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REVIEW

Recommendations for the prevention and diagnosis of asthma in children: Evidence from international guidelines adapted for Mexico

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Abstract
Background: With the availability of high-quality asthma guidelines worldwide, one possible approach of developing a valid guideline, without re-working the evidence, already analysed by major guidelines, is the ADAPTE approach, as was used for the development of National Guidelines on asthma.
Methods: The guidelines development group (GDG) covered a broad range of experts from medical specialities, primary care physicians and methodologists. The core group of the GDG searched the literature for asthma guidelines 2005 onward, and analysed the 11 best guidelines with AGREE-II to select three mother guidelines. Key clinical questions were formulated covering each step of the asthma management.

Results: The selected mother guidelines are British Thoracic Society (BTS), GINA and GEMA 2015. Responses to the questions were formulated according to the evidence in the mother guidelines. Recommendations or suggestions were made for asthma treatment in Mexico by the core group, and adjusted during several rounds of a Delphi process, taking into account: 1. Evidence; 2. Safety; 3. Cost; 4. Patient preference – all these set against the background of the local reality. Here the detailed analysis of the evidence present in BTS/GINA/GEMA sections on prevention and diagnosis in paediatric asthma are presented for three age-groups: children with asthma $\leq$5 years, 6–11 years and $\geq$12 years.
Conclusions: For the prevention and diagnosis sections, applying the AGREE-II method is useful to develop a scientifically-sustained document, adjusted to the local reality per country, as is the Mexican Guideline on Asthma.

Introduction

According to estimates of the World Health Organisation and the International Forum of Respiratory Societies, there are between 235 and 300 million people worldwide suffering from asthma[1] and in Mexico it is calculated that 7% of the population has asthma.[2,3] The General Directory for Health Information (DGIS, by its initials in Spanish) reported that asthma accounted for 20% of the hospitalisations for respiratory illnesses in 2013, with a 0.03% fatality rate.[4] It has been observed that among the different institutes that provide medical care in Mexico, there is a lack of harmonisation regarding the management of patients with asthma. In general, there are still multiple aspects that are sensitive to improvement in the prevention, diagnosis and treatment of this disease in Mexico.

Therefore, the National Institute of Respiratory Diseases (INER, by its initials in Spanish), in a joint effort with the Mexican Society of Pulmonology and Thoracic Surgery and members of the Mexican College of Clinical Immunologists and Allergists (SMNyCT and CMICA, by their initials in Spanish) convened thirteen national professional societies to join efforts and develop a National Asthma Guideline. Aware of the high-quality guidelines that already exist worldwide on asthma, it was decided to use the ADAPTE approach[5] to develop a transculturation of the fused evidence of three of the best and most recent asthma guidelines globally available. The objective of the *Guía Mexicana del Asma* (GUIMA) 2017 project was to develop an evidence-based, practical guideline on the prevention, diagnosis and treatment of asthma, including asthma exacerbations. The guideline moreover had to have a solid base among specialists and primary health care physicians throughout the country.

The herein presented paper represents the collective evidence of the three international guidelines, selected as 'Mother' guidelines, and their fused recommendations for the prevention and diagnosis of asthma in children, adapted to the Mexican reality by a group of 56 local experts and primary care doctors, representing 13 national medical societies and two methodologists. In a subsequent paper the evidence on asthma treatment in children shall be presented.

Methods

A core group, in charge of the coordination and content of the guideline was created, consisting of eight expert pulmonologists and allergists. Subsequently, presidents of 13 professional societies, whose members treat patients with asthma in Mexico, were invited to assign 3–5 of their members to be integrated into the broad Guideline Development Group (GDG), consisting of 50 physicians. Other members of the GDG were methodologists, respiratory therapists and a specialised nurse. In the course of 19 months, three face-to-face meetings were held, and the rest of the work, including the Delphi rounds, was done via electronic communication.

For the development of GUIMA 2017 we followed the ADAPTE approach for transculturation of guidelines.[5] Briefly, first the SCOPE document was created, explicitly defining the scope of the guideline. It was decided the analysis would include some aspects of asthma prevention, and an in-depth review of asthma diagnosis, treatment and diagnosis and treatment of the asthma attack, in both children and adults. After defining the scope, a literature search was conducted for asthma guidelines, yielding a total of 40 guidelines. The quality of the 11 most prominent and recent ones was evaluated with AGREE-II by two members of the core-team per guideline.[6] Finally, the best three guidelines were selected: the British Thoracic Society Asthma Guideline (BTS) 2014,[7] the Global Initiative on Asthma (GINA) 2015,[8] and its update in 2016[9] and the Guía Española del Manejo del Asma (GEMA) 2015.[10] These function as the 'mother' guidelines, from where the evidence is recollected to make GUIMA.

The next step was to develop the critical route of the asthma management process, for primary, secondary and tertiary asthma health care. After that the core group developed clinical questions, to cover each phase of the asthma management process, from prevention, to diagnosis, to treatment. Subsequently, the three mother-guidelines were searched for evidence to sustain the replies to the clinical questions and their corresponding recommendations. During the next stage each clinical question and its reply was analysed against the background of the Mexican reality, and a final set of suggestions and recommendations was drawn by

Box 1: Steps in the development of *Guía Mexicana del Asma* (GUIMA) 2017.

I. Selection of the guideline (GL) development group:
   i. Executive Committee for Administration (JS), Content (DLL) and Financial support (JCV)
   ii. Core group for GL development (4 pulmonologists and 4 allergists) [coordinating DLL and MCCS]
   iii. Three methodologists, involved in all stages of development
   iv. National Medical Societies, most related to the care of patients with asthma, giving autonomy to their Presidents to assign 3–5 members as collaborators for the guideline.
II. Elaboration of the document containing the objectives and the scope of the GL (SCOPE document)
III. Literature search for worldwide available asthma guidelines
IV. Evaluation of the quality of the GLs with AGREE II (2 evaluators/GL), and their adaptability to Mexican reality
V. According to IV, selection of the three best GLs as 'Mother Guidelines'
VI. Development of flow-diagram of the different phases of asthma management, from diagnosis, to treatment, including crisis
VII. Formulation of key clinical questions for each asthma management step, using the PICO method
VIII. Answering of key clinical questions according to scientific evidence in Mother Guides, assigning level of evidence and recommendation
IX. With the complete Guideline Development Group fine-tuning of text of recommendations, using a Delphi process of several blocks and rounds
X. Integration of guideline text, based on the evidence set of key clinical questions
XI. Review final GL text with the complete Guideline Development Group, external reviewers (experts, legislators)
XII. Completion of the final GL document

the core-group. These were then submitted to the opinion of the broad GDG. Delphi rounds were employed to obtain the opinion and corrections of all members of the broad GDG. During the last face-to-face meeting final details of the recommendations were discussed and corrected, and the GL text was integrated. See Box 1 for the different steps in the development process.

The results of step IX, Box 1, related to the clinical questions on asthma prevention and diagnosis in children are presented here, with their level of evidence and recommendation, fused from the three 'mother-guidelines'. A brief clarification in the context of the Mexican reality accompanies the recommendation per question. To 'recommend' or to 'suggest' a certain action we used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach,[11] in which a soft recommendation (suggestion) or strong recommendation is given, depending on the quality of the evidence, the cost and safety of a certain action or medication and the patient's preference. In the evidence column, the combined evidence from the three mother guidelines is depicted. In case of discordance between the mother guidelines, the original papers on which the evidence levels are based were reviewed, to come to a final level of evidence evaluation. In the final column, the joint level of recommendation is stated. For the separate evidence and recommendation analysis per guideline (before fusion), see the online repository. After each clinical question and the proposed reply for Mexico, the results of the Delphi rounds are stated, reflecting the level of acceptability and concordance among the GDG members with regards to the recommendation for Mexico.

Results

Table 1 through Table 4 show the analysis of the recommendations and suggestions, as present in the mother guidelines and set in the context of Mexico. The results of the Delphi process can be found at the end of each question, including the level of agreement among the members of the GDG and the number of rounds that were necessary to come to agreement.

Issues related to the prevention of asthma are analysed in Table 1. The first part of the asthma diagnosis process, including the steps leading to suspecting the diagnosis of asthma is analysed in Table 2. The whole analysis of the diagnostic part starts off with the note that asthma is a heterogeneous entity, with a mostly clinical diagnosis. Thus, no strong evidence-based recommendations, related to its diagnosis, can be made. Table 3 explores the different tests that can be used to confirm the diagnosis of asthma. Finally, Table 4 focuses on establishing asthma severity and levels of asthma control.

Discussion and conclusion

Analysing the results of the fusing of evidence from our three mother guidelines, it can be concluded that in the majority of the clinical questions the replies from the three guidelines are similar or complementary. For asthma prevention, there are only two firm recommendations: (1) avoidance of exposure to tobacco smoke, and (2) avoidance of the frequent intake of paracetamol (PCM) or broad-spectrum antibiotics (BSAB) between 0 and 12 months of age. Furthermore, it can be suggested to avoid living close to highly transited roads, in favour of the rural environment. Paediatric vaccination should be carried out with no restriction, just as for the population at large; pets at home should be allowed and there should be no restrictions to the mother's diet. To date, no medication exists that can avoid asthma development. For the diagnosis of asthma, the level of evidence is low, and in some cases absent, leaving only expert opinion to make suggestions. Generally, the presence of at least two of the four clue symptoms of asthma: wheeze, cough, dyspnoea or chest tightness, varying over time in presence and severity should raise the firm suspicion of asthma. The confirmation of asthma should be sought with the second line tests that demonstrate airflow obstruction and its variability over

Table 1 Clinical questions on the prevention of asthma, level of evidence and recommendation.

Clinical question	GUIMA: Recommends/ suggests yes/no	Mother guidelines' level of...	
		Evidence	Recommendation
P1. For non-allergic people: Does the ownership of cats or dogs modify the prevalence of asthma?	No recommendation. Exposure to cat could give some protection (2++)	1-	B
Does mite exposure modify the development of asthma?	No recommendation	1-	A
We do not give any suggestion regarding pets at home since a review of 11 birth cohorts in Europe did not find a link between the presence of animals at home during childhood and an increase or decrease in the prevalence of asthma. (1-) Nor do we give a recommendation to reduce exposure to home dust mites as a primary prevention measure for asthma. Several randomised trials with multifaceted interventions showed a reduction in asthma development, but the intervention consisted of maternal breast feeding or polyhydrolysed formulae, a late introduction of solids and a reduction in the exposure to house dust all together; so the effect of each of these factors individually is not known. In Mexico, humidity in practically the entire republic is at such a level that it favours the growth of mites; It will be very difficult to create intradomiciliary climates sufficiently dry to stop the mites from multiplying.			
The results of the Delphi Panel for this recommendation were mean= 8.5, standard deviation= 0.95, median= 9, min= 6, max= 9, percentile 25= 8, percentile 75= 8.5 Agreement was reached in the second round with 91% of scores in range from 7-9 for Appropriateness.			
P2. For non-allergic children: Does vaccination affect the prevalence of asthma?	Does not affect, We recommend vaccination	2+	B
We recommend children to be vaccinated, as paediatric vaccination does not affect the development of asthma. □ Good clinical practice: In children at risk for a Respiratory Syncytial Virus (RSV) infection, e.g. children with a history of prematurity (<35 weeks of gestation), children with bronchopulmonary dysplasia, or with a congenital heart disease with significant haemodynamic impact, Palivizumab reduced the likelihood of wheezing in the 1st year of life (evidence 2+). Whether this reduces the risk of developing asthma is to be investigated. Moreover, its availability and cost has to be taken into account.			
The results of the Delphi Panel for this recommendation were mean= 8.0, standard deviation= 1.07, median= 8, min= 6, max= 9, percentile 25= 7.7, percentile 75= 8.0 Agreement was reached in the second round with 87% of scores in range from 7-9 for Appropriateness.			
P3. For non-allergic people: A change in environment affects the prevalence of asthma …	Limited evidence		
A. Is living in a rural setting a protective factor for asthma?	We suggest Yes	2++	C
B. Does living close to high traffic roads augment asthma prevalence?	We suggest Yes	2++	C
We suggest that a rural and less polluted environment might be favourable and might avoid the development of asthma. High-quality case-control studies have shown that the rural environment, and especially exposure to endotoxins, reduces the risk of developing asthma, as living near a highly trafficked road increases this risk.			
The results of the Delphi Panel for this recommendation were mean= 7.1, standard deviation= 1.49, median= 7, min= 3, max= 9, percentile 25= 6.5, percentile 75= 8 Agreement was reached in the first round with 73% of scores in range from 7-9 for Appropriateness.			
P4. For non-allergic children: Does exposure to environmental tobacco smoke increase the likelihood of asthma?	We recommend Yes	2+	A-B
We recommend that all children avoid environmental tobacco smoke exposure as a primary prevention measure for wheezing and persistent asthma. Parents should be informed about such risk. □ Good clinical practice: GUIMA experts also recommend to avoid smoking during pregnancy (active or passive), as exposure to tobacco smoke increases the risk of allergies in the newborn.			
The results of the Delphi Panel for this recommendation were mean= 8.7, standard deviation= 0.46, median= 9, min= 8, max= 9, percentile 25= 8.5, percentile 75= 9 Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
P5. In children and adults: Does smoking increase the incidence of asthma?			
Children	We recommend Yes	2	B
Adults	We suggest Yes	3	C
We recommend that children and we suggest that adults avoid smoking (tobacco) as a primary prevention measure for asthma. In adolescents smoking doubled the risk of developing asthma within six years (level of evidence 3).			
The results of the Delphi Panel for this recommendation were mean= 8.8, standard deviation= 0.41, median= 9, min= 8, max= 9, percentile 25= 9, percentile 75= 9, Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
P6. For non-allergic people: Does a healthy diet ('Mediterranean diet', diet rich in antioxidants, vit D + E, etc.) reduce the prevalence of asthma?	We suggest Yes	2+	C
There exist consistent data from observational studies that a Mediterranean diet and a diet rich in fresh fruit and vegetables is associated with a lower incidence of asthma, particularly in childhood.			
The results of the Delphi Panel for this recommendation were mean= 7.1, standard deviation= 0.96, median= 7, min= 6, max= 9, percentile 25= 6.5, percentile 75= 7. Agreement was reached in the first round with 73% of scores in range from 7-9 for Appropriateness.			
P7. For non-allergic people, does a hypoallergenic diet of the pregnant or lactating mother reduce the incidence of asthma in her child?	We recommend No	1+	A
We do not recommend that pregnant or lactating women follow a hypoallergenic diet to reduce the risk of developing asthma in the newborn.			

Table 1 (*Continued*)

The results of the Delphi Panel for this recommendation were mean= 7.9, standard deviation= 1.73, median= 9, min= 4, max= 9, percentile 25= 7, percentile 75= 9. Agreement was reached in the first round with 73% of scores in range from 7-9 for Appropriateness.			
P8. In infants: Does breastfeeding reduce the prevalence of wheezing or asthma?	We recommend Yes, but unsure it reduces asthma	2+	B
Breastfeeding is recommended as a point of good paediatric practice, although its effect on the reduction in the prevalence of asthma is not conclusive.			
The results of the Delphi Panel for this recommendation were mean= 7.5, standard deviation= 1.36, median= 8, min= 5, max= 9, percentile 25= 7, percentile 75= 8.5 Agreement was reached in the first round with 80% of scores in range from 7-9 for Appropriateness.			
P9A. In the general paediatric population: A. Can any medication prevent the development of asthma? (Primary prevention)	We recommend No	1+	A
P9B. Does the frequent intake of paracetamol (PCM) or broad-spectrum antibiotics (BSAB) between 0-12 months of age favour the development of asthma?	We recommend Yes	PCM 1+ BSAB 1-	B
We recommend physicians to consider there is no medication that reduces the risk of developing asthma in children (e.g. antihistamines, probiotics). We recommend reducing the intake of paracetamol (1+) and broad-spectrum antibiotics (1-) during pregnancy and the first year of life to reduce the risk of developing asthma.			
The results of the Delphi Panel for this recommendation were mean= 8, standard deviation= 1.43, median= 9, min= 3, max= 9, percentile 25= 8, percentile 75= 8.0 Agreement was reached in the second round with 87% of scores in range from 7-9 for Appropriateness.			

time: pre-post bronchodilator spirometry, serial peak flow measurements or a therapeutic trial. The mother guidelines differ somewhat in the exact cut-off points used in these tests.

In small children, the modified asthma predictive index could be used to try to evaluate the risk of developing asthma in children 0–3 years old with a history of four wheezing episodes. A personal or family background of atopy increases the risk of developing asthma and its severity.

Challenge testing could be of help in patients with the suspicion of asthma, who fail to demonstrate airflow obstruction or reversibility. These tests are normally reserved for third level health care, with the exception of the exercise challenge test that could be performed at any level, as long as the patients are closely observed during the testing. It is suggested not to use the fraction of exhaled nitric oxide (FeNO) test to confirm asthma, but as a measure of airway inflammation it can be of use for the follow-up in eosinophilic asthma. On the contrary, the demonstration of specific immunoglobulin E to a certain allergen is recommended at any age, when asthma symptoms flare after allergen exposure.

For the follow-up of the patients with asthma, again the level of evidence is mostly 2+ (low evidence), with a level of recommendation C. The asthma control test (ACT) is suggested by the mother guidelines, as are serial peak flow measurements and simple spirometry. The mother guidelines agree on a list of several factors that might indicate the risk of developing an asthma exacerbation (see Table 4, last rows).

Conclusion

We have shown how to take advantage of well-designed globally available guidelines for the development of a national guideline. It is possible to take the evidence from the best existing guidelines, analyse it in detail, fuse it and adjust it, according to local knowledge and reality, to come to a national recommendation for certain medical actions. We have applied this schedule for the development of the Mexican Asthma Guidelines and presented the section of prevention and asthma diagnosis in children in this article, which shall be followed by a similar analysis of asthma treatment in children.

Ethical disclosures

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

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Conflict of interest

The following co-authors reported receiving honoraria as a speaker, support for congress attendance and/or grants of the indicated companies: DLL: AstraZeneca, Boehringer Ingelheim, MSD, Novartis, Grunenthal, Meda, Sanofi, UCB,

Table 2 Clinical questions on when to suspect the diagnosis of asthma, level of evidence and recommendation.

Clinical question	GUIMA: Recommends/ suggests yes/no	Mother guidelines' level of... Evidence	Recommendation
D1. In patients ≥ 6 years: The diagnosis of asthma is based on three points? I. Presence of more than one of the clue symptoms: a. wheeze b. cough c. dyspnoea d. chest tightness II. + Variability of symptoms III. + Variable airflow obstruction.	We suggest: yes	3	D
The diagnosis of asthma should be suspected in the presence of characteristic clinical signs and symptoms; the main ones are: wheezing (the most characteristic), cough (usually paroxysmal and nocturnal predominance), dyspnoea (respiratory distress) and chest tightness; Which show a variable pattern and are often exacerbated or induced by triggers. None of these symptoms and signs are specific for asthma, so the clinical diagnosis should be confirmed, with test(s) showing variable airflow obstruction			
The results of the Delphi Panel for this recommendation were mean= 8.4, standard deviation= 0.63, median= 8, min= 7, max= 9, percentile 25= 8, percentile 75= 9. Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
D2. In patients ≥ 6 years, for the diagnosis of asthma: A clue characteristic of the respiratory symptoms is their variability? a. Come and go with time b. Fluctuation in intensity c. Worse in the night/past midnight/on awakening d. Exacerbate with exercise, laughing, contact with allergens, cold air e. Exacerbate with viral illnesses f. Exacerbate with the ingestion of NSAIDs or beta-blocking agents (BTS)	We suggest: yes	3	D
Symptoms suggestive of asthma are characterised by their variability (variation or fluctuation in symptoms, pulmonary function over time, even within one day), both in intensity and frequency, they usually present predominantly at night, at dawn or on awakening and may be induced or exacerbated by multiple potential triggers (viral infections, exercise, allergens, tobacco smoke, certain drugs, weather changes, among others).			
The results of the Delphi Panel for this recommendation were mean= 8, standard deviation= 1.43, median= 9, min= 3, max= 9, percentile 25= 8, percentile 75= 8.0 Agreement was reached in the first round with 87% of scores in range from 7-9 for Appropriateness.			
D3. Are airway hyper-reactivity and inflammation secondary characteristics of asthma?	We recommend: yes	2+	B
Patients with asthma have two pathophysiological characteristics: **airway inflammation** and **bronchial hyperreactivity** (BHR) that are closely related. The inflammatory pattern includes an increase in the number of mast cells, activated eosinophils, natural Killer cells and Th2 lymphocytes, which release mediators that cause the symptoms. Airway structural cells also produce inflammatory mediators that facilitate the persistence of inflammation. The cellular interactions that make this inflammatory process possible are through cellular mediators and molecules (cytokines, chemokines, leukotrienes, histamine, nitric oxide, etc.) with diverse functions. BHR consists of a variable airflow limitation and appearance of symptoms of variable presentation to stimuli that are usually innocuous in people without asthma. The mechanisms involved in bronchial hyperreactivity are the constriction of the bronchial smooth muscle, thickening of the bronchial basement membrane (mainly due to oedema, structural changes and smooth muscle constriction), and hyperexcitability of cholinergic sensory nerve fibres which may induce exaggerated bronchoconstriction and mucus secretion, in response to pro-inflammatory stimuli. The degree of BHR correlates partially with the clinical severity of asthma and with some markers of inflammation.			
The results of the Delphi Panel for this recommendation were mean= 8.6, standard deviation= 0.63, median= 9, min= 7, max= 9, percentile 25= 8.25, percentile 75= 9 Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
D4. In patients ≥ 6 years presenting with the respiratory symptoms described above: are there any specific clinical details in the personal or family history that can increase or decrease the probability of the diagnosis of asthma? **THE PROBABILITY OF ASTHMA IS INCREASED IF:** • Personal history of atopy (AD, AR) • Family history of atopy or asthma • Diffuse wheeze on auscultation • Reduced FEV_1 or PEF with no other explanation (serial or historic values) • Eosinophilia with no other explanation **THE PROBABILITY OF ASTHMA IS DECREASED IF:** • Cough as an isolated symptom • Chronic productive cough, with no wheeze nor dyspnoea • Repetitively normal physical exam of the chest while symptomatic • Dysphonia • Symptoms only with colds • Smoking history of importance (e.g. > 20 pack-years) • Cardiac pathology • Dyspnoea accompanied by light-headedness, dizziness or paraesthesia • Exercise-induced dyspnoea with noisy inspiration. • Normal FEV_1 or PEF when symptomatic*	We suggest: yes	3	D
Asthma is a heterogeneous entity that results from complex interactions between environmental and genetic factors. None of the symptoms and characteristic signs are totally specific to asthma, so it is sometimes not easy to confirm the diagnosis. However, there are details in the personal and family history and in the clinical behaviour of the disease, whose presence or absence can increase or decrease the probability of having asthma. Confirmatory tests may be used for this purpose. The characterisation of various asthma phenotypes has allowed to integrate in the context of the disease certain groups of patients with probably different etiologies but specific demographic, clinical and / or pathophysiological characteristics. However, the different studies have not clearly established the clinical utility of sub-classification of asthma by phenotypes.			

Table 2 (*Continued*)

The results of the Delphi Panel for this recommendation were mean= 8.4, standard deviation= 0.74, median= 8.5, min= 7, max= 9, percentile 25= 8, percentile 75= 9. Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
D5. In patients ≥ 6 years with respiratory symptoms suggestive of asthma: Does the absence of wheezing discards asthma?	We suggest: no	3	D
Although data from observational studies have established that wheezing is the most characteristic clinical sign of asthma, the clinical heterogeneity characteristic of the disease can sometimes cause the sign to be absent or not referred to as part of the semiology. We suggest considering that its absence during the history taking or the physical examination (like any other characteristic symptom of asthma) is not enough to rule out the diagnosis.			
The results of the Delphi Panel for this recommendation were mean= 7.9, standard deviation= 2.11, median= 8.5, min= 1, max= 9, percentile 25= 8, percentile 75= 9. Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
D6. In patients ≤ 5 years: Might making the diagnosis of asthma be a challenge? Because: • Respiratory symptoms (sporadic cough and wheezing) are common during viral respiratory infections in children without asthma, particularly in the 0-2-year-old • Routine tests to demonstrate airflow obstruction are lacking	We suggest: yes	4	D
In patients < 5 years of age the diagnosis of asthma may be difficult to establish due to the clinical similarity of respiratory manifestations secondary to infections (viral). These patients are often called "early transient wheezers," whose clinical presentation and tendency to recurrence can lead to diagnostic confusion, especially in children younger than 2 years. Confirmation of the diagnosis in this group of patients is complicated, mainly due to the technical difficulty to perform pulmonary function tests.			
The results of the Delphi Panel for this recommendation were mean= 7.9, standard deviation= 1.69, median= 9, min= 4, max= 9, percentile 25= 8, percentile 75= 9. Agreement was reached in the first round with 79% of scores in range from 7-9 for Appropriateness.			
D7. In patients ≤ 5 years: One suspects the diagnosis of asthma if? More than one of the clue respiratory symptoms are present, periodically or recurrently, varying in intensity and frequency: a. wheeze b. cough c. dyspnoea d. chest tightness	We suggest: yes	3	D
Given the difficulty in performing and interpreting confirmatory tests for asthma in children < 5 years of age, the diagnostic suspicion of the disease lies in the intermittent and/or recurrent occurrence of respiratory symptoms, generally in the absence of clinical data of infection. Although in some cases respiratory tract infections trigger the symptoms, which confers diagnostic complexity. In epidemiological studies, it has been shown that asthma begins in early childhood in more than 50% of cases.			
The results of the Delphi Panel for this recommendation were mean= 7.7, standard deviation= 1.20, median= 8, min= 5, max= 9, percentile 25= 7, percentile 75= 8.75. Agreement was reached in the first round with 86% of scores in range from 7-9 for Appropriateness.			
D8. For preschool children, with more than three wheezing episodes per year during the first 3 years of life: is the asthma predictive index a valuable tool to predict the risk of persistent asthma?	We suggest: yes	3	D
Based on birth-cohort studies, some tools have been developed for predicting childhood asthma risk. The best known is the Asthma Predictive Index (Castro et al.), developed from the data of children of the Tucson cohort study (Martínez et al.). However, these score-based instruments obtained on the basis of the presence of certain factors, have modest predictive values (VPP 77%, VPN 68%), and therefore lack sufficient precision to make reliable forecasts. With this reservation and in the absence of other more precise instruments, we suggest its use, interpreting its results with caution.			
The results of the Delphi Panel for this recommendation were mean= 7.5, standard deviation= 1.34, median= 7.5, min= 5, max= 9, percentile 25= 7, percentile 75= 8.75 Agreement was reached in the first round with 86% of scores in range from 7-9 for Appropriateness.			
D9. According to the age group and the acute of chronic presentation of the respiratory symptoms, should differential diagnoses be considered? See tables per age group in online repository.	We suggest: yes	3	D
We suggest that the suspicion of asthma always obliges the clinician to make a differential diagnosis with other diseases, according to the age group, the frequency and the characteristics of the symptoms. The range of differential diagnoses is very broad and is described in table ***.			
The results of the Delphi Panel for this recommendation were mean= 8.6, standard deviation= 0.63, median= 9, min= 7, max= 9, percentile 25= 8.25, percentile 75= 9. Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
D10. Does a personal or family history of allergy increase the predisposition or the severity of asthma?	We suggest: yes	2++	C
The family and / or personal history of allergy in the majority of children > 3 years represents a risk factor for asthma and its intensity. Transverse and cohort studies have established allergic sensitisation (particularly expressed as allergic rhinitis or eczema coupled with a family history of asthma) as one of the most important risk factors that increase the likelihood for the diagnosis of asthma. Phenotypically, allergic asthma can behave as severe asthma or difficult to control asthma, in some situations with high allergenic exposure.			
The results of the Delphi Panel for this recommendation were mean= 7.9, standard deviation= 1.21, median= 8.5, min= 6, max= 9, percentile 25= 7, percentile 75= 9. Agreement was reached in the first round with 86% of scores in range from 7-9 for Appropriateness.			

Table 3 Clinical questions on tests that confirm the diagnosis of asthma,[a] level of evidence and recommendation.

Clinical question	GUIMA: Recommends/ suggests yes/no	Mother guidelines' level of...	
		Evidence	Recommendation
D11. Is pre- and post-bronchodilator spirometry the first-choice diagnostic test to document variable expiratory airflow obstruction? Does it have an adequate diagnostic precision?			
Children < 5 years	We suggest: no	2+	C
Children 5-6 years	We suggest: yes	2+	D
Children > 6 years	Recommend: yes	2+	C
D11a. In patients ≥ 6 years with respiratory symptoms suggestive of asthma: Do normal spirometric values, when the patient is asymptomatic, discard asthma?	Recommend: no	2+	C
In patients with a clinical profile suggestive of asthma, spirometry (baseline and post bronchodilator) is recommended as the first-line test to demonstrate a variable expiratory airflow obstruction**, mainly in children over 6 years of age and adults, given its diagnostic accuracy, its non-invasive nature and its easy availability. Young children may have difficulty performing the correct technique, so it is suggested with reservation as a diagnostic complement in children from 5 to 6 years. We do not suggest its use in children <5 years. A normal spirogram in a patient with history or symptoms suggestive of asthma is not sufficient to rule out the disease, given the fluctuating nature of the obstructive process, characteristic of the disease, so that such an outcome should be carefully evaluated. In case of doubt, we suggest taking serial pulmonary function tests. ** In a baseline spirometry with adequate technique and reproducible results, an obstructive airflow pattern is defined as an FEV_1 / FVC ratio <80% of the predicted value in adults and <80-85% of the predicted value in children. The reversibility test is considered positive if the FEV_1 increases> 12% and 200 mL (BTS 400mL) relative to baseline 15 minutes after administration of 400 µg salbutamol in aerosol.			
The results of the Delphi Panel for this recommendation were mean= 8.6, standard deviation= 0.65, median= 9, min= 7, max= 9, percentile 25= 8, percentile 75= 9 Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
D12. Is it possible to use complementary objective tests to confirm the variable airflow limitation?	We suggest: yes	2+	C
D12a. **Increase in diurnal variability of PEF for a period of 2 weeks (amplitude % mean)***			
Children < 2 years	We suggest: no	N/A	D
Children 2-5 years	We suggest: yes	2+	C
Children > 6 years	We suggest: yes (PEF variability >12%)*	2+	C
* Each guideline uses different cut-points: BTS ≥ 12% GINA children: >13% GEMA ≥ 20%			
D12b. **Increase in FEV_1 >12% after 4-6 weeks of a therapeutic trial with moderate-high ICS****			
Children < 2 years	We suggest: no	N/A	N/A
Children 2-5 years	We suggest: yes	2+	C
Children > 6 years	We suggest: yes	2+	C
** Each guideline uses a different schedule: - BTS: beclomethasone IDM 400 mcg/d for 6-8 weeks - GINA: 4 weeks de "controller treatment" - GEMA: 2-3 weeks fluticasone with IDM 1500-2000 mcg/d.			
D12c. **Increase in FEV_1 >12% after a therapeutic trial with prednisone 30 mg/day PO for 15 days ***			
Children < 2 years	We suggest: no	N/A	N/A
Children 2-5 years	We suggest: no	2+	D
Children > 6 years	We suggest: yes	2+	C
*** *Each guideline uses a different schedule:* - BTS: Prednisone 30 mg/day for 15 days - GINA: 4 weeks of "controller treatment" - GEMA: 2-3 weeks of prednisone 40 mg/day			
Complementarily, we suggest the use of other strategies to confirm reversible airflow limitation, particularly in patients older than 6 years and adults. The diagnostic value of these complementary tests will increase if more than one type of test is done. The increase in diurnal peak flow variability (PEF) in two-week records will give the clinician results in the medium term with a degree of regular accuracy (low sensitivity [~ 25%], medium specificity), With wide variability, so it will probably be more useful for the monitoring of the patient with established asthma than for the initial diagnosis. Some pre-school children may be able to perform the manoeuvre to obtain PEF, so we suggest its use in this age group, although its results should be evaluated with caution. In patients with uncertain diagnosis, therapeutic trials may be performed with inhaled corticosteroids (over 2 years) or systemic (over 6 years) with a pre-post reversibility test (ΔFEV_1) **. The mother guides consider different dosing schedules and different test periods, so a consensus is proposed (see table) to facilitate its application in Mexico. □ **Point of good clinical practice**: In patients younger than 5 years the criterion will be improvement in clinical parameters given the difficulty to obtain FEV_1			
The results of the Delphi Panel for this recommendation were mean= 8.1, standard deviation= 1.00, median= 8, min= 6, max= 9, percentile 25= 7.25, percentile 75= 9 Agreement was reached in the first round with 93% of scores in range from 7-9 for Appropriateness.			
D13. In patients in whom asthma is suspected, but who have normal pulmonary function tests: Should bronchial hyper-reactivity be identified with challenge testing?	We suggest: yes	3	C

Table 3 (*Continued*)

D13a. **Exercise Challenge testing?**			
Children < 2 years	We suggest: no	2+	D
Children 2-5 years	We suggest: yes**	2+	D
Children > 6 years	We suggest: yes	2+	C
(drop of FEV_1>12% from baseline)****			
**** GEMA: drop of >20% from baseline			
D13b. **Direct challenge testing?** (PC_{20} with methacholine <8 mg/mL, histamine)			
Children < 2 years	We suggest: no	2+	C
Children 2-5 years	We suggest: no	2+	C
Children > 6 years	We suggest: yes	2+	C
D13c. **Indirect challenge testing (Hypertonic saline, mannitol)?**			
Children < 2 years	We suggest: no	2+	C
Children 2-5 years	We suggest: no	2+	C
Children > 6 years	We suggest: no	2+	C
We suggest that in case of clinical suspicion of asthma and (almost) normal pulmonary function tests, in children older than 6 years and adults, challenge tests should be considered to document bronchial hyperreactivity (drop in ΔFEV1 post challenge). These tests are performed without current corticosteroid treatment or signs of an upper respiratory infection. The decision to perform these tests should be based on the individual clinical context and a careful medical history. In children under 6 years of age, it is suggested that these challenges be avoided due to the difficulty of obtaining objective measurements of airflow obstruction and the potential irritative effect of some agents (with the exception of the exercise challenge, which is simple to do, reproducible and with high specificity, even in the small child, see below). Indirect tests (such as exercise or mannitol) in untreated patients, are estimated to have a median sensitivity and a high specificity. For direct challenges, particularly with methacholine (PC20 <8mg / mL), high sensitivity and medium specificity have been reported. In Mexico, these complementary tests (except for exercise challenges) are performed only in some third level health care units. **Point of good clinical practice**: In patients <5 years the criterion will be the change in clinical parameters given the difficulty to obtain FEV_1 **Point of good clinical practice**: With the exception of occupational asthma, where it is important to recognise the causal agent even for legal reasons, in Mexico challenge testing is usually not necessary, given the difficulty of finding centres with adequate supplies and personnel (usually third level health care) to perform the correct protocols.			
The results of the Delphi Panel for this recommendation were mean= 8.1, standard deviation= 1.00, median= 8, min= 6, max= 9, percentile 25= 7.25, percentile 75= 9 Agreement was reached in the first round with 79% of scores in range from 7-9 for Appropriateness.			
D14. **Third level** In children in whom asthma is suspected and who show airflow obstruction in PFT, however who have no reversibility after bronchodilator and with negative tests for bronchial hyper-reactivity: - Should FeNO testing be considered a useful diagnostic tool?			
Children < 2 years	We suggest: no	2+	D
Children 2-5 years	We suggest: no	2++	D
Children ≥ 6 years (normal range <30 ppb)	We suggest: no	2++	C
(Only without current use of ICS and with no respiratory tract infections)			
We suggest considering FeNO (indirect marker of eosinophilic inflammation) in cases of uncertain diagnosis with suggestive clinical data, but absent or incomplete reversibility and with negative challenge tests for bronchial hyperreactivity. In adults not treated for asthma, high sensitivity and medium specificity have been reported with a good body of evidence, so we recommend its use in individuals with adequate inclusion criteria (see table) that are treated at the third level of care. In children between 1 and 5 years, reference values have been established; However, the results are usually highly variable with very low specificity for this age group. Therefore, this test is not considered a sensitive or specific marker for the diagnosis of childhood asthma, so we suggest not to use it in the initial diagnostic protocol. It is suggested that it could be more useful if used as an established asthma monitoring tool, especially in patients not treated with corticosteroids.			
The results of the Delphi Panel for this recommendation were mean= 8.1, standard deviation= 1.00, median= 8, min= 6, max= 9, percentile 25= 7.25, percentile 75= 9. Agreement was reached in the first round with 79% of scores in range from 7-9 for Appropriateness.			
D15. In patients of any age with asthma symptoms after allergen exposure: Should atopic sensitisation be demonstrated (with skin prick tests and/or specific IgE testing in serum)?	Recommend: yes	2++	B
Based on results from open and observational clinical trials, we recommend in any age group that patients, presenting with symptoms suggestive of allergy and tests that confirm asthma, and who have a personal or family history of allergic diseases or who have asthma symptoms on allergen exposure, should be tested in vivo (skin prick testing, preferably) or in vitro to determine allergic sensitisation.1)			
The results of the Delphi Panel for this recommendation were mean= 7.5, standard deviation= 1.91, median= 8, min= 3, max= 9, percentile 25= 7, percentile 75= 9. Agreement was reached in the first round with 86% of scores in range from 7-9 for Appropriateness.			
D16. When asthma is suspected in a child: Should a chest X-ray be taken for the diagnosis?	We suggest: no	2+	D
In children and adults, observational studies have concluded that a chest X-ray will only be necessary in certain cases, such as atypical symptoms, severe symptoms or clinical data suggesting differential diagnoses, and we suggest: not to use it as part of the initial diagnostic protocol for asthma.			
The results of the Delphi Panel for this recommendation were mean= 7.6, standard deviation= 1.65, median= 8, min= 3, max= 9, percentile 25= 7, percentile 75= 9. Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			

1 The diagnosis of allergic asthma will be based on the concordance between the medical history and the diagnostic test results.

[a] The diagnosis of allergic asthma will be based on the concordance between the medical history and the diagnostic test results.

Table 4 Clinical questions on how to evaluate asthma severity and levels of asthma control, level of evidence and recommendation of Mother guidelines and conclusions of GUIMA.

Clinical questions	GUIMA: Recommends/ suggests yes/no	Mother guidelines' level of...	
		Evidence	Recommendation
D17 In general: In Children ≥ 6 years, for home monitoring of disease activity and asthma control can we use…	We suggest ACT: yes	2+	C
a. Asthma control test (ACT)? b. Peak flow measurements? c. Spirometry? d. Impulse oscillometry? e. Exhaled nitric oxide? f. Sputum eosinophils? g. Bronchial challenge to detect hyper-reactivity (Methacholine etc.)? h. Metabolites in urine (LT4, PCE)?	We suggest: PEF yes For c-h: Recommend no	2+	C
ACT (Asthma Control Test): The tool allows control of symptoms through a standardised four-question questionnaire that assesses disease control. It is validated for use in the daily clinic and there are validated translations into Spanish for the paediatric version (children 4-11 years) and the general version; In longitudinal studies, the ACT proved to be a reliable, valid tool, sensitive to detect a change in asthma control over time. However, its reliability in detecting poorly-controlled asthma is somewhat limited. Therefore, it is not recommended as the only asthma-control assessment tool. *PEF (Peak Expiratory Flow):* we suggest the use of PEF. It can be used to assess the response to treatment and to triggers. Excessive PEF variation suggests pulmonary hyperreactivity and suboptimal treatment and increases the risk of exacerbations, thus may be useful in monitoring the control of patients with asthma. A reduction in PEF may indicate an exacerbation and the need for adjustment of asthma management. *The self-control diary* uses a combination of symptoms/signs and PEF as measures of asthma control. Its purpose is to guide the adjustment of treatment at home, in case of loss of asthma control or when the patient is facing an exacerbation.			
The results of the Delphi Panel for this recommendation were mean= 8.4, standard deviation= 1.01, median= 9, min= 6, max= 9, percentile 25= 8, percentile 75= 9 Agreement was reached in the first round with 93% of scores in range from 7-9 for Appropriateness.			
D18- At the **first** and **second** level of health care: In patients ≥ 6 years with asthma, for the out-patient monitoring of disease activity and asthma control, we can use…: a. Asthma control test (ACT)? b. peak flow measurements?	 Suggest yes Suggest yes	 2+ 2+	 C C
c. Spirometry? d. Exhaled nitric oxide? e. Sputum eosinophils?	Suggest yes Recommend No Recommend No	2+ x x	C x x
ACT: Can be used at the first level of care to quickly identify patients requiring more detailed assessment and to identify patients with poorly-controlled asthma. *PEF:* Suggested to assess response to treatment and identify triggers. Excessive PEF variation suggests suboptimal treatment and increases the risk of exacerbations. Periodic PEF measurement is suggested on a long-term basis in patients with severe asthma, who sometimes have poor perception of airflow limitation. *FEV1:* Suggested to monitor the severity of the obstruction. A low FEV1 is associated with an increased risk of exacerbations. In a prospective study of children with asthma and those who were not using inhaled steroids (ICS), children who had FEV1 between 99-80%, 79-60%, and <60% had a chance of having an asthma attack 1, 3, 1.8, and 4.8 times greater than children with FEV1 equal to or greater than 100%. * While the FEV1/FVC ratio detects the presence of obstruction, FEV_1 gradients its severity. In the first and second level of medical care we recommend not to use FeNO or eosinophilia in sputum as follow-up measures due to lack of availability.			
The results of the Delphi Panel for this recommendation were mean= 8.1, standard deviation= 1.38, median= 8.5, min= 4, max= 9, percentile 25= 8, percentile 75= 9. Agreement was reached in the first round with 93% of scores in range from 7-9 for Appropriateness.			
D19. At the **third** level of health care: In children with asthma: for the out-patient monitoring of disease activity and asthma control, we can use…: a. Asthma control test (ACT)? b. peak flow measurements? c. Spirometry? d. Exhaled nitric oxide? e. Impulse oscillometry? f. Sputum eosinophils? g. Bronchial challenge to detect hyper-reactivity (Methacholine etc.)? h. Metabolites in urine (LT4, PCE)?	 a. Suggest yes b. Suggest yes c. Suggest yes d-e. Weak suggestion yes f-h. We recommend No	 2+ 2+ 2+ 1+ 2+ 4 4 4	 C C C C C D D D
FeNO, as a marker of airway inflammation, could be a predictor of response to inhaled steroid therapy (ICS). Increased FeNO levels predict relapse after ICS withdrawal; However, a meta-analysis showed that adjustment of treatment according to FeNO levels does not improve the outcome of asthma and does not add benefits when compared to traditional follow-up. FeNO is not routinely suggested for use. Oscillometry is suggested only in children <5 years, although more evidence is required to fully support its use. Cytological analysis of sputum could be used in the assessment of the control of adult patients with severe asthma, but not routinely.			
The results of the Delphi Panel for this recommendation were mean= 8.0, standard deviation= 1.47, median= 9, min= 4, max= 9, percentile 25= 7, percentile 75= 9. Agreement was reached in the first round with 93% of scores in range from 7-9 for Appropriateness.			
D20.- Patients ≥ 6 years with asthma are considered well controlled if in the last 4 weeks, they have had: • < 2 times / week symptoms	We suggest: yes	4	D

Table 4 (*Continued*)

• No night-time wakening • < 2 times / week use of rescue inhaler • No self-limiting of physical activities, due to asthma			
Its use is suggested to classify the degree of control of the disease and as a method to fine-tune the treatment. It is recommended in two mother guides (GINA and GEMA). Although the BTS suggests treating a poorly-controlled patient with symptoms three or more times per week, Mexican experts consider that there is already a lack of control from symptoms or use of rescue medication two or more times per week.			
The results of the Delphi Panel for this recommendation were mean= 8.4, standard deviation= 0.85, median= 9, min= 7, max= 9, percentile 25= 8, percentile 75= 9 Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			
D21. In patients ≥ 6 years with asthma: What factors increase the risk of developing exacerbations? 1. Use of more than one SABA vial per month 2. Inadequate use of the inhaled steroid (poor adherence, poor inhalation technique) 3. Low FEV_1 (especially if <60%) 4. Psychosocial or socioeconomic problems 5. Comorbidities 6. Pregnancy 7. Sputum eosinophilia 8. Eosinophilia in peripheral blood	We recommend yes	1. 2+ 2. 2+ 3. 2+ 4. 2+ 5. 1+ 6. 2+ 7. 2+ 8. 2+	B-C
We recommend to identify patients who monthly use more than one vial of salbutamol. In a randomised controlled trial the frequent use of salbutamol was significantly associated with the development of adverse effects in the future. The use of salbutamol for two days during two weeks was associated with severe exacerbations. The use of ICS is recommended, because patients using one or more ICS inhalers per month for one year had a significantly lower risk of having near-fatal or fatal asthma. FEV_1 monitoring <60% was recommended because in a retrospective cohort study the FEV_1 decline was found to be responsible for asthma attacks (FEV_1 <60% OR of 2.1 [95% CI 1.3-3] compared to FEV_1 <80 % with OR 1.4 [95% CI 1-2-1.6]) It is suggested to identify factors such as environmental tobacco smoke exposure and positive sensitivity to dog or cat, as in a cohort study these factors were associated with groups at highest risk for hospitalisation. It is recommended to consider obesity as a risk factor, since in a retrospective study GI-III obesity was associated with worsening of asthma severity (OR: 4.23, 95% CI: 1.61-11.06, P = 0.003, II / III: OR: 2.76, 95% CI: 1.08-7.09, P = 0.03). It was associated with increased exacerbations requiring oral steroids, an increased time of inhaled steroid use and an increased IgE, and neutrophil level. In patients with stable asthma, an increase in eosinophils was found to be associated with moderate to high risk of exacerbations. During pregnancy, it has been established that up to 20% will require some intervention, 6% will require hospital admission, exacerbations mostly occur at the end of the second trimester, the main triggers are viral infections and poor adherence to inhaled corticosteroid treatment. Women with severe exacerbations are at risk for low birth weight infants. Use of steroids may reduce the risk of exacerbations during pregnancy.			
The results of the Delphi Panel for this recommendation were mean= 8.4, standard deviation= 0.84, median= 9, min= 7, max= 9, percentile 25= 8, percentile 75= 9. Agreement was reached in the first round with 100% of scores in range from 7-9 for Appropriateness.			

Pfizer, TEVA, GSK, Amstrong, Siegfried, DBV technologies. MDCCS: Takeda. MAJC: Janssen, MSD. SJRT: Boehringer Ingelheim. BDRN: Sanofi, MSD, Grunenthal. JALP: Mead & Johnson Nutricionales, Meda. JAOM: UCB, AstraZeneca, Sanofi. JVR: A2DAHT. NRP: MSD, AstraZeneca, Boehringer Ingelheim. CGG: AstraZeneca. DAMH: Senosiain. HHRG: Abbvie, Novartis, Roche. HLM: Aerosol Medical Systems. JGV: Novartis, Sanofi. JLMR: AstraZeneca.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.aller.2017.05.011.

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