

Global guidelines for asthma management

Summary of the current status and future challenges

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KEY WORDS

asthma, current control, future risk, inhaled corticosteroids, treatment

ABSTRACT

The Global Initiative for Asthma (GINA) is an initiative started in the early 1990s to develop guidelines for asthma diagnosis and management that were applicable to both developed and developing countries. GINA now recommends that achieving overall asthma control is the goal of therapy. Overall asthma control consists of 2 domains: to achieve day-to-day (or current) asthma control and to minimize future risk measured by the absence of asthma exacerbations, the prevention of accelerated decline in lung function over time, and no side effects from medications. The GINA treatment paradigm consists of 5 treatment steps. At each step a preferred option and other alternatives are identified. Step 1 is as needed (prn) rapid-acting inhaled β_2 -agonist. The other 4 treatment steps include a controller option, ranging from low-dose inhaled corticosteroids (ICSs) as the preferred treatment option at Step 2, to high-dose ICSs plus long-acting inhaled β_2 -agonist combinations together with oral corticosteroids at Step 5. Once the level of asthma control has been established, consideration should be given to reducing the amount of treatment. By contrast, if asthma is uncontrolled, treatment needs to be increased to the next step. In an effort to remain current, a yearly update, based on an extensive review of the previous year's peer-reviewed literature on asthma management, is available on the web version of the GINA guidelines.

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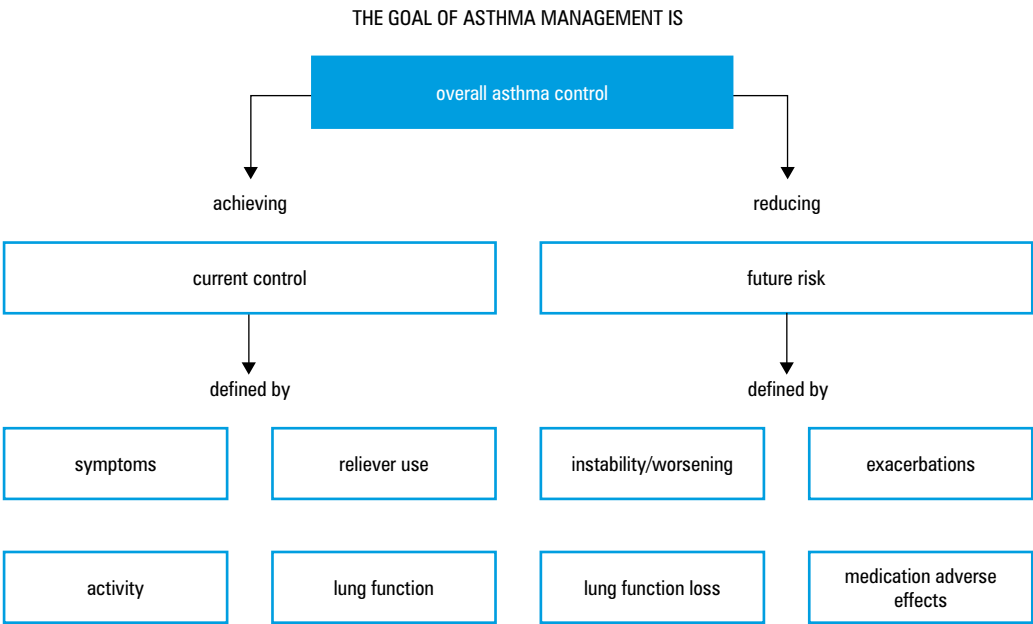
Introduction Recommendations for the diagnosis and treatment of asthma were initially developed in the late 1980s, with Australia and Canada being the first to publish asthma management guidelines.^{1,2} In these guidelines, the recommendations for treatment were considered in a stepwise manner, with the starting treatment step being established based on an estimate of the severity of the patient's asthma.¹⁻³ This paradigm continued for more than 15 years. Eventually, however, it became clear that this approach was limiting the implementation of the guidelines, because many physicians could not establish the degree of asthma severity, as this assessment involves both the inherent severity of asthma and the response to treatment.

The Global Initiative for Asthma (GINA) is an initiative developed in the early 1990s, under the auspices of the National Heart, Lung and Blood Institute of the National Institutes of Health in the United States and the World Health

Organization. Its initial purpose was to develop asthma diagnosis and management guidelines that were applicable to both developed and developing countries, because so far asthma guidelines had been country-specific.

Since its inception, GINA has undergone 4 major iterations. The third of these was the first asthma management guideline to be rigorously evidence-based and the fourth is described below. All asthma management guidelines agree on the importance of establishing a correct diagnosis of asthma. This should be done, whenever possible, by using objective measures to document variable airflow obstruction and/or airway hyperresponsiveness (AHR), to support the clinical suspicion generated by the patient's symptoms. This is necessary because asthma symptoms are not specific, and without objective measures demonstrating variable airflow obstruction and/or AHR, an incorrect diagnosis may be made. In addition, the guidelines have been very

FIGURE 1 The concept of overall asthma control consists of 2 domains: obtaining current (day-to-day) control and reducing future risk



consistent in the objectives of treatment, in identifying what is meant by ideal asthma control, and in stepwise approach to increasing or reducing the medications needed by the patient to maintain control.

Asthma control The concept of asthma control has always existed in treatment guidelines. However, physicians were often confused by the terms “asthma control” and “asthma severity”. It was perceived that well-controlled asthma was synonymous with mild asthma and poorly controlled asthma was synonymous with severe asthma. This perception is not correct.⁴ Severity is the intensity of the underlying disease process before treatment and control is the adequacy of the response to treatment. Patients with severe asthma, if treated appropriately, can be well controlled and patients with mild asthma, if they fail to follow treatment guidelines, will have inadequately controlled asthma. The goals of asthma management are the same for all degrees of asthma severity. Although patients with severe asthma will often be more difficult to control with an intervention, effective treatment can potentially fully control patients with severe asthma. For these reasons, the most recent iteration of the GINA guidelines have not used a severity grading to identify treatment needs, but rather has focused on targeting asthma control as the parameter to determine treatment needs.

The original descriptions of asthma control require the patient to experience no daytime or night-time symptoms, require very infrequent rescue β_2 -agonist use, have no limitation on day-to-day activities, and have lung function values close to normal.² More recently, however, an additional concept has been added to indicate that overall asthma control consists of 2 domains. One is achieving day-to-day (or current) asthma control as described above. The second

domain is to minimize future risk to the patient by ensuring the absence of asthma exacerbations, the prevention of accelerated decline in lung function over time, and no side effects from medications (FIGURE 1).^{5,6}

Current asthma control has been measured in a number of different ways. The first study to use asthma control as the primary outcome was the Gaining Optimal Asthma Control (GOAL) study,⁷ which used a categorical scale to identify totally controlled or well-controlled asthma. GINA uses a slightly different scale to identify controlled, partly controlled or uncontrolled asthma.⁷ These scales were developed based on expert opinion. There are also a number of validated numerical scales developed to quantify asthma control. These include the Asthma Control Questionnaire (ACQ),⁸ the Asthma Control Test,⁹ and the Asthma Therapy Assessment Questionnaire.¹⁰ The most widely used of these assessment tools in clinical trials to date is the ACQ, which was developed using expert opinion and originally contained 7 items; however, a 5-item version (ACQ-5) has been validated for use in clinical trials and epidemiological surveys.¹¹ GINA or GOAL criteria for asthma control provide similar results, but the ACQ-5 is more responsive to change in a clinical trial setting than a categorical scale.¹²

In addition, the American Thoracic Society and the European Respiratory Society jointly formed a working group to review the important components of asthma control and to make recommendations about their measurement. A summary of their recommendations is now available.¹³

This approach to asthma management is both more logical (as achieving good asthma control is the main outcome objective of treatment) and much easier to grasp as a clinical concept. Asthma control can be assessed quickly and treatment decisions made much easier than previously. The management of an asthmatic patient

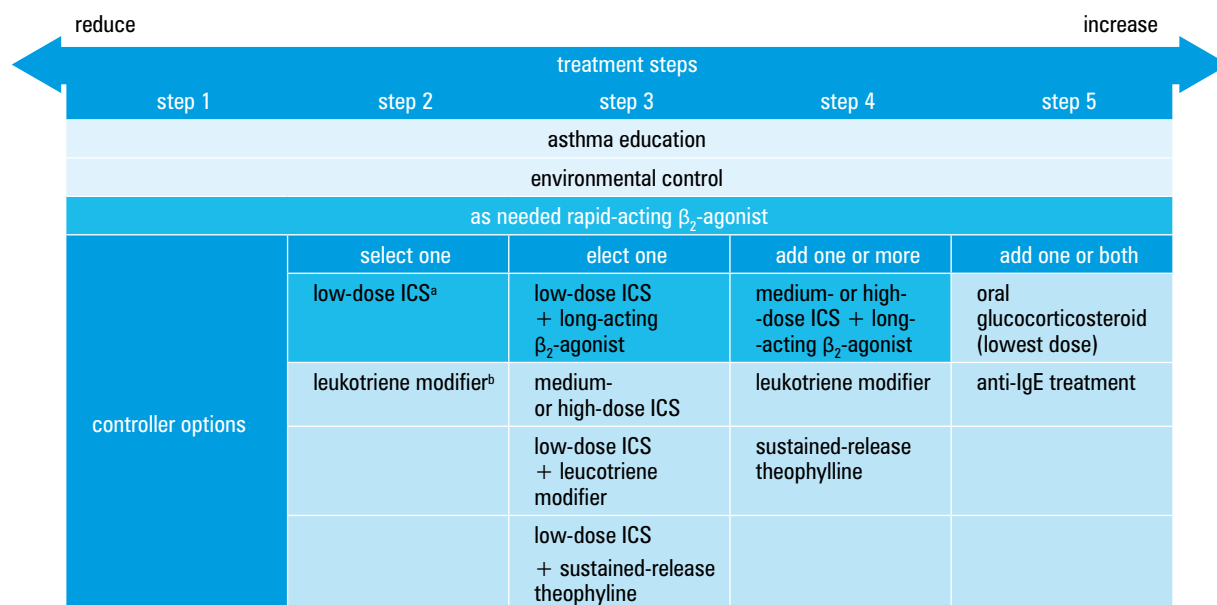


FIGURE 2 Stepwise approach to asthma therapy as recommended by the GINA guidelines. Abbreviations: ICS – inhaled corticosteroid, IgE – immunoglobulin E. **a** inhaled ICS, **b** receptor antagonist or synthesis inhibitors

becomes an iterative process, where asthma control is assessed by the health care practitioner at an initial assessment visit and a decision made on the treatment needed. The patient is then evaluated at the next appointment to decide whether asthma control has been achieved. If so, then treatment is continued or reduced; if not, then treatment is increased.

The best outcome for the patient is to achieve ideal asthma control, where the patient is asymptomatic all of the time, has normal lung function and no limitations in activities or side effects from medications. However, the GINA guidelines recognize that not all patients will achieve such a beneficial result from treatment. Uncontrolled asthma is when patients have symptoms needing rescue medication more than twice per week and/or having airflow obstruction (the forced expired volume in one second [FEV₁] <80% predicted normal, or the ratio of the FEV₁ to vital capacity [FEV₁/VC] <70% predicted normal). These patients need an increase in treatment. The GINA guidelines have also identified that there are patients whose asthma is not controlled, and for whom an increase in treatment may be recommended, but requires discussion between the patient and the health care professional. These patients are considered partly controlled and the correct treatment decision may be not to change the treatment plan. In addition, the importance of patient education about the disease, its causes, and treatment options continues to be stressed.

Treatment steps in GINA The GINA asthma treatment paradigm consists of 5 steps of treatment (FIGURE 2). At each step a preferred option and other alternatives are identified. Step 1 is as needed (prn) rapid-acting inhaled β_2 -agonist. The other 4 treatment steps include a controller option, ranging from low-dose inhaled corticosteroids (ICSs) as the preferred treatment option at Step 2 to high-dose ICSs and long-acting

inhaled β_2 -agonists (LABAs) combinations plus oral corticosteroids at Step 5. Once the level of asthma control has been established, a decision is made about the treatment. If asthma is controlled, consideration should be given to reducing the amount of treatment. By contrast, if asthma is uncontrolled, treatment needs to be increased to the next step.

The most effective controller therapy for asthma is ICS. Low doses of ICS alone can often provide good asthma control in both children and adults,^{14,15} and this approach remains the treatment recommendation for GINA Step 2. There is no convincing evidence that regular use of combination therapy with ICS and inhaled LABAs provides any additional benefit for milder patients.¹⁴ ICS treatment not only improves current control, but greatly reduces the risk of severe asthma exacerbations.^{14,15} Severe asthma exacerbations are associated with an accelerated decline in lung function in patients with newly diagnosed asthma, and ICS treatment can reduce this risk of lung function decline, even in patients who experience exacerbations while taking ICS treatment.¹⁶

Another issue which needs to be considered when making a decision to start ICS treatment in mild asthma is the potential for side effects. ICSs are not metabolized in the lungs and every molecule of ICS that is administered into the lungs is absorbed into the systemic circulation. Studies in patients with mild persistent asthma have used low doses of ICS (maximal doses 400 mcg/day). There is a wealth of data demonstrating the safety of these low doses, even used long-term, in adults.¹⁷ However, a significant reduction in growth velocity has been demonstrated with low doses of ICS in children.¹⁵ This is unlikely to have any effect on the final height of these children, as the one study that has followed children treated with ICS to final height, did not show any detrimental effect, even with a moderate daily ICS dose.¹⁸

Leukotriene receptor antagonists (LTRAs) are another treatment in Step 2, but they are less effective than low-dose ICSs.¹⁹ There are considerable interindividual and intraindividual differences in responses to any therapy. This is also true for response to treatment with ICS and LTRA in both adults and children.²⁰ While on average ICSs improve almost all asthma outcomes more than LTRAs, there may be some patients who show a greater response to LTRAs. Currently, it is not possible to accurately identify these responders based on their clinical, physiological, or pharmacogenomic characteristics.

Step 3 treatment is for those patients whose asthma is not well controlled on low doses of ICS alone (≤ 500 mcg of beclomethasone or its equivalent for other ICS in adults, and ≤ 250 mcg in children). Combination therapy with ICS and a LABA is the preferred treatment option in these patients. This is because the use of combination treatment of ICS and LABA for moderate persistent asthma has also been demonstrated to improve all indicators of asthma control, when compared with ICS alone.^{7,21} It is important to note that the evidence of the enhanced benefit of combination therapy with ICS and LABA exists mainly in adult asthmatics. Another recently described treatment approach for the management of patients at Step 3 or higher is the use of an inhaler containing the combination of budesonide (ICS) and formoterol (LABA), both as maintenance and as relief therapy, which has been shown to reduce the risk of severe asthma exacerbations when compared with the other approaches studied, with an associated reduction in oral corticosteroid use.^{22,23}

Several studies have compared clinical benefit when LTRAs are added to ICS in patients with moderate persistent asthma in both adults and children.^{24,25} The addition of LTRAs to ICS may modestly improve asthma control compared with ICS alone, but this strategy cannot be recommended as a substitute for increasing the dose of ICS. In addition, LTRAs have been shown to be less effective than LABAs when combined with ICS.²⁶

There has been a lot of concern raised about the safety of LABA use in asthmatic patients.²⁷ These unwanted effects have included severe asthma exacerbations requiring hospitalization, life-threatening exacerbations requiring intubations, and asthma-related death. This concern is the result of the results of an initial large randomized trial of the LABA salmeterol compared with the short-acting inhaled β_2 -agonist, salbutamol,²⁸ and a more recent trial of salmeterol added to usual therapy.²⁹ In addition, a systematic review of data for both salmeterol and formoterol raised concerns.³⁰ These studies, however, were conducted in clinical settings in which inhaled steroids were not mandated as a background treatment. Two meta-analyses of the effect of LABAs in combination with ICS have subsequently been reported,^{31,32} which did not show an increased

risk for hospitalizations or serious adverse events, while the relative effect on asthma-related mortality and asthma-related intubation and ventilation could not be assessed because of the very low frequency of these events.

Step 4 treatment is recommended for patients not controlled on low doses of ICS/LABA combinations. The most effective approach is to increase the dose of the ICS/LABA combination.^{21,33} Additional add-on therapy also includes LTRAs, although the combination of ICS/LABA and LTRAs has not been extensively evaluated. A recently published study has demonstrated that a long-acting inhaled anticholinergic (tiotropium bromide) is as effective a bronchodilator as the LABA salmeterol when added to ICS;³⁴ however, there is no currently available information on the benefit of ICS plus tiotropium in reducing asthma exacerbations, which are effectively reduced by ICS/LABA combinations.

There are a small percentage of patients who do not respond adequately to even high doses of ICS/LABA combinations and they need Step 5 treatment. This population disproportionately consume health care resources related to asthma. Often these patients will require oral corticosteroids in addition to ICS/LABA combinations, in an effort to achieve asthma control. Another potential treatment option for these patients is omalizumab, which is a recombinant humanized monoclonal antibody against immunoglobulin E (IgE).³⁵ This anti-IgE antibody forms complexes with free IgE, thus blocking the interaction between IgE and effector cells, and reduces serum concentrations of free IgE. When compared with placebo in patients on moderate to high doses of ICSs, omalizumab reduces asthma exacerbations and enables a small, but statistically significant, reduction in the dose of ICS. However, this treatment has not been compared with proven additive therapies such as ICS/LABAs, which are less expensive.

Some patients who are requiring oral corticosteroids to manage asthma, have a persisting airway eosinophilia, as measured by an increase in the numbers of eosinophils in induced sputum. Two recent studies have demonstrated clinical benefit, as measured by a reduction or elimination of the need for oral corticosteroids³⁶ or a reduction in severe asthma exacerbations,³⁷ when such patients have been treated with a monoclonal antibody directed against the cytokine, interleukin-5 (IL-5). This antibody directed against IL-5 is, however, not yet approved by regulatory bodies for use in the treatment of asthma.

A very important component of the GINA guidelines is the recommendation that, once asthma control has been achieved, the treatment is stepped down to identify the best treatment options and doses for each patient. There are many fewer studies that have provided insights into the best way to step down treatment than are available for stepping up treatment. The available evidence, however, suggests that when asthma is controlled with low-dose ICS, once-daily dosing

is recommended,^{38,39} when medium-to-high dose ICS is being used, a 50% reduction in the dose should be attempted at 3-month intervals;³⁸ when a combination ICS/LABA is being used, the dose of ICS should be reduced by 50%, while maintaining the dose of the LABA.⁴⁰ If low-dose ICS/LABA is still maintaining asthma control, the LABA can be discontinued.

Recommendations for children 5 years and younger

The GINA guidelines have recently published recommendations for the diagnosis and treatment of young children with asthma.⁴¹ There are several important differences in the management of asthma in young children when compared with older children and adults. Firstly, making a diagnosis of asthma in young children is more difficult. This is because symptoms such as wheezing and cough are also common in children who do not have asthma. In addition, the objective measurements needed to be confident of a diagnosis of asthma, particularly lung function measurements cannot be made in this age group. However, a presumptive diagnosis of asthma can be made in young children, based largely on symptom patterns and on a careful clinical assessment of family history and physical findings. The presence of atopy provides additional predictive support, as early allergic sensitization increases the likelihood that a wheezing child will have asthma.

A second important difference between young children and older children and adults is that there are many fewer clinical trials upon which to base treatment recommendations in young children. Despite this limitation, there are sufficient studies available to make strong recommendations, as in older children and adults, that ICS treatment is the cornerstone of management. Several studies have demonstrated improved lung function and number of symptom-free days, and reduced symptoms, need for additional medication, caregiver burden, systemic corticosteroid use, and exacerbations.⁴²⁻⁴⁴ An alternative treatment option is LTRAs, which improve some asthma outcomes in young children, but less well than ICSs.⁴⁵ The role of LTRAs as add-on therapy to ICS in young children has not been evaluated.

Future issues for the GINA guideline The current GINA guideline is shorter than previous iterations, but is still 92 pages long. There are, however, "pocket guides" to help improve implementation of the guidelines. It is the implementation of guidelines such as GINA, which remains a major hurdle. This means that many physicians managing asthma are unaware of the recommendations and the evidence which supports them. GINA has developed an implementation committee to develop methods for improving this aspect of the guidelines. In addition, the GINA guideline remains rigorously evidence-based and, in an effort to be current (with the most recent studies included), a yearly update, based on an extensive review of the previous year's peer-reviewed

literature on asthma management, is available on the web version of the GINA guidelines (www.ginasthma.com).

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Światowe wytyczne postępowania w astmie

Stan obecny i perspektywy

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SŁOWA KLUCZOWE

astma, bieżąca
kontrola, glikokortyko-
steroidy wziewne,
leczenie, ryzyko
w przyszłości

STRESZCZENIE

Światowa Inicjatywa Zwalczania Astmy (Global Initiative for Asthma – GINA) powstała na początku lat 90. XX w. w celu opracowania wytycznych rozpoznawania i leczenia astmy, które miałyby zastosowanie zarówno w krajach rozwiniętych, jak i w krajach rozwijających się. GINA zaleca obecnie przyjęcie jako celu leczenia uzyskanie całościowej kontroli astmy. Całościowa kontrola astmy ma dwie składowe. Pierwsza to uzyskanie codziennej (bieżącej) kontroli astmy. Druga to zminimalizowanie ryzyka w przyszłości, co wyraża się niewystępowaniem zaostrzeń astmy, zahamowaniem przyspieszonej utraty czynności płuc z biegiem czasu oraz niewystępowaniem działań niepożądanych stosowanych leków. Algorytm leczenia według GINA obejmuje 5 stopni ciężkości astmy. Dla każdego stopnia jest określone leczenie preferowane oraz alternatywne. W 1. stopniu stosuje się doraźnie (w razie potrzeby) szybko działający β_2 -mimetyk wziewny. Leczenie w pozostałych 4 stopniach obejmuje stosowanie leku kontrolującego chorobę: od glikokortykosteroidów (GKS) wziewnych w małej dawce jako preferowane leczenie w 2. stopniu po GKS wziewne w dużej dawce w połączeniu z długo działającym β_2 -mimetykiem wziewnym i GKS doustnym w 5. stopniu. Gdy osiągnięta zostanie kontrola astmy, należy rozważyć zmniejszenie intensywności leczenia. Z kolei gdy astma nie jest dobrze kontrolowana, należy zwiększyć intensywność leczenia, przechodząc na wyższy stopień. Aby wytyczne GINA były zawsze aktualne, co roku dokonuje się ich aktualizacji na podstawie przeglądu piśmiennictwa dotyczącego postępowania w astmie, opublikowanego w ostatnim roku, dostępnego na stronie internetowej tych wytycznych.

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Zgłoszono sprzeczność interesów:

Paul M. O'Byrne jest członkiem
rady doradczej dla firm
AstraZeneca, Biolipox, GSK, Merck,
Nycomed, Topigen, Resistentia
i Wyeth; otrzymuje honoraria
za wykłady od powyższych firm,
a także od Chiesi i Ono Pharma
oraz dofinansowanie na badania
od AstraZeneca, Boehringer
Genentech, GSK, Medimmune,
Merck, Pfizer i Wyeth.

Pol Arch Med Wewn. 2010;

120 (12): 511-517

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Erratum

Buyukhatipoglu H, Sezen Y, Yildiz A, Bas M, Kirhan I, Ulas T, Turan MN, Taskin A, Aksoy N. N-acetylcysteine fails to prevent renal dysfunction and oxidative stress after noniodine contrast media administration during percutaneous coronary interventions. *Pol Arch Med Wewn.* 2010; 120 (10): 383-389.

In the title on page 383, “noniodine” should be stated as “nonionic”; in the title on page 389, “niejodowego” should be stated as “niejonowego”.