Mini-Symposium: Asthma Phenotypes

Steroid responsiveness and wheezing phenotypes

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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. 3–7 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 episode, in a child ≤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...
significant reversibility to inhaled β2-agonists or corticosteroids. 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 findings. 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. 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 been considered. 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. 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 over the course of the study. 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 and meta-analyses of randomised trials, which confirmed its superiority over placebo and leukotriene receptor antagonists. 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. 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 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). 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. As the latter study included children with interims 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. Only recently has this recommendation been withdrawn in the view of the lack of effectiveness reported by several randomized controlled trials. 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). 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
The discordance between the responsiveness to high-dose inhaled corticosteroids in preschool-aged children with viral-induced asthma, but not as step-up therapy in children and adults with multi-trigger asthma, underlines the importance of phenotype-specific treatment. Yet, for each phenotype and treatment, there is some degree of variability in the magnitude of response to ICS and LTRA in preschool-aged children whether with multi-trigger or viral-induced asthma.27 Considering the flat dose-response curve of corticosteroids, a good response should be expected with a low-dose of inhaled corticosteroids for children with multi-trigger asthma.28 In the face of a poor response, a trial of therapy with an alternate drug or step-up strategy with careful documentation of response is advised. On the other hand, the possibility that quadrupling, but not doubling, the daily dose of inhaled steroids may be effective for reducing the severity of exacerbations25 would further support the contention that viral infections induce a certain degree of “corticoreistance”, as they are the most frequent asthma triggers.29

Oral corticosteroids

The evidence-based management of acute asthma includes inhaled β₂-agonists for all patients, systemic (usual oral) corticosteroids for those with moderate and severe asthma or unsatisfactory response to inhaled β₂-agonists, and repeated doses of inhaled β₂-agonists and anticholinergics for severe exacerbations.1,6 The latter two recommendations independently reduce admission rates by 25% in studies of combining preschool- and school-aged children as well as adults.30,31 Of all treatments, oral corticosteroids are by far the most effective for preventing hospital admissions.

Of note, recommendations are severity-specific; patients with mild asthma do not appear to benefit from oral corticosteroids. The delay of action of oral corticosteroids of 3 to 4 hours, spearheaded the concept of the “golden first hour of treatment,” supporting early and aggressive asthma management.31 This explains the apparent ineffectiveness of clinical care pathways in which the early timing of corticosteroids was not stressed or applied. Although recommendations are relatively similar across age groups, the evidence for preschool-aged children is weaker due to their underrepresentation in relevant trials. (Figure 3).

Importantly, the accumulating evidence suggests heterogeneity in the magnitude of response to oral corticosteroids. Indeed, while most children and adults with moderate or severe acute asthma respond sufficiently well to be discharged within 5-6 hours of intake, a substantial proportion (36%) are admitted,31 presumably because of a delayed or poorer response to oral corticosteroids. Moreover, in a large placebo-controlled randomized controlled trial of 700 children aged 10-60 months with mild-to-moderate viral-induced wheezing, oral corticosteroid was not superior to placebo for reducing the length of stay in hospital or improving the Pediatric Respiratory Assessment Measure clinical score, despite adequate power.5 Critics have suggested that the absence of responsiveness to oral corticosteroids may due to: (1) a large proportion of children with bronchiolitis (with asthma documented in only 16% of children); (2) mild disease severity not requiring corticosteroids; (3) insufficient corticosteroids dosage (1 mg/kg of prednisolone) and (4) the prolonged stay in hospital perhaps not supported by severity.13 Yet, this study elicited a major discomfort regarding acute asthma management in young children, raising the possibility that preschool-age and/or viral triggers may be responsible for the poor apparent responsiveness.

Similar concerns could be raised in view of the non-response of children to home-administered oral corticosteroids. Indeed, a Cochrane review aggregated two trials testing parent-initiated oral corticosteroids vs. placebo in 303 children aged 1 to 18 years with
intermittent wheezing illness including asthma and “viral wheeze”. Oral corticosteroids failed to reduce hospital admissions, unscheduled medical reviews, symptoms scores, bronchodilator use, or days lost from work or school. In fact, in a subgroup analysis, preschoolers treated with prednisolone paradoxically experienced a higher rate of unscheduled medical visits compared to those receiving placebo. Although preschool age and perhaps viral trigger may again be cited as causal, the following hypotheses were also raised to explain the lack of efficacy of parent-initiated treatment in view of the efficacy of physician-initiated oral corticosteroids: (1) the lower severity of exacerbations managed at home compared to those leading to a physician visit and (2) the difficulty for parents of making an accurate assessment of severity and need for oral corticosteroid treatment in their child.

Although in all trials, study design or confounding issues were raised, the possibility that preschool-aged children with viral-induced phenotype may show decreased responsiveness to oral corticosteroids cannot be dismissed. The untangling of age vs. trigger(s) prompted us to examine potential determinants of responsiveness.

**POTENTIAL CLINICAL DETERMINANTS OF RESPONSE**

**Upper respiratory tract infections (URTIs)**

URTIs, usually viral in origin, are the most frequent (60-80%) triggers of asthma exacerbation in children of all ages. RSV, parainfluenza virus, and rhinovirus are frequently implicated in children under two years old, while picornavirus, coronavirus, and influenza are usually associated with asthma in older children. In adults with acute asthma, viral infection is associated with longer hospital admission and increased sputum neutrophils, suggesting that a predominantly neutrophilic airway inflammation may respond poorly to oral corticosteroids. In a study of children aged 3-36 months, those infected with rhinovirus showed fewer relapses when treated with oral prednisone compared to placebo, suggesting that rhinovirus did not impair responsiveness to corticosteroids. In a placebo-controlled trial of 283 young children with wheezing, prednisolone did not significantly decrease the overall time to discharge; however, it reduced by half the length of stay in children infected with picornavirus and by fourfold that of children with enterovirus, suggesting that response may be organism-dependent. Clearly, oral corticosteroids may not be as effective in patients with viral infections as in those without, perhaps due to neutrophilic airway inflammation, a condition associated with poor response to corticosteroids. Moreover, response may be organism-specific, a hypothesis that requires careful documentation of aetiology in future studies.

**Exposure to tobacco smoke**

In an adequately powered trial, a 2-week treatment with prednisone showed marked blunting of response in adult smokers, with an improvement in forced expiratory volume in 1 second of 237 mL (95% CI: 43, 431) in never-smokers compared to no significant change that is, 47 (-148, 243) mL in current smokers. A blunted response to inhaled corticosteroids was also documented in adult smokers in randomized controlled trials. While the mechanism behind the lack of response is not known, one can certainly point to smoking's direct toxicity, pro-inflammatory action, or interference with the transcription of genes associated with corticosteroid response. Indeed, smoking has frequently been associated with airway neutrophilia. In paediatrics, exposure to tobacco smoke has been associated with a higher incidence of URTIs and prevalence of asthma, and a greater severity of exacerbations. However, the impact on the therapeutic response has not been documented in children, as asthma trials have not examined or failed to report subgroup analyses on environmental tobacco smoke exposure or active smoking. Yet, heavier environmental tobacco smoke exposure in preschoolers who spend more time at home than school-aged children may explain a poorer response in young children. The questions to be addressed are whether smoking adolescents with a short smoking history and children with environmental tobacco exposure would respond as well to oral corticosteroids as those not exposed.

**Other determinants**

In addition to age, perceived asthma phenotype, alleged trigger(s), and tobacco smoke exposure, a number of other factors could possibly modulate the responsiveness to oral corticosteroids, including gender, race, and other environmental triggers.

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**Table: Relative Risk of Hospital Admission**

<table>
<thead>
<tr>
<th>Study</th>
<th>CS Events</th>
<th>Placebo Events</th>
<th>Relative Risk (Random) 95% CI</th>
<th>Weight %</th>
<th>Relative Risk (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connell 1994</td>
<td>622</td>
<td>655</td>
<td>0.75 (0.61, 0.92)</td>
<td>56.3</td>
<td>0.90 (0.72, 1.13)</td>
</tr>
<tr>
<td>Connell 1996</td>
<td>686</td>
<td>655</td>
<td>1.05 (0.87, 1.26)</td>
<td>39.1</td>
<td>0.90 (0.72, 1.13)</td>
</tr>
<tr>
<td>Scarnone 1983</td>
<td>111</td>
<td>104</td>
<td>1.08 (0.72, 1.61)</td>
<td>2.5</td>
<td>0.90 (0.72, 1.13)</td>
</tr>
<tr>
<td>Shir 1987</td>
<td>53/73</td>
<td>61/59</td>
<td>0.87 (0.56, 1.37)</td>
<td>15.7</td>
<td>0.90 (0.72, 1.13)</td>
</tr>
<tr>
<td>Tal 1990</td>
<td>47/67</td>
<td>47/67</td>
<td>1.00 (0.80, 1.28)</td>
<td>7.1</td>
<td>0.90 (0.72, 1.13)</td>
</tr>
<tr>
<td>Wolfson 1994</td>
<td>17/42</td>
<td>15/48</td>
<td>1.10 (0.69, 1.80)</td>
<td>0.7</td>
<td>0.90 (0.72, 1.13)</td>
</tr>
<tr>
<td><strong>Total (50% CI)</strong></td>
<td><strong>210</strong></td>
<td><strong>190</strong></td>
<td><strong>1.02 (0.90, 1.14)</strong></td>
<td><strong>50.3</strong></td>
<td><strong>1.00 (0.80, 1.28)</strong></td>
</tr>
</tbody>
</table>

**Figure 3.** The figure depicts the individual study and pooled odds ratio of patients who required hospital admission, comparing children with moderate or severe asthma (baseline forced expiratory volume in 1 second of <75% of predicted) who were vs. were not treated with systemic corticosteroids. Of note, the two trials by Connell et al. included children aged 18 months and over, those by Scarnone et al. and Shir and colleagues, children aged 1 to 17 years; the study by Tal et al., 6-60 months, and the trial by Wolfson and colleagues, children aged 4 to 18 years; the proportion of children aged 1-3 was not reported. For each study, the width of each horizontal line represents the 95% CI around the point estimate (black square). The size of the square representing the point estimate is proportional to the relative weight (% weight) of each trial in the pooled summary estimate (diamond). The vertical line is the line of no effect (Odds ratio = 1.0).
were shown to correlate with response to corticosteroids, with associations replicated in several cohorts.\textsuperscript{51–53} Identified polymorphisms are summarized in Table 1. Genotyping should be strongly considered in clinical therapeutic studies to advance our understanding of the heterogeneity of response to corticosteroids and importantly, to better characterize the phenotypes of responders and poor responders for the clinician.

**Potential Mechanistic Pathways Modulating Responsiveness to Corticosteroids**

Two promising mechanistic pathways may explain variations in the magnitude of response to oral corticosteroids, namely (1) gene polymorphisms that may reveal potential gene-environment interactions and (2) the type of airway inflammation.

**Gene Polymorphisms**

There is increasing evidence that inherited genes are not a deterministic genotype, but rather a genotype that encodes a potential range of phenotypes that will develop in response to a variety of environmental triggers. Consequently, variations in genes that modulate response to corticosteroids may predispose some people to environmentally-induced problems, such as smoke- or viral-induced asthma. Two major groups of genes are of interest: (1) those affecting susceptibility to asthma and specific phenotypes and (2) those directly interfering with response to corticosteroids by coding for major components of the pathway involved in corticosteroid action (Table 1). In the first group, 8 key polymorphisms in 7 genes have been identified; they can be divided into those coding for xenobiotic metabolizing enzymes and those coding for mediators of inflammation and immunity, specifically the ones demonstrated to affect lung function, disease severity and interaction with exposure to environmental tobacco smoke.\textsuperscript{43} The selected polymorphisms affect gene function with top-ranking single nucleotide polymorphisms in a number of association studies. TGFBI polymorphisms were found to correlate with disease severity;\textsuperscript{44} CC16 polymorphisms play a role in the development and persistence of the asthma phenotype in childhood;\textsuperscript{45} CD14 polymorphisms have been linked to pathogenesis of asthma and lung function in smokers.\textsuperscript{46} The ORMDL3 gene confers susceptibility to early-onset asthma, particularly through interaction with early life exposure to environmental tobacco smoke;\textsuperscript{47} GSTM1 null and GSTP1 genotypes have been associated with an increased risk of asthma\textsuperscript{48} and rapid decline of lung function among smokers.\textsuperscript{49} The ADRB2 receptor gene was found to contribute to the occurrence of wheeze among children who were exposed to tobacco smoke in utero and early childhood.\textsuperscript{50}

In the second group of genes, that is, those affecting the corticosteroid pathway, three genes (CHRH1, TBX21 and FCER2)
SUMMARY

Marked heterogeneity in responsiveness to corticosteroids has been observed, whether inhaled corticosteroids as daily controller therapy, pre-empptive therapy with inhaled and oral corticosteroids at onset of flare-ups, and systemic corticosteroids in the emergency management of children with acute asthma are considered. There is increasing evidence that, in contrast to those with allergic or multi-trigger asthma, preschool-aged children with viral-induced asthma may display a certain degree of corticosteroid resistance, requiring higher doses of corticosteroids to overcome it. Other than design and confounding issues including mixed diagnoses, heterogeneous phenotypes and mild severity, other determinants of responsiveness may include age, trigger, tobacco smoke exposure, and genetic make-up. The mechanistic pathway for “corticoresistance” may originate from an interaction between genetic and environment, leading to non-eosinophilic or mixed eosinophilic/neutrophilic inflammation. Maintenance low-dose inhaled corticosteroids remain the cornerstone of the management of multi-trigger asthma of any age, while they show no evidence of effectiveness in children with viral-induced asthma. If a trial of daily montelukast is insufficient to control episodes, episodic high-dose inhaled corticosteroids with careful monitoring of medication use and growth may be considered for viral-induced asthma. Phenotype-specific treatment of children with asthma should be the focus of future research endeavours.

CONFLICT OF INTEREST

Francine M. Ducharme has received research funds, travel support, fees for speaking and/or consulting fees from GlaxoSmithKline, Merck Frosst Inc, Merck Canada, Novartis, and Nycomed.

PRACTICE POINTS

- Confirm the diagnosis of asthma and ascertain the phenotype.
- For young children with viral-induced asthma,
  - Nasal hygiene and inhaled β2-agonists is the mainstay of pre-emptive management of episodes.
  - Daily preventative controller medication use with low dose inhaled corticosteroids are not recommended.
- A trial of montelukast may be considered, although it has not been shown to reduce rescue oral corticosteroids.
- Pre-emptive high-dose inhaled corticosteroids could be considered in children whose episodes remain poorly controlled, with 2 or more episodes requiring rescue oral steroids and/or admission in the preceding 12 months and should be administered with careful monitoring of medication use and growth.
- Pre-emptive oral corticosteroids have not been proven effective.
- For multi-trigger asthma,
  - Daily preventative controller medication use with low dose inhaled corticosteroids is the cornerstone of the treatment; it is and the most effective means to prevent and alleviate the severity of episodes.
  - Nasal hygiene and inhaled β2-agonists should be added as needed during episodes.
  - Dose-doubling of inhaled corticosteroids is not recommended.
- Pre-emptive oral corticosteroids have not been proven effective.

RESEARCH DIRECTIONS

- Examine whether the following factors are determinant of responsiveness to oral and inhaled corticosteroids: Age, gender, race, asthma phenotype, asthma trigger, presence and etiology of viral respiratory infection, and tobacco smoke exposure.
- Develop clinical tools to assist in correctly identifying the phenotype and key determinants of responsiveness.
- Confirm that the type and amount of airway inflammation modulates the response to corticosteroids in children with asthma.
- Identify genotype linked to the viral-induced phenotype.
- Test the hypothesis that gene-environmental interaction modulates the response to corticosteroids in children with asthma.
- Conduct intervention trials, focused on a specific phenotype or stratified on phenotype to explore phenotype-specific response to therapy.

References


42. Wark PA, Gibson GS, Johnston SL. Exacerbations of asthma: addressing the triggers and treatments. Monaldi Arch Chest Dis 2001;56:429–35.


