Development and implementation of guidelines in allergic rhinitis - an ARIA-GA2LEN paper

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POSITION PAPER

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ARIA; asthma; EAACI; EFA; GA^{2}LEN; IPCRG; rhinitis.

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Abstract

The links between asthma and rhinitis are well characterized. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines stress the importance of these links and provide guidance for their prevention and treatment. Despite effective treatments being available, too few patients receive appropriate medical care for both diseases. Most patients with rhinitis and asthma consult primary care physicians and therefore these physicians are encouraged to understand and use ARIA guidelines. Patients should also be informed about these guidelines to raise their awareness of optimal care and increase control of the two related diseases. To apply these guidelines, clinicians and patients need to understand how and why the recommendations were made. The goal of the ARIA guidelines is to provide recommendations about the best management options for most patients in most situations. These recommendations should be based on the best available evidence. Making recommendations requires the assessment of the quality of available evidence, deciding on the balance between benefits and downsides, consideration of patients' values and preferences, and, if applicable, resource implications. Guidelines must be updated as new management options become available or important new evidence emerges. Transparent reporting of guidelines facilitates understanding and acceptance, but implementation strategies need to be improved.

Abbreviations
ARIA, Allergic Rhinitis and its Impact on Asthma; CARAT, Control of Rhinitis and Asthma Test; EAACI, European Academy of Allergology and Clinical Immunology; EFA, European Federation of Allergy and Airways Diseases Patients Associations; GA^{2}LEN, Global Allergy and Asthma European Network; GRADE, Grading of Recommendation, Assessment, Development, and Evaluation; IPCRG, International Primary Care Respiratory Group.

Allergic rhinitis and asthma represent a global health problem in both children and adults. Allergic diseases are common worldwide. In some countries, they affect over 40% of the young adult population, and their prevalence is increasing. Allergic rhinitis adversely affects social life, school performance, and work productivity (1), particularly in patients with severe disease (2). Rhinitis symptoms have a detrimental effect on academic performance (3). Some medications to treat these diseases can increase functional impairment (4). Moreover, the costs incurred by subjects with rhinitis are substantial. Nonallergic rhinitis, another common problem, is a heterogeneous group of diseases less well understood and controlled than allergic rhinitis (5).

Epidemiologic studies consistently show that asthma and rhinitis frequently co-exist in the same subjects throughout the world (1, 6). Rhinitis, often self-reported, is also a significant problem for patients with asthma (7). The prevalence of asthma in subjects without rhinitis is usually $<2\%$, whereas the prevalence of asthma in patients with rhinitis varies from 10% to over 40%. Asthma appears more prevalent in patients with persistent and more severe rhinitis (8–12). Most patients with allergic or nonallergic asthma have rhinitis (6, 13). There is a probable association between the severity of asthma and rhinitis or rhinosinusitis (14–18).

Clinicians are confronted with various treatment choices to manage allergic rhinitis. This contributes to considerable variation in clinical practice, and patients, clinicians, and other health care professionals worldwide are faced with uncertainty about the relative merits and downsides of the various treatment options (1, 19). Clinical practice guidelines for the management of allergic rhinitis have been developed over the past 15 years and have improved the care of patients with allergic rhinitis (20). Allergic Rhinitis and its Impact on Asthma (ARIA) was the first in the field of these evidence-based guidelines (21). ARIA was developed in collaboration with specialists in allergy, primary care physicians, and patient representatives from the European Federation of Allergy and Airways Diseases Patients Associations (EFA). Several guidelines have recently been published, including those from the International Primary Care Respiratory Group (22), the British Society of Allergy and Clinical Immunology (BSACI) (23), the American Academy of Allergy, Asthma and Clinical Immunology, the American College of Allergy, Asthma and Immunology (24) and the ARIA 2008 Update (1). ARIA and its update as well as the Spanish Asthma Management Guide (25) are the only guidelines, which assess the management of patients with both allergic rhinitis and asthma in the same document. These guidelines were based on various evidence-based models, but none except the latest ARIA Revision used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach – a systematic and transparent way of developing health care recommendations (26, 27).

The methodology for the development of guidelines is essential for their validity and acceptance in the clinical community. Methodologists without important conflicts of interest should be involved (28, 29, 30) with input from all stakeholders, including physician experts, and patients. The majority of patients with allergic rhinitis and asthma are treated by primary care physicians (31, 32) and therefore it is important that these physicians should be involved in the development and implementation of such guidelines (33). However, in primary care, there is an inadequate implementation of guidelines for allergic and chronic respiratory diseases. One of the reasons for this lack of implementation is the lack of involvement of primary care practitioners in the guideline development process in respiratory medicine and their potential lack of understanding the true intent of a clinical practice guideline. In regard to rhinitis and allergy, there is indeed a need for more awareness of the links between rhinitis and asthma as well as an improved global management readily applicable to primary care and patients. Patient organizations have a key role in contributing and objectively interpreting available evidence, such as evidence on patient values and preferences.

Similarly to the development of guidelines, the management of patients should be undertaken using a comprehensive approach. Physicians, in particular primary care providers, need to understand that asthma and rhinitis are similar disease processes and may be different manifestations of the same disease. To satisfy patient expectations, both asthma and rhinitis should be appropriately diagnosed and controlled, and attempts should be made to prevent their occurrence. Thus, rigorous, unbiased guidelines are needed and should be developed for easy understanding and application by all physicians, health professionals, and patients. An example of such a guideline adapted from ARIA is proposed for the management and control of allergic rhinitis and its major comorbidity, asthma.

Guideline development using GRADE in allergic rhinitis

GRADE

The 'Guidelines for WHO Guidelines' recommend using a specific, uniform grading system (34). The GRADE approach is recommended by the WHO (26) and is being used increasingly by a number of prominent organizations throughout the world (35–40). It grades recommendations on two levels – strong and weak (an alternative term is conditional) and quantifies evidence into four categories – high (in symbolic language: four plus), moderate (three plus), low (two plus), and very low (one plus) (26, 41). While the quality of evidence is one of the factors influencing the strength of a recommendation, these strengths are also influenced by a balance between the benefits and downsides, values and preferences, and considerations around resource utilization (42) (Table 1).

Development of ARIA Revision using GRADE

The ARIA 2010 Revision was developed following the GRADE approach (43) by the ARIA guideline panel (Fig. 1).

Table 1 Grading the strength of recommendations and quality of evidence in the ARIA guidelines according to the GRADE system

Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable consequences	Implications (for patients, clinicians, and policy makers) and interpretation of the quality of evidence
Strong recommendation		
High-quality (four plus: ⊕⊕⊕⊕) evidence	Desirable consequences clearly outweigh undesirable consequences, or vice versa	Patients: Most people in your situation would want the recommended course of action and only a small proportion would not Clinicians: Most patients should receive the recommended course of action Policy makers: The recommendation can be adapted as a policy in most situations There is confidence that the true effect lies close to that of the estimate of the effect. Further research is unlikely to change the confidence in the estimate of effect
Moderate-quality (three plus: ⊕⊕⊕◯) evidence	Desirable consequences clearly outweigh undesirable consequences, or vice versa	Patients: Most people in your situation would want the recommended course of action and only a small proportion would not Clinicians: Most patients should receive the recommended course of action Policy makers: The recommendation can be adapted as a policy in most situations There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research (if performed) is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
Low-quality (two plus: ⊕⊕◯◯) evidence	Desirable consequences clearly outweigh undesirable consequences, or vice versa	Patients: Most people in your situation would want the recommended course of action and only a small proportion would not Clinicians: Most patients should receive the recommended course of action Policy makers: The recommendation can be adapted as a policy in most situations The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
Very low-quality (one plus: ⊕◯◯◯) evidence (these recommendations are very rarely issued)	Desirable consequences clearly outweigh undesirable consequences, or vice versa	Patients: Most people in your situation would want the recommended course of action and only a small proportion would not Clinicians: Most patients should receive the recommended course of action Policy makers: The recommendation can be adapted as a policy in most situations The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Weak recommendation		
High-quality (four plus: ⊕⊕⊕⊕) evidence	Desirable consequences closely balanced with undesirable consequences	Patients: The majority of people in your situation would want the recommended course of action, but many would not Clinicians: Be prepared to help patients to make a decision that is consistent with their own values Policy makers: The recommendation can be adapted as a policy in most situations There is confidence that the true effect lies close to that of the estimate of the effect. Further research is unlikely to change the confidence in the estimate of effect
Moderate-quality (three plus: ⊕⊕⊕◯) evidence	Desirable consequences closely balanced with undesirable consequences	Patients: The majority of people in your situation would want the recommended course of action, but many would not Clinicians: Be prepared to help patients to make a decision that is consistent with their own values

Table 1 (Continued)

Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable consequences	Implications (for patients, clinicians, and policy makers) and interpretation of the quality of evidence
		Policy makers: The recommendation can be adapted as a policy in most situations There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research (if performed) is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
Low-quality (two plus: ⊕⊕◯◯) evidence	Uncertainty in the estimates of desirable and undesirable consequences; desirable consequences may be closely balanced with undesirable consequences	Patients: The majority of people in your situation would want the recommended course of action, but many would not Clinicians: Be prepared to help patients to make a decision that is consistent with their own values Policy makers: The recommendation can be adapted as a policy in most situations The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
Very low-quality (one plus: ⊕◯◯◯) evidence (this recommendation is very rarely issued)	Major uncertainty in the estimates of desirable and undesirable consequences; desirable consequences may be closely balanced with undesirable consequences	Patients: The majority of people in your situation would want the recommended course of action, but many would not Clinicians: Be prepared to help patients to make a decision that is consistent with their own values Policy makers: The recommendation can be adapted as a policy in most situations The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Adapted from Schünemann et al. (26) and Brozek et al. (27).
GRADE, Grading of Recommendation, Assessment, Development, and Evaluation; ARIA, Allergic Rhinitis and its Impact on Asthma.

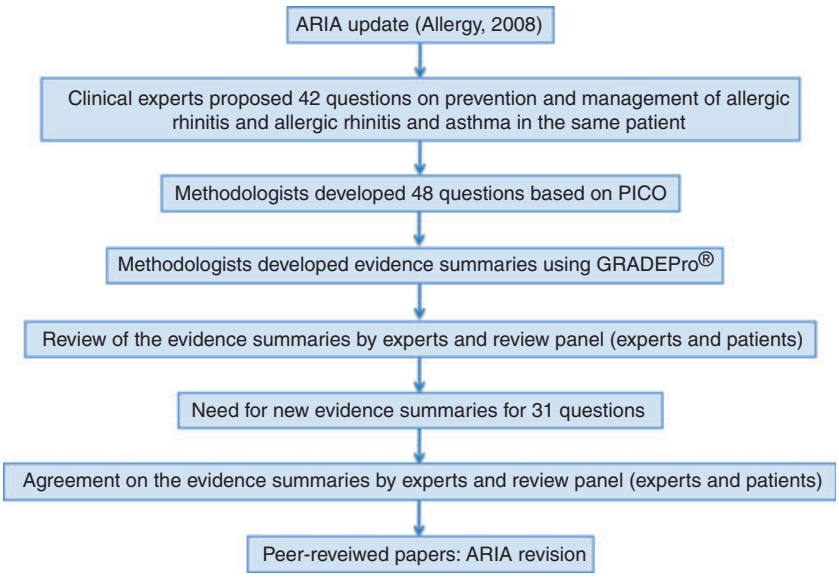

Figure 1 Development of Allergic Rhinitis and its Impact on Asthma revision.

Group composition

The guideline panel included two methodologists who developed evidence summaries with the help of an information scientist with experience in GRADE and two biostatisticians. Eight clinicians with experience in treating allergic rhinitis and asthma in adults and children were also members of the panel.

Formulation of questions and rating the importance of outcomes

The ARIA guideline panel identified 42 clinical problems requiring guidance. These general disease-oriented problems led to 48 specific, structured clinical questions based on the Population, Intervention, Comparison, and Outcome (PICO) approach (44) (Table 2). Only the ARIA guidelines approached the management of comorbid allergic rhinitis and asthma in the same patient.

An evidence summary (evidence profile and narrative summary) was prepared for each question using the GRADE approach. The following patient-important outcomes were identified: development of any allergy, allergic rhinitis, and/or asthma; presence and severity of nasal, ocular, and bronchial symptoms; exacerbations of asthma; hospitalization for asthma; quality of life; work/school performance; adverse effects; and resource utilization. For this revision of the ARIA guidelines, the authors did not formally assess the relative importance of each outcome, but used an informal assessment by the guideline panel for agreeing on which outcomes were critical, which were important and which were not important to patients (45).

Preparation of evidence summaries

One or more evidence profiles were prepared for most questions following the GRADE approach (27, 46) and using the GRADEPRO© software version 3.1 (47).

The evidence summaries were based on existing up-to-date, well-prepared systematic reviews identified by searching MEDLINE, the Cochrane Library, reference lists of the most recent narrative reviews, related systematic reviews, or studies on this subject. Systematic reviews were supplemented, as necessary, with additional randomized trials (until August 2007 and for selected clinical questions until January 2009). When recent valid systematic reviews were unavailable, rigorous systematic reviews were not performed, but MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for relevant studies. Where possible, the results of identified studies using meta-analysis were used. The identified original studies were evaluated to inform judgements about the underlying evidence as long as they addressed the relevant PICO question. The reporting of most trials did not employ the approach recommended by the CONSORT statement (48).

Table 2 Key questions of Allergic Rhinitis and its Impact on Asthma Revision

Should allergen avoidance methods or strategies be used by parents to avoid the development of allergic disease in children?
Should occupational allergen avoidance methods or strategies be used to avoid the development of allergic disease?
Should patients with allergic rhinitis and/or conjunctivitis use H1-antihistamines, glucocorticosteroids, antileukotrienes, chromones, decongestants, or ipratropium bromide? What is the relative effect of each of these medications?
Should allergen-specific immunotherapy be used in patients with allergic rhinitis? What is the effect of subcutaneous, intranasal, and sublingual-specific immunotherapy?
Should complementary and alternative treatments be used to treat allergic rhinitis?
Should medications for the treatment of allergic rhinitis be used in patients to treat concomitant asthma?

Panel meetings

Two meetings were held to discuss the clinical questions and the results of the evidence reviews, as well as to agree on recommendations. The panel agreed that recommendations would be based on a formal consensus of the panel and that voting would be used solely if agreement could not be reached through discussion. Agreement on the type and wording of the recommendations that reflect their strength was also reached during the panel meeting by consensus. No recommendation required voting. There was no disagreement after discussion.

Balancing desirable and undesirable consequences of management options and developing recommendations

Evidence profiles were made available before, during and after the meetings. Formulating the recommendations included consideration of the quality of evidence, desirable and undesirable consequences of following the recommended course of action, and values and preferences of those for whom the recommendations are intended. For most of the recommendations, resource utilization (cost) was also taken into account (37). Statements about the underlying values and preferences as well as the remarks are integral parts of the recommendations and serve to facilitate accurate interpretation. They should not be omitted when citing or translating recommendations in the ARIA GRADE guidelines. The expression 'values and preferences' refers to the relative worth or importance of a healthy state of mind or the consequences of a decision to follow a particular course of action (i.e., the relative weight one attributes to particular benefits, risks, burdens and costs to determine their balance).

Consultation

A consultation process for the ARIA GRADE guidelines included 80 clinicians: allergists, pediatricians, primary care physicians, otolaryngologists, and pulmonary specialists from a variety of countries as well as three members of patient organizations to review the guidelines. As a result, additional searches were performed for more recent studies for 31 questions.

Update and adaptation of guidelines

Guidelines are living documents. As for any guideline document, the ARIA guidelines will have to be revised, primarily because:

- The science and evidence concerning rhinitis is evolving, and guidelines are based on published evidence up to a fixed point in time.
- For many clinical questions, there were no systematic reviews of current evidence available. This document will be updated when such reviews are available and if any major new research is published or new medications become available.
- These guidelines cover only some of the many possible clinical questions; the authors believe that the most important ones are currently addressed.

Many other questions relevant to the management of allergic rhinitis and its impact on asthma have been identified as potentially important. ARIA will develop a process to register and prioritize additional questions to be included in subsequent revisions. Topics that were identified during the consultation as potential priorities for update and additional evidence reviews include:

- Recommendations on using special formulas containing hydrolyzed protein for the prevention of allergic diseases in infants.
- Relative effectiveness and safety of different homeopathic methods and herbal medicines.
- Recommendations on using intranasal saline to treat allergic rhinitis.
- Recommendations on the prevention and treatment of the complications of allergic rhinitis.
- Refinement of the recommendations on the use of particular medications to treat intermittent/seasonal or persistent/perennial allergic rhinitis.

The guidelines should be applicable to all countries, all settings and, in particular, to low and middle-income countries. In the first set of ARIA guidelines, the management of allergic rhinitis was carefully considered in developing countries, taking into account affordability and availability of medications as well as the WHO essential lists of medicines (21). In the GRADE Revision, 16 experts from developing countries have drafted or reviewed the recommendations. As an example, a very careful approach was used, in particular for oral H_1-antihistamines. In the former WHO list, only chlorphenyramine was accepted, but in the latest revisions, alternative medications were listed (49). Experts and reviewers discussed in great length the relative risk/benefit ratio of these drugs (19).

Adaptation of these guidelines by an expert panel will be necessary in some circumstances. Moreover, guidelines may require adaptation for local circumstances and must be culturally appropriate and acceptable. Depending on when such a process occurs, a publication co-authored by WHO suggests that the following steps should be taken (50):

- Appoint a guideline committee comprising clinicians and methodologists.
- Determine the scope of the guidelines.
- Define the clinical questions to be addressed.
- Update the evidence-based tables, as necessary.
- Review the recommendations in the guidelines (the recommendations may need to be modified at a national level, depending on the local values, availability of medications, and costs).
- Disseminate the guidelines, with a 'use by' date.
- Develop a method to obtain feedback and plans for review and update.

The update of these ARIA GRADE guidelines is planned for December 2011.

Applicability of guidelines to the general patient population and research needs

There is a clear need to perform real-life studies to provide concrete evidence that the applicability of evidence obtained in mechanistic randomized controlled trials appropriately reported (48, 51) translates into daily practice settings (52). Such studies should be well designed, appropriately carried out, and answer clinical questions that are highly relevant for clinical practice. Moreover, they should be reported using appropriate methodology (53, 54). Finally, studies need to be conducted in special populations, including young children, elderly patients, patients with occupational allergic rhinitis and asthma, and patients in low-resource countries.

Implementing guidelines

In allergic rhinitis, two cluster, randomized trials have been performed comparing free treatment choice by physicians with guideline-based treatment. The first study was carried out on patients with seasonal allergic rhinitis consulting primary care physicians of three countries (Belgium, France, UK). The guideline-based strategy used the International Consensus of Rhinitis (55) and a visual analog scale to assess the severity of nasal or conjunctival symptoms (56). The second study was carried out with specialists in France. This guideline-based strategy used ARIA and a visual analog scale to assess the severity of combined nasal or conjunctival symptoms (20). Both studies showed that guideline-based management of allergic rhinitis is more effective than free treatment choice.

Implementation and dissemination of guidelines

Guidelines are sometimes difficult to apply (57), especially by users who need a rapid answer to a question about a patient without reading the entire document. A first step for a better understanding of the ARIA revision using GRADE is available (43) and summarizes 48 questions. For maximum transparency, the evidence profiles are available in an online supplementary document to inform those who require more complete information.

The appropriate dissemination of guidelines is essential as a start to implementation. Derivatives of guidelines (such as pocket guides, web-based activities, questionnaires, web-based documents) should follow the guideline recommendations

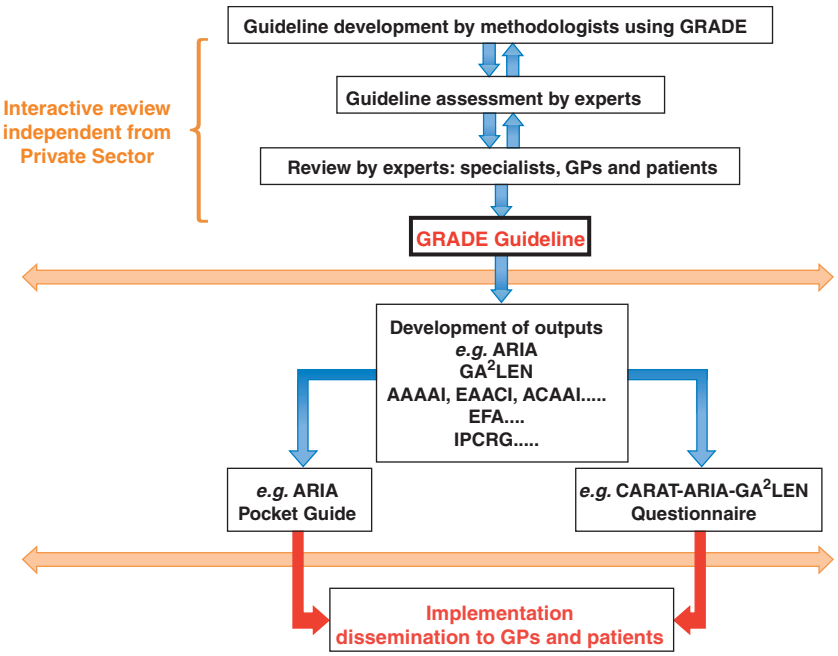

Figure 2 From guideline development to implementation.

exactly. As with the 2008 ARIA Pocket Guide, translated into more than 50 languages, we plan to disseminate the 2010 update internationally. Specialists and primary care physicians should be encouraged to use the guidelines and should be involved in the production of guideline summaries and educational materials derived from that guideline. There is an important need to disseminate the outputs to all involved in patient care. Pharmacists should also be aware as they are often the first portal approached by the patient. Patients likewise should be informed about these guidelines to create awareness of available treatments and to raise expectations. Simple fact sheets for patients should also be available (Fig. 2).

A question to be addressed in evaluating the efficacy of implementation is to obtain a validated and simple combined questionnaire to assess asthma and rhinitis in the same patient and to inform patients and physicians about the impact of the combined disease on quality of life, and school and work performance. This could be used as a tool for physician consultation or to give to patients before the consultation. As an example, in Portugal, a simple questionnaire (CARAT) includes 10 questions on the diagnosis of rhinitis and asthma in the same patient and the impact of these diseases on quality of life (58). This tool was developed using a comprehensive set of methodological steps ensuring its design quality and validity. Additional validation studies to assess the psychometric properties of the questionnaire have been completed for patients with asthma who also suffer from rhinitis (59). The GA^{2}LEN network (60) covers all countries and regions of Europe and offers all the advantages needed to rapidly test the CARAT in different languages and to provide a first tool to implement ARIA guidelines by primary care physicians and their patients. In addition, the ARIA online, interactive rhinitis and asthma questionnaires (http://www.whiar.org) can be used to identify comorbidities, to diagnose rhinitis and asthma as well as rhinitis severity and asthma control, and to compose letters to patients' physicians about the findings of the questionnaires. These questionnaires have been validated in large studies (SACRA).

The development of guidelines and educational outputs, their translation and validation are a prerequisite for successful guideline implementation. Implementation involves changing the behavior of physicians, health care professionals, and patients. Specifically targeted tools, special networks, and complementary strategies are needed. Evidence should be applied (and further obtained) for the effectiveness of various methods of guideline dissemination.

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