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COWS' MILK PROTEIN ALLERGY GUIDELINES: IS THE MESSAGE GETTING THROUGH?

Cows' milk protein allergy (CMPA) has been shown to be the most common food allergy in infants and young children and, therefore, healthcare professionals need to know current management guidelines to optimally treat children with this allergy.

Several guidelines have been published to help healthcare professionals not only to identify symptoms, but also to guide maternal elimination diets and suitable hypoallergenic formulas for prescription. However, are the messages of these guidelines getting through and are we getting better at the diagnosis and management of CMPA?

CMPA can present as either immunoglobulin E (IgE) or non-IgE mediated allergy.¹ The main distinctions between these two types of allergy is whether IgE is involved in the pathophysiology and the onset of symptoms. In IgE-mediated CMPA, symptoms occur within two hours of exposure to cows' milk and non-IgE mediated CMPA symptoms usually set in from two hours and up to a couple of days after the ingestion of cows' milk.² In addition to the timing of onset of symptoms, there are distinct differences in the type of symptoms, with IgE-mediated allergy leading to acute skin rashes, facial swelling and in the worst case scenario, cardio-respiratory compromise (called anaphylaxis). Conversely, non-IgE mediated symptoms affect mainly the gastrointestinal tract and skin and can lead to diarrhoea (with/without blood in stool), vomiting, constipation, severe abdominal discomfort and/or atopic dermatitis.³



The recent EuroPrevall data has found that the prevalence of CMPA Europe-wide, based on double blind food challenges, was below 1%.⁴ From this cohort, the United Kingdom (UK) had one of the highest incidence rates at 1.28%. Following this publication, several researchers have highlighted concerns that the study design may have not adequately identified non-IgE mediated CMPA.^{5,6} A UK birth cohort study has shown that 2-3% of one- to three-year-olds can be confirmed as having a CMPA, but this still does not adequately reflect the prevalence of non-IgE mediated CMPA. Nevertheless, CMPA has been shown to be the most common food allergy seen in infants and young children and, therefore, healthcare professionals do need to know current management guidelines to optimally treat children with this allergy.



Table 1: Summary of first line hypoallergenic feed recommendation

Clinical presentation	MAP guidelines	BSACI guidelines*
Anaphylaxis	AAF	AAF
Acute urticaria or angioedema	Mild-moderate EHF Severe +/- poor growth AAF	EHF
Atopic eczema/dermatitis	Mild-moderate EHF Severe +/- poor growth and/or breastfed top up AAF	If requiring a top up formula when breastfed AAF otherwise EHF
Eosinophilic Oesophagitis	AAF	AAF
Gastroesophageal reflux disease	Mild-moderate EHF Severe +/- poor growth AAF	EHF
Cows' milk protein-induced enteropathy	Mild-moderate EHF Severe +/- poor growth AAF	EHF unless severe in which case AAF
Food Protein Induced Enterocolitis Syndrome	AAF	AAF
Proctocolitis	Mild-moderate EHF Severe +/- poor growth AAF	EHF

* The BSACI guidelines indicate an AAF formula in any conditions mentioned if food allergies are multiple, growth faltering is present and reactions are severe

CURRENT GUIDELINES

In the last 10 years, 11 guidelines have been published in the English language worldwide on the diagnosis and management of CMPA.^{2,7-10} Of these, three are from the UK and include the Milk Allergy guidelines for Primary care (MAP),¹¹ the British Society for Allergy and Clinical Immunology (BSACI) guidelines for secondary and tertiary care¹² and the National Institute for Clinical Excellence (NICE) Clinical Knowledge Series on CMPA.¹³ These guidelines in regard to both diagnosis and management are very similar and provide guidance on the diagnosis of CMPA and the management, including information on the maternal elimination during breastfeeding, calcium and vitamin supplementation and hypoallergenic formulas.

For the diagnosis of IgE-mediated CMPA, either skin prick or specific IgE-testing for cows' milk provides useful support in addition to the allergy focused history, but in primary care, often these tests are not available and healthcare professionals will require to place the child on a cows' milk elimination diet until supervised challenges or test results are available to confirm the diagnosis.¹⁴ For non-IgE mediated CMPA, there is currently no valid test to guide the healthcare professionals to the diagnosis of CMPA and, therefore, a cows' milk elimination diet with symptom improvement, followed by deterioration with re-introduction, remains the best method for diagnosis.

As the majority of children present in early childhood with this allergy,¹⁵ a cows' milk maternal

elimination diet will be required in breastfed infants. In non-breast fed children, a hypoallergenic formula will be required. A hypoallergenic formula has <1% immunoreactive protein on in vitro testing and should be tolerated by 90% of children with a CMPA (with a 95% confidence interval).¹⁶ The MAP and BSACI guidelines both recommend first line choices for a variety of cows' milk allergic conditions (Table 1). In principle, the guidelines indicate that for the majority of children with mild to moderate IgE/ non-IgE mediated CMPA, an extensively hydrolysed formula (EHF) is appropriate. However, if they have anaphylaxis, faltering growth and/or are exclusively breastfed with symptoms, then an amino acid formula (AAF) is indicated. In addition, if an EHF does not lead to symptom improvement, a trial of an AAF is warranted.^{11,12} The aforementioned suggestions are well substantiated by published evidence and are in line with international guidelines and the majority of guidelines from other countries.^{2,17-19}

Quality of life for both the family and the child has been associated with symptom severity and foods eliminated and, therefore, is directly linked to optimal dietary management of CMPA.²⁰ Breast milk and/or a hypoallergenic formula contributes to the majority of nutrients in the young infant and, therefore, does not only have an impact on symptoms resolution but also on growth. It is, therefore, important for healthcare professionals to familiarise themselves with formula choices (Table 1).

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WHAT IS HAPPENING IN PRACTICE?

Breast milk remains the best source of nutrition in children, also in those with CMPA and should be promoted as far as possible. A maternal elimination diet may be required, in particular in non-IgE mediated CMPA. Unfortunately, the UK has one of the worst breastfeeding rates in the world, which healthcare professionals need to be aware of and support practice as far as possible.²¹ This means that the majority of children with suspected CMPA will be on a cows' milk formula and require intervention using a hypoallergenic formula. In 2010, Sladkevicius et al²² found that on average it took 2.2 months before infants with suspected CMPA were prescribed with the first clinical nutrition preparation and on average it took 3.6 months before the diagnosis of CMPA was made. Since that publication, above-mentioned guidelines on how to diagnose and manage CMPA in the UK were published and there was an assumption that this would improve the identification and treatment of children with this allergy. However, a recent study by Lozinsky et al²³ indicated that the average time for diagnosis continued to be around 2.2 months according to parents surveyed, and 48% of cases were diagnosed by the GP followed by 21% by paediatricians, 13% by the health visitor and in 5% by a dietitian.

Why has the diagnosis and initiation of suitable treatment for CMPA therefore not improved significantly since the publication of UK guidelines? Could it be that we do have a case of guideline overload, where healthcare professionals do not know which guidelines to follow, or are they confused with the content of guidelines? Many trusts have also developed their own guidelines for feed prescriptions based on local CMPA population and feed

contracts. We do, therefore, have a situation where healthcare professionals are exposed to international, UK national and local guidelines, which understandably can be confusing.

In addition, there has been the belief in primary care, that CMPA is rare and that many primary care physicians would not deal with this diagnosis on a regular basis and, therefore, further education on this topic may have not received so much priority. However, in a study by Lozinsky et al,²³ in the 12-month period prior to completing the survey in primary care, 52% of the GPs diagnosed ≥ 3 children with CMPA and 65% managed ≥ 3 cases already diagnosed with this allergy. It is, therefore, an allergy that most healthcare professionals, even in primary care will be regularly exposed to.

Has the current financial climate contributed to a delay in commencing optimal dietary management? There has been more pressure placed on healthcare professionals to ensure cost savings and that includes evaluating the prescribing of hypoallergenic formulas. A recent review by the National Healthcare System (NHS) London Procurement Partnership indicated that the cost per annum on the NHS for the management of CMPA was 23.6 million.²⁴ That survey found that the cost a year per patient on an EHF was £1,853 and AAF £3,161.²⁵

Data has indicated that in Europe, the UK has the highest consumption on AAF; undoubtedly this does need review, but one has to take into account that the EuroPrevall study also indicated the highest prevalence of CMPA in the UK, which may also imply that we have a higher number of children with severe CMPA.²⁶

Due to the cost implication of hypoallergenic formula, further guidelines were introduced in 2014 by the NHS PresQIPP,²⁷ providing a traffic



light style guidance on first, second and third line feed choices based on specific commercial EHF's and AAF's, that take cost of hypoallergenic formulas into account. Using these guidelines, first line choice is always an EHF, which in theory should be suitable for the majority of children; however, second line choice is another EHF before an AAF is prescribed. Many children who would have had numerous feed changes prior to trialling hypoallergenic formulas will, therefore, potentially have further feed changes before symptom improvement may be achieved. This does not only delay the diagnosis, but from the survey from Lozinsky et al,²³ almost 47% of parents reported feelings of exhaustion, 55.7% had stress or anxiety related to their child's health and 33% of fathers reported a delay in going back to work due to their child's food allergy. Sladkevicius et al²² found that, in particular, frequent hypoallergenic feed changes have a health economic impact. Children from that study who remained on the same feed throughout their treatment had on average 17-19 GP visits, whereas those who required feed changes needed >20 visits over the same period of time. Therefore, getting the management right from the start may consequently also relieve work pressures from already stretched primary healthcare practitioners.

THE FUTURE

Prescott et al²⁸ recently described the increase of food allergy as the second wave of the allergy epidemic, with the first wave occurring 50 years ago with asthma and allergic rhinitis. All healthcare professionals, therefore, will need to become more familiar with food allergic conditions. There is a general recognition that education on both recognition and management

of CMPA is key to improving the delay in initiation of suitable treatment.

A recent survey in dietetic competencies related to food allergy in the UK, Australia and North America, found that many dietitians did not feel competent in developing an elimination diet, food challenges and managing feeding difficulties.²⁹ Reeves et al³⁰ together with the Food Allergy Specialist Group of the British Dietetic Association, developed a one-day competency-based study day on CMPA. The results of that study day have indicated this as a useful format to improve both knowledge and competencies in CMPA. The course is currently run through the BDA in different areas of the UK (www.bda.uk.com/publications/events/160601cma) and has repeatedly yielded positive results. However, it is important to note that the majority of children will first present to their general practitioner and/or health visitor. It is, therefore, crucial that education is focused on the healthcare professionals who will be the first port of call for parents. The challenge is to make the education easily accessible, time effective and practical within the current financial climate.

CONCLUSION

The diagnosis and management of CMPA remains a challenge. Several guidelines have been published to help healthcare professionals to not only identify symptoms, but also to guide maternal elimination diets and suitable hypoallergenic formulas for prescription. In addition to following these guidelines, it is important to ensure a patient-centred approach as this may not only improve the time to symptom resolution and, therefore, parent journey of CMPA, but may also reduce healthcare visits in an already stretched service.