

Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA): A summary report

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The 2nd Milan Meeting on Adverse Reactions to Bovine Proteins was the venue for the presentation of the first consensus-based approach to the management of cow's milk allergy. It was also the first time that the Grading of Recommendations, Assessments, Development, and Evaluation approach for formulating guidelines and recommendations was applied to the field of food allergy. In this report we present the contributions in allergen science, epidemiology, natural history,

evidence-based diagnosis, and therapy synthesized in the World Allergy Organization Diagnosis and Rationale for Action against Cow's Milk Allergy guidelines and presented during the meeting. A consensus emerged between discussants that cow's milk allergy management should reflect not only basic research but also a newer and better appraisal of the literature in the light of the values and preferences shared by patients and their caregivers in partnership. In the field of diagnosis, atopy patch testing and microarray technology have not yet evolved for use outside the research setting. With foreseeable breakthroughs (eg, immunotherapy and molecular diagnosis) in the offing, the step ahead in leadership can only stem from a worldwide organization implementing consensus-based clinical practice guidelines to diffuse and share clinical knowledge. (J Allergy Clin Immunol 2010;126:1119-28.)

Key words: Cow's milk allergy, epidemiology, amino acid formula, hydrolyzed milk formula, soy formula, hydrolyzed rice formula, skin prick test, specific IgE, oral immunotherapy, Grading of Recommendations, Assessments, Development, and Evaluation approach

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The World Allergy Organization's (WAO) Food Allergy Special Committee's Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines were presented during the 2nd Meeting on Adverse Reactions to Bovine Proteins in Milan, Italy, on February 4 and 5, 2010. Because current recommendations in Europe and the United States are a decade old,^{1,2} diagnosis and treatment of cow's milk allergy (CMA) practice guidelines were in need of a reappraisal reflecting recent literature.³ DRACMA encompasses recommendations for the diagnosis and treatment of IgE-mediated CMA.⁴ The full set is available in Boxes E1 and E2 (available in this article's Online Repository at www.jacionline.org),³ and selected conclusions are included in this report.

The DRACMA guidelines are the fruit of a 2-year WAO commitment targeted toward an audience of allergists, general practitioners, pediatricians, gastroenterologists, dermatologists, and nutrition and food chemistry specialists. Patient advocacy and industry focus groups and physicians and their charges, all stakeholders in DRACMA, are invited to participate in its implementation through professional bodies, through the soon-to-be posted dedicated DRACMA pages on the WAO Web site (>3.6 million hits in 2009), or both.⁵

Abbreviations used

AD:	Atopic dermatitis
CMA:	Cow's milk allergy
DRACMA:	Diagnosis and Rationale for Action against Cow's Milk Allergy
GRADE:	Grading of Recommendations, Assessments, Development, and Evaluation
OFC:	Oral food challenge
OIT:	Oral immunotherapy
PICO:	Patient Intervention Comparison Outcome
sIgE:	Specific IgE
SPT:	Skin prick test
WAO:	World Allergy Organization

CMA: BASIC SCIENCE

Proteins involved in CMA

Cow's milk contains approximately 20 potentially sensitizing proteins (some recognized as major allergens), which are found in the whey and casein fractions, including α -lactalbumin (Bos d 4), β -lactoglobulin (Bos d 5), BSA (Bos d 6), bovine immunoglobulins (Bos d 7), and casein allergens (Bos d 8)^{6,7} collectively (see Table E1 in this article's Online Repository at www.jacionline.org). The comparative electrophoretic profiles of other genera and species are shown in Fig E1 (available in this article's Online Repository at www.jacionline.org). The effect of industrial processing (pasteurization, ultra-high-temperature heating, or dry blending for cow's milk formula) on the antigenic/allergenic properties of cow's milk proteins is minimal or absent.⁸ However, according to 1 study, up to 70% of children might tolerate milk in baked products,⁹ potentially improving their quality of life.¹⁰ Higher temperatures and longer exposure to heat in baking might account for this. For choosing an alternative to cow's milk, potential cross-reactivity (caused by protein sequence homology between related species) should be considered of clinical relevance. At present, cross-reactivity cannot be ruled in or out by species phylogeny, although conserved protein sequences are often cross-reactive (see Table E2 in this article's Online Repository at www.jacionline.org).^{11,12} Alternatives from other mammals (eg, mare and camel) should be clinically evaluated for suitability from a nutritional and allergy point of view.

Epidemiology of CMA

Food allergy was reported by 40% of 5- to 16-year-olds but confirmed by challenge in only 5% of cases.¹³ In a European telephone survey of more than 44,000 contacts, 5 million claimed to be allergic to milk. Adult women were making most of these claims. Milk was the food most often reported by or for children (38.5%) and was the second most often implicated food in adults (26%).¹⁴ Challenge-based studies remain the exception rather than the rule.¹⁵ More than 20 studies have dealt with self-perceived or parentally perceived CMA over the last 20 years in preschoolers,¹⁶⁻²⁵ school-aged children (5-16 years),^{13,26-29} and young adults.³⁰⁻³⁶ Self-report prevalence varies between 1% and 17.5% in preschoolers, 1% and 13.5% in 5- to 16-year-olds, and 1% and 4% in adults (see Fig E2 in this article's Online Repository at www.jacionline.org). CMA peaks during the first year of life and tends to subside later in a temporal pattern that appears unique among food allergies.³⁷⁻⁴¹ Sensitization surveys in the general population are few (see Fig E3 in this article's Online Repository

at www.jacionline.org).^{15,17,19,20,22,34,42} The Isle of Wight birth cohort tested 543 children at 1, 2, and 3 years of age and found 0.37% of infants, 0.92% of 2-year-olds, and 0.55% of 3-year-olds to be sensitized to cow's milk.⁴³ In the German Multicentre Allergy Study sensitization decreased from 4% at 2 years to 1% at 10 years.⁴⁴ In cross-sectional studies a CMA prevalence of 0.6% to 2.5% of preschoolers, 0.3% of older children and teens, and less than 0.5% of adults is reported (see Fig E2).^{20,45-47} Geographic differences, blinding (still rare), and method of standardization remain unmet needs of epidemiologic research, as are high-quality, challenge-controlled, community surveys (see the section on diagnosis).⁴⁸ On the whole, rates of CMA, in line with other food allergies, seem to be on the increase.^{49,50}

Pathogenesis of CMA: IgE and non-IgE mediated

CMA presents in 3 clusters of immune mechanisms. The IgE-mediated forms are characterized by acute onset and involve 1 or more target organs, such as the skin (urticaria and angioedema), the respiratory system (rhinoconjunctivitis and asthma), and the gastrointestinal tract (nausea, vomiting, and diarrhea). The cell-mediated, non-IgE forms are of delayed or chronic onset, with enterocolitis and proctocolitis as frequent clinical presentations (Table I).^{3,51-77} A "mixed" IgE and non-IgE setting, also with a delayed or chronic onset, might present as atopic dermatitis (AD) or as one of the eosinophilic gastroenteropathies (CMA phenotypes).

In common with other food allergies, genetic predisposition, infections, and intestinal microflora alteration, as well as age at first exposure, maternal diet, antigen transmission through breast milk, and the nature, quantity, and frequency of antigen load, are factors promoting oral tolerance or sensitization to cow's milk.⁷⁸ The integrity of the intestinal epithelial barrier, which controls allergen load to the immunocompetent cells of the mucosa-associated immune system, plays a key role in the onset of both IgE- and non-IgE-mediated forms. The delicate balance between oral tolerance and hypersensitivity is regulated by active immune mechanisms involving specialized regulatory T cells.⁷⁹ Serum milk-specific IgG antibodies and T cells have been reported in the Peyer patches of healthy infants,⁸⁰ as has an antigen-specific suppression of cellular or humoral responses after oral exposure.⁸¹ Cell-mediated CMA has been far less studied than IgE-mediated forms. Polarization of T cells specific for cow's milk toward the T_H2 phenotype has been reported with IgE-mediated CMA; in contrast, a T_H1-skewed type of response mediates non-IgE-mediated CMA in children. T-cell clones from children with acute IgE-mediated CMA produce mainly IL-4 and IL-13, whereas T-cell clones from cow's milk-tolerant patients are characterized by a marked production of IL-10 and IFN- γ , thus suggesting a key role for IL-10 in the induction of tolerance to cow's milk. However, cow's milk-specific T-cell responses *per se* do not induce CMA because specific T_H1, T_H2, and regulatory T-cell subsets have been described in both healthy and allergic subjects.⁸⁰ A T_H2-skewed cytokine pattern, dominated by IL-13, IL-5, and IL-4, has also been reported in T-cell clones in a CMA/AD setting. In contrast, a T_H1-skewed response is dominant in T-cell clones from infants without CMA.⁸² Clinically, most IgE-mediated and non-IgE-mediated forms of CMA are outgrown during late childhood. T-cell clones with a T_R1 phenotype (producing IL-10 and IFN- γ) have been recovered in children who became spontaneously tolerant to cow's milk proteins. An association between naturally occurring regulatory

TABLE I. Clinical manifestations of CMA

I. Gastrointestinal reactions	
<ul style="list-style-type: none"> • Oral allergy syndrome (rare in pediatric patients) • Lip swelling is a commonly observed manifestation during food challenge procedures.⁵¹ 	
Immediate gastrointestinal allergy	
<ul style="list-style-type: none"> • Vomiting (described in children both isolated and as part of allergic/anaphylactic reactions) • Diarrhea (usually in, but not limited to, delayed reactions⁵²) 	
CMA in short bowel syndrome	
<ul style="list-style-type: none"> • Greater than 50% of these patients are also allergic to cow's milk, according to 1 case study.⁵³ 	
II. IgE-mediated respiratory reactions	
<ul style="list-style-type: none"> • Rhinitis occurs in ±70% of patients during oral cow's milk challenge, and asthma occurs in less than 8%.⁵⁴⁻⁵⁶ • Reactions rarely occur in isolation.⁵⁷ • Reactions correlate with severe CMA.^{3,58} • Asthma makes for the worst prognosis in children with anaphylaxis. • Asthma in patients with CMA is of particular severity.^{3,59} • Respiratory symptoms in patients with CMA can progress to respiratory allergy.⁶⁰ • Inhalation of milk vapor has been associated with severe respiratory tract reactions.^{61,62} 	
III. IgE-mediated skin reactions	
Acute urticaria or angioedema	
<ul style="list-style-type: none"> • Urticaria is a feature of most anaphylactic reactions to cow's milk. • Urticaria with inhalation⁶³ or accidental skin contact⁶⁴ is often severe. 	
Contact urticaria	
<ul style="list-style-type: none"> • Pattern varies from irritant to allergic contact dermatitis. • Generalized eczematous rash (systemic contact dermatitis) is present. • Contact reactions are frequent in patients with AD.⁶⁵ 	
IV. Late-onset reactions	
<ul style="list-style-type: none"> • Symptoms not IgE mediated • Mostly localized in the gastrointestinal tract • Typically develop 1 to several hours or even days after ingestion • No reliable laboratory tests to diagnose late-onset CMA: IgE test results are negative 	
Skin	<ul style="list-style-type: none"> • AD
Gastrointestinal tract	<ul style="list-style-type: none"> • Gastroesophageal reflux disease • Allergic eosinophilic esophagitis • Food protein–induced enterocolitis syndrome • Cow's milk protein–induced enteropathy • Constipation • Severe irritability (colic) • Food protein–induced gastroenteritis and proctocolitis
Respiratory system	<ul style="list-style-type: none"> • Milk-induced chronic pulmonary disease • Heiner syndrome
V. AD	
<ul style="list-style-type: none"> • AD is most often present as an eczematous lesion (after ingestion or contact). • AD can involve both IgE-mediated and non-IgE-mediated skin responses. • Less than 30% of children with moderate-to-severe AD have food allergy, and CMA is the second most common food allergy in this population.⁶⁶ • The earlier the age of onset, the greater the severity and frequency of high of cow's milk sIgE levels.⁶⁷ • Appropriate diagnosis and elimination diets frequently lead to symptom improvement.⁶⁸ 	
VI. Gastrointestinal syndromes	
Symptoms frequently include nausea, vomiting, abdominal pain, diarrhea, and, with chronic disease, malabsorption and failure to thrive or weight loss.	

(Continued)

TABLE I. (Continued)

<ul style="list-style-type: none"> • Food protein–induced enterocolitis syndrome, the primary cause of which is CMA^{69,70} • Cow's milk–induced enteropathy syndrome and secondary lactose malabsorption⁷¹ • Cow's milk–induced proctocolitis syndrome (relatively benign disorder)⁷² • Gastroesophageal reflux disease–like symptoms^{73,74} • Eosinophilic esophagitis⁷⁵ • Constipation • Irritable bowel syndrome⁷⁶
VII. Milk-induced chronic pulmonary disease⁷⁷
<ul style="list-style-type: none"> • Heiner syndrome is a very rare form of pulmonary hemosiderosis caused by CMA. • Young children typically present with recurrent pulmonary infiltrates associated with chronic cough, tachypnea, wheezing, rales, recurrent fevers, and failure to thrive. • Milk-precipitating antibodies are found in the serum. • Symptoms generally resolve after an elimination diet.

T cells (CD25⁺ CD27⁺ forkhead box protein 3^{high+} cytotoxic T lymphocyte–associated antigen 4⁺ CD127^{low} cells) and the onset of tolerance to milk has been found.⁸³

CMA: CLINICAL SCIENCE

CMA phenotypes: Immediate and delayed reactions

From a clinical point of view, patients with CMA can present with a bewildering variety of symptoms. The classification of immune-mediated reactions to cow's milk into immediate (typically IgE-mediated) or late-onset (non-IgE-mediated or cell-mediated) reactions still holds true. Currently defined as “a severe systemic or generalized severe allergic reaction,”⁸⁴ cow's milk–induced anaphylaxis can be life-threatening and occur at any time to within minutes and up to 2 hours after ingestion of dairy products. Like any food-induced anaphylactic reaction, CMA can present with skin,⁸⁵⁻⁸⁷ respiratory tract,⁸⁸⁻⁹⁰ and gastrointestinal⁹¹ symptoms (Table I, parts I to VII). Cardiovascular collapse, syncope, or incontinence are the hallmarks of the most severe forms. Food-dependent exercise-induced anaphylaxis has also been reported in children with previous milk allergy, either after achieving tolerance⁹² or after oral desensitization protocols.⁹³ In the United Kingdom milk ingestion was the cause of fatal anaphylaxis in 4 cases over 10 years and was involved in 10.9% of fatal or near-fatal anaphylactic episodes.⁹⁴ Milk is one of the leading foods accounting for epinephrine use.⁹⁵ Cow's milk has thus far been subject to cautionary labeling both in Europe and the United States,⁹⁶ but the similar labeling of milk as an ingredient of pharmaceutical preparations has not been required, and several cases of anaphylaxis caused by milk in medicinal fillers, such as lactose, have been reported.⁹⁷⁻⁹⁹ Goat's and ewe's milks have also been implicated in anaphylactic reactions.^{100,101}

Unusual clinical presentations of CMA

Unusual clinical presentations are as much a feature of CMA as one might expect from such a ubiquitous allergen source in food and the environment as milk (Box 1).¹⁰²⁻¹¹²

BOX 1: Unusual clinical manifestations and routes of exposure

Manifestation		
Constipation	See Table I	Iacono et al ¹⁰²
Heiner syndrome	See Table I	Moissidis et al ¹⁰³
Unusual routes of exposure		
Skin contact	Direct or indirect contact in bathtub into which a few drops of milk were spilled by a younger brother	Liccardi et al ¹⁰⁴
Mucous membrane contact	Kiss	Hallett et al ¹⁰⁵
	Vaginal contact	Liccardi et al ¹⁰⁶
Inhalation	Milk vapor or casein powder	Bonadonna et al, ¹⁰⁷ Vargiu et al ¹⁰⁸
Environmental exposure		
Poor food labeling	Labeling of commercially prepared foods might not be accurate	Joshi et al ¹⁰⁹
Hidden or contamination in other foods	Contamination in restaurants or factories	Muñoz-Furlong et al ¹¹⁰
	Ignorance of catering personnel	
Hidden or contamination in medications	In lactose	Nowak-Wegrzyn et al ¹¹¹
	In dermatologic preparations or injectable corticosteroids	Eda et al ¹¹²

The natural history of CMA

CMA is primarily of pediatric onset,¹¹³⁻¹¹⁵ is generally outgrown, and is often the first stage of the “allergic march.” The take-home message about the latest developments regarding the natural history of CMA is reviewed in Table II.^{1,38,116-135}

CMA GUIDELINES: METHODS**The Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) approach for developing management guidelines in patients with CMA**

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group defines quality of evidence as the extent of confidence that estimates of effect for an outcome (including diagnostic accuracy estimates) are correct. An estimate of such an effect therefore underpins a recommendation in guidance/guideline formulation.¹³⁶⁻¹⁴¹ GRADE is used by more than 50 international organizations, including the World Health Organization, the Centers for Disease Control and Prevention, the Allergic Rhinitis in Asthma Guidelines, and the American Thoracic Society. Considerations of health benefits and harms, burden of disease, patient preferences, and resource use lead to specific and explicit recommendations for patients and caregivers.

Using and searching for evidence to guide clinical practice requires formulating research questions before turning to the literature.¹⁴² Key considerations (ie, patient [P]; intervention, including diagnostic tests or strategies [I] or exposure [C; and outcomes [O]) combine to form the Patient Intervention Comparison Outcome (PICO) format for this purpose. Evidence was collected by an independent panel of researchers who conducted systematic reviews of the published evidence for all PICO questions.³ Randomized controlled trials and observational evidence were considered when available or relevant. GRADE is a

system for evaluating the quality of evidence, as well as a systematic and transparent approach to develop recommendations (and their relative strength) for clinical practice use, also specifying the strength of these recommendations. Four grades of evidence are used: high, moderate, low, and very low quality. Five factors decrease the confidence in an estimate of an effect and consequently decrease its grade, and 3 factors increase it (see Table E3 in this article’s Online Repository at www.jacionline.org). The strength (strong/weak or “conditional”) of a for-or-against recommendation expresses the degree of confidence with which the desirable effects outweigh the undesirable effects of the intervention. A recommendation for action requires the consideration of the magnitude of the expected benefit/downside tradeoff in view of all patient outcomes, associated values/preferences, and resource use (see Table E4 in this article’s Online Repository at www.jacionline.org). Panel deliberation and consensus after consideration of the factors listed in Table E4 allow the recommendations to be formulated reflecting the quality of evidence, the strength of the recommendations themselves, and the inclusion of patients’ values and preferences. Thus the GRADE stepped approach, which requires and reflects judgmental and stakeholder inputs, comprehensively and explicitly facilitates the scrutiny and transparency of these judgments throughout the guideline development process.

GRADE assessment of the diagnostic tests in patients with CMA, their diagnostic properties, and consequences for use in daily practice

An oral food challenge (OFC) with cow’s milk is the reference standard for the diagnosis of CMA. However, it is resource intensive and not easily performed or interpreted and might carry a significant risk of anaphylaxis. In many parts of the world, it is not realized in clinical practice precisely because of the above reasons. Thus the DRACMA panel research question was whether reducing OFCs was possible though better deployment of skin prick tests (SPTs) or cow’s milk-specific IgE (IgE) *in vitro*

TABLE II. Natural history of CMA at a glance

Temporal pattern:

In the 1990s, a Danish birth cohort study found that more than 50% of children outgrow their CMA at 1 year of age.^{116,117} Subsequent studies have reported a longer duration of CMA, with tolerance developing in 51% of patients within 2 years after diagnosis.

Tolerance:

Referral studies indicate that 80% of patients achieve tolerance within 3 to 4 years. In several studies children with delayed reactions became tolerant faster than those with immediate reactions.¹¹⁸⁻¹²¹

Duration:

In retrospective studies the duration of CMA differs in different settings.¹ In a population of breast-fed infants with cow's milk-induced allergic proctocolitis, tolerance developed between 6 and 23 months.

Onset:

The onset of CMA is related to antigen exposure. A cow's milk avoidance diet, once thought of as the only treatment for CMA, has recently been challenged by opposite theories on the basis of human and animal studies.

Risk factors:

A family history of progression to atopic asthma, rhinitis, eczema, early respiratory symptoms with skin and/or gastrointestinal symptoms, or severe symptoms are considered risk factors for persistent CMA.

A larger wheal diameter on SPTs with fresh milk significantly correlates with CMA persistence. A smaller eliciting dose on OFCs also correlates with longer duration of CMA.¹²⁰

Severe symptoms reported at diagnosis are consistent with the worse prognosis for duration.^{120,123-125} Children with earlier or more severe AD have a higher prevalence of early-onset bronchospasm compared with those with AD or mild AD.³⁸

Phenotypes:

There might be different CMA phenotypes that, once identified, could lead to personalized treatment strategies for different populations of atopic patients.

Tolerance factors:

Low milk-specific IgE levels correlate with earlier onset of tolerance, and a 99% reduction in sIgE concentrations over 12 months translates into a 94% likelihood of achieving tolerance to cow's milk protein within that period.

Tolerance of cow's milk protein might correlate with reduced concentrations of IgE- and IgG-binding casein epitopes, and an involvement of tertiary or linear casein epitope structures has been hypothesized.¹²⁶⁻¹²⁹ However, the maintenance of tolerance in atopic patients is associated with persistently increased milk-specific IgG4 antibody concentrations.¹³⁰ Tolerance of cow's milk protein might correlate with a shift toward IgA^{131,132} and reduced concentrations of T-cell epitopes of casein in either IgE-mediated or non-IgE-mediated allergy.^{133,134} Tolerance maintenance is associated with persistently increased milk-specific IgG4 antibody concentrations.¹³⁵

determinations. Following the GRADE Working Group approach for making recommendations, the panel formulated several specific clinical questions and specified outcomes of interest,³ such as patient-oriented consequences of taking into account being correctly or incorrectly classified as allergic to cow's milk, the consequences of indeterminate results, the complications of tests, and resource use. The panelists carried out a systematic review of all available evidence that addressed these questions. Thirty-six studies were included in the final qualitative analyses.³ The combined accuracy of the SPTs and sIgE measurements were estimated, the risk of bias in the studies included was assessed by using the Quality Assessment of Studies of Diagnostic Accuracy tool, and the panelists' ratings (from 1 to 10) of the quality of supporting evidence for each outcome of interest were reported.¹⁴³ The cutoff values for positivity of SPT results and sIgE determinations reported in most studies in the literature are a greater than 3-mm wheal diameter and a greater than 0.35 kU/L sIgE level, respectively. The guideline panel concluded that there was insufficient evidence to support recommendations of other cutoff values. The overall quality of the evidence was either low or very low because of the risk of bias and unexplained heterogeneity in the results of individual studies. Based on estimated combined accuracy, we calculated the numbers of patients who experience particular consequences of being correctly or incorrectly classified as having CMA. The DRACMA guideline panel considered the balance of desirable and undesirable consequences, the quality of available evidence, patients' values and preferences, and the resource implications of each diagnostic option. The panel made several recommendations for the use of SPTs and sIgE measurements as a single test or in combination

in patients with high, average, or low initial probability of IgE-mediated CMA. The panel also made 2 recommendations for further research on allergen microarrays and component-resolved diagnostics before they can be used in clinical practice. The 6 clinical research questions identified by the panelists (who screened 3877 articles³) deal with issues regarding the settings of high, medium, and low suspicion of CMA. Below is the summary of the recommendations presented by the panelists.

CMA: DIAGNOSIS

The recommendations on diagnosis using SPTs and sIgE determinations are reported in **Box E1**.^{3,144} According to these recommendations, a child with a recent cutaneous reaction immediately after the ingestion of a meal including milk (high probability of IgE-mediated CMA) must have his or her diagnosis based on a challenge. If not easily feasible, a positive SPT result or IgE determination will surrogate the reference test with an acceptable accuracy: with a 5% to 6% false-positive rate, only 1 in 20 patients will be misclassified as having CMA and will receive an unnecessary exclusion diet. If these sensitization test results are negative, a challenge must be done to diagnose or exclude CMA.

Vice versa, a negative sensitization test result in a child with mild eczema (low probability of CMA) will exclude the condition in most cases. In this case, given the 2% to 4% of false-negative results, an allergic reaction (possibly mild) will be possible in 1 in 25 to 50 patients misclassified as not having CMA although actually being allergic to cow's milk. Regarding the use of the atopy patch test for CMA diagnosis, the low correlation with skin tests for single allergens and the unsatisfactory reproducibility

BOX 2: What DRACMA brings to the treatment of CMA³**General treatment principles**

- Apply strict avoidance of all cow's milk protein in food.
- Consider a maternal elimination diet in breast-fed infants.
- Use a replacement formula in formula-fed children <2 years of age.
- It is often possible to switch to a milk-free diet in children >2 years of age.
- Continue elimination diet until tolerance has developed.
- Provide intramuscular adrenaline autoinjector to children at risk of anaphylaxis.

Clinical goals

- Remission of cow's milk-induced symptoms
- Prevention of accidental ingestion of cow's milk proteins
- Prevention of inhalation or skin contact with cow's milk
- Avoidance of cross-reactive milk proteins (buffalo's, goat's, or ewe's milk)
- Monitoring of nutritional adequacy of elimination diets, especially if maintained for prolonged periods
- Patient education to improve adherence

Problems

- Inadvertent intake (labeling and level of dietary education)
- Misconceptions about safety of partially hydrolyzed formula, heated milk products, or homologous nonbovine milk formula (eg, goat's milk formula)
- Taste aversion for treatment formula
- Poor intake and feeding difficulties or refusal to feed
- Risk of decreased growth velocity
- Other confounding food allergies (eg, egg, soy, or wheat)

How long should an elimination diet be maintained?

- Prolonged elimination diets might adversely affect nutritional outcomes, particularly if poorly supervised.
- The aim is to normalize elimination diets as soon as feasible.
- Patients on elimination diets require regular reassessment of tolerance (SPTs, sIgE antibody measurements, and diagnostic OFCs).
- Dairy products are often tolerated by 2-3 years of age.
- In case of unremitting CMA beyond 2 years of age, consider shifting from replacement formula to a milk-free diet.

Maternal elimination diet

- Encourage continued breast-feeding.
- A maternal elimination diet might be useful if there is clear evidence of ongoing clinical allergic reactions after maternal cow's milk ingestion while the infant is exclusively breast-fed.
- A maternal elimination diet is not required if the infant tolerates breast milk while the mother is on an unrestricted diet (eg, previous reaction occurred to supplemental cow's milk formula or dairy products).
- Monitor maternal protein and calcium intake (1.2 g of calcium daily in divided doses), as supervised by a dietician.

of food atopy patch tests in children argue against their widespread clinical use in diagnosing CMA.^{145,146}

CMA: TREATMENT**Dietary treatment**

Thus far, the only treatment of CMA is strict avoidance of cow's milk proteins, which nevertheless carries a number of drawbacks, as outlined in Box 2. Planning a dietary regimen avoiding all cow's milk proteins from dairy or processed food products for these infants and children should be backed by a collaborative effort between scientific societies, clinical specialists, primary care physicians, and caregivers. For infant foods in particular, lists of acceptable foods and suitable substitutes in line with national recommendations and clinical settings must be drafted from various sources and adapted to suit the individual subject's needs and values.¹⁴⁷ It is DRACMA's contention that all dietary interventions and avoidance strategies be re-evaluated with patients and their families on a yearly basis, ideally after OFCs carried out under medical supervision (see the section on diagnosis). The panelists' consensus was that to fulfill the nutritional requirements of young children, a substitute formula should be prescribed until at least 2 years of age. This

applies to most countries in the world. As a rule, extensively hydrolyzed formulae are the first choice, except in patients with anaphylaxis and eosinophilic esophagitis.³ Soy formulae should never be prescribed during the first 6 months of life.³ Where available, rice-based hydrolysates can adequately substitute extensively hydrolyzed cow's milk proteins.³

Prescribing a nutritionally adequate diet

Formulating the diet of infants and children during the CMA workup requires careful evaluation of nutritional aspects on a strictly individual basis.¹⁴⁸ The aim is to achieve a balanced calorie/protein ratio and amino acid composition and an adequate calcium source.^{149,150} Noncompliance with recommendations can lead to inappropriate diets, sometimes with dramatic effects.¹⁵¹ The literature supports the nutritional safety of cow's milk substitutes both during the first¹⁵² and second¹⁵³ semesters of life.

Experimenting with immunotherapy for CMA

Animal studies have shown that, under certain circumstances, tolerance can develop through apoptosis on exposure to high

antigen loads.¹⁵⁴ Different studies have shown that the tendency of T cells to become tolerant can be triggered by the ingestion of minimal quantities of the incriminated allergen.^{155,156} The wide array of allergens that can be introduced in the diet is an obvious risk factor for allergy very early on, when the immune system is still functionally immature, and the jury is still out on whether early contact with a potential antigen can modulate the response of the organism either toward hyperresponsiveness or tolerance.¹⁵⁷⁻¹⁶⁰ In this context oral immunotherapy (OIT) has been attempted for at least a decade, with mixed success. In some cases OIT has been supplemented with IFN- γ ¹⁶¹ or mAbs. From these studies, it is shown that standard OIT can increase the threshold of reactivity in about 80% of patients with CMA. However, mild adverse reactions are very common, and occasionally more severe reactions occur (approximately 1 in 100 doses resulted in multisystem reactions).¹⁶²⁻¹⁶⁹ Taken together, these studies leave an important question unanswered: Are we dealing with desensitization or induced tolerance? Only prospective studies will tell.

FUTURE DEVELOPMENTS

Microarray technology is progressing apace toward a future in which allergen testing can be carried out on a microchip. However, several paradigmatic shifts are necessary before this can occur, and this is reflected in the GRADE recommendations in the absence of more studies with larger samples and wider allergy applications. DRACMA recommends allergen microarrays and component-resolved diagnostics to be used only in the context of well-designed studies investigating their accuracy against OFCs for diagnostic purposes.

Another promising approach is represented by insights afforded by molecular studies of the underlying immune mechanisms mediated through specific IgA, IgG, IgE, and regulatory T-cell expression in patients with CMA.⁸³ These developments might lead to clinical breakthroughs in the near future, hopefully leading to tests assisting clinicians in characterizing phenotypical expression of CMA and thus defining patients' prognostic profiles.¹⁷⁰

In conclusion, DRACMA should contribute to research by focusing a worldwide awareness to deal with the unmet needs that current CMA research has identified. Toward these goals, the WAO provides an instrument and a forum to generate solutions to clinical aspects of the problem and to coordinate energies from the multidisciplinary approaches needed to tackle the problem of CMA.

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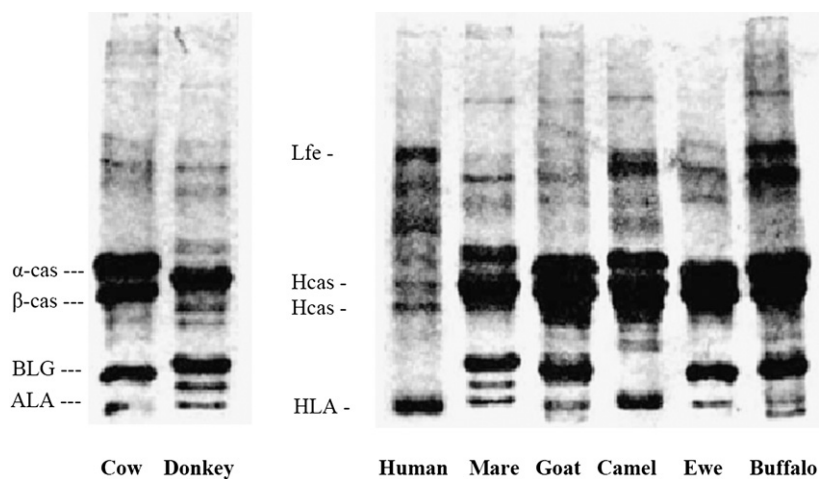


FIG E1. SDS-PAGE of cow's milk. *ALA*, Bovine α -lactalbumin; *α -cas*, bovine α -casein; *β -cas*, bovine β -casein; *BLG*, bovine β -lactoglobulin; *Hcas*, Human casein; *HLA*, human lactalbumin; *Lfe*, human lactoferrin.

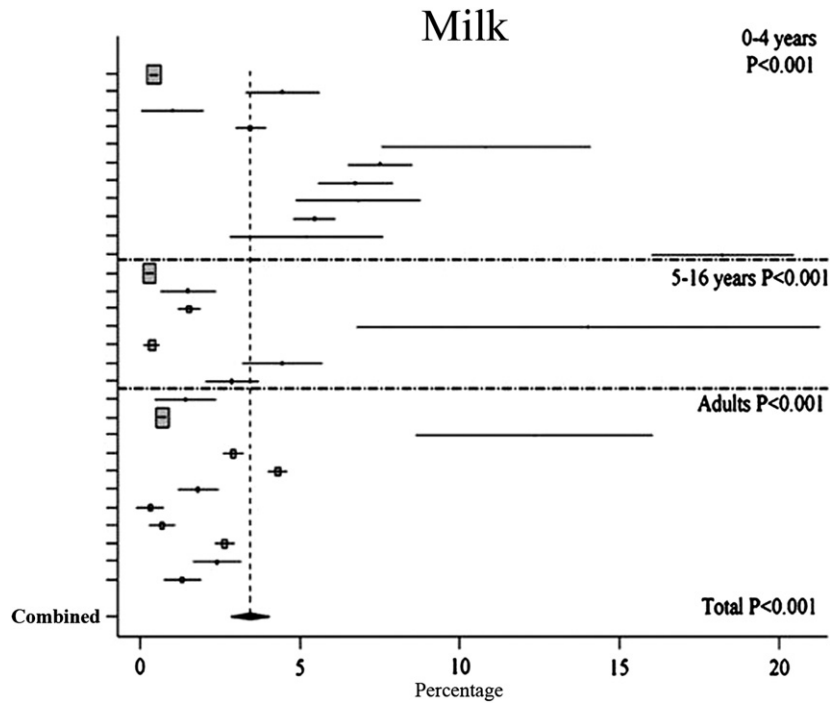


FIG E2. Self/parental report of CMA stratified by age. *P* values connote the level of heterogeneity by age group and in total.

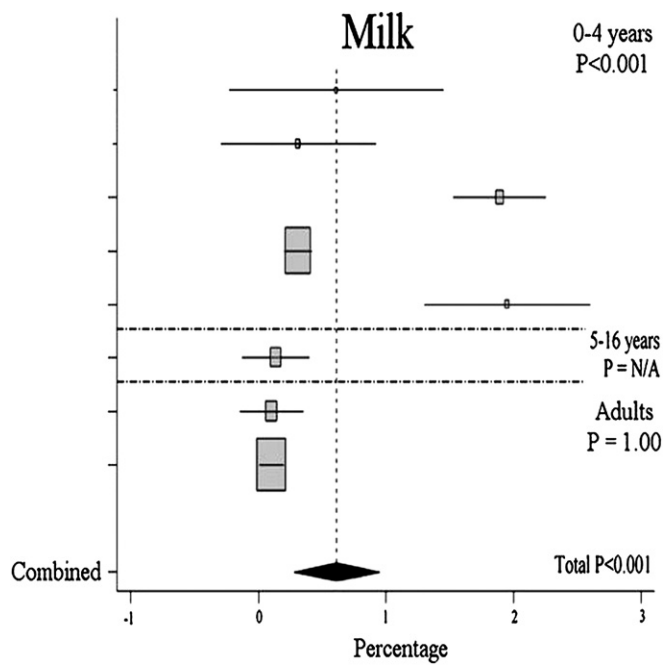


FIG E3. Prevalence of symptoms and sensitization (tested by means of SPTs or IgE antibody assays) and stratification by age. *P* values connote the level of heterogeneity by age group and in total. *N/A*, Not applicable.

BOX E1: Recommendations for the diagnosis of CMA

Should SPTs be carried out for the diagnosis of IgE-mediated CMA in patients with suspected CMA?

Recommendation 1

In settings in which an OFC is considered a requirement for making a diagnosis of IgE-mediated CMA, we recommend using an OFC with cow's milk as the only test without performing an SPT as a triage or an add-on test to establish a diagnosis (strong recommendation/very low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding resource consumption and the risk of anaphylactic reactions at home in patients who would be misclassified by an SPT alone. It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when an OFC is performed. This recommendation also places a high value on avoiding any unnecessary treatment in patients who would be incorrectly classified by an SPT as allergic to cow's milk.

Remark

This recommendation applies to clinical practice settings. In research settings there might be compelling reasons to perform an SPT even though a food challenge with cow's milk is being done.

Recommendation 2

In settings in which an OFC is not considered a requirement in all patients suspected of IgE-mediated CMA, in patients with high pretest probability of CMA, we suggest using an SPT with a cutoff value of 3 mm or greater as a triage test to avoid an OFC in those in whom the result of an SPT turns out positive (conditional recommendation/low quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding burden, resource use, and very likely anaphylactic reactions during the OFC (approximately 50% to 70% of food challenges avoided). It places a lower value on unnecessary treatment of around 1 in 20 patients misclassified as allergic to cow's milk (5% to 6% false-positive results).

Remarks

A high pretest probability of CMA (approximately 80%) can be estimated based on the history and would represent, for instance, patients who experienced an anaphylactic reaction in the past.

Recommendation 3

In settings in which an OFC is not considered a requirement in all patients suspected of IgE-mediated CMA, in patients with an average pretest probability of CMA, we suggest using an OFC with cow's milk as the only test without performing an SPT with a cutoff value of 3 mm or greater as a triage or an add-on test to establish a diagnosis (strong recommendation/very low-quality evidence).

Underlying values and preferences

This recommendation places a high value on avoiding resource consumption and the risk of anaphylactic reactions at home in a large proportion of patients who would be incorrectly classified by an SPT alone. It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when an OFC is performed. This recommendation also places a high value on avoiding any unnecessary treatment in patients who would be incorrectly classified by an SPT as allergic to cow's milk.

Remarks

An average pretest probability of CMA (approximately 40%) can be estimated based on the history and presenting symptoms and would represent the majority of situations.

Recommendation 4

In settings in which OFCs are not considered a requirement in all patients suspected of IgE-mediated CMA, in patients with a low pretest probability of CMA, we suggest using an SPT with a cutoff value of 3 mm or greater as a triage test to avoid an OFC in those in whom the result of an SPT turns out negative (conditional recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding burden and resource use with an OFC (approximately 70% of challenges avoided). It places a lower value on avoiding an allergic reaction (possibly a mild one) in around 1 in 25 to 50 patients misclassified as not having CMA although actually allergic to cow's milk (2% to 4% false-negative results).

Remarks

A low pretest probability of CMA (approximately 10%) can be estimated based on the history and would represent, for instance, patients with unexplained gastrointestinal symptoms (eg, gastroesophageal reflux).

Should *in vitro* sIgE determination be carried out for the diagnosis of IgE-mediated CMA in patients suspected of CMA?

(Continued)

BOX E1. (Continued)

Recommendation 1.

In practice settings in which an OFC is a requirement in all patients suspected of IgE-mediated CMA, we recommend using an OFC with cow's milk as the only test without measuring a cow's milk-specific IgE level as a triage or add-on test to establish a diagnosis (strong recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding resource consumption and the risk of anaphylactic reactions at home in patients who would be misclassified by a milk-specific IgE test alone. It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when an OFC is performed. This recommendation also places a high value on avoiding any unnecessary treatment in patients who would be incorrectly classified based on milk-specific IgE measurement as allergic to cow's milk.

Remark

This recommendation applies to clinical practice settings. In research settings there might be compelling reasons to perform SPTs even though a food challenge with cow's milk is being done.

Recommendation 2.

In settings in which an OFC is not a requirement, in patients with a high pretest probability of IgE-mediated CMA, we suggest using cow's milk-specific IgE with a threshold of 0.7 IU/L to avoid an OFC if a result of milk-specific IgE measurement turns out positive (conditional recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding burden, resource use, and very likely anaphylactic reactions during an OFC (food challenges would be avoided in 50% of patients with milk-specific IgE results ≥ 0.7 IU/L). It places a lower value on unnecessary treatment of around 1 in 20 patients misclassified as allergic to cow's milk (5% false-positive results).

Remarks

A high pretest probability of CMA (approximately 80%) can be estimated based on the history and would represent, for instance, patients who experienced an anaphylactic reaction in the past

Recommendation 3.

In settings in which an OFC is not a requirement in all patients suspected of IgE-mediated CMA, in patients with an average pretest probability of IgE-mediated CMA, we suggest using an OFC with cow's milk as the only test without measuring milk-specific IgE levels as a triage or add-on test to establish a diagnosis (conditional recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a high value on avoiding resource consumption and the risk of anaphylactic reactions at home in a large proportion of patients who would be incorrectly classified by a milk-specific IgE test alone. It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when an OFC is performed. This recommendation also places a high value on avoiding any unnecessary treatment in patients who would be incorrectly classified by a milk-specific IgE test as allergic to cow's milk.

Remarks

An average pretest probability of CMA (approximately 40%) can be estimated based on the history and presenting symptoms and would represent the majority of clinical situations. Using higher cutoff values (eg, 2.5 IU/L) might be of benefit; however, we believe the available evidence does not allow us to make a recommendation to support any recommendation.

Recommendation 4.

In practice settings in which an OFC is not a requirement in all patients suspected of IgE-mediated CMA, in patients with a low pretest probability of IgE-mediated CMA, we suggest using milk-specific IgE measurement with a cutoff value of 0.35 IU/L as a triage test to avoid an OFC in those in whom the result of milk-specific IgE measurement turns out negative (conditional recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding burden and resource use with an OFC (approximately 50% to 70% of food challenges avoided). It places a lower value on avoiding an allergic reaction (possibly a mild one) in around 1 in 20 to 50 patients misclassified as not having CMA (2% to 5% false-negative results).

Remarks

A low pretest probability of CMA (approximately 10%) can be estimated based on the history and would represent, for instance, patients with unexplained gastrointestinal symptoms (eg, gastroesophageal reflux).

Should *in vitro* sIgE antibody determination be used for diagnosis in patients with suspected CMA and a positive SPT result?

(Continued)

BOX E1. (Continued)

Recommendation 1.

In patients with a low initial probability of IgE-mediated CMA who have a positive SPT result (≥ 3 mm), we suggest an OFC rather than measuring the cow's milk-specific IgE level with a cutoff value of 0.35 IU/L (conditional recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding unnecessary treatment in patients who would be misclassified by a milk-specific IgE test alone. It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when an OFC is performed.

Recommendation 2.

In patients with an average or high initial probability of IgE-mediated CMA who have a positive SPT result (≥ 3 mm), we suggest measurement of cow's milk-specific IgE with a cutoff value of 0.35 IU/L to avoid a food challenge test in those in whom the result of milk-specific IgE turns out positive (conditional recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding resource consumption and the burden of an OFC (approximately 20% of food challenges would be avoided in patients with an average initial probability of CMA and approximately 40% in those with a high initial probability). It places a lower value on unnecessary treatment of a small proportion of patients who would be misclassified as having CMA (3% false-positive results in patients with an average initial probability of CMA and 1% in those with a high initial probability).

Remarks

An average pretest probability of CMA (approximately 40%) can be estimated based on the history and presenting symptoms and would represent the majority of situations. A high pretest probability of CMA (approximately 80%) can be estimated based on the history and would represent, for instance, patients who experienced an anaphylactic reaction in the past.

Should *in vitro* sIgE determination be used for the diagnosis of CMA in patients suspected of CMA with a negative SPT result?

Recommendation 1

In patients with a low initial probability of IgE-mediated CMA who have a negative SPT result, we recommend measuring cow's milk-specific IgE levels as a triage test to avoid a food challenge test in those in whom the result of the milk-specific IgE test turns out negative (strong recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding burden and resource use with an OFC (approximately 60% of tests avoided). It places a lower value on avoiding an allergic reaction (possibly a mild one) in around 1 in 50 patients misclassified as not having CMA (false-negative result).

Remarks

A low pretest probability of CMA (approximately 10%) can be estimated based on the history and would represent, for instance, patients with unexplained gastrointestinal symptoms (eg, gastroesophageal reflux).

Recommendation 2

In patients with an average initial probability of IgE-mediated CMA who have a negative SPT result, we suggest an OFC rather than measuring cow's milk-specific IgE levels (conditional recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding resource consumption and the risk of anaphylactic reactions at home in patients who would be misclassified as not having CMA by means of SPTs and milk-specific IgE tests. It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when an OFC is performed.

Remarks

An average pretest probability of CMA (approximately 40%) can be estimated based on the history and presenting symptoms and would represent the majority of situations.

Recommendation 3

In patients with a high initial probability of IgE-mediated CMA who have a negative SPT result, we recommend an OFC rather than measuring cow's milk-specific IgE levels (strong recommendation/low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding resource consumption and the risk of anaphylactic reactions at home in a large proportion of patients who would be misclassified as not having CMA by SPTs and milk-specific IgE tests.

(Continued)

BOX E1. (Continued)

It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when an OFC is performed.

Remarks

A high pretest probability of CMA (approximately 80%) can be estimated based on the history and would represent, for instance, patients who experienced an anaphylactic reaction in the past.

Should allergen microarrays or component-resolved diagnostics be used for the diagnosis of IgE-mediated CMA in patients suspected of CMA?

Recommendation 1

We suggest that allergen microarrays are used only in the context of well-designed and well-executed studies that investigate the accuracy of commercially available allergen microarrays compared with OFCs with cow's milk in patients suspected of IgE-mediated CMA.

Recommendation 2

We suggest that more well-designed and well-executed studies of component-resolved diagnostics compared with OFCs with cow's milk be performed in patients suspected of IgE-mediated CMA.

BOX E2: DRACMA recommendations for treatment of CMA

Should amino acid formula, extensively hydrolyzed whey or casein formula, soy formula, or rice formula be used in children with IgE-mediated CMA?

Recommendation 1

In children with IgE-mediated CMA at high risk of anaphylactic reactions (prior history of anaphylaxis and currently not using extensively hydrolyzed milk formula), we suggest amino acid formula rather than extensively hydrolyzed milk formula (conditional recommendation/very low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding possible anaphylactic reactions and a lower value on avoiding the direct cost of amino acid formula in settings in which the cost of amino acid formula is high.

Remarks

In controlled settings a trial feeding with an extensively hydrolyzed milk formula might be appropriate.

Recommendation 2

In children with IgE-mediated CMA at low risk of anaphylactic reactions (no prior history of anaphylaxis or currently on extensively hydrolyzed milk formula), we suggest extensively hydrolyzed milk formula over amino acid formula (conditional recommendation/very low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding the direct cost of amino acid formula in settings in which the cost of amino acid formula is high. In settings in which the cost of amino acid formula is lower, the use of amino acid formula might be equally reasonable.

Remarks

Extensively hydrolyzed milk formula should be tested in clinical studies before being used. If a new formula is introduced, one should carefully monitor whether any adverse reactions develop after first administration.

Recommendation 3

In children with IgE-mediated CMA, we suggest extensively hydrolyzed milk formula rather than soy formula (conditional recommendation/very low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding adverse reactions to soy formula and a relatively low value on an inferior acceptance of the extensively hydrolyzed formula and resource use. In settings in which the relative importance of resource expenditure is lower, an alternative choice might be equally reasonable.

Remarks

Soy should not be used in the first 6 months of life because of nutritional risks.

Recommendation 4

In children with IgE-mediated CMA, we suggest extensively hydrolyzed milk formula rather than extensively hydrolyzed rice formula (conditional recommendation/very low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on wide availability of extensively hydrolyzed milk formula relative to hydrolyzed rice formula.

Recommendation 5

We suggest that more well-designed and well-executed randomized trials comparing soy formula with extensively hydrolyzed rice formula be performed in patients suspected of having IgE-mediated CMA.

Remarks

There is very sparse evidence suggesting a possible benefit from using extensively hydrolyzed formula compared with soy formula, but more research is needed to confirm these observations.

Should oral immunotherapy be used in patients with CMA?

Recommendation

In patients with IgE-mediated CMA, we recommend that clinicians do not administer oral immunotherapy with cow's milk unless this is done in the context of formal clinical research (strong recommendation/very low-quality evidence).

Underlying values and preferences

This recommendation places a relatively high value on avoiding serious adverse effects of oral immunotherapy and a relatively low value on the increased probability of desensitization to milk.

TABLE E1. Chemical characteristics of cow's milk proteins

Protein	Allergen*	Amount (g/L)	Percent total protein	MW (kd)	No. of AAs
Whey proteins		~30	80		
α_{s1} -Casein		12-15	29	23.6	199
α_{s2} -Casein		3-4	8	25.2	207
β -Casein	Bos d 8	9-11	27	24.0	209
γ_1 -Casein				20.6	180
γ_2 -Casein		1-2	6	11.8	104
γ_3 -Casein				11.6	102
κ -Casein		3-4	10	19.0	169
Caseins		~5.0	20		
α -Lactalbumin	Bos d 4	1-1.5	5	14.2	123
β -Lactoglobulin	Bos d 5	3-4	10	18.3	162
Immunoglobulin	Bos d 7	0.6-1.0	3	160.0	
BSA	Bos d 6	0.1-0.4	1	67.0	583
Lactoferrin		0.09	Traces	800.0	703

AA, Amino acid; MW, molecular weight.

*Chapman MD, Pomés A, Bretieneder H, Ferreira F. Nomenclature and structural biology of allergens. *J Allergy Clin Immunol* 2007;119:414-20.

TABLE E2. Sequence homologies between milk proteins (as a percentage relative to cow's milk proteins)¹²

Protein	Goat	Ewe	Buffalo	Sow	Mare	Donkey	Dromedary	Human
α -Lactalbumin	95.1	97.2	99.3	74.6	72.4	71.5	69.7	73.9
β -Lactoglobulin	94.4	93.9	96.7	63.9	59.4	56.9	Absent	Absent
Serum albumin	—	92.4	—	79.9	74.5	74.1	—	76.6
α ₁ -Casein	87.9	88.3	—	47.2	—	—	42.9	32.4
α ₂ -Casein	88.3	89.2	—	62.8	—	—	58.3	—
β -Casein	91.1	92.0	97.8	67.0	60.5	—	69.2	56.5
γ -Casein	84.9	84.9	92.6	54.3	57.4	—	58.4	53.2

—, Allergen is not present in the Swiss-Prot DataBank.

TABLE E3. The GRADE approach: Hierarchy of evidence

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Randomised trials	High	Risk of Bias (limitations in design or execution of studies)	Large effect Large Very large	A/High (four plus: ⊕ ⊕ ⊕ ⊕)
		Inconsistency	Dose response Evidence of a gradient	B/Moderate (three plus: ⊕ ⊕ ⊕ ○)
Observational studies	Low	Indirectness		C/Low (two plus: ⊕ ⊕ ○ ○)
		Imprecision Publication bias	All plausible residual confounding Would reduce a demonstrated effect Would suggest a spurious effect if no effect was observed	D/Very low (one plus: ⊕ ○ ○ ○)

TABLE E4. Strength of recommendations from guidelines according to the GRADE approach

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The higher the quality of evidence, the more likely there will be a strong recommendation.
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely weak a recommendation is warranted.
Values and preferences	The greater the variability in values and preferences or uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention (ie, the more resources consumed), the less likely a strong recommendation is warranted.