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Review

Symptom *versus* exacerbation control: an evolution in GINA guidelines?

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***Abstract*:** The article traces the concept of asthma control within GINA guidelines over the past 25 years. In the first 15 years after 1995, the main objective of asthma management was to obtain the control of all clinical and functional characteristics of asthma. A landmark study (GOAL) showed for the first time that a good control of asthma is a reasonable outcome that can be achieved in a large proportion of asthmatics with a regular appropriate treatment. In the following years, more emphasis was placed on the role of exacerbations as critical manifestations of poor asthma control, whose frequency is associated with excessive FEV1 decline and increased risk of death. Accordingly, the 2014 GINA report makes a clear distinction between the control of the day-by-day symptoms and the reduction in the risk of severe exacerbations, stating that both conditions should be obtained. The 2019 update included a significant change in the management of mild asthma, prioritizing the prevention of exacerbations to that of mild symptoms. This view was repeated in the 2021 update, where the prevention of exacerbations, together with an acceptable symptom control with a minimal use of rescue medication, appeared to be the real main goal of asthma management. While a discrepancy between current symptoms and exacerbations may be present in mild asthma, a significant relationship between these two features is observed in moderate-severe asthma: a persistent poor symptom control is a major risk factor for exacerbations, whereas achieving symptom control through regular treatment is associated with a reduction in exacerbation rate. Thus, the opinion that frequent symptoms are not important in the absence of acute exacerbations should be discouraged, whereas education of patients to a good symptom perception and to improve adherence to regular treatment should be implemented. Furthermore, the persistence of risk factors, such as increased airway inflammation, even in a patient with minor daily symptoms, should be considered for optimizing treatment.

Keywords: asthma control, asthma exacerbation, GINA guidelines, regular pharmacologic treatment, rescue medication use

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Introduction

Asthma is defined as a complex combination of symptoms of different type and severity, with functional abnormalities mainly represented by variable airway obstruction which may progress to a persistent non-fully reversible airway obstruction.[1] Typical asthma symptoms include dyspnea, chest tightness, cough, and wheezing, which may vary largely over time, and are often triggered by typical factors, such as exposure to irritants, allergens, viral infection, or exercise. Symptoms may change in severity over time, and sometimes may require urgent pharmacologic treatment (rapid-onset inhaled beta2-agonists and/or oral corticosteroids) or an urgent medical visit; these events are called exacerbations. All these features are responsible for a limitation in the activities of

- **Minimal (ideally no) chronic symptoms**
- **Minimal (infrequent) exacerbations**
- **No emergency visits**
- **Minimal (ideally no) need for «as needed» use of beta2-agonists**
- **No limitations on activities, including exercise**
- **PEF circadian variation of less than 20 percent**

Figure 1. Control of asthma according to Global Initiative for Asthma (GINA) in documents between 2002 and 2005.
Adapted from Global Initiative for Asthma, www.ginasthma.org.

daily life and for a poor quality of life, and also, in a limited number of patients, for an increased risk of death.

The aim of asthma management should be to obtain a significant reduction (ideally the complete absence) of asthma symptoms, to achieve a better pulmonary function, and to allow the patients to have a normal or almost normal life, including physical activity; the acute deterioration of asthma symptoms (exacerbations) should be prevented. According to that, asthma may be considered under control when all these outcomes are achieved, and the risk of future events is minimized.

Since the publication of the first recommendations or guidelines for asthma management, the attempt was to produce a practical schematic assessment of all these clinical features, in order to modify the pharmacologic and non-pharmacologic treatment to obtain an almost complete remission of the disease.

In this article, we reconsider the evolution in the GINA recommendations over time, regarding the main outcomes to achieve in asthma management, and we critically discuss the greater weight attributed to asthma exacerbations compared with the day-by-day symptom control, in relationship with the potential progression of the disease.

The history of the evolution of the concept of 'asthma control' in GINA guidelines

The first GINA document was published in 1995, with the aim to promote a better management of asthma, in view of a growing prevalence of asthma and asthma-related mortality.[2] At that time, the main objective of asthma management was to obtain the control of all clinical manifestations of asthma: minimizing daytime and nocturnal symptoms as well as rescue medication use, preventing as much as possible any limitation in daily life, improving pulmonary function, and preventing exacerbations (Figure 1). These outcomes in asthma management were confirmed in the following updated versions of the document, which became widely diffused and quoted all over the world.

Reaching and maintaining the control was therefore the main outcome of asthma management, and some short questionnaires (such as ACQ and ACT) were developed and validated for a standardized assessment of symptoms.[3,4] However, when using these questionnaires in large populations of asthmatic patients recruited in the normal clinical activity, the overall level of asthma control was found to be poor,[5] raising some concern about the possibility to reach a good asthma control in real life.

The GOAL study had the objective to verify if a total control of asthma might be reached and maintained over the following months.[6] In this attempt, total control was defined as a complete remission of all clinical manifestations of asthma in the last 8 weeks (Figure 2). Because this ambitious aim was considered difficult to obtain, a well-controlled asthma was also considered as a possible outcome of the treatment. The well-controlled asthma included minimal daily symptoms requiring rescue medication use, but no exacerbations or limitation in daily life (Figure 2). The results of the study showed that, depending on the baseline severity of asthma (as assessed

	Well controlled	Totally controlled
Each week	**2 or more of**	**All of**
Daytime symptoms	≤ 2 days with symptom score > 1[a]	None
Rescue ß2-agonist use	Use on ≤ 2 days and < 4 occasions/wk	None
Morining PEF	≥ 80% predicted every day	> 80% predicted every day
	All of	
Night-time awakening	None	None
Exacerbations[b]	None	None
Emergency visits	None	None
Treatment-related adverse events	None enforcing change in asthma therapy	None enforcing change in asthma therapy

Figure 2. Definition of well-controlled and totally controlled asthma used in the GOAL study.
Adapted from: Bateman *et al.*[6]
[a]Symptom score: 1 was defined as 'symptoms for one short period during the day'. Overall scale: 0 (*none*) to 5 (*severe*).
[b]Exacerbations were defined as deterioration in asthma requiring treatment with oral corticosteroid or emergency department visit or hosptalization.

Characteristic	Controlled (All of the following)	Partly controlled (Any present in any week)	Uncontrolled
Daytime symptoms	Twice or less per week	More than twice per week	3 or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for rescue/ "reliever" treatment	Twice or less per week	More than twice per week	
Lung function (PEF or FEV_1)	Normal	< 80% predicted or personal best (if known) on any day	
Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side effects)			

Figure 3. Levels of asthma control according to Global Initiative for Asthma (GINA) in documents between 2006 and 2013.
Adapted from Global Initiative for Asthma, www.ginasthma.org.

by the level of asthma treatment performed at the enrollment visit), total control was reached in a minority of patients (up to 50% of steroid naive patients), while a well-controlled asthma was reached in up to 80% cases in the same group of steroid naive patients. The GOAL study represented a true cornerstone in asthma management: a *well-controlled* asthma was then considered a reasonable outcome to be obtained in a large part of asthmatic patients with a step-up strategy, and the persistence over time of the regular treatment led to a progressive, albeit mild, improvement of asthma control, a significant reduction of asthma exacerbations and a significant improvement in the quality of life.[6,7] After that, what should be considered a controlled, partially

Asthma symptom control			Levels of asthma symptom control		
			Well controlled	Partly controlled	Uncontrolled
In the past 4 weeks has the patient had:					
• Daytime asthma symptom nore than twice/week?	Yes □	No □	None of these	1-2 of these	1-2 of these
• Any night waking due to asthma?	Yes □	No □			
• Reliever needed more than twice/week?	Yes □	No □			
• Any activity limitation due to asthma?	Yes □	No □			
Risk factors for poor outcomes					
Assess the risk for: • Exacerbations • Fixed airflow limitation • Medication side-effects					
Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations. *Measure FEV1 at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.*					

Figure 4. GINA assessment of asthma control in adults, adolescents, and children 6–11 years, according to GINA documents from 2014.
Adapted from: Global Initiative for Asthma, www.ginasthma.org, update 2014.
GINA, Global Initiative for Asthma.

controlled, or uncontrolled asthma was clearly defined (Figure 3).

In the following years, more emphasis was placed on the role of acute asthma exacerbations, which were more and more considered as critical manifestations of a poor asthma control. Frequent exacerbations were associated with an excessive decline in FEV1[8,9] and with an increased risk of death,[10] in comparison with patients without exacerbations. In general, severe exacerbations, defined as the need for a short course of systemic corticosteroids, for an emergency department visit or for hospitalization for asthma, were considered as the expression of a poor asthma control, associated with day-by-day frequent symptoms, rescue medication use and limitation in daily life. Although a strict association between exacerbation rate and poor symptom control was expected, some observations suggested that severe exacerbations might occur even in patients with a seemingly good symptom control.[11] In the attempt to minimize the risk of exacerbations, new pharmacologic strategies were considered, namely, the use of an ICS/formoterol combination as regular treatment plus as needed (so-called SMART/MART strategy). Several randomized clinical trials demonstrated that this approach was as least as effective as a regular treatment with other ICS/LABA combinations plus SABA as needed, in the prevention of severe exacerbations, with a significant reduction in the cumulative exposure to ICS[12–14]; however, the presence of even minor symptoms requiring the use of rescue medication may be considered as a sign of an incomplete asthma control, particularly when these events are frequently reported (Figure 3).

The distinction between the control of the day-by-day symptoms and the reduction in the risk of severe exacerbations became more evident in the major revision of the GINA document published in 2014.[15] Together with a new definition of asthma ('. . . a heterogenous disease . . .') focusing on the different asthma phenotypes and endotypes which may require a different approach in the management, the distinction between symptom control and reduction in the future risk, mainly represented by the risk of future exacerbations, excessive decline in pulmonary function and side effects of the pharmacologic treatment became clearer (Figure 4). In this new approach, it was clearly stated however that both symptom control and reduction in the future risk should be obtained.[6] By applying the new definition of asthma control, which included the occurrence of exacerbations, a higher proportion of asthmatic patients originally recruited in the GOAL study analysis would have achieved control, with an additional proportion reaching total control. It

must also be considered that the evolution of the GINA approach over time has led to tolerate occasional symptoms not requiring a treatment step-up. Taken together, these observations confirm that an ICS/LABA combination is the preferred approach over ICS alone in controlling the disease manifestations.[16]

The 2019 update of the GINA document included a significant change in the management of mild asthma, with rescue ICS/formoterol as first option in step 1 and in step 2 (in this case as an alternative to the regular use of low dose ICS).[17] This change was due to the recent publication of the two Sygma studies.[18,19] The aim of these studies was to investigate which was the best strategy for the management of patients with mild asthma who are frequently treated in clinical practice with SABA alone as needed and who have poor adherence to the regular treatment with low dose ICS as recommended in step 2 and sometimes in step 1 of the previous guidelines. These patients may have occasional symptoms but may experience severe exacerbations, and their frequent use of SABA may have negative effects. In this updated GINA document, much emphasis was placed on the potential risk of severe exacerbations and death due to the use of SABA without concomitant ICS administration, leading then to the indication of using ICS/formoterol combination as rescue medication in mild asthma. Because the use of rescue ICS/formoterol could be due to the presence of mild symptoms, the concept of symptom control appeared to become less important than the prevention of exacerbations; indeed, in the last 2022 document, GINA stated that the use of ICS-formoterol reliever, divided dichotomously in $\leqslant 2$ *versus* >2 days/week, should not be included in the composite assessment of symptom control. However, the patient's average frequency of as needed ICS-formoterol use over the past 4 weeks should be assessed and taken into account when the patient's maintenance controller dose is reviewed.[20]

This *distinction* between symptom control and prevention of exacerbations was therefore reinforced in the GINA document 2022,[20] in which two different tracks of treatment were reported: the first (the preferred one) using always ICS/formoterol combinations as rescue medication (without or with regular use of the same combinations), and the second one, using ICS alone in mild asthma and other ICS/LABA combinations for regular use in steps 3 to 5. Therefore, it become even clearer that, according to this view, mild symptoms may be well tolerated because they do not cause any relevant limitation in daily life, while the prevention of exacerbation is the real main goal of asthma management.

Main outcomes of asthma management as reported in other national guidelines

The main outcome in asthma management has been defined in different ways in several national asthma guidelines (Table 1). We reported only data from the most recently updates of national guidelines published from 2017, when the changes in GINA guidelines became apparent. In general, all these guidelines derived from the contribution of several key opinion leaders in United Kingdom, United States, Japan, and Australia reported that the main outcome of asthma management should be the control of all clinical and functional characteristics of asthma. Furthermore, prevention of exacerbations (often called in different ways) is included in the aim of asthma management, in addition to symptom control.[21–26]

Daily symptoms and exacerbations: which relationship?

Daily symptoms of asthma are easily collected, often using specific simple questionnaire, such as ACT and ACQ, and they may clearly show the level of current asthma control, allowing doctors and patients to modify asthma management. The limit of this approach is that mild symptoms are frequently underestimated and minimized by the patients who do not consider these symptoms responsible for relevant limitations in daily life. Patients often underestimate the potential impact of mild symptoms in the progression of the disease, and in general their knowledge of the possibility of preventing these mild symptoms by a regular pharmacologic treatment is quite poor. In this situation, a regular treatment may be considered a useless effort not devoid of possible negative side effects.

Poor asthma control is associated with several negative outcomes both in children[27] and in adults.[28] In these studies, asthma control has been evaluated according to the old GINA guidelines, with an integrated assessment of day and night symptoms, rescue medication use, limitation in

Table 1. Summary of the principal objectives in the management of asthma in different recent national guidelines.

Document	Main objectives	Notes	Ref.
NICE 2017, UK	Good control defined as: • Daily symptoms ⩽ 3 times/week • Daily rescue medication ⩽ 3 times/week • Nocturnal symptoms ⩽ 1	No special mention on exacerbations Control assessed by ACT or other questionnaires	21
British guidelines 2019	Complete control defined as: • no daytime symptoms • no night-time awakening due to asthma • no need for rescue medication • no asthma attacks • no limitations on activity including exercise • normal lung function (in practical terms (FEV1 and/or PEF > 80% predicted or best) • minimal side effects from medication.	Apparently, all these features should be satisfied, in order to obtain the control of the disease	22
Expert Panel Report 2020, USA	Clinical assessment should be done, using • Asthma exacerbations • Asthma control (ACT, ACQ) • Asthma quality of life (AQLQ)	Additional points: - *both exacerbation prevention and symptom control should be considered* - no mention of ICS/formoterol only as needed (in mild asthma, adults and adolescents should use regular ICS at low dose)	23
Japanese guidelines 2020	I. Symptom control II. Avoidance of future risk 1. To prevent decline of respiratory function 2. To prevent death due to asthma 3. To prevent adverse effects caused by therapeutic agents	Additional points - regulate airway inflammation - maintain normal respiratory function: No mention of ICS/formoterol only as needed (in mild asthma, adults and adolescents should use regular ICS at low dose)	24
Australian Asthma Handbook 2020	- minimize impact of asthma on quality of life - optimize asthma symptom control with the minimal medication (number of medicines and doses) necessary - minimize risk of flare-ups and loss of lung function - minimize adverse effects of treatment	Additional points - engage the person in managing their asthma - ICS/formoterol is recommended as rescue medication in mild asthma	25

ACQ, asthma control questionnaire; ACT, asthma control test; AQLQ, asthma quality of life questionnaire; FEV1, forced espiratory volume in the first second; ICS, inhaled corticosteroids; NICE, national institute of health and care excellence; PEF, peak expirstpary flow.

daily life, and reduction in pulmonary function. Poor asthma control was associated with lower cardiovascular fitness and higher prevalence of obesity and learning disability in children, and with a significant reduction in 10 out of 15 domains of the 15-dimensional health-related quality-of-life (15D-HRQoL) questionnaire in adults.[27,28]

Exacerbations are considered the major manifestations of a poor asthma control. They may be considered as the emerging top of an iceberg, where persistent symptoms, limitation in daily life, and persistent airway inflammation represent the submerged part. This relevant role of exacerbations is due to the clear demonstration that they are associated with severe acute events (emergency department access, hospitalization, and death)[29] and a progressive decline in FEV1.[9] However, one major risk factor for exacerbations is a persistent poor control of asthma symptoms (frequently due to an incorrect pharmacologic management, poor compliance, and wrong use of the devices), but other features (comorbidities, increased biomarkers of airway inflammation, persistent exposure to allergens or irritants) are independent risk factors for exacerbations even in the presence of an apparently good asthma control (Figure 4).[15,17]

A major problem in considering exacerbation rate as the major outcome of asthma management is also the vague definition of asthma exacerbation.

This is a clinical definition, based mainly on the reported severity of asthma symptoms requiring a change in the current treatment, more often a short course of oral corticosteroids.[30] The healthcare utilization, such as emergency department visit or hospitalization, is another variable that is often used to assess the severity of exacerbation, although it is affected by the clinician's judgment. It follows that the definition of exacerbation may include a wide range of severity, from mild increase in daily symptoms to severe asthma attacks requiring urgent medical attention. Some patients and doctors are prone to require a short course of oral corticosteroids in the presence of a mild increase in symptoms, while other patients do not request medical attention even when asthma symptoms deteriorate significantly. Accordingly, a clear distinction between a progressive loss of asthma control and an acute exacerbation is difficult.[31] Therefore, in a single case, the definition of an asthma exacerbation would require an accurate assessment of clinical and functional data, in order to have a comparable way for the evaluation of the different patients.

In any case, there is a significant relationship between symptom control and exacerbation risk: achieving symptom control is associated with a reduction in exacerbation rate (Figure 5).[32] A recent review suggests that high ACT scores are strongly related to the achievement of symptom control, but moderately associated with a reduction in the exacerbation rate.[33] The relationship between symptom control and exacerbation rate may be different according to the level of asthma severity: in mild asthma, current symptoms may be occasionally reported, while exacerbation rate may be higher, and this is the basis of the recent recommendation to use ICS/formoterol combinations as needed.[17] In contrast, in moderate-severe asthma, current symptoms and exacerbations are more strictly related, and in these cases a regular treatment able to minimize current symptoms is also able to prevent exacerbations. Therefore, the choice between regular preventing treatment and rescue medication use may be made on the basis of the frequency and severity of current symptoms; unfortunately, the cut-off level of daily symptoms to be considered as expression of persistent asthma is arbitrary, and no clear scientific evidence has been obtained on the fact that two asthma symptoms or less in a week may be considered as indicative of controlled asthma.

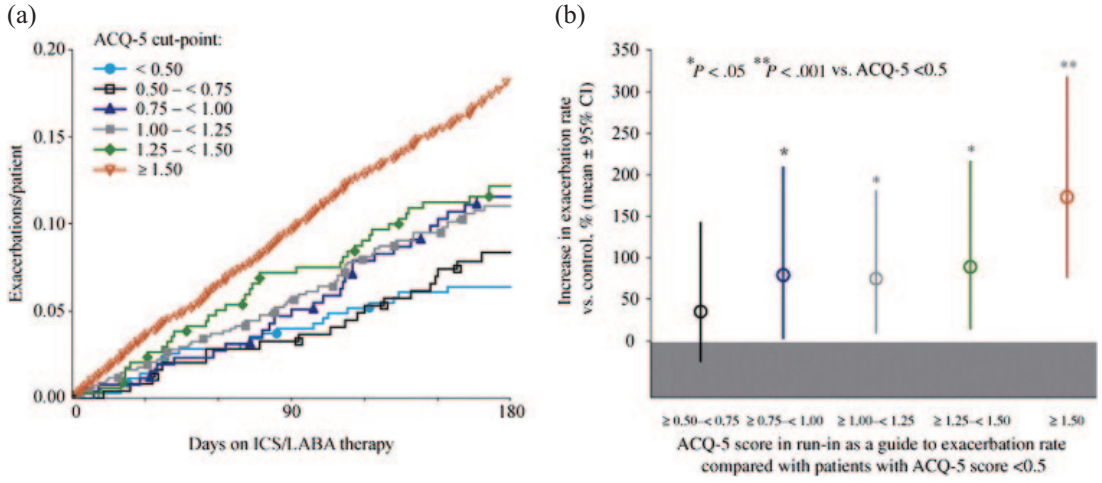

Figure 5. Current level of control may predict the risk of future exacerbations: (a) Future risk of exacerbations using ACQ-5 at randomization as a predictor. Mean number of exacerbations over time stratified by ACQ-5 at randomization. (b) Data pooled from all patients randomized to budesonide/formoterol maintenance and reliever therapy or higher maintenance dose ICS/LABA plus SABA ($n = 5480$). ACQ-5 < 0.50, $n = 355$; ACQ-5 $\geqslant 0.50$–<0.75, $n = 250$; ACQ-5 $\geqslant 0.75$–<1.00, $n = 261$; ACQ-5 $\geqslant 1.00$–<1.25, $n = 686$; ACQ-5 $\geqslant 1.25$–<1.50, $n = 345$; ACQ-5 $\geqslant 1.50$, $n = 3583$.
Adapted from Bateman *et al.*[32]

Conclusion

Considering the many components of asthma and the pathologic and functional features which underly the clinical manifestations of asthma, we believe that the major goal of asthma management should be to obtain the control of both daily symptoms and exacerbations, thus leading to an acceptable quality of life, including usual physical activity, no limitation in daily life and good mental status. Although the relationship between these two components of asthma control may be different in the single patient and mainly between mild and moderate-severe asthma, both these components are responsible for a poor outcome of the disease and should be appropriately managed.

We believe that the opinion that mild unfrequent symptoms are not important in the absence of acute exacerbations should be discouraged, while we suggest that a greater attention is devoted to the real level of daily symptoms of the patients. We believe that, although strategies aiming to reduce the major clinical manifestations of asthma (such as severe exacerbations) when compliance to regular treatment is low, are welcome and effective, the attention to educate the patient to a good symptom perception and to improve adherence to regular treatment, when needed, should be implemented. In this attempt, the decision of being tolerant with mild symptoms but preventing acute exacerbation (thus probably undertreating asthma regularly) *versus* completely preventing symptoms and exacerbations (probably overtreating asthma regularly) should be considered in each single patient, according to the clinical characteristics and risk factors. This point is also considered in the recent GINA guidelines, which recommend considering also an individually based approach in deciding treatment in a single patient.[17]

Furthermore, the persistence of risk factors for the loss of asthma control, including comorbidities and increased biomarkers of airway inflammation, in a patient with apparently minor daily symptoms should be considered for optimizing the treatment and to prevent negative outcomes (both severe exacerbations and progressive decline in pulmonary function due to airway remodeling). In moderate-severe asthmatics, strategies aiming to normalize sputum eosinophilic counts or exhaled nitric oxide levels have been demonstrated to be effective or quite promising in reducing asthma exacerbations[34–36]; whether blood eosinophilia may be similarly effective as a surrogate marker of airway inflammation in mild-moderate asthmatics should be more extensively investigated.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Manuela Latorre: Conceptualization; Data curation; Writing – original draft.

Riccardo Pistelli: Conceptualization; Writing – review & editing.

Giovanna Elisiana Carpagnano: Data curation; Writing – review & editing.

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