

Critical Analysis of Asthma Guidelines: Are They Really Evidence-Based?

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Recent years have seen a growing reliance on “evidence-based” guidelines or consensus statements, in which rigorous, explicit methods are used to translate the complex findings of scientific research into operational recommendations for medical care. Various factors can affect the validity of the conclusions they express, however. The purpose of this review was to compare the levels of evidence supporting treatments for acute asthma in adults according to 3 of the most important guidelines. It seems that even though these guidelines are based on an approach that is more or less rigorous, there are considerable gaps and inconsistencies that compromise their validity. Our main sources of information should therefore be those that apply the best research designs, namely randomized controlled trials or meta-analyses of such trials with consistent results and a low probability of bias.

Key words: *Guidelines. Consensus. Asthma. Evidence-based medicine. Therapeutics.*

¿Están verdaderamente basadas en la evidencia las guías sobre el asma? Un análisis crítico

En los últimos años se ha producido un movimiento creciente hacia el uso de métodos explícitos y rigurosos que conduzcan al desarrollo de guías o consensos “basados en la evidencia”, capaces de convertir los complejos hallazgos de la investigación científica en recomendaciones operativas del cuidado médico. Sin embargo, diferentes factores son potencialmente capaces de afectar a la validez de sus conclusiones. El objetivo de esta revisión consistió en realizar un análisis comparativo de los niveles de evidencia asignados a los tratamientos del asma aguda en el adulto en 3 de las guías más importantes sobre asma. Se puede concluir que, a pesar de que estas guías se desarrollaron con una metodología más o menos rigurosa, presentan importantes carencias o incongruencias que pueden comprometer su validez. En consecuencia, nuestras fuentes prioritarias de información deben ser las de mayor calidad metodológica, es decir, los ensayos aleatorizados y controlados o los metaanálisis de ensayos aleatorizados y controlados con resultados consistentes y baja probabilidad de sesgo.

Palabras clave: *Guías. Consensos. Asma. Medicina basada en la evidencia. Tratamiento.*

Introduction

Clinical guidelines are defined by “the systematic development of recommendations that have the aim of helping the practicing physician and the patient make decisions related to the specific circumstances of health care.”¹ In the last decade, consensus statements or clinical guidelines have become increasingly important in clinical practice. Many of the daily decisions concerning patients or operative aspects of the management of health centers, and even decisions made by health managers, are therefore influenced by such documents. The marked increase in

the number of guidelines published can largely be attributed to problems faced primarily in the health systems of countries of Europe, North America, Australia, and New Zealand, that is, the sharp increase in health costs along with increased demand, new and costly technologies, as well as the repercussions of the aging of the population, in combination with the desire of health professionals to offer (and the patients to receive) the best possible medical care. Thus, practicing physicians, health managers, and health policy makers see the guidelines as a means to providing more uniform and efficient health care, and to reducing the gap between what physicians actually do and what the scientific evidence indicates.^{2,3}

The main potential benefit of these guidelines or consensus statements is improved medical care for patients. Guidelines can make medical care more uniform and thus improve its quality.⁴ Furthermore, they help ensure that patients are better informed about their therapeutic options,

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something which in turn will allow them to influence the development of health policies. However, the availability of good guidelines does not ensure their use in everyday clinical practice.^{4,5} Systematic reviews of the strategies for modifying the behavior of health professionals show that use of predominantly passive means of dissemination and the implementation of guidelines through publication in scientific journals does not significantly alter behavior.⁶ This is because, to a certain extent, physicians, patients, and managers differ in how they define quality of health care. The chances that guidelines will be effective will depend on factors such as the strategies used for their development, dissemination, and implementation.

Perhaps the most important limitation of guidelines is that their recommendations might not be correct or valid. Those responsible for drafting the guidelines may err in their assessment of what is best for the patient in 2 fundamental ways. First, the scientific evidence underpinning the different recommendations might not exist, or be confusing or misinterpreted. Only limited aspects of medical knowledge have been widely studied in an appropriate fashion with well-designed sufficiently powered studies. Often, studies may be available that can provide biased conclusions or ones that cannot be readily generalized due to methodological limitations. The search for evidence itself may also be partial and limited by the judgment of those who draft the guidelines, with the result that evidence is fitted to their preconceived ideas. Second, recommendations are often influenced by the opinions, beliefs, values, and clinical experience of the experts who develop them. Thus, the evaluations and the treatments that the authors considered beneficial for their patients are more highly recommended than other options which might in fact be superior.⁷ The guidelines can therefore provide inaccurate scientific evidence so compromising the quality of health care that the patients receive.

Although, traditionally, most guidelines were developed through expert panels sponsored by professional societies and other groups, in recent years there has been a growing movement towards the use of explicit and rigorous methods that lead to the development of "evidence-based" guidelines, able to translate complex findings of scientific research into operational recommendations for medical care.⁸⁻¹⁰ Most guidelines are still formed, however, from an amalgam of experience, expert opinion, and scientific evidence.

The aim of this review was to perform a comparative analysis of 3 of the most important guidelines for asthma with regard to recommendations on management of asthma crises in adults. In particular, the levels of evidence assigned to the treatments were compared and the validity of the classification of this evidence was assessed.

Methods

Three of the guidelines or consensus statements on asthma from groups with greatest worldwide prestige were selected: *a)* the Global Initiative for Asthma (GINA), revised in 2006¹¹; *b)* the Expert Panel Report (EPR) of the National Program for the Education and Prevention of Asthma published by the National Heart, Lung, and Blood Institute,¹² updated in January 2007 and

only available on the Internet; and *c)* the British Guideline on the Management of Asthma, drafted by the British Thoracic Society and the Scottish Intercollegiate Guidelines Network (SIGN), in the version updated in November 2005, also only available in electronic format.¹³ The 3 guidelines, which are "evidence based," present various details on the methodology used, such as the time periods considered, search strategies for new evidence (all are updates of previous versions), study inclusion criteria, and number of new studies found, among other points. Of the 3 guidelines, EPR-3 contains the most detailed description of methodology. Finally, while all the guidelines provide an explicit description of the definitions of the different levels of evidence, only 2 of them provide grades of recommendations.^{12,13}

Due to space constraints, the analysis of the guidelines was limited to the sections on treatment of asthma crises in adults. The 3 guidelines were compared in terms of the levels of evidence assigned to each of the treatments. In addition, the references cited to support the levels of evidence were identified in order to check whether the articles cited did indeed reflect the level of evidence assigned.

Results

Table 1 shows the definitions of the levels of evidence used in each of the guidelines. In all cases, these levels were based on the design and the methodological quality of the studies. Two of the 3 consensus statements (GINA and EPR-3) shared the same definition. Both these guidelines take as reference a publication in which a critical evaluation of how the meta-analyses published on asthma treatment are done. This publication does not appear to treat the question of methodological quality of scientific studies in general.¹⁴ The evidence is summarized in 4 categories, with randomized, controlled trials (RCTs) occupying the highest or level A category. It is particularly noteworthy that the meta-analyses of RCTs are considered evidence category B. On the other hand, the British guidelines also have 4 levels evidence based on the system developed by the SIGN¹⁵; of these, only the 2 lower categories show reasonable overlap with the categories C and D of GINA and EPR-3. In contrast, the 2 higher levels (1 and 2) are significantly different to categories A and B, and each of these higher levels is divided into 3 subcategories. Moreover, meta-analyses are considered the most convincing evidence. Finally, level 2 is made up of cohort studies or case-control studies, which would correspond to evidence category C of GINA and EPR-3.

Only 2 of the 3 guidelines present grades of recommendations (Table 2). The EPR-3 establishes 2 very broad, poorly-defined levels. In contrast, the British guidelines establish 4 levels defined in detail and based, as for the levels of evidence, on the SIGN system.¹⁵ In view of these differences, a comparison of the guidelines is rendered impossible.

Despite certain overlap, comparison of the 3 guidelines with regard to management of acute asthma attacks revealed numerous discrepancies (Table 3). The 3 essentially agree on the use of short-acting β_2 -agonists (level A in GINA and EPR-3 and 1+ in the British guidelines). All advise against intravenous administration of short-acting β_2 -agonists, antibiotics, theophylline, and indicate the use of

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TABLE 1
Comparative Analysis of the Definitions of the Levels of Evidence Used in the Guidelines Considered

GINA and EPR-3		BG	
Level of Evidence	Definition	Level of Evidence	Definition
A	RCT. Rich body of data. Evidence comes from well-designed studies with a consistent pattern of findings. A large number of studies with a substantial number of patients are required	1++	High-quality meta-analyses, systematic review of RCTs, or RCTs with a low risk of bias
		1+	Well-conducted meta-analyses, systematic review of RCTs, or RTCs with low risk of bias
		1-	Meta-analyses, systematic review of RCTs, or RCTs with high risk of bias
B	RTC. Limited body of data. Evidence comes from studies with limited number of patients, or from subgroup or post-hoc analyses, or meta-analyses of RCTs or studies with inconsistent results	2++	High-quality systematic review of case-control studies or cohort studies. High-quality systematic review of case-control studies or cohort studies with low risk of bias and high probability that the relationship is causal
		2+	Well-conducted case-control studies or cohort studies with low risk of bias and moderate probability that the relationship is causal
		2-	Case-control studies or cohort studies with high risk of bias or high probability that the relationship is not causal
C	Nonrandomized or observational studies. The evidence comes from nonrandomized studies or uncontrolled or observational studies	3	Nonanalytic studies, for example, case reports
D	Expert opinion. These are based on clinical experience or knowledge that cannot be included in category C	4	Expert opinion

Abbreviations: BG, British guidelines; EPR-3, Expert Panel Report (EPR) of the National Program for the Education and Prevention of Asthma; GINA, Global Initiative for Asthma; RCT, randomized controlled trials.

the combination of β_2 -agonists and ipratropium bromide, although the levels of evidence do not always coincide. In contrast, some treatments, although discussed by the guidelines, were not assigned any level of evidence or considered as therapeutic options. For example, no mention is made of the use of inhaled adrenaline and noninvasive

ventilation in GINA; formoterol in an emergency-room setting in EPR-3; or inhaled formoterol, levalbuterol, adrenaline, and magnesium in the British guidelines. The British guidelines affirm that no studies have been published on antileukotrienes for treatment of asthma crises when in fact several RTCs had been published before 2005.¹⁶⁻¹⁸

TABLE 2
Comparative Analysis of the Grades of Recommendation in the Guidelines Considered

Guideline	Grade of Recommendation	Definition
GINA	—	—
EPR-3	Recommends Should or could be considered	Strongly recommends Indicates a weak recommendation
BG ^a	A	At least 1 meta-analysis, systematic review of RCTs or RCTs rated as 1++, directly applicable to the target population; or a uniform body of evidence consisting of studies rated as 1+, directly applicable to the target population, demonstrating consistent results
	B	A body of evidence that includes studies rated as 2++, directly applicable to the target population, demonstrating consistent results; or extrapolated evidence from studies rated as 1++ or 1+
	C	A body of evidence including studies rated as 2+, directly applicable to the target population, demonstrating consistent results; or extrapolated evidence from studies rated as 2++
	D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Abbreviations: BG, British guidelines; EPR-3, Expert Panel Report (EPR) of the National Program for the Education and Prevention of Asthma; GINA, Global Initiative for Asthma; RCT, randomized controlled trials.

^aThe grade of recommendation reflects the strength of evidence to support the recommendation, not the clinical significance of the evidence.

TABLE 3
Comparative Analysis of Management of Acute Asthma According to the Guidelines Studied

	GINA	EPR-3	BG
Oxygen	Goal: SaO ₂ >90%. It is recognized that hyperoxia can produce hypercapnia, particularly in patients with the most severe forms of the disease	Goal: SaO ₂ >90%	Use of high FiO ₂ (40%-60%) for all patients through use of high-flow masks. Goal: SaO ₂ 92%. Low risk of hypercapnia due to hyperoxia (2+)
Short-acting inhaled β ₂ -agonists	Use of repeated dosing (A). MDI is equivalent to nebulization	Use of repeated dosing (A). In moderate crises, MDI is equivalent to nebulization. In severe cases, nebulization is preferred	High doses at regular intervals (1+). In patients with most severe disease, nebulization is recommended
Formoterol	Similar efficacy to short-acting β ₂ -agonists	Not mentioned for treatment in the emergency room	Evidence not mentioned
Levalbuterol	Modest bronchodilatory effect	Levalbuterol incorporated as short-acting β ₂ -agonist	Evidence not mentioned
Adrenaline	SC or IV route not indicated. Inhaled route not mentioned	SC route not recommended. Inhaled route not mentioned	Evidence not mentioned
Continuous vs intermittent nebulization	Inconsistent results	Continuous nebulization might be more effective in patients with severe disease	Continuous nebulization is equivalent, but might be more effective in patients with most severe disease (PEF<50%) (1+).
Short-acting IV β ₂ -agonists	No evidence of efficacy	No benefit (B)	Inhaled route preferred (1++)
Short-acting β ₂ -agonists in combination with ipratropium bromide	Multiple doses ↑ bronchodilation (B), ↓ admissions to hospital (A)	Multiple doses ↑ bronchodilation (B), ↓ admissions to hospital (A)	Fewer admissions to hospital and faster recovery (1++)
IV aminophylline	Minimal role	Not recommended (A)	Not effective (1++)
Systemic corticosteroids	Should be used in all exacerbations except mild ones (A). The oral route is preferred as it is equivalent and cheaper. Reduces the relapse rate (B)	In patients with moderate and severe asthma, or in those who do not respond to treatment (A); oral equivalent to IV. Oral route is preferred as it is less invasive	Mortality, relapses, and admissions to hospital are reduced (1++). Administer orally to all patients
Inhaled corticosteroids	Compared to placebo or systemic corticosteroids, ↑ bronchodilatation (B)	Possible beneficial effect. Insufficient evidence to replace systemic corticosteroids by inhaled ones (B)	No benefit provided (1++)
IV magnesium	Only in patients with severe disease (FEV ₁ , 25%-30%) (A)	Patients with severe disease (PEF<25%) to avoid intubation (B)	Effective in patients with more severe disease or poor response (1++)
Inhaled magnesium	Beneficial (A)	Can be beneficial	Evidence not mentioned
Helium-oxygen	No evidence to support systematic use	Use in patients with PEF<25% to avoid intubation (B)	Not recommended (1+)
Antileukotrienes	Few data for determining their role	Insufficient data (D)	No studies published in acute asthma
Antibiotics	Role unclear	Not recommended (B)	Not indicated (1++)
Noninvasive ventilation	Evidence not mentioned	Insufficient evidence (D)	Cannot be recommended because there are no RCTs

Abbreviations: BG, British guidelines; EPR-3, Expert Panel Report (EPR) of the National Program for the Education and Prevention of Asthma; FEV₁, forced expiratory volume in 1 second; FiO₂, fraction of inspired oxygen; GINA, Global Initiative for Asthma; IV, intravenous; MDI, metered dose inhaler; PEF, peak expiratory flow; RCT, randomized controlled trials; SaO₂, arterial oxygen saturation; SC, subcutaneous.

Other inconsistencies include, in the EPR-3, the lack of studies cited to support the recommendation for the use of levalbuterol, support for helium-oxygen mixture in order to avoid intubation in patients with severe disease, even though this hypothesis has not been tested in clinical trials, and the omission of 2 important meta-analyses, one of which was a Cochrane review.^{19,20} On the other hand, the

recommendation (level 1+) in the British guidelines concerning the lack of usefulness of a helium-oxygen mixture is only supported by 2 RCTs published in 1999, with no mention made of any of the meta-analyses performed on this topic. With regard to the use of systemic corticosteroids, GINA and EPR-3 indicate their use in patients with moderate and severe asthma crises, as well

as in those who do not respond to initial treatment (the GINA recommendation is based on 2 meta-analyses, one of which refers exclusively to hospital patients²¹). In contrast, the British guidelines establish use of systemic corticosteroids in all patients regardless of whether they are admitted to hospital or not, without any supporting evidence either for hospital patients or outpatients. In particular, the British guidelines establish a beneficial effect of corticosteroids in terms of lower mortality, with no reference to support that affirmation. For the same guidelines, the affirmation that intravenous magnesium is effective in patients with most severe disease or with poor initial response is based solely on a meta-analysis from 2000, which analyzed 7 studies although only 3 included patients with severe disease.²² Important RCTs carried out at a later date were omitted.²³ Both the EPR-3 and the British guidelines claim that no RCTs have been conducted for use of noninvasive mechanical ventilation, when at least 1 such study has been published.²⁴ Also of note is the preference for nebulization instead of metered-dose inhalers for administration of short-acting bronchodilators in asthma patients with severe crises (EPR-3 and British guidelines). The 2 meta-analyses discussed in the EPR-3 to support this recommendation do not actually favor this preference but rather affirm the equivalence of the 2 methods.^{25,26} In the case of the British guidelines, despite establishing the equivalence of the 2 systems beforehand (based on a meta-analysis), use of nebulizers is subsequently recommended. Finally, both GINA and EPR-3 recommend the use of oxygen therapy with a view to maintaining arterial oxygen saturation above 90%. GINA also recognizes the negative effect that use of high fractions of inspired oxygen might have, particularly in patients with severe disease. In contrast, the British guidelines recommend the use of high fractions of inspired oxygen in all patients and state that the risk of triggering hypercapnia is low. It should be noted that these guidelines support this statement with 4 references to articles published between 1968 and 1991, although none actually support such a therapeutic approach.²⁷⁻²⁹ In fact, few controlled studies have evaluated the effect of hyperoxia in patients with acute asthma.^{30,31}

Conclusions

The aim of this review was to perform a comparative analysis of 3 of the most important guidelines for asthma with regard to recommendations on management of asthma crises in adults. It can be concluded that, although these guidelines used an "evidence-based" approach, substantial deficiencies and inconsistencies might compromise their validity. As discussed earlier, the recommendations given by guidelines or a consensus statement may be affected by several factors. This analysis uncovered elements that point to a possible contribution from all of them. In fact, on the one hand, we found several important omissions of studies such as meta-analyses or RCTs to support a recommendation. In addition, certain well-known treatments were not considered. Second, in several instances, evidence to support certain recommendations was erroneously or partially interpreted. Finally, it is very

likely that the opinions, experience, or values of some of the experts who participated in drafting the guidelines played a role, an observation which could explain certain biases in literature selection or recommendations.

The last few years has seen a substantial increase in the number of published guidelines or consensus statements. In particular, the growing use of explicit methodology and development of "evidence-based" guidelines has increased the validity of the guidelines and contributed substantially to their improved reputation in medical circles. However, the significant weaknesses uncovered in the present study invite us to maintain a cautious and critical attitude toward their recommendations. We should not accept the maxim that a treatment has to be included in clinical guidelines to be respectable. Guidelines are not textbooks that provide a balanced and reliable summary of the role of different treatments. We should also remember that when assessing the evidence of a given treatment, our main sources should be those with the highest methodological quality, that is, RCTs or meta-analyses of RCTs with uniform results and a low probability of bias.

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