

POSITION PAPER

Position Paper on management of mild asthma in childhood. A statement proposed by the SIMRI Asthma Committee and approved by the SIMRI Advocacy Council and Executive Committee

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ABSTRACT

Mild asthma in children and adolescents has traditionally been considered a less impactful condition characterized by infrequent symptoms. However, emerging evidence recognizes it as a chronic inflammatory disease with potential for severe, life-threatening exacerbations. Recent evidence and guidelines highlight the need for a paradigm shift in the management of mild asthma, moving away from exclusive reliance on short-acting beta2-agonists (SABA), towards proactive, inflammation-targeted asthma management across pediatric age groups. Non-pharmacological interventions—such as avoiding exposure to tobacco smoke, promoting healthy lifestyles, addressing psychosocial factors, and controlling environmental triggers—are equally critical to improving outcomes. A holistic, personalized approach that incorporates both medical and lifestyle interventions is pivotal for effective control of mild asthma, reduction of exacerbation risks, and improvement of long-term outcomes and quality of life in pediatric patients.

This statement summarizes current evidence and presents the official recommendations of the Italian Pediatric Respiratory Society (IPRS, Società Italiana per le Malattie Respiratorie Infantili/Ente Terzo Settore—SIMRI/ETS) to guide best practices in the management of mild asthma in childhood.

IMPACT STATEMENT

Mild asthma in children has long been viewed as a minor condition with occasional symptoms. However, new evidence identifies it as a chronic inflammatory disease capable of triggering severe, potentially life-threatening exacerbations. Current research and updated guidelines call for a shift in management—moving beyond exclusive reliance on short-acting beta2-agonists toward a proactive, inflammation-focused approach. This statement presents the latest evidence and outlines the official recommendations of the Italian Pediatric Respiratory Society (IPRS, Società Italiana per le Malattie Respiratorie Infantili/Ente Terzo Settore – SIMRI/ETS) to support best practices in managing mild asthma in childhood. The statement aims to play a key role in advancing national standards for care.

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KEY WORDS

Children; inflammation; inhaled corticosteroids; management; mild asthma.

INTRODUCTION

Asthma is one of the most common chronic diseases in all age groups. It is estimated that its prevalence is increasing worldwide, that can be explained by increased diagnosis of mild asthma (1, 2), which frequency ranges between 50% and 75% among asthmatic patients (3). The definition of mild asthma differs across studies and between guidelines. Its clinical variability adds to the challenge: symptoms can be occasional, or triggered only by specific risk factors. This sporadic nature makes it difficult to determine the precise amount of medication needed to maintain effective control (4). Therefore, an important research need is to determine a definition of the disease that accurately reflects the heterogeneity and risks noted in these patients (5). According to Global Initiative for Asthma (GINA) mild asthma is asthma that is suitable to receive Step 1-2 of treatment (1). Remarkably, the diagnosis of "mild" asthma does not prevent patients from an underappreciated exacerbation burden (6, 7); severe or even fatal exacerbations account for 30% to 40% of exacerbations requiring emergency care with an estimated frequency between 0.12 and 0.77 episodes per patient-year (3). Growing evidence propose several mechanisms underlying the increased adverse events in mild asthmatic patients,

particularly those that regularly use Short Acting beta2 Agonists (SABAs) (8). First, the acute symptoms relief obtained with SABA may mask patients' perception of asthma worsening. Moreover, they can have a desensitization and downregulation of the $\beta 2$ -receptors resulting in failure of rescue SABA treatment during an exacerbation; this mechanism can be compensated using corticosteroids that mediates transcription of the $\beta 2$ -receptors-gene (9). Finally, $\beta 2$ -agonists have been suggested to exert pro-inflammatory effects through a shift in the human type-1/type-2 cytokine balance toward a type-2 response (10) (**Figure 1**). Notably, inflammation of the bronchial mucosa with eosinophilic infiltrates (11) and airway remodeling have already been demonstrated even in children with mild asthma (12).

Thus, patients with mild asthma should be considered patients with a chronic inflammatory condition with mild and infrequent symptoms, but still at risk of severe to fatal exacerbations, who can benefit of anti-inflammatory relievers.

In November 2024, the British Thoracic Society (BTS), the National Institute for Health and Care Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN) released an updated guideline, revising recommendations on the diagnosis, treatment, and

Problems with SABA-Only Treatment

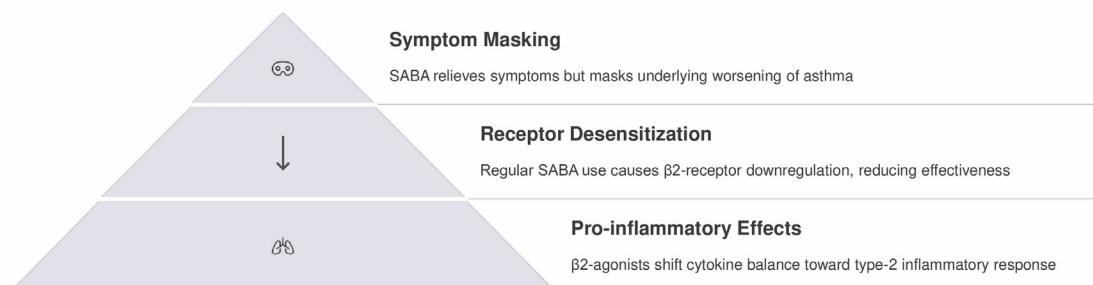


Figure 1. Problems with SABA-Only Treatment.

monitoring of asthma (13). In addition, the update of the GINA Report has been published very recently (1) and even recently has been discussed on Lancet Respiratory Medicine (14).

Starting from these key documents, the present statement outlines the current evidence and provides the official recommendations of the Italian Pediatric Respiratory Society (IPRS, Società Italiana per le Malattie Respiratorie Infantili – SIMRI/ETS) to support best practices in the management of mild asthma in children and adolescents.

REDEFINING THE TREATMENT OF MILD ASTHMA IN CHILDREN AND ADOLESCENTS

Recent updates to asthma guidelines issued by BTS, NICE, and SIGN have introduced significant changes to treatment strategies in patients with asthma. In detail, for individuals aged 12 years and older with newly diagnosed asthma, the guidelines recommend offering a low-dose ICS/formoterol combination inhaler as needed (anti-inflammatory reliever -AIR- therapy). This recommendation is based on evidence comparing three approaches: 1) SABA as needed; 2) Regular low-dose ICS plus SABA as needed; 3) As-needed ICS/formoterol (AIR).

ICS-based strategies (AIR or regular ICS) consistently outperform the SABA-only approach in reducing asthma exacerbations and improving asthma control (15, 16). The AIR strategy significantly reduces severe exacerbations compared to both SABA-only and regular ICS/SABA regimens (17, 18). Moreover, when compared to as-needed SABA alone, the use of as-needed low dose ICS/formoterol avoids the need for daily ICS, where adherence is often poor, and simplifies asthma management by using a single medication for both relief and maintenance therapy. The use of ICS-formoterol may also have a role in management of exercise-induced bronchoconstriction (EIB), as there is evidence that it improves symptoms control as well as regular ICS treatment with a substantially lower total steroid dose and is superior to SABA monotherapy (19). Health economic analyses demonstrated that as-needed AIR therapy is more cost-effective than regular ICS plus SABA (20). Taking into account the available evidence, the guidelines support adoption of as-needed AIR therapy as a first-line strategy in adolescents with newly diagnosed asthma and suggests that patients currently managed on SABA-only regimens should be switched to

as-needed AIR therapy. Moderate-dose MART (maintenance and reliever therapy) to people aged 12 and over with asthma that is not controlled on low-dose MART is offered as medicine combination and sequencing in people aged 12 and over.

For currently people with confirmed asthma that is not controlled on using regular low-dose ICS plus SABA as needed or regular low-dose ICS/LABA (long-acting beta₂ agonist) combination inhaler plus SABA as needed or regular low-dose ICS and supplementary therapy (leukotriene-receptor antagonists, LTRA) plus SABA as needed or regular low-dose ICS/LABA combination inhaler and supplementary therapy (LTRA) plus SABA as needed, change treatment to a low-dose ICS/formoterol combination inhaler used as needed (as-needed AIR therapy) is recommended.

For children aged 5–11 years with newly diagnosed asthma, the recommended initial treatment is a regular use twice-daily of low-dose ICS with as-needed SABA. A recent systematic review and network meta-analysis showed that regular ICS use may be the most effective treatment for preventing exacerbation and increasing lung function in children with mild asthma, while no supporting evidence for the use of as-needed ICS/formoterol is available (21).

With regard to MART therapy for children whom asthma is not controlled on low-dose ICS plus SABA as needed, BTS/NICE/SIGN 2024 recommend the increasing to moderate-dose MART therapy or considering moderate-dose ICS/LABA maintenance treatment (with or without an LTRA, depending on previous response) based on the use of a dry powder inhaler. When a child has uncontrolled asthma and is assessed as unable to manage the MART regimen, BTS/NICE/SIGN 2024 recommend to add a LTRA (for a trial period of 8 to 12 weeks, unless there are side effects, then stop it if it is ineffective) or offer twice daily low-dose ICS/LABA combination inhaler plus SABA as needed.

Overall, the guideline revisions advocate a shift from traditional SABA-dominated regimens towards more consistent use of anti-inflammatory therapies, particularly ICS/formoterol. These recommendations are supported by both clinical and economic evidence. Importantly, the guidelines underscore the need for individualized therapy, considering inhaler technique, adherence, and patient preference.

The latest GINA report introduces a nuanced, evidence-based framework for managing asthma in adolescents and children. Central to the update is the stratification of treatment into two tracks for adolescents (**Figure 2**).

Track 1 (preferred): as-needed low-dose ICS/formoterol. **Track 2 (alternative):** step 1, SABA as needed, with concurrent administration of low-dose ICS (either via a combination ICS-SABA inhaler or by taking ICS immediately after SABA use); step 2, daily low-dose ICS maintenance therapy, with SABA as needed for symptom relief. Track 1 is favored due to its superior efficacy in reducing severe exacerbations compared with Track 2, while providing comparable symptom control. Clinical trials demonstrate reductions in emergency department visits or hospitalizations compared to SABA-only therapy, and to regular low-dose ICS plus SABA as needed (22-24). The use of ICS plus formoterol is supported by formoterol's rapid bronchodilatory action—faster than that of other LABAs like salmeterol—and by the concept that increasing ICS dosing during symptom flare-ups may help prevent exacerbations (25). The combination of budesonide-formoterol is the suggested formulation, as other combinations, such as beclomethasone/formoterol, have not been studied for as-needed use. The

usual dose of as-needed budesonide-formoterol for mild asthma is a single inhalation of 200/6 mcg (delivered dose 160/4.5 mcg) taken whenever symptoms relief is needed. The maximum total daily dose of formoterol for both reliever and controller use is 72 mcg (equivalent to a delivered dose of 54 mcg). Treatment can be administered using either a Dry Powder Inhaler (DPI) or a pressurized Metered Dose Inhaler (pMDI). This approach is preferably recommended for: 1) step-down treatment for patient whose asthma is well controlled on low-dose MART with ICS-formoterol or on regular low-dose ICS with as-needed SABA; 2) initial asthma treatment for patients previously using SABA alone. Moreover, it is recommended for patients with low adherence, since reliance on SABA-only poses increased risks. Notably, ICS-formoterol should not be used as a reliever in patients already on a maintenance ICS-LABA regimen containing a LABA other than formoterol.

Indications for Track 2 include both patients with asthma symptoms occurring less (Step 1) and more than twice a week (Step 2). Indeed, the Track 2 should be considered when Track 1 is not possible or not preferred by patients who have no exacerbations with the current treatment. In patients aged 6–17 years with mild asthma, the as-needed combination of ICS/SABA showed a

Treatment Recommendations for Adolescents (≥12 Years)



Track 1 (Preferred)

Low-dose inhaled ICS-formoterol as an as-needed reliever and controller (Step 1 - 2)

- Reduces risk of severe exacerbations
- Avoids need for daily ICS where adherence is often poor
- Simplifies management with single medication

Track 2 (Alternative)

Low-dose inhaled ICS whenever SABA is required (Step 1)

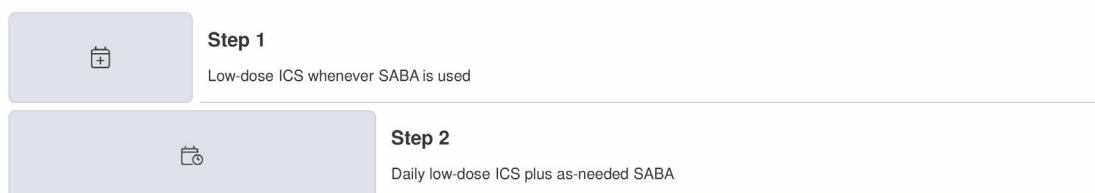
Low-dose maintenance ICS plus as-needed SABA (Step 2)

- Using separate inhalers or combination of ICS and SABA

(1) Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2025. Updated May 2025. Available at: www.ginasthma.org

Figure 2. Treatment Recommendations for Adolescents (≥12 Years) (1). Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2025. Updated May 2025. Available at: www.ginasthma.org.

Treatment Recommendations for Children (6-11 Years)



(1) Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2025. Updated May 2025. Available at: www.ginasthma.org

Figure 3. Treatment Recommendations for Children (6-11 Years) (1). Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2025. Updated May 2025. Available at: www.ginasthma.org.

similar effect compared to regular ICS use in terms of asthma control and exacerbation frequency, with lower cumulative ICS exposure over the year (26). There is also strong evidence that this strategy reduces the risks of severe exacerbations, than as-needed use of SABA alone (27). At last, evidence supports the superiority of daily ICS—even at low doses—over SABA-only treatment in terms of reducing exacerbations, improving lung function, and alleviating symptoms (21).

When choosing between the two recommended tracks, GINA emphasizes the need to consider: the presence of one or more non-modifiable risk factors for exacerbations or progressive loss of lung function; the patient's attitude toward self-management and ability to accurately perceive symptoms; and previous treatment experiences, including any potential side effects.

With respects to adolescents, a more conservative approach is outlined in younger children (age 6-11 years), due to limited evidence for ICS/formoterol use in this population (**Figure 3**). Accordingly, treatment for patients in this age group using SABA for symptoms relief less than twice per week should be as-needed SABA, combined with administration of low-dose ICS at each instance of symptom occurrence (Step 1), as poor treatment adherence is highly likely in this group of patients; Step

2 involves regular daily low-dose ICS therapy, supplemented with as-needed SABA.

OPTIMIZING ASTHMA TREATMENT

Asthma control can be usually achieved through tailored pharmacological treatment. However, nonpharmacological strategies should also be considered and implemented. Data from twenty-eight thousand five hundred eighty-four asthma patients (≥ 18 y) from nationwide Swedish asthma cohort study reported that over 50% of patients treated for mild/moderate asthma had an uncontrolled disease and non-pulmonary treatable traits (TTs), such as smoking, may affect asthma control negatively (28). As a matter of fact, it has been shown that both non-healthy lifestyles and environmental triggers determine detrimental effects on the airways which might cause worsening of symptoms and lower response to treatments. Therefore, to optimize asthma management patients and caregivers should be continuously educated on the risks deriving from avoidable risk factors. Firstly, it is well known that exposure to environmental tobacco smoke worsens asthma control and symptoms: many studies have shown that both active and passive smoking (including second and third

hand exposure) have negative effects on the bronchial mucosa mainly by promoting inflammation, by causing direct tissue damage and by favoring the development of allergy and airway hyperreactivity (29). As a consequence, every form of tobacco smoke exposure must be avoided, especially in children, who are particularly vulnerable. Notably, in active smokers, the risk of worse symptom control and reduced lung function is higher and associated with marked reduced response to ICS, so that such habit should be routinely screened among adolescents. Recently, evidence showed that also exposure to active and passive vape from both e-cigarette and heated tobacco products increases the risk of respiratory symptoms and asthma exacerbations and is not harmless as commonly thought and must be avoided as well (30-33).

As for pollution, exposure to air pollutants should be reduced as much as possible, due to their well-known detrimental effects on the airways. Traffic and industry-related gaseous pollutants, including nitrogen dioxide, sulfur dioxide, ozone, together with particulate matter cause disruption of epithelial integrity, exert a pro-inflammatory effect and induce oxidative stress, thus worsening asthma inflammation and airway hyperreactivity (34-36). Children are particularly at risk due to their inclination to play outside, usually on the ground, and to put their hands on their mouths, not mentioning their higher respiratory rates and immaturity of the respiratory and immune systems (37). Notably, in asthmatic patients outside physical activity should be promoted, but considering the quality of air. Regarding indoor pollution, in addition to tobacco smoke the most common source of pollution are heating devices and cooking behaviors, together with building materials, furnishings and products used for household cleaning and maintenance (38). Caregivers must be educated accordingly to improve the quality of their household air (39). Frequent windows opening can be useful, avoiding days in which outdoor air quality is poor. Indoor mold must be detected and removed due to its pro-inflammatory and irritant effects on the airways. Airborne allergens exposure, such as to house dust mite, should be avoided or at least reduced, even if there is limited evidence on the efficacy of such strategy on asthma control.

Secondly, healthy lifestyles must be encouraged. In particular, patients with asthma should be doing regu-

lar physical activity, which has been shown to be able to improve cardiopulmonary fitness, asthma control and quality of life (40, 41). In patients with exercise-induced asthma symptoms, maintenance treatment must be carefully reviewed and stepping up could be useful to better control their condition. However, premedication with SABA or ICS-formoterol before exercising could be considered on a case-by-case basis. Moreover, a healthy diet (meaning rich in fruits and vegetables) should be followed, not only to maintain adequate weight, but also for its benefits on general health (42). As for asthma control, fruits and vegetables might improve symptoms control through their anti-inflammatory properties as well as modulation effects on the immune system and microbial composition in both the gut and lungs (43, 44).

Last but not least, mental health and emotional stress must be evaluated and managed when appropriate, especially in adolescents, in which signs or symptoms of anxiety and depression must be detected early. Psychiatric comorbidities reduce asthma control and quality of life and are usually associated with overall lower medication adherence (45).

MANAGEMENT OF MILD ASTHMA IN CHILDHOOD: WHAT DOES SIMRI SUGGEST?

The adoption of AIR strategies in mild asthma aims to decrease underlying inflammation and potentially reduce the risk of exacerbations (46), while reducing cumulative steroid exposure (22, 24, 26), and providing a way for patients with inconsistent maintenance use to receive ICS whenever reliever medication is used (47). SIMRI advocates for improved management of mild asthma in children and adolescents, supporting AIR strategies while highlighting some critical points that need to be addressed.

First of all, clinical evidence supporting ICS-SABA therapy in children remains limited. Questions persist regarding the optimal ICS dosage for intermittent use in this population and more research is needed to evaluate safety, efficacy, and the potential for long-term effects. Misunderstanding the "as-needed" concept may lead to overuse, mirroring past challenges observed with SABA-only treatment. Nonetheless, the convenience of ICS-SABA single inhaler therapy can improve patient adherence. Having one device for both control and symp-

Table 1. Main benefits and barriers of AIR strategies in childhood asthma.

Benefits	Barriers
Reducing airways inflammation	Limited evidence in children
Reducing risk of future exacerbations	Regulatory discrepancies among countries
Improving treatment adherence	Poor clinicians' awareness
Reducing cumulative steroid exposure	Inconsistent prescribing habits among specialists and primary care providers

tom relief simplifies the regimen, reduces confusion, and improves inhaler technique, especially in younger patients. Inhaler design can play a significant role in patient acceptance and adherence, which are critical for effective asthma management. Adolescents in particular may benefit from DPIs, which are more discreet and easier to use than pMDIs with spacers (48). Any-way, we believe that tailoring therapy to each patient remains essential. While both ICS-SABA combination inhalers and separate ICS plus SABA regimens are viable options, the best approach depends on individual needs, preferences, and treatment goals (49).

With regard to ICS-formoterol, evidence for this combination in children is poor. Key trials like SYGMA included only small numbers of adolescents, and they were criticized for being overly controlled and lacking external validity, as patients demonstrated unusually high inhaler adherence rates that do not reflect real-world practice. Moreover, real-world data in younger children are lacking (48). Consequently, while current asthma guidelines, including GINA's dual-track framework, provide flexibility in treatment options for adolescents, where both ICS-SABA and ICS-formoterol are considered appropriate options, a gap of knowledge regarding treatment in children still exists. Nonetheless, the combination of budesonide-formoterol is the only suggested formulation, as other combinations have not been studied for as-needed use. In this context, fluticasone propionate has substantially advantageous peculiarities for asthma therapy, including a stronger topical anti-inflammatory activity than budesonide and beclomethasone (50-52), and quick achievement of protective effect (53). Moreover, its systemic availability occurs solely via absorption from lungs, whereas for the other ICS oral bioavailability also needs to be considered (54).

Additionally, concerns about overuse of as-needed ICS-formoterol persist. Although no serious safety signals have been reported, inappropriate or excessive

use could lead to overtreatment or, conversely, inadequate control of inflammation. Ultimately, while the ICS-formoterol AIR approach shows promise, more pediatric-specific research is needed. Until robust data are available, clinicians should apply this strategy cautiously, guided by ongoing monitoring and individual patient response (48).

It should also be acknowledged that, in spite of potential benefits, the adoption of AIR strategies remains limited in real-world practice due to several barriers (**Table 1**). These include regulatory restrictions, clinical uncertainty, and inconsistent prescribing habits (47). Notably, the use of ICS-formoterol as a reliever without maintenance therapy remains off-label in many countries, underscoring significant regulatory discrepancies (55). It should be also emphasized that good asthma control depends not only on appropriate prescribing but also on patient self-management. This includes recognizing symptom worsening and adjusting therapy accordingly. On the other hand, clinicians should base decisions on thorough assessments of asthma severity, lung function, symptom patterns, adherence, and inhaler technique. Regular follow-up and therapy adjustment based on the patient's response and monitoring for side effects, should be part of routine care and shared decision-making with families. In summary, whether as-needed ICS-formoterol is truly superior and suitable to replace maintenance ICS in all patients with mild asthma remains a subject of debate. The choice should be tailored to the individual, taking into account patient preferences and their risk of asthma-related complications. In line with the European Respiratory Society, we suggest adolescents in GINA treatment steps 1 or 2 use either strategy (56), being regular ICS therapy considered for those with low lung function, and in particular if lung function is worsening. Finally, education of caregivers and patients is recommended as a core component of pediatric asthma management (57). Providing clear, age-appropriate informa-

tion about the disease, the role of each medication, and the importance of symptom monitoring can significantly improve adherence and empower families to take an active role in care. This education should also include practical training on correct inhaler technique, recognition of early warning signs of exacerbations, and appropriate use of action plans.

CONCLUSIONS

In accordance with current guidelines, SIMRI endorses the adoption of AIR strategies as a foundational treatment for mild asthma (**Table 2**). Nonetheless, we highlight the urgent need for additional randomized controlled trials involving large pediatric populations and testing different ICS/formoterol combinations for as-needed use other than budesonide/formoterol. However, pharmacological treatment alone is not sufficient; non-pharmacological interventions are equally critical. Multidisciplinary collaboration among healthcare providers, caregivers, and patients is essential to achieving long-term, meaningful outcomes. Therefore, a proactive and holis-

tic approach should be embraced as the new standard for managing mild asthma in children and adolescents.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

The authors declare that they have no conflicts of interest relevant to the content of this article.

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Authors' contributions

Conceptualization, GF and SLG; writing - original draft preparation, GF, MEDC, GFen, RN, and FP; writing - review and editing, GF and SLG; supervision, SLG. All authors have read and agreed to the submitted version of the manuscript.

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Table 2. SIMRI recommendations on management of mild asthma in children and adolescents.

- 1 Mild asthma must be considered as a chronic inflammatory condition capable of sudden, severe, and potentially life-threatening exacerbations.
- 2 Treatment strategies must target the underlying pathophysiology of asthma.
- 3 Treatment for adolescents aged 12 years and older should be as-needed ICS-formoterol (a single inhalation as needed is recommended, with a maximum daily dose of 72 mcg of formoterol) or as-needed SABA combined with administration of low-dose ICS at each instance of symptom occurrence; regular daily low-dose ICS therapy supplemented with as-needed SABA is suggested for adolescents with low lung function, and in particular if lung function is worsening.
- 4 Treatment for children aged 6 to 11 years using SABA for symptoms relief less than twice per week should be as-needed SABA, combined with administration of low-dose ICS at each instance of symptom occurrence; regular daily low-dose ICS therapy supplemented with as-needed SABA is suggested when symptoms occur more than twice per week.
- 5 Tailoring therapy to each patient remains essential: the best approach depends on individual needs, preferences, and treatment goals.
- 6 Avoidance of environmental tobacco smoke and exposure to vapors from e-cigarettes or heated tobacco products is recommended to mitigate asthma symptoms and inflammation, as well as reducing exposure to air pollutants and aeroallergens.
- 7 Encouraging a healthy lifestyle, including regular physical activity and a diet rich in fruits and vegetables, is recommended to improve asthma outcomes.
- 8 Screening for mental health issues like anxiety and depression is recommended, as these conditions are known to negatively impact asthma control and treatment adherence, especially during adolescence.
- 9 Education of caregivers and young patients is recommended to ensure adherence and foster long-term management success.
- 10 Assessing and managing mild asthma should be conducted in a holistic manner based on multidisciplinary collaboration among healthcare providers, caregivers, and patients in order to achieve sustained outcomes.

Data sharing and data accessibility

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to the nature of the survey and the anonymized dataset, no individual identifiable information is included. Data sharing will be considered for academic and research purposes in compliance with applicable data protection regulations.

Publication ethics

The authors declare that this manuscript is original, has not been previously published, and is not under

consideration for publication elsewhere. All authors have approved the final version of the manuscript and agree with its submission to this journal. The authors affirm that the work complies with the highest standards of research integrity. No data have been fabricated, manipulated, or falsified. The manuscript is free from plagiarism, and all sources and contributions have been appropriately acknowledged. The authors confirm adherence to ethical principles regarding authorship, data transparency, and responsible communication of scientific results.

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