

UPDATES ON ASTHMA: IMPACT OF THE GINA 2023 GUIDELINES ON THE TREATMENT AND CLASSIFICATION OF EXACERBATIONS

Ana Elisa Nunes da Rocha Dias

Faculdade ZARNS - Itumbiara

Itumbiara-GO

<https://orcid.org/0000-0001-5005-542X>

Maria Angélica Otero de Melo dos Reis

Universidad Nacional de Rosario (UNR)

Rosario - Argentina

<https://orcid.org/0000-0002-1681-9614>

Natália de Souza Alvarenga Barbosa

Faculdade da Saúde e Ecologia Humana
(FASEH)

Vespasiano - MG

<https://orcid.org/0009-0006-6976-4166>

Ana Clara Campos de Melo

Faculdade de Minas (FAMINAS-BH)

Belo Horizonte - MG

<https://orcid.org/0009-0008-5834-6502>

Amanda Carolina Zicatti da Silveira

Pontifícia Universidade Católica de São Paulo
(PUCSP)

São Paulo - SP

<https://orcid.org/0000-0001-8963-9553>

All content in this magazine is licensed under a Creative Commons Attribution License. Attribution-Non-Commercial-Non-Derivatives 4.0 International (CC BY-NC-ND 4.0).



Abstract: Objective: To investigate the changes proposed by GINA 2023 in the treatment and classification of asthma exacerbations, with a focus on how these changes influence the clinical management of the disease. **Methods:** Bibliographic review using the database: Pubmed – Medline. Therefore, with the search terms in combination with the terms (Asthma) AND (Treatment) AND (GINA). 449 articles were found and after applying the research strategy and selection criteria, 17 articles were selected to compose the study. **Review:** The changes introduced in the Global Initiative for Asthma (GINA) guidelines and their impacts on asthma management were explored. The new recommendations emphasize personalized patient action plans, early use of oral corticosteroids (OSCs) for moderate to severe exacerbations, and dosage adjustments of inhaled corticosteroids (ICS) to reduce the need for OSCs. Furthermore, they highlight the importance of biological therapy for severe cases and discourage the routine use of antibiotics, except in proven lung infections. The personalized approach aims to improve asthma control, reduce exacerbations and improve patients' quality of life, reflecting the complexity of the disease and the need for adaptive treatments based on ongoing assessments. **Final considerations:** The new guidelines promote a more personalized and adaptive approach, improving symptom control and reducing serious exacerbations. The introduction of biological therapies for severe asthma offers effective options for patients unresponsive to conventional treatments. Effective implementation of the guidelines requires collaboration between healthcare professionals, patients and healthcare systems, as well as ongoing training and awareness about treatment adherence. Future studies must focus on optimizing personalized therapies and investigating new biomarkers.

Keywords: GINA 2023 Guidelines; Asthma; Treatment.

INTRODUCTION

Asthma is a common respiratory disease characterized by chronic inflammation of the airways, often associated with bronchial hyperreactivity. This condition can cause symptoms such as dyspnea, cough, wheezing and angina, in addition to other respiratory signs that vary in time, intensity and limitation of expiratory airflow. Such changes are triggered by various stimuli, including allergens, environmental irritants, physical exercise, climate changes and viral respiratory infections (Levy et al., 2022; Jenkins; Bateman; Sears; O'byrne, 2020).

Additionally, the World Health Organization (WHO) estimates that more than 339 million people are affected by asthma globally, with 417,918 deaths attributed to the disease in 2016. This data underscores the importance and impact of the Global Initiative on Asthma (GINA), established in 1993 by the WHO and the US National Heart, Lung, and Blood Institute. GINA develops and annually updates evidence-based guidelines for the management of asthma in adults and children, aiming to reduce morbidity and mortality associated with the disease.

Thus, GINA contributes significantly to the awareness, prevention and management of asthma worldwide.

In 2023, GINA updated its guidelines, recommending the combined use of a short-acting bronchodilator or fast-acting beta agonist (ABAR) and inhaled corticosteroids (IC), taken together or in sequence, during asthma exacerbations in adults and adolescents, when the CEI + formoterol combination is not available or affordable. This update was based on a clinical trial that demonstrated that patients treated with budesonide and salbutamol had a lower risk

of serious exacerbations compared to the use of salbutamol alone (Jenkins; Bateman; Sears; O'byrne, 2020).

Furthermore, the 2023 guidelines emphasize that the combination of inhaled corticosteroids with formoterol (a long-acting bronchodilator) remains the preferred treatment approach for flares or as maintenance therapy in adults and adolescents. GINA now advises against treating asthma exclusively with ABAR in adults, adolescents and children aged 6 to 11 years, as although ABARs are effective in quickly relieving symptoms, their use alone is associated with an increased risk of death from asthma and does not significantly reduce the risk of severe exacerbations (FitzGerald et al., 2019; Agache et al., 2021). Therefore, this article proposes to explore in depth the GINA 2023 updates on the treatment and classification of asthma exacerbations, evaluating their potential to improve clinical outcomes and reduce the global burden of the disease. However, successful implementation of the guidelines depends on collaboration between healthcare professionals, patients and healthcare systems to ensure equitable access to necessary resources and an effective response to the individual needs of asthmatic patients.

METHODOLOGY

Bibliographic searches were conducted in the PubMed- MEDLINE (Medical Literature Analysis and Retrieval System Online) database, using a defined search strategy. The search terms “(Asthma) AND (Treatment) AND (GINA)” were used in the aforementioned search strategy to identify relevant publications. This initial search resulted in the identification of 449 articles. For the selection of articles, precise inclusion and exclusion criteria were established. The inclusion criteria limited the selection to articles published in the last five years (2019

to 2024), which directly addressed the themes proposed for this research. Studies such as systematic review, meta-analysis, randomized clinical trial, REALITI-A study, observational study, cohort study, pragmatic study and guidelines were considered (GINA, 2023).

On the other hand, the exclusion criteria eliminated duplicate articles, those available only in abstract form, and works that did not directly meet the proposal studied or that did not meet the other inclusion criteria. After applying the selection criteria, 17 articles were chosen from the PubMed database to compose the collection of this study. This methodology ensures a rigorous approach to selecting evidence, providing the basis for the analysis of the GINA 2023 updates on the management of asthma exacerbations.

REVISION

The Global Initiative for Asthma (GINA) guidelines, established in the early 1990s, aim to reduce the prevalence, morbidity, and mortality associated with asthma through a coordinated approach to research and global action. Updated annually, these guidelines reflect advances in asthma research and clinical practice, keeping healthcare professionals globally informed with evidence-based, patient-focused practices. In 2023, GINA introduced significant changes to strategies for managing asthma exacerbations, promoting a more personalized approach adjusted to the severity of symptoms.

These updates highlight the recommendation that all patients have an asthma action plan, adjusted to their age, current treatment and level of disease control. This plan must provide guidance on how to recognize and respond to worsening symptoms, adjusting relief and/or maintenance medication and using oral corticosteroids (OSC) when necessary. It is important to highlight that GINA 2023 emphasizes the early use of OSC for moderate

to severe exacerbations, changing previous practices that reserved OSC for more severe cases.

Guidance includes initiating CEO as detailed in the written action plan, usually involving a short course (e.g., 40–50 mg/day for 5–7 days for adults), especially when there is rapid deterioration or inadequate response to inhaled medication. This focus is founded on the ability of CEOs to save lives in severe exacerbations, despite the recognized risks associated with repeated courses, such as sleep disturbances, increased appetite, mood changes and more serious risks such as diabetes, cataracts, heart failure and osteoporosis. This review of the GINA guidelines reinforces the need for careful, individualized management of asthma, ensuring that both healthcare professionals and patients are well-equipped to manage exacerbations effectively, minimizing the overall impact of the disease and its associated treatments.

In this context, according to Price et al. (2018), in an extensive study with a broad asthmatic population starting systemic corticosteroids (CES), both for acute and maintenance treatment, and followed for an average period of more than 7 years, it was observed that the increase in cumulative exposure and Daily intake of CES places patients at high risk of CES-related adverse outcomes, negatively affecting quality of life. Furthermore, some outcomes may be correlated with cumulative effects.

Systemic corticosteroids have been shown to accelerate the resolution of exacerbations and prevent relapses, and are recommended for use in all exacerbations, except the mildest, in adults, adolescents and children aged 6 to 11 years (GINA, 2023). The updated guidelines highlight the importance of adjusting the dose of inhaled corticosteroids (ICS) during periods of exacerbation, suggesting a temporary dose increase as an alternative to the use of OSCs

in mild to moderate exacerbations. This approach aims to reduce the side effects of oral steroids while maintaining effectiveness in controlling symptoms.

Early intervention with ICS, such as budesonide/formoterol, which has anti-inflammatory properties when symptoms begin to worsen, may explain the benefits of this regimen in reducing exacerbations compared to maintaining inhaled corticosteroids (ICS)/beta agonists. long-acting (ABLA) plus ABAR as needed for relief, as ABARs do not address the underlying inflammation that triggers symptoms. Comparatively, studies show that the MART (Budesonide/Formoterol Maintenance and Relief) regimen results in higher levels of asthma control compared to conventional guideline-based practices. Reducing maintenance treatment to the lowest dose required is an essential principle of asthma management, aiming to avoid excessive treatment and minimize adverse effects (Jenkins; Bateman; Sears; O'byrne, 2020).

The GINA 2023 guidelines indicate that the need for CSO can be reduced by optimizing inhalation therapy, including attention to inhaler use technique, aiming to minimize the risk of exacerbations and the adverse effects of CSO. It is recommended that patients who are not currently taking controller medication begin ICS therapy, as treating asthma with ABAR alone is no longer recommended. Furthermore, the occurrence of an exacerbation requiring medical care indicates an increased risk of future exacerbations.

Updates to the Global Initiative for Asthma (GINA) 2023 guidelines illustrate continued progress in understanding asthma as a heterogeneous disease, requiring an equally diverse therapeutic approach. Notably, the new guidelines emphasize personalizing treatment by adjusting it to disease severity, patient-specific triggers, and response to previous treatments.

The use of inhaled corticosteroids (ICS) remains the mainstay of maintenance treatment, but now guidelines suggest a more dynamic assessment of the dose required, aiming to administer the lowest effective dose to maintain control of the disease and minimize side effects.

Inhaled albuterol (albuterol) remains the standard bronchodilator for treating acute asthma exacerbations. However, recent studies in emergency departments indicate similar efficacy and safety with the use of formoterol and the budesonide-formoterol combination (GINA, 2023).

Singh et al. (2022) emphasize that non-adherence to CIS therapies or excessive dependence on short-acting bronchodilators can compromise the effective management of asthma, negatively impacting the patient's general health. Regular daily regimens of CEI and ICS/ABLA have been observed to provide greater bronchoprotection compared to budesonide/formoterol as needed (MART), even while maintaining low systemic activity. Furthermore, coadministration of CEI with long-acting bronchodilators (ABLA) is recommended for patients who do not achieve adequate asthma control with CEI alone, highlighting the effectiveness of this combination in improving lung function and reducing exacerbations.

According to Jenkins, Bateman, Sears, and O'byrne (2020), study data confirm that patients treated with the MART budesonide/formoterol regimen achieved equal or greater control of asthma symptoms compared to ICS/ABLA plus ABAR regimens. with consistently lower rates of exacerbations and a lower annual need for oral corticosteroids.

GINA 2023 specifies that, for adults and adolescents, the combination of a rapid-onset ABLA (formoterol) and a low-dose CEI (budesonide or beclomethasone) in a single inhaler, both for maintenance and relief,

has been shown to be effective in improved control of asthma symptoms and reduced exacerbations requiring oral corticosteroids and hospitalizations compared to the same or higher dose of CEI or ICS-ABLA with ABAR as needed (Evidence A). This approach has also proven effective in reducing exacerbations in children aged 4 to 11 years (Evidence B).

The guidelines also expand the discussion on the use of biological treatments for cases of severe asthma that do not respond to conventional therapies. These include medications such as monoclonal antibodies, which act against specific molecules involved in the pathogenesis of the disease. The use of these treatments depends on the accurate identification of asthma, providing highly personalized therapy that targets the underlying mechanisms of the disease in each individual. The introduction and increasing use of biological products in recent years has revolutionized the treatment of severe asthma.

Studies indicate that patients with severe non-atopic asthma showed better disease control after one year of treatment with omalizumab, similarly to patients with allergic asthma. A significant reduction in unplanned visits to health services and school or work absenteeism was observed. Furthermore, 75.92% of patients who initially received oral corticosteroids were able to discontinue their use. A decrease in healthcare costs and significant benefits were also reported in a large case study that looked at the impact of benralizumab in individuals with severe eosinophilic asthma with a suboptimal response to mepolizumab (Agache et al., 2021).

Additionally, it is stated that the evidence does not support the routine use of antibiotics in the treatment of acute exacerbations of asthma, except when there is strong evidence of pulmonary infection, such as fever and purulent sputum or radiographic evidence of pneumonia. According to Hiles et al. (2019), long-term azithromycin treatment prevents

asthma exacerbations and may be especially beneficial in patients with severe asthma who frequently experience two or more exacerbations per year. Reducing the use of oral corticosteroids is a primary goal in the management of asthma, and azithromycin may help achieve this goal in patients with eosinophilic inflammation. To minimize antibiotic resistance, it is recommended that the prescription and monitoring of azithromycin use be carried out by a specialist pulmonologist. Supporting the long-term use of azithromycin, which has been shown to be effective in reducing exacerbations in both eosinophilic and non-eosinophilic asthma.

The guideline updates also highlight the importance of a personalized, stratified approach to the management of asthma exacerbations, reflecting the complexity of this condition and the need for adaptive treatments based on ongoing patient assessment.

GINA specifies that the severity of exacerbations must be assessed based on several clinical indicators, such as the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation and lung function. Immediate treatment with fast-acting bronchodilators such as salbutamol (albuterol) and oxygen therapy are crucial. If the patient exhibits signs of a severe exacerbation, such as drowsiness, confusion, or decreased breath sounds, immediate transfer to an intensive care unit is recommended.

Mommers et al. (2023) reinforce that GINA advocates a scalable treatment model, where the intensity of medication can be adjusted up or down based on the control of asthma symptoms. This dynamic approach allows treatments to be personalized to individual needs, potentially reducing the need for hospitalizations through more effective management at home or in primary care for less severe cases.

The introduction of new classification criteria for exacerbations by GINA could have significant implications for the diagnosis and management of asthma, allowing a clearer distinction between mild, moderate and severe exacerbations. This helps clinicians determine the severity of a patient's condition more effectively, adjusting treatment appropriately and providing clear guidance for escalating or reducing therapies. After discharge from hospital, it is crucial that follow-up includes regular assessments by the doctor, ensuring that the patient maintains good control of symptoms and that any potential for relapse is minimized through a well-structured asthma action plan and ongoing treatment strategy. This includes prescribing regular maintenance treatments that may include inhaled corticosteroids and long-acting bronchodilators, and a brief course of oral OSCs to stabilize any residual inflammation after an exacerbation.

The study conducted by Jo et al. (2019) investigated the effectiveness of budesonide-formoterol reliever therapy compared to maintenance treatment with budesonide plus terbutaline as needed in adults with mild to moderate asthma. This study revealed that as-needed use of budesonide-formoterol was more effective in preventing severe exacerbations than maintenance budesonide plus as-needed terbutaline, with a relative ratio of 0.69, indicating a significant decrease in the risk of severe exacerbations (Jo et al., 2019). Additionally, the safety analysis included all participants who received at least one dose of study treatment, reinforcing the robustness and applicability of the results in the real-world care setting. The study highlighted not only the efficacy in reducing exacerbations, but also the safety of the treatment regimen, with comparable adverse events between treatment groups.

Personalization of asthma treatment, as evidenced in this study, allows for a more targeted and efficient approach, especially considering individual variability in treatment response and disease progression. These results are crucial for clinical practice as they demonstrate that less intensive treatment regimens, which are easier for patients to follow, can be equally effective, particularly in a context of often imperfect adherence and challenges in managing mild to severe asthma. Therefore, this study provides valuable evidence for the implementation of the GINA 2023 guidelines, encouraging a more flexible and personalized approach to asthma treatment, aligned with individual patient needs and promoting better disease control with a lower medication burden (Jo et al., 2019).

The study conducted by Beasley et al. (2019) provides a valuable perspective on treatment strategies for mild asthma using budesonide–formoterol as as-needed reliever therapy. This regimen resulted in a significant reduction in the risk of severe asthma exacerbations compared to as-needed use of a short-acting β 2-agonist (SABA), and showed similar efficacy to maintenance therapy with budesonide plus as-needed SABA. This study highlights the effectiveness of budesonide–formoterol used as needed in reducing the rate of annual exacerbations compared to the group that used albuterol as needed. The annualized rate of exacerbations in the budesonide–formoterol group was significantly lower than that in the albuterol group, and did not differ significantly from the budesonide maintenance group. Beasley et al. (2019) discuss how treatment personalization can be challenging due to variability in patient responses. However, they also recognize the opportunity to utilize new diagnostic tools and biomarkers to guide therapy more precisely, which could significantly improve long-term

disease control. On the other hand, Sobieraj et al. (2018) provide a critical analysis of how treatment personalization, based on robust evidence, can lead to significant improvement in clinical outcomes, reducing exacerbations and improving disease control. Recent studies provide robust evidence supporting new treatment strategies, expanding clinicians' understanding of the complexity of asthma management and the most effective methods for mitigating asthma exacerbations.

The study by Nwaru et al. (2020) illustrates the relationship between excessive use of short-acting beta-agonists (SABA) and a significant increase in the risk of severe exacerbations and mortality in patients with asthma. This finding highlights the importance of reviewing prescription methods and rigorously monitoring the use of SABA, aspects emphasized in GINA updates that seek to reduce dependence on these medications and encourage combined use with inhaled corticosteroids for more effective control. Additionally, the study conducted by McKeever et al. (2018) highlights that temporarily increasing the dosage of inhaled glucocorticoids, as part of a self-management plan, reduced the incidence of severe exacerbations, supporting the approach of dose adjustment as asthma control deteriorates. This strategy is consistent with the direction adopted by GINA, which suggests dynamic adjustments to medication based on regular assessments of asthma control, promoting a more personalized and adaptive approach to treatment.

The new guidelines also emphasize the need for a personalized approach that aligns with each patient's clinical reality, a change that aims to not only improve asthma control, but also patients' quality of life. This personalization is key as it allows treatments to be more specifically aligned to individual needs, reducing the risk of serious

exacerbations through more precise and proactive disease control.

The implementation of these new guidelines in clinical practice requires continuous updating by healthcare professionals, ensuring that they are able to apply these advanced concepts in the daily management of asthma. The robust evidence available and the clear direction of the 2023 GINA guidelines highlight the need for a shift away from the practice of prescribing based solely on symptoms, moving towards management based on a deeper understanding of asthma pathophysiology and the impact of treatments on patients' long-term outcomes.

FINAL CONSIDERATIONS

The updates to the GINA 2023 guidelines were discussed, highlighting their implications for the treatment and classification of asthmatic exacerbations, with the main changes in recommendations being the emphasis on the combined use of short-acting bronchodilators and inhaled corticosteroids during exacerbations, the early introduction of corticosteroids oral administration for moderate to severe exacerbations, and the

personalization of maintenance treatment with inhaled corticosteroids. Analysis of the guidelines demonstrated that the updates have the potential to significantly improve asthma management by promoting a more personalized and adaptive approach that adjusts to individual patient needs. Personalizing treatment can lead to better symptom control and a reduction in severe exacerbations, improving the quality of life of asthmatic patients. Furthermore, the introduction of biological therapies for cases of severe asthma represents a significant advance in the treatment of the disease, providing effective therapeutic options for patients who do not respond to conventional treatments. However, effective implementation of these guidelines requires close collaboration between healthcare professionals, patients, and healthcare systems. Continuous training of professionals and awareness among patients about the importance of adherence to treatment are fundamental to the success of new therapeutic strategies. Furthermore, future research must focus on optimizing personalized therapies and investigating new biomarkers that can guide treatment more precisely.

REFERENCES

AGACHE, Ioana, *et al.* Advances and highlights in asthma in 2021. **Allergy**, v. 76, n. 11, p. 3390-3407, 2021.

BEASLEY, Richard, *et al.* Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma. **N Engl J Med**, v.380, n.21, p.2020-2030, 2019.

FITZGERALD, J Mark, *et al.* The burden of exacerbations in mild asthma: a systematic review. **ERJ Open Research**, v. 6, n. 3, 2019.

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023.

HARDY, Jo, *et al.* Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. **The Lancet**, v. 394, n. 10202, p. 919-928, 2019.

HILES, Sarah A, *et al.* Does maintenance azithromycin reduce asthma exacerbations? An individual participant data meta-analysis. **Eur Respir J**, v.54, n.5, 2019.

JENKINS, Christine R ; BATEMAN, Eric D; SEARS, Malcolm R ; O'BYRNE, Paul M. What have we learnt about asthma control from trials of budesonide/formoterol as maintenance and reliever?. **Respirology**, v. 25, n. 8, p. 804-815, 2020.

LEVY, Mark L, *et al.* Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. **NPJ Prim Care Respir Med**, v.33, n.1, p.7, 2023.

MCKEEVER, Tricia, *et al.* Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations. **N Engl J Med**, v.378, n.10, p.902-910, 2018.

MOMMERS, Irene, *et al.* Real-World Dispensing Patterns of Inhalation Medication in Young Adult Asthma: An Inception Cohort Study. **Clin Epidemiol**, v.15, p.721-732, 2023.

NWARU, Bright I, *et al.* Overuse of short-acting β 2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. **Eur Respir J**, v.55, n.4, 2020.

PILETTE, Charles, *et al.* REALITI-A study: real-world oral corticosteroid-sparing effect of mepolizumab in severe asthma. **J ALLERGY CLIN IMMUNOL PRACT**, v.10, n.10, p.2646-2656, 2022.

PRICE, David B, *et al.* Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. **J Asthma Allergy**,v.11, p.193-204, 2018.

REDMOND, Charlene, *et al.* Socioeconomic disparities in asthma health care utilization, exacerbations, and mortality: A systematic review and meta-analysis. **J Allergy Clin Immunol**,v. 149, n. 5, pág. 1617-1627, 2022.

SINGH, Dave, *et al.* New Versus Old: The Impact of Changing Patterns of Inhaled Corticosteroid Prescribing and Dosing Regimens in Asthma Management. **Adv Ther**, v.39, n.5, p.1895-1914, 2022.

SOBIERAJ, Diana M, *et al.* Association of Inhaled Corticosteroids and Long-Acting β -Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. **JAMA**, v.319,n.14, p.1485-1496, 2018.

ZER, Beth A ; KRUSE, Jacklyn M; GLOVER, Jon J. Evaluation of adherence to guideline-directed therapy and risk factors for exacerbation in mild asthma: a retrospective chart review. **Allergy, Asthma & Clinical Immunology**, v. 20, n. 1, p. 27, 2024.