Nutritional Support in Paediatric Patients (1)  

Module 4.2  
Food Allergy:  
Prevention and Treatment - Cow’s Milk Allergy

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Learning Objectives

To discuss current evidence and recommendations on the prevalence, natural history, clinical manifestations, diagnosis, management, and prevention of cow’s milk allergy.

Contents

1. Introduction  
2. Definitions  
3. Prevalence  
4. Major allergens  
5. Natural history  
6. Clinical manifestations  
7. Diagnosis  
8. Management of cow’s milk allergy  
9. Oral tolerance induction  
10. Prevention of cow’s milk allergy  
11. Summary  
12. References

Key Messages

- Cow’s milk allergy (CMA) is a reproducible adverse reaction to a cow’s milk protein caused by immunological reactions;  
- In developed countries, the prevalence of confirmed CMA is approximately 0.5-3%;  
- The diagnostic approach includes performing a medical history, physical examination, diagnostic elimination diets, skin prick tests, specific IgE measurements, and oral food challenges;  
- Strict avoidance of the offending allergen is the only therapeutic option;
• Oral immunotherapy is being studied, but it is not yet recommended for routine clinical practice;
• For primary prevention of allergy, exclusive breastfeeding for at least 4 months and up to 6 months is desirable;
• Infants with a documented hereditary risk of allergy (i.e., an affected parent and/or sibling) who cannot be breastfed exclusively should receive a formula with confirmed reduced allergenicity, i.e., a partially or extensively hydrolyzed formula, as a means of preventing allergic reactions, primarily atopic dermatitis;
• Soy protein formulae have no role in the prevention of allergic disease;
• Complementary foods can be introduced between 4 and 6 months of age;
• Avoidance or delayed introduction of solid foods beyond 4-6 months for allergy prevention is not recommended.

1. Introduction

Cow’s milk allergy (CMA) is common in infants and children. A clear understanding of the various aspects of CMA, including its epidemiology, clinical manifestations, diagnosis, management, and primary prevention, is important for health care professionals involved in the care of children with food allergies.

The objective of this module is to summarize recent evidence on CMA. Preference was given to evidence and recommendations from scientific societies published in the last 9 years (2009-2018). Among them, there are documents focusing on food allergy in general or specifically on CMA. The first group includes documents developed by the US National Institute of Allergy and Infectious Diseases (NIAID, 2010) (1) or International Collaboration in Asthma, Allergy and Immunology (International Consensus ON, ICON, 2012) (2), and the European Academy of Allergy and Clinical Immunology (position paper: Food allergy and anaphylaxis guidelines, 2014) (63). The second group includes documents focusing specifically on CMA, and they were developed by the World Allergy Organization (WAO, 2010) (2), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, 2012) (3), and most recently, the British Society for Allergy and Clinical Immunology (BSACI, 2014) (4).

2. Definitions

The nomenclature of allergy varies. The terminology proposed by the European Academy of Allergology and Clinical Immunology, and later revised and updated by the World Allergy Organization, is currently used to ensure proper communication between health care professionals (1, 5, 6). For terms relevant to this module, see Table 1.
### Table 1

#### Allergy definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitization</td>
<td>A positive skin prick test and/or detectable specific IgE irrespective of the method or cut-off values and irrespective of clinical reactions.</td>
</tr>
<tr>
<td>Allergy</td>
<td>A hypersensitivity reaction initiated by specific immunologic mechanisms.</td>
</tr>
<tr>
<td>Food allergy</td>
<td>An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.</td>
</tr>
<tr>
<td>Cow’s milk allergy</td>
<td>A reproducible adverse reaction to a cow’s milk protein caused by immunological reactions.</td>
</tr>
<tr>
<td>Proven cow’s milk allergy</td>
<td>Cow’s milk allergy documented by controlled elimination/challenge procedures.</td>
</tr>
<tr>
<td>Non-allergenic hypersensitivity</td>
<td>An adverse reaction to milk that does not involve an immune mechanism. It is traditionally termed ‘cow’s milk intolerance’.</td>
</tr>
</tbody>
</table>

### 3. Prevalence

CMA is the most common cause of food allergy in infants and children. In developed countries, the prevalence of CMA in children is estimated to be approximately 0.5% to 3% (7, 8). In breastfed infants, the CMA prevalence is estimated to be 0.5% (9).

However, a recent systematic review concluded that the evidence for the prevalence of food allergy is greatly limited by a lack of uniformity of the criteria for making a diagnosis. Consequently, it remains unclear whether the prevalence is increasing (9), although some data suggest it (2).

### 4. Major Allergens

The major allergens of cow’s milk are 4 casein fraction proteins (αs1-, αs2-, β-, and κ-casein) and 2 whey proteins (α-lactalbumin and β-lactoglobulin) (10).

### 5. Natural History

CMA is frequently outgrown during childhood or adolescence, although data on the resolution of CMA vary. In general, the prognosis is better for non-IgE-mediated CMA, which is more likely to be transient. In contrast, IgE-mediated CMA is more likely to persist longer (5).

Children with highly elevated milk-specific IgE levels, multiple food allergies, and/or concomitant asthma and allergic rhinitis tend to have more persistent disease (5, 11). One recent study found that in children with CMA, low levels of IgE binding to cow’s milk and specific IgE binding to α-lactalbumin, β-lactoglobulin, κ-casein, and αs1-casein correlate with a greater likelihood of developing tolerance to cow’s milk (12). Another recent study evaluated which clinical and laboratory factors predict resolution of CMA within the first 5 years of life (13). The investigators concluded that milk-specific IgE levels, skin prick test results, and the severity of atopic dermatitis were predictors of CMA resolution. A web-based calculator to determine the prognosis of children with CMA is available at www.cofargroup.org. Validation studies are still needed (5).
6. Clinical Manifestations

CMA mainly affects children during the first 2 years of life. Affected children usually present with symptoms within the first 6 months of life. One review documented that most infants develop symptoms of CMA before 1 month of age, often within 1 week after the introduction of cow's milk proteins (9). Very rarely, the onset is after 12 months of age (5). Affected children have one or more symptoms, involving one or more organ systems.

Table 2 features characteristics of the four major categories of immune-mediated adverse food reactions. These are as follows: IgE-mediated, non-IgE-mediated, mixed, and cell-mediated reactions (1). Table 3 summarizes symptoms of food-induced allergic reactions.

Clinical features suggestive of IgE-mediated CMA include a combination of typical presenting symptoms such as urticaria and/or angioedema with vomiting and/or wheeze. IgE-mediated reactions generally occur immediately, within minutes to 2 hours after ingestion of cow's milk protein. Signs and symptoms most commonly involve the skin, then the gastrointestinal tract and, least frequently, the respiratory system or cardiovascular system. The spectrum of reactions ranges from mild (the majority) to life-threatening anaphylaxis (5, 14). The latter occurs rarely. However, cow's milk is one of the most common foods, in addition to peanuts and tree nuts, responsible for an anaphylactic reaction (15). Evidence of sensitization (presence of specific IgE) is typical (15).

Clinical features suggestive of non-IgE-mediated CMA include delayed reactions (beyond 2 hours after ingestion) that typically involve the gastrointestinal tract and/or skin (16). Non-IgE-mediated disorders include food protein-induced enterocolitis syndrome (entire gastrointestinal tract), food protein-induced enteropathy (small bowel), food protein-induced proctitis and proctocolitis (rectum and colon), coeliac disease, and food-induced pulmonary haemosiderosis (Heiner's syndrome) (15).

Clinical features of mixed IgE- and non-IgE-mediated reactions, with either humoral and/or cell-mediated mechanisms, also typically involve the gastrointestinal tract and/or skin, and they include atopic dermatitis (eczema) and allergic eosinophilic gastrointestinal disorders.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Disorder</th>
<th>Key features</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-mediated (acute onset)</td>
<td>Urticaria/angioedema</td>
<td>Triggered by ingestion or direct skin contact (contact urticaria); food commonly causes acute (20%) but rarely chronic (2%) urticaria</td>
<td>SPT and/or sIgE measurement</td>
</tr>
<tr>
<td>Oral allergy syndrome (pollen associated, food allergy syndrome)</td>
<td>Pruritus, mild oedema confined to oral cavity; uncommonly progresses beyond mouth (~7%) or to anaphylaxis (1% to 2%); might increase after pollen season</td>
<td>SPT and/or sIgE measurement Fresh (raw food) prick-prick testing</td>
<td></td>
</tr>
<tr>
<td>Rhinitis, asthma</td>
<td>Symptoms might accompany a food-induced allergic reaction but rarely an isolated or chronic symptom; might also be triggered by inhalation of aerosolized food protein</td>
<td>SPT and/or sIgE measurement</td>
<td></td>
</tr>
<tr>
<td>Immediate gastrointestinal</td>
<td>Immediate isolated vomiting (more often, gastrointestinal symptoms are</td>
<td>SPT and/or sIgE measurement</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Associated with anaphylaxis</td>
<td>Anaphylaxis</td>
<td>Rapidly progressive, multiple organ system reaction can include cardiovascular collapse</td>
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<tr>
<td>-----------------</td>
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<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Delayed food-induced anaphylaxis to mammalian meats</td>
<td>Several-hour delay after ingestion</td>
<td>Serum test for IgE to α-Gal</td>
<td>SPT and/or sIgE measurement</td>
</tr>
<tr>
<td>Food-associated, exercise-induced anaphylaxis</td>
<td>Food triggers anaphylaxis only if ingestion followed temporally by exercise</td>
<td>SPT and/or sIgE measurement</td>
<td>Component testing Exercise test (might be poorly reproducible)</td>
</tr>
<tr>
<td>Mixed IgE antibody-associated/cell-mediated (delayed-onset/chronic)</td>
<td>Atopic dermatitis</td>
<td>Associated with food in ~35% of children with moderate-to-severe rash</td>
<td>SPT and/or sIgE measurement</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic gastrointestinalopathies</td>
<td>Symptoms vary with site(s)/degree of eosinophilic inflammation. Oesophageal: dysphagia, pain. Generalized: ascites, weight loss, oedema, obstruction</td>
<td>Empiric diets</td>
</tr>
<tr>
<td></td>
<td>Food protein-induced enterocolitis syndrome</td>
<td>Primarily affects infants Chronic exposure: emesis, diarrhoea, poor growth, lethargy Re-exposure after restriction: emesis, diarrhoea, hypotension (15%) 2 hours after ingestion</td>
<td>SPT and/or sIgE measurements are typically negative but can become positive APTs not helpful</td>
</tr>
<tr>
<td></td>
<td>Food protein-induced allergic proctocolitis</td>
<td>Mucus-laden bloody stools in infants</td>
<td>Empiric diets</td>
</tr>
<tr>
<td></td>
<td>Heiner syndrome</td>
<td>Rare disorder; pulmonary infiltrates, upper respiratory tract symptoms, failure to thrive, iron deficiency anaemia</td>
<td>No evidence of IgE; might have precipitating milk-specific IgG antibodies</td>
</tr>
<tr>
<td></td>
<td>Coeliac disease</td>
<td>Autoimmune disorder leading to enteropathy and malabsorption; occurs in persons with a genetic disposition and is triggered by gliadin, a gluten protein found in wheat and related grains</td>
<td>Serologies (while ingesting wheat including IgA against tissue transglutaminase, gliadin), HLA typing (for DQ2/DQ8), and biopsies</td>
</tr>
<tr>
<td></td>
<td>Cell-mediated allergic contact dermatitis</td>
<td>A form of eczema in response to chemical haptens that are additives or naturally occurring in foods</td>
<td></td>
</tr>
</tbody>
</table>

APT, atopy patch test; sIgE, specific IgE; SPT, skin prick test
<table>
<thead>
<tr>
<th>Target organ</th>
<th>Immediate symptoms</th>
<th>Delayed symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Erythema</td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Morbilliform eruption</td>
<td>Morbilliform eruption</td>
</tr>
<tr>
<td></td>
<td>Angiooedema</td>
<td>Angiooedema</td>
</tr>
<tr>
<td></td>
<td>Eczematous rash</td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>Pruritus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conjunctival erythema</td>
<td>Conjunctival erythema</td>
</tr>
<tr>
<td></td>
<td>Tearing</td>
<td>Tearing</td>
</tr>
<tr>
<td></td>
<td>Periorbital oedema</td>
<td>Periorbital oedema</td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>Nasal congestion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rhinorrhoea</td>
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</tr>
<tr>
<td></td>
<td>Sneezing</td>
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<tr>
<td></td>
<td>Laryngeal oedema</td>
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</tr>
<tr>
<td></td>
<td>Hoarseness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry staccato cough</td>
<td></td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>Cough</td>
<td>Cough, dyspnoea, and wheezing</td>
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<tr>
<td></td>
<td>Chest tightness</td>
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<tr>
<td></td>
<td>Dyspnoea</td>
<td></td>
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<tr>
<td></td>
<td>Wheezing</td>
<td></td>
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<tr>
<td></td>
<td>Intercostal retraction</td>
<td></td>
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<tr>
<td></td>
<td>Accessory muscle use</td>
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<tr>
<td>Gastrointestinal (oral)</td>
<td>Angiooedema of lips, tongue, or palate</td>
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</tr>
<tr>
<td></td>
<td>Oral pruritus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tongue swelling</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal (lower)</td>
<td>Nausea</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Colicky abdominal pain</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Reflux</td>
<td>Reflux</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>Diarrhoea</td>
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<tr>
<td></td>
<td></td>
<td>Haematochezia</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Cardiovascular</td>
<td>Tachycardia (occasionally bradycardia in anaphylaxis)</td>
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<tr>
<td></td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
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<tr>
<td></td>
<td>Fainting</td>
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<tr>
<td></td>
<td>Loss of consciousness</td>
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</tr>
<tr>
<td>Miscellaneous</td>
<td>Uterine contractions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sense of “impending doom”</td>
<td></td>
</tr>
</tbody>
</table>

### 7. Diagnosis

Algorithms for the evaluation of infants and children presenting with symptoms suggestive of CMA have been developed by a number of organizations, including ESPGHAN (Fig. 1). A comparison of the diagnostic approaches proposed by various organizations is presented in Table 4.
In all cases of suspected CMA, performing a medical history, physical examination, diagnostic elimination diets, skin prick tests (SPTs), specific IgE (sIgE) measurements, and oral food challenges are central (1, 3, 4, 15). An open or single-blind challenge is often sufficient, depending on the patient’s history, age, symptoms, etc. However, performing a double-blind, placebo-controlled, oral food challenge remains the gold standard for diagnosis of food allergy (17). In order to standardize the procedures, standards for office-based oral food challenges (18), as well as for double-blind, placebo-controlled, oral food challenges, have been published (19). One recent systematic review investigated the accuracy of tests used to diagnose food allergy. It was concluded that the evidence base is limited, and thus, interpretation is difficult (20). Overall, the SPT and sIgE measurements appear sensitive, although not specific, for diagnosing IgE-mediated food allergy. For cows’ milk allergy:

- APT – sensitivity 53% (33 to 72); specificity 88% (76 to 95)
- SPT – sensitivity 88% (76 to 94); specificity 68% (56 to 77)
- sIgE – sensitivity 87% (75 to 94); specificity 48% (36 to 59)

In contrast to IgE-mediated CMA, diagnostic tests for non-IgE-mediated manifestations of CMA are limited. The diagnosis is mostly reliant on the clinical history, physical examination, and results of the elimination diet with subsequent milk reintroduction. The latter is the diagnostic gold standard (5). Screening tests, such as skin prick tests, specific IgE tests, and atopy patch tests, have been shown to lack specificity and sensitivity (1).

**Tests not recommended.** Tests such as Vega (electrodermal) testing, cytotoxic testing, iridology, kinesiology, food-specific IgG testing, pulse testing, and hair analysis are not recommended for allergy diagnosis (due to the lack of scientific rationale and the lack of reliability and reproducibility) (5, 21).

![Fig. 1. Algorithm for children with symptoms suggestive of cow’s milk allergy recommended by ESPGHAN (5).](image)
Table 4
Cow’s milk allergy. Comparison of diagnostic approaches recommended by various organizations

<table>
<thead>
<tr>
<th></th>
<th>WAO 2010(3)</th>
<th>ESPGHAN 2012 (4)</th>
<th>BSACI 2014 (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target audience</strong></td>
<td>Physicians everywhere</td>
<td>Practical guidelines (audience not specified)</td>
<td>Clinicians in secondary and tertiary care</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Oral food challenge (OFC)</strong></td>
<td>Yes</td>
<td>The diagnosis of CMA starts with suspicion and ends with an OFC.</td>
<td>Yes</td>
</tr>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specific IgE</strong></td>
<td>See Table 5</td>
<td>Useful diagnostic test (at any age)*</td>
<td>slgE levels ≥0.35 kU/L have been used to support a clinical diagnosis</td>
</tr>
<tr>
<td><strong>Skin prick test (SPT)</strong></td>
<td>See Table 5</td>
<td>Useful diagnostic test (at any age)*</td>
<td>Weal size ≥5 mm (≥2 mm in younger infants) is strongly predictive of CMA</td>
</tr>
<tr>
<td><strong>Total IgE</strong></td>
<td>Not addressed</td>
<td>No benefit over specific IgE</td>
<td>Not addressed</td>
</tr>
<tr>
<td><strong>Atopy patch test</strong></td>
<td>Not specifically addressed</td>
<td>Not recommended (outside research setting)</td>
<td>Not addressed</td>
</tr>
<tr>
<td><strong>Intradermal tests</strong></td>
<td>Not addressed</td>
<td>Should not be performed</td>
<td>Not addressed</td>
</tr>
<tr>
<td><strong>Specific IgG/IgG subclass antibodies against CMP</strong></td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Other unorthodox tests</strong></td>
<td>Not addressed</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

* Combination of specific IgE and skin prick test is not necessary

** Examples include basophil histamine release/activation, lymphocyte stimulation, mediator release assay, facial thermography, gastric juice analysis, hair analysis, applied kinesiology, provocation neutralization, cytotoxicity assay, and electrodermal testing.
### Table 5
Tests for specific IgE and skin prick tests in various settings and in different patients (3)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Specific IgE</th>
<th>Skin prick test</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFC done routinely in all patients suspected of IgE-mediated CMA</td>
<td>No need to test for specific IgE. OFC only.</td>
<td>No need for SPT. OFC only.</td>
</tr>
<tr>
<td>OFC is not a requirement; high pretest probability of IgE-mediated CMA</td>
<td>Test for specific IgE using a threshold of ≥0.7 IU/L. If IgE level is ≥0.7 IU/L, OFC may be avoided.</td>
<td>Perform SPT. Cut-off value of ≥3 mm. If SPT ≥3 mm, OFC may be avoided.</td>
</tr>
<tr>
<td>OFC is not a requirement; an average pretest probability of IgE-mediated CMA</td>
<td>Do not test for specific IgE. Perform OFC only.</td>
<td>Perform SPT. Cut-off value of ≥3 mm. If SPT ≥3 mm, OFC may be avoided.</td>
</tr>
<tr>
<td>OFC is not a requirement; low pretest probability of IgE-mediated CMA</td>
<td>Test food-specific IgE level using a threshold of ≥0.35 IU/L. If IgE level is &lt;0.35 IU/L, avoid OFC.</td>
<td>Perform SPT. Cut-off value of ≥3 mm. If SPT&lt;3 mm, avoid OFC.</td>
</tr>
</tbody>
</table>

CMA, cow's milk allergy; OFC, oral food challenge; SPT, skin prick test.

### 8. Management of Cow’s Milk Allergy

Currently, the cornerstone of management of CMA is the strict avoidance of offending food antigens (22).

For breastfed infants, mothers should be advised to continue breastfeeding while avoiding consumption of dairy products. The mother will require calcium supplements while on a dairy-free diet (3, 4, 5).

For non-breastfed infants, milk substitutes are available. Standards have been developed for the composition of the milk substitutes. These substitutes are as follows:

- Extensively hydrolyzed formula of cow’s milk protein
- Amino acid formula
- Soy formula
- Rice extensively hydrolyzed formula
- Soy hydrolyzed formula

The choice of the milk substitute depends on the patient’s age, severity of symptoms, and the nutritional value of the milk substitute. In general, the recommendations made by scientific organizations with regard to available substitutes are consistent and are highlighted below.

- **Extensively hydrolyzed formulas**
  - The American Academy of Pediatrics defines extensively hydrolyzed formulae as those containing only oligopeptides that have a molecular weight <3000 Da (39).
  - Extensively hydrolyzed formulas may be used in children with CMA.

- **Amino acid formulas**
  - The formulas contain free amino acids as the only nitrogen source.
Amino acid formulas may be used as first-line treatment for CMA, but their high cost is a limiting factor.

As per BSACI recommendations (5), amino acid formulas are usually used in infants with 1) multiple food allergies; 2) severe CMA; 3) allergic symptoms or severe atopic eczema when exclusively breastfed; 4) severe forms of non-IgE-mediated CMA, such as eosinophilic oesophagitis, enteropathies, and food protein induced enterocolitis syndrome (FPIES); 5) faltering growth; and 6) reactions to or refusal to take extensively hydrolyzed formula who are at nutritional risk.

- **Soy formulas**
  - Soy formulas should not be used in infants with food allergy during the first 6 months of life.
  - If soy protein formulas are considered for therapeutic use in patients with food allergy after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.

- **Amino acid formula vs. extensively hydrolyzed whey or casein formula**
  - In children with IgE-mediated CMA at high risk of anaphylactic reactions (prior history of anaphylaxis and currently not using extensively hydrolyzed milk formula), the use of amino acid formula rather than extensively hydrolyzed formula is recommended.
  - In children with IgE-mediated CMA at low risk of anaphylactic reactions (no prior history of anaphylaxis or currently on extensively hydrolyzed milk formula), the use of an extensively hydrolyzed milk formula rather than an amino acid formula is recommended.

- **Extensively hydrolyzed whey or casein formula vs. soy formula**
  - In children with IgE-mediated CMA, the use of extensively hydrolyzed milk formula rather than soy formula is recommended. However, soy formula should anyway not be used during the first 6 months of life.

- **Extensively hydrolyzed whey or casein formula vs. extensively hydrolyzed rice formula**
  - In children with IgE-mediated CMA, the use of extensively hydrolyzed milk formula rather than extensively hydrolyzed rice formula is recommended (one reason is the much wider availability of the former). New data on extensively hydrolyzed rice protein-based formula compared with extensively hydrolyzed cow’s milk protein-based formula are now available (23).

- **Soy formula vs. extensively hydrolyzed rice formula**
  - More research is needed.

- **Partially hydrolyzed formula**
  - The American Academy of Pediatrics defines partially hydrolyzed formulas as those containing reduced oligopeptides that have a molecular weight generally of <5000 Da (39).
  - Partially hydrolyzed formulas should not be used for the treatment of suspected or proven CMA or for the diagnostic exclusion diet.
Other milks. Children with CMA should not be fed preparations based on unmodified milk of other mammalian species (such as sheep, buffalo, horse, or goat milk) or unmodified soy or rice milk because of a high rate of possible allergic cross-reactivity and insufficient nutritional value (3). Similarly, ‘milk beverages’, such as those based on almond, coconut, hazelnut, oat, potato, rice, or soya, are not recommended because of their nutritional inadequacy. Compared with cow’s milk, most of them are low in energy and extremely low in protein (5).

Need for calcium. If a suitable milk substitute is used in an adequate amount, further supplementation may not be needed. In other circumstances, children should be assessed for mineral and/or vitamin deficiencies. Calcium supplementation (also phosphorus and vitamin D) is necessary. In general, if dairy intake is below 500 ml, assessment by a dietitian is recommended (5).

Growth and nutritional concerns. If not adequately monitored, exclusion diets may lead to nutritional deficiencies and poor growth (24). Comorbidities such as atopic dermatitis or feeding difficulties due to eosinophilic oesophagitis may further contribute to inadequate nutrient intake. Considering these concerns, scientific organizations recommend use of an age-appropriate milk substitute in children younger than 2 years of age and food counselling.

Duration of milk exclusion diet. Children with CMA on a milk exclusion diet should be re-assessed every 6-12 months from 12 months of age to assess for the possibility of reintroduction of cow’s milk. The BSACI proposed as a guide a ‘milk ladder’, i.e., the classification of cow’s milk ranging from less allergenic (to be offered initially) to more allergenic (5). In brief, reintroduction should start with baked milk products, as baking (or thermal processing) reduces allergenicity. More allergenic products such as uncooked cheese and cow’s milk are only recommended for use in subjects who have achieved full tolerance to baked milk products.

Management of anaphylaxis. One recent systematic review found no robust studies investigating the effectiveness of adrenaline (epinephrine), H1-antihistamines, systemic glucocorticosteroids, or methylxanthines in the management of anaphylaxis (25).

Even if the evidence is limited, the first-line treatment for anaphylaxis is epinephrine (both in the outpatient setting [autoinjector] or in a hospital setting). Other medications used in the management of anaphylaxis include antihistamines or anti-inflammatory drugs (systemic or topical steroids) (23). The latter are the main therapy in cases of eosinophilic oesophagitis or gastroenteritis in which dietary restriction was not feasible or had failed to improve the disease (26).

Probiotics. The WAO and the EAACI recently concluded that no single probiotic supplement or class of supplements has been demonstrated to influence the course of any allergic manifestation or long-term disease efficiently, or to be sufficient to do so (27, 64).

One randomized controlled trial (RCT) published subsequently to the WAO document found that the addition of Lactobacillus rhamnosus GG (LGG) to the therapeutic formula has an impact on acquisition of tolerance. In this RCT, otherwise healthy infants with CMA were randomly assigned to receive extensively hydrolyzed casein formula (n = 55),
extensively hydrolyzed casein formula with LGG (n = 71), hydrolyzed rice formula (n = 46), soy formula (n = 55), or amino acid–based formula (n = 33). Oral food challenges were performed after 12 months to assess acquisition of tolerance. The rate of tolerance after 12 months was significantly higher in the groups receiving extensively hydrolyzed casein formula (43.6%) or extensively hydrolyzed casein formula with LGG (78.9%) compared with the other groups: hydrolyzed rice formula (32.6%), soy formula (23.6%), and amino acid–based formula (18.2%). Repeat studies are needed.

9. Oral Tolerance Induction

A number of experimental strategies for managing IgE-mediated food allergy are currently being investigated. The best studied is oral tolerance induction as a treatment option in subjects who do not outgrow their allergy. Two recent meta-analyses of RCTs (one of them additionally included observational studies) on oral immunotherapy for IgE-mediated CMA showed that oral immunotherapy, compared to use of an elimination diet alone, increased the likelihood of achieving full tolerance to cow's milk (desensitization). However, the development of long-term tolerance was unlikely (29, 30). One limitation of oral immunotherapy is an increased risk of adverse effects, although they are mostly mild and self-limiting. Moreover, currently, there are no standardized protocols, which further limits the routine clinical use of oral immunotherapy. One form of oral immunotherapy is the use of extensively heated milk (also egg) protein. Recent studies involving children reacting to unheated milk (or egg) documented that they tolerate extensively heated (baked) milk products (31, 32). It has been suggested that an oral challenge to extensively heated milk may be considered in children with CMA (under physician supervision). However, studies with baked-milk products are still limited, and guidelines do not recommend them for routine use in clinical practice.

10. Prevention of Cow’s Milk Allergy

Diet during pregnancy or lactation
Currently, specific allergen avoidance is not recommended (15, 33). However, the role of diet during pregnancy and lactation remains unclear, and data remain conflicting (mainly with regard to the role of peanut intake during pregnancy) (34, 35). Use of an elimination diet during pregnancy may have unfavourable effects on maternal and/or fetal nutrition.

Breastfeeding
Exclusive breastfeeding may help to prevent allergic disease by decreasing exposure to exogenous antigens, protecting against infections, promoting gastrointestinal mucosal maturation and the development of gut microbiota, and conferring immunomodulatory and anti-inflammatory benefits (36). Overall, the evidence on the effects of breastfeeding is inconsistent, showing a protective effect, no effect, or even a predisposing effect (37). These inconsistent results do not mean that breastfeeding does not have a significant effect. Rather, these inconsistencies likely reflect a variety of methodological problems associated with investigating breastfeeding in studies. These problems include an inability to randomize and blind; the retrospective design of many studies and the potential for parental recall bias; imprecise definitions of the intervention with no clear distinction between ‘exclusive breastfeeding’
and ‘any breastfeeding’; the lack of strict diagnostic criteria for allergic diseases; and, finally, reverse causation. Despite the controversy, experts agree that even if breastfeeding does not provide a strong protective effect, it should be promoted for its nutritional, immunological, and psychological benefits. Exclusive breastfeeding for at least 4 months, but preferentially up to 6 months, is recommended (34, 38).

**Dietary products with reduced allergenicity**

- **Hydrolyzed formula**
  One recent overview of reviews followed by a systematic review of subsequently published trials concluded that certain extensively hydrolyzed casein formulas and certain partially hydrolyzed whey formulas are appropriate for reducing the risk of allergy in infants at high risk when formula feeding is initiated. Thus, in high-risk infants, when breastfeeding is not possible, hydrolysates of documented safety and efficacy have an indication for infant feeding up to the age of 4 to 6 months (39). Current recommendations also agree that infants with a documented hereditary risk of allergy (i.e., an affected parent and/or sibling) who cannot be breastfed exclusively should receive a formula with confirmed reduced allergenicity, i.e., a partially or extensively hydrolyzed formula, as a means of preventing allergic reactions, primarily atopic dermatitis (1, 40).

- **Soy protein formula**
  One meta-analysis of 3 RCTs found that in infants at high risk of allergy who were unable to be completely breastfed, feeding with soy formula compared to cow’s milk formula did not reduce the risk of allergies in later infancy and childhood (41). Soy protein formulae have no role in the prevention of allergic diseases (42, 43).

- **Amino acid-based formula**
  There are no studies on the consumption of amino acid-based formulae for allergy prevention.

**Timing of introduction of complementary food**

Earlier guidelines that recommended extended avoidance/delayed introduction of solid foods, specifically of potentially allergenic foods, are being replaced by guidelines recommending early exposure.

No effect of the delayed introduction of solid foods on the prevalence of food allergies has been suggested by the results of a number of prospective birth cohort studies (e.g., GINI Study (44), LISA Study (45), KOALA Study (46), Generation R Study) (47). A population-based, cross-sectional study, which involved 2589 infants, found that the introduction of cooked eggs at 4 to 6 months might protect against egg allergy at the age of 1 year, irrespective of eczema status. These findings represented the first clear evidence to support a paradigm shift in infant feeding by challenging the notion that delaying egg introduction might protect against egg allergy.

Current recommendations from the scientific societies agree that there is no convincing scientific evidence that the avoidance or delayed introduction of potentially allergenic foods (e.g., cow’s milk protein [except for whole cow’s milk], eggs, peanuts, tree nuts, fish, and seafood) beyond 4-6 months reduces allergies in infants considered to be at increased risk for the development of allergic diseases or in those not considered to be at increased risk.
Recently, several intervention trials, e.g. LEAP (Learning Early About Peanut Allergy; www.leapstudy.co.uk), LEAP-On, EAT (Enquiring About Tolerance; www.eatstudy.co.uk) have shown another light on food allergy prevention (64, 65, 66). Waiting for more formal guidelines the WAO and nine other scientific societies jointly published a Consensus Communication highlighting the necessity to support early peanut introduction in at risk infants (67). The approach to the introduction of other solids remains open to evaluation. More extensive guidelines will be announced in the near future from the NIAID expert panel on food allergy and EAACI Guidelines Group (69).

**Probiotics and/or prebiotics**

It has been suggested that improved hygiene and the reduced exposure of the immune system to microbial stimuli early in childhood contribute to the rising number of allergic disorders worldwide (48).

There are differences in the neonatal gut microbiota that may precede or coincide with the early development of atopy. Atopic subjects have more clostridia and tend to have fewer bifidobacteria than non-atopic subjects (49). There is evidence suggesting a crucial role for a balanced commensal gut microbiota in the maturation of the early immune system.

A number of recent meta-analyses have suggested that probiotics are effective in preventing eczema, particularly if the probiotics are administered both pre- and postnatally (50, 51, 52). However, one major limitation of all of these meta-analyses is that all of them pooled data obtained from different probiotic strains, with no analyses based on individual probiotic strains. Based on a qualitative and narrative review, the World Allergy Organization recently concluded that probiotics do not have an established role in the prevention of allergy (28). Like probiotics, prebiotics and synbiotics may potentially affect the development and severity of allergic disease (53, 54, 55). However, evidence regarding these products is even more limited.

**Long-chain polyunsaturated fatty acids (LCPUFA)**

It has been hypothesized that the low consumption of n-3 LCPUFA (e.g. oily fish), typical of the diet in many Westernized countries, results in reduced maternal consumption of n-3 LCPUFA, favours more proinflammatory n-6 LCPUFA, and contributes to the development of allergy and asthma (56).

Epidemiological studies do suggest an association between the intake of fish oil and a reduced risk of allergy (57).

In contrast to the epidemiological data, a meta-analysis (search date: 2008) of 10 publications (representing 6 RCTs) found no clear evidence of a benefit with regard to reducing the risk of allergic sensitization or developing a favourable immunological profile with use of n-3 or n-6 LCPUFA (58).

More recent evidence suggests that the timing of the intervention may play an important role. The Docosahexaenoic Acid to Optimise Mother Infant Outcome (DOMInO) randomized controlled trial found that while maternal n-3 LCPUFA supplementation (900 mg/day) during pregnancy did not reduce the overall incidence of IgE-associated allergies in the offspring’s first year of life, it reduced the risk of atopic eczema and egg sensitization (59).

In contrast, n-3 LCPUFA supplementation carried out exclusively during the postnatal period demonstrated mixed results, with one trial showing no effect (60) and another suggesting only a transient effect on symptoms of respiratory disease (61). Further research is needed to establish the optimal timing of n-3 LCPUFA supplementation and its long-term effects.
Other nutritional interventions
A recent systematic review and meta-analysis of observational trials (no RCTs were identified) concluded that although the evidence is weak, it is nevertheless supportive with respect to the consumption of vitamins A, D, and E; zinc; fruit and vegetables; and a Mediterranean diet for the prevention of atopic disease, namely asthma (62). For LCPUFA, vitamins, and other micronutrients used for allergy prevention, no specific recommendations exist and further studies are needed.

11. Summary
This module reviews current recommendations regarding CMA, the most common food allergy in young children. The diagnostic approach includes performing a medical history, physical examination, diagnostic elimination diets, skin prick tests, specific IgE measurements, and oral food challenges. Strict avoidance of the offending allergen is the only therapeutic option. Oral immunotherapy is being studied, but it is not yet recommended for routine clinical practice. For primary prevention of allergy, exclusive breastfeeding for at least 4 months and up to 6 months is desirable. Infants with a documented hereditary risk of allergy (i.e., an affected parent and/or sibling) who cannot be breastfed exclusively should receive a formula with confirmed reduced allergenicity, i.e., a partially or extensively hydrolyzed formula, as a means of preventing allergic reactions, primarily atopic dermatitis. Avoidance or delayed introduction of solid foods beyond 4-6 months for allergy prevention is not recommended.
12. References


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