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

Alessandro Fiocchi, MD, Holger J. Schünemann, MD, PhD, Jan Brozek, MD, Patrizia Restani, PhD, Kirsten Beyer, MD, Riccardo Troncone, MD, Alberto Martelli, MD, Luigi Terracciano, MD, Sami L. Bahna, MD, Fabienne Rach, MD, Motohiro Ebisawa, MD, Ralf G. Heine, MD, FRACP, Amal Ass’ad, MD, Hugh Sampson, MD, Elvira Verduci, MD, G. R. Bouygue, MSc, Carlos Baena-Cagnani, MD, Walter Canonica, MD, and Richard F. Lockey, MD

Milan, Naples, and Genoa, Italy, Hamilton, Ontario, Canada, Berlin, Germany, Shreveport, La, Toulouse, France, Kanagawa, Japan, Melbourne, Australia, Cincinnati, Ohio, New York, NY, Cordoba, Argentina, and Tampa, Fla

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

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, diagnosis and treatment of cow’s milk allergy (CMA) practice guidelines were in need of a reappraisal reflecting recent literature. DRACMA encompasses recommendations for the diagnosis and treatment of IgE-mediated CMA. The full set is available in Boxes E1 and E2 (available in this article’s Online Repository at www.jacionline.org), 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.

From the Department of Child and Maternal Medicine, Melloni Hospital, Milan; the Departments of Clinical Epidemiology and Biostatistics and of Medicine, McMaster University, Hamilton; the Department of Pharmacological Sciences, Università degli Studi di Milano, Milan; Charité Klinik für Pädiatrie m.s. Pneumologie und Immunologie, Berlin, Germany; the Department of Pediatrics, Federico II Hospital, University of Naples; the Paediatric Division, Department of Child and Maternal Medicine, University of Milan Medical School at the Melloni Hospital; Pediatrics and Medicine, Allergy and Immunology, Louisiana State University Health Sciences Center, Shreveport; Allergologie, Hôpital des Enfants, Pôle Médicochirurgical de Pédiatrie, Toulouse, France; the Department of Allergy, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Kanagawa; the Department of Allergy and Immunology, Royal Children’s Hospital, University of Melbourne, Murdoch Childrens Research Institute, Melbourne; the Division of Allergy and Immunology, Cincinnati Children’s Hospital Medical Center; the Jaffe Food Allergy Institute, Mount Sinai School of Medicine, New York; the Department of Pediatrics, University of Milan; the Division of Immunology and Respiratory Medicine, Department of Pediatrics, Infantile Hospital Cordoba, Cordoba; the Allergy and Respiratory Diseases Clinic, Department of Internal Medicine, University of Genoa; and the Division of Allergy and Immunology, University of South Florida College of Medicine, Tampa.

Disclosure of potential conflict of interest: A. Fiocchi has received support from the World Allergy Organization (WAO); he is chairman of the American College of Allergy, Asthma, and Immunology’s (ACAAI) adverse reactions to foods committee and the WAO’s food allergy special committee. H. J. Schünemann and J. Brozek have received research support from the WAO. K. Beyer has received research support from the European Union, Food Allergy and Anaphylaxis Network (FAAN), Phadia, Paul Ehrlich Institute, and the German Foundation. S. L. Bahna has received research support from Pharming and speaker’s honoraria from Abbott, and is president of the ACAAI. R. G. Heine is on scientific advisory boards for Nutricia Australia and Nestle Nutrition Institute Australia, and has received lecture honoraria from Nutricia Australia. H. A. Sampson has consulted for Allertech Therapeutics, LLC; has received research support from the Food Allergy Initiative (FAI) and the National Institutes of Health / National Institute of Allergy and Infectious Diseases; is a consultant/scientist/advisor for FAI; and is part-owner of Herbal Springs, LLC. The remaining authors declare that they have no relevant conflicts of interest to disclose.

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Reprint requests: Alessandro Fiocchi, MD, Department of Child and Maternal Medicine, Melloni Hospital, Via Melloni, S2 Milan-I 20123. E-mail: allergy@tin.it.

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) 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). 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 1).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 Th2 phenotype has been reported with IgE-mediated CMA; in contrast, a Th1-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 Th1, Th2, and regulatory T-cell subsets have been described in both healthy and allergic subjects.82 A Th2-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 Th1-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 Th1 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 factors promoting oral tolerance or sensitization to cow’s milk.
Skin

I. Gastrointestinal tract

Symptoms frequently include nausea, vomiting, abdominal pain, diarrhea, and, with chronic disease, malabsorption and failure to thrive or weight loss.

Immediate gastrointestinal allergy

- Vomiting (described in children both isolated and as part of allergic/anaphylactic reactions)
- Diarrhea (usually in, but not limited to, delayed reactions

CMA in short bowel syndrome

- Greater than 50% of these patients are also allergic to cow’s milk, according to 1 case study.

II. IgE-mediated respiratory reactions

- Asthma makes for the worst prognosis in children with anaphylaxis.
- Asthma in patients with CMA is of particular severity.
- Respiratory symptoms in patients with CMA can progress to respiratory allergy.
- Inhalation of milk vapor has been associated with severe respiratory tract reactions.

III. IgE-mediated skin reactions

- Acute urticaria or angioedema
- Contact urticaria
- Pattern varies from irritant to allergic contact dermatitis.
- Generalized eczematous rash (systemic contact dermatitis) is present.

IV. Late-onset reactions

- Symptoms not IgE mediated
- Mostly localized in the gastrointestinal tract
- Typically develop 1 to several hours or even days after ingestion

Table I. Clinical manifestations of CMA

<table>
<thead>
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<tbody>
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<td>- Oral allergy syndrome (rare in pediatric patients)</td>
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<td>- Lip swelling is a commonly observed manifestation during food challenge procedures.</td>
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Contact reactions are frequent in patients with AD.

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<td>- AD is most often present as an eczematous lesion (after ingestion or contact).</td>
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<td>- AD can involve both IgE-mediated and non–IgE-mediated skin responses.</td>
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<td>- 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.</td>
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<td>- The earlier the age of onset, the greater the severity and frequency of high of cow’s milk sIgE levels.</td>
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<td>- Appropriate diagnosis and elimination diets frequently lead to symptom improvement.</td>
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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).
The natural history of CMA

CMA is primarily of pediatric onset,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5} 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 through 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. 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.

**Duration:**
In retrospective studies the duration of CMA differs in different settings. 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.

**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. However, the maintenance of tolerance in atopic patients is associated with persistently increased milk-specific IgG4 antibody concentrations.

CMA: DIAGNOSIS

The recommendations on diagnosis using SPTs and sIgE determinations are reported in Box E1. 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 theatopy patch test for CMA diagnosis, the low correlation with skin tests for single allergens and the unsatisfactory reproducibility.
of food atopy patch tests in children argue against their widespread clinical use in diagnosing CMA.135,146

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 first 6 months of life.3

Experimenting with immunotherapy for CMA

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

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 (e.g., gastroesophageal reflux).

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

<table>
<thead>
<tr>
<th>Protein</th>
<th>Allergen*</th>
<th>Amount (g/L)</th>
<th>Percent total protein</th>
<th>MW (kd)</th>
<th>No. of AAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whey proteins</td>
<td></td>
<td>~30</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>αs₁-Casein</td>
<td></td>
<td>12-15</td>
<td>29</td>
<td>23.6</td>
<td>199</td>
</tr>
<tr>
<td>αs₂-Casein</td>
<td></td>
<td>3-4</td>
<td>8</td>
<td>25.2</td>
<td>207</td>
</tr>
<tr>
<td>β-Casein</td>
<td>Bos d 8</td>
<td>9-11</td>
<td>27</td>
<td>24.0</td>
<td>209</td>
</tr>
<tr>
<td>γ₁-Casein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ₂-Casein</td>
<td></td>
<td>1-2</td>
<td>6</td>
<td>11.8</td>
<td>104</td>
</tr>
<tr>
<td>γ₃-Casein</td>
<td></td>
<td></td>
<td></td>
<td>11.6</td>
<td>102</td>
</tr>
<tr>
<td>κ-Casein</td>
<td></td>
<td>3-4</td>
<td>10</td>
<td>19.0</td>
<td>169</td>
</tr>
<tr>
<td>Caseins</td>
<td></td>
<td>~5.0</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Lactalbumin</td>
<td>Bos d 4</td>
<td>1-1.5</td>
<td>5</td>
<td>14.2</td>
<td>123</td>
</tr>
<tr>
<td>β-Lactoglobulin</td>
<td>Bos d 5</td>
<td>3-4</td>
<td>10</td>
<td>18.3</td>
<td>162</td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>Bos d 7</td>
<td>0.6-1.0</td>
<td>3</td>
<td>160.0</td>
<td></td>
</tr>
<tr>
<td>BSA</td>
<td>Bos d 6</td>
<td>0.1-0.4</td>
<td>1</td>
<td>67.0</td>
<td>583</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td></td>
<td>0.09</td>
<td>Traces</td>
<td>800.0</td>
<td>703</td>
</tr>
</tbody>
</table>

AA, Amino acid; MW, molecular weight.

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

<table>
<thead>
<tr>
<th>Protein</th>
<th>Goat</th>
<th>Ewe</th>
<th>Buffalo</th>
<th>Sow</th>
<th>Mare</th>
<th>Donkey</th>
<th>Dromedary</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Lactalbumin</td>
<td>95.1</td>
<td>97.2</td>
<td>99.3</td>
<td>74.6</td>
<td>72.4</td>
<td>71.5</td>
<td>69.7</td>
<td>73.9</td>
</tr>
<tr>
<td>β-Lactoglobulin</td>
<td>94.4</td>
<td>93.9</td>
<td>96.7</td>
<td>63.9</td>
<td>59.4</td>
<td>56.9</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>—</td>
<td>92.4</td>
<td>—</td>
<td>79.9</td>
<td>74.5</td>
<td>74.1</td>
<td>—</td>
<td>76.6</td>
</tr>
<tr>
<td>αs₁-Casein</td>
<td>87.9</td>
<td>88.3</td>
<td>—</td>
<td>47.2</td>
<td>—</td>
<td>—</td>
<td>42.9</td>
<td>32.4</td>
</tr>
<tr>
<td>αs₂-Casein</td>
<td>88.3</td>
<td>89.2</td>
<td>—</td>
<td>62.8</td>
<td>—</td>
<td>—</td>
<td>58.3</td>
<td>—</td>
</tr>
<tr>
<td>β-Casein</td>
<td>91.1</td>
<td>92.0</td>
<td>97.8</td>
<td>67.0</td>
<td>60.5</td>
<td>—</td>
<td>69.2</td>
<td>56.5</td>
</tr>
<tr>
<td>γ-Casein</td>
<td>84.9</td>
<td>84.9</td>
<td>92.6</td>
<td>54.3</td>
<td>57.4</td>
<td>—</td>
<td>58.4</td>
<td>53.2</td>
</tr>
</tbody>
</table>

—, Allergen is not present in the Swiss-Prot DataBank.
**TABLE E3.** The GRADE approach: Hierarchy of evidence

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial quality of a body of evidence</th>
<th>Lower if</th>
<th>Higher if</th>
<th>Quality of a body of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised trials</td>
<td>High</td>
<td>Risk of Bias (limitations in design or execution of studies)</td>
<td>Large effect</td>
<td>A/High (four plus: Ⓞ Ⓞ Ⓞ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inconsistency</td>
<td>Dose response Evidence of a gradient</td>
<td>B/Moderate (three plus: Ⓞ Ⓞ Ⓞ)</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Low</td>
<td>Indirectness</td>
<td></td>
<td>C/Low (two plus: Ⓞ Ⓞ Ⓞ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imprecision</td>
<td>All plausible residual confounding Would reduce a demonstrated effect Would suggest a spurious effect if no effect was observed</td>
<td>D/Very low (one plus: Ⓞ Ⓞ Ⓞ)</td>
</tr>
</tbody>
</table>
TABLE E4. Strength of recommendations from guidelines according to the GRADE approach

<table>
<thead>
<tr>
<th>Factors that can strengthen a recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of the evidence</td>
<td>The higher the quality of evidence, the more likely there will be a strong recommendation.</td>
</tr>
<tr>
<td>Balance between desirable and undesirable effects</td>
<td>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.</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The greater the variability in values and preferences or uncertainty in values and preferences, the more likely a weak recommendation is warranted.</td>
</tr>
<tr>
<td>Costs (resource allocation)</td>
<td>The higher the costs of an intervention (ie, the more resources consumed), the less likely a strong recommendation is warranted.</td>
</tr>
</tbody>
</table>