

Global Initiative for Asthma (GINA) guidelines: 15 years of application

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Claus Kroegel

Department of Pneumology & Allergy, Medical Clinics I, Friedrich-Schiller-University, Erlanger Allee 101, D-07740 Jena, Germany
Tel.: +49 364 193 249 131
Fax: +49 364 193 249 132
claus.kroegel@med.uni-jena.de

The Global Initiative for Asthma (GINA), founded in 1993, embodies a network of public health organizations and medical societies, as well as other individuals concerned with asthma. Its first report, published in 1995 and entitled 'A Global Strategy for Asthma Management and Prevention', has been widely adopted, providing the foundation for asthma guidelines in many nations across the world. To this effect, the report has not only been translated into several languages but has also been frequently updated. Since its establishment 15 years ago, GINA has undergone two major paradigm shifts. The first was the change in the late 1990s from an opinion- to an evidence-based approach for the management of asthma severity. The second, an even more radical shift, was seen in 2006, when the revised GINA guidelines involved the classification of asthma severity according to the level of control as a guide to treatment. In order to classify asthma control, elements such as the significance of the partnership between the patient and caregiver, patient education, guided self-management and treatment goals were introduced. In addition to compiling guidelines and reports for the management of asthma, GINA is actively involved in organizing and coordinating the World Asthma Day, regional initiatives and GINA symposia. On the whole, during the 15 years since their original publication in 1995, the GINA guidelines have provided the basis for many national asthma strategies around the world. This course is most likely to continue in the future. In this paper, the history of the development of the guidelines and other issues regarding the GINA project will be addressed.

KEYWORDS: • asthma control • asthma guideline • asthma management and prevention • asthma severity • GINA • Global Initiative for Asthma • paradigm shift in asthma

Asthma is defined as a clinical syndrome characterized by airway inflammation, variable lung function and airways hyper-responsiveness [1–5,101]. Worldwide, an estimated 300 million people suffer from asthma and this number is expected to increase to 400 million by 2025 [6–8,101]. Moreover, asthma is believed to be responsible for approximately 250,000 annual deaths worldwide. As a result, asthma accounts for a substantial global socio-economic burden [5,101]. Although there is convincing evidence that asthma cannot always be adequately controlled with current treatments [9–11], the development of guidelines for the diagnosis and management of asthma has provided an important means of allowing the implementation of current knowledge into daily clinical practice [12–15].

History

Approximately 30 years ago, the circumstances regarding asthma and allergy were worse than

they are today. Many anti-asthmatic drugs in common use today were not available at that time, and the role of anti-inflammatory drugs for the treatment of asthma had yet to be established. At the time, asthma was associated with recurrent symptoms, disabling side effects due to treatment and epidemics with high mortality rates [16]. For example, outbreaks of fatalities due to asthma among individuals aged between 15 and 64 years have been repeatedly recorded in New Zealand since 1976 [17], where peak mortality rates were more than four times pre-epidemic rates. In addition, in Australia, the prevalence of asthma almost doubled between 1984 and 1994 [18]. At the same time, disease prevalence also increased in Western Europe, the USA and Australasia, with hospital admissions increasing by an astonishing 20-fold in children, and by three- to fivefold in adults between 1960 and 1985. This wave of asthma also spread to developing countries that had adopted a 'Westernized'

lifestyle. Although the upsurge in asthma deaths in New Zealand was eventually found to partly be related to an overuse of fenoterol [19], explanations regarding the increase in the occurrence of asthma observed in other parts of the world have remained elusive [20,21].

This alarming trend compelled groups of professionals involved in asthma in individual countries to convene with the view to preparing guidelines relating to the diagnosis and management of asthma. Since then, a number different national and international guidelines and documents have been produced worldwide (TABLE 1) [1–5,21–34,102,103], aiming at alerting and educating not only healthcare professionals but also government officials, policy-makers and regulatory authorities of this marked increase in the

prevalence of asthma and other atopic diseases. Among them, the Global Initiative for Asthma (GINA) guidelines are probably the most internationally recognized framework for the diagnosis and management of asthma.

GINA guidelines

The National Heart, Lung and Blood Institute (NHLBI); (USA) launched the GINA project 15 years ago, under the direction of Claude L'Enfant, in collaboration with the WHO. Teams of international leading asthma experts collaborate to design GINA's strategy. GINA's aims and objectives include:

- Increase awareness of asthma and its public-health consequences
- Educate asthma patients and their relatives

Table 1. Summary of selected guidelines on the diagnosis and treatment of asthma.

Guidelines	Publication year	Description/characteristics	Ref.
First guidelines on asthma (Australia and New Zealand)	1986	Expert-based recommendations based on severity	[17]
EPR-1 and 2 NHLBI/NAEPP	1990–1991 Update 1997	Opinion-based; places major emphasis on diagnosis (including classification of asthma) and management (including a step-by-step approach to asthma treatment) Severity grading based on level of symptoms, use of reliever medications, airflow limitation and variability	[1,2]
BTS	1990 Updates 1993 and 1995	Guidelines for the management of asthma in adults already became available in 1990. Consensus-based; places major emphasis on diagnosis and treatment of adult asthma. The 1993 update included childhood asthma	[21–26]
International consensus report on asthma	1992	Represents an international consensus statement providing a general approach to asthma management developed on the basis of guidelines from 11 nations	[3]
GINA 1. The Global Strategy for Asthma Management and Prevention Report	1995 Updates annually (1999–2002)	Includes sections on epidemiology and the pathogenesis and prevention of asthma, as well as chapters on treatment and education. Guidelines place major emphasis on diagnosis (including classification of asthma) and management (including a step-by-step approach to asthma treatment)	[4]
The Paediatric Asthma: Best Practices guidelines	1998	Translates the NAEPP guidelines into recommendations for easy use by general pediatricians. The guidelines also acknowledge the differences in assessment and management for very young children (age ≤5) with asthma	[27]
BTS and SIGN	1996 Updates 2003 and 2008	Originally published in 1996 as two separate guidelines (BTS and SIGN) Sections on primary care management of asthma and management of acute asthma added in 1998 and 1999, respectively Since 2003, joint production by BTS and SIGN of comprehensive asthma guidelines using evidence-based methodology	[22,28,102]
Canadian	1990 Updates 1999, 2001 and 2005	The first guideline to use the evidence-based approach. Control and severity included in the 1999 revised guidelines. The latest version highlights young childhood asthma and asthma-prevention strategies	[29–31]
EPR-3 NHLBI/NAEPP	2007	Evidence-based disease grading according to control by means of day- and night-time symptoms and physical activity, reliever medications, airflow limitation (FEV ₁ or PEF), quality of life and frequency of exacerbations	[5]
IPAG and IPCRG guidelines for primary care	2005 and 2006	Guidelines focus on the primary care approach to asthma and combines asthma, rhinitis and COPD. Also provide diagnosis and treatment tracks for clinical practice	[32–34,103]

BTS: British Thoracic Society; COPD: Chronic obstructive pulmonary disease; EPR: Expert Panel Report; FEV₁: Forced expiratory volume in 1 s; GINA: Global Initiative for Asthma; IPAG: International Primary Care Airways Group; IPCRG: International Primary Care Respiratory Group; NAEPP: National Asthma Education and Prevention Program; NHLBI: National Heart, Lung and Blood Institute; PEF: Peak expiratory flow; SIGN: Scottish Intercollegiate Guidelines Network.

Table 2. Materials and activities available from GINA to help improve the delivery of care for asthmatics.

Guideline title	Description
Asthma Management and Prevention	A practical guide for public health officials and healthcare professionals: highlights from the workshop report
Pocket Guide for Asthma Management and Prevention	A summary of patient care information for primary healthcare professionals
What You and Your Family Can do about Asthma	A patient information booklet. The complete report includes technical discussions on asthma and asthma management, as well as specific citations from the scientific literature
Instructions for Inhaler and Spacer Use	Diagrams and step-by-step instructions on the correct use of various inhaler and spacer devices available worldwide. Printable and downloadable slides can be used for patient education
Spacer Devices	An introduction to spacers for healthcare professionals: how, when and why these devices should be used
GINA Teaching Slide Set	Powerpoint slide set summarizing GINA's objectives, documents and management recommendations, with background information on asthma and the burden of this disease

GINA: Global Initiative for Asthma.

- Promote research into the identification of factors associated with increased asthma prevalence
- Support studies on the correlation between asthma and the environment
- Reduce asthma morbidity and mortality
- Improve asthma management
- Increase access to effective asthma therapy

An additional goal of the GINA initiative is to facilitate collaborations between existing state and other programs aimed at combating chronic respiratory diseases. In contrast to other guidelines (TABLE 1), the GINA guidelines use a comprehensive global approach for the prevention and control of chronic respiratory diseases from the very start, with a special emphasis on developing countries. In order to achieve these goals, GINA organizes a spectrum of activities and events (e.g., World Asthma Day and GINA symposia) in addition to releasing printed material (TABLE 2).

During the early 1990s, GINA set out to draw up recommendations for the care and management of asthma that were to be based on top scientific data. To this purpose, the GINA Scientific Committee devised a sophisticated system to review the worldwide literature regarding asthma management, resulting in the publication in 1995 of the first guidelines, entitled 'Global Strategy for the Diagnosis and Management of Asthma'. Today, one of the main tasks of the GINA Scientific Committee is to regularly update the guidelines, which, on their completion, are available free of charge on the GINA website [104].

The updated 2006 and 2007 GINA guidelines contain several important new themes. In addition to relevant pharmacological treatments, the importance of a patient–doctor partnership, patient education, defining individual treatment goals, guided self management, reduced exposure to triggers and the treatment of comorbidities are emphasized. The most significant amendment, however, relates to a fundamental change in the approach to asthma management. The two latest updates recommend using the level of asthma control, rather than asthma severity, as the

key feature for the classification and management of asthma, as well as for treatment decisions. These aspects will be discussed in more detail later.

The strength of a recommendation reflects the extent to which we can be confident that the desirable effects of an intervention outweigh any undesirable effects. It is determined by the balance between the desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resource use [35]. Indeed, the quality of clinical guidelines depends on the evidence and the judgments they are based on [36]. The GINA guidelines followed the grading system of the Agency for Health Care Policy and Research, which has been a reference for many years (TABLE 3) [37].

Paradigm shifts

The Global Initiative for Asthma not only pioneered the development of guidelines for the control and management of asthma, but also were among the first to introduce two major paradigm shifts (FIGURE 1). The first shift involved the conversion from opinion-based to evidence-based consensus guidelines. The second change concerned the global distribution of a consensus report to substitute severity-based treatment guidance with a control-based therapy approach.

Opinion- versus evidence-based approaches

During the 1990s, many guidelines and recommendations, including the GINA guidelines, were based upon expert opinion, since very few data from randomized clinical trials regarding the disease process were available. Although 'only' opinion-based, the results provided a framework for the development of later revisions using evidence-based methodology. The turn of the century marked the period during which 'evidence-based medicine' (EBM) established itself as an essential component in the preparation of guidelines (FIGURE 1).

The Global Initiative for Asthma adopted the new evidence-based methodology for the 2002 guideline update. EBM aims to provide a logical and convenient framework that allows an

Table 3. Description of level of evidence used in the GINA guidelines.

Evidence category	Source of evidence	Description
A	RCTs, rich body of data	Evidence is from end points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants
B	RCTs, limited body of data	Evidence is from end points of interventional studies that include only a limited number of patients, <i>post hoc</i> or subgroup analysis of RCTs, or meta-analyses of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation or the results are somewhat inconsistent
C	Nonrandomized trials, observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies
D	Panel consensus judgment	Category D is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The panel consensus is based on clinical experience or knowledge that does not meet the criteria listed above

RCT: Randomized controlled trial.

assessment of the quality and relevance of clinical studies in an unbiased manner [38]. Therefore, clinical practice guidelines based on evidence obtained from randomized controlled trials are considered the most rigorous and accurate. However, EBM-based guidelines have a number of inherent shortcomings, which need to be considered when applying the recommendations in a clinical practice setting [39,40]. For instance, group probabilities derived from EBM-based data analyses cannot be safely applied to individuals. Thus, the conclusions raised from EBM are not applicable to the entire population of asthmatic patients, and tend to overvalue the specific modalities it tests. In addition, EBM in its hierarchy of evidence does not take into account the safety and efficacy of medical interventions, and neglects elucidation of within-group variability. Finally, the artificial nature of EBM-based conclusions often restrict their applicability to overly simple interventions [40].

Severity- versus control-based approaches

Initially, for over a period of more than 10 years, the GINA guidelines recommended assessing and monitoring asthmatic patients according to disease severity. Four classes of asthma severity were recognized: mild intermittent, mild persistent, moderate persistent and severe persistent. The categories were based on history of daytime and night-time asthma symptoms, exacerbations and measurements of lung function (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 s [FEV₁], as well as the morning-to-evening variability of PEFR.

Classification according to disease severity clearly had an important educational impact (Box 1). It permitted:

- Assessment of the prognosis and the level of treatment required to obtain control
- Choice of initial treatment in a patient with newly diagnosed asthma
- Standardized communication among healthcare providers over patients
- Prediction of asthma-related costs and resource utilization

As asthma severity does not directly reflect the activity of a highly variable disease [102], a second major paradigm shift has led GINA to recommend classifying asthma according to three levels of disease control (TABLE 4) [41–44,104,105]:

- Controlled
- Partly controlled
- Uncontrolled

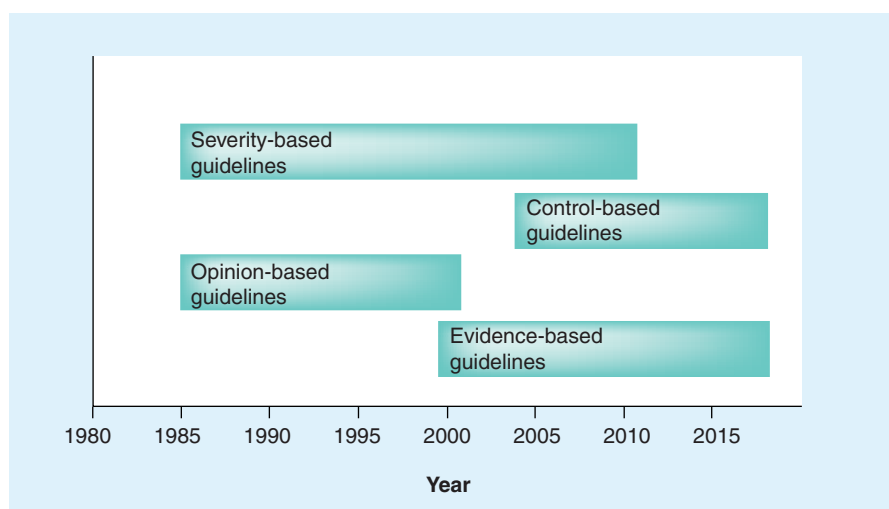


Figure 1. Paradigm change in the conception of guidelines for the management and treatment of asthma.

Box 1. Potential disadvantages of severity-based classification for asthma guidelines.

- Severity classification has not been validated as a clinical tool, undermining physicians' beliefs and their confidence in the utility of this aspect of the guidelines
- Application of severity-based classification is difficult in practice, and although severity classification must be applied to patients with no treatment, this is not always the case, even at initial diagnosis
- An assessment of the effect of treatment over time, one of the most relevant clinical objectives, is not achieved with the severity classification, since response to treatment is extremely heterogeneous among asthmatic patients with asthma of similar severity
- Severity is not a static feature in asthma, but rather is dynamic and variable, rendering the classification of a patient's disease at a single point in time misleading and, moreover, adverse for adjusting the treatment
- The use of severity as an outcome measure has limited value in predicting the required treatment and the response to that treatment
- Severity classification also has limited reliability due to a significant discrepancy in severity evaluation between physicians, resulting in considerable differences in treatment decisions

Although disease control was always considered the ultimate goal of asthma therapy, the concept of control as a guide to therapy is relatively new [41–43]. Level of control was first introduced in the 1999 revision of the Canadian guidelines (TABLE 4) [30,45] and was followed by a number of publications and studies that addressed 'control' as a major end point. It was believed that periodic assessment of asthma control was of clinical relevance [46–51]; however, the revised GINA guidelines in 2006 represented the first globally distributed asthma guidelines adopting this concept of disease control (TABLE 4) [104]. Although other

guidelines, such as the Expert Panel Report-3 [5] have followed suit, the concept of asthma disease control has not been adopted as rigorously as by GINA.

Concepts of asthma severity and control are important in the evaluation of patients and their response to treatment; however, the terminology is not standardized and the terms are often used interchangeably. Asthma control refers to the extent to which the manifestations of asthma have been reduced or removed by treatment. Its assessment should incorporate the dual components of current clinical control (e.g., symptoms, reliever use and lung

Table 4. Assessment of control in the Canadian, BTS, NHLBI and GINA guidelines.

Criteria	Goals (definition of asthma control)			
	<i>Canadian (1999)</i> [30]	<i>NAEPP (2007)</i> [5]	<i>BTS/SIGN (2008)</i> [102]	<i>GINA (2007)</i> [104]
Daytime symptoms	<4 days/week	≤2 days/week	No daytime symptoms	None (or minimal)
Limitations of activities	Normal	None	No limitations in activity, including exercise	None
Nocturnal symptoms/night-time awakening	<1 days/week	≤2 times/month	No night-time awakening due to asthma	None
Need for reliever/rescue treatment	<4 days/week	≤2 days/week	No need for rescue medication	None (or minimal)
Validated questionnaires		ATAQ (score 0) ACQ (score ≤ 0.07) ACT (score ≥ 20)		
Lung function (PEF or FEV ₁)	>85% of personal best, ideally 90%	>80% of predicted/personal best	Normal lung function (in practical terms FEV ₁ and/or PEF > 80% predicted or best)	>80% of predicted
PEF circadian variation	<15% of diurnal variation	PEF circadian variation ≥ 20%		
Exacerbations*	Mild, infrequent	0–1 times/year	No exacerbations	None (or minimal)
Absence from work or school	None			
Emergency visits		No emergency visits		
Treatment-related adverse effects		Should be considered	Minimal side effects	

*Exacerbations are defined as any worsening of asthma symptoms requiring emergency intervention.

ACQ: Asthma control questionnaire; ACT: Asthma control test; ATAQ: Asthma therapy assessment questionnaire; BTS: British Thoracic Society; FEV₁: Forced expiratory volume in 1 s; GINA: Global Initiative on Asthma; NAEPP: National Asthma Education and Prevention Program; NHLBI: National Heart, Lung and Blood Institute; PEF: Peak expiratory flow; SIGN: Scottish Intercollegiate Guidelines Network.

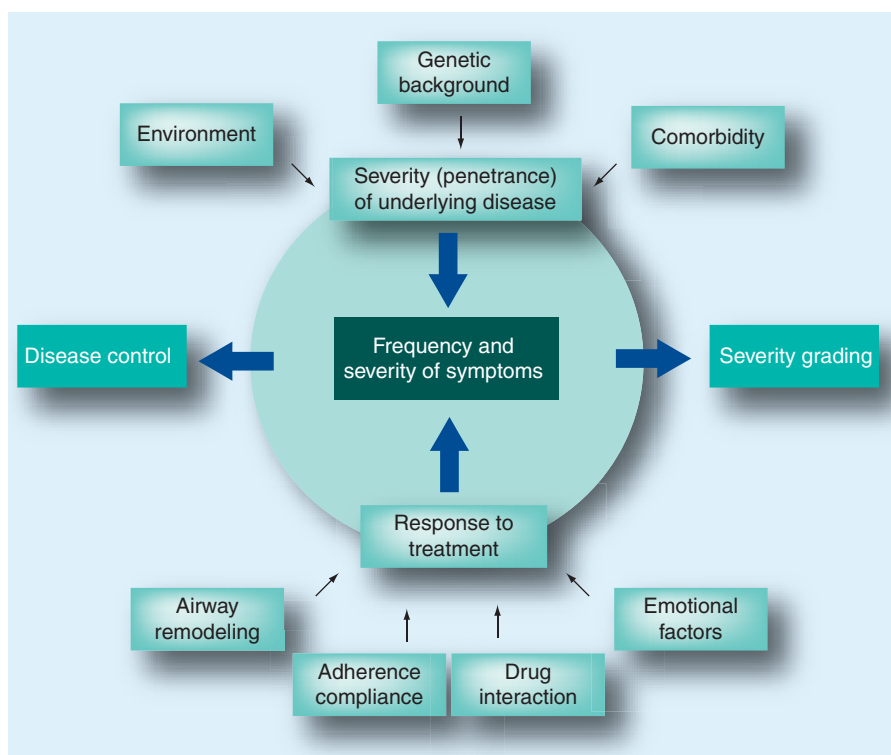


Figure 2. Factors associated with asthma severity and asthma control.

function) and future risk (e.g., exacerbations and lung function decline). The most clinically useful concept of asthma severity is based on the intensity of treatment required to achieve good asthma control – that is, severity is assessed during treatment. Severe asthma is defined as the requirement for high-intensity treatment. Asthma severity may be influenced by the underlying disease activity and by the patient's phenotype, both of which may be further described using pathological and physiological markers. These markers can also act as surrogate measures for future risk [52].

Both disease control and severity classifications are based on symptoms, exacerbations, impact on daily life, use of rescue medications and variations in lung function, making it difficult to identify distinct facets of the two concepts (FIGURE 2) [49]. However, each concept has features that direct their usage and interpretation (TABLE 5). Disease control reflects the level of disease stability within a given severity stratum (i.e., patients with severe or difficult-to-treat asthma) and denotes the clinical manifestation of asthma, as well as the responsiveness to treatment. Moreover, control may be regarded as one of the main treatment targets, together with the prevention of deterioration in long-term lung function, and can thus be considered the main component of therapeutic decisions. Control may also be understood as a threshold – a level at which a satisfactory disease state is achieved. Therefore, while severity reflects the inherent status of disease, control provides an indication of the adequacy of treatment. Disease control is also independent of individual differences between asthmatics with respect to the severity of the clinical manifestation and the variability

of disease activity, as well as the effect of exacerbations and treatment. Thus, classifying and treating asthma according to the level of control rather than according to the severity of disease is likely to be closer to the practical approach [46–50]. In other words, the concept of control is easier to understand both by the patient and by professional healthcare providers. This may be of particular importance, as easy-to-use approaches regarding treatment decisions are more likely to be accepted and applied in a clinical setting [50].

Control versus severity

The issue on asthma control versus severity dates back 15–20 years. At that time, there was a degree of confusion regarding both terms and no clear distinction between control versus severity was established (TABLE 5). For example, one of the major problems was that poorly controlled asthma was frequently mislabeled as severe asthma. Even today, there is some confusion regarding the distinction between severity and control, in particular in clinical practice.

However, in order to understand the meaning of asthma classification, there is a need for clearly separate concepts of control and severity [52].

The 2006/2007 GINA guidelines declare that severity is only to be used for scientific purposes. However, as indicated previously (TABLE 5), although severity is associated with a number of disadvantages regarding its use as a treatment guide in chronic asthma, are these reasons enough to completely disregard 'severity' and totally rely on 'control' as suggested by the GINA guidelines? The answer here is a resounding 'no'.

This above answer can be justified by the fact that severity and control of chronic asthma describe two different aspects of the condition and each concept has features that direct their usage and interpretation (FIGURE 3). Control indicates a quality of disease manifestations, but does not reflect the endogenous severity status of the underlying inflammation [12,51,53]. By contrast, severity refers to an endogenous disease component and describes relatively stable, intrinsic aspects of asthma, such as genetic factors and the duration of disease. Thus, severity and control describe two different things. Severity presents an important feature not only for the initial assessment of a patient but also for characterizing the underlying severity of chronic disease manifestation.

On the other hand, the use of control as a sole guide also has its limitations. For instance, control does not reflect the endogenous disease expression or the severity of the underlying inflammation [37]. As with severity, the term 'control' is neither standardized nor clearly defined [52]. In fact, current guidelines use different asthma scores for assessing the level of control

(TABLE 4). Moreover, although assessment of control may be faster to achieve, the length of duration for the assessment remains a matter of debate. Finally, both individual and other subjective factors may influence control. Taken together, severity and control describe two different aspects of asthma. Therefore, a more appropriate approach to guide asthma management would be to use both the 'control' and 'severity' concepts in a complementary manner.

FIGURE 3 illustrates the potential relationship between control and severity. It may serve as a guide as to how severity can be retained, and a composite description of asthma severity and control is feasible. For instance, if a given patient classified as having a severity of grade II suffers an infectious exacerbation with loss of disease control, the patient may be designated as suffering from uncontrolled mild persistent asthma. Or, if a patient initially classified as having moderately persistent asthma becomes free of symptoms under appropriate treatment with inhalative corticosteroids and long-acting β_2 -agonists, he or she should now be referred to as having controlled mild-to-moderate persistent asthma. As can be concluded from the scheme, changes of disease control occur rapidly from mild and controlled to exacerbation, usually over hours or a few days. FIGURE 3 also points to the clinical observation that control in severe persistent asthma is almost impossible to achieve.

It will be interesting to observe whether measuring disease inflammation may help to evaluate control or severity of asthma. In addition to clinical evaluation, the incorporation of exhaled nitric oxide (FeNO) measurement in evaluating asthma may lead to better pharmacotherapy and guidance in adjusting the dosage of anti-inflammatory agents, and more positive long-term disease outcomes. However, measuring FeNO or other parameters of asthmatic inflammation is too time-consuming and not cost-effective enough to become an established marker in clinical routine. It also remains to be seen whether such a parameter will actually add any substantial information relevant to the clinical management of asthma and to the clinical decision-making process.

Impact of the GINA guidelines

What impact has the publication of the GINA initiative had on asthma management practices during the past 15 years? Since its initiation, the GINA guidelines on asthma have made available an internationally recognized framework for the diagnosis and management of the condition. The GINA guidelines have

Table 5. Differences between the concepts of asthma disease control and severity.

Severity	Control
<i>Feature</i>	
Represents an endogenous component of disease (status)	Corresponds to the current clinical manifestation of disease
<i>Variability in time</i>	
Long-term variation (months to years)	Short-term variation (hours to weeks)
<i>Progress in time</i>	
Slow progress	Rapid progress
<i>Precipitating factors</i>	
Environmental factors Genetic factors?	Environmental, allergen exposure, infection and noncompliance
<i>Significance</i>	
Facilitates communication among healthcare providers over patients	Facilitates evaluation of responsiveness to treatment
Allows choice of initial treatment in a new patient	Allows adapting treatment level to the current disease status
Determines level of treatment necessary to obtain control	Characterizes the ultimate treatment goal
<i>Depends on</i>	
Endogenous disease expression (genetics) Unrestricted and persistent exposure to precipitating environment	Acute exposure to precipitating environment Level of environmental exposure Compliance/adherence The patients perspective Cost the public is willing to pay

been widely adopted, extensively distributed, and translated into over 50 languages. In this way, GINA has significantly contributed to a broad awareness of the problems associated with asthma, both at the regional and global levels. This is because GINA effectively combines available scientific evidence and practical advice on the clinical management of asthma, thus demonstrating that translating current scientific knowledge into clinical practice is a valid pathway for tackling a specific health problem.

Future of the GINA guidelines

In the future, the GINA guidelines will probably continue their success as being the standard epitome for the diagnosis and treatment of asthma around the globe. Representing a 'living guideline', constant reviews of the literature and regular annual revisions must continue. While this point is self-explanatory, the true challenge will be to further improve the implementation of the guidelines. In this context, a challenge for the coming years will be to work with primary healthcare providers and public-health officials in various countries to meet local needs and identify the barriers to implementation of asthma management recommendations. In addition, the guidelines need to be assessed with respect to their efficacy, accuracy, acceptance and user friendliness in clinical practice. In addition, there

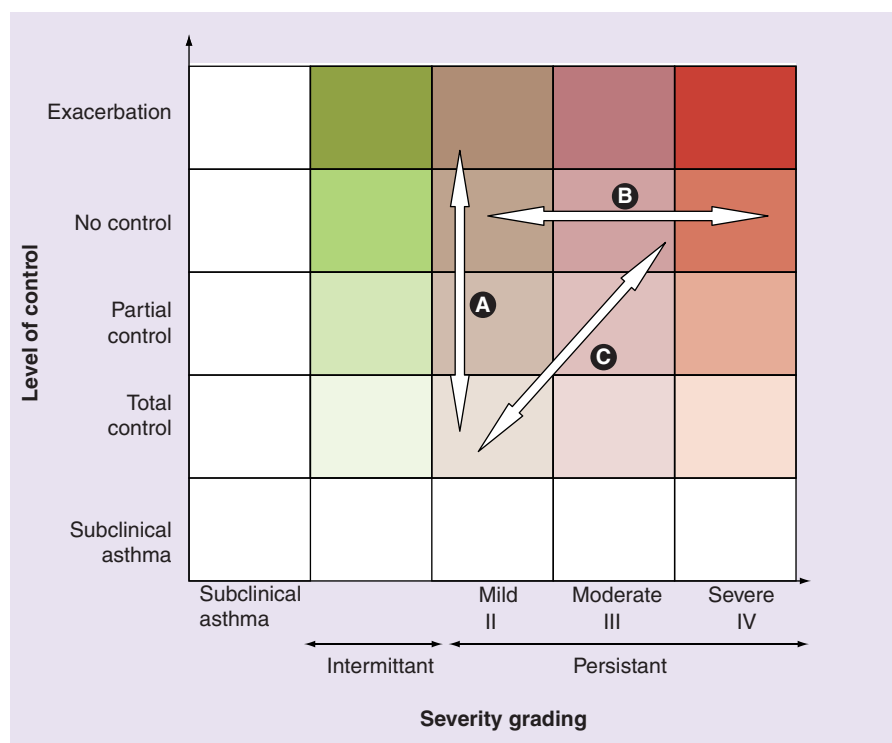


Figure 3. Schematic representation of the relationship between disease manifestation based on asthma severity grading and level of control.

Theoretically possible courses of asthma: **(A)** Rapidly occurring change of disease control from mild controlled to an exacerbation (e.g., infectious exacerbation), usually occurring over hours or days; **(B)** Progress of disease severity from mild uncontrolled to severe uncontrolled, usually occurring over a period of months or years; **(C)** Progress of disease from mild controlled to moderate uncontrolled.

is a need to define reliable tools for assessing control and its relationship to asthma. More importantly, it will be indispensable to integrate the two concepts of 'control' and 'severity' as a guide to asthma treatment in a user-friendly manner, in order to facilitate acceptance by both healthcare professionals and patients. Furthermore, it will be important to initiate more pragmatic clinical trials and well-designed observational trials designed to evaluate the effectiveness of therapies in real-world settings. Hence, the cost of asthma treatment has thus far been neglected in the recommendations. However, pricing of asthma medications has become a topic that requires urgent attention, as inadequate medical facilities and meagre financial resources prevent the application of guidelines and recommendations in many locations. Thus, the recommendations must be adapted to fit local practices and available healthcare resources. Finally, as a small number of asthmatics suffer from the most severe form of the disease and remain difficult to treat, GINA should also address the potential new treatment options for these 'untreatable' patients, such as interferon [54], even if controlled trials are not available.

In the years to come, guidelines such as those published by GINA will continue to be required, as many patients' asthma still remains uncontrolled, and data from ongoing studies provide either new treatment possibilities or a better understanding of the current treatments.

Expert commentary

A number of new drugs being developed for the treatment of asthma will become available within the next few years. An important strategy for simplifying asthma management and improving adherence involves using novel bronchodilators and drug combinations. The incorporation of once-daily dose-administration drugs such as the ultra-long-acting β_2 -agonists (e.g., indacaterol, arformoterol and carmoterol) or new long-acting antimuscarinic agents (e.g., aclidinium, NVA-237 [glycopyrrolate] and OrM3) may improve both compliance and overall clinical outcomes. Development of modern inhalers containing a once-daily dual-action ultra-long-acting β_2 agonist (LABA) plus long-acting anticholinergic (LAMA) combination is also likely to simplify treatment regimens. Similarly, dimer molecules in which both pharmacological principles are present (so-called M3 antagonist- β_2 agonist [MABA] bronchodilators) will revolutionize the field and open the door for a novel range of combination products. It is probable that the generation of once-daily dual-action ultra-LABA plus LAMA combination products may serve as a basis for improved triple therapy combinations,

through coformulation with novel inhaled corticosteroids and other current anti-inflammatory compounds (e.g., inhaled PDE4 inhibitors) for patients with asthma (and chronic obstructive pulmonary disease). These developments will significantly alter the guideline recommendations.

There is also an increasing number of biologic drugs under development, opening alternative therapeutic avenues. Biologics have revolutionized the treatment of rheumatoid arthritis, Crohn's disease, certain types of cancer and multiple sclerosis, and are likely to revolutionize the treatment of asthma. The first biologic approved for asthma in 2003, known as Omalizumab (Xolair®), is a monoclonal antibody that binds to free IgE, preventing the immunoglobulin from engaging mast cells and basophils, thus hindering the downstream inflammatory cascade that usually results in degranulation and the release of histamine [55]. Interestingly, there is circumstantial evidence that anti-IgE therapy also interferes with allergen processing and may even alter the course of the disease [55,56]. Similar observations with the immune modifier IFN- α have been also made in asthma and Churg-Strauss syndrome [KROEGEL C, UNPUBLISHED DATA] [57]. Thus, although still speculative, there may indeed be a possibility of altering the immune dysregulation underlying asthma and other related diseases. If this holds true, it will radically change our approach to asthma treatment and consequently the treatment recommendations put forward by any guidelines.

Five-year view

In the future, guidelines, including the GINA guidelines, will become the standard epitome for the diagnosis and treatment of asthma around the globe. In addition, the efficacy, accuracy and acceptance of the guidelines will increase. In order to further improve implementation and application of the guidelines, primary healthcare providers and public-health officials in various countries need to reduce the barriers to the implementation of asthma management recommendations. In the future, asthma will be classified according to both disease concepts of 'control' and 'severity' as a guide to asthma treatment. Furthermore, the cost of asthma treatment will become an additional integrated

feature of the guidelines. Finally, recommendations will address the management of asthma subtypes, in particular severe persistent 'untreatable' forms of the disease, even if controlled trials are not available.

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Key issues

- The Global Initiative for Asthma (GINA) was launched 15 years ago in 1993, in collaboration with the National Heart, Lung and Blood Institute, the NIH and the WHO.
- In 1995, GINA published its first consensus report on asthma treatment that aimed at increasing the implementation of innovative treatment forms into daily clinical practice. This report has since been regularly revised and updated.
- In addition, GINA also engages in other activities, such as organizing the World Asthma Day, regional educational initiatives and regular scientific symposia.
- The GINA guidelines and reports have been widely adopted and translated in several languages, thus providing the foundation for asthma guidelines worldwide.
- The GINA guidelines pioneered two major paradigm shifts. First, the transition from an opinion-based to an evidence-based approach in the late 1990s and, second, the shift from severity to control as guide to the treatment of asthma in 2006.
- During the past 15 years, the GINA guidelines have played a leading role in disseminating information concerned with asthma and have had a substantial educational impact regarding standardizing asthma care around the world.
- The global significance of the GINA guidelines is likely to continue in future.

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Papers of special note have been highlighted as:

- of interest
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Affiliation

- Claus Kroegel, MD, PhD, FCCP
Consultant Professor of Internal Medicine, Pneumology and Allergy, Department of Pneumology & Allergy, Medical Clinics I, Friedrich-Schiller-University, Erlanger Allee 101, D-07740 Jena, Germany
Tel.: +49 364 193 249 131
Fax: +49 364 193 249 132
claus.kroegel@med.uni-jena.de

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