McWilliam et al. World Allergy Organization Journal (2023) 16:100830
http://doi.org/10.1016/j.waojou.2023.100830

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines update – X – Breastfeeding a baby with cow's milk allergy

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ABSTRACT

Cow's milk allergy is rare in exclusively breastfed infants. To support the continuation of breastfeeding an infant after diagnosis with a cow's milk allergy, it is critical to examine the evidence for and against any form of cow's milk elimination diet for lactating mothers. In this narrative review, we highlight the lack of high-quality evidence, hence subsequent controversy, regarding whether the minuscule quantities of cow's milk proteins detectable in human milk cause infant cow's milk allergy symptoms. Current clinical practice recommendations advise a 2–4 week trial of maternal cow's milk dietary elimination for: a) IgE-mediated cow's milk allergy only if the infant is symptomatic on breastfeeding alone; b) non-IgE-mediated associated symptoms only if the history and examination strongly suggest cow's milk allergy; and c) infants with moderate to severe eczema/atopic dermatitis, unresponsive to topical steroids and sensitized to cow's milk protein. There should be a clear plan for home reintroduction of cow's milk into the maternal diet for a period of 1 week to determine that the cow's milk elimination is responsible for resolution of symptoms, and then subsequent reoccurrence of infant symptoms upon maternal cow's milk reintroduction. The evidence base to support the use of maternal cow's milk avoidance for the treatment of a breastfed infant with cow's milk allergy is of limited strength due to a lack of high-quality, adequately powered, randomised controlled trials. It is important to consider the consequences of maternal cow's milk avoidance on reducing immune enhancing factors in breast milk, as well as the potential nutritional and quality of life impacts on the mother. Referral to a dietitian is advised for dietary education, along with calcium and vitamin D supplementation according to local recommendations, and a maternal substitute milk should be advised. However, for most breastfed infants with cow's milk allergy maternal cow's milk dietary elimination will not be required, and active support of the mother to continue breastfeeding is essential.

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http://doi.org/10.1016/j.waojou.2023.100830
Received 4 May 2023; Received in revised from 2 October 2023; Accepted 3 October 2023
Online publication date xxx

Keywords: Breastfeeding, Infant, IgE-mediated cow's milk allergy, Non-IgE-mediated cow's milk allergy, Maternal nutrition

INTRODUCTION

Breast-feeding (see Figs. 1 and 2) is the optimal way to feed a baby, with health, social, economic, and environmental benefits. Breastfeeding not only provides immediate nutrition and antibodies against many communicable diseases, but also has long-term benefits to both the mother and child.[1] Thus, to support the continuation of breastfeeding an infant after diagnosis with a cow's milk allergy (CMA), it is critical to examine the evidence for and against any form of cow's milk (CM) elimination diet for lactating mothers. Many guidelines in the past have recommended reducing or eliminating the intake of cow's milk in the breastfeeding mother's diet of a baby with a CMA.[2–6] The World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) 2010 guideline was also of this opinion, although this recommendation was not the result of a systematic review. Since 2010, the recommendation of a maternal CM elimination diet was maintained in practically all guidelines,[7–14] albeit with different nuances such as the possibility of an unrestricted diet for the breastfeeding mother in cases of mild or absent symptoms.

In this narrative review we will summarise the current guidelines/recommendations regarding breastfeeding an infant with CMA; and outline the current evidence on the presence of CM proteins in human milk, consequences of maternal CM avoidance on other breast milk compositional factors, and nutritional and quality of life impacts of a CM elimination diet on the mother. We will highlight the lack of high-quality evidence, hence subsequent controversy, regarding whether the minuscule quantities of CM proteins detectable in human milk cause infant IgE-mediated or non-IgE mediated CMA symptoms in breast fed infants.

Prevalence and symptoms of cow's milk allergy in breastfed infants

Three European birth cohorts that followed infants for the first year of life, and assessed the infants for CMA, confirmed by oral CM challenge, have reported a CMA incidence of 1.9–2.2%.[15–17] In these birth cohorts, the incidence of CMA in exclusively breastfed infants (prior to the introduction of any breast milk substitutes or solid foods) was determined to be 0.4–0.8 %. In 2 of these cohorts,[15,16] the diagnosis of CMA in exclusively breastfed infants was made following the resolution of symptoms after maternal dietary elimination of CM protein and reoccurrence of identical symptoms after maternal CM challenge. The symptoms observed in the exclusively breastfed infants included atopic dermatitis/eczema, urticaria, colic, diarrhoea, vomiting, recurrent wheezing, and rhinitis,[15,16] and the age

Fig. 1 Breastfeeding infant

Fig. 2 Breastfeeding infant

of onset of symptoms ranged from 2 to 12 weeks of age.[15] Of importance to note was that in the cohort in Denmark by Host et al,[15] after newborn hospital nursery records were examined, it was identified that all 9/1749 (0.5%) infants in the birth cohort who developed CMA while still thought to be exclusively breastfed, had actually been given CM based breast milk substitutes during the first 3 days of life providing approximately 0.4–3.0 g of beta-lactoglobulin (BLG). Host et al[15] concluded that the early neonatal exposure to CM proteins may have sensitized the infants, and then subsequent exposure to minute amounts of CM proteins in breast milk may act as booster doses eliciting allergic reactions.

IgE-mediated CMA in breast fed infants

Case reports of confirmed, medically diagnosed IgE-mediated allergic reactions in exclusively breastfed infants are limited. More common are the immediate (usually within 1–2 h) symptoms following direct infant ingestion of cow's milk protein via breast milk substitutes or solid foods (such as in cereal with added cow's milk or yoghurt). To our knowledge, there has been only 1 case report[18] of anaphylaxis in a young breastfed CMA infant. However, this case is complicated as the first episode of anaphylaxis occurred after the third feed of a casein-based breast milk substitute. Current clinical practice guidelines[10] do not recommend routine maternal CM protein avoidance for infant IgE-mediated CMA unless symptoms are evident whilst the infant is exclusively breastfeeding. However, practice does seem to be variable. Wangberg and colleagues[19] recently conducted a web-based survey of 133 breastfeeding mothers of children with IgE-mediated food allergies. This survey identified that following food allergy diagnosis in their child, 43% mothers reported they were advised by their health care provider to continue breastfeeding without dietary restriction, 17% were advised to avoid eating the food(s) their child was allergic to, and for 29% this concern was not addressed. A minority of mothers (12%, n = 16/133) reported their child experienced an "allergic reaction" to breastmilk; however, an allergist evaluated only 4 of these to be "likely IgE-mediated reactions"; all 4 children had multiple IgE-mediated food allergies, and it was not asked which specific food allergen the mother had consumed prior to the described allergic reaction in the child. Thus, most mothers of children with diagnosed IgE-mediated food allergies participating in this recent survey could consume the food their child was allergic to without their child experiencing IgE-mediated food allergy symptoms.

Non–IgE-mediated gastrointestinal CMA in breast fed infants

Symptoms of non-IgE-mediated food allergies typically occur several hours to days after food allergen consumption.[20] Non–IgE-mediated gastrointestinal food allergies include Food Protein Induced Enterocolitis Syndrome (FPIES), Eosinophilic Oesophagitis (EoE), food protein-induced allergic proctocolitis, food protein-induced allergic enteropathy, and food protein-induced dysmotility disorders (gastro-oesophageal reflux disorder and constipation).[20] Some gastrointestinal manifestations of non-IgE-mediated allergies triggered by CM protein may be experienced by exclusively breastfed infants. The most common presentation being food protein-induced allergic proctocolitis,[20] where symptoms usually start within the first month of life and include blood (sometimes seen with mucous) in bowel movements. Most publications to-date report case series or case reports, with the 2020 European Academy of Allergy and Clinical Immunology (EAACI) Position Paper on Diagnosis and Management of Non-IgE Gastrointestinal Allergies in Breastfed Infants[20] providing an excellent summary of these. To our knowledge, there has only been 1 randomised controlled trial (RCT) investigating the treatment of proctocolitis by comparing CM dietary elimination by the mother and/or infant (n = 19) to no treatment (n = 21) for 1 month,[21] with 27 infant participants who were exclusively breastfed. In this trial, CMA was diagnosed in only 7 (18%) infants by dietary elimination and provocation testing, and a CM elimination diet did not affect the duration of rectal bleeding. Hence, CMA was less common than previously believed among infants with symptoms of proctocolitis, which highlights the importance of a maternal/infant CM challenge in infants who become symptom-free during CM dietary avoidance to reduce false-positive

CMA diagnoses. In this trial, for most of the participants the cause of the proctocolitis was unknown, but an association with viral infection was seen in some participants. To our knowledge, there have been no published reports of Eosinophilic Oesophagitis (EoE) in exclusively breastfed infants.

The overall incidence of FPIES has been recently estimated to affect 15.4/100 000 per year in Australian children under 2 years of age.[22] In this Australian study, Mehr et al[22] surveyed 230 children with FPIES, and identified 8 children who had parent-reported symptoms on recall of being exclusively breastfed, and where CM in the maternal diet was parent-reported to be the cause of their FPIES symptoms. There have been a few other case reports published[23-26] where exclusively breastfed infants diagnosed with FPIES have been reported to experience symptoms after maternal CM protein ingestion; however, overall it is extremely uncommon to see FPIES in exclusively breastfed infants in clinical practice.[20]

As there are no diagnostic tests available, the diagnosis of non-IgE-mediated CMA in an exclusively breastfed infant relies on resolution of infant symptoms upon exclusion of CM from the maternal diet for a period of 2–4 weeks and infant symptom reoccurrence upon maternal diet CM reintroduction.[20] However, this can be problematic as some symptoms of non-IgE-mediated CMA, especially the dysmotility disorders of gastro-oesophageal reflux disease and constipation, are prevalent in the general population. Furthermore, up to 25% of infants experience colic symptoms, typically defined as full force crying for at least 3 h per day, on at least 3 days per week, for at least 3 weeks.[27] Colic appears to be more frequent in the first 6 weeks of life and usually resolves by 3 months of age.[27] The first reports of maternal diet being linked to colic symptoms were as early as 1921,[28] and from the early 1980s, a series of studies[29-33] suggested a reduction in crying time with maternal diet modifications. It was suggested that up to 25% of infants with colic could respond to maternal diet CM exclusion. However, a 2018 Cochrane Database systematic review[27] of dietary interventions for treating infant colic highlighted the limitations of the earlier studies and concluded "evidence of the effectiveness of dietary modifications for the treatment of infantile colic is sparse and at significant risk of bias". In summary, with a lack of available high-quality evidence, a 2020 EAACI position paper[20] could only make grade C or D level evidence-based recommendations regarding the use of maternal CM elimination diets for managing gastrointestinal symptoms associated with presumped non–IgE-mediated CMA in breastfed infants.

Eczema/atopic dermatitis in breast fed infants

Infant eczema/atopic dermatitis is common affecting around 1 in 5 infants,[34,35] but the role of environmental or food allergens in eliciting and maintaining eczema skin lesions remains unclear.[36] Most often, eczema flares appear to be triggered by a range of other irritants (such as soaps, fabrics, chemicals, and climatic/temperature changes) or for no obvious reason. Furthermore, as eczema flares are typically delayed 6–48 h after exposure to allergens or other irritants, any specific association with food allergen ingestion is difficult to diagnose. A 2008 Cochrane Database systematic review[37] concluded that there may be some benefit to an egg-free diet in infants with suspected egg allergy who also have positive specific IgE to eggs, but other exclusion diets, including CM avoidance, were not found to be efficacious in unselected eczema/atopic dermatitis populations. This Cochrane review also concluded that "future studies should be appropriately powered focusing on participants with a proven food allergy".[37] The 2014 Guidelines of care for the management of atopic dermatitis (Section 4) by Sidbury et al,[36] recommend that even if food allergies are present, effective treatment for eczema/atopic dermatitis should still include good skin care and topical therapies. As with non-IgE-mediated gastrointestinal CMA, if a maternal CM elimination diet is commenced for suspected CMA in an infant with eczematous symptoms, it is essential that maternal CM challenge reintroduction is undertaken as spontaneous resolution of eczema often occurs.[38] This was illustrated in the study by Cant et al[39] where 37 eczematous infants were studied to see whether changes in their mothers' diets affected their skin condition. However, only 6/37 (16 %) infants were reported to have their eczema improve after maternal diet exclusion of

egg and cows' milk and worsen when egg and cows' milk were reintroduced into the mother's diet. Furthermore, prolonged avoidance of food allergens, especially in infants with eczema, may place the infant at increased risk of food allergy by missing an important window of exposure period for food allergen tolerance development during infancy.[40]

Presence of cow's milk protein allergens in human milk

CM derived proteins have been detected in human milk samples in previous observational and interventional studies (as reviewed in Gamirova).[41] These studies have been conducted in a range of countries with culturally varied maternal diets, including Europe,[42–47] Asia,[48,49] and the United States.[50] β-Lactoglobulin (BLG) was the most commonly measured CM protein, with bovine casein[51] levels measured only in 1 study. Detectable quantities of these CM proteins have consistently only been measured in very small concentrations of nanograms per millilitre, with average concentrations of BLG ranging from 1.23 ng/ml[49] to 4.4 ng/ml,[45] which is one million times lower than the BLG level (3.3 g/l = 3 300 000 ng/ml) in fresh cow's milk. On a few occasions women have had notably higher BLG levels detected, with the highest measured concentration being 800 ng/ml in an observational study.[42] Overall, concentrations of CM proteins detected in breast milk vary widely, irrespective of the amounts consumed by the mother and the timing of consumption, with BLG detected in only 42% of samples collected in observational studies and in 52% of samples collected in interventional studies.[41] Inter-women variations in BLG concentrations were found even within the same study after ingestion of the same amount of cow's milk. Physiological differences in food protein absorption in the maternal gut and secretion into breast milk are likely to be influencing these results. The transfer of medications into breastmilk for example often depends on the medication properties (such as molecule size and lipid solubility), along with maternal plasma concentration, maternal plasma protein binding, volume of breastmilk, and stage of lactation.[52] Hence, further mechanistic studies are required to understand the maternal characteristics that may predict which women are more likely to secrete CM proteins in their breast milk.

In the trials summarised in a recent systematic review,[41] the most common intervention[41] was pasteurised CM as an unmodified drink, with maternal consumption volumes ranging from 200 ml[48] to 500 ml[44] as a single ingestion. The effects of cooking and/or food processing of dairy foods, and other CM containing foods (for example baked goods) on CM protein detection in human milk samples, has not been investigated. This is important for future research studies in this field as maternal intake of 1 cooked egg has been shown to result in higher egg protein (ovalbumin) concentrations in breast milk when compared to maternal ingestion of 1 raw egg.[53]

In a recent study in Thailand,[49] after maternal ingestion of 240 ml of CM, the level of BLG in breast milk increased from 0.58 ng/ml (IQR 0.38–0.88) to 1.23 ng/ml (IQR 1.03–2.29), $p < 0.001$. In this study, BLG was detected in all samples from 4 mothers of CMA infants; however, the BLG levels were not different from those measured in mothers of 15 healthy infants. Thus, it appears that the quantities of CM proteins secreted into breast milk cannot explain which infants are more likely to show symptoms associated with CMA.

A recent systematic review[41] has estimated that the probability of an IgE-mediated allergic reaction in a food allergic infant breastfed by a woman consuming the relevant food allergen can be estimated as less than 1 in 1000 infants. Specifically for CM, the probability of having sufficient quantities of CM proteins within a single breastfeed to elicit an IgE-mediated allergic reaction in a breastfed infant was estimated at one in 2893 infants.[41] The authors of this systematic review[41] also conclude that the probability of non-IgE-mediated reactions to food proteins in breastmilk is still unclear due to lack of evidence. It is likely that threshold data are different for breastfed infants with non–IgE-mediated CMA, however thresholds of reactivity in infants with non–IgE-mediated CMA are usually higher.[54,55]

Cross-reactive potential with human milk proteins

Another important consideration which also requires further evidence generation is the question

of whether there are cross-reactive proteins (or protein fragments) between CM and human milk proteins. Occasionally, exclusively breastfed infants with CMA remain symptomatic despite strict maternal CM and dairy food avoidance. Järvinen et al[56] identified that some endogenous human milk proteins (including α-lactalbumin) are recognized by specific IgE from infants and children with CMA. In another study by Monti et al,[46] anti-CM BLG antibodies were found to cross-react with a fragment from the N-terminal end of human milk protein lactoferrin, where three regions of this fragment exhibit sequence homology with a sequence contained in cow's milk BLG. These findings were further supported by the findings of Bertino et al[43] who identified that protein components from human milk lactoferrin, human milk β-casein and human milk α-lactalbumin were found to cross-react with antibodies to CM BLG. Thus, this potential for cross-reactions between human milk and CM proteins further complicates recommendations to mothers breastfeeding a baby with CMA.

Consequences of maternal CM avoidance on other immune enhancing breast milk factors

In addition to potentially containing food allergens, breastmilk is an essential source of immunoglobulins and immune complexes, immune cells and their cytokines/chemokines, growth factors, human milk microbiome, immunomodulatory nutrients, and human milk oligosaccharides. Breast milk composition of some immunoglobulins and immune complexes, and immunomodulatory nutrients can be modulated by the maternal diet. Hence, any elimination of CM and dairy foods from the maternal diet not only removes CM proteins from breastmilk but also removes associated beneficial immune and immunomodulatory factors.

Maternal CM avoidance during breastfeeding has been associated with lower breast milk levels of CM-specific IgA and IgG4 antibodies and the development of CMA in infants.[57] This highlights the potential protective benefit of maternal CM consumption against infant CMA via CM-specific IgG4 and IgA in breast milk. High concentrations of CM-specific IgA in breast milk can reduce the transfer of CM allergens through the infant gut lumen, suggesting that CM-specific IgA may prevent excessive, uncontrolled CM allergen uptake from breast milk. Along with lower concentrations of BLG-specific IgA, Järvinen et al[58] have also identified that concentrations of cytokines IL-1β and IL-10 were also lower in breast milk from mothers of infants with CMA.

Immunomodulatory nutrients are those which are known to have effects on immune function. Observational studies have linked higher maternal intakes (with most studies assessing consumption during pregnancy) of immunomodulatory nutrients, including omega-3 fatty acids, vitamin D, antioxidant vitamins (A, C and E), prebiotics, zinc, and magnesium to reduced child allergic diseases.[59] Thus, it is important to consider that CM and dairy foods (see Fig. 3) are good dietary sources of some immunomodulatory nutrients, especially vitamin A, zinc, and magnesium. There are limited studies investigating maternal dietary intakes during lactation; however, in a recent Swedish observational study (n = 508),[60] an increased maternal intake of CM during lactation, confirmed with biomarkers (fatty acids C15:0 pentadecanoic acid and C17:0 heptadecanoic acid) in the maternal blood and breast milk, was associated with a lower prevalence of physician-diagnosed infant food allergy. These fatty acid biomarkers are commonly used as biomarkers for dairy food intake as they are only synthesized in the cow's rumen by the bacterial flora.[61] Pentadecanoic acid (15:0) in breast milk at 4 months postpartum was also directly associated with lower prevalence of infant food allergy. A reverse causation explanation of this result was reduced as this association remained even when the infants with allergic

Fig. 3 Cow's milk protein containing dairy foods, including cow's milk, yogurt, and cheeses

symptoms prior to the maternal dietary survey completion were excluded from the analysis. Hence, one must raise the question of whether CM and dairy food elimination from a maternal diet may reduce infant breast milk ingestion of other protective immunomodulatory nutrients and have the unintended consequence of increased risk of the infant developing other food allergies.

Nutritional disadvantages to the mother following a CM avoidance diet

Maternal dietary restriction of CM and dairy foods may significantly reduce the mother's nutrient intakes of energy, protein, calcium, phosphorus, riboflavin (B2), pantothenic acid (B6), cyanocobalamin (B12), and vitamins A and D (in countries where cow's milk is fortified with vitamin D). During lactation, a woman requires an additional energy intake of 2000 kJ/day (approx. 500 Cal/day) and 1.1 g/kg protein above her usual energy and protein daily nutritional requirements,[62] as well as increased needs for many other vitamins and minerals (specifically Vitamins A, B group, C, D, E, and zinc).[62] While calcium requirements are not increased during lactation many women have usual intakes that are less than the recommended 1000 mg/day (equivalent to 850 ml/day of CM or an alternate beverage fortified to 120 mg calcium per 100 ml). An interesting study by Adams et al[63] identified increased bone turnover in breastfeeding mothers who were eliminating CM and dairy foods in their diet despite sufficient calcium supplementation of 1000 mg/day. These mothers following CM free diets were also found to have lower energy, protein, and phosphorus dietary intakes when compared to mothers on unrestricted diets.[63]

Another potential disadvantage of elimination of dairy foods by lactating mothers is avoidance of yoghurt and other fermented dairy foods, the most common source of probiotics for many women. Although probiotic supplements are available to be taken separately, consuming fermented dairy foods also provide additional maternal gut health benefits. The bacterial enzymes in fermented dairy foods transform lactose into lactic acid and other milk carbohydrates into oligosaccharides with prebiotic properties which enhance beneficial gut microbiome composition profiles.[64] With increasing evidence of improved health outcomes of a beneficial gut microbiome composition, this is another important maternal disadvantage to consider when maternal CM avoidance is recommended. Hence, if a mother is advised to avoid CM while breastfeeding a baby with a CMA it is essential that she receives detailed and regular expert dietary advice from a Dietitian, experienced in allergy and maternal and child health, to ensure maternal nutritional adequacy is achieved.[65]

Impacts on maternal quality of life while following a CM avoidance diet

In addition to the nutritional consequences of CM exclusion diets on a breastfeeding mother there are also several potential negative impacts on quality of life. CM and CM-based ingredients are ubiquitous in the diet and considerable food literacy is required to be able to substitute ingredients in recipes and accurately interpret packaged food labels. This can place a huge time burden on families that cannot rely on pre-made meals and foods. Food is also an important part of many cultural celebrations and social events, therefore some women may find CM avoidance to be socially restrictive. Finally, there is the potential for feelings of guilt or anxiety that the infant is experiencing symptoms due to foods in the maternal diet which may negatively impact on a mother's desire or willingness to continue breastfeeding. In the case series study by De Boissieu and colleagues[66] it was reported that 2/6 (33%) mothers decided to use an extensively hydrolysed breast milk substitutes for their infant rather than to continue to breastfeed and follow a maternal dietary restriction for the treatment of their infant with food allergy symptoms. Previous studies have not incorporated maternal quality of life measures to assess the impacts of maternal CM restriction, so this should be incorporated in future study designs. Detailed dietary advice from a Dietitian who specialises in food allergy will reduce the impact of maternal dietary restriction by increasing the mother's knowledge of nutritionally equivalent substitutes, label reading and suitable products to prepare and purchase.[65]

Breastfed infants whose symptoms improve after maternal CM restriction

There have been a few studies which have examined the effects of maternal CM restriction

followed by maternal CM challenge on the "allergic" symptoms of breastfed infants. These include case series,[15,66-68] a case-control study[69] and RCTs.[29,33,39]

The cases series evidence[15,66-68] was flawed by open (non-blinded) maternal CM challenges, variations in challenge doses, small sample sizes of <20 participants, and many women who commenced dietary restriction did not follow through with the CM challenge. In most case series, limited or no attempts were also made to objectively quantify (score) infant symptom improvement with maternal CM restriction and deterioration with maternal CM challenge.

In the case-control study (17 cases and 10 control infants) by Järvinen et al,[69] the maternal CM challenge involved a standardised protocol of increasing doses of CM protein over 2 days followed by free consumption of CM. This enabled the determination that an average volume of 700 ml (range 100–2300 ml) of maternal CM ingestion was required to elicit predominately eczema and gastrointestinal symptoms in these breastfed infants. Given the nature of these symptoms, and that all but one of these infants had a negative skin prick test to cow's milk, the infants studied in this case-control study appear to predominately have non-IgE mediated CMA. Unfortunately, in this case-control study,[69] as was the design in the case series studies, the maternal CM challenges were non-blinded nor placebo controlled.

There have been 3 RCTs[29,33,39] using a cross-over study design with double-blinded, placebo-controlled CM challenges. The choice of an ideal placebo challenge should be a low-allergenic food, such as the potato starch which was used in the trial by Jakobsson and Lindberg,[33] but unfortunately the other 2 trials[29,39] used potentially allergenic soy protein for the placebo challenges, which may explain the lack of difference in infant symptoms observed. The beneficial effect of maternal CM dietary restriction on infant colic symptoms found in the early 1980s trial conducted by Jakobsson and Lindberg[33] still requires corroboration in more RCTs. This is due to the participant selection criteria likely biasing the results towards a beneficial response, as mothers were selected for trial participation only if after an initial period of maternal CM avoidance their infant's symptoms improved and then returned on maternal open CM challenge. These RCTs[29,33,39] had small participant numbers (n = 16–20 only per trial) and did not describe the use of power calculations to determine adequate sample sizes.

Thus, despite some reported beneficial responses to alleviate infant symptoms in case series or case-control studies, and personal and clinical experience supporting the existence of infants whose symptoms appear to respond to maternal dietary changes, there is a lack of high-quality evidence and mechanistic understanding around this phenomenon.

Other maternal dietary components that may transfer through breastmilk and elicit infant symptoms

Unrelated to infant "allergic" reactions, maternal consumption of alcohol, spices, and other foods have also been reported to influence infant behaviours, particularly infant distress and crying.[70] Many parents search for organic causes and commonly attribute infant crying behaviours to components of the maternal diet, but research into this is weak and difficult to conduct. Yet there is a proliferation of unsubstantiated maternal dietary modifications that are promoted via breastfeeding support forums, social media groups and the lay literature that fosters the potential widespread self-restriction of diets by breastfeeding mothers looking for options they can control.

In a recent Australian online survey study by Iacovou and colleagues,[71] 966/1262 (77%) survey respondents reported avoiding some foods/beverages in their diet while breastfeeding. The reasons for maternal dietary avoidance were most commonly: baby being unsettled (31%), baby having wind/gas (29%), colic (11%), and crying (10%), and the most common foods/beverages avoided were alcohol (79%), coffee (44%), chili (22%), cabbage (20%), onion (20%), and garlic (16%). This survey identified that 245/1262 (19%) breastfeeding mothers had eliminated CM/dairy foods, but one-third did not substitute with calcium-rich alternatives, and only a few (4%) sourced advice from a Dietitian. Hence, although health professional advice and

guidelines recommend maternal dietary restriction to manage symptoms in breastfed infants in only limited situations, it is important to also acknowledge the potential widespread practice of dietary self-restriction by breastfeeding mothers.

A recent systematic review[72] highlighted that infant behaviours impact feeding decisions and breastfeeding continuation. This review draws special attention to the importance of preventing misinformation, especially that which implies that normal infant behaviours are abnormal and results in undermining the breastfeeding self-efficacy of mothers. Strategies around feed positioning and settling techniques by a maternal-child health nurse or lactation consultant to assist in managing crying and unsettled behaviour, as well as fostering an understanding of normal infant behaviour are important. A key message in this recent review was that health care staff need to be trained in providing anticipatory advice to parents on usual infant behaviours to prevent unnecessary changes in feeding strategies.

Current recommendations and guidelines

IgE-mediated CMA

Maternal CM dietary avoidance for breastfed infants with IgE-mediated CMA is not recommended unless the infant is symptomatic on breastfeeding alone [10].

Eczema/atopic dermatitis

For breastfed infants with moderate to severe eczema/atopic dermatitis, unresponsive to topical steroids and sensitized to cow's milk protein, a trial of maternal CM avoidance may be recommended [38].

Non-IgE-mediated CMA

A trial of maternal CM avoidance is only advised if the history and examination strongly suggest CMA [10].

Trial of maternal CM avoidance if required

Current guidelines advise that if a trial of a strict elimination of CM and CM containing foods from the maternal diet appears warranted then this should only occur initially for 24 weeks. Then there should be a clear plan for home reintroduction of CM into the maternal diet for a period of one week to determine that the CM elimination is responsible for resolution of symptoms, and then recurrence of infant symptoms upon maternal CM reintroduction. Referral to a dietitian is advised for dietary education, along with calcium and vitamin D supplementation according to local dietary recommendations, and a maternal substitute milk should be advised [10]. Active support of continued breastfeeding is essential [10].

Future research required

Research in this field is not straightforward due to the inherent complexity of multiple maternal dietary influences on breast milk composition, difficulty in accurately measuring it, and interplay with infant feeding patterns and infant phenotypes, as well as variations in parenting responses to infant behaviours. There however remains enormous scope for the addition of high-quality new evidence, especially harnessing systems biology approaches to examine combinations of influencing factors on the maternal-infant pair. Along with quantitative observed infant symptom improvement after maternal CM avoidance, and blinded CM/placebo maternal challenges, future adequately powdered RCTs should also incorporate measures to assess the potential impacts of CM avoidance on maternal quality of life, and any resulting premature cessation of breastfeeding. Greater mechanistic understanding in this field will also enable the design of targeted future personalized medicine style interventional RCTs on the effects of maternal CM protein inclusion compared to avoidance diets when breastfeeding a baby with CMA.

In conclusion

With significant variation between mothers breastfeeding a baby with CMA we cannot apply a "one size fits all" approach to our advice and recommendations. Furthermore, despite some international expert consensus recommendations for maternal CM avoidance to treat breastfed infants with CMA, the evidence to support these recommendations are of limited strength due to a lack of high-quality, adequately powered, RCTs. It is likely that more than 99% of infants with IgE-mediated CMA will tolerate breastmilk from a mother consuming CM and CM containing foods without having an allergic reaction. Furthermore, we must not lose sight of the other consequences of maternal CM avoidance on reducing immune enhancing factors in breast milk, nutritional, financial, and social impacts on the mother, which ultimately also burden her family and community. Finally, active support of the mother to continue breastfeeding is essential.

Abbreviations

BLG, beta-lactoglobulin; CM, cow's milk, CMA, cow's milk allergy; EAACI, European Academy of Allergy and Clinical Immunology; EoE, Eosinophilic Oesophagitis; FPIES, Food Protein Induced Enterocolitis Syndrome; RCT, randomised controlled trial.

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Funding

This document was supported by the World Allergy Organization. VMcW was supported by a Royal Children's Hospital Clinician-Scientist Fellowship, and DJP was supported by a Telethon Kids Institute Ascend Fellowship.

Author contributions

DJP initially conceptualized the study. VMcW, MJN, EV, DJP, contributed to data collection. DJP drafted the first version of the manuscript. All authors approved the final version of the manuscript.

Ethics approval

Ethics approval was not required for this study as it is a narrative review.

Consent for publication

All authors approved the final version and its submission.

Declaration of competing interest

VMcW reports speaker honoraria and advisory panel consultancy outside the submitted work for Nutricia, Abbott and Nestle Nutrition Institute, MJN reports speaker honoraria from Nestle Nutrition Institute outside the submitted work, EV has nothing to disclose, DJP reports advisory panel consultancy outside the submitted work for Nestle Nutrition Institute.

WAO DRACMA Guideline Group, Declaration of competing interests: S Arasi, S Bahna, Bognanni, J Brozek, D Chu, L Dahdah, Piotr Dziechciarz, E Galli, R Kamenwa, H Li, A Martelli, R Pawankar, H Schunemann, R Targino, L Terracciano, and A Warner have no conflicts to disclose. Relationships reported related to the submitted work: IJ Anstotegui – Abbott, Amgen, Astra Zeneca, Bayer, Bial, Faes Farma, Hikma, Menarini, Merck, Mundipharma, Roxall, Sanofi, Stallergenes, UCB. A Assa'ad – Aimmune Therapeutics, DBV Technologies, Astella, ABBVIE, Novartis, Sanofi, FARE, NIH and an intellectual property patent

licensed to Hoth. R Berni Canani – Ch.Hansen, Danone, DVB, Humana, iHealth, Kraft Heinz, Mead Johnson, Nestlè, Novalac, Nutricia, Sanofi. M Bozzola – Danone C Dupont – Nestle Health Science, Nestle France, Nutricia, Novalac, Sodilac, Abbott, Danone, and stock ownership at DBV Technologies. M Ebisawa – DBV Technologies, Mylan, ARS Pharmaceuticals, Novartis. A Fiocchi – Abbott, Danone. G Lack – FARE, National Peanut Board (NPB), The Davis Foundation, Action Medical Research, UK Food Standards Agency, Medical Research Council, DBV Technologies, Mission Mighty Me, Novartis, Sanofi-Genyzme, Regeneron, ALK-Abello, Lurie Children's Hospital. A Nowak-Wegrzyn – Nestle, Nutricia, Novartis, Gerber, Aimmune. N Papadopoulos – Novartis, Nutricia, HAL Allergy, Menarini/Faes Farma, Sanofi, Mylan/Meda, Biomay, AstraZeneca, GSK, MSD, ASIT Biotech, Boehringer Ingelheim, Gerolymatos International SA, Capricare. M Said – Nestle, Nutricia, Abbott, Bayer for Anaphylaxis Australia. J Spergel – DBV Technologies, Regeneron, Sanofi, and Aimmune. H Szajewska – Ausnutria, Cargill, Danone, Else Nutrition, Hipp, Nestle, and Nestle Nutrition Institute. Y Vandenplas – Abbott Nutrition, Biogaia, Biocodex, By Heart, CHR Hansen, Danone, ELSE Nutrition, Friesland Campina, Hero, Hypocrata, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, Orafti, Phacobel, Phathom Pharmaceuticals, Sari Husada, United Pharmaceuticals (Novalac), Wyeth, Yakult. C Venter – Reckitt Benckiser, Nestle Nutrition Institute, Danone, Abbott Nutrition, Else Nutrition, and Before Brands, DBV Technologies. S Waserman – Novartis-basic science work on peanut allergy, Aimmune-peanut OIT trial, Medical Advisor to Food Allergy Canada, and Pfizer, Bausch, Kaleoconsultant for epinephrine autoinjectors. GWK Wong – Nestle, Danone.

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