Reply to: GINA 2021: Asthma in Pre-School Children and SABA-Only Treatment

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on behalf of the authors of "Global Initiative for Asthma (GINA) Strategy 2021 – Executive summary and rationale for key changes".

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From the Authors:

We thank Professors Baraldi and Piacentini for their interesting comments on the Global Initiatives for Asthma (GINA) 2021 recommendations for asthma management in children 5 years and younger. They raise the important question why the recommendation against using short-acting beta₂-agonist (SABA)-only treatment for children, adolescents and adults 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” the patient to over-rely on this medication. The authors also pose the pertinent question as to whether the pathophysiology of asthma in preschool children is different than in older children, and subsequently why the preferred medication option in step 1 of the GINA strategy in these age groups should not be similar: i.e., the use of low dose ICS whenever a reliever inhaler is given, instead of 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 β₂-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 multi-trigger wheeze. 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 pre-emptively at onset of symptoms that would
typically precede development of an exacerbation) with daily ICS, episodic or daily montelukast, or SABA-only treatment. These studies mostly, but not always, found these treatment strategies equally beneficial in reducing asthma exacerbations compared with SABA alone. However, the ICS doses used in the episodic treatment studies were much higher than those recommended at Step 1 for other age groups. The Individualized Therapy for Asthma in Toddlers (INFANT) study provides some of the most useful data to inform this discussion. Differential treatment response was assessed using three strategies: daily ICS; daily montelukast; and ICS co-administered with as-needed SABA. In this study, children with allergic sensitization and blood eosinophils ≥300/µl 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: firstly, these were preschool children who were eligible by US guidelines for Step 2 treatment (regular ICS or montelukast), not Step 1; secondly, there was no SABA-only comparator, and thirdly 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, 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. 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.
REFERENCES


