diagnosis and management algorithm).

Figure 6: Role of the Dietitian in CMA Management

All infants with a confirmed diagnosis of CMA should be referred to a dietitian to:

- Ensure nutritional adequacy and growth through use of alternative products and assess need for micronutrient supplementation
- Support families regarding weaning progression/textures and order of introduction of allergens
- Provide practical, individualised advice to ensure cows' milk is strictly avoided and advise on adaptation of family meals to allow for sharing, role modelling, etc.
- Provide eating behavioural management strategies when food avoidance is an issue
- Review appropriateness of prescribed hypoallergenic formulas for age and advise on transition onto standard milk alternatives
- Provide a range of supporting resources, e.g. cows' milk free diet sheet, pictorial leaflets of free from dairy alternatives, recipes, signposting to allergy support networks, social media and free from product finder apps
- Advise on re-challenging and ensure against unnecessary long-term exclusion of foods

Figure 7: Suggested Ongoing Management of CMA in Primary Care

- Monitoring of growth and nutrition on a 6-12 monthly basis
- Identification and management of emerging comorbidities – ideally GPs/other specialist healthcare professional should conduct an annual review of all children with CMA, including a physical examination and review of medications relating to atopy/allergies
- Attempts to minimise the impact of having CMA on the quality of life
- Ongoing provision of dietetic supervision as required by families until they are able to self-manage the condition or it has been outgrown and normal diet re-established
- Recognition of development of tolerance and appropriateness of re-challenging; usually on a 3-6 monthly basis for non-IgE mediated CMA

Management of mild to moderate confirmed non-IgE mediated cows' milk allergy

Referral to a dietitian with appropriate competencies is essential if a diagnosis has been confirmed,^{13,14} to not only ensure that cows' milk is avoided in the infant's diet but also to address growth and nutritional deficits at the time of diagnosis³² and feeding problems that can arise as a result of CMA in the short³³ and longer term³⁴ (see **Figure 6**).

There needs to be a co-ordinated approach for the ongoing management of CMA amongst GPs, health professionals in both primary and secondary care and parents/carers focusing on key issues as outlined in **Figure 7**.

Reintroduction with cows' milk to determine acquisition of tolerance

Based on current knowledge of mild to moderate CMA, a consensus was reached that re-challenging with cows' milk to assess acquisition of tolerance should first occur around 9-12 months of age, once a full six month period of strict cows' milk exclusion has taken place and, ideally, once integration onto family meals has successfully been established.¹⁴ Subsequent re-challenging episodes can occur at 3-6

monthly intervals, depending upon levels of tolerance - i.e. if unable to tolerate small amounts of baked milk, then re-challenging should be left for six months, whereas if they now tolerate products containing baked milk, e.g. biscuit, more frequent attempts at moving up the ladder can be tried, as long as symptoms following a reaction are not overly debilitating.

Whilst there is complete exclusion of cows' milk protein, consideration needs to be given as to whether it is safe to undertake the re-challenge at home or in a supervised setting (see **Figure 8**). The reintroduction is usually carried out in the form of a graduated 'Milk Ladder', starting with highly baked forms of cows' milk where the matrix effect of wheat and fat, high temperatures and time all play a role in reducing the allergenicity of milk proteins³⁵ (see **Figure 2** to access iMAP Milk Ladder guide and recipes).

The iMAP Milk Ladder differs from the original MAP Ladder as it has had to accommodate the different foods and feeding practices across the world. It has been simplified to only six steps, the first few baked steps being lower sugar, healthier versions than the original biscuits and muffins and requiring use of the iMAP recipes accompanying the Ladder. The revised Ladder refers to the need for healthcare supervision, and ideally a dietitian will support the reintroduction process and individualise the Milk Ladder

stages based on the child's previous symptoms, sensitivity to trace amounts of cows' milk protein and previous re-challenge attempts.

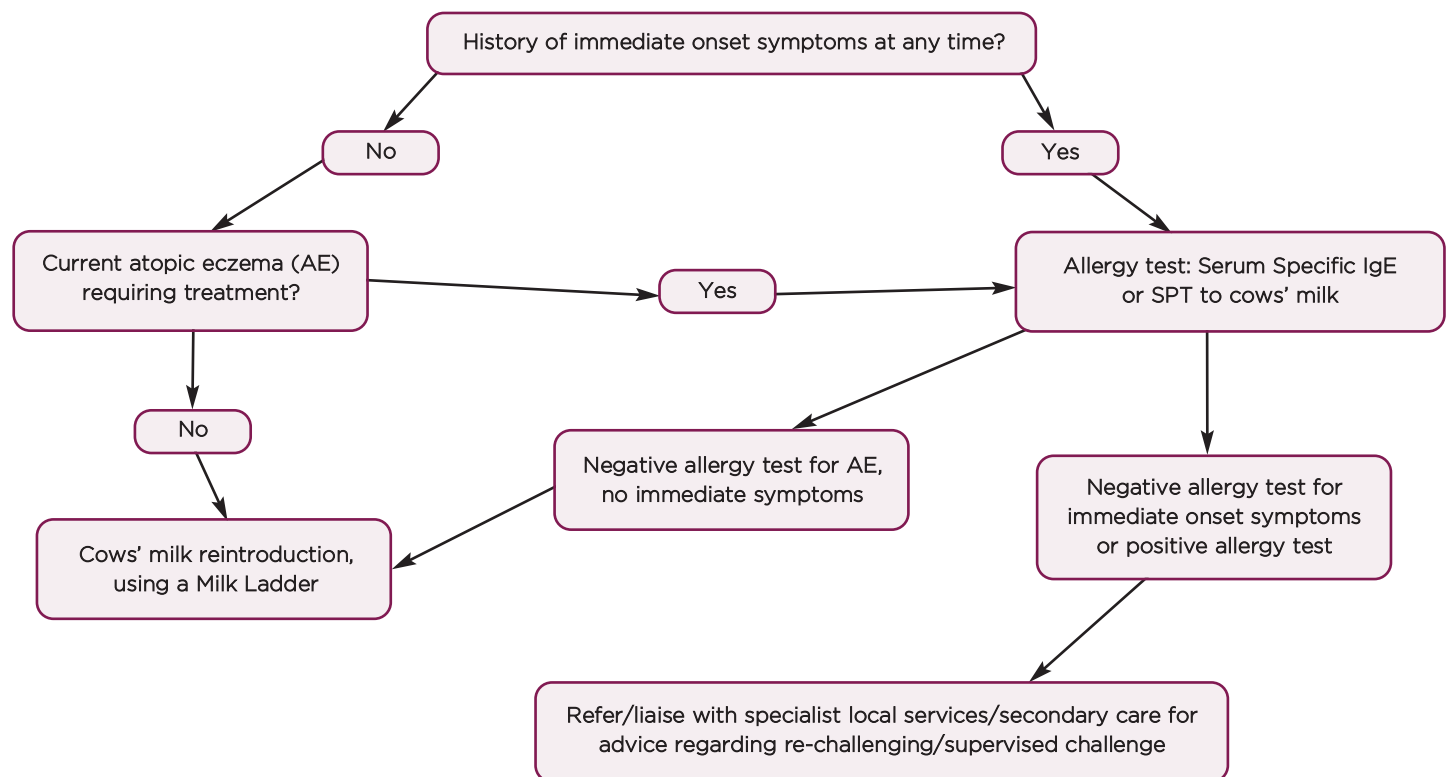
Referral

In accordance with NICE (2011)⁴, referral to secondary care/specialist allergy service should occur for on-going diagnostic assessment and management in infants who have:

- Had a systemic allergic reaction (acute or delayed)
- Strong clinical suspicion of IgE mediated cows' milk allergy but allergy test results are negative
- Confirmed IgE mediated food allergy and concurrent asthma
- Faltering growth or severe acute gastrointestinal reactions despite a cows' milk exclusion trial.

The benefits of having access to a tertiary specialist allergy service are that it ensures that the paediatrician, who will be an expert in allergy, is supported by a multi-disciplinary team consisting of specialist dietitians, nurses and, ideally, a clinical psychologist. The tertiary specialist allergy service should also have ready access to other relevant medical specialists, such as gastroenterology and dermatology, to support provision of a seamless service for patients and their families. Unfortunately, these services are not available in every city across the UK.

Figure 8: Algorithm to Guide Cows' Milk Re-Challenging Process at Home or Under Supervision



Conclusion

CMA is one of the most common food allergies affecting children worldwide, presenting predominantly as mild to moderate, non-IgE mediated allergy commencing within the first few months of life.³² Since there are no effective laboratory methods for the diagnosis of this disorder, a cows' milk exclusion trial followed by re-challenge should be undertaken in a timely manner to avoid nutritional and growth deficits that can result from lack of recognition of this condition, not to mention a reduction in quality of life for the family. Recognition of infants who fall outside the typical non-IgE mediated presentation also need to be identified quickly and referred on to specialist services.

The original MAP Guideline has been shown to positively change UK prescribing patterns.³⁶ It is hoped that the updated iMAP Guideline, with all the supporting practical tools and algorithms, will aid primary care teams, such as GPs and community health professionals (e.g. health visiting teams and community clinical pharmacists), to work better with families to further improve the cost effectiveness and quality of their care and ensure that community dietitians are proactively involved in this alliance.

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Easier sugar swaps with Hermesetas

Whilst government targets to reduce daily calories from free sugars to less than 5 per cent¹ is great news for our health this has also bought about some practical challenges – with the achievement of these guidelines being one.

Sweeteners, like Hermesetas, have an important role to play by helping to reduce the amount of sugar in the diet. There are two types of sweeteners that can be used:

- low calorie sweeteners (LCS), e.g. aspartame. These only need to be used in tiny amounts and provide zero calories.
- bulk sweeteners e.g. xylitol. These are used in larger amounts and help provide structure to products.

Sweeteners are classed as food ingredients, meaning that they are strictly regulated in Europe and given an 'E number' to show that they have been tested and approved for use.



fact:

A review² of 16 randomised controlled trials found that switching sugar for LCS reduced average daily calorie intake by 10%.

Product	Contains	Equivalent in sweetness
Hermesetas mini sweeteners	Saccharin & Sucralose	1 tablet = 1 teaspoon of sugar.
Hermesetas granulated	Saccharin & Cyclamate	1 cup sugar = 1 cup Hermesetas.
Hermesetas liquid	Saccharin & Cyclamate	10 drops (0.5 ml) = 1 teaspoon of sugar. 5ml = 50g sugar.
Hermesetas SteviaSweet	Steviol Glycosides	1 tablet = 1 small teaspoon of sugar.

Hermesetas, a LCS, provides a food choice for people who are looking to sweeten foods and drinks without adding extra unnecessary calories

See www.hermesetas.co.uk for recipes



1. Scientific Advisory Committee on Nutrition (SACN) (2015) Carbohydrates and health. London: SACN. www.gov.uk/government/publications/sacn-carbohydrates-and-health-report 2. de la Hunty A et al. (2006) *Nutr Bull* 31: 115-128.

