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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

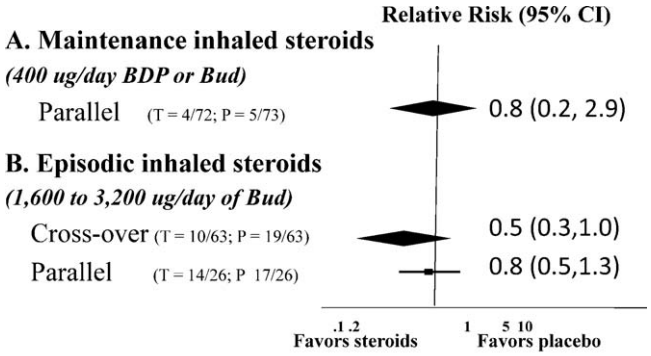

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Figure 1. The figure depicts the pooled relative risk of patients experiencing one or more exacerbation requiring rescue systemic glucocorticoids (1 count per patient) comparing in (A) maintenance inhaled steroids compared to placebo and in (B) episodic 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

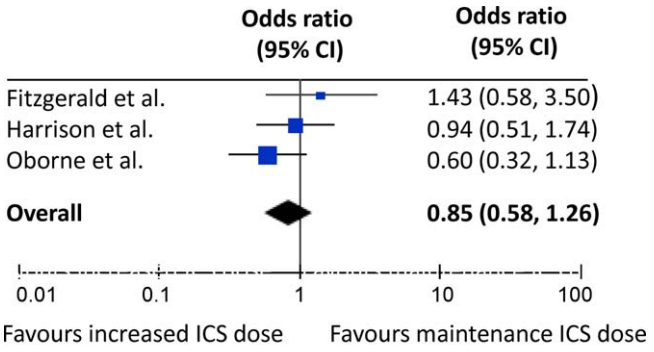

Figure 2. The figure depicts the individual and pooled odds ratio of patients experiencing 1 or more exacerbation requiring rescue systemic glucocorticoids (1 count per patient) comparing doubling (Fitzgerald et al. and Harrison et al.) or quadrupling (Oborne et al.) the dose of inhaled corticosteroids vs. maintaining the usual dose, at the onset of exacerbations. 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). The analysis was conducted by intention-to-treat in all randomised patients.

trend towards a 50% reduction in the rate of rescue oral corticosteroids, with improved symptoms and parent preference.[3] (Figure 1B) The efficacy of the approach was recently confirmed in a recent trial where the initiation of high-dose fluticasone (1500 μg/day) at the onset of an exacerbation was associated with a 50% reduction in the need for rescue oral corticosteroids and a 20% reduction in other markers of severity and duration of exacerbations.[4] While clearly effective this strategy was associated with a small but significant reduction in growth.

Leukotriene receptor antagonists

In terms of alternate treatment, the Pre-empt trial suggested modest effect of intermittent montelukast over placebo. The parallel-group placebo-controlled trial involved 220 children aged 2 to 14 years of age with physician-diagnosed intermittent asthma and who, between episodes, were asymptomatic with no asthma medications. Intermittent montelukast was associated with a 28.5% reduction in health care utilisation, modest reductions in symptoms, school and parent-work absenteeism, but no group difference in the use of rescue oral corticosteroids or rescue inhaled β2-agonists. Admittedly, a substantial proportion of children was older than 3 years and may have had unrecognised persistent asthma.

The only available head-to-head comparison study of intermittent budesonide, intermittent montelukast and placebo by Bacharier and colleagues[26] suggests no important group difference in preschool-aged children with viral-induced asthma. The study compared 1 mg twice daily of nebulized budesonide, 4 mg of montelukast and placebo in 238 children aged to 1 to 4 years with moderate to severe intermittent wheezing associated with upper respiratory tract infections and minor symptoms between episodes.[26] There was no group difference in episode-free days, health care use, quality of life or growth, but a non-significant trend towards less use of rescue oral steroids in children treated with high dose budesonide (38.5%) compared to those on montelukast (46.8%) or placebo (55.3%), p = 0.15, suggesting the possibility of insufficient power. An update of the Cochrane review is in progress to aggregate these additional trials and should confirm the effectiveness of high-dose inhaled corticosteroids in preschool-aged children with viral-induced asthma.

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 exacerbations[25] would further support the contention that viral infections induce a certain degree of "corticoresistance", as they are the most frequent asthma triggers.[29]

Oral corticosteroids

The evidence-based management of acute asthma includes inhaled ß$_2$-agonists for all patients, systemic (usually oral) corticosteroids for those with moderate and severe asthma or unsatisfactory response to inhaled ß$_2$-agonists, and repeated doses of inhaled β$_2$-agonists and anticholinergics for severe exacerbation.[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.[2] 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 requring 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

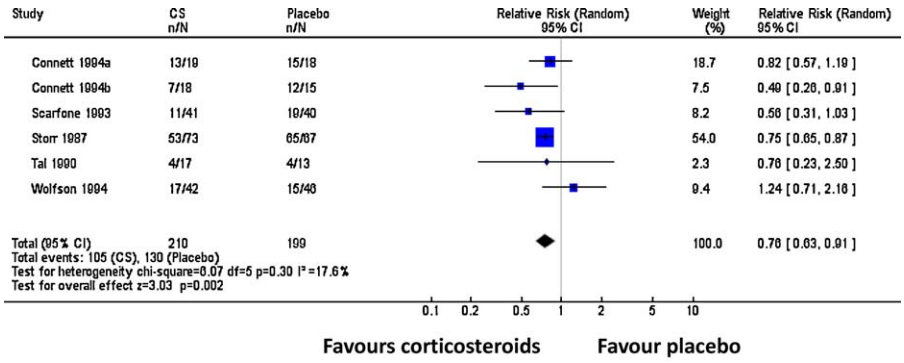

Figure 3. The figure depicts the individual study and pooled odds ratio of patients who required hospital admission, comparing children with moderate or severe asthma (baseline forced expiratory volume in 1 second of <75% of predicted) who were vs. were not treated with systemic corticosteroids. Of note, the two trials by Connett et al. included children aged 18 months and over, those by Scarfone et al. and Storr 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).

intermittent wheezing illness including asthma and "viral wheeze".[32] 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 (URTI)

URTIs, usually viral in origin, are the most frequent (60-80%) triggers of asthma exacerbation in children of all ages.[33] 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.[34] In adults with acute asthma, viral infection is associated with longer hospital admission[35] 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.[36] 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-dependant.[37] 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.[38] A blunted response to inhaled corticosteroids was also documented in adult smokers in randomized controlled trials.[39] 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.[38] 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.[40] 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[41] 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,[7] alleged trigger(s),[42] and tobacco smoke exposure, a number of other factors could possibly modulate the responsiveness to oral corticosteroids, including gender, race, and other environmental triggers.

Table 1
Summary of polymorphisms in subset of candidate genes of relevance for asthma phenotype and corticosteroid response

Gene		Location	Position/ SNP Annotation	Reference
TGFB1[1]	Transforming growth factor-beta	Promoter	C-509T	*Grainger DJ, Hum Mol Genet, 1999; Silverman, Am J Respir Crit Care Med, 2004*
		Coding	T869C	*Li H, Hum Genet, 2007; Sharma S, Am J Respir Crit Care Med, 2009*
CD14[1]	Monocyte differentiation antigen CD14	Promoter	C-159T	*Zhou H, Respir Med, 2009*
CC16[1]	Clara cell 16 kDa secretory protein	5'UTR	A38G	*Laing IA, Clin Exp Allergy, 2009*
ADRB2[1]	Beta-2-adrenergic receptor	Coding	Arg16Gly	*Wang C, Pediatrics, 2008*
GSTM1[1]	Glutathione S-transferase M1	Gene deletion	GSTM1 null genotype	*Tamer L, Respirology, 2004; Kamada F, Int Arch Allergy Immunol, 2007*
GSTP1[1]	Glutathione S-transferase P1	Coding	Ile105Val	*HE JQ, Am J Respir Crit Care Med, 2002*
ORMDL3[1]	Orosomucoid 1-like 3 (Orm1-like protein 3)	Intronic	A/C	*Bouzigon E, NEJM, 2008*
CRHR1[2]	Corticotropin-releasing hormone receptor 1	Intronic	A/G	*Tantisira KG, Hum Mol Genet, 2004*
TBX21[2]	T-box 21	Coding	H33Q	*Tantisira KG, Proc Natl Acad Sci U S A, 2004*
		Promoter	T-1514C G-999A T-1993C	*Suttner K, J Allergy Clin Immunol, 2009*
FCER2[2]	Fc fragment of IgE, low affinity II, receptor for (CD23)	Intronic	T2206C	*Tantisira KG, J Allergy Clin Immunol, 2007*

[1]Relevance for asthma phenotype
[2]Relevance for corticosteroid response

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.[43] The selected polymorphisms affect gene function with top-ranking single nucleotide polymorphisms in a number of association studies. *TGFB1* polymorphisms were found to correlate with disease severity;[44] *CC16* polymorphisms play a role in the development and persistence of the asthma phenotype in childhood;[45] *CD14* polymorphisms have been linked to pathogenesis of asthma and lung function in smokers.[46] The *ORMDL3* gene confers susceptibility to early-onset asthma, particularly through interaction with early life exposure to environmental tobacco smoke;[43,47] *GSTM1* null and *GSTP1* genotypes have been associated with an increased risk of asthma[48] and rapid decline of lung function among smokers.[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.[50]

In the second group of genes, that is, those affecting the corticosteroid pathway, three genes (*CHRH1*, *TBX21* and *FCER2*) were shown to correlate with response to corticosteroids, with associations replicated in several cohorts.[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.

Airway inflammation

There is increasing evidence that eosinophilic asthma is more responsive to corticosteroids than non-eosinophilic asthma. Using induced sputum, three distinct inflammatory cell patterns have been reported during paediatric exacerbations: non-eosinophilic (<2.5% eosinophils) in 22%; eosinophilic (≥2.5% eosinophils) in 43%; and combined eosinophilic/neutrophilic (≥2.5% eosinophils and >54% neutrophils) in 35% of children. Contrary to adult findings and criteria, paucigranular inflammation has not been described in acute paediatric athma.[54] A higher proportion of sputum neutrophils is associated with smoking[38] and with viral infection.[35,55] This non-eosinophilic inflammatory phenotype in adults has been associated with poor response to corticosteroids.[56] In contrast, sputum eosinophils and eosinophil cationic protein increase with exposure to allergens and decrease with corticosteroid treatment, suggesting good response of eosinophilic inflammation to corticosteroids.

Recognizing that most exacerbations in children and adults are caused by viral infections,[29,33] the relative "corticoresistance" of neutrophilic inflammation associated with URTIs would explain both the ineffectiveness of dose-doubling of inhaled corticosteroids and the potential effectiveness of dose-quadrupling at the onset of exacerbations.[25] It would also explain the efficacy of short courses of high-dose fluticasone at the onset of URTIs to decrease the severity and duration of exacerbations, in preschool-aged children who were carefully selected for viral-induced asthma phenotype,[4] a finding supported by a prior Cochrane review.[3]

In other words, there is increasing evidence that gene-environmental interaction influences the type and amount of airway inflammation, which in turn modulates the response to corticosteroids in children with asthma. An ongoing cohort study is testing this hypothesis in acute paediatric asthma and, importantly, exploring clinical characteristics and promising markers of poor response.

SUMMARY

Marked heterogeneity in responsiveness to corticosteroids has been observed, whether inhaled corticosteroids as daily controller therapy, pre-emptive 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 preventive 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 preventive 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

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention Global Initiative for Asthma. [updated 2009 December 1; cited 2011 Jan 3]. Available from: http://www.ginasthma.org.
2. Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;**360**:329–38.
3. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database System Rev* 2000;**2**. CD001107.
4. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;**360**:339–53.
5. Global strategy for asthma management and prevention. Global Initiative for Asthma (GINA). [updated 2008; cited 2009 Jul 3]. Available from: http://www.ginasthma.org.
6. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guidelines on the management of asthma - A national clinical guideline British Thoracic Society. [updated 2009; cited 2011 Jan 3]. Available from: http://www.brit-thoracic.org.uk/clinical-information/asthma/asthma-guidelines.aspx.
7. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;**63**:5–34.
8. Myers TR. Pediatric asthma epidemiology: incidence, morbidity, and mortality. *Respir Care Clin N Am* 2000;**6**:1–14.
9. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *New Engl J Med* 1995;**332**:133–8.
10. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics* 2006;**118**:1774-93.
11. Corneli HM, Zorc JJ, Mahajan P, Shaw KN, Holubkov R, Reeves SD, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007;**357**:331–9.
12. Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R, et al. Epinephrine and dexamethasone in children with bronchiolitis.[see comment]. *New Engl J Med* 2009;**360**:2079–89.
13. Ducharme FM, Zemek RL, Schuh S. Oral corticosteroids in children with wheezing. *N Engl J Med* 2009;**360**:1674.
14. Brand PLP, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;**32**:1096–110.
15. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. *Lancet* 2003;**361**:1071–6.
16. Ducharme FM, Di Salvio F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database System Rev* 2004. CD002314.
17. Adams NP, Bestall JC, Jones PW, Lasserson TJ, Griffiths B, Cates C. Inhaled fluticasone at different doses for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005. CD003534.
18. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *New Engl J Med* 2006;**354**:1985–97.
19. Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995;**72**:317–20.

20. Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;**171**:315–22.
21. National Heart Lung and Blood Institute. Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. Bethesda, MD: NIH; 2002. Report No.: NIH publication No 02-3659.
22. Lemiere C, Bai T, Baltzan M, Bayliff C, Becker A, Boulet LP, et al., On behalf of the Canadian Asthma Consensus Group of the Canadian Thoracic Society. Adult Asthma Consensus Guidelines Update 2003. *Can Respir J* 2004;**11**:9a–18a.
23. Bousquet J, Clark TJ, Hurd S, Khaltaev N, Lenfant C, O'Byrne P, et al. GINA guidelines on asthma and beyond. *Allergy* 2007;**62**:102–12.
24. Lougheed MD, Lemiere C, Dell SD, Ducharme FM, Fitzgerald JM, Leigh R, et al. Canadian Thoracic Society Asthma Management Continuum - 2010 Consensus Summary for children six years of age and over, and adults. *Can Respir J* 2010; **17**:15–24.
25. Quon BS, Fitzgerald JM, Lemiere C, Shahidi N, Ducharme FM. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. [Review]. *Cochrane Database of Systematic Reviews (10):CD007524, 2010* 2010;CD007524.
26. Bacharier LB, Phillips BR, Zeiger RS, Szefler SJ, Martinez FD, Lemanske Jr RF, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;**122**:1127–35.
27. Bacharier LB, Guilbert TW, Zeiger RS, Strunk RC, Morgan WJ, Lemanske Jr RF, et al. Patient characteristics associated with improved outcomes with use of an inhaled corticosteroid in preschool children at risk for asthma. *J Allergy Clin Immunol* 2010;**123**:1077–82.
28. Zhang L, Axelsson I, Chung M, Lau J. Dose Response of Inhaled Corticosteroids in Children With Persistent Asthma: A Systematic Review. *Pediatrics* 2011;**127**: 129–38.
29. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *Brit Med J* 1995;**310**:1225–9.
30. Plotnick L, Ducharme FM. Should inhaled anticholinergics be added to beta2-agonists in acute pediatric asthma? A systematic review of randomized controlled trials. *British Medical Journal* 1998;**317**:971–7.
31. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001;**1**:CD002178.
32. Vuillermin P, South M, Robertson C. Parent-initiated oral corticosteroid therapy for intermittent wheezing illnesses in children. *Cochrane Database Syst Rev* 2006;**3**:CD005311.
33. Johnston SL, Pattemore PK, Sanderson G, Smith S, Campbell MJ, Josephs LK, et al. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am J Respir Crit Care Med* 1996;**154**. t-60.
34. Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005;**24**:S217–22.
35. Wark PA, Johnston SL, Moric I, Simpson JL, Hensley MJ, Gibson PG. Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. *Eur Respir J* 2002;**19**:68–75.
36. Jartti T, Lehtinen P, Vanto T, Hartiala J, Vuorinen T, Makela MJ, et al. Evaluation of the Efficacy of Prednisolone in Early Wheezing Induced by Rhinovirus or Respiratory Syncytial Virus. [Article]. *Pediatr Infect Dis J* 2006;**25**:482–8.
37. Jartti T, Lehtinen P, Vanto T, Vuorinen T, Hartiala J, Hiekkanen H, et al. Efficacy of prednisolone in children hospitalized for recurrent wheezing. *Pediatr Allergy Immunol* 2007;**18**:326–34.
38. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma.[see comment]. *Am J Respir Crit Care Med* 2003;**168**:1308–11.
39. Chalmers GW, MacLeod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;**57**:226–30.
40. Chilmonczyk BA, Salmun LM, Megathlin KN, Neveux LM, Palomaki GE, Knight GJ, et al. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children [see comments]. *New Engl J Med* 1993;**328**:1665–9.
41. Chang MY, Hogan AD, Rakes GP, Ingram JM, Hoover GE, PlattsMills TA, et al. Salivary cotinine levels in children presenting with wheezing to an emergency department. *Pediatr Pulmonol* 2000;**29**:257–63.
42. Wark PA, Gibson PG, Johnston SL. Exacerbations of asthma: addressing the triggers and treatments. *Monaldi Arch Chest Dis* 2001;**56**:429–35.
43. Bouzigon E, Corda E, Aschard H, Dizier MH, Boland A, Bousquet J, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma.[see comment]. *New Engl J Med* 2008;**359**:1985–94.
44. Sharma S, Raby BA, Hunninghake GM, Soto-Quiros M, Avila L, Murphy AJ, et al. Variants in TGFB1, dust mite exposure, and disease severity in children with asthma. *Am J Respir Crit Care Med* 2009;**179**:356–62.
45. Laing IA, de Klerk NH, Turner SW, Judge PK, Hayden CM, Landau LI, et al. Cross-sectional and longitudinal association of the secretoglobin 1A1 gene A38G polymorphism with asthma phenotype in the Perth Infant Asthma Follow-up cohort. *Clin Exp Allergy* 2009;**39**:62–71.
46. Zhou H, Alexis N, Almond M, Donohue J, LaForce C, Bromberg P, et al. Influence of C-159T SNP of the CD14 gene promoter on lung function in smokers. *Respir Med* 2009;**103**:1358–65.
47. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;**448**:470–3.
48. Tamer L, Calikoglu M, Ates NA, Yildirim H, Ercan B, Saritas E, et al. Glutathione-S-transferase gene polymorphisms (GSTT1, GSTM1, GSTP1) as increased risk factors for asthma. *Respirology* 2004;**9**:493–8.
49. He JQ, Ruan J, Connett JE, Anthonisen NR, Pare PD, Sandford AJ. Antioxidant gene polymorphisms and susceptibility to a rapid decline in lung function in smokers. *Am J Respir Crit Care Med* 2002;**166**:323–8.
50. Wang C, Salam MT, Islam T, Wenten M, Gauderman WJ, Gilliland FD. Effects of in utero and childhood tobacco smoke exposure and beta2-adrenergic receptor genotype on childhood asthma and wheezing. *Pediatrics* 2008;**122**:e107–14.
51. Tantisira KG, Lake S, Silverman ES, Palmer LJ, Lazarus R, Silverman EK, et al. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. *Human Molecular Genetics* 2004;**13**:1353–9.
52. Tantisira KG, Hwang ES, Raby BA, Silverman ES, Lake SL, Richter BG, et al. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. *Proceedings of the National Academy of Sciences of the United States of America* 2004;**101**:18099–104.
53. Tantisira KG, Silverman ES, Mariani TJ, Xu J, Richter BG, Klanderman BJ, et al. FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma. *J Allergy Clin Immunol* 2007;**120**:1285–91.
54. Gibson PG, Norzila MZ, Fakes K, Simpson J, Henry RL. Pattern of airway inflammation and its determinants in children with acute severe asthma. *Pediatr Pulmonol* 1999;**28**:261–70.
55. Pizzichini MM, Pizzichini E, Efthimiadis A, Chauhan AJ, Johnston SL, Hussack P, et al. Asthma and natural colds. Inflammatory indices in induced sputum: a feasibility study. *Am J Respir Crit Care Med* 1998;**158**:1178–84.
56. Pavord ID, Shaw DE, Gibson PG, Taylor DR. Inflammometry to assess airway diseases. *Lancet* 2008;**372**:1017–9.