GINA 2021: the missing pieces in the childhood asthma puzzle

The Global Initiative for Asthma (GINA) 2021 report has now been published, with landmark changes for the improvement of asthma prevention and management.[1] The report raises important points about paediatric asthma treatment; although 50–75% of children and adolescents are classified as having mild asthma, 30–40% of all severe exacerbations occur in this group. The risk is reduced by inhaled corticosteroid-containing treatment and by avoiding short-acting β_2-agonist-only therapy.

In the 2021 GINA report, children aged 6–11 years with symptoms occurring less than twice per month (step 1) are recommended to take inhaled corticosteroids whenever given short-acting β_2-agonists as rescue therapy. From a pathophysiological point of view, this recommendation is supported by the evidence that inhaled corticosteroids enhance the expression of β_2-adrenergic receptors in the airways, helping to prevent severe exacerbations.[2] When symptoms occur at least twice a month—but less frequently than daily (step 2)—inhaled corticosteroids as maintenance therapy is recommended. If less symptom control occurs, maintenance and reliever therapy with a very-low-dosed or low-dosed inhaled corticosteroid–formoterol combination is included in the list of preferred controllers at step 3 and 4, respectively.[1] Finally, the 2021 GINA report recommends that, at any step of asthma severity, reliever treatment includes as-needed short-acting β_2-agonists or inhaled corticosteroid–formoterol. Many doctors ignore the danger of overusing short-acting β_2-agonists alone. Indeed, one of the key messages from the report is to avoid, at any age, the use of short-acting β_2-agonists alone as rescue therapy (box 3–4), and the available evidence fully supports this recommendation.[1]

Following the novel GINA recommendations, three major questions about paediatric asthma appear unanswered. First, there are no indications on the duration of inhaled corticosteroid–formoterol combination therapy when used as reliever treatment in case of asthma worsening. For paediatricians, this information is of importance when treating both children aged 6–11 years (step 3–4, when the inhaled corticosteroid–formoterol combination is used as reliever treatment in the context of maintenance and reliever therapy) and adolescents (when the fixed combination of inhaled corticosteroids and long-acting β_2-agonists is used as needed at any step; track 1).

Second, in individuals aged 12 years and older, the maximum recommended number of inhalations per day of the budesonide–formoterol combination is 12 (formoterol 54 µg and budesonide 960 µg delivered dose, respectively).[1] It is unclear whether this recommendation can be applied also to children aged 6–11 years. Finally, in the only paediatric study available of mild-to-moderate asthma, budesonide–formoterol was also effective and safe in children as young as 4 years.[3] Indeed, the management of preschool children with asthma symptoms is still an open issue. Evidence suggests that regular inhaled corticosteroids is a better strategy than intermittent short-acting β_2-agonists and inhaled corticosteroids in young children with aeroallergen sensitisation and increased blood eosinophils.[4] Yet preschool children with severe episodic wheezing, in whom intermittent inhaled corticosteroids are recommended, might be safely treated with budesonide–formoterol.[5] However, variable phenotypic heterogeneity and different responses to asthma medications in early life are considerable challenges that make it difficult to amend current guidelines in preschool children. More studies are needed to establish whether a different treatment from daily inhaled corticosteroids would also apply to young children requiring higher treatment steps.

Regulatory approval of medicines differs from country to country, and many recommendations are off-label in various countries (eg, inhaled corticosteroid–formoterol for intermittent therapy), particularly for children. Indeed, investigators and the pharmaceutical industry should do trials in children to provide the data needed to broaden the indications for these products. Only in this way can we hopefully fill in the missing pieces in the childhood asthma treatment puzzle.

We declare no competing interests.

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1 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. May, 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf (accessed June 3, 2021).
2 Sin DD, Man SF. Corticosteroids and adrenoceptor agonists: the compliments for combination therapy in chronic airways diseases. *Eur J Pharmacol* 2006; **533:** 28–35.
3 Bisgaard H, Le Roux P, Bjåmer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006; **130:** 1733–43.
4 Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016; **138:** 1608–18.
5 Abrams EM, Shaker M, Greenhawt M, Fernandes RM, Sinha I. Treatment of mild-to-moderate asthma in childhood and adolescence in 2021. *Lancet Respir Med* 2021; **9:** 443–45.

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