



GERD and Cow's Milk Allergy

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Abstract

Gastroesophageal reflux disease (GERD) is currently listed by the European Academy for Allergy and Clinical Immunology, the European Society for Pediatric Gastroenterology Hepatology and Nutrition and other food allergy associations as a possible non-Immunoglobulin E (IgE) mediated food allergic disorder. Published studies have indicated that in up to around 40% of children, this may be associated with cow's milk allergy (CMA). However, the challenge is not only distinguishing between food protein and non-food protein driven GERD, as both exhibit the same symptoms, but also to be able to distinguish between acute vomiting as a result of an IgE-mediated reaction or Food Protein-Induced Enterocolitis Syndrome (FPIES). The elimination of cow's milk and its derivatives should only be considered once standard treatment, which includes avoiding overfeeding and thickening of feed, has been trialled, and/or when atopic co-morbidities and/or other symptoms associated with non-IgE-mediated allergies are present. A 2–4 week elimination of cow's milk, which may entail a maternal elimination in breastfed infants or suitable formula with proven hypoallergenicity with complementary food free-from cow's milk protein (CMP). The reintroduction of cow's milk, with re-appearance of symptoms, is a critical step for the confirmation of the diagnosis and to avoid the unwarranted elimination. Mother and child should be supported with optimal dietetic support, including vitamin (i.e., vitamin D) and mineral supplements (i.e., calcium) to avoid excessive weight loss for the mother and ongoing growth and development for the child. The prognosis of cow's milk allergy-associated GERD is good with most children becoming tolerant between 1 and 3 years of age.

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Introduction

Food allergy is defined as a reproducible immune-mediated reaction towards a food allergen and can be either Immunoglobulin E (IgE) or non-IgE mediated [1]. IgE-mediated allergies, typically occur immediately and up to 2 h after the ingestion of the trigger foods and common symptoms include urticaria, angioedema, hives, eczema, respiratory symptoms (i.e., wheezing), acute vomiting and in severe cases anaphylaxis [2]. Non-IgE-mediated allergies are delayed in the presentation of symptoms, usually occurring >1 h to 48 h after ingestion of the trigger food [3]. Symptoms typically affect the skin (i.e., eczema) and/or gastrointestinal tract, including acute (within 1–4 h after exposure), severe vomiting (i.e., food protein-induced enterocolitis syndrome (FPIES)) [4], persistent vomiting, diarrhea with/without blood in the stools, abdominal pain, vomiting (acute and chronic) and these symptoms may be associated with faltering growth [3].

There is a wide range in challenge proven prevalence of food allergies in children <5 years of age, ranging from <1% in Turkey to 10% in Australia [5, 6]. The most common trigger foods in pediatric IgE and non-IgE-mediated food allergy includes cow's milk, hen's egg, soya, wheat, peanuts, tree nuts, fish, and shellfish [7]. Cow's milk allergy (CMA) [8], one of the most common food allergies <1 year of age, has a challenge proven incidence of <1% in Europe, according to the EuroPrevall study, but great variation was seen between countries [9]. This study is to date, the only population-based study that has assessed through a double-blind food challenge both IgE and non-IgE-mediated CMA and found that the latter had a prevalence ranging from 0.13% to 0.72%, with the UK having more children with non-IgE- than IgE-mediated CMA [9]. Methodological concerns have been highlighted in particular related to the recognition of symptoms of non-IgE-mediated allergies, so it is likely that the incidence of this delayed allergy is much higher.

Gastroesophageal reflux disease (GERD) is currently listed by the European Academy for Allergy and Clinical Immunology (EAACI) [10], the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) [11] and other food allergy associations as a possible non-IgE-mediated food allergic disorder [2, 12]. However, the role of food allergens as a cause of GERD remains controversial [13].

The Role of Cow's Milk Protein (CMP) in GERD

The joint ESPGHAN-North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) guidelines on GERD from 2009 already recognized the possible role of CMA [8, 14] and has further increased in

prominence in the treatment pathway in the updated guidelines from 2018, with the consideration of a cow's milk elimination diet prior to the use of medication in infants <1 year of age [15]. Cavataio et al. published a study in the year 2000 on 204 prospectively recruited infants <1 year of age with the diagnosis of GERD and found that 41.8% of these patients had challenge proven CMA [16]. In addition to this study, Borrelli et al. [17] found through 48-h multichannel intraluminal impedance-pH monitoring that children with proven CMA had more total reflux and weakly acidic reflux episodes during CMP challenge. A recent study by Omari et al. [18], found that the elimination of CMP significantly improved GERD symptoms in infants with non-IgE-mediated CMA when compared with controls. That study also showed improved esophageal peristaltic function and mucosal integrity, increased acid clearance and esophageal mucosal impedance [18]. Several further studies have also found a high prevalence of CMA in children with GERD, in particular those resistant to standard treatment [17, 19–21]. The challenge, however, highlighted by all publications is the difficulty in not only distinguishing between food protein and non-food protein driven GERD as both exhibit the same symptoms, but also to be able to distinguish between acute vomiting as a result of an IgE-mediated reaction or Food Protein-Induced Enterocolitis Syndrome [3]. From the published studies, CMA may be more relevant in infants with severe and persistent GERD with associated food aversion, faltering growth and other gastrointestinal symptoms commonly associated with non-IgE-mediated allergies, but also atopic manifestations including atopic dermatitis and/or urticaria and rhinitis [17, 22].

Diagnosis

As CMP-associated GERD is recognized as a possible non-IgE-mediated food allergy [23, 24]. A small number of studies have assessed the role of skin prick testing, patch testing, serum IgE measurement, IgG and IgG4 for the diagnosis of non-IgE-mediated food allergy per se, but none have yielded results supporting their routine use for the diagnosis of CMP-associated GERD or any other non-IgE-mediated condition [25, 26]. However, if the infant exhibits symptoms of an IgE-mediated food allergy and/or has eczema, the use of specific IgE testing and/or skin prick test as part of a food allergy focused history may be indicated to support a diagnosis [2, 27]. The role of endoscopy, pH-manometry, and other tests are discussed in Chap. 3 and should be considered where applicable as part of the diagnostic work-up, in particular with the overlapping symptoms of GERD (food protein and non-protein induced) and eosinophilic esophagitis (EoE). See Table 11.1.

The primary diagnostic tool therefore for CMP-associated (and other food protein) GERD is a trial elimination diet, with symptom improvement, followed by the reintroduction of CMP with symptom deterioration [11, 24, 28, 29]. This elimination diet should only be considered for children with GERD, who have failed standard treatment, which includes avoiding overfeeding and thickening of feed, as per ESPGHAN/NASPGHAN guidelines and/or have atopic co-morbidities and/or other

Table 11.1 Diagnostic work-up for cow's milk-induced GERD

General symptoms	Atopic co-morbidities	Food allergy focused history	Allergy test
Vomiting with discomfort Faltering growth Epigastric pain Excessive crying Feeding difficulties Back arching during feed Poor sleep	Atopic dermatitis Existing IgE-mediated allergies Other non-IgE-mediated allergies (i.e., rectal bleeding, diarrhea) Recurrent wheezing	When did symptoms appear in relation to breast/bottle feeding and complementary foods? Specific foods involved?	Skin prick/specific IgE test only required if symptoms of IgE-mediated allergy present and/or eczema

symptoms associated with non-IgE-mediated allergies [15, 27, 30, 31]. Studies on the length of diagnostic elimination diets vary between 24 hours to 4 months [32]. Three review publications [20, 32, 33] recommended a 2–6 weeks avoidance period of cow's milk, and two guideline papers [34, 35] recommend a 2–4 week period of CMP avoidance in GERD. Although the publication by Lozinsky et al. [36] was not specifically aimed at infants with GERD, it collected data on a cohort with non-IgE-mediated allergies, including food protein-induced GERD and found that 98% had symptom improvement after a 4 week elimination diet, although complete resolution of symptoms may require a longer and full resolution of symptoms may not occur in all infants. This implies that a minimum of 2 weeks is required to start seeing symptom improvement, but symptom resolution may only occur in some after 6 weeks, in particular, if symptoms are severe. It is, however, important to individualize the length of elimination and use clinical judgement when suggesting a diagnostic elimination diet as this may be influenced by the following factors:

1. Severity of symptoms
2. Breastfed/bottle fed
3. Whether complementary food has been introduced
4. Nutritional status (growth and vitamin and mineral status) of the mother/infant
5. Psychological well-being of the family

While the elimination and reintroduction diagnostic approach is highlighted in all current guideline papers, specific guidance on how to reintroduce CMP is scarce. A double-blind supervised challenge remains the gold standard also for the diagnosis of CMP-associated GERD, however, this is not practical for many healthcare systems, as reactions may take days to occur, which has a significant fiscal burden to either parents or healthcare system. Studies have shown that reintroduction of CMP (and other offending food allergens) can be performed safely at home, if IgE-mediated symptoms or FPIES are absent, but this requires sufficient time for monitoring symptoms, guidance on how to reintroduce and most importantly how parents should assess reactions [34, 37].

Publications have varied greatly in the method for CMP reintroduction for diagnostic purposes, and to date, no standard approach exists, as with IgE-mediated

allergies. The iMAP allergy guidelines specific for mild to moderate non-IgE-mediated CMA have suggested that breastfeeding mothers should reintroduce cow's milk and its derivatives over 1 week back in their diet and monitor symptoms. For formula-fed infants, a 1 week reintroduction regime has also been suggested, ending with at least 210 mL of CMP-based formula per day [24]. While these suggestions are not evidence based, there seems to be consensus amongst healthcare professionals that one should at least aim for a "normal portion" of CMP according to the child's age to confirm or refute the diagnosis. For cow's milk, a normal portion is considered 120–240 mL of infant formula or cow's milk for toddlers [38].

Dietary Management in Proven CMP-Induced GERD

Cow's milk and its derivatives is a primary source of nutrition for the breastfeeding mother as well as for the non-breastfed infant and during complementary feeding [11, 39, 40]. The elimination of CMP increases the risk of growth faltering/excessive weight loss post-pregnancy and vitamin and mineral deficiencies for both the infant and breastfeeding mother are well-reported [39, 41]. It may also be that the infant/breastfeeding mother is not only eliminating cow's milk but soya and other food allergens. Soya is commonly reported as concomitanted allergen in particular in non-IgE-mediated cow's milk allergy [36, 42, 43]. However, data differs between countries. It is therefore crucial that parents receive dietary advice, ideally from a registered dietitian/nutritionist, not only on what to avoid, but how to replace the macro and micronutrients from cow's milk and other allergens (Table 11.2), as this has shown to improve growth and micronutrient status [44].

Breastmilk in the Management of GERD

Limited data exists on the presence of CMA in breastfed infants. However, in a prospectively recruited cohort of breastfed children by Høst et al. [45] 0.5% of the 2.2% children diagnosed with an IgE-mediated CMA presented while being exclusively breastfed. There is paucity of data on the incidence and severity of GERD in breastfed infants, but it is estimated that about 25% of infants (both breastfed and bottlefed) suffer from troublesome regurgitation [46].

Cow's/goats and/or sheep milk protein can transfer through human milk in the form of β -lactoglobulin (levels range from 0.9 to 150 $\mu\text{g/L}$), which is unique to most mammalian milks and can elicit symptoms of CMA and may therefore also be involved in CMP-associated GERD [24, 47–49]. Breastfeeding is strongly supported by EAACI, ESPGHAN/NASPGHAN and other food allergy guidelines as the best source of nutrition to support growth, development, and the immune system [11, 24, 28, 49, 50]. In 2019, the EAACI position statement outlining the management and diagnosis of non-IgE-mediated allergies in breastfed infants was published highlighting the importance of supporting breastfeeding, ideally in line with the World Health Organization (WHO) of exclusive breastfeeding until 6 months of

Table 11.2 Cow's milk sources its nutritional contribution and possible alternatives

Potential sources ^a	Macro- and micronutrients	Food alternatives
Cow's milk (fresh, UHT, evaporated, condensed, dried) butter, butter oil, buttermilk	Protein, energy, vitamins A, D, and B12, riboflavin, pantothenic acid, calcium, phosphorus	Dairy free spreads, olive/sunflower/coconut/canola oil
Cream		Fortified coconut/pea/nut/soya ^b based yoghurts/cheese
Cheese		Plant-based fortified drinks (see guidance below on milk alternatives)
Yogurt, fromage-frais		Baked goods without butter/milk/cheese/cream
Casein, caseinates, hydrolyzed casein, sodium caseinate		
Curd		
Ghee		
Lactoglobulin		
Lactose—(food grade)		
Milk solids, non-fat milk solids		
Whey, hydrolyzed whey, whey powder, whey syrup sweetener		

^a This list is not exhaustive and may differ between countries

^b Soya may also be eliminated in some infants

age [51, 52]. Breastfeeding mothers should receive support to maintain breastfeeding and their dietary adequacy needs to be considered at all time, which may include the supplementation of calcium, vitamin D, iodine, and other micronutrient as appropriate to their elimination diet and their nutritional status [48, 53]. An unwarranted elimination diet should always be avoided as this poses a nutritional risk to the mother and may impact on the quantity and quality of the breastmilk [54].

Formulas for CMA in the Management of GERD

Many guidelines on the diagnosis and management of CMA, include suggested formulas suitable for the management of CMA, when breastmilk is insufficient or not available [2, 28, 49, 50]. All formulas that are being used for the management of CMA should be tested and conform to current guidelines on hypoallergenicity, which requires a product to be tolerated by 90% of children with a challenge proven CMA at 95 confidence interval and support normal growth [55, 56]. All guidelines suggest an extensively hydrolyzed formula [EHF] based on either casein, whey or rice, as first-line treatment for CMP-associated GERD (Table 11.3) [57]. However, the impact of growth faltering on formula choice should also be taken into account and is discussed in some of the guidelines. Several studies have shown improved catch-up growth, in particular, longitudinal growth with amino acid formulas (AAF) possibly related to the resolution of mild ongoing gastrointestinal inflammation [58, 59]. In addition, the involvement of multiple organ systems and multiple food allergies may also require the consideration of an AAF as first-line formula [60, 61].

In recent years, studies have been published using formulas that have specifically been designed for CMP-associated GERD. There are now thickened EHF casein,

Table 11.3 Summary of guidelines for first-line formulas for GERD

DRACMA (2010)	ESPGHAN (2012)	Australian Guidelines (2009)	BSACI (2014)	iMAP (2017)
EHF ^a	No specific mention for GERD but EHF is recommended as first-line formula for most presentation of CMA	EHF if <6 months Soy if >6 months EHF if >6 months if also presenting with faltering growth	EHF (unless faltering growth then AAF)	EHF

^a When hydrolyzed rice formulas are available, these can also be considered as first-line formulas for GERD

rice and AAF formulas with proven hypoallergenicity suitable for this population [62–65]. The studies by Dupont et al. [64, 66] and Vandenplas et al. [63] also assessed regurgitation episodes, crying and sleeping time. In children that had challenge proven CMA, both thickened and un-thickened extensive hydrolysates were equally effective in the resolution of symptoms and supported growth. In the study by Dupont et al. [64] significantly more children had better quality of sleep and less irritability with a thickened AAF and several studies have shown improved stool frequency and consistency [64] [63]. These formulas are not yet included in any of the CMA guidelines.

As mentioned above, soy is a commonly reported concomitant allergen in children with non-IgE-mediated CMA. While some data indicates that up to 50% have a concomitant allergy to soy in non-IgE-mediated CMA [42, 43], this is not the same in other studies and very limited data exists on soy being a culprit food in GERD [67, 68]. While all European, Australasian, and American guidelines do not recommend the use of soy-based formulas below 6 months of age for any CMA (Table 11.3) [11, 24, 49, 57], careful consideration in regards to local resources and the cost to families and healthcare system needs to be taken into account when considering soy-based formula as an option for a non-breastfed infant with CMP-associated GERD [12, 69].

Complementary Feeding in Infants with GERD

Complementary food should ideally be introduced, as per WHO guidelines, around 6 months of age. It is acknowledged in all of the allergy prevention guidelines, that outside of the culprit food, the introduction of other food allergens, including egg, wheat, soy (if not eliminated), peanut, tree nuts and fish, should not be delayed beyond 6 months of age [70–72]. In fact, when eczema and/or IgE-mediated egg allergy is present, the early introduction of peanuts, in countries where peanut allergy is prevalent is recommended [71, 73].

Furthermore, studies have also indicated that increasing the diversity of foods, may also have a positive impact on the further prevention of food allergies, possibly through improving the gut microbiome [74–76]. The expansion of complementary foods does not only play a role in the contribution of nutrients and the

microbiome, but also in the development of oral motors skills and the prevention of feeding difficulties [77]. Feeding difficulties are commonly reported in infants with GERD, ranging from breast to bottle aversion to texture hypersensitivity [78]. In a study published by Rommel et al. [79], who assessed the underlying diagnosis of 700 children with feeding difficulties, 60% presented with GERD as an underlying diagnosis. While this is well-recognized in GERD, limited data is available on feeding difficulties in children with CMP-associated GERD. To date, only one retrospective study has been published on feeding difficulties in the whole spectrum of non-IgE-mediated FA diagnoses, including GERD [80]. In that study, 30% of children had feeding difficulties, as noted by clinicians in the medical notes, with the most commonly reported being a texture hypersensitivity (Table 11.4). More data exists in EoE, where similar symptoms are present, in particular in the infants with early onset of EoE compared to CMP-associated GERD [81]. In the publication on EoE up to 90% of children have maladaptive feeding behavior [82, 83].

Many parents will report worsening of their infant's GERD to other foods, including fruit and vegetables that have traditionally been classified as "hypoallergenic." There is paucity on data on other trigger foods outside of CMP and other common allergens. However, many alternative practitioners and websites may advocate for the elimination of various foods (i.e., acidic fruit and vegetables), which may limit the infants' complementary diet significantly, increasing the risk for nutritional deficiencies. While, hypersensitivity reactions may occur to other foods, healthcare professionals should guard against unwarranted dietary elimination and understand the impact of food characteristics (i.e., protein content, osmolality, fat content and particle size) on gastric emptying to recognize patterns and therefore possible trigger foods. Any elimination of complementary foods outside of CMP should always be followed up by a timely reintroduction.

Natural History of CMP-Induced GERD

The prognosis of CMP-induced GERD is poorly described and difficult to establish; however, it is assumed that tolerance occurs at least within the age range previously described for other non-IgE-mediated allergies, which can be as early as 1 year of age, according to the EuroPrevall study on both IgE- and non-IgE-mediated allergy but may be as late as 3 years of age for some [9, 84].

Table 11.4 Feeding difficulties commonly seen in infants with GERD [80]

Feeding difficulties reported in infancy
Breastfeed or bottle refusal/aversion
Gagging on textured foods
Sealing of mouth and pushing spoon away
Crying when seeing the spoon
Extended mealtimes

The DRACMA Guidelines [28], ESPGHAN [11], and iMAP guidelines [34] suggest that after a period of avoidance, usually between 6 and 12 months, periodic reintroductions of cow's milk should occur to determine if tolerance has developed and this should also occur for CMP-associated GERD. There is currently no consensus on how reintroductions should occur in children with confirmed CMP-associated GERD. Several countries have adopted a milk ladder approach, which introduces milk proteins in a very gradual manner, starting from lower doses of less allergenic forms of milk, such as baked goods and advances slowly, as tolerated. While the efficacy of milk ladders has yet to be established, it has the potential of improvement in quality of life using this method of reintroduction has been recognized [69, 85]. Meyer et al. [37] has recently published their experience with using the ladder approach for the common allergens in a cohort of children with non-IgE-mediated allergy, including CMP-associated GERD. That study indicated that many children needed 2–5 attempts at the milk ladder due to ambiguous results, because of concomitant illness and/or teething impacting on the outcome. Whatever method is used for reintroduction, it is important that this is not delayed and that parents are adequately supported with reintroductions to not delay the process and also provide an accurate answer on tolerance.

Conclusion

CMP-associated GERD is a recognized non-IgE-mediated condition that is difficult to distinguish from GERD not associated with a food allergy. It is therefore important when an elimination diet is commenced to already discuss the reintroduction of CMP with the parents as an essential diagnostic step. GERD has a significant impact on the quality of life of parents and the further elimination of CMP may compound this impact [86]. At all times, the nutritional status of the breastfeeding mother and infant should be at the center of the management of CMP-associated GERD.

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