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Textbook of Pediatric Gastroenterology, Hepatology and Nutrition

Editors
Anupam Sibal
Sarath Gopalan

Co-Editors
Yogesh Waikar
Rajeev Khanna
Ishaq Malik
Prasanth K Sobhan

Foreword
Kathleen B Schwarz



2nd Edition

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Chapter 8

Cow's Milk Protein Allergy

Laura Carucci, Serena Coppola, Ilaria Di Sessa, Erika Caldaria, Roberto Berni Canani

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INTRODUCTION

Cow's milk allergy (CMA) is one of the most common food allergies (FA) in childhood, affecting up to 3% of the pediatric population. It also represents the primary cause of food-induced anaphylaxis in children. The prevalence, persistence, and severity of CMA dramatically increased in the last two decades under the pressure of environmental factors in genetically predisposed individuals. This condition imposes a significant cost to healthcare systems as well as to families, and it has emerged as one of the most expensive allergic diseases. Most of the costs are related to CMA management. The mainstay of CMA treatment is the elimination from the diet of cow's milk proteins (CMP). If breastfeeding is not available, the child must be fed with special formulas during infancy and later in the life if the disease persists. These formulas emerged as the primary cost driver for CMA management. Indeed, it has been estimated that the cost to feed a child with CMA is 2.5–6 times higher compared to a child fed by standard formula. Medical visits and drug costs significantly contribute to increasing the direct cost of CMA, as well as work and school absenteeism dramatically impacts the indirect costs of the disease. The economic burden and the anxiety of allergic reactions detrimentally impact the quality of life (QoL) of patients and their caregivers. Finally, CMA could increase the risk of developing other chronic conditions later in life, contributing to further worsening the scenario.

PATHOPHYSIOLOGY AND NATURAL HISTORY OF COW'S MILK ALLERGY

Cow's milk allergy derives from a breakdown of immune tolerance against CMP due to a negative interaction between genetic and environmental factors. Immune tolerance is an active process of unresponsiveness to food antigens. It is actively influenced by the gut microbiome (GM) and their metabolites. This phenomenon is called the GM–immune system axis. Growing evidence suggests that several environmental factors, including cesarean delivery, infections, drug use, and dietary habits (i.e., the Western diet) could have a role in facilitating the occurrence of CMA. Indeed, operating on an unfavorable genetic background, these factors may impair the GM, with consequent alterations of the GM–immune system axis. The perturbation of this axis could lead to a breakdown of immune tolerance and to CMA occurrence. On the other hand, Mediterranean diet, vaginal delivery, and breastfeeding could positively modulate the axis and may represent an effective approach to preventing CMA.

Many subjects with CMA develop tolerance to CMP by the age of 5 years. The acquisition of immune tolerance is just one of the steps of CMA's natural history; indeed, these patients have an increased risk of developing other immune and nonimmune-mediated diseases later in the life. It is known that early life CMA could be the first step of allergic march (AM), which affects up to 45% of CMA children, but recent evidence has shown that these patients have also an increased risk of developing celiac disease, eosinophilic esophagitis (EoE), functional gastrointestinal (GI) disorders (FGIDs), inflammatory bowel diseases (IBD), psychiatric disorders, such as autistic spectrum disorders (ASD) attention-deficit hyperactivity disorder (ADHD), and obsessive–compulsive disorder (OCD) **(Fig. 1)**. The pathogenesis of these events is still largely unknown, but increasing evidence suggests that a perturbation of GM could lead to alterations in the GM–immune system axis, which is strictly connected to the GM–brain axis, influencing the occurrence the natural history of CMA and other conditions later in life.

PHENOTYPES OF COW'S MILK ALLERGY

Cow's milk allergy may present with different phenotypes based on the immune mechanisms: Immunoglobulin

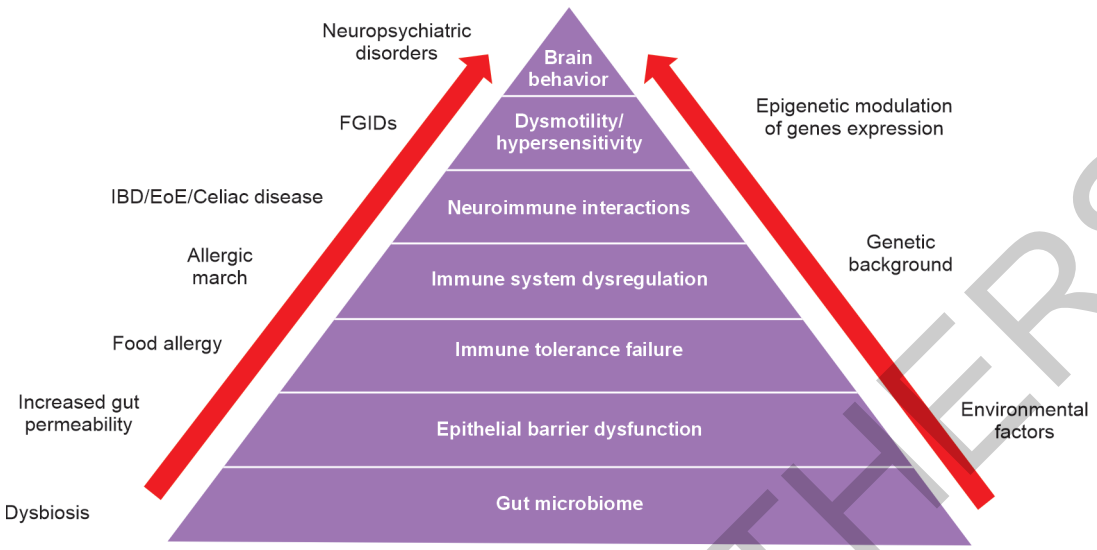


Fig. 1: *Food allergy pyramid*. Clinical studies suggested that pediatric patients with CMA could present an increased risk of developing other conditions such as allergic disorders (i.e., the allergic march), inflammatory bowel diseases (IBD), celiac disease, eosinophilic esophagitis (EoE), functional gastrointestinal disorders (FGIDs), and neuropsychiatric disorders (such as autism spectrum disorders and ADHD syndrome). Several genetic factors are implicated in the pathogenesis of these conditions, but evidence suggests the pivotal role of gut microbiome dysbiosis (induced by environmental factors such as cesarean section, formula feeding, drug use, unhealthy dietary habits, etc.) as the "first hit" in the development of alterations of the gut barrier and of the immune system development and function (responsible for the occurrence of CMA, allergic march, celiac disease, EoE, and IBD) and dysregulation of the brain–gut–immune system axis (responsible for the occurrence of FGIDs and neuropsychiatric disorders), at least in part through a modulation of epigenetic mechanisms. (ADHD: attention deficit hyperactivity disorder; CMA: cow's milk allergy)

E (IgE), non-IgE, or mixed. Children with IgE CMA may present GI (i.e., vomiting and diarrhea), cutaneous (i.e., erythema, itching, urticaria, and angioedema), respiratory, and/or systemic symptoms up to the most severe reaction, anaphylaxis, occurring within 2 hours after CMP exposure. The occurrence is most common in the first 3 years of age, but the IgE-mediated CMA could occur at any age.

Non-IgE CMA is mainly characterized by subacute or chronic GI symptoms with an onset usually after 6–72 hours after the ingestion of CMP-containing foods. The occurrence is usually in the first year of life, and the affected infants may present bloody stools, delayed vomiting, crying, and chronic diarrhea with the risk of malnutrition and failure to thrive. Non-IgE CMA classically includes the following phenotypes:

- Food protein-induced allergic proctocolitis *(FPIAP)*, which is characterized by bloody and mostly mucous stools in otherwise healthy infants. The symptoms begin within the first months of life, usually in the first two. It affects both exclusively breastfed and formula-fed infants, although it appears to be slightly more common in exclusively breastfed infants (60%). The most common offending triggers are CMP (76%), followed by hen's egg (16%), soy (6%), and corn (2%).
- Food protein-induced enteropathy *(FPE)* is characterized by chronic diarrhea and intermittent vomiting. The symptoms begin in the first year of life, and if they persist, they will lead to poor weight gain, failure to thrive, and villous atrophy. Some children develop an iron-deficiency anemia, associated with the presence of occult blood in the stools. The most common offending triggers are CMP and soy. The anatomopathological findings are villus atrophy, crypt hyperplasia, an increased number of intraepithelial lymphocytes, and eosinophilic infiltration. The main differential diagnosis is with celiac disease. Clinically and pathologically, they are indistinguishable, but the typical celiac disease antibodies are absent in FPE and the age at onset is typically different.
- Food protein-induced enterocolitis syndrome *(FPIES)* is considered a heterogenous disorder with a wide spectrum of clinical phenotypes. These are based on: (1) Time and duration of the symptoms; (2) Age of presentation; (3) Positivity of specific IgE (sIgE) to the causal food. Thus, we can classify FPIES into

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acute, chronic, later onset, and atypical. Acute FPIES usually presents in infancy with repetitive, protracted vomiting that begins 1–4 hours after food ingestion. Vomiting is often accompanied by lethargy and pallor and can be followed by diarrhea. Some patients have an isolated fever peak, and severe cases can progress to hypothermia, methemoglobinemia, and hypotension, mimicking sepsis. Children are asymptomatic between episodes and have normal growth, and these typical symptoms commonly disappear within 24 hours. Chronic FPIES is less well characterized. In this presentation, the symptoms occur over several days or weeks and do not have a clear relationship with the offending food. Children have intermittent but progressive vomiting and/or diarrhea, failure to thrive, or poor weight gain. The severe form can develop dehydration and hypovolemic shock. In chronic FPIES, once the offending food is removed from the diet, the symptoms subside within 2 weeks, but re-exposure to it triggers the typical symptoms of acute FPIES. When the disease onsets in adolescence or adulthood, the symptoms appear after years of tolerance to the food and the predominant symptoms are, in most cases, colic abdominal pain and diarrhea. Although FPIES is considered a non-IgE- FA, in some patients, it is possible to detect sIgE against the causal food. This form of presentation is known as atypical FPIES, and it seems to have a protracted course, with a further risk of developing IgE-mediated symptoms. Any food can trigger FPIES; however, the most causative foods are CMP and soy.

- Food protein-induced motility disorders *(FPIMD)* are a group of diseases characterized by motility disorders including colic, gastroesophageal reflux disease, and constipation due to CMA. These are common disorders in infancy, but they can also be caused by CMA, when FPIMD symptoms are persistent, do not improve with standard treatment, improve with a CMP elimination diet, and recur after CM exposure. Other signs/symptoms of atopy, such as atopic dermatitis and faltering growth, are frequently associated with FPIMD.

DIAGNOSIS OF COW'S MILK ALLERGY

The diagnosis of CMA is based on an allergy-focused clinical history, full physical examination, results of allergy screening tests, and response to the elimination diet and to oral food challenge (OFC). Indeed, the diagnosis may be confirmed without OFC if the patient experienced typical signs/symptoms of FPIES after ingestion of a single food vomiting in the 1–4-hours period after the ingestion of the suspected food, in the absence of classic IgE-mediated allergic skin or respiratory symptoms, in combination with ≥2 minor criteria (lethargy, pallor, diarrhea 5–10 hours after food ingestion, hypotension, hypothermia, increased neutrophil count of ≥500 neutrophils above the baseline count) and in case of a convincing history of IgE-mediated CMA with positive skin prick tests (SPT) and/or sIgE.

Allergy-focused Clinical History and Clinical Evaluation

Attention should be given to the presenting symptoms/signs that may indicate CMA, as well as the timing of symptoms' onset, the infant's feeding history and habits, and the possible reproducibility of the reaction. In most infants, CMA symptoms can be clinically recognized as either IgE, non-IgE, or mixed onset **(Table 1)**. Information regarding other allergic comorbidities, like personal and familial history of allergic disease, as well as any other potential risk factors should be evaluated. History of allergic disease in first-degree family members has long been recognized as a risk factor for allergic diseases. Living in an industrial versus a rural environment, cesarean section, and administration of medication such as antibiotics and proton-pump inhibitors early in life have been known for many years to be risk factors for FA occurrence. This may be related to a difference in GM development. The timing of formula and complementary feeding introduction in early life is also a long-standing debate. The latest European Academy of Allergy and Clinical Immunology (EAACI) guidelines on FA prevention highlighted how formula consumption in the first week of life could facilitate the occurrence of CMA; on the contrary, two most recent guidelines showed that rather than early milk-based formula introduction, the most important aspects for FA prevention are the early introduction of all allergenic foods in age-appropriate forms once the infant has shown interest and to keep it in their diet regularly, ideally several times each week.

A full clinical evaluation should include anthropometric, cardiovascular, GI, respiratory, and skin evaluation, to look for some potential allergic signs, including atopic dermatitis, abdominal distension, constipation, mucous and/or bloody stools, anal erythema, hives, angioedema, irritability, and failure to thrive. Most recently, a clinical score, the NAPFA score,

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TABLE 1: Allergy-focused clinical history for CMA.

Non-IgE-mediated	*Questions*	*IgE mediated*
Eating: Cow's milk formula, or breastfed with dairy exposure through the mother's diet	Exposure	• *Eating*: Cow's milk formula fed or breastfed with dairy exposure through the mother's diet is the most common • *Skin contact*: Rare • *Inhalation*: Rare
• *Age*: In the first year of life, most common in the first months of life • *Symptoms onset*: Insidious, subacute, or chronic, 1–24 hours after ingestion	Timing	• *Age*: All ages, most common in the first 3 years of life • *Symptoms onset*: Acute, in 2 hours after ingestion
• *Symptoms recurrence*: 1–24 hours after ingestion; sometimes it is difficult to recognize the allergen • *Symptoms resolution*: 2–14 days during the exclusion diet	Reproducibility	• *Symptoms recurrence*: Always acute symptoms in 2 hours with exposure • *Symptoms resolution*: In a few hours, exclusion diet and drugs are needed to resolve symptoms (i.e., antihistamines, corticosteroids, or adrenaline)
Skin: Eczema • *Gut*: Nausea, vomiting, reflux, dysphagia, sialorrhea, colic, abdominal pain behavior, diarrhea, constipation, mucous and/or bloody stools, and anal erythema • *Systemic*: Hypotension, pallor, lethargy, irritability, colic, persistent crying, faltering growth, malabsorption, and shock	Symptoms	• *Skin*: Urticaria, angioedema, eczema, and pruritus • *Respiratory*: Acute onset of cough, wheeze, stridor, acute clear rhinorrhea, and nasal obstruction *Gut*: Nausea, vomiting, abdominal pain, and diarrhea • *Systemic*: Hypotension, sleepiness, impending doom, anxiety shock, and collapse

(CMA: cow's milk allergy)

have been suggested as a useful tool for faciliating the food allergy diagnosis in children.

Determination of Specific Serum Immunoglobulin E and Skin Prick Test

The role of specific serum IgE (sIgE) and SPT may help in confirming the diagnosis in IgE CMA with a clear allergy history. In a systematic review and meta-analysis by the EAACI, SPT and sIgE were compared with double-blind OFCs (DBPCFCs). When the analysis was restricted to CMA, pooled sensitivities were high [88% (95% CI 76–94)] for SPT and [87% (95% CI 75–94)] sIgE. The specificities decreased to 68% (95% CI 56–77) and 48% (95% CI 36–59) for SPT and sIgE, respectively. Therefore, if the history and clinical presentation are suggestive of IgE CMA, sIgE or a SPT for CMP is useful in the diagnostic workup. The 95% positive predictive value for sIgE in children <2 years old was 5 kU/L and >15 in older children. The choice of test should be guided by local availability and relative and absolute contraindications for the SPT, which include severe eczema/dermographism, recent anaphylaxis, significant comorbidities such as cardiovascular disease or arrhythmias, and use of antihistamines or other medications that cannot be discontinued and may interfere with its proper interpretation.

Atopy Patch Test

The atopy patch test (APT) has been proposed as a diagnostic tool for identifying the culprit food in children with non-IgE CMA. A meta-analysis showed that APT has a high specificity of 94% (95% CI 0.88–0.97) in the group of patients affected by FPIMD. Data showed a high pooled specificity of 96% (95% CI 0.89–0.98) and the highest accuracy of APT in patients affected by CMA [area under the curve (AUC) = 0.93]. Despite these encouraging results, due to the lack of standardized test substances and most studies being performed on mixed or IgE FA, APT are not recommended for routine diagnosis of FA, but they could be effective in identifying causative food in children with FPIMD, especially if CMA is suspected.

Component Resolved Diagnostics

Component-resolved diagnostics detects sIgE to allergenic molecules or the epitope of the allergen. In a systematic

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review of selected components, including components of CMP, the reported sensitivity-specificity were: Bos d 4 (α-lactalbumin), 62.0 and 87.5% (with a cut off value defining a positive test of >0.01 kUa/L), and 50.0 and 93.0% (at >0.1 fluorescent intensity (FI); Bos d 5 (β-lactoglobulin), 82.0 and 62.5% (at >0.35 kUa/L), and 23.8 and 95.3% (at >0.1 FI); Bos d 8 (caseins), 88.0 and 56.3% (at >0.35 kUa/L). Among the α-, β-, and κ-caseins, κ-casein had the highest accuracy with a sensitivity and specificity of 38.1 and 88.4% (at >0.1 FI), respectively. Since there are only a few conducted studies to date, it remains challenging to draw firm conclusions, and further research to establish clinically relevant cutoff values, risk assessment, and cost-effectiveness of component-resolved diagnostics is needed.

Diagnostic Cow's Milk Elimination Diet

Symptoms and signs of CMA involve the skin (urticaria, angioedema, and atopic eczema/dermatitis), the GI tract (i.e., vomiting, colic, abdominal pain, diarrhea, and constipation), and the respiratory tract (rhinorrhea, sneezing, cough, and dyspnea), up to systemic reactions (cardiovascular collapse). Reactions are mostly triggered by CMP ingestion but can also be triggered by inhalation of and skin contact with milk.

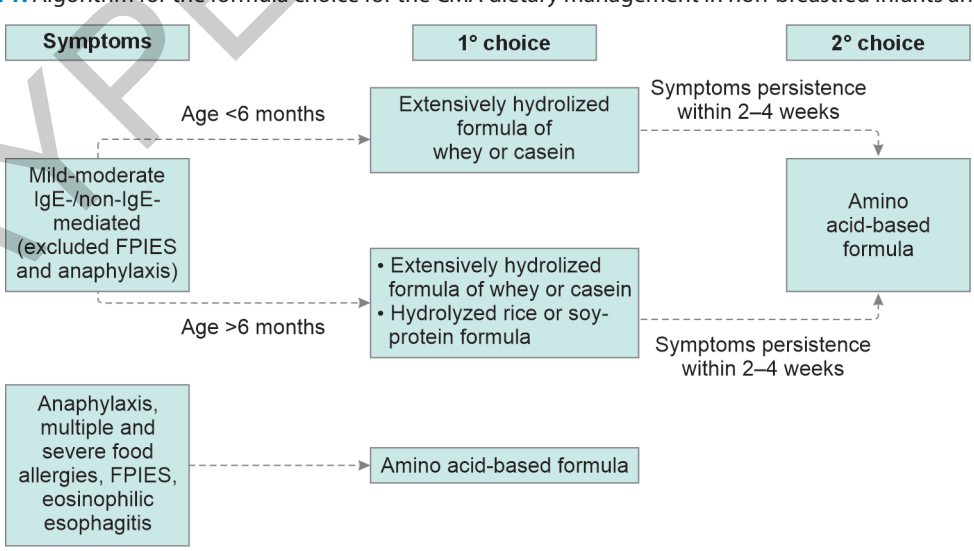
In non-IgE CMA, the diagnostic elimination diet typically requires 4 weeks before reintroduction, while for IgE CMA the time window may be shorter (1–2 weeks) due to the faster improvement in this form. The formula choice for the diagnostic elimination diet is based on the severity of clinical symptoms **(Flowchart 1)**. If symptoms persist, the diet needs to be carefully reevaluated, as potential food allergens may have been missed or another diagnosis should be considered.

Oral Food Challenge

Oral food challenge consists in the exposure to suspected food causing FA to confirm FA diagnosis and to evaluate the development of immune tolerance. An OFC is mandatory in the workup of infants with CMA, except for those presenting with a clear history of IgE CMA or of anaphylaxis together with high levels of sIgE, and for patients presenting the diagnostic criteria of FPIES after ingestion of single food. OFC could be performed in different ways: Open, single, or double blinded. DBPCFC is the gold standard for FA diagnosis, but it is also the most complicated and expensive OFC procedure. It should be used for research purposes and in clinical practice when evaluating subjective symptoms with possible psychological interference (e.g., abdominal pain), late reactions, or chronic symptoms (e.g., moderate to severe atopic dermatitis, isolated GI reactions, or chronic urticaria).

If objective symptoms are expected, an open OFC could be performed to confirm the CMA diagnosis. The protocols and setting of CMP administration vary based on the CMA type. In cases of suspected IgE or FPIES CMA, the OFC should always be carried out under medical supervision in a hospital setting with intravenous access. In others, non-IgE CMA, the challenge can be done at home.

Flowchart 1: Algorithm for the formula choice for the CMA dietary management in non-breastfed infants and children.



(CMA: cow's milk allergy; FPIES: food protein-induced enterocolitis syndrome; IgE: immunoglobulin E)

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In the hospital setting, full emergency equipment and medications (epinephrine, antihistamines, and steroids, as well as ondansetron and saline solution) should be available, and the different OFC protocols should be adopted based on the clinical history (IgE vs. FPIES CMA). The IgE CMA protocol consists of seven growing doses of food with a semilogarithmic increase in protein concentration: 3–10–30–100–300–1,000–3,000 mg, corresponding to 0.1, 0.3, 0.9, 3, 9.1, 30.3, and 90.9 mL of fresh milk every 15–30 minutes. If severe immediate reactions are expected, the OFC should start with a drop on the lips followed by a stepwise increasing dosing of small volumes at 30-minute intervals. Patients should be observed for at least 2 hours following the maximum dose or the resolution of signs/symptoms in case of reaction. If no reaction occurs during the OFC, CM should be continued at home every day with at least 200 mL/day for at least 2 weeks. The parents should be trained to recognize and to report any late reactions.

In FPIES-suspected patients, the OFC protocol requires a challenge dose of 0.3 g of food protein per kilogram of body weight with a maximum total of 3 g of protein (range 0.06–0.6 g/kg body weight). The total dose should be divided in three equal doses, each administered every 30 minutes, and the patient remains under observation for at least 6 hours from the last dose or for 6 hours after symptom resolution in case of a positive OFC result.

In all other forms of non-IgE CMA, there are no standardized protocols, but a gradual reintroduction up to the total appropriate age doses in 7 days has been suggested. The symptoms of non-IgE CMA could generally occur in 48–72 hours but also up to 7–14 days in some cases; for this reason, the OFC period should last at least 7 days before the first medical evaluation. Further evaluation at 14 and 30 days since OFC starting should also be carried out to surely confirm the non-IgE CMA.

DIETARY MANAGEMENT OF COW'S MILK PROTEIN ALLERGY

Dietary management of CMA involves the strict elimination of all sources of CMP from the child's diet. Experienced dietary counseling should be included in the management of all CMA pediatric patients, playing a pivotal role in improving the quality of life of CMA patients and their caregivers. The three nutritional intervention cornerstones for the management of CMA pediatric patients' are:

1. Preventing allergic reactions
2. Avoiding nutritional deficits and nutritional status alterations
3. Stimulating the immune tolerance acquisition and protecting against the occurrence of other atopic manifestations through active diet therapy

Preventing Allergic Reactions

Patients and their caregivers should be carefully educated about allergen avoidance to prevent accidental ingestion of CMP.

Patients and caregivers must scrutinize food labels to identify any presence of milk or its derivatives. Ingredients such as casein, whey, lactose, and various milk proteins may be hidden under different names, making it essential to be thorough and knowledgeable about potential aliases for cow's milk. Additionally, being aware of common terms like "may contain milk" or "produced in a facility that processes milk" is crucial to avoid inadvertent exposure to allergens due to cross-contamination.

Caregivers and individuals responsible for preparing food for these patients must be meticulous in checking ingredient lists for hidden sources of milk or its derivatives. Cross-contamination is a significant concern, and it is essential to use separate cutting boards, utensils, and cooking equipment for foods that contain or may contain cow's milk. Thoroughly cleaning surfaces and kitchen tools after each use is crucial to minimize the risk of accidental exposure. When dining out or ordering food, it is imperative to communicate the allergy to restaurant staff to ensure proper handling and preparation of meals. Educating family members, friends, and caregivers about the severity of CMA and the importance of avoiding cross-contact is vital for the safety of the individual with the allergy. Maintaining a strict and vigilant approach to food preparation and consumption is key in safeguarding individuals with CMA from inadvertent exposure and potential allergic reactions.

Furthermore, due to the high cross-reactivity with CMP of sheep, goats, buffalo, ibex, deer, donkey, camel, and horse milk, patients and their caregivers should be aware of cross-reactions that may occur and should strictly avoid the consumption of these alternative milks.

Avoiding Nutritional Deficit and Nutritional Status Alterations

Cow's milk is an important source of nutrients such as calcium, phosphorus, vitamin D, B_2, B_5, B_{12}, proteins, and lipids, and an inappropriate elimination of cow's milk could determine nutrient deficit and faltering growth.

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For breastfeeding mothers, the elimination of cow's milk and dairy products from their diet is crucial to prevent the transmission of allergenic proteins through breast milk. Mothers should receive supplements of calcium (1 g/day) and vitamin D [600 IU/day].

For infants with CMA who are not breastfed, substitute hypoallergenic formulas are recommended as suitable alternatives. These formulas provide the essential nutrients required for growth and development while minimizing the risk of allergic reactions. There is a relatively wide choice of nutritionally adequate formulas for CMA infants, differing by the protein source and the size of the peptides: Extensively hydrolyzed formula (HF) of whey or casein, plant-based formulas (hydrolyzed rice and soy protein formulas), and amino acid-based formula (AAF). The formula choice should be based on symptoms and age of the patient, on the nutritional composition, and on the allergy severity **(Flowchart 1)**. An extensive HF of whey or casein proteins should be the first choice. The use of an AAF is recommended as the first choice in patients with anaphylaxis, faltering growth, multiple and severe complex GI FA, acute and chronic severe FPIES, and EoE not responding to an extended exclusion diet to avoid any risk of sensitization and as the second choice in FA children presenting symptoms persistence within 2–4 weeks of using extensively HF. Formula based on soy protein could be chosen after the establishment of tolerance to soy protein for infants >6 months because of the risk of coallergy, who do not tolerate the extensive HF taste, or for its more affordability; formula based on rice protein may be considered in infants who refuse or do not tolerate extensively HF or in vegan families.

To avoid nutrient deficits in the first semester of life, calcium supplementation should be evaluated considering the amount and the composition of the hypoallergenic formula consumed. In the second semester, with the introduction of solid foods, the consumption of formula progressively decreases, and calcium supplementation could be required when the formula intake is <500 mL/day. Moreover, in CMA patients who do not reach immune tolerance within the first year of age, calcium supplementation should be considered for the entire duration of the exclusion diet. Since calcium absorption decreases from 30–40% to 10–15% in cases of vitamin D deficiency, both calcium and vitamin D should be supplemented. The supplementary dose of calcium can vary from 500 mg/day in infancy and toddlerhood to 1,000 mg/day or more during adolescence, remaining below the maximum tolerable dose according to the recommended intake per age. Regarding vitamin D supplementation, patients at risk for vitamin D deficiency had a daily requirement of 400–1,000 IU in the first years of life and 600–1,000 IU from 1 to 18 years.

Finally, close monitoring of the dietary intake of macro- and micronutrients and body growth is of pivotal importance during the nutritional counseling to prevent or correct nutritional status alterations and to promote a varied diet leading to normal feeding behavior. The nutritional follow-up through the evaluation of body growth parameters and relative percentiles/z-scores should be performed at 1, 2, and 4 months in the first semester of life and every 3 months in the second semester. After the first year, the anthropometric measurements should be performed every 6–12 months. The nutritional intake assessment should be performed at least once a year in CMA patients with normal growth or two or more times per year when patients present an alteration in the body growth pattern.

Active Diet Therapy

The traditional dietary management of CMA has changed in the last few years, moving from a passive approach based on the strict elimination diet of cow's milk to a proactive one, able to change the CMA course. The discovery of the pivotal role of selected dietary factors in influencing immune system development and function has introduced the "immunonutrition" concept. The application of the "immunonutrition" approach in the management of CMA paved the way to the concept of "active diet therapy," an integrated dietary strategy able to facilitate the acquisition of immune tolerance and prevent the occurrence of other atopic manifestations.

This strategy consists of an integrated, multistep approach. The first one is the continuation of breastfeeding if available. Mothers of breastfed CMA patients should avoid from their diet CMP-containing foods and should adopt an optimal adherence to a healthy dietary pattern, able to positively modulate the GM–immune system axis (e.g., the Mediterranean diet). When breast milk is unavailable, the choice of a substitute hypoallergenic formula should be based not only on allergenicity and nutritional features but also on the potential to modulate the natural history of the disease. Several evidences have reported that among hypoallergenic formulas, only the protein fraction derived from extensively hydrolyzed casein formula (EHCF) could activate several tolerogenic

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mechanisms, through at least in part an epigenetic regulation of gene expression, with a central role in the maintenance of immune homeostasis and tolerance.

When solid food introduction starts, other dietary strategies can be applied in formula- and breastfed CMA children. First of all, caregivers should be educated about the importance of a complementary feeding based on the Mediterranean diet for their children, considering the beneficial and antiallergic effects of this pattern. Then, the possibility to introduce processed foods containing CMP to stimulate immune tolerance acquisition represents a novel therapeutic approach that should be considered. Indeed, allergenic characteristics of proteins can change during food processing with a reduction of protein allergenicity. The "milk ladder" approach could be adopted both to promote the immune tolerance acquisition to cow's milk and to increase the diet variety and improve the patients' quality of life. This approach includes a step-by-step consumption of CMP, starting from fewer (baked) to more (fresh) allergenic forms of milk. The tolerance and introduction in the diet of foods containing milk could determine a better prognosis of CMA. Finally, the last stage of the "active diet therapy" is oral immunotherapy (OIT), which could be considered in older children (>4–5 years of age) with persistent CMA. This strategy provides the administration of increasing quantities of milk under medical supervision until achieving tolerance. Unfortunately, one of the main limiting steps of OIT is the high percentage of patients who cannot tolerate it, so the adjunctive use of biologics, such as omalizumab, that by improving OIT safety could be another promising strategy.

CONCLUSION

The prevalence and severity of pediatric CMA have increased dramatically in the last decades under the pressure of environmental factors in genetically predisposed individuals. Among environmental factors, nutrition plays a pivotal role. Diet is one of the most relevant modifiable factors, representing a potential target for the prevention and treatment of CMA. Indeed, immune system development and function could be modulated by an active diet strategy. This approach, modulating the GM composition, could influence the natural history and then the risk of developing other conditions later in life.

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The second edition of *Textbook of Pediatric Gastroenterology, Hepatology and Nutrition* highlights the significant advancements in the field of pediatric digestive and liver disorders. With expert contributions from both Indian and International Specialists, this expanded edition features 45 chapters—eight more than the original edition—offering in-depth coverage of key topics such as inflammatory bowel disease, neurogastroenterology, celiac disease, and cow's milk protein allergy. It also addresses recent developments in genetics, endoscopy, and liver transplantation. Thoughtfully crafted as both a trusted teaching resource and a practical reference, this edition is an essential guide for postgraduate students, general pediatricians, and pediatric gastroenterologists and hepatologists committed to enhancing pediatric care.



Anupam Sibal MBBS MD FIAP FIMSA FRCP(Lon) FRCP(Glas) FRCPCH FAAP set up the Pediatric Gastroenterology and Hepatology unit at Indraprastha Apollo Hospital, New Delhi (1997), the first in the private sector in India. He helped establish the first successful Liver Transplant Program in India in 1998. The Apollo Liver Transplant Unit has to its credit more than 4800 solid organ transplants including 595 in children. He has been serving as the Group Medical Director, Apollo Hospitals Group, since 2005. He served as the President, Global Association of Physicians of Indian Origin (GAPIO) from 2020 to 2022 and Member, Institute Body, Postgraduate Institute of Medical Education and Research, Chandigarh, India from 2009 to 2014. He edited the first edition of *Textbook in Pedaitric Gastroenterology, Hepatology and Nutrition*. He has to his credit 165 publications, 16 chapters, and more than 400 national and international lectures. He is the Author of the national bestseller, "*Is Your Child Ready to Face the World*"?



Sarath Gopalan MD (PGIMER, Chandigarh) Fellowship in Pediatric Gastroenterology and Clinical Nutrition (UK) MAMS FIAP is a practicing Pediatric Gastroenterologist and Hepatologist in New Delhi, India for the past 30 years. He is currently a Senior Consultant at the Madhukar Rainbow Children's Hospital, New Delhi. He graduated from the Madras Medical College, Chennai, Tamil Nadu, in 1986; completed his postgraduation in pediatrics from Postgraduate Institute of Medical Education and Research, Chandigarh; and subsequently pursued his Fellowship in Pediatric Gastroenterology and Clinical Nutrition from the Institute of Child Health, University of Birmingham, UK. He is currently a Member of the Nutrition Subcommittee of APPSPGHAN (Asian Pan Pacific Society of Pediatric Gastroenterology, Hepatology and Nutrition) and also the National President, Nutrition Society of India.

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