It has been suggested that desensitization and downregulation of β_2-receptors, with a loss of bronchodilator response and proinflammatory effects of β_2-agonists (3), are responsible for the increase in adverse events observed with regular β_2-agonist treatment. Adding ICS to SABAs improves airway inflammation, enhances β_2 adrenergic receptor expression, and reduces downregulation of β_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 β_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. ■

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References

1. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, *et al.* Global Initiative for Asthma strategy 2021: executive summary and rationale for key changes. *Am J Respir Crit Care Med* 2022;205: 17–35.
2. Carroll W, Clayton S, Frost S, Gupta A, Holmes S, Nagakumar P, *et al.* If it's "only" asthma, why are children still dying? *Arch Dis Child* 2020;105: 494–498.
3. Kersten ETG, Koppelman GH, Thio BJ. Concerns with beta2-agonists in pediatric asthma—a clinical perspective. *Paediatr Respir Rev* 2017;21: 80–85.
4. Bush A, Dalziel SR, Byrnes CA, Hatter L, Beasley R. Has the time come to end use of the blue inhaler? *Lancet Respir Med* 2021;9: e51.
5. Saglani S, Payne DN, Zhu J, Wang Z, Nicholson AG, Bush A, *et al.* Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007;176:858–864.
6. Jackson DJ, Bacharier LB. Inhaled corticosteroids for the prevention of asthma exacerbations. *Ann Allergy Asthma Immunol* 2021;127: 524–529.

Reply to Baraldi and Piacentini

From the Authors:

We thank Prof. Baraldi and 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 β_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 β_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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other age groups (1). The INFANT (Individualized Therapy for Asthma in Toddlers) study (5) provides some of the most useful data to inform this discussion. In that study, differential treatment response was assessed using three strategies: daily ICS, daily montelukast, and ICS coadministered with as-needed SABA. Children with allergic sensitization and blood eosinophils $\geqslant 300/\mu l$ were more likely to respond to daily ICS, but children without either of these features were as likely to respond to regular ICS as to symptom-driven ICS. However, there are three key caveats: first, these were preschool children who were eligible by U.S. guidelines for step 2 treatment (regular ICS or montelukast), not step 1; second, there was no SABA-only comparator; and third, we do not know if these findings are applicable in a wider range of settings, particularly in regions where blood eosinophilia may reflect helminth infection rather than asthma or atopy.

For children 6–11 years of age, the GINA step 1 recommendation for taking low-dose ICS whenever SABA is taken is based on two studies that combined this age group with adolescents (6, 7). We suspect that this approach may also be effective and safe in preschool children likely to have asthma; however, to change or extrapolate treatment recommendations, clinical trial evidence is needed, and to date no randomized clinical trials have been conducted to examine this regimen compared with SABA alone in children 5 years and younger. Thus, for preschool children with infrequent wheezing episodes, we currently recommend treatment with as-needed SABA (step 1), depending on the symptom pattern, and recommend that we should frequently assess, adjust, and review response to obtain the best personalized asthma management for children 5 years and younger. ■

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References

1. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, *et al.* Global Initiative for Asthma strategy 2021: executive summary and rationale for key changes. *Am J Respir Crit Care Med* 2022;205: 17–35.
2. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, *et al.* GINA 2019: a fundamental change in asthma management. Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019;53:1901046.
3. Robinson PFM, Fontanella S, Ananth S, Martin Alonso A, Cook J, Kaya-de Vries D, *et al.* Recurrent severe preschool wheeze: from prespecified diagnostic labels to underlying endotypes. *Am J Respir Crit Care Med* 2021;204:523–535.
4. Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, Bakel LA, Parkin PC, *et al.* Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. *Pediatrics* 2016;137:e20154496.
5. Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, *et al.*; NIH/NHLBI AsthmaNet. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138: 1608–1618.e12.
6. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, Mauger DT, *et al.* Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377:650–657.
7. Sumino K, Bacharier LB, Taylor J, Chadwick-Mansker K, Curtis V, Nash A, *et al.* A pragmatic trial of symptom-based inhaled corticosteroid use in African-American children with mild asthma. *J Allergy Clin Immunol Pract* 2020;8:176–185.e2.