

Asthma 2



Diagnosis, management, and prognosis of preschool wheeze

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Preschool children (ie, those aged 5 years or younger) with wheeze consume a disproportionately high amount of health-care resources compared with older children and adults with wheeze or asthma, representing a diagnostic challenge. Although several phenotype classifications have been described, none have been validated to identify individuals responding to specific therapeutic approaches. Several risk factors related to genetic, prenatal, and postnatal environment are associated with preschool wheezing. Findings from several cohort studies have shown that preschool children with wheeze have deficits in lung function at 6 years of age that persisted until early and middle adulthood, suggesting increased susceptibility in the first years of life that might lead to persistent sequelae. Daily inhaled corticosteroids seem to be the most effective therapy for recurrent wheezing in trials of children with interim symptoms or atopy; intermittent high-dose inhaled corticosteroids are effective in moderate-to-severe viral-induced wheezing without interim symptoms. The role of leukotriene receptor antagonist is less clear. Interventions to modify the short-term and long-term outcomes of preschool wheeze should be a research priority.

Burden of preschool asthma and wheeze

Preschool children (ie, those aged 5 years or younger) have higher asthma morbidity than do any other age group, with 48% of preschool children with asthma reporting an asthma attack in the preceding year.¹ The annual rate of emergency department visits is 23–42 per 1000 for preschool children with asthma, compared with less than 15 per 1000 for those aged 6–70 years.² The same pattern exists for the rate of hospital admissions.^{2,3} In developing countries, wheeze and asthma in preschool children can be falsely diagnosed as pneumonia and undertreated because definitions of these disorders overlap, leading to increased morbidity and mortality in this age group.⁴ Thus, the worldwide economic burden of poor asthma control in preschool children is very important.⁵ Preschool wheeze is also highly prevalent; about a third of children aged 1–6 years in Europe and the USA have wheezed in the preceding 6 months,⁶ and almost 50% of children report at least one episode of wheeze in the first 6 years of life.⁷ This finding concords with a reported prevalence of preschool wheeze of 22% among Canadian children aged 0–5 years.¹

Diagnostic challenge

Wheezing is not a disorder; it is a symptom manifested by a continuous whistling sound occurring during breathing that suggests narrowing or obstruction in some part of the respiratory airways. The diagnosis and management of wheeze in preschool children is challenging because this symptom can be associated with many diseases and, unless the disorder has been accurately identified, its management is as elusive and imprecise (because of misclassification) as the management of abdominal pain or fatigue. It is thus essential to identify the correct diagnosis behind this symptom, a substantial challenge in preschool children.

The two most frequent causes of wheezing in young children are clearly bronchiolitis and asthma, but

diagnosis of these disorders has been fraught with difficulties, resulting in many children being labelled as so-called wheezers for lack of a precise diagnosis. Less frequent causes of wheezing include congenital anatomical abnormalities, foreign body aspiration, other pulmonary disorders (eg, cystic fibrosis), and cardiac, immune, and gastrointestinal disorders; these possibilities should be considered, particularly in atypical cases or in patients who do not respond to therapy.

Bronchiolitis is the most common acute viral infection of the lower respiratory tract in the first year of life.⁸ Similar to asthma, its peak incidence is in autumn and winter. 10% of children are affected in the first year of life, and 90% have been affected by the age of 2 years.⁹ Respiratory syncytial virus is the most frequent cause, with several other viruses implicated. Although bronchiolitis is generally benign, 10% of affected children need admission to hospital, with an overall mortality rate of 0.2–0.5%.⁸ Bronchiolitis is usually defined as the first episode of wheezing (in the USA and Canada) or

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This is the second in a *Series* of two papers about asthma

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Search strategy and selection criteria

We searched MEDLINE, Current Contents, PubMed, and the Cochrane Library with the keywords “wheeze* or asthm*” and “preschool* or pre-school*” and one of the following: “cohort*”, “randomised or randomized or randomly or trial”, “risk factors”, “remission or recurrence”, “(steroid* or corticosteroid) and (inhal*)”, “leukotriene* or leukotriene* or anti-leukotriene or antileukotriene or montelukast”. Because 2167 trials about preschool wheeze have been published in French or English between January, 1980, and January, 2014, we did a non-systematic review of these articles, giving priority to systematic reviews, randomised controlled trials, larger studies, and articles published in high-quality journals. Two authors independently extracted data for the meta-analysis.

respiratory crackles (in the UK) with clinical evidence of viral infection (eg, coryza or fever) in a child younger than 12–24 months.^{10,11} Infection of bronchioles leads to airway oedema, inflammation, mucus plugging, bronchospasm, and necrosis, all of which contribute to airway obstruction.¹⁰ Bronchiolitis responds poorly to bronchodilators,¹² epinephrine,¹³ humidified oxygen,¹⁴ anticholinergics,¹⁵ and corticosteroids.¹⁶ It can respond better to hypertonic saline nebulisation¹⁷ and a combination of therapies targeting the various pathophysiological mechanisms.¹⁸ By contrast, asthma in preschool children responds well to bronchodilators¹⁹ and inhaled corticosteroids.²⁰ So, why is diagnosis of the underlying disorder presenting as wheezing in preschool children so difficult?

Part of the answer is that bronchiolitis is frequently the first of a series of wheezing illnesses in children who will subsequently be diagnosed with asthma; this sequence has alimented the debate as to whether bronchiolitis uncovers a predisposition or causes the development of asthma.²¹ Another reason might stem from the old belief that asthma does not exist in preschool children, perhaps because many preschool children who wheezed no longer had symptoms by the age of 6 years,⁷ or because confirmatory lung-function testing is traditionally available only by 6 years of age. In school-aged children (aged ≥ 6 years) and adults, the diagnosis of asthma is supported by objective documentation of at least partly reversible obstruction and airway hyper-responsiveness, usually by spirometry.^{22–25} Important advances have been made in lung function tests in preschool children, but their use remains restricted to specialised paediatric laboratories.²⁶ Thus, in absence of lung-function testing, the diagnosis of asthma in younger children is usually based on a series of clinical criteria (symptom pattern, family history, and physical findings) and the absence of an alternative diagnosis.^{22,24,25,27,28} Between bronchiolitis and asthma lay many children who seemingly fall, at least for a period, between the two entities, for example, those with a first episode of wheezing illness after 12 months of age that is unresponsive to asthma therapy; in view of these diagnostic dilemmas, some task forces even hesitate to recommend to make a diagnosis of asthma in young children.²⁸

Phenotypes of wheeze

In the past 15 years, many efforts have been devoted to prediction of the risk of ongoing asthma at school age throughout cohort studies to identify different phenotypes of wheezing in preschool children in which to test different management strategies and perhaps offer early therapy. One of the first classifications (early persistent, late-onset, and transient wheezing), proposed in 1999 by Martinez and colleagues,⁷ described the association between the age of onset of wheezing and the outcome (remission or persistence) at 6 years of age based on the

Tucson birth cohort study. Since then, several studies have replicated these phenotypes,²⁹ some with slight variations based on the time of onset of wheeze,^{30,31} but all are based on the longitudinal trajectory of wheeze. The prognostic value and the differential risk factors associated with individual wheeze trajectory are also well documented, suggesting a different pathogenesis for distinct trajectories. For example, children with persistent wheeze have substantially worse lung function at age 3 years²⁹ and higher airway resistance at age 4 years³² than do children with intermittent wheeze, whereas atopy has been associated with persistent,³³ late-onset,³⁴ and intermediate-onset wheeze,³¹ a subphenotype between early-onset and late-onset wheeze. Furthermore, studies have documented differential associations between these wheeze phenotypes and genetic variants in the 17q21 locus, the most consistently replicated region for its association with childhood asthma.^{35,36} Specifically, variants in this region are strongly associated with persistent wheeze, with little evidence of association with other wheeze phenotypes.³⁷ Another study³⁸ documented an association between 17q21 genetic variants and the risk of asthma after 6 years of age, but only among children with a wheezing illness related to human rhinovirus in early childhood, suggesting a gene-by-environment interaction for asthma.

Although the classification based on longitudinal symptomatology is epidemiologically useful, it has little clinical value because no good biomarkers or predictors are available that allow the prospective prediction of which trajectory a child with wheeze will follow. Thus, several studies have used hypothesis-free analytical approaches using baseline characteristics, lung function, airway responsiveness, and atopy to identify distinct phenotypes.^{39,40} Although these phenotype classifications are attractive because they are based on patient characteristics that are available at baseline, they have not been validated prospectively. Since 2008, other phenotypical classifications proposed by international paediatric groups (eg, the European Respiratory Society and PRACTALL), based on the temporality of symptoms (episodic or persistent) and asthma triggers (viral only, allergens, exercise, or multitrigger), have been recommended to better support therapeutic decisions.^{28,41} These classifications have been widely used in recent therapeutic trials. Yet, even in tertiary care paediatric settings, the use of such classifications has been limited by substantial between-physician and (importantly) inpatient variations in phenotype over time, such that the phenotype can change in up to 55% of children.^{42,43}

Using the Tucson birth cohort, the asthma predictive index (API) was developed by Castro-Rodríguez and colleagues,⁴⁴ using the age at onset of wheezing, frequency of wheezing, parental history of asthma, wheezing without colds, eczema, allergic rhinitis, and eosinophilia in an attempt to better predict outcome at 6 years of age using a loose and a stringent index.⁴⁴ Children aged 3 years

or younger with few risk factors for ongoing asthma symptoms by school age (negative API) were frequently referred to as having transient wheezing, whereas those with a positive API were labelled as having persistent asthma. Subsequently, other predictive indices were derived from other birth cohorts (eg, the Avon Longitudinal Study of Parents and Children [ALSPAC] and the Dutch Prevention and Incidence of Asthma and Mite Allergy [PIAMA])³⁰ and aimed to predict whether the child will meet the definition of asthma aged 6–10 years.^{45,46} Although these so-called asthma predictive scores have substantially shaped the classification of wheezing phenotypes and improved understanding of the epidemiology of preschool wheezing, they have five main limitations regarding the therapeutic approach of wheeze in preschool children: their positive predictive values and sensitivities were quite low, particularly in children with repeated wheeze;^{47,48} independent validation of these indices in different populations from those in which they were derived has not been published;^{47,49} although often used to stratify or select patients in therapeutic trials, there is controversial evidence as to whether children with positive and negative asthma predictive scores respond differently to therapeutic approaches;^{50,51} although not necessarily promoted as such, children perceived at low risk of ongoing asthma by school age are often believed to deserve less preventive therapy, whereas those at higher risk are recommended more intensive therapy, an assumption that has not been verified; and importantly, there is accumulating evidence suggesting that the disappearance of symptoms might not correlate with the absence of sequelae.⁵²

In summary, several classifications of wheeze phenotypes have been proposed so far, each with its limitations. Although imperfect and offered as prediction methods, the asthma predictive scores curiously became intimately related, not only to the phenotypes, but also to the diagnostic criteria of preschool asthma.²⁷ We believe that it is crucial to dissociate current diagnosis from the prediction of remission. Aligned with the definition in school-aged children and adults, the diagnosis of asthma can be made clinically and whenever possible, using non-invasive lung-function tests in preschool children.²⁶ Diagnostic criteria remains the finding of reversible variable airway obstruction that can be confirmed by a therapeutic trial with inhaled bronchodilators or corticosteroids as suggested by the Global Initiative for Asthma.²² In view of the heterogeneity of preschool wheezing, the most important advances in diagnosis should be made with the use of objective tools, whether existing or to be developed, to document airway obstruction and reversibility by measurement of airway calliper (lung function),²⁶ and to ascertain the type and amount of airway inflammation (eg, with non-invasive inflammatory markers, including metabolomics)⁵³ applicable to young children. Similarly, these tools should be applied to ascertain phenotypes associated with

different therapeutic responses and prognosis,²⁹ and overcome the documented inpatient variability reported over time.^{42,43} These aims should be research priorities.

The goal of this Series paper is to assess the preventable risk factors, evidence for present therapeutic approaches, and long-term prognosis of children with preschool wheeze and asthma. All phenotypes of preschool wheeze and asthma are considered in this Series paper, but wheeze arising from bronchiolitis and other comorbid conditions (eg, cardiac disorders, anatomical malformations, or other pulmonary diseases) are specifically excluded.

Risk factors for early wheeze

Genetic influences and prenatal environment

The heterogeneity of preschool wheeze is defined by unique interactions between the child's genetic makeup and prenatal and postnatal environmental factors. Indeed, there is increasing evidence that genes encode a potential range of phenotypes that can develop in response to many environmental triggers. Recent advances in technology have identified several common genetic variants associated with asthma⁵⁴ through genome-wide association studies or candidate-gene analyses. However, most of these variants have not been replicated in other studies. One exception is the 17q21 locus, containing the *ORMDL3* and *GSDMB* genes, which is the most consistently replicated genetic risk factor for childhood asthma.^{35,36} Recent studies have documented a larger effect of this locus among children exposed to environmental tobacco smoke in early life⁵⁵ and in children with early life respiratory infections,^{38,56} suggesting gene-by-environment interactions. Although the identification of these genetic risk factors has provided new insight into the pathogenesis of asthma, the variants themselves only account for a small proportion of the heritability of asthma.⁵⁷ Thus, other factors (eg, gene–gene or gene–environment interactions) clearly have important roles, through epistatic or epigenetic mechanisms.

Maternal smoking has been associated with transient early wheezing (wheezing by age 3 years but not at age 6 years).⁷ By contrast, late-onset wheezing (no wheezing by age 3 years but wheezing by age 6 years) was associated with maternal asthma, male sex, and early-onset rhinitis, whereas persistent wheezing (wheezing by age 3 years and at age 6 years) was associated with maternal asthma, wheezing frequency, child diagnosis of asthma, and atopy.⁷ Of interest, women with severe and uncontrolled asthma during pregnancy were 27% more likely to give birth to a child diagnosed with asthma before age 12 years than were mothers with mild, moderate, or severe asthma whose asthma was well controlled.⁵⁸ If asthma control and severity during pregnancy affect the incidence of asthma in offspring, they could conceivably also affect long-term asthma control and the course of the disease among offspring with asthma or atopy,⁷ although this suggestion has not been proven.

Findings from a birth cohort study^{59,60} in Perth, Australia, showed impaired lung function at 1 month of age and persistent airway hyper-responsiveness at 12 months of age in significantly more children with persistent asthma aged 11 years than in their peers. In 411 children at risk for asthma, investigators of a Copenhagen birth cohort study⁶¹ also reported a significant airflow deficit at 1 month of age in children who subsequently developed asthma by age 7 years. Two main hypotheses might account for the occurrence of reduced lung function in infancy and asthma symptoms in preschool age—a genetic predisposition, or a factor associated with pregnancy (eg, uncontrolled maternal asthma, smoking, or maternal attitude towards medication)⁶²—which could affect not only disease incidence but also asthma progression in infancy, preschool years, and throughout childhood.

Postnatal environment

Several risk factors in infancy have been associated with preschool wheeze, mainly stemming from observational

studies; further studies are needed to establish the underlying mechanisms. These factors include rapid weight gain in infancy⁶³ and environmental exposures such as tobacco smoke,⁶⁴ traffic-related particles and endotoxins,^{65–67} paracetamol,^{68,69} daycare attendance, and older siblings,^{64,70} with daycare attendance and older siblings increasing exposure to respiratory viruses and thus the risk of preschool wheezing illnesses. Breastfeeding⁶³ seems to be protective. Although these environmental factors affect the risk of preschool wheeze, they are not necessarily risk factors for the development of asthma. We focus on respiratory viral infections and weight gain in infancy, two of the risk factors associated specifically with the subsequent development of asthma.

Several findings support the multiple-hit hypothesis, in which respiratory viral infections in a period of increased susceptibility in infancy, combined with atopic sensitisation, could play a key part in the pathogenesis of asthma.^{71–73} Whether the association is causal or simply unearths a genetic susceptibility remains unclear. Up

	Patient population							Intervention		Study duration	
	Age	Phenotype	Interim symptoms	API *	Atopy†	Eczema	Rhinitis	Active (daily dose)	Control		
Daily controller therapy											
Daily ICS vs placebo											
Storr et al (1986) ⁹³	1–5 years	Recurrent asthma	Yes	..	..	41%	..	Beclometasone dipropionate 300 µg (nebuliser)	Placebo	24 weeks	
Wilson et al (1995) ⁹¹	0.7–6 years	EVW	Minimum	..	..	..	..	Budesonide 400 µg	Placebo	4 months	
Bisgaard et al (2004) ⁹⁰	1–3 years	Recurrent wheeze	NR	..	35%	..	..	Fluticasone 200 µg	Cromoglycate	52 weeks	
Guilbert et al (2006) ⁹²	2–3 years	Wheezing and positive API	None	..	59%	54%	..	Fluticasone 200 µg	Placebo	24 months	
Castro-Rodríguez et al (2009) ^{20‡}	1 month to 5 years	Wheezing or asthma	Mixed	..	..	..	..	Various ICS and doses	Placebo	4–36 weeks	
Brand et al (2011) ⁴⁷	2–6 years	Asthma, plus positive API and skin test	Yes	..	..	..	..	Ciclesonide 40, 80, or 160 µg	Placebo	24 weeks	
Daily ICS vs pre-emptive ICS											
Papi et al (2009) ⁵⁰	1–4 years	Wheezing	Yes	+ or –	..	..	..	Beclometasone dipropionate 800 µg (nebuliser)	Beclometasone dipropionate 800 µg plus salbutamol 1600 µg (nebuliser) as needed	12 weeks	
Zeiger et al (2011) ⁹⁵	1–5 years	Wheezing and positive API	No	+	..	..	..	Beclometasone dipropionate 500 µg (nebuliser)	Beclometasone dipropionate 2000 µg (nebuliser) for 1 week	12 months	
Daily LTRA vs placebo											
Bisgaard et al (2005) ⁹⁶	2–5 years	EVW	Minimum§	..	35%	..	..	Montelukast 4 mg daily	Placebo	12 months	
Valovirta et al (2011) ⁹⁷	6 months to 5 years	Two or more asthma episodes	None	..	..	30%	50%	Montelukast 4 mg daily	Placebo	12 months	
Daily LTRA vs pre-emptive LTRA											
Valovirta et al (2011) ⁹⁷	6 months to 5 years	Two or more asthma episodes	None	..	..	30%	50%	Montelukast 4 mg daily	Montelukast 4 mg for 12 days	12 months	
(Table continues on next page)											

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	Patient population							Intervention		Study duration
	Age	Phenotype	Interim symptoms	API *	Atopy†	Eczema	Rhinitis	Active (daily dose)	Control	
(Continued from previous page)										
Pre-emptive controller therapy										
Pre-emptive LTRA vs pre-emptive ICS										
Bacharier et al (2008) ⁴¹	12–59 months	≥2 EVW	Minimum	60% +	50%	25%	..	Montekulast 4 mg for 7 days	Budesonide 1 mg twice a day for 7 days	12 months
Pre-emptive high-dose ICS vs placebo										
McKean et al (2000) ^{100‡}	1–5 years	EVW	None	..	NR	..	..	Budesonide or beclometasone dipropionate 1600–3200 µg per day for 5–7 days	Placebo	1–2 years
Svedmyr et al (1999) ⁹⁹	1–3 years	EVW or EVA	Minimum	..	24%	35%	..	Budesonide 1600 µg per day for 3 days then 800 µg for 7 days	Placebo	12 months
Bisgaard et al (2006) ⁸⁴	0–3 years	EVW	None	..	6%	..	..	Budesonide 400 µg per day for 14 days	Placebo	36 months
Bacharier et al (2008) ⁴¹	12–59 months	≥ 2 EVW: 60% API	Minimum	60% +	50%	25%	..	Budesonide 1 mg twice a day for 7 days	Conventional therapy	12 months
Ducharme et al (2009) ⁹⁸	1–5 years	EVA	None	..	18%¶	15%	..	Fluticasone 750 µg twice a day for 10 days (maximum)	Placebo	9 months
Papi et al (2009) ⁵⁰	1–4 years	Wheezing	Yes	+ or –	..	..	..	Beclometasone dipropionate 800 µg plus salbutamol 1600 µg (nebuliser as needed)	Placebo	12 weeks
Pre-emptive LTRA vs placebo										
Robertson et al (2007) ¹⁰¹	2–14 years	Intermittent asthma	None	..	..	64%	51%	Montekulast 4 mg (for 5 years or younger; 5 mg otherwise) for 7–20 days	Placebo	12 months
Bacharier et al (2008) ⁴¹	12–59 months	≥2 EVW	Minimum	60% +	50%	25%	..	Montekulast 4 mg (for 5 years or younger; 5 mg otherwise) for 7 days	Conventional therapy	12 months
Valovirta et al (2011) ⁹⁷	6 months to 5 years	Two asthma episodes or more	None	..	..	30%	50%	Montekulast 4 mg (for 5 years or younger; 5 mg otherwise) for 12 days	Placebo	12 months

All reported studies are randomised controlled trials, with the exception of two systematic reviews of randomised controlled trials. API=asthma predictive index. ICS=Inhaled corticosteroids. EVW=episodic viral-induced wheeze. EVA=episodic viral-induced asthma. LTRA=leukotriene receptor antagonists. NR=not reported. *API, developed by Castro-Rodríguez,²⁷ reported as positive or negative. †Atopy suggested by positive skin tests to aeroallergens unless otherwise stated. ‡Meta-analysis of randomised controlled trials. §Randomised controlled trial included an unspecified proportion of children with interim symptoms. ¶Atopy suggested by elevated serum IgE concentrations.

Table: Description of randomised controlled trials and systematic reviews related to preschool wheezing or asthma

to 50% of children will have at least one lower-respiratory-tract viral infection with wheezing before school age,⁷ with human rhinovirus and respiratory syncytial virus being the most commonly identified. Several studies have documented an association between early infection with human rhinovirus or respiratory syncytial virus with increased risk of school-age asthma, especially in infants with a family history of atopy.^{74–76} Although most of these studies focused on school-age asthma, Lemanske and colleagues⁷⁵ reported that wheezing illness with human rhinovirus infection in the first year of life was the strongest predictor of wheezing in the third year of life (odds ratio [OR] 6·6). The age of the first wheezing illness could have prognostic value to determine subsequent asthma risk, because infection with human rhinovirus or respiratory syncytial virus in the first year of life was associated with a particularly high risk of asthma at age 6 years in a cohort⁷⁷ at high risk of atopy (OR 31·7, 6·5, and 2·5 for human rhinovirus infection in the third,

second, and first year of life, respectively). Several mechanisms have been proposed to account for the role of viral infections in the inception of asthma. Human rhinovirus infection increases mediators of airway remodelling in vitro, such as VEGF⁷⁸ and EGFR,⁷⁹ and upregulates genes associated with interferon and airway remodelling pathways,⁸⁰ suggesting that an early lung insult during the susceptible preschool years can lead to long-term sequelae. Whether respiratory bacterial infections, recently associated with acute wheezing episodes,⁸¹ are also determinants of the long-term prognosis remain to be explored. In addition to viral exposures, host factors such as allergic sensitisation in early childhood⁸² and deficiencies in interferon responses⁸³ might modify the risk for asthma development in susceptible individuals. Whether early therapy can modify these associations remains to be shown.⁸⁴

Accelerated weight gain (but not length gain) in infancy has been associated with asthma symptoms in the

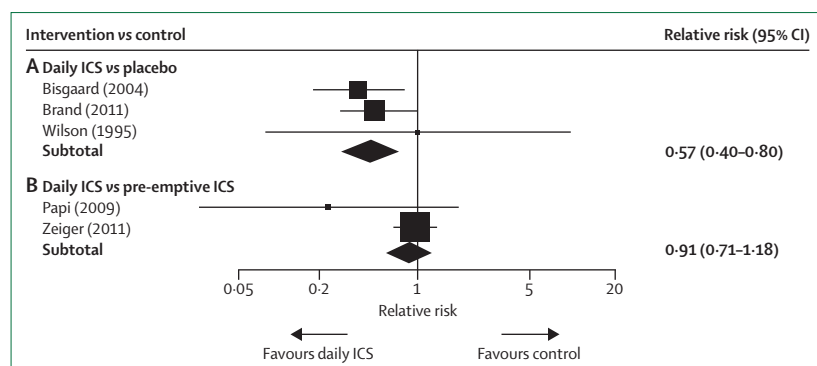


Figure 1: Relative risk of patients with exacerbations needing rescue oral corticosteroids

Pooled relative risk (fixed effect model) of preschool children with wheeze or asthma experiencing exacerbations treated with rescue oral corticosteroids, comparing daily ICS with placebo (A) and pre-emptive high-dose ICS (B). The width of horizontal line represents the 95% CI around the point estimate (solid square). The size of the point estimate represents relative weight (% weight) of each trial in the pooled summary estimate (diamond). The vertical line is the line of no effect (relative risk 1.0). ICS=inhaled corticosteroids.

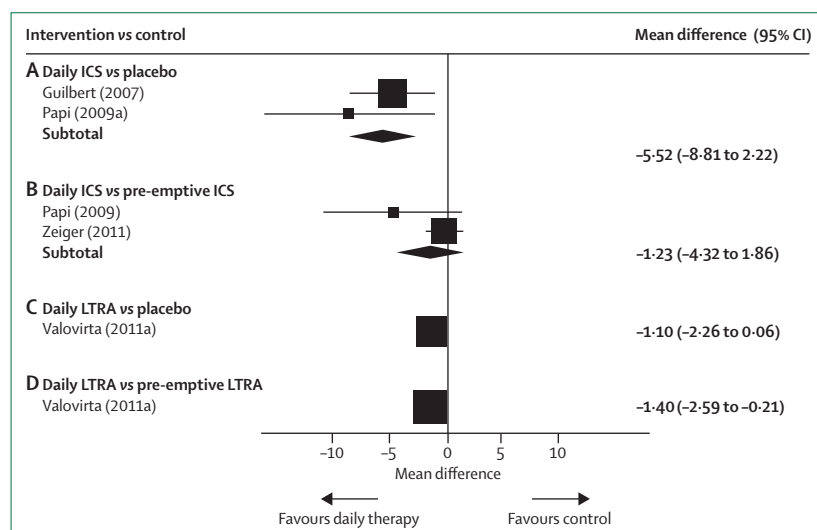


Figure 2: Mean group difference of percentage of asthma-free days

Mean group difference (fixed effect model) of percentage of asthma-free days (defined as no asthma symptoms and no use of rescue bronchodilators) in preschool children with wheeze or asthma, comparing daily ICS with placebo (A), daily ICS with pre-emptive high-dose ICS (B), daily LTRA with placebo (C), and daily LTRA with pre-emptive LTRA (D). Of note, in the study by Papi and colleagues,⁵⁰ the percentage of symptom-free days is given because the investigators assumed that in the absence of symptoms, there would be no use of rescue bronchodilators. The width of horizontal line represents the 95% CI around the point estimate (solid square). The size of the point estimate represents relative weight (% weight) of each trial in the pooled summary estimate (diamond). The vertical line is the line of no effect (relative risk 1.0). ICS=inhaled corticosteroids. LTRA=leukotriene receptor antagonist.

preschool years. In the Generation R Study⁶³ (a prospective cohort study of pregnant women and their offspring), weight gain from birth to 3 months of age was positively associated with the risk of wheezing, shortness of breath, and persistent phlegm in the first 4 years of life, independent of fetal growth patterns. Investigators of another Dutch birth cohort⁶⁵ documented an association between rapid weight gain in the first 3 months of life and reduced forced expiratory volume in 1 s (FEV₁) at 5 years of age, independent of birthweight. These findings are corroborated by other

studies.^{86,87} The mechanisms underlying these associations are not completely understood. The rapid acquisition of adipose tissue could be associated with increased obesity-related cytokines (adipokines), leading to a chronic state of inflammation.⁸⁸ This inflammatory state might in turn adversely affect lung growth and the developing immune system,⁸⁹ which could contribute to the development of asthma.

Effects of therapy on health outcomes

Available evidence

The evidence supporting therapy in preschool children is fraught with several problems, namely international differences in diagnosis of asthma and preschool wheeze, secular changes in the definition of wheezing phenotypes, and recent change in the focus from asthma severity to asthma control. The number of randomised controlled trials and systematic reviews of trials contributing to the evidence remains fairly small, yet the strength of the accumulated evidence regarding the management of preschool asthma or wheezing is definitively increasing (table).

Daily controller therapy

In a systematic review of 29 trials of preschool children with recurrent wheezing or asthma published up to 2008, Castro-Rodríguez and Rodrigo²⁰ reported a significant benefit for daily inhaled corticosteroids in the risk of exacerbations of all severity (RR 0.59, 95% CI 0.59–0.67), the risk of withdrawals due to exacerbations (RR 0.52, 95% CI 0.43–0.63), in symptoms (standardised mean difference [SMD] 0.93, 95% CI 0.49–1.37), β_2 -agonist use (SMD 0.63, 95% CI 0.30–0.63), and in the improvement in FEV₁ (weighted mean difference [WMD] 0.06, 95% CI 0.05–0.09). However, a post-hoc analysis suggested a stronger effect for exacerbations in children with asthma than in those with wheezing (RR 0.50 vs 0.65, $p=0.04$). We did a meta-analysis of more recent trials of preschool children and those not included in the aforementioned review; in studies combining a mixed population of children with or without atopy and a positive API, daily inhaled corticosteroids reduced the risk of exacerbations needing rescue oral corticosteroids by more than 40% compared with placebo (RR 0.57, 95% CI 0.40–0.80; figure 1).^{20,90–94} With only two trials of preschool children with recurrent wheeze, with and without a positive API, there is insufficient evidence to draw firm conclusions about the relative efficacy of daily doses of inhaled corticosteroids compared with pre-emptive high-dose inhaled corticosteroids (figure 1).^{50,95} Therapy with daily inhaled corticosteroids must be sustained to maintain benefit, because a 1-year treatment cessation is associated with similar frequency of symptoms as reported in the placebo group.⁹² Of interest, in a cohort study⁶¹ of high-risk infants followed up from birth to 7 years of age, about 40% of the airflow obstruction reported at 7 years of age in children with asthma was

already present at 1 month of age, suggesting prenatal or perinatal programming. This finding might also identify a window of opportunity for intervention in the preschool years. As yet, there are no long-term trials of children followed up until the age of 6 years to determine if sustained controller therapy introduced in the preschool years could prevent lung function impairment in children with wheezing or asthma symptoms.

Compared with placebo, daily leukotriene receptor antagonists in episodic wheezing with interim symptoms are not associated with a significant reduction in the risk of rescue oral corticosteroids.⁹⁶ Treatment with daily leukotriene receptor antagonists was associated with a reduction in overall exacerbations in one trial⁹⁶ but not in another,⁹⁷ and no significant change in asthma-free days in any trial.^{96,97} Data are not reported graphically because of incomplete reporting.

Compared with placebo, there was a statistically significant group difference in favour of daily inhaled corticosteroids in the percentage of asthma-free days (figure 2), which is consistent with findings from the study by Bisgaard and colleagues⁹⁰ showing a significantly increased proportion of children treated with daily fluticasone with 75% or more symptom-free days compared with children receiving placebo. There was no statistically significant group difference in asthma-free days between daily and pre-emptive inhaled corticosteroids,^{50,95} or between daily leukotriene receptor antagonists and either pre-emptive leukotriene receptor antagonists or placebo⁹⁷ (figure 2).

Pre-emptive controller therapy

Pre-emptive high-dose inhaled corticosteroids reduced the risk of exacerbations needing rescue oral corticosteroids by more than 30% (RR 0.68 [95% CI 0.53–0.86]) in children with moderate-to-severe viral-induced intermittent asthma (figure 3).^{51,98,99} These findings lend support to the preliminary findings from a meta-analysis¹⁰⁰ of two crossover trials published in 2000, in which we documented a reduction almost reaching statistical significance in the risk of rescue oral steroids in patients receiving pre-emptive high-dose inhaled corticosteroids (RR 0.53, 95% CI 0.27–1.04). These findings did not translate to a statistically significant group difference for asthma-free days (figure 4). Of note, pre-emptive medium doses of inhaled corticosteroids at the first and subsequent wheezing episodes in infancy do not prevent progression from episodic to persistent wheezing, and convey no statistically significant symptom relief.⁸⁴ In the individual trials reporting these outcomes, the effect of pre-emptive leukotriene receptor antagonists was not significantly different from that of placebo or of pre-emptive inhaled corticosteroids to prevent rescue oral corticosteroids or reduce asthma-free days (figures 3, 4),^{51,97,101} although findings from a trial¹⁰¹ of children aged 2–14 years showed a significant reduction in use of

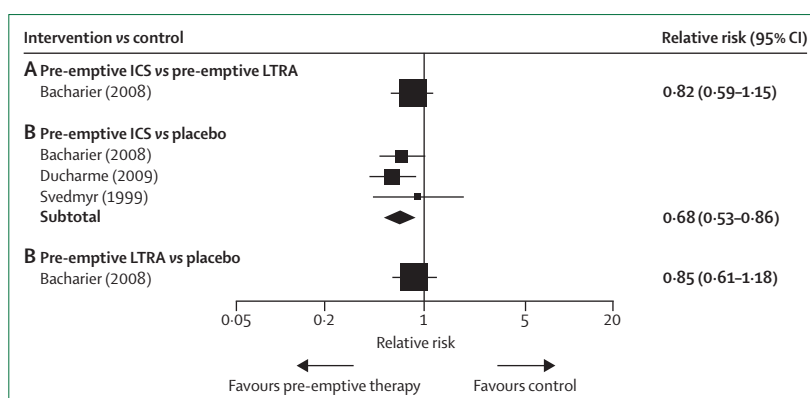


Figure 3: Pooled relative risk of patients with exacerbations needing rescue oral corticosteroids
Pooled relative risk (fixed effect model) of preschool children with wheeze or asthma experiencing exacerbations treated with rescue oral corticosteroids comparing pre-emptive high-dose ICS with pre-emptive LTRA (A), pre-emptive ICS with placebo (B), and pre-emptive LTRA with placebo (C). The width of horizontal line represents the 95% CI around the point estimate (solid square). The size of the point estimate represents relative weight (% weight) of each trial in the pooled summary estimate (diamond). The vertical line is the line of no effect (relative risk 1.0). ICS=inhaled corticosteroids. LTRA=leukotriene receptor antagonist.

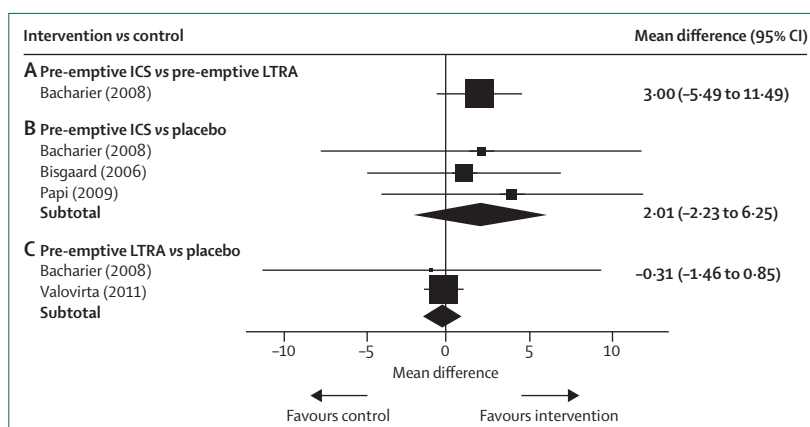


Figure 4: Mean group difference of percentage of asthma-free days
Mean group difference (fixed effect model) of percentage of asthma-free days (defined as no asthma symptom and no use of rescue bronchodilators) in preschool children with wheeze or asthma, comparing pre-emptive ICS with pre-emptive LTRA (A), pre-emptive ICS with placebo (B), and pre-emptive LTRA with placebo (C). Of note, Bisgaard and colleagues⁸⁴ and Papi and colleagues⁵⁰ reported the percentage of symptom-free days, because the investigators assumed that in the absence of symptoms, there would be no use of rescue bronchodilators. The width of horizontal line represents the 95% CI around the point estimate (solid square). The size of the point estimate represents relative weight (% weight) of each trial in the pooled summary estimate (diamond). The vertical line is the line of no effect (relative risk 1.0). ICS=inhaled corticosteroids. LTRA=leukotriene receptor antagonist.

health-care resources, symptoms, and school and parental work absenteeism.

Few adverse health events, including growth suppression, have been systematically documented in trials, thus preventing a meta-analysis of adverse events. From the few data available, daily low-dose⁹² and intermittent high-dose⁹⁴ inhaled corticosteroids are associated with a small (but statistically significant) effect on growth compared with placebo, with a group difference of 1.1 cm for daily low-dose inhaled corticosteroids and 0.6 cm for intermittent high-dose inhaled corticosteroids, equivalent to a four percentile difference. The potential for overuse of intermittent high-dose

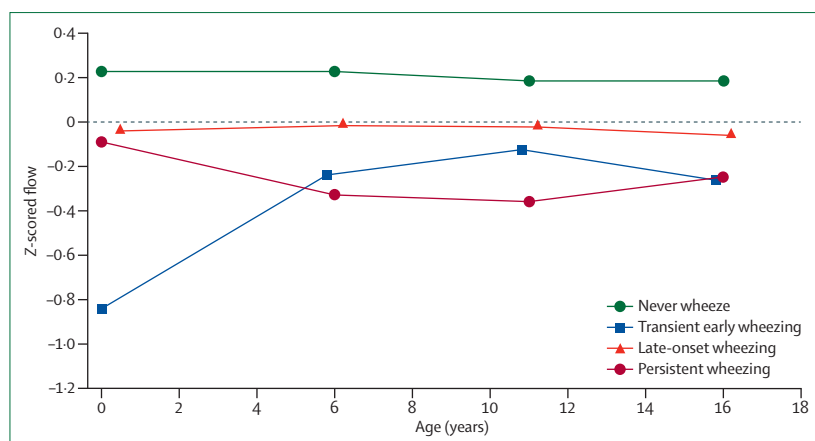


Figure 5: Maximum respiratory flow by age in preschool children with wheeze

Cross-sectional Z scores of height-adjusted maximum expiratory flows at the age of 2–4 months and 6, 11, and 16 years for the preschool wheezing groups in the Tucson Children's Respiratory study.¹¹³ The Z score shows how many SDs from the mean a participant's value lies. Participants with persistent wheezing began life with flows that do not differ from those of their peers with late-onset wheeze or those who never wheeze, but had decreased flows relative to these other groups by the age of 6 years. By contrast, participants with transient early wheezing had early and persistent reductions flows. Reprinted from Morgan and colleagues¹¹³ by permission of the American Thoracic Society.

inhaled corticosteroids both by parents and physicians has led to calls for caution in use of this strategy. Findings from a systematic review¹⁰² of randomised controlled trials, predominantly of prepubertal school-aged children, showed a significant molecule dependency in the magnitude of growth suppression associated with inhaled corticosteroids in disfavour of beclomethasone dipropionate and budesonide.¹⁰² In the absence of solid data for preschool children, selection of the safest molecules and careful monitoring of growth seems to be the most prudent approach for either option.

These findings suggest the benefit of daily low-dose inhaled corticosteroids for children with repeated wheezing episodes and asthma (recognising that most studies included or focused on children with interim symptoms or atopy), and intermittent high-dose inhaled corticosteroids for toddlers with apparent moderate-to-severe viral-induced wheezing with no interim symptoms (ie, those with two or more exacerbations needing a visit to the emergency department or rescue oral corticosteroids). The evidence for leukotriene receptor antagonists is less compelling, partly because of the paucity of trials. In view of the difficulty in recognition of the phenotypes, initiation of therapy with daily inhaled corticosteroids in any child with substantial symptoms seems reasonable; for patients who do not respond to this therapy, intermittent high-dose inhaled corticosteroids could be considered in those with moderate-to-severe viral-induced asthma. Several questions remain unanswered, namely the frequency and severity of episodes warranting initiation of daily therapy, optimum duration of therapy, and the balance between safety and effectiveness of each option in this age group.

Prognosis

Asthma remission and persistence

In population-based studies, the symptoms of most preschool children with wheeze will remit by school age. In the Tucson Children's Respiratory Study,⁷ almost 60% of children with wheeze before the age of 3 years had stopped wheezing by age 6 years. In a cohort¹⁰³ of infants who wheezed before 30 months of age, 63% were in remission at age 6 years. Authors of a large population-based study of Canadian children diagnosed with asthma before age 6 years reported that 48% were in remission by age 12 years.¹⁰⁴ However, children with an asthma-related admission to hospital or at least four physician visits during the first year after diagnosis were at increased risk of persistent asthma at age 12 years, suggesting that the severity or intensity of symptoms might lead to (or predict) long-term effects.¹⁰⁴ Larger and more recent birth cohorts such as the ALSPAC and PIAMA studies have documented similar patterns, in which most cases of preschool wheeze are transient early wheeze.³⁰ Although the symptoms of most children with wheeze seem to remit later in life, some of these children go on to have persistent symptoms or relapse in adulthood after a period of remission.^{105–107}

Lung function

Despite a seemingly benign prognosis regarding symptoms, findings from birth cohorts have consistently shown that, as a group, preschool children with wheeze have permanent deficits in lung function at 6 years of age.⁵² Indeed, several longitudinal cohort studies—initiated in 1957 (Melbourne, Australia),^{105,108} 1958 (UK),¹⁰⁹ 1972 (New Zealand),¹⁰⁷ and the 1980s (USA),⁶⁴ when use of daily anti-inflammatory therapy was infrequent—offer a good picture of the natural history of paediatric asthma up to 42 years of age. Their findings consistently show an average deficit of about 10% of predicted values in FEV₁ and a 5% lower ratio of FEV₁ to forced vital capacity in adolescents and adults who had asthma symptoms before the age of 6 years than in peers who did not wheeze (figure 5).^{105,108,109} These deficits are probably established by 4 years of age or younger, suggesting early airway remodelling and irreversible long-term effects on lung growth and function.^{7,110,111} There is indeed convincing evidence of airway remodelling with reticular membrane thickening and eosinophilic inflammation documented in preschool children aged 1–3 years with chronic wheezing and in children as young as 10 months of age.^{111,112} These findings suggest not only that preschool children with wheeze have permanent deficits in lung function at 6 years of age, but also that growth patterns of lung function established by 6 years of age generally continue into early adulthood to middle adulthood.

Modulation of medium-term and long-term prognosis by patient characteristics

Age at onset, asthma morbidity in early life, and age at remission of symptoms seems to affect medium-term

and long-term outcomes. Children with transient early wheezing and persistent early wheezing had decreased lung function compared with children with wheezing onset after 6 years of age and those without wheeze, suggesting an effect of early lung insult in all preschool children, irrespective of age at onset and remission, if any.¹¹³ However, there is conflicting data about whether or not children with transient wheezing sustain irreversible impairments in lung growth.¹¹⁴ Other than age at onset, asthma morbidity in early life seems to affect long-term outcomes. Indeed, although outcomes are generally good in children with a small number of wheezing episodes, those with the worst asthma control (ie, frequent and severe symptoms in early childhood) seem to have a high probability of continuing symptoms with impaired lung function in adult life.^{105,108} Thus, children with repeated wheezing episodes needing emergency department visits and hospital admissions are at increased risk of impaired lung growth. Asthma morbidity, persistence, or recurrence into adulthood also seems to be affected by asthma symptoms in early life. 63% of individuals with newly diagnosed asthma at 22 years of age had wheezing occurring in the first 3–6 years of life.¹¹⁵ Additionally, the risk of hospital admission for asthma in early adulthood was associated with onset of asthma in preschool age, frequent respiratory symptoms, and reduced lung function at 9 years, with patients admitted to hospital more than once in early adulthood having even earlier onset of symptoms, more allergies, and more impairment of lung function than did those with a single admission.¹¹⁶ Collectively, these findings underscore the importance of age at onset and severity and intensity of symptoms in early childhood for long-term asthma morbidity in adulthood.

Gap in implementation

Most preschool children with recurrent and persistent asthma symptoms do not receive daily anti-inflammatory drugs because of uncertainties in diagnosis or phenotype,⁴² paucity of solid evidence-based recommendations, perceived unclear treatment benefit, physician discomfort in prescribing long-term controller therapy, alternative intermittent treatment options,¹¹⁷ and low parental compliance to recommended therapy.^{118,119} Children who do receive drugs often have an undue delay between onset of disease and initiation of long-term therapy with controller medications. Many children are treated with pre-emptive inhaled corticosteroids, but at lower doses than have not been proven to be effective.

Conclusions

Long-term health outcomes and the effects of therapy in different phenotypes remain unclear. Other than the variability in phenotype definition, confounders include age at onset, severity, delay between onset of symptoms and the initiation of first controller medication, choice of controller medication, intraindividual therapy change

over time, in addition to pattern, adherence, persistence,¹⁰⁴ and overall use of asthma controller by the patient. Importantly, irrespective of phenotype, researchers need to document whether asthma control achieved rapidly after the initial diagnosis in early childhood predicts medium-term and long-term disease evolution (remission, persistence, and recurrence); acute-care use of health resources (morbidity); and consequently health-care costs.

Preschool children consume disproportionately high amounts of health-care and economic resources for wheezing and asthma; they also represent the most susceptible age group at risk for irreversibly impaired lung growth. Whether the susceptibility is genetically determined, associated with pregnancy-related events, or increased by the onset, severity, or frequency of symptoms occurring early in life at a crucial time of rapid lung growth, long-term studies point to events that play out in the first few years of life. Studies showing that children with persistent wheezing after 6 years of age started life with reduced lung function at 1 month point not only to genetic causes, but also to the possibility of modifiable pregnancy-related factors. Cohort studies show that wheezing illnesses in the first 3–6 years of life are associated with impaired lung function into childhood and adulthood and, for those who experience remission, an increased risk of relapse and higher morbidity in early and middle adulthood. Growth patterns of lung function established by age 6 years generally continue into early adulthood and on to middle adulthood, setting the stage for lifelong persistent asthma, and might put people at risk for the development of chronic obstructive pulmonary disease. Thus, the seeds of chronic airways dysfunction in early and middle adulthood are sown in early life. Daily inhaled corticosteroids are clearly beneficial to achieve asthma control and prevent exacerbations in a mixed population of wheezing children; high-dose pre-emptive corticosteroids are effective in children with moderate-to-severe viral-induced exacerbations with no interim symptoms. Whether prevention of early respiratory infections or early controller therapy can modify the natural history of disease remains to be examined. The ability to favourably modify the long-term outcome of preschool-aged wheeze is a major public health priority.

Contributors

FMD did the literature search, the systematic review of randomised controlled trials and meta-analyses, extracted and interpreted data, and wrote the report. SMT focused the literature review on post-natal environment and contributed to the overall report. BC participated in the data extraction and meta-analysis of therapeutic trials.

Declaration of interests

FMD has received research funds, honorarium as speaker, and consulting fees from GlaxoSmithKline, Merck Frosst, Merck Canada, Novartis, and Takeda. SMT and BC declare no competing interests.

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