

Cow's milk allergy as a global challenge

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Purpose of review

Cow's milk is a leading cause of food allergy especially in infants and children.

'Diagnosis and Rationale for Action against Cow's Milk Allergy' published by the World Allergy Organization has underlined that there is not enough information concerning geographical trends in cow's milk allergy (CMA) in children or adults. Experts from Australia, Asia, North America, Latin America, the Middle East and Europe have gathered together in a 2-day meeting in order to present various regional approaches to CMA. This report is a summary of the information that was presented at this meeting.

Recent findings

Even though there seems to be uniformity concerning the diagnosis and treatment of CMA, the diagnostic approach to CMA shows variations among different regions. Common concerns were inadequate applications of challenge tests for the diagnosis and inadequate supply of the cow's milk substitute formulas.

Summary

CMA is a global challenge and collaboration of the national and international scientific communities is essential to produce and update practical guidelines for CMA.

Keywords

children, cow's milk allergy, food allergy, food allergy guidelines, pediatrics

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Introduction

According to the reports published by Centers for Disease Control and Prevention in 2008, the prevalence of food allergy in childhood has increased by 18% between 1997 and 2007 [1]. Cow's milk is one of the leading causes of food allergy especially in infants and children. Recently, the World Allergy Organization (WAO) published 'Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA)', the first guideline in the field [2•]. DRACMA underlines that there is not enough information concerning geographical trends in cow's milk allergy (CMA) in children or adults. To fill in this gap of knowledge, a panel was organized during DRACMA presentation meeting 'Adverse reactions to bovine proteins' [3], in which specialists from Australia, Asia, North America, Latin America, the Middle East and Europe presented regional approaches to CMA. This paper reflects the gaps, opportunities and pitfalls of CMA management in different contexts.

Australia

There are no current national prevalence data. A prospective community-based prevalence study determined that the clinical characteristics of the participants may affect the prevalence of food allergy. Results from this

questionnaire showed that those who declined participation were more likely to have infants that were already safely ingesting allergic foods or had no family history of allergy. This may tend to artificially increase the prevalence of food allergy identified from the responder population in our study [4]. In 1999, with 2% prevalence, CMA was the second most common food allergy after hen's egg in Australian infants [5]. The medical records from Australia indicate a 12-fold increase in demand for consultations related to food allergy (and a seven-fold increase in confirmed food allergy) between 1995 and 2006 [6]. In Australia, most of the children with suspected CMA are evaluated by general practitioners or pediatricians and then referred to the specialists. The tertiary-level pediatric allergy centers are located in five different cities in Australia. In addition to the pediatric allergist, the other specializations including pediatric gastroenterologist, pediatric dermatologist and general pediatricians are involved in care of infants diagnosed with CMA.

A national guideline for the use of infant formulas to treat cow's milk protein allergy (an Australian consensus panel opinion) was published in 2008 [7]. This consensus puts clearly the indications for use of soy, extensively hydrolyzed formula (eHF) and amino acid formulas (AAFs) in the treatment of CMA under Australian conditions in

general and pediatric practice. The AAF is recommended as first choice in anaphylaxis and eosinophilic oesophagitis, eHF for infants under 6 months of age for treating immediate but nonanaphylactic CMA, food protein-induced enterocolitis syndrome, atopic eczema, gastrointestinal symptoms and food protein-induced proctocolitis and soy formula is recommended for the same reasons for infants over 6 months of age. Only if a specialist prescribes the eHF initially, the health insurances reimburse the formulas. Moreover, the AAFs are reimbursed if the infant cannot tolerate eHF or soy. However, soy formula is not funded in Australia. Extensively hydrolyzed casein, rice or soy-based formulas are not available in Australia (and New Zealand). Increased clinical services and better access to pediatric allergist care are needed to limit referral delay and undertreatment. The management of children with CMA needs to involve training of primary and secondary care practitioners rather than predominantly relying on tertiary-level specialists.

Asia

In Japan, a Food Allergy Management Guideline appeared in 2005 and was revised in 2008 [8]. In Singapore, a national guideline was published in 2010 with the partial support by the Japanese guideline format ([http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Guidelines/Clinical_Practice_Guidelines/Management%20of%20Food%20Allergy_Final\(A5\).pdf](http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Guidelines/Clinical_Practice_Guidelines/Management%20of%20Food%20Allergy_Final(A5).pdf)). National guidelines are also in the course of publication in Korea and China. However, few epidemiological data are available although CMA is the second most frequent food allergy encountered by children from birth to 15 years of age in Japan, Korea, Singapore and China and the third most frequent food allergy in Thailand. When the diagnosis is challenge-confirmed, Japan's CMA prevalence in children 3 years old is 2.5%. Immediate allergic food-induced reactions and their causative foods fall within the remit of general practitioners, pediatricians, internists, dermatologists and otolaryngologists regardless of patients' age. Cutaneous reactions are present in 90% of patients with immediate food reactions, followed by respiratory (32%), mucosal (28%) and gastrointestinal (17%) symptoms and shock (11%) [9]. Among infants, cow's milk (27.4%) is the second causative food in immediate-type reactions. When accidental intakes are factored in, CMA is the second causative food for these reactions in children from 0 to 10 years of age. The children who developed anaphylactic shock ($n=283$) are classified according to causative foods and cow's milk intake is the second most frequent cause (22.3%) of anaphylaxis after egg. In Asian countries, CMA is diagnosed mostly by pediatricians and then by allergists and general practitioners and rarely by dermatologists or nutrition specialists. The pattern of CMA diagnosis varies across Asian countries. The oral food challenge is a

Key points

- 'Diagnosis and Rationale for Action against Cow's Milk Allergy' which is a publication of the WAO underlines that there is not enough information concerning geographical trends in cow's milk allergy (CMA) in children or adults.
- This paper reflects the gaps, opportunities and pitfalls of CMA management in different contexts. Current diagnosis and management of CMA does not represent a consistent systematic approach in different regions of the world and even in the same country.
- Although some countries have national or regional guidelines, the high variability of the diagnostic procedures is still a problem among different centers.
- In order to bring a systematic and global approach, the application of a universal guideline that respects regional cultural differences on CMA is mandatory.

routine diagnostic procedure in Japan and is practiced in 264 hospitals where pediatric specialty training centers are available. However, challenges are rarely carried out in Hong Kong, Singapore and Thailand and their use is limited to specialists, whereas in Korea and China they are not performed at all. Japan is the only nation where the National Health Service reimburses oral food challenge tests. The diagnosis of food allergy is mostly carried out as a hospital and office procedure in Japan, Hong Kong and Singapore. In Thailand, diagnostic procedures are only performed in-office. Diagnostic interventions and substitute formula prescriptions are not reimbursed anywhere in Asia. Substitute formulas such as eHF and AAFs are available in Japan, Singapore and Thailand. Goat's milk and chicken-based 'milk' are also proposed as alternatives for patients with CMA. Specific oral tolerance induction for CMA is practiced only in a limited number of hospitals, which are highly specialized in Japan and Hong Kong.

The USA

The current diagnosis and management of CMA do not represent a consistent systematic approach. CMA in children in the USA is overshadowed by peanut allergy. Without documentation, the label of CMA or intolerance is frequently applied to babies who spit up and to infants with vomiting, diarrhea, constipation or colic, frequent crying or insufficient sleep. Formula changes are frequently made to partially or completely hydrolyzed cow's milk, lactose-free, soy or AAFs. Parental education on avoidance is cursory. Thus, potentially cow's milk allergic infants are fed with cheese or yogurt and, at 1 year of age, are given homogenized cow's milk. More recently, primary care physicians have started ordering serum specific IgE 'pediatric panels', and interpret any positive

result as cow's milk as allergy and prescribe avoidance, still rather loosely.

The best estimate of the prevalence of CMA at 3.8% in infants up to 12 months of age comes from the Infant Feeding Practice Study [10]. When diagnostic oral food challenge is carried out, prevalence decreases up to 0.9%.

At the time of the conference there was only one published practice parameter in the USA that addresses the diagnosis and management of food allergy in general [11^{••}]. In 2008, the National Institute of Health and specifically the National Institute of Allergy and Infectious Diseases began the development of the Guidelines for the Diagnosis and Management of Food Allergy in the United States to meet a long-term need for harmonization of best clinical practices related to food allergy across medical specialties [12[•]]. An independent evidence-based literature search was commissioned in order to generate the Guidelines using the Grading of Recommendations Assessment, Development and Evaluation approach to classify the strength of the evidence. The guidelines addressed IgE-mediated food allergy in general, whereas cow's milk was addressed specifically in the section on natural history of food allergy. The guidelines also outlined gaps in knowledge in the area of food allergy. The guidelines emphasized that the diagnosis of food allergy is to be based on history, skin and blood tests as well as oral food challenges [13^{••}].

The oral food challenge procedure is used routinely for the diagnosis of CMA in nine highly experienced hospitals in the USA. The oral food challenges are carried out mostly for hen's egg, peanut and cow's milk and less frequently for soy and wheat [13^{••}]. In general, pediatricians are the specialists who diagnose food allergies in the USA, whereas allergists evaluate a minority of patients. Allergists or dermatologists are consulted when the clinical picture is complicated by additional food allergies or by comorbid conditions, when the allergy persists beyond the generally expected 1 year of age or when severe reactions recur. Dermatologists are called in only when eczema is moderate-to-severe and not responsive to topical therapy. Most patients are diagnosed in-office and all diagnostic procedures are reimbursed, including oral food challenges, but at a relatively low rate. Substitute formulas are dispensed to infants on the Women, Infant and Child (WIC) program but are not a covered benefit from commercial insurances. Only formulas administered by a nasogastric tube or a gastrostomy tube are reimbursed by commercial insurance. Partially hydrolyzed, totally hydrolyzed milk formulas, soy milk and AAFs are available as substitutes for cow's milk and recommended based on age or severity of the CMA. Rice-based hydrolysate available at grocery stores, but not specifically formulated for infants and toddlers is

occasionally used. Specific oral tolerance induction with cow's milk is under investigation only as a research procedure.

In Canada, Health Canada and Allergy, Genes, and Environment Network of Centres of Excellence (*Allergen*) are supporting the Surveying Canadians to Assess the prevalence of common food Allergies and Attitudes towards food Labelling and Risk (SCAAALAR) study, a research initiative led by McGill and McMaster Universities. This large Canadian survey on the prevalence of food allergies was launched in June 2008 (www.hc-sc.gc.ca). Results released in July 2010 included only a survey on peanut, tree nuts, shellfish, fish and sesame but not cow's milk (http://www.hc-sc.gc.ca/fn-an/securit/allerg/res-prog/allergen_research-eng.php).

A Guide to Food Labeling and Advertising was initially published by the Canadian Food Inspection Agency in 1963 and has received two amendments in 1993 and 2003. In the 'Guide', labeling of dairy products (milk and cow's milk) is discussed in Section 9.4. On the website of the CFIA (www.inspection.gc.ca), milk is listed among the food causing most allergic reactions. The list includes: peanuts, tree nuts [almonds, Brazil nuts, cashews, hazelnuts (filberts), macadamia nuts, pecans, pine nuts, pistachios, walnuts], sesame seeds, milk, eggs, seafood (fish, crustaceans, shellfish), soy, wheat and sulphite. Infant formulas available in Canada as alternative to cow's milk-based formulas are soy formulas and eHF. Rice-based formulas are not available.

Not much is published on food allergy from Mexico [14]. However, in personal discussions by the author with Mexican allergists, cow's milk and eggs are the common food allergens in children. There is heavy reliance on breast-feeding because formula is expensive. Substitutes for breast milk and cow's milk would include soy formula.

South America

Data on the prevalence of CMA and severity of disease are lacking for Latin America. The only CMA diagnosis and management guideline is from Argentina [15]. However, this guideline was prepared by a small group of pediatric gastroenterologists and nutritionists and clear recommendations regarding in-vivo or in-vitro allergy diagnosis are lacking. Double-blind placebo-controlled food challenge (DBPCFC) is the 'gold standard' among the different diagnostic tools. However, it is mentioned as an exceptional intervention. The open challenge is recommended in clinical daily practice in office and hospitals. In Argentina, available cow's milk substitutes include soy, cow's milk hydrolysates and AAFs. Roughly the cost is between 140 and 450 Argentinean pesos (ARG \$) per 450 g (EUR € 34–84). Some social health insurance mainly related to the unions, as well as private

insurance cover about 20–80% of the cost. In the public health system that takes care of deprived population, these substitutes are not covered at all. Thus, there is an urgent need to design an epidemiological study in order to gain insights about the prevalence and severity of CMA in Latin America.

The Middle East

In the Middle East, the prevalence of food allergy in the general population is not well known and there are no national or regional guidelines for food allergy. However, there are some reports that have investigated CMA within limited geographical entities. Orhan *et al.* [16] reported that the parent-reported food allergy is 5.7% in children aged between 6 and 9 years old in the Black Sea region of Turkey but the prevalence of food allergy and CMA confirmed by the DBPCFC is only 0.8 and 0.1%, respectively. According to various studies published from Turkey, Israel, Iran, Saudi Arabia and the United Arab Emirates, it is clear that the diagnosis of CMA is based on a clear history of allergic reaction to cow's milk plus evidence of specific IgE to cow's milk by skin prick tests and/or blood tests [17–26]. In addition to these tests, open challenge tests are frequently used. In Turkey, the challenge tests are used only in a limited number of highly experienced pediatric allergy centers in the universities. Generally, allergists, pediatricians, pediatric gastroenterologists, primary care physicians and – rarely – dermatologists order the specific tests. The misinterpretation of a positive specific IgE to cow's milk as CMA is not a rare problem among primary care physicians. Unfortunately, it results in unnecessary elimination of cow's milk for some children.

Another common problem in Turkey is the misconception that allergy tests can only be applied to children older than 5 years of age. Generally the pediatric allergist applies the skin prick tests and open challenge tests in children with suspected CMA. DBPCFCs are done only for research purposes. CMA is diagnosed more commonly in hospitals than in offices. The social health security system reimburses all the diagnostic procedures and the substitute formulas until 2 years of age as long as a specialist documents the diagnosis in written form. Soy-based eHF and AAFs are all available. Goat's milk is available but not recommended to children with CMA and soy milk is generally recommended after 1 year of age in Turkey. However, Shabo *et al.* [27] from Israel showed that the administration of camel milk is safe in children with CMA. Specific oral tolerance induction is applied only in one center for research purposes in Turkey. At Hacettepe Children's Hospital in Ankara, CMA was the second most frequent allergy next to hen's egg in children with food allergies [28]. Among the children with CMA, the majority had another food allergy in addition to cow's milk. In addition to cow's milk and hen's egg, tree

nuts and peanuts are the common causes of food allergies. Forty-six percent of patients with CMA presented with anaphylaxis. The self-injected epinephrine is not widely available and is not prescribed as frequently as needed in patients with a history of the anaphylaxis.

Europe

In several European countries including Austria, Belgium, Denmark, Finland, Germany, Greece, Italy, Poland, Slovenia and Switzerland, the self-perception of food allergy is reported between 1.7 and 11.7% in children (<18 years old), 1.8 and 7.1% in adults [29]. CMA is the most frequent reported food allergy on the telephone survey. The studies [30–47,48[•],49–52] evaluating food allergy by different methods including report, skin prick tests and DBPCFC tests revealed that food allergy ranges between 7.2 and 38%, 2.8 and 5.2% and 0.1 and 5%, respectively. There are two guidelines available in Germany, which offer recommendations for diagnostic pathways and therapeutic approaches in children and adolescents with suspected or proven CMA [53,54]. The diagnostic steps for CMA involve medical history, specific IgE measurement, skin prick and prick-to-prick tests and finally provocation tests consisted of DBPCFC as the gold standard diagnostic tools and open challenge tests. All the steps and evaluation of the reactions during the process of DBPCFCs are detailed in this guideline. The response to the questionnaire survey determined that food challenge tests were performed regularly in 122 institutions from Germany (50.2%) and 17 from Austria (54.8%) [55]. Among the centers making DBPCFC tests, only 18 institutions, which are mainly rehabilitation centers, performed more than 50 provocation tests per year. This questionnaire revealed that the procedures of the food challenge tests have high variability in the number of titration steps, time interval, ratio of verum and placebo, source of placebo, the person who observes the test, time points for checking the immediate and late phase reactions between clinics and different tests procedures in the same clinic. Another variability observed about the food challenges is the type of the test: 56 clinics (54%) performed only open challenges, 47 clinics have experiences with blinded challenges and six clinics (5.8%) perform only blinded challenges in Germany and Austria. Relatively high costs to perform DBPCFC do not pay off: in consequence mainly open challenges are used for CMA diagnosis. The therapeutic options are allergen avoidance and the use of adequate formulas (eHF or AAFs). In Germany, therapeutic administration of cow's milk substitute formulas is reimbursed since 2005 only if proven (DBPCFC) CMA, upon special request directly at the insurance company.

Specific oral tolerance induction is a possible future therapy of food allergy for selected patients. Today it is not recommended except in controlled studies.

Conclusion

The prevalence of CMA is variable among different age groups in different countries but seems to range between 0.1 and 4.2% in children. In many regions of the world cow's milk, egg and peanut seem to be the most common causes of food allergy [56].

Current diagnosis and management of CMA do not represent a consistent systematic approach in different regions of the world and even in the same country. Although some countries have national or regional guidelines, the high variability of the diagnostic procedures is still a problem among different centers. In order to bring a systematic and global approach, a detailed guideline is mandatory.

It is clear that there is not a uniform approach about the use of specific IgE, skin prick tests and food challenge tests. The cow's milk-specific IgE and skin prick tests as diagnostic tools are widely used. A common problem is the misinterpretation of any positive specific IgE to cow's milk in children as CMA. Obviously, this misinterpretation results in unnecessary avoidance of cow's milk in many instances. A clear and step-by-step guide for the diagnosis and surveillance of the children with CMA is essential for the correct interpretation of laboratory tests.

The oral food challenge test is not a routine procedure in many places. The food challenge tests are used only in some regions and the type of the challenge tests used shows a great variability even in the same country. It seems that even the countries with national guidelines have not been able to standardize the oral challenge tests. Even though the DBPCFC is perceived as the golden standard for the diagnosis of food allergy, the number of the allergy centers performing DBPCFC routinely is limited all over the world. DBPCFC tests are time-consuming and are costly especially in terms of health-care personnel. Therefore, DBPCFC tests are used generally only for research purposes. Mainly the allergists diagnose the CMA but general practitioners, family physicians and different specialists such as pediatricians, internal medicine specialists, dermatologists, gastroenterologists and otolaryngologists (ENT specialist) are involved in the routine diagnosis and more often in the treatment of the immediate and chronic symptoms.

The substitute formulas recommended by DRACMA that are amino-acid-based formula, extensively hydrolyzed whey or casein formula, soy formula or rice extensively hydrolyzed formula are available in the majority of the regions and countries. However, reimbursement of the diagnostic interventions and cow's milk substitutes show great variability among countries. The ratio of the reimbursement varies from 100% to the reimbursement

of only low-income patients or no imbursement in several regions. There are no commonly accepted criteria to select an alternative for cow's milk. In addition to eHF and AAFs a large spectrum of alternatives including goat's milk, mare's milk, donkey's milk, pig's milk camel's milk, chicken-based milk is available depending on the cultural behaviors. The specific oral tolerance induction for CMA is a new approach for the treatment of food allergy and it is applied only in a limited number of highly specialized centers and today it is not recommended as a routine therapeutic tool except in controlled studies.

This panel about CMA as a global challenge clearly showed that collaboration of the national and international scientific communities is essential to update and produce practical guidelines for CMA. A universal guideline that takes into consideration regional cultural differences is needed for standardizing management of CMA worldwide.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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