

Current practice and recent trends in preventing and treating CMPA

DRACMA Guidelines

Alessandro Fiocchi

Among several recently published clinical practice guidelines for the prevention and management of pediatric food allergies, the 2010 *Diagnosis and Rationale for Action against Cow's Milk Allergy* (DRACMA) guidelines represent the first consensus-based approach specific to the management of cow milk protein allergy (CMPA).¹ Focusing on diagnosis and management, rather than prevention, the authors of DRACMA applied the principles of evidence-based medicine to provide information intended to help physicians choose the most appropriate of several available alternatives to conventional cow milk based infant formula for babies with CMPA. Having reviewed 1,579 published studies, they concluded that a cow milk substitute should ideally: 1) be safe and non-allergenic, particularly for infants with severe CMPA, for which reason partially hydrolyzed formulas (pHF) are not recommended for treatment; 2) be nutritionally adequate, with no evidence of impaired growth or deficiency in protein, iron, vitamins or minerals; 3) be user friendly, and enhance quality of life for the users and their families at the lowest possible cost and, importantly, not taste unpleasant.

Key DRACMA recommendations include:²

- Safety is the overarching concern for children at high risk for anaphylactic reactions; amino-acid-based formulas (AAF) should therefore be used to avoid potential anaphylaxis, even if this is the most costly option.
- For children who are not at high risk of anaphylaxis, extensively hydrolyzed formula (eHF) may be favored over AAF, by virtue of its similar safety and lower cost. eHF should be tested in clinical studies before being used and when a new

“DRACMA guidelines allow physicians the flexibility to work within their recommendations to tailor treatment to patients’ individual circumstances”

Alessandro Fiocchi

formula is introduced for the first time, the patient should be carefully monitored for any adverse reactions that may develop.

- For children with immunoglobulin E (IgE) mediated CMPA, eHF is preferred to soy, which, despite being cheaper, may cause adverse reactions and growth deficit; however, soy may be a reasonable alternative in settings where the relative importance of affordability is greater. Soy should not be used in first 6 months of life, because of nutritional risks.
- Other mammal milks are not recommended due to the high cross-reactivity of sheep and goat milk, and nutritional problems with equine and camel milk.

Importantly, DRACMA is based not only on scientific evidence, but also real life, in which patient values, preferences and circumstances bear strongly on treatment outcomes. The DRACMA guidelines allow physicians the flexibility to work within their recommendations to tailor treatment to patients’ individual circumstances. Cost considerations were very important in shaping the guidelines. In general, AAF is 2.5 times more expensive than eHF and three times more expensive than soy formula. In countries/regions where soy is far cheaper than eHF, for example Brazil, Iran and Bulgaria, or low income settings where a slight price differential matters much more to buyers, the cheaper cost may override the high value placed on avoiding adverse reactions.

From Department of Child and Maternal Medicine, University of Milan Medical School, Melloni Hospital, Milan, Italy

In choosing the most appropriate treatment for CMPA, physicians should take into account the seriousness of the condition, the family's ability to pay and readiness to deal with failed dietary therapy, and the probability of refusal due to unpalatability.

In terms of cost, eHF is generally the best option; however, up to 10% of infants with CMPA may have allergic reactions to eHF, whereas none react to AAF.

Australia and New Zealand

John Sinn

Australia has among the highest prevalence of food allergies in the world, especially CMPA, which affects 2% of children. If there is a history of CMPA, the first strategy to treat CMPA is eliminating cow milk in maternal diet whilst breastfeeding. As there is a high cross reactivity with egg and peanuts these should also be avoided in the first instance. If the symptoms improve, egg and peanuts can be reintroduced one by one after 4 weeks, and cow milk after 6 months. For formula-fed babies, AAF is the first-line option for treating anaphylaxis and eosinophilic esophagitis, but an initial trial of eHF is recommended for other immediate non-anaphylactic food reactions and AAF is a second-line option.³ In practice, however, far more AAF is prescribed than strictly indicated. For example, although eHF is the recommended first-line for non-IgE mediated allergy it is very little used because of the 10% failure rate, and AAF tends to be used more often. An interesting study from Japan showed that compared to conventional infant formula, pHF decreased the severity of atopic dermatitis and had immunomodulatory effects,⁴ but this remains controversial, despite provisional evidence that pHF may be beneficial in CMPA. It is increasingly common, however, to desensitize infants with mild to moderate CMPA by feeding small quantities of pHF.

From Royal North Shore Hospital and The Children's Hospital, Westmead, The University of Sydney, Australia

“Soy is no longer recommended to prevent CMPA”

John Sinn

As eHF and AAF are expensive to purchase, the Australian government subsidizes these to assist parents to manage children with severe allergies. AAF can only be prescribed by allergist, immunologist or gastroenterologist. eHF can be prescribed by pediatricians.⁵ Unlike AAF and eHF, the price of non-subsidized soy-based formula is similar to conventional cow milk formula and it is a safe and nutritious alternative for the 85% of infants with IgE-associated CMPA who are not allergic to soy.⁶ However, soy is very rarely used and has a high discontinuation rate. Unprocessed soy milk has a different amino acid profile from cow milk, impairs zinc and iodine absorption and is associated with hypothyroidism, and has high aluminum and manganese levels,⁷ so it is important that children are given only soy formula, which has additives that compensate for these shortcomings. Nevertheless, soy formula still has high phytoestrogen levels and due to concerns about potentially adverse reproductive hormonal effects in both females⁸ and males,⁹ is not recommended for children younger than 6 months. Since a Cochrane review that showed no difference in the incidence of eczema between infants fed soy versus cow milk,¹⁰ soy is no longer recommended to prevent CMPA¹¹

China

Hu Yan

The prevalence of food allergy in China appears to have increased over the last 10 years, following a similar trend to most developing regions. Between 1999 and 2009, food allergy prevalence doubled from 3.5% to 7.7% ($p = 0.017$), with a parallel increase in positive skin-prick test (SPT) response from 9.9% to 18.0% ($p = 0.002$).¹² Similar to an earlier study in Chongqing, China, where challenge-proven prevalence of egg allergy was 2.5% and cow milk was 1.3,¹³ egg, followed by cow milk, shrimp and fish, was the most common food allergen. These allergies most commonly trigger reactions involving the skin, followed by the gastrointestinal and respiratory tracts.

Current management of CMPA in China involves administering hypoallergenic formulas. A recent study compared the therapeutic effects of three common hypoallergenic formulas on infants with CMPA;¹⁴ 22 were fed AAF, 21 eHF, and 17 soy formula, with follow-up at 1, 2, 3 and 6 months. Results at 6 months favored AAF and eHF, which

“Between 1999 and 2009, food allergy prevalence doubled”

Hu Yan

maintained normal growth, whereas the group fed soy formula had a pronounced decline in growth rate. In addition, AAF and eHF more effectively relieved atopic symptoms than soy formula, as shown by SCORing Atopic Dermatitis (SCORAD) remission velocity.

Health professionals in China have striven to formulate appropriate recommendations for diagnosing and treating infant-onset food allergies. They also conduct national training tours to acquire and disseminate information on the current status and latest thinking in food allergy management. Experts are currently developing evidence-based guidelines to bridge identified gaps on allergy referral, management of anaphylaxis, diagnosis, food allergen avoidance education, and appropriate selection of milk-based formula.

From Affiliated Children's Hospital of Chongqing, Medical University, Chongqing, China

Indonesia

Soemadiono

Epidemiologic data suggest increasing prevalence of asthma, allergic rhinitis and atopic dermatitis in Indonesia over the past 20 years. This rising trend spawns other health issues, including high treatment costs, the allergic march, and documented malnutrition in older children with food allergies. Primary prevention to counteract these threats to public health is a paramount priority.

In Indonesia, physicians use a simple and convenient an allergy-detection score card to identify infants at high risk. These cards enable pediatricians, obstetricians, general practitioners and midwives to provide standardized information.

Exclusive breastfeeding for at least 4 to 6 months is recommended as an inexpensive and effective way to protect against allergies. A local study found high-risk infants who were not exclusively breast-fed to be at greater risk for developing atopic dermatitis.¹⁵ In the absence of breast milk, pHF is an acceptable and affordable substitute. Pregnant mothers are strongly advised to quit smoking and avoid tobacco smoke as there is a direct correlation between increased IgE in newborn cord blood and cigarette smoke exposure during pregnancy, which may suggest an increased risk of allergies.¹⁶ Current guidance, is to begin introducing solid food at 4 months. Although preliminary evidence suggested

“Pregnant mothers are strongly advised to quit smoking and avoid tobacco smoke”

Soemadiono

that early introduction of solid foods may increase the risk of allergies, no clinical data support the hypothesis that delaying the introduction of solids until after 6 months prevents CMPA.¹⁷

Diagnosis and management of CMPA in Jakarta is based on recommendations by the Indonesia Paediatrician Association, with algorithms determined by whether the mother prefers to breastfeed or use formula. Infants with CMPA who are exclusively breast-fed should continue to receive breast milk until 9–12 months of age. If no symptoms develop during re-exposure, the infant may resume a normal diet; otherwise, an elimination diet should continue for 6 months. Formula-fed infants with CMPA may benefit from eHF or AAF, which should be given until 9–12 months. If no symptoms develop during re-exposure, they may resume normal cow milk formula; otherwise, an elimination diet should be continued for 6 months. If eHF or AAF are not available, soy-based formula is an acceptable alternative; however, this can only be given to infants aged 6 months or above. AAF is preferred in cases of severe CMPA, due to the 10% failure rate of eHF to resolve the symptoms.

From Child Health Department, Medical Faculty University Gajah Mada/Dr Sardjito Hospital, Jakarta, Indonesia

Malaysia

Nur Atiqah Ng Abdullah

Malaysia is no exception to the worldwide spread of food allergy. While published national data are scarce, cow milk is recognized as the most common food allergen. In this context, the Malaysian Society of Allergy and Immunology, in cooperation with the Malaysian Paediatric Association, recently published *Guidelines for the Management of Cow's Milk Protein Allergy 2012 (CMPA in Children)*.¹⁸ Based solely on currently available scientific evidence and/or best clinical practice, the document is intended to facilitate a practical approach to the care and management of allergic children. It provides frontline pediatricians, primary care physicians and allied healthcare providers with information about inappropriate substitute or elimination diets, the importance of accurate diagnosis, and locally-relevant issues (eg, cost/availability of infant formulas and religious dietary laws).

The basis of a confirmatory diagnosis is a thorough medical history, complemented by

From Pantai Hospital, Kuala Lumpur, Malaysia

“Dietary elimination is the key principle for managing CMPA”

Nur Atiqah Ng Abdullah

diagnostic tests including double-blind placebo-controlled food challenge, open food challenge, SPT, and serum cow milk-specific IgE test. Dietary elimination is the key principle for managing CMPA. Substitute formulas are not necessary in breast-fed infants or children more than 2 years old; however, they are mandatory for formula-fed infants or those below 2 years of age.¹⁸ Family history is an important element in prevention strategies for CMPA that can sway decisions to appropriate screening and early treatment and allow for tailored patient education and management.

The Malaysian guideline recommends exclusive breastfeeding for at least 4 months and switching to an infant formula with documented reduced allergenicity. There is no evidence indicating the preventative effect of maternal elimination of potential food allergens during pregnancy or breastfeeding.

Singapore

Anne Goh

The true prevalence of CMPA in Singapore is uncertain. Existing figures tend to be overestimates, due to over-reporting by concerned parents. In a preliminary study, the prevalence of self-reported CMPA was 2.0%, whereas convincing history indicated a lower figure of 1.6%. Another local study reported a similar discrepancy, with parents reporting food allergies in approximately 20% of the sample population, whereas SPT only indicated 12% food allergen sensitization. Nonetheless, such prevalence does warrant appropriate management and prevention measures to prevent adverse health consequences.

Management of CMPA in Singapore is based on the approach used for any IgE-mediated food allergy, starting with taking a detailed patient history that includes types of symptoms, the time these occur after ingesting food, age, and family history of allergy. Diagnostic tests, specialist referral and elimination diet are prescribed according to the severity of allergic reactions the patient develops. Regular follow-up and monitoring for tolerance are also essential elements of this symptom-based approach to management.

Children with IgE-mediated CMPA are advised to avoid goat and/or sheep's milk due to the 90% likelihood of cross-reactivity with cow milk.

From Department of Paediatrics, KK Women's and Children's Hospital, Singapore

“Patients should be strongly reminded about cross-reacting allergens in other foods, or allergens ‘hidden’ in food labels”

Anne Goh

Shifting to soy-based formula is also recommended; if such formula is not well-tolerated, allergic children may be fed eHF or AAF. Food avoidance is the cornerstone of long-term CMPA management. Patients should be strongly reminded about cross-reacting allergens in other foods, or allergens ‘hidden’ in food labels. They should also be advised to take precautions during high-risk situations (eg, dining out). In the event of acute food allergic reactions, an EpiPen[®] and a written anaphylaxis action plan should be immediately at hand. Developing tolerance to cow milk is possible and 80% of allergic children do so by age 3 to 5 years. The decision to reintroduce cow milk products should be based on SPT and levels of specific IgE. On the other hand, treatment for non-IgE mediated cow milk allergy is limited to using eHF, or AAF if eHF is not tolerated. To date, there are no preventive strategies recommended by health practitioners in Singapore. The use of pHF or eHF is neither approved nor discouraged, while there is no strong evidence confirming its preventive effects in CMPA.

Thailand

Jarungchit Ngamphaiboon

CMPA has become increasingly prevalent in Thailand recently, since milk-containing products have been marketed to pregnant women, who would not take cow milk as part of the usual Thai diet. However, the diverse manifestations of CMPA make diagnosis challenging. Unlike other countries, respiratory rather than skin symptoms are the most common, followed by a diversity of gastrointestinal symptoms. Atopic dermatitis accounts for more than 70% of skin manifestations and the most common respiratory symptoms are rhinitis (37%), blocked nose (32%), and recurrent wheeze (21%). Another notable symptom is failure to thrive, which affects 10%.

The Royal College of Pediatricians of Thailand, Thai Pediatric Society of Gastroenterology and Hepatology, Society of Pediatric Nutrition of Thailand, and The Allergy, Asthma and Immunology Association of Thailand published joint national guidelines for the management of CMPA in 2012. The nutritional principles include continuing breastfeeding and avoiding cow milk and dairy products from any type of food, prescription of any nutritionally adequate and safe diet, referral to a pediatric specialist in case of severe symptoms, and monitoring of nutritional and growth status every 3–6 months after commencing treatment. Nursing mothers should take calcium supplements if necessary. It is recommended to eliminate other allergenic foods from the maternal diet, and if symptoms do not improve, to investigate the child for other food allergies. In formula-fed infants, special hypoallergenic formula should be given depending on the severity of symptoms, patients' age, affordability, availability and palatability. Soy-based formula, eHF, AAF and modular formula are possible substitutes. However, replacement formula may not be necessary for children older than 2 years who get sufficient nutrition from solid food. In case of anaphylaxis or other severe symptoms, eHF or AAF should be tried first, with modular formula

“There are discrepancies between the guidelines and real-life practice”

Jarungchit Ngamphaiboon

prescribed by a pediatrician if either first-line option is not tolerated. Soy formula, eHF, or AAF are options for immediate IgE-mediated reactions, and eHF, AAF, modular formula or soy formula for non-IgE-mediated and mixed type allergies, again based on patient tolerability. Substitute formula prescriptions are not reimbursed in Thailand.

However, there are discrepancies between the guidelines and real-life practice. For example, CMPA symptoms may not become apparent as early as expected; most CMPA patients cannot be accurately diagnosed within the first year or until they are more than 3 years old. Also, CMPA is not self-limited by age; in reality, it takes at least 1 year after treatment for mild symptoms to resolve, 3 years for moderate symptoms, and 5 years for severe symptoms. The outcome will therefore depend on a patient's age at definitive diagnosis and their management. Detailed history taking is important to making an early diagnosis. IgE test results are often misinterpreted and although confirmatory oral food challenge is recommended, most parents are reluctant to subject their children to this. The guideline makes no recommendations concerning the duration to evaluate for pass or fail after testing infant formula, whereas in practice, the duration to evaluate for pass or fail is 2 weeks or more. Although not included in the guideline, pHF is used in cases of mild IgE and non-IgE mediated food allergy. The guideline makes no comment on supplementary foods, but these are usually started between the ages of 4–6 months, with egg after 6 months, seafood after 2 years and peanut after 3 years. Neither are there specific recommendations for prevention. In practice, breastfeeding for 6 months is encouraged. In cases where breastfeeding for 6 months is not possible, eHF or pHF can be substituted and introduction of common allergenic foods should be delayed. Soy formula cannot be used for prevention.

From Department of Pediatrics, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

References

1. Fiocchi A, Schünemann HJ, Brozek J, Restani P, Beyer K, Troncone R, et al. Diagnosis and Rationale for Action Against Cow's Milk Allergy (DRACMA): a summary report. *J Allergy Clin Immunol*. 2010;126:1119-28.e12.
2. Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, et al; World Allergy Organization (WAO) Special Committee on Food Allergy. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. *Pediatr Allergy Immunol*. 2010;21(Suppl 21):1-125.
3. Kemp AS, Hill DJ, Allen KJ, Anderson K, Davidson GP, Day AS, et al; Australian consensus panel. Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion. *Med J Aust*. 2008;188:109-12.
4. Jin YY, Cao RM, Chen J, Kaku Y, Wu J, Cheng Y, et al. Partially hydrolyzed cow's milk formula has a therapeutic effect on the infants with mild to moderate atopic dermatitis: a randomized, double-blind study. *Pediatr Allergy Immunol*. 2011;22:688-94.
5. Australian Government Department of Health and Ageing. Schedule of Pharmaceutical Benefits [Internet] 2012 Oct. [cited 2012 Oct 25]. Available from: <http://www.pbs.gov.au/publication/schedule/2012/10/2012-10-01-general-schedule.pdf>
6. Zeiger RS, Sampson HA, Bock S, Wesley Burks Jr A, Harden K, Noone S, et al. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr*. 1999;134:614-22.
7. Lönnerdal B, Cederblad A, Davidsson L, Sandström B. The effect of individual components of soy formula and cows' milk formula on zinc bioavailability. *Am J Clin Nutr* 1984;40:1064-70.
8. Zung A, Glaser T, Kerem Z, Zadik Z. Breast development in the first 2 years of life: an association with soy-based infant formulas. *J Pediatr Gastroenterol Nutr*. 2008;46:191-5.
9. Tan K, Walker M, Morris K, Greig I, Mason J, Sharpe R. Infant feeding with soy formula milk: effects on puberty progression, reproductive function and testicular cell numbers in marmoset monkeys in adulthood. *Hum Reprod*. 2006;21:896-904.
10. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev*. 2006;(4):CD003741.
11. United Kingdom Department of Health. Chief Medical Officer's Update 37. London: Department of Health, 2004.
12. Hu Y, Chen J, Li H. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. *Pediatr Int*. 2010;52:820-4.
13. Chen J, Hu Y, Allen KJ., Ho MHK, Li H. The prevalence of food allergy in infants in Chongqing, China. *Pediatr Allergy Immunol*. 2011;22:356-60.
14. Yan J, Chen J, Li H, Hu Y. Evaluation of therapeutic effects of three hypoallergenic formulae in infants with cow's milk protein allergy. *Zhonghua Er Ke Za Zhi*. 2011;49:501-5.
15. Budiastuti M, Wandita S, Sumadiono. Exclusive breastfeeding and risk of atopic dermatitis in high risk infant. *Berkala Ilmu Kedokteran*. 2007;39:192-8.
16. Hasanah L, Sumadiono, Wandita S. Correlation between total immunoglobulin E (IgE) of newborn cord blood and cigarette smoke exposure during pregnant mother [abstract]. *Paediatrica Indonesiana*. 2010;50(Suppl).
17. Sari R, Ni Luh Putu H, Faturrahman D, Barlianto W. Timing of solid food introduction and the development of cow milk allergy in Saiful Anwar General Hospital, Malang [abstract]. *Paediatrica Indonesiana*. 2010;50(Suppl).
18. Malaysian Society of Allergy and Immunology. Guidelines for the Management of Cow's Milk Protein Allergy 2012 (CMPA in Children) [Internet]. 2012. [cited 2012 Oct 25]. Available from: http://www.allergysai.org/file_dir/6296706325048109343baa.pdf
19. Ngamphaiboon J, Chatchatee P, Thongkaew T. Cow's milk allergy in Thai children. *Asian Pac J Allergy Immunol*. 2008;26:199-204.
20. The Royal College of Pediatricians of Thailand. Clinical practice guideline for the management of cow's milk protein allergy, 2012.