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## Global Initiative for Asthma 2021: Asthma in Preschool Children and Short-Acting $\beta_2$ -Agonist-Only Treatment

To the Editor:

We read with interest the Global Initiative for Asthma (GINA) 2021 executive summary by Reddel and colleagues (1), which summarizes key recommendations for asthma management and the evidence underpinning recent changes. A landmark new recommendation for adolescents and children >6 years of age is that short-acting  $\beta_2$ -agonists (SABAs) be given in combination with inhaled corticosteroids (ICS) to reduce the risk of severe exacerbations and asthma-related death (2).

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It has been suggested that desensitization and downregulation of  $\beta_2$ -receptors, with a loss of bronchodilator response and proinflammatory effects of  $\beta_2$ -agonists (3), are responsible for the increase in adverse events observed with regular  $\beta_2$ -agonist treatment. Adding ICS to SABAs improves airway inflammation, enhances  $\beta_2$  adrenergic receptor expression, and reduces downregulation of  $\beta_2$  adrenergic receptors (1, 3). In this regard, it has been suggested that regulatory bodies should mandate the use of SABAs alone as off label (4).

In the section on the management of asthma in children 5 years and younger, the GINA 2021 recommendation is to “provide inhaled SABA for relief of wheezing episodes.” Do we have evidence to indicate that asthma in a 6-year-old is any different from asthma in a child 4–5 years old? To our knowledge, the downregulation of  $\beta_2$  adrenergic receptors is not age dependent, and eosinophilic airway inflammation occurs in the airways of preschool children with asthma, too (5). Data from several studies show that the prompt use of intermittent high-dose ICS therapy is effective in preventing symptoms from progressing to exacerbation in 35% of cases among preschool-aged children with intermittent asthma or recurrent virally triggered wheezing (6). The GINA working group also warns that starting treatment with SABAs trains parents and patients to regard it as their primary asthma treatment, particularly if training starts in the early years of life.

In light of these considerations, we suggest that the GINA recommendation for children >6 years old that low-dose ICS be taken whenever SABAs are taken should apply to preschool-aged children as well. It would be of great interest to pediatricians to have some feedback on this issue from the authors of the GINA 2021 executive summary. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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## Reply to Baraldi and Piacentini

From the Authors:

We thank Prof. Baraldi and Prof. Piacentini for their interesting comments on the Global Initiative for Asthma (GINA) 2021 recommendations for asthma management in children 5 years and younger (1). They raise the important question of why the recommendation against using short-acting  $\beta_2$ -agonist (SABA)-only treatment for children, adolescents, and adults (2) was not also applied to preschool children. The authors' arguments for applying the same approach to preschool children echo the rationale of the GINA Science Committee for implementing these changes in older age groups: namely, concerns around the risks of SABA-only treatment, the benefit of regular or as-needed inhaled corticosteroids (ICS), and that starting with SABA alone “trains” patients to be overly reliant on these medications. The authors also pose the pertinent question as to whether the pathophysiology of asthma in preschool children is different than in older children and, consequently, why the preferred medication option in step 1 of the GINA strategy in these age groups should not be similar: that is, the use of low-dose ICS whenever a reliever inhaler is given, instead of a SABA alone. We take this opportunity to further discuss the differences in evidence and management of asthma in these age groups of children.

As suggested by the authors, eosinophilic airway inflammation and downregulation of  $\beta_2$ -adrenergic receptors are indeed observed in children of all ages; however, many younger children with recurrent wheeze do not have evidence of eosinophilic airway inflammation, even among those with severe multitrigger wheeze (3). Furthermore, there are currently insufficient clinical trial data to support the efficacy and safety of as-needed low-dose ICS at step 1 in preschool children. Several randomized clinical trials in preschool children have compared episodic high-dose ICS (given preemptively at the onset of symptoms that would typically precede the development of an exacerbation) with daily ICS, episodic or daily montelukast, or SABA-only treatment (4). These studies mostly, but not always, have shown these treatment strategies to be equally beneficial in reducing asthma exacerbations compared with SABA alone (4). However, the doses of ICS used in the episodic treatment studies were much higher than those recommended at step 1 for

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