

# New Perspectives in the Management of Mild to Moderate Asthma in Children

This article was published in the following Dove Press journal:  
*Journal of Asthma and Allergy*

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**Abstract:** Mild to moderate asthma makes up the greatest proportion of all asthma severities in childhood. Children who are treated with steps 1–2 are defined as having mild asthma and step 3 as having moderate asthma, according to the guidelines. Although many studies focused on the management of severe asthma over the last decade, there have also been important changes and improvements in the management of mild to moderate asthma. In this article, new perspectives in the management of children with mild to moderate asthma will be reviewed and compared according to the two major guidelines.

**Keywords:** asthma, mild, moderate, long-acting inhaled bronchodilators, treatment

Mild to moderate asthma is defined according to the frequency of symptoms and risk of exacerbations in the Global Initiative for Asthma Guideline (GINA) and National Asthma Education and Prevention Program Expert Panel Report 3.<sup>1,2</sup> Another definition of mild to moderate asthma in the GINA guidelines is non-severe asthma which can be controlled by steps 1–3 treatment.<sup>1</sup> Although mild to moderate asthma constitutes the majority of childhood asthma, it is also a heterogeneous group as severe asthma.<sup>3</sup> Data on phenotypic characterization of mild to moderate asthma is limited.<sup>3,4</sup> Predictors of poor outcomes such as exacerbations or persistent airflow obstruction are still largely unknown.<sup>3</sup> Treatment options and studies on predictors of response to treatments in mild to moderate asthma are very limited.<sup>5</sup> Besides, mild asthma is no longer regarded as an easy condition to manage considering the severe exacerbation risk (0.12 and 0.77 severe exacerbations per patient per year).<sup>6</sup> Furthermore, compliance to regular controller medication is worse in mild, but also in the moderate spectrum of, asthma compared to severe asthma, that may be the main reason of severe exacerbations in these groups.<sup>7</sup>

The risk of severe exacerbation even in the mildest spectrum of asthma led to major changes in the management of this category. As sufficient data was accumulated, the use of a combination of inhaled corticosteroid (ICS)-formoterol in a single inhaler as maintenance and reliever treatment and a low dose ICS taken whenever short-acting beta<sub>2</sub>-agonist (SABA) is taken was recommended in an effort to overcome the problems of compliance and severe exacerbation. Additionally, specific allergen immunotherapy is suggested as an add-on treatment in selected allergic asthmatic patients. Lastly, the guidelines included the Food and Drug Administration's announcement about the

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requirement of a boxed warning about the risk of serious mental health adverse effects with montelukast.<sup>8</sup>

In this review, new perspectives in the management of children with mild to moderate asthma will be discussed and compared according to treatment steps and age groups in GINA<sup>1,9</sup> and National Heart, Lung, and Blood Institute (NHLBI)<sup>10</sup> guidelines.

## Step 1

Step 1 treatment is recommended for mild intermittent asthma. In this group, symptoms are less than two days a month with no risk factors for future exacerbations according to GINA guidelines.<sup>9</sup> The new treatment recommendations in GINA and NHLBI asthma guidelines at steps 1–3 are given in a table for each age group (Table 1).

## Teens (≥12 Years Old)

There are new recommendations for “preferred controller and reliever options” in adolescents ≥12 years old with asthma in GINA guideline.<sup>1,9</sup> SABA-only treatment is no longer recommended for adolescents with mild asthma because of the risk of death<sup>11</sup> and urgent health care utilization<sup>12</sup> related to asthma, although they may have good control of their asthma symptoms.<sup>13</sup> As-needed, a low dose ICS-formoterol combination is both the preferred controller and reliever treatment options in this step. The basis for these treatment options comes from indirect evidence (therefore classified as evidence B) provided by two randomized controlled trials (RCTs) where adolescents ≥12 years are also included with adults.<sup>14,15</sup> In the first study, it was demonstrated that the as-needed budesonide-formoterol group was superior to the as-needed

**Table 1** New Recommendations in the Treatment of Mild to Moderate Asthma According to the GINA and NHLBI Guidelines

		GINA	NHLBI
Step 1	Teens	As-needed low dose ICS-formoterol*	No new recommendations
		Low dose ICS taken whenever SABA taken <sup>#</sup>	
	6–11 years old	Low dose ICS taken whenever SABA taken <sup>#</sup>	No new recommendations
	Preschool age	No new recommendations	As-needed SABA and add short course daily ICS at the start of RTI
Step 2	Teens	As-needed low dose ICS-formoterol <sup>†</sup>	Low dose ICS taken whenever SABA taken <sup>†</sup>
			**SCIT as adjunct treatment to standard pharmacotherapy
	6–11 years old	Low dose ICS taken whenever SABA taken <sup>#</sup>	**SCIT as adjunct treatment to standard pharmacotherapy
	Preschool age	No new recommendations	No new recommendations
Step 3	Teens	Daily and as-needed low-dose ICS-formoterol <sup>‡</sup>	Daily and as-needed low-dose ICS-formoterol <sup>‡</sup>
			**SCIT as adjunct treatment to standard pharmacotherapy
	6–11 years old	No new recommendations	Daily and as-needed low-dose ICS-formoterol*
			**SCIT as adjunct treatment to standard pharmacotherapy (for 5–11 year olds)
	Preschool age	No new recommendations	Low dose ICS-LABA and as-needed SABA (for ≤3 years old)*
			Daily and as-needed low dose ICS-formoterol (for 4 years old)*

**Notes:** \*Preferred controller and reliever treatment option in this age group. <sup>#</sup>Other controller option in this age group. <sup>†</sup>Second preferred controller and reliever treatment option in this age group. <sup>‡</sup>Low dose ICS-formoterol is the reliever only for patients prescribed budesonide-formoterol maintenance and reliever therapy. \*\*Conditional recommendation. Data from Global Initiative for Asthma (GINA)<sup>1,9</sup> and National Asthma Education and National Heart, Lung, and Blood Institute, National Institutes of Health.<sup>10</sup>

**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub>-agonist; SABA, short-acting beta<sub>2</sub>-agonist; RTI, respiratory tract infection; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual allergen immunotherapy; HDM, house dust mite.

terbutaline group when considering symptom control. In addition, exacerbation rates with as-needed budesonide-formoterol and regular daily budesonide regimens were similar and lower compared to terbutaline group.<sup>14</sup> In the second study, the annual rate of severe exacerbation was not inferior in the group using as-needed budesonide-formoterol than daily regular budesonide maintenance therapy.<sup>15</sup>

“Other controller option” newly recommended in step 1 for adolescents  $\geq 12$  years is low dose ICS taken whenever SABA taken. This option depends on indirect evidence from studies that included patients eligible for step 2 treatment separate from or in combination with ICS and SABA inhalers.<sup>16,17</sup> This may be an option, especially in those who have difficulty in adhering to daily low dose ICS therapy and in mild patients with infrequent symptoms, while decreasing future risks of exacerbations compared to as-needed SABA-only treatment. In addition, it may be an alternative option for countries where fixed budesonide-formoterol or beclomethasone-formoterol combinations are either not available or affordable. On the other hand, there is no new recommendation at this step for adolescents in the NHLBI guidelines.<sup>10</sup>

## 6 - 11-Year-Old Children

There are two new options presented under “other controller options” in the 2019 and 2020 revisions of the GINA guidelines: low dose ICS taken whenever SABA is taken or daily low dose ICS.<sup>1,9</sup> These recommendations based on the data from an RCT involving children aged  $\geq 6$  (TREXA study),<sup>16</sup> and a real-world open-label trial involving African-American children aged 6–17 years by Sumino et al.<sup>17</sup> In the TREXA trial, rescue beclomethasone (as-needed beclomethasone with SABA in separate inhalers) was shown to decrease the risk of exacerbations by more than a third, compared to SABA only treatment.<sup>16</sup> In the other study, it was shown that asthma control and exacerbations were no different in those who use as-needed beclomethasone with SABA from those who use beclomethasone on a daily basis.<sup>17</sup> These two studies showed that rescue ICS with SABA in separate inhalers resulted in lower ICS exposure<sup>17</sup> and growth impairment,<sup>16</sup> compared to daily low dose ICS which preserves its place as the “other controller option” in the GINA guideline at this step.<sup>1</sup> There is no new recommendation for 6- to 11-year-old children in the NHLBI guidelines.<sup>10</sup>

## Preschool Children ( $\leq 5$ Years Old)

The evidence is accumulating much more slowly in this age group because of the difficulty of definite asthma diagnosis, transition between symptom patterns and challenges of planning research compared to older age groups. There is still no change in either preferred controller or reliever options in step 1 in GINA 2020 guideline.<sup>1</sup> Nevertheless, a trial of controller treatment who use SABA more than twice a week in a month is recommended by expert opinion under “preferred options” in the GINA guideline since the 2019 update.<sup>9</sup> The use of intermittent high dose ICS with as-needed SABA for intermittent viral induced wheezing attacks with no interval symptoms, is recommended as the “other option” in the GINA guidelines.<sup>1,9</sup> This is a conditional recommendation for 0- to 4-year-old children with recurrent wheezing in the NHLBI 2020 asthma guidelines and it is suggested it should be started at the onset of an apparent respiratory tract infection.<sup>10</sup> There are three RCTs referred to for this recommendation.<sup>18–20</sup> two of them also assessed growth.<sup>18,19</sup> One of them found a 5% lower gain in height<sup>19</sup> and the other did not find an effect on linear growth.<sup>18</sup> Therefore clinicians are recommended to discuss this issue with parents and make close monitorization of growth if they decide to use this intermittent treatment regimen.<sup>10</sup>

## Step 2

Step 2 asthma treatment is recommended for mild persistent asthma patients whose symptoms are more than 2 days a month but not daily.<sup>1</sup>

## Teens ( $\geq 12$ Years Old)

As-needed low dose ICS-formoterol combination was given as a second option under the “preferred controller” section for adolescents  $\geq 12$  years old, where it may also be used as preferred reliever option as a new recommendation starting from 2019 in the GINA guidelines.<sup>1,9</sup> The evidence for this option was provided by SYGMA 1–2 studies.<sup>14,15</sup> This recommendation stems from the fact that the annual number of attacks and the rate of severe attacks are not-inferior in as-needed ICS-formoterol group compared to daily low dose ICS group.<sup>14,15</sup> Although benefits of daily use of ICS (reduction in severe attacks, hospitalization and mortality) are well known,<sup>11,21,22</sup> treatment compliance is an important issue in mild asthma. Therefore, this option may be a good choice for teens

with poor treatment compliance.<sup>23</sup> On the other hand, this treatment regimen is not recommended in step 2 in the NHBLI guidelines.<sup>10</sup>

At this step, NHBLI makes a new conditional recommendation of as-needed ICS and SABA used concomitantly which was given under the “other controller option” in the GINA guidelines.<sup>1,10</sup> Supporting data comes from two studies using low dose ICS taken when SABA was taken in separate inhalers in children between 5 and 18 years old.<sup>16,17</sup> This treatment choice when compared with a daily low dose ICS has similar effects on asthma control, asthma quality of life and frequency of asthma exacerbations, as well as infrequent side effect profiles.<sup>10</sup> This option may be a good alternative for patients whose compliance is poor with daily low dose ICS. However, the NHBLI guidelines warns clinicians about the fact that teens with low or high perception of symptoms may not be good candidates for as-needed ICS and SABA use concomitantly.<sup>10</sup>

Subcutaneous allergen immunotherapy (SCIT) was proposed as a new conditional recommendation as adjunct treatment to standard pharmacotherapy in allergic individuals whose asthma is controlled according to the NHBLI guidelines between steps 2 and 4.<sup>10</sup> Patients who have demonstrated allergic sensitization and evidence of worsening asthma symptoms after acute (e.g., pets), seasonal (e.g., pollens), or chronic exposure to allergens (e.g., dust mites) were stated as candidates for this treatment if they perceive a high value on possible small improvements in some aspects of asthma outcomes with tolerable side effects.

## 6- to 11-Year-Old Children

There are two new recommendations for this age group at step 2. One is as-needed low dose ICS and SABA concomitant use in separate inhalers as described in the GINA guidelines since 2019<sup>1,9,16,17</sup> and the other is SCIT as adjunct treatment to standard pharmacotherapy as described in the NHBLI guidelines with the same indications given in teens.<sup>10</sup>

## Preschool Children (≤5 Years Old)

There is no new recommendation in either the GINA or NHBLI guidelines for this age group at Step 2.

## Step 3

Step 3 treatment is recommended for moderate persistent asthma.<sup>1</sup> Moderate asthma is defined as daily symptoms

are much more common (most days) or waking up at night due to asthma occur at least once a week in GINA guideline.<sup>1</sup>

## Teens (≥12 Years Old)

There are two new changes at this step in GINA guideline since 2019 and NHBLI guideline.<sup>1,9,10</sup> The first one is similar in both guidelines in the preferred reliever option as low dose ICS-formoterol for patients prescribed maintenance and reliever therapy.<sup>1,9</sup> However, ICS-formoterol fixed combination should not be used as the reliever for patients taking combination ICS-LABA medications with a different LABA. This recommendation is made because ICS-formoterol maintenance and reliever option has been shown to significantly reduce severe attacks and provide a similar level of control compared to either fixed dose ICS-formoterol or high-dose ICS maintenance treatment plus SABA.<sup>24</sup> The NHBLI guidelines comment that ICS-formoterol maintenance and reliever option might not be necessary for patients whose asthma is well controlled with ICS-LABA combination and SABA as quick relief. On the other hand, patients with a severe exacerbation in the previous year are particularly good candidates for ICS-formoterol maintenance and reliever option to reduce exacerbations depending on the evidence.<sup>10,25</sup>

Maintenance and reliever treatment is recommended either with beclometasone-formoterol<sup>26</sup> or budesonide-formoterol<sup>27</sup> combinations in a single inhaler but studies involving children and adolescents were made with only budesonide-formoterol combinations.<sup>25,28–30</sup> The maximum total daily dose of formoterol used in these studies did not exceed 54 mcg for ages 12 years and older.<sup>10,25,28,29</sup>

The second change in the guidelines is related with specific allergen immunotherapy. In the GINA guidelines sublingual allergen immunotherapy for asthmatic patients with allergic rhinitis sensitized to house dust mite is suggested as additional treatment choice to standard treatment under “other controller options”.<sup>1,9</sup> In NHBLI guideline, sublingual immunotherapy is not recommended because Food and Drug Administration did not support the use of it for allergic asthma.<sup>10</sup> On the other hand, NHBLI guideline makes a conditional recommendation for SCIT with pets, pollens, house dust mites for patients who are sensitized and show a clinically meaningful increase in asthma symptoms upon exposure to these allergens.<sup>10</sup>

## 6- to 11-Year-Old Children

In this age group, only NHBLI guideline made a new recommendation with ICS-formoterol in a single inhaler for maintenance and reliever as the preferred option for children between 5 and 11 years old.<sup>10</sup> There are four randomised controlled studies<sup>25,28–30</sup> referred for this recommendation, two of which included also children younger than 11 years old.<sup>25,30</sup> All studies found a significant decrease in severe attacks in patients using ICS-formoterol in a single inhaler for maintenance and reliever compared either to the same dose ICS-formoterol and SABA or increased dose of ICS and SABA. In addition, two of them demonstrated a better growth with ICS-formoterol in a single inhaler for maintenance and reliever compared to higher dose of ICS.<sup>25,30</sup> The guideline recommends this option with moderate certainty of evidence for children 4–11 years old.<sup>10</sup> There is no new recommendation for this age group in the GINA guidelines at Step 3.<sup>1</sup>

## Preschool Children (≤5 Years Old)

There is a no new recommendation for this age group in the GINA guidelines, but a major new treatment option only in NHBLI guidelines in this age group.<sup>1,10</sup> For children ≤ 3 years old, the NHBLI guidelines showed daily low dose ICS-LABA as maintenance and SABA as preferred reliever treatment in a figure without any recommendation or explanation about it. For preschool children (4 years old) however, the NHBLI guideline recommends low dose ICS-formoterol in a single inhaler for maintenance and reliever with moderate evidence of certainty for children 5–11 years old.<sup>25,30</sup>

There is no study investigating ICS-formoterol in a single inhaler for maintenance and reliever in preschool children younger than 4 years old. There are 3 studies that used fluticasone-salmeterol combination as ICS-LABA for maintenance and SABA for quick relief that included children 5 years and younger.<sup>31–33</sup> In the first study, it was shown that 26 weeks long fixed dose fluticasone-salmeterol combination did not differ in severe asthma exacerbations requiring hospitalization compared to the same dose fluticasone-use alone in children 4–11 years old.<sup>31</sup> The second study included 300 children aged 8 months to 4 years in a randomized, double-blind fashion with either fixed dose fluticasone propionate 80 mcg/salmeterol 25 mcg combination or the same dose of fluticasone propionate for 8 weeks.<sup>33</sup> Fluticasone propionate-salmeterol combination did not show superior

efficacy in mean total asthma symptom scores to fluticasone propionate although no clinically significant differences in safety were noted with fluticasone propionate/salmeterol usage.<sup>33</sup> The last study, which was observational, used fluticasone propionate-salmeterol combination treatment in children younger than 5 years old with a mean duration of  $12.45 \pm 9.14$  months. They showed an 89% reduction in hospitalizations, a 71% reduction in exercise-related asthma symptoms and an 81% reduction in nocturnal asthma symptoms.<sup>32</sup> However, the rate of ICS treatment before initiation of fluticasone-salmeterol combination was very low in this study (only 19%), which may bias their results. Therefore, we believe that there is still no sufficient data to recommend the use of any ICS-LABA combinations as a controller in children under 4 years old.<sup>31–33</sup>

## Conclusion

Both the GINA and NHBLI asthma guidelines revised the document depending on recent evidence. They mainly recommended two new treatment choices in mild to moderate childhood and adolescent asthma: ICS-budesonide in a single inhaler as maintenance and reliever and low dose ICS taken whenever SABA taken. However, these recommendations do not match with respect to treatment steps at each age group which leads to a discrepancy between these two guidelines. Guidelines may help clinicians in planning the treatments, however, interpretation of the same evidences may differ depending on different issues. Therefore, a personalized treatment strategy may be needed not only for the severe spectrum of the disease but also for mild to moderate asthma in childhood.

## Abbreviations

ICS, Inhaled corticosteroids; GINA, Global Initiative for Asthma; LABA, Long-acting beta<sub>2</sub>-agonist; NHLBI, National Heart, Lung, and Blood Institute; RCT, Randomized controlled trial; SABA, Short-acting beta<sub>2</sub>-agonist; SCIT, Subcutaneous Allergen Immunotherapy.

## Disclosure

The authors have no conflicts of interest to declare for this work.

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