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Mini-Symposium: Asthma Phenotypes

Steroid responsiveness and wheezing phenotypes

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EDUCATIONAL AIMS

The reader will be able to:

- Examine the evidence supporting the variation in effectiveness of oral and inhaled corticosteroids across paediatric asthma phenotypes
- Highlight key determinants that may modulate the response to corticosteroids
- Review effective phenotype-specific treatment options

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SUMMARY

Oral corticosteroids are the cornerstone of management of acute moderate or severe asthma whilst preventive inhaled corticosteroids are the mainstay of the preventive management of children with asthma. Yet, variation in the magnitude of response to corticosteroids has been observed. There is increasing evidence that preschool-aged children with viral-induced asthma may display a certain degree of corticosteroid resistance, requiring higher doses of corticosteroids to overcome it. The identification of determinants of responsiveness is complicated by design issues, including heterogeneous populations of children with asthma and bronchiolitis or of children with viral-induced and multi-trigger asthma phenotypes in published trials. Potential key determinants of responsiveness may include age, trigger, phenotype, tobacco smoke exposure and genotype. The mechanistic pathway for corticoresistance may originate from a gene-environment interaction, leading to non-eosinophilic airway inflammation. The clinician should carefully confirm the diagnosis of asthma and ascertain the phenotype to select appropriate phenotype-specific therapy.

Oral corticosteroids are the cornerstone of management of acute, moderate or severe asthma whilst preventive inhaled corticosteroids are the mainstay of daily management of children with asthma.[1] Yet, several reports have recently shaken the belief that they are equally effective for all patients with asthma, suggesting, for instance, that preschool children with viral-induced wheezing are somewhat corticosteroid-resistant.[2–4]

DIAGNOSIS OF ASTHMA

The definition of asthma in children and adults required the documentation of both airway obstruction and reversibility/hyper-reactivity.[5–7] The same concept applies to preschool-aged children who are too young or sick to cooperate with standard spirometry. In these children, airway obstruction is documented by classical signs (cough, decreased air entry, wheezing), symptoms (cough, wheezing, dyspnoea, expectorations), accessory muscle use and impaired air exchange parameters. Reversibility is reflected by the improvement following bronchodilator and/or corticosteroids; and hyper-reactivity is supported by deterioration upon exposure to specific triggers.[8;9] Children meeting these criteria can be diagnosed with asthma at the very first episode, thus avoiding unnecessary delays in treatment.

In infants and toddlers, it is critical to distinguish asthma from bronchiolitis. Bronchiolitis is clinically defined as the first wheezing illness, in a child $\leq$12 months; respiratory syncytial virus (RSV) is the most frequent pathogen.[10] Although they display similar signs and symptoms of airway obstruction, children with bronchiolitis don't fit the definition of asthma as they do not show

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significant reversibility to inhaled β2-agonists or corticosteroids.[11] The only exception is evidenced by a recent multicentre bronchiolitis trial reporting no response to each individual drug, but unexpectantly, a significant response with the combination of high-dose oral steroids (dexamethasone) and nebulised adrenergic agonist (epinephrine); the study is currently being replicated to confirm the findngs.[12] To reduce the risk of misclassification with bronchiolitis, two or three wheezing episodes are commonly required for the diagnosis of asthma for children aged 12 (or 24) months or less.

In general, therapeutic studies of preschool wheezing are often difficult to interpret as they generally included heterogeneous wheezing groups. Indeed, the inclusion of children with bronchiolitis and asthma probably explain the poor response to oral corticosteroids in studies including infants and toddlers.[2,13] Careful attention to the population under study is thus critical in the interpretation of the literature.

PHENOTYPE

While many classifications have been proposed, two main phenotypes have considered.[14] Viral-induced asthma refers to children with exacerbations solely triggered by viral respiratory infections with no symptoms between episodes. This phenotype pertains almost exclusively to very young children, those aged 1 to 3 years, with symptoms resolved by the age 6 years.[9] In a recent trial, 85% of children with viral-induced asthma were aged 1 to 3 years; those aged 4-6 years evolved towards multi-trigger asthma during the course of the study.[4] In contrast, children with symptoms triggered by two or more factors (e.g., viral infection, weather, activity, allergens) usually have symptoms between episodes; they are referred to as having multi-trigger asthma (formerly called "persistent" asthma).

VARIATION IN TREATMENT EFFECTIVENESS ACROSS PHENOTYPES

Maintenance inhaled corticosteroids

National and international guidelines recommend daily inhaled corticosteroids as the cornerstone of the therapy for children with multi-trigger asthma. In school-aged children and adults, this recommendation is based on solid evidence, derived from several randomized controlled trials[15] and meta-analyses of randomised trials, which confirmed its superiority over placebo and leukotriene receptor antagonists.[16,17] In preschool children with multi-trigger asthma, the evidence supporting the efficacy of maintenance inhaled corticosteroids is less abundant but no less convincing. The PEAK trial involved 285 children aged 2 to 3 years with a high risk of asthma, that is, with four episodes or more in the prior year, and either one major risk factor (parental history of asthma or personal history of atopic dermatitis) or two of three minor risk factors (allergic rhinitis, eosinophilia, and wheezing without colds). More than 57% of enrolled children had positive aeroallergen skin tests, suggesting allergic or multi-trigger asthma in the majority of children.[18] Low dose daily fluticasone for two years was associated with a significant reduction in episode-free days, rescue bronchodilator use, and exacerbations requiring rescue oral corticosteroids and significantly improved lung function over placebo. The efficacy of daily maintenance inhaled corticosteroids to improve symptoms and prevent exacerbations in patients of all ages with multi-trigger asthma is clearly established.

In preschool-aged children with viral-induced asthma, daily inhaled corticosteroids have not been shown to be superior to placebo. In a study involving 161 children with viral-induced wheezing and no or minimal symptoms between episodes, there

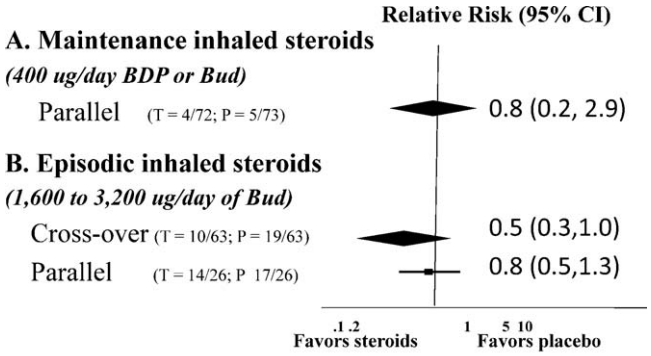

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Figure 1. The figure depicts the pooled relative risk of patients experiencing one or more exacerbation requiring rescue systemic glucocorticoids (1 count per patient) comparing in (A) maintenance inhaled steroids compared to placebo and in (B) episodic high dose inhaled corticosteroids compared to placebo. The width of each horizontal line represents the 95% CI around the point estimate (black square). The pooled estimates are represented by diamonds. The vertical line is the line of no effect (Relative Risk = 1.0).

was no group difference in rescue oral corticosteroids, admission, symptom severity, and duration of episodes between treatment with low dose Budesonide (400 ug/day) vs. placebo (Figure 1A).[19] Admittedly, the study was small and underpowered to identify a significant difference in important outcomes such as episodes requiring rescue oral corticosteroids. Of interest, in 549 children aged 2 to 5 years with viral-induced asthma, but including children with symptoms between exacerbations, daily montelukast did not show any group difference in rescue oral corticosteroids it appeared more effective than placebo for reducing the frequency and severity of exacerbations.[20] As the latter study included children with interim symptoms between episodes, it is unclear whether the observed benefits primarily apply to children with multi-trigger or those with viral-induced asthma.

Although the literature is scarce, there is no current evidence supporting the efficacy of daily maintenance corticosteroids in preschool-aged children with viral-induced asthma, while this strategy is clearly effective in children with multi-trigger asthma.

Pre-emptive high dose inhaled corticosteroids

For several years, national and international consensus statements had recommended the dose-doubling of inhaled corticosteroids as home management of exacerbation in children and adults with multi-trigger asthma.[21–23] Only recently has this recommendation been withdrawn in the view of the lack of effectiveness reported by several randomized controlled trials.[1,6,24] Indeed, a 2010 Cochrane review reported no evidence of the superiority of dose-doubling and dose-quadrupling of inhaled corticosteroids over placebo as home management of exacerbations; one small paediatric trial of dose-doubling contributed data to this review (Figure 2).[25] Only a subgroup analysis performed *per protocol* suggested that quadrupling the dose of inhaled corticosteroids may be beneficial for reducing the need for physician-initiated rescue oral corticosteroids in adults; caution is advised however, for the interpretation of subgroup analyses. Overall, the evidence would suggest that, in patients with multi-trigger asthma, the most effective strategy for preventing and reducing the severity of exacerbations remains simply the daily intake of inhaled corticosteroids.

In contrast, in preschool-aged children with viral-induced asthma (with no symptoms between exacerbations), high-dose inhaled corticosteroids (1,600 to 3,200 ug/day of budesonide) at the onset of an upper respiratory tract infection appears effective. Indeed, a Cochrane review of three trials showed a non-significant