



How guideline can shape clinical practice globally: the diagnosis and rationale for action against cow's milk allergy experience

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Purpose of review

Allergic diseases are increasing worldwide and are considered an important public health problem causing severe and even life-threatening reactions. The creation of guidelines aims to help clinicians improving the quality of diagnosis and management of such diseases. Clinical practice guidelines alone are not sufficient and there is a need for implementation strategies for their introduction into daily practice. We report here the main international allergy guidelines with a more focused look on the Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines and their effect on clinical practice.

Recent findings

DRACMA guidelines have clearly modified the approach to cow's milk allergy (CMA) from its diagnosis to treatment tailoring the choices for each patient. Although they strongly recommend oral food challenge for diagnosing CMA, they also indicate that it may not be necessary in many cases with the introduction of the pretest probability of CMA. Studies on the implementation of DRACMA guidelines show how they influenced the formula market, making appropriate treatments more affordable.

Summary

DRACMA reconciled international differences in the diagnosis and management of CMA. They introduced the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology in the field of food allergy and highlighted the importance for meta-analyses to be able to adapt recommendations to the local context.

Keywords

allergy, development and evaluation, diagnosis and rationale for action against cow's milk allergy, grading of recommendations assessment, guideline, milk, treatment

INTRODUCTION

Allergic diseases are increasing worldwide and are considered an important public health problem because they affect children and adults, causing severe and even life-threatening reactions. Among the aims of globally established scientific allergy societies, the creation of guidelines points to help clinicians improving the quality of diagnosis and management of such diseases. Guidelines may smooth out the variations existing between the different centers in the different countries of the world. The production of clinical practice guidelines alone is not sufficient and there is a need for implementation strategies for their introduction into daily practice.

We report here the main international allergy guidelines with a more focused look on the diagnosis and rationale for action against cow's milk allergy

(DRACMA) guidelines and their effect on clinical practice.

GLOBAL ALLERGY GUIDELINES

The Global Initiative on Asthma (GINA) was launched in 1993 in collaboration with the National Heart, Lung, and Blood Institute; the National

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KEY POINTS

- The use of implementation approaches helps guidelines to reach physicians everywhere improving the quality of diagnosis and clinical care.
- The DRACMA guidelines have clearly modified the approach to CMA from its diagnosis to treatment, tailoring the choices for each patient by taking into account the values, preferences, and remarks of each context.
- The DRACMA guidelines strongly recommend OFC for diagnosing CMA to avoid the risk of anaphylactic reactions at home in false negative sensitization tests, unnecessary treatment for false positive cases, and inappropriate resource utilization, but they also indicate that challenge may not be necessary in those cases with a high pretest probability of CMA and positive sensitization tests.
- DRACMA guidelines have been able to decrease the cost of an AAF by 30% in Italy, modifying the balance of recommendations for a substitute formula.

Institutes of Health (USA); and the WHO. It produced a consensus report on asthma treatment, which aimed to bridge the gap between the various treatment options and implemented innovative treatments into daily clinical practice. The first report published in 1995, 'A Global Strategy for Asthma Management and Prevention', was translated into several languages, widely adopted, and discussed. It provided the foundation for several asthma guidelines worldwide. GINA and other guidelines were primarily based on consensus of expert opinion; however, in the late 1990s, they underwent a major paradigm shift from opinion to evidence-based classification as the foundation for asthma management. In the 2006 revision, a second considerable shift involved the classification of asthma according to the level of disease control as a guide to treatment.

A major revision of the GINA report was published in 2014, and updated in 2015, then recently in March 2018 [1]. It witnesses an evolving understanding of heterogeneous airways disease, a broader evidence base, increasing interest in targeted treatment, and evidence about effective implementation approaches. During development of the report, the clinical utility of recommendations and strategies for their practical implementation were considered in parallel with the scientific evidence.

Similarly, Allergic Rhinitis and its Impact on Asthma (ARIA), a nongovernmental initiative in collaboration with WHO through the Global Alliance Against Chronic Respiratory Diseases, created a state-of-the-art document for the specialist as well as for the general practitioner and other healthcare

professionals dealing with allergic rhinitis. It was intended to update their knowledge of allergic rhinitis, to highlight its impact on asthma, to provide an evidence-based documented revision on diagnostic methods and treatments, and to propose a stepwise approach to management. An important achievement of ARIA was also to propose a new classification for allergic rhinitis into 'intermittent' or 'persistent', and 'mild' or 'moderate/severe' disease according to symptoms and quality of life impairment. Another important aspect was to consider comorbidities of allergic rhinitis for instance the eye involvement and paranasal sinuses, which are an integral part of the respiratory tract.

The ARIA document, first published in 2001 [2] and revised in 2008 [3], 2010 [4], and 2016 [5^{*}], was not conceived as a standard of care document for individual countries. It was provided as a basis for physicians, healthcare professionals, and organizations in various countries to facilitate the development of relevant local standard of care documents for their patients.

Regarding urticaria, the first international guideline was generated in 2004 as the result of a consensus reached during a panel discussion in the second International Consensus Meeting on Urticaria, a joint initiative of the European Academy of Allergy and Clinical Immunology Dermatology Section and the Global Allergy and Asthma European Network. It covered, in two articles, the definition and classification of urticaria, and the management of this disease [6,7]. Since 2008, World Allergy Organization (WAO)'s participation in the panel also begun [8–10]. This collaboration ensured that the consensus included European and global regional differences in viewpoint and provided a basis for improved comparison of future studies.

These guidelines are regularly updated, and the most recent versions of 2013 and 2018 used the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) methodology and merged them in single documents [11,12^{*}]. They have recently been compared to the American and Asian guidelines [13,14]. The American practice parameter [15] and the Asian guidelines [16,17] are in agreement with the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/WAO guidelines on most points regarding the definition, cause, diagnosis, and management, but subtle differences do exist and after the comparisons, the latter resulted to be the most comprehensive document and should serve as the consensus document on the diagnosis and management of chronic, spontaneous urticaria.

Always among the WAO missions and to respond to a lack of global protocols regarding the

assessment and management of anaphylaxis, the WAO Anaphylaxis Special Committee developed in 2010 the WAO Anaphylaxis guidelines [18]. Published in early 2011, these guidelines provided a global perspective on patient risk factors, triggers, clinical diagnosis, treatment, and prevention of anaphylaxis, thus they have been widely disseminated and used for information about anaphylaxis.

In 2012–2013, primary advances occurred in the characterization of patient phenotypes, in the development of component resolved diagnosis, in epinephrine research, and in immunotherapy to prevent food-induced anaphylaxis. For this reason, two updated versions of the guidelines have been published to insert the news in the mentioned fields [19,20].

In 2014–2015, major advances were related rather to patient risk factors and cofactors that amplify anaphylaxis, and greater insights were made into anaphylaxis triggers such as food, venom, and drugs, as well as idiopathic anaphylaxis. High-quality observational studies confirmed the importance of prompt injection of epinephrine in reducing hospital admissions and anaphylaxis fatalities. The 2015 update [21[¶]] reports all the novelties in the abovementioned topics.

Another field in which WAO wanted to respond to unmet needs is that of the management of cow's milk allergy (CMA). WAO special committee on food allergy brought together pediatric allergists, food allergists, and other experts in a panel to rationalize the whole management process of IgE-mediated CMA from workup to treatment and developed the DRACMA guidelines [22]. Up to 2008, clinical practice parameters for the treatment of CMA consisted mainly of national allergy society position articles reflecting local views and needs. These were aimed at different treatment strategies, not always evidence-based. For these reasons, it was decided that clinical practice guidelines issued on behalf of WAO would apply the GRADE methodology even though for the first time in the field of food allergy.

GUIDELINES' IMPLEMENTATIONS STRATEGIES

The relevance of guidelines is widespread recognized as pivotal. Overall, their dissemination is interpreted as articulating a 'standard of care', a standard that has political, sociological, and even legal ramifications when compared with day-to-day practice. Notwithstanding, guidelines are not always translated to policy or practice [23]. Their limited use contributes to omission of beneficial treatments, preventable harm, suboptimal patient outcomes or experiences, or waste of resources [24].

The implementation science aims to identify barriers, choose and tailor implementation strategies to optimize their clinical impact [25,26]. In particular, implementation approaches and strategies have been categorized [27] and include characteristics of the recommended practice and patient, provider,

Table 1. Main implementation strategies

Professional
Identify barriers Distribute guideline material Advertise guideline material Present guideline materials at meetings Educate individuals about guideline intent/benefits Educate groups about guideline intent/benefits Recruit an opinion leader who recommends implementation Achieve consensus that guideline should be implemented Provide reminders to individuals/groups about intent/benefits Provide alerts when practice deviates Provide feedback on compliance Provide feedback about patients (outcome data, self-report) Provide feedback from patients Provide feedback from healthcare professionals Print material (summary, algorithm, referral forms, so on) Tailor guideline Enable self-audit (training, material)
Financial
<i>Health professional</i> Incentive (individual financial reward or benefit for compliance) Incentive (group or institutional financial reward or benefit) Grant or allowance to individual (not tied to compliance) Grant or allowance to group/institution (not tied to compliance) Penalty (individual, for noncompliance) Penalty (group/institution, for noncompliance) Change in reimbursement (add/remove/substitute)
<i>Patient</i> Incentive (individual financial reward/benefit for compliance) Grant or allowance (not tied to compliance) Penalty (for noncompliance) Incentive (individual nonfinancial reward/benefit for compliance)
Organizational
<i>Health professional</i> Additional human resources (number/type) Reallocated or new role Create an implementation/multidisciplinary team Communication between distant health professionals Improve health professional satisfaction (nonfinancial)
<i>Patient</i> Consumer participation in governance
Structural changes
Organizational structure (including reorganization) Setting/site of service delivery Physical structure, facilities, or equipment Information/communication technology Quality improvement, performance measurement system Method of service delivery Integration of services Risk management provisions (including insurance coverage)
Regulatory
Legislation or regulation (which enforces or mandates) Ownership or affiliation Licensing, credentialing, or accreditation
Patient/consumer
Education (single or group) Counseling Group interaction (via social media) Print material (summary, so on) Reminder

Adapted with permission [23].

institutional and system-level factors (Table 1). There is evidence that many guidelines are implemented using educational approaches – such as workshops – directed at health professionals or patients. Educational approaches are often combined with other more complex interventions such as organizational, financial, or regulatory strategies, which require large-scale change and/or considerable funding [28]. However, the use of single versus multiple implementation approaches and strategies remains controversial and the choice of the most effective tools should be defined case by case [29].

IMPLEMENTATION TOOLS ACTIVATED FOR DIAGNOSIS AND RATIONALE FOR ACTION AGAINST COW'S MILK ALLERGY

The missions of DRACMA Guidelines are to provide physicians everywhere with a management tool to deal with CMA from suspicion to treatment, to inform the decision level of the appropriate diagnostic and therapeutic strategies on CMA, and to inform the public about the importance of the problem of food allergy and CMA in particular. To succeed is their missions, many actions have been taken as part of their strategic implementation.

The DRACMA document, in its 19th and final section, set itself some recommendations for the implementation of the guidelines:

- (1) DRACMA publication: *WAO Journal*, April 2010.
- (2) Milan Meeting proceedings: *Journal of Allergy and Clinical Immunology* 2010.
- (3) GLOBal Resources In Allergy educational modules.
- (4) World allergy societies' endorsement and input sought.
- (5) World sister societies' endorsement and input sought.
- (6) DRACMA symposia during allergy and nutrition society meetings.
- (7) Outreach toward patient organizations.
- (8) Creation of an international bureau for dissemination and update of WAO DRACMA guidelines.

To achieve these goals, a DRACMA Implementation Committee was formed and worked on the different points and successfully joined the majority them. Apart from its publication in the *WAO Journal*, the original version of DRACMA was copublished in *Pediatric Allergy and Immunology (PAI)* [30], once again with an open access, where it was the most downloaded article in 2011, the second in 2012, and the third in 2013. The publication in the *WAO Journal* was the most accessed article in 2011 and 2012. Up to 1 November 2018, according the Scopus data,

306 articles cited the two versions. A summary report was published after the 2nd Milan Meeting on Adverse Reactions to Bovine Proteins in February 2010, where the guidelines were presented for the second time [31] after their first exposition in Buenos Aires. It has been cited 138 times thus far, with a 6.2 field-weighted citation impact. The systematic review and meta-analysis proposing the recommendations for oral immunotherapy in CMA [32] has been cited 118 times with a 6.02 field-weighted citation impact.

DRACMA guidelines were also directly translated into national languages, to overcome communication barriers in Italy [33], in South America with the Spanish translation [34], in China [35,36], and a shortened version with the recommendations in France [37]. In Mexico, the DRACMA recommendations were incorporated in a large specific guideline [38].

Other publications involving some DRACMA panelists together with those of GRADE have been made those years to highlight the importance of applying the GRADE methodology in the construction of recommendations in clinical practice [39–41].

After the Milan Meeting and the publication of DRACMA, 93 WAO-affiliated national Allergy Societies endorsed the guidelines and implemented them. Many of the national meetings of these societies hosted lectures on the topic. DRACMA was presented in many countries, including the United States, France, Italy, Brazil, Chile, Argentina, Kenya, Egypt, Thailand, and Malaysia, to name a few. In addition, some Allergy Societies outside of WAO, for example, the Iranian, invited WAO lecturers to present DRACMA.

EFFECTS OF DIAGNOSIS AND RATIONALE FOR ACTION AGAINST COW'S MILK ALLERGY ON GLOBAL CLINICAL PRACTICE

First of all, DRACMA recommendations substantially modified the practice in diagnosing CMA [42]. Before DRACMA, very often oral food challenge (OFC) was not part of the diagnostic workup and indicated only after an elimination period of a few months or upon a specialist's advice in more severe cases. This exposed whole populations to overdiagnosis of CMA and to excessive use of elimination diets. Although the DRACMA guidelines strongly recommend OFC for diagnosing CMA to avoid the risk of anaphylactic reactions at home in false negative sensitization tests, unnecessary treatment for false positive cases, and inappropriate resource utilization, they also indicate that challenge may not be necessary in many cases. It is in

this context that we see the novelty of the inclusion of the CMA pretest risk assessment. Assessing the clinical history, physicians can determine the diagnostic likelihoods estimating the pretest probability of CMA. As examples, the pretest probability will be low in cases of atopic dermatitis or gastroesophageal reflux disease, average in case of immediate reactions, or high in case of anaphylaxis. In the latter, physicians reach a highly probable diagnosis using simpler diagnostic tests such as skin prick tests and/or specific IgE determination. OFCs remain necessary in all cases of high uncertainty. The search for replacement tests has been very active in the past years. Specific IgE cutoff points, skin prick tests diameters, and/or atopy patch test have been proposed as replacement tests. In DRACMA, the limits of these diagnostic practices are clearly indicated

and their possible use is reevaluated. Atopy patch test is not considered useful in the diagnosis of IgE-mediated CMA.

The other area in which DRACMA guidelines heavily influenced clinical practice is CMA treatment [43,44²²].

Every recommendation reports the outcome that was considered most relevant (Table 2). Outcomes and their ranking were not arbitrarily chosen, but selected from the literature by the expert panel. This method allows the pediatrician to tailor treatment of CMA to changing conditions while observing the recommendations.

As the cost of the same formula differs substantially from country to country, the implementation of the recommendations may differ. In recommendation 7.2, for example, extensively Hydrolyzate

Table 2. Guidelines for choosing a replacement formula

Question 7 Should amino acid formula, extensively hydrolyzed whey or casein formula, soy formula, or rice formula be used in children with IgE-mediated CMA?	
Recommendation 7.1	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 where the cost of amino acid formulas is high Remarks. In controlled settings, a trial feeding with an extensively hydrolyzed milk formula may be appropriate
Recommendation 7.2	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 where the cost of amino acid formula is high. In settings where the cost of amino acid formula is lower, the use of amino acid formula may 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 if any adverse reactions develop after first administration
Recommendation 7.3	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 utilization. In settings where relative importance of resource expenditure is lower an alternative choice may be equally reasonable. Remarks. Soy should not be used in first 6 months of life, because of nutritional risks
Recommendation 7.4	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. We suggest that more well designed and executed randomized trials comparing soy formula to extensively hydrolyzed rice formula are performed in patients suspected of IgE-mediated CMA Remarks. There is very sparse evidence suggesting possible benefit from using extensively hydrolyzed formula compared with soy formula, but more research is needed to confirm these observations

CMA, cow's milk allergy.
Adapted with permission [22].

Formula (eHF) is preferred to amino acid formula (AAF), if there is no risk of anaphylaxis. The reason for this approach is the high cost of AAF formula (see 'values and preferences'). Elaborating on these considerations, an Italian company decided in 2012 to decrease the cost of their AAF by 30%, so that it dropped from 2.4 to 2 times that of eHF. This did modify the balance of recommendations for a substitute formula and, for example, when facing a child with cow's milk protein-induced atopic dermatitis, it became easier to advise an AAF against an eHF. Although such decisions ideally include economic modeling, the factors in the equation generated in the mind of every single pediatrician will be manifold, but it is certain that they will include the seriousness of the condition, the assessable economic capacity of the family, the psychological readiness of the family to meet with failure of the dietary therapy, and the probability of the refusal of the child in front of the scarce palatability of the formula itself. The problem is compounded by the fact that on the Italian market, in contrast with many others, extensively hydrolyzed rice formulas are also available and have been assessed as similar to eHFs from a nutritional point of view by the systematic review carried out as part of DRACMA. This example illustrates how DRACMA guidelines did influence the formula market, making appropriate treatments affordable to larger layers of population. Naturally, this is only one of the factors for an appropriate care.

In recommendation 7.3, eHFs are preferred over soy formulas to avoid untoward reactions to soy. These recommendations deeply change the traditional approach to the choice of a substitute formula. As an example, soy formulas, widely used, are a second-line choice because of possibility of secondary sensitization and to nutritional drawbacks. In contexts where soy formula is cheaper than eHF and extensively hydrolyzed rice formulas are unavailable (e.g., Iran and Brazil), this recommendation should be diversely applied in the face of wider social and economic disparities. In any case, soy formula cannot be considered under 6 months of age.

CONCLUSION

The DRACMA guidelines have clearly modified the approach to CMA from its diagnosis to treatment tailoring the choices for each individual patient. They are under a process of an update in which they will include non-IgE-mediated forms of CMA which are still lacking global evidence-based protocols.

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Conflicts of interest

There are no conflicts of interest.

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

- of special interest
- of outstanding interest

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Comprehensive analysis of DRACMA, the first global guidelines containing all the recommendations, evidence profiles, and literature search algorithms on CMA.