



Challenges and choices in the pharmacological treatment of non-severe pediatric asthma: A commentary for the practicing physician

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ABSTRACT

In recent years, asthma research has focused intensely on the severe part of the disease spectrum, leading to new treatments, mostly therapeutic monoclonal antibodies. However, severe asthma accounts for not more than 2% of asthma in the pediatric population. Therefore, non-severe asthma remains a major health problem in children, not only for patients and parents but also for healthcare professionals such as general practitioners, pediatricians and allergists who take care of these patients. It is thus essential to identify and put in context novel concepts, applicable to the treatment of these patients. Recent evidence suggests benefits from using anti-inflammatory treatment even for the mildest cases, for whom until now only symptomatic bronchodilation was recommended. Likewise, “reliever” medication may be better combined with an inhaled corticosteroid (ICS). Among “new” treatments (for children), ICS formulation in ultrafine particles has showed promise and tiotropium is gaining access to the pediatric population. Maintenance and reliever therapy (MART) is an option for moderate disease. Most importantly, personalized response to medications appears to be considerable, therefore, it may need to be taken into account. Overall, these new options provide opportunities for multiple new management strategies. The deployment of such strategies in different populations remains to be evaluated.

Keywords: Mild asthma, Moderate asthma, Pharmacotherapy, MART, Treatment

INTRODUCTION

The goals of asthma management are to minimize symptoms and decrease the risk of adverse outcomes, including the risks of acute

exacerbations, persistent airflow obstruction, and adverse effects of medications.

To achieve this goal, appropriate pharmacological treatment should be accompanied by optimum use of non-pharmacological strategies and

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treatment of modifiable risk factors regardless of the severity of the disease.¹ These include, but are not limited to:

- Education of patients for self-management and providing a written asthma action plan
- Teaching correct inhaler technique
- Environmental control for airway irritants such as tobacco smoke
- Environmental control for specific allergens such as house dust mites, molds and animals
- Weight loss for overweight and obese children
- Treatment of co-morbidities such as allergic rhinoconjunctivitis, psychosocial problems and reflux disease.

Recent years have witnessed significant advances in the pharmacological treatment of asthma, especially with respect to personalized treatment using biologicals. However, these advances have mostly focused on severe asthma and have been particularly in the adult population. Since severe asthma accounts for a high amount of burden regarding all aspects of the disease, this is understandable. On the other hand, it is also true that severe asthma is quite rare in children and probably accounts for not more than 2% of the asthma cases observed in this population.^{2,3} Even though taxonomically childhood covers 0–18 years, with respect to asthma and asthma treatment, preschoolers have particular characteristics,⁴ while adolescents (children, 12–18 years) have most often been grouped together with adults. However, it should be noted that representation of subjects aged 12–18 is quite small in most “adult” studies.

In summary, much of the recent medical literature concerning asthma treatment has focused on adult patients with severe asthma even though there are important new findings and several remaining challenges in the treatment of non-severe asthma in children.⁵ Since the vast majority of the patients seen in clinical practice by general practitioners, pediatricians, and allergists are children with non-severe asthma, it is essential to apply the new knowledge to the treatment of these patients.

According to the European Respiratory Society (ERS) and the American Thoracic Society (ATS), severe asthma is defined as asthma that requires treatment with guideline-suggested medication of GINA steps 4–5 for the past year, or systemic corticosteroids for at least 50% of the past year, to prevent it from becoming uncontrolled, or which remains uncontrolled despite therapy. Since steps 4 and 5 involve the use of high dose inhaled corticosteroid – long-acting beta agonist (ICS-LABA), systemic corticosteroids and finally the use of biologicals, for all practical purposes, *non-severe asthma* can be defined as asthma that can be controlled without the need to use high dose ICS-LABA which comprise the vast majority of patients in the 6–12 year age group.

With this intention, a group of pediatric asthma specialists was commissioned by the World Allergy Organization (WAO) to produce a commentary aiming to summarize and discuss the new findings that have recently accumulated in the treatment of children with non-severe asthma aged 6–12 years, in order to reach the main goals of asthma treatment both within the control and risk domains (Fig 1).

When the burden of asthma is low

Based on validated epidemiological studies, the “intermittent” and “mild persistent” asthma phenotypes represent the great majority in the pediatric age group.⁶ Nevertheless, appropriate management is still a matter of debate,

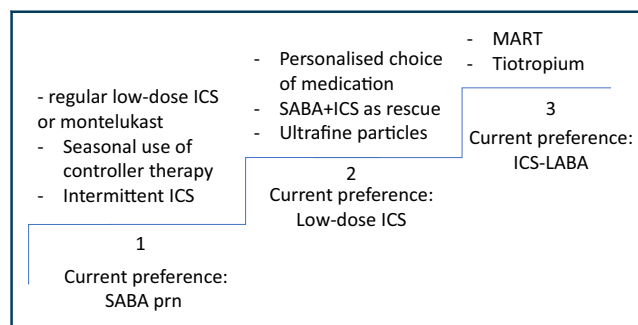


Fig. 1 New exploratory approaches for the pharmacological management of non-severe asthma. Although they are presented according to the well-known stepwise ladder, several of them can be used throughout the spectrum of non-severe disease, depending on the phenotypic characteristics of the patient. ERS: European Respiratory Society. ATS: American Thoracic Society. GINA: Global Initiative for Asthma. ICS: Inhaled corticosteroid. LABA: Long acting beta agonist

particularly focused on the following dilemma: Knowing that asthma is a chronic inflammatory airway disease, do children with episodic exacerbations need chronic anti-inflammatory medication? If so, what is the benefit/risk ratio of regular intake of inhaled corticosteroids in this population?

Up to now, pediatric asthma guidelines recommend that a symptom-based approach is acceptable for mild asthma treatment, rather than treating the underlying disease, reinforcing health care professionals' and parents' perception of short acting beta (β) 2 agonists (SABA) as an acceptable unique treatment for the mildest cases.⁷ However, albeit rare, a significant number of adverse events have long been associated with SABA use; these are either due to lack of selectivity with their receptors [β 2 adrenoceptors (β 2ARs)], such as tachychardia, arrhythmia, tremor and headache or β 2AR desensitization resulting in loss of the bronchoprotective effect or exacerbation of airway inflammation and its consequences.⁸ More severe side effects include sudden constriction of the bronchial airways, or paradoxical bronchospasm, hypokalemia, and in rare cases serious cardiovascular side effects such as myocardial infarction.⁹ In addition, poor asthma control has strongly been associated with infrequent controller medication use and concomitant SABA overuse.¹⁰

Despite the presence of airway inflammation, the recommended step 1 therapy remains as needed SABA in children with infrequent symptoms.¹¹ Due to lack of efficacy studies on controller medication in this subset of asthmatics, daily low dose ICS is only recommended for children with persistent symptoms or at high risk for an exacerbation. More recently, the introduction of regular low dose ICS, or leukotriene receptors antagonists (LTRAs), has been proposed as an alternative for intermittent and mild persistent asthma. Regular use of ICS has been shown to reduce asthma symptoms, decrease the risk for exacerbations, and improve quality of life in a significant proportion of children.¹² Moreover, a meta-analysis in preschoolers with asthma showed improved lung function and reduced symptoms with daily ICS compared to intermittent treatment, however, with no significant differences in respect to exacerbations.¹³ Daily controller therapy may also be

recommended at time periods when suboptimal control is anticipated such as in autumn, when returning to school or exposure to clinically relevant aeroallergens and viral upper respiratory tract infections.¹⁴ It is clear that daily ICS do not confer any disease-modifying effect in established childhood asthma or toddlers with emerging asthma.¹⁵ LTRAs are an alternative controller medication which has shown efficacy in children with concomitant allergic rhinitis and in preschoolers.¹⁶

Nevertheless, use of SABA is reinforced by the almost immediate relief provided by them compared with the less perceivable benefit of an ICS.¹⁷ It is advisable that depending on the frequency and persistence of even mild symptoms or in the presence of continuous findings doctors should highlight the chronic inflammatory character of the disease and necessity of appropriate treatment in order to potentially minimize SABA overuse.¹⁷ Then, the need for benefit/risk analysis of daily ICS in low burden patients arises. Recent data support ICS safety for short periods of time, while safety of daily use, especially at high doses with regards to reduction of growth rate, remains a matter of debate.¹⁶ Hypothalamic-pituitary-adrenal (HPA) axis dysfunction should be evaluated in children with long-term moderate or high ICS doses; there is not much doubt about low or intermittent regimens being safe. In children that need higher doses, treatment with a lower strength ICS can be considered.

In children with intermittent or viral-triggered symptoms, intermittent ICS use has been shown to be effective in terms of asthma symptoms and frequency of exacerbations, even at low doses.¹⁸ Nevertheless, efficacy of intermittent ICS is lower than daily ICS in most studies, but comparable to daily LTRAs, while safety concerns have been reported in case of frequent high dose ICS utilization.¹⁹

When asthma activity becomes persistent: choice of medication

When asthma activity becomes persistent, chronic anti-inflammatory treatment is unavoidable. There are several options as outlined in GINA steps 2 and 3; however, identifying the clinical

and/or laboratory biomarkers that may aid in the choice of medication is a major challenge, particularly in younger children.

One major issue is the choice between inhaled corticosteroids and LRTAs. While the available evidence clearly suggests that ICS have higher efficacy, the ease and simplicity of taking an oral leukotriene antagonist, and the concern of adverse events from chronic corticosteroid use, are important parameters that determine the choice of medication particularly among primary care physicians and health care professionals.

School age children with lower lung function and markers of type 2 inflammation (i.e. IgE, FeNO, eosinophilia) preferentially respond to low dose inhaled steroid. In these patients low dose ICS should be considered first line treatment.²⁰⁻²² LRTAs, while less effective than ICS for most patients, are an option for patients who cannot, or prefer to not, use an ICS or have concomitant allergic rhinitis.²³ A high urinary LTE₄ level (which may not be readily measurable) and/or low (or no) levels of indicators of allergic inflammation may help predict a favorable response.²⁰ More recently, a triple crossover head-to-head study between as-needed ICS given with as-needed SABA, daily ICS, and LTRAs in preschool children demonstrated that the probability of best response to daily ICS was higher in those with an allergic sensitization and blood eosinophil counts > 300 μ /l.²⁴

How much ICS is necessary to counter the adverse effects of ongoing respiratory inflammation is not clear. Recent work has shown that in children with mild-to-moderate persistent asthma treated with daily inhaled glucocorticoids, quintupling the dose at the early signs of loss of asthma control did not reduce the rate of severe asthma exacerbations or improve other asthma outcomes and may be associated with diminished linear growth.²⁵

Even though the daily use of ICS has been the cornerstone in the management of persistent asthma, poor adherence has always been a major problem leading to suboptimal control in a large proportion of patients. As stated above, the long-term use of ICS in children has generally been considered to be safe. However, a possible long-term suppressive effect on growth remains a key

concern. An early observational study in Denmark suggested that asthmatic children who had been treated with ICS for a mean of 9 years were able to achieve adult heights similar to their non-asthmatic siblings.²⁶ On the other hand, the long-term results of the Childhood Asthma Management Program revealed that children randomized to receive budesonide achieved mean adult height 1.2 cm lower when compared to those in the placebo group.²⁷

Another issue related to the long-term use of ICS, especially at higher doses, is the risk of adrenal crisis. Adrenal crisis may occur in patients managed with ICS with a higher prevalence in those under chronic use rather than in those with short courses of treatment. A survey carried out in the UK suggests that acute adrenal crisis may be more frequent than expected and that higher doses of ICS should gradually be reduced due to the risk of triggering an adrenal crisis.²⁸ There are even studies suggesting that ICS, even at medium doses, can have some impact on the HPA axis. For instance, Cavkaytar et al. showed that 66% of children treated with ICS for 6 weeks or more showed a level of baseline serum cortisol below 15 μ g/dL (4.66-12.90 μ g/dL), and of these 11.6% (7.7% of the total sample of 91 children) had a suppressed response to a low-dose adrenocorticotropin (ACTH) stimulation test (LDAT). The use of ICS at moderate-to-high doses [>176 and > 264 μ g/day fluticasone propionate-hydrofluoroalkane] for at least 7 months distinguished participants with HPA axis suppression (HPA-AS) from those with a normal HPA axis. More importantly, the cut-off value for predicting axis suppression was around 300 μ g per day of fluticasone.²⁹

Taken together, these studies suggest that even though ICS are safe and effective, patients should be carefully monitored regarding adverse events especially at higher doses, and physicians should aim at optimal asthma control with the lowest dose of ICS possible.

These studies have indicated that the low dose ICS treatment is both safe and effective in the treatment of children with mild persistent asthma. However, as stated above, some children have exacerbations even with good day-to-day control, and in addition many discontinue treatment after

becoming asymptomatic. These children inevitably become the target of an “as-needed approach”. The question then remains how to approach this group. In the randomized, double-blind, placebo-controlled Treating Children to Prevent Exacerbations of Asthma (TREXA) study,¹⁸ the investigators enrolled children and adolescents with mild persistent asthma aged 5–18 years and compared four groups: 1) regular ICS and ICS plus albuterol as rescue (combined group) 2) Regular ICS and placebo plus albuterol as rescue (Daily ICS group); 3) regular placebo and ICS plus albuterol as rescue (rescue ICS group); 4) Regular placebo with placebo plus albuterol as rescue (placebo group). The study has shown that the most effective treatment to prevent exacerbations is daily ICS. Compared with the placebo group, the frequency of exacerbations was lower in the daily, combined, and rescue groups. Frequency of treatment failure was 23% in the placebo group, compared with 5.6% in the combined, 2.8% in the daily, and 8.5% in the rescue groups. From a safety perspective, compared with the placebo group, linear growth was 1.1 cm less in the combined and daily arms, but not the rescue group. The investigators concluded that ICS as rescue medication with albuterol might be an effective step-down strategy for children with well controlled, mild asthma because it is more effective at reducing exacerbations than rescue salbutamol alone. In addition, with this approach the use of daily inhaled ICS treatment and related side effects such as growth impairment can therefore be avoided. Hence, ICS plus a SABA on an as-needed basis rather than beta agonist alone, can be considered as an option. Unfortunately, a combined preparation of ICS plus salbutamol is still not available, and this strategy can only be achieved with two different preparations.

When asthma is not controlled with daily ICS treatment: stepping up

When asthma is still not adequately controlled despite the use of low dose ICS, there are several options including an increase of dosage ICS, addition of a LABA or the addition of LTRA to low dose ICS. A crossover comparison of the three commonly used step-up protocols – adding LABA,

increasing the dose of ICS monotherapy, or adding LTRA, demonstrated that the best response occurred most frequently with the LABA step-up, but this was not uniform across all children.³⁰ White race and higher baseline score on the Asthma Control Test predicted a better response to the addition of LABA. Therefore, individual assessment in such patients is important in determining the personal best combination for each individual. The effect of race is being comprehensively studied in the recently completed Best African American Response to Asthma Drugs Trial (NCT01967173). A more recent study demonstrated that combination therapy with fluticasone and salmeterol provides equivalent or better asthma control to ICS monotherapy. The risk of a serious asthma related event was similar between fluticasone-salmeterol and fluticasone-only groups.³¹ As there is no sufficiently robust evidence for children younger than 4 years of age, the regular use of ICS-LABA under that age cannot be recommended at the moment.

Another possibility in stepping up from monotherapy with ICS is the so called Single Maintenance And Reliever Therapy (SMART) which may reduce the risk of exacerbations compared to budesonide alone.³² In a recently published systematic review with meta-analysis,³³ this approach was associated with a lower risk of asthma exacerbations and compared ICS (with or with no LABA) and SABA as reliever treatment. This analysis also included data obtained from 341 children aged 4–11 years that came from a single trial.³⁴ In this group SMART was associated with a reduced risk of asthma exacerbations compared with a higher dose of ICS as the controller therapy (RR, 0.55 [95%CI, 0.32 to 0.94]); or the same dose of ICS and LABA as the controller therapy (RR, 0.38 [95%CI, 0.23 to 0.63]).

Beyond these “traditional” options, the addition of long acting anti-muscarinic (LAMA) agent has also been evaluated as add-on therapy. In adult asthma, tiotropium is a recognized treatment option when the disease is not well controlled despite the use of ICS and LABA.³⁵ More recently, tiotropium has also been tested as an add-on treatment in pediatric trials and was found to improve lung function at a dose of 5 mcg daily.^{36–}

³⁸ In a small controlled trial, a similar trend in clinical efficacy and safety was found with tiotropium alone or as add-on treatment in preschool children.³⁹

OTHER CONSIDERATIONS IN THE TREATMENT OF NON-SEVERE ASTHMA IN CHILDREN

Treatment with ultrafine particle ICS

Inflammation in asthma mainly involves the large airways, but there is histopathological evidence that the small airways are involved as well⁴⁰ and may contribute to poor asthma control. As control of asthma by ICS requires delivery to both small and large airways, the differing particle size of ICS could potentially impact both efficacy and safety outcomes.⁴¹ Compared with larger particles, extrafine hydrofluoroalkane beclomethasone dipropionate (HFA-BDP) with a mass median aerodynamic diameters (MMAD) of 1~2 μm have a lower oropharyngeal deposition (20-30% vs >80%) and a higher lung deposition (50-60% vs 10-20%) compared to chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone.⁴² Systematic reviews and meta-analyses of RCT comparing extrafine to fine particle ICS have yielded conflicting results, summarized in Table 1.⁴³⁻⁴⁶

In childhood asthma, initiating or stepping up the ICS dose with ultrafine-particle ICS rather than with standard-size-particle ICS was found more effective and showed similar effectiveness to add-on LABA.⁴⁷ Furthermore, adjusted respiratory-related health care costs were significantly lower for HFA-beclomethasone than for fluticasone.⁴⁸ These findings challenge guidelines that recommend adding a LABA as the first choice for stepping up when asthma is not controlled by ICS monotherapy.⁴⁷ Spacers are usually used with pressurized metered-dose inhalers (pMDIs) to eliminate the need for coordinating inhalation with actuation. However, there was no evidence that prescribed spacer devices are associated with improved asthma outcomes for extrafine- or fine-particle ICS administered by pMDI, challenging long-standing assumptions that spacers should improve pMDI effectiveness.⁴⁹

Adherence and its monitoring

Suboptimal adherence to asthma medications is very common in children with asthma and is associated with poor disease control and reduced quality of life. Commonly reported factors leading to persistent non-adherence are unawareness of non-adherence by both parents and health care providers, a lack of parental drive to achieve high adherence and ineffective parental problem-solving behavior.⁵⁰ High stress levels among asthmatic children and/or their caregivers is another noticeable factor. In a prospective school-based population of inner-city asthmatic children, higher non-adherence scores and high caregiver stress were associated with worse asthma morbidity.⁵¹ Another report noted that increased caregiver negative health beliefs were significantly and negatively associated with an objective measure of ICS adherence in preschool age.⁵²

Adherence levels can be overestimated when considering only secondary adherence (following the medication recommendations for a defined period) and ignoring primary adherence (first filling of a prescription). In a prospective study on two databases of asthmatic children and adults, secondary adherence to ICS was found poor in both children and adults while primary adherence was low in adults only. The authors concluded that integrated primary and secondary adherence (IPSA) measure leads to more valid estimates of adherence to ICS.⁵³

Adherence was calculated using medication possession ratio (MPR) and ratio of controller to total asthma drug in a population-based cohort study from a primary care database containing medical records of 176,516 children, aged 5-18 years. Adherence to ICS was generally low with only 31% of the patients having an MPR ≥ 0.8 . Characteristics of children with good adherence were compatible with more severe asthma, suggesting that adherence is driven by treatment need or intensity of medical follow-up.⁵⁴ Accordingly, children with non-severe asthma are expected to have lower adherence rates and should be targeted for adherence-improvement programs.

Electronic adherence monitoring with daily reminder alarms is likely to be of significant benefit

Authors/year	Study description	Treatment and control groups	Main outcome
Lasserson et al. ⁴ /2006.	Systematic review. Nine studies (1265 participants). Two studies were conducted in children. All studies were of short duration (three to twelve weeks)	CFC or HFA-propelled FP vs HFA-propelled extrafine BDP	No significant difference between FP and extrafine HFA-BDP on FEV ₁ or peak flow at a dose ratio of 1:1. Individual studies reported non-significant findings in symptom scores and quality of life questionnaires.
Chen et al. ⁵ /2015.	Metanalysis. Five studies involving 949 asthmatic patients	Extrafine HFA-BDP versus BUD	Extrafine HFA-BDP at half of daily dose is equivalent to BUD in improving lung function (FEV ₁ , morning and evening PEF) and use of rescue medication, without increasing adverse events in patients with asthma.
El Baou et al. ⁶ /2017.	Systematic review and metanalysis. Twenty-three independent trials. Children and adults	Standard particle size FP and FP/SAL versus small particle size comparators (BDP, BDP-F or CIC). Eight studies evaluated FP versus BDP, 11 evaluated FP versus CIC, one evaluated FP/SAL versus BDP and three evaluated FP/SAL versus BDP-F	No clinically significant differences in efficacy (on mean change from baseline FEV ₁ , morning PEF and FEF _{25-75%} predicted) or safety were observed comparing small and standard particle size ICS medications for the treatment of asthma
Sonnappa et al. ⁷ /2018	Systematic review and metanalysis. Seven studies with 33,453 subjects aged 5-80 years	Six studies used extrafine beclomethasone propionate and 1 study used both extrafine beclomethasone propionate and extrafine ciclesonide versus fine-particle ICSs	Extrafine ICSs have significantly higher odds of achieving asthma control with lower exacerbation rates at significantly lower prescribed doses than fine-particle ICSs.

Table 1. Meta-analyses comparing extrafine and standard particle size ICSs. ICSs: inhaled corticosteroids; CFC: chlorofluorocarbon; HFA: hydrofluoroalkane; FP: fluticasone propionate; BDP: beclomethasone dipropionate; BUD: budesonide; SAL: salmeterol; CIC: ciclesonide

in the routine management of asthmatic children. A randomized controlled trial on 6-16-year-old children revealed adherence rates in the intervention group (70%), versus 49% in the control group. There was no significant impact on the Asthma Control Questionnaire (ACQ) results but children in the intervention group required significantly fewer courses of oral steroids and fewer hospital admissions.⁵⁵ In a multicentre randomized controlled trial, 209 children (aged 4-11 years) using ICS were given a real-time medication monitoring (RTMM) device for 12 months. The intervention group also received tailored short message service (SMS) reminders,

sent only when a dose was at risk of omission. Mean adherence was higher in the intervention group: 69.3% versus 57.3% (difference 12.0%, 95% CI 6.7%-17.7%). This e-monitoring improved adherence to ICS, but not asthma control, quality of life, or exacerbations.⁵⁶

Treatment options to prevent autumn exacerbations

Childhood asthma exacerbations peak in the autumn season in many geographic locations. This is probably related to the dynamics of viral infections and allergen exposure when children

return to school. The Seasonal Asthma Exacerbation Predictive Index (saEPI) appears to be a good tool to evaluate which children are unlikely to have an asthma exacerbation in autumn.¹⁴

Short-term targeted treatment can potentially prevent autumn asthma exacerbations. In a randomized, double-blind, double placebo-controlled, multicenter clinical trial, the Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) study, adding omalizumab to ongoing guidelines-based care among inner-city youth, before return to school, reduced autumn asthma exacerbations requiring ICS or hospital admission in the 90 days after school return to 11.3%, compared to 21.0% in those receiving placebo (odds ratio 0.48, 95% confidence interval 0.25 to 0.92).⁵⁷ According to a Cochrane systematic review, there was no evidence of an effect of LTRAs in reducing autumn exacerbations. Sending a seasonal medication reminder letter did not reduce the number of children requiring an unplanned healthcare contact.⁵⁸

CONCLUSION

Even though severe asthma attracts increasing attention from the scientific community as well as from the pharmaceutical industry, treatment of non-severe, mild-to-moderate asthma remains to be an important challenge for the practicing physician for a number of reasons. First, due to its high prevalence in the community, it has very important public health implications. Second, due to the heterogenous character of the disease, children across the whole spectrum of severity can have severe exacerbations.⁵⁹ Therefore, control of the disease is of utmost importance to prevent deaths from asthma attacks. Finally, since it comprises the majority of patients treated on an outpatient basis, medical professionals need to be continually updated on this.

Asthma management requires a multifaceted approach involving many strategies in addition to pharmacotherapy. Even though children with non-severe asthma with Th2 signature such as atopy, eosinophilia, and high nitric oxide respond favorably to low dose ICS, clinical, laboratory, and genetic biomarkers that will aid in defining the best strategy for the initial treatment and stepping up in

the individual child with non-severe asthma awaits the results of further research and remains to be an intriguing challenge in the field.

Author contributions

All authors contributed equally to the development of the paper. All authors approved the final version.

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