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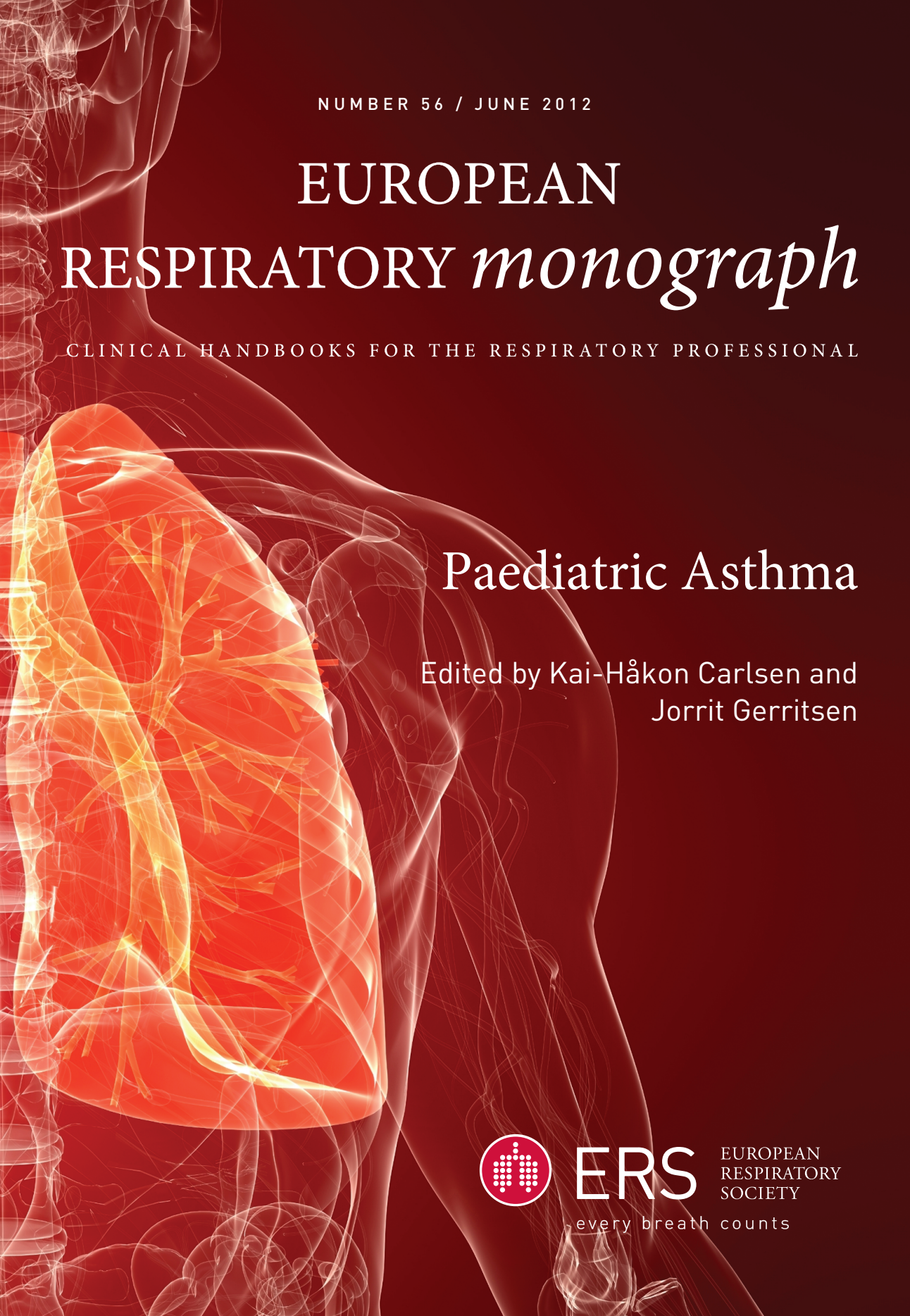

Paediatric Asthma

Edited by Kai-Håkon Carlsen and Jorrit Gerritsen

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Paediatric Asthma

Edited by Kai-Håkon Carlsen and Jorrit Gerritsen

Editor in Chief
Tobias Welte

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This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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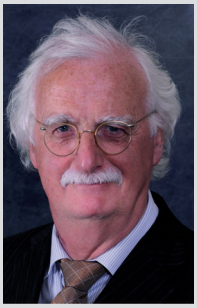
Guest Editors

Kai-Håkon Carlsen

Kai-Håkon Carlsen is Professor of Paediatric Respiratory Medicine and Allergology at the University of Oslo (Oslo, Norway), senior consultant of the Paediatric Clinic of Oslo University Hospital and Professor of Sports Medicine at the Norwegian School of Sports Sciences (Oslo). He was President of the European Paediatric Respiratory Society (1991–1993), President of the Norwegian Society of Allergy and Immunopathology (1989–1993), Head of the Paediatric Assembly of the European Respiratory Society (ERS) (1997–2001), Chair of the ERS School (2002–2005) and Chair of the European Lung Foundation (2007–2010). He has also been an Associate Editor of the European Respiratory Journal (*ERJ*) (1998–2003), an Associate Editor of *Acta Paediatrica* (2008–2011) and a member of the editorial board of *Allergy* (1999–2011). He has been a member of the editorial board of *Paediatric Allergy and Immunology* since October 1997. Kai-Håkon was also a member of the editorial board of *Paediatric Pulmonology* (1997–2004) and the first Chief Editor of *Breathe*, the educational journal of the ERS (2004–2005). He gave the prestigious Jean-Claude Yernault Lecture at the ERS Annual Congress in September 2007 and received the Life Time Achievement Award of the Paediatric Assembly of the ERS in 2010. Kai-Håkon is presently a member of the Tobacco Control Committee of the American Thoracic Society (ATS), has been a member of several Task Forces of the ERS, ATS and the European Academy of Allergy and Clinical Immunology (EAACI), and is presently part of the ERS/ATS Task Force on Bronchial Hyperresponsiveness, the ERS Task Force on Rare Lung Diseases and the Paediatric Asthma ICON Task Force of EAACI.



Jorrit Gerritsen

Jorrit Gerritsen served as Secretary and Head of the Paediatric Assembly of the ERS, and was President of the ERS from 2009 to 2010. He has been involved in follow-up studies of asthma from childhood to adulthood, epidemiological studies, studies on the role of the environment, the large Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort study, studies on genetics of asthma and studies on cystic fibrosis. He was Editor of the *Dutch Paediatric Journal* and several other respiratory journals, and is an Associate Editor of the *ERJ*. He has been involved, as first author or as co-author, in more than 220 peer-reviewed international publications, has published several books, and has participated in writing chapters of international books.

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Preface

There is no question about it: in terms of morbidity and healthcare costs, asthma is the most important respiratory disease in children and adolescents. Both research and clinical development have been tremendously successful over the last few decades, and understanding about the genetics, molecular biology, pathophysiology and clinical implications of asthma have been greatly improved. We have become aware that paediatric asthma is not a homogenous disease, but is very heterogeneous, with various clinical phenotypes that need different diagnostic and therapeutic approaches. Like bronchial malignancy, asthma may be one of the first diseases in which personalised, phenotype-driven medicine could be possible in the next few years. However, such an approach will not only have medical implications but will raise a number of questions with regard to educational programmes for physicians and patients, and will give a focus on pharmacoeconomic considerations.

Asthma research driven by paediatricians has produced impressive results in the past, and this will also be the case in the future. The winners of all of these ongoing efforts are the patients, as good research leads to better care with an improved quality of life.

This issue of the *European Respiratory Monograph* summarises the current knowledge on paediatric asthma but also focuses on future developments. I want to congratulate the Guest Editors for this excellent *Monograph*, which should be of interest to paediatricians but also to general medical doctors and pulmonary specialists treating adults. I am convinced that they will find this *Monograph* useful in daily practice.

Editor in Chief
Tobias Welte

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Introduction

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Paediatric asthma remains a health problem on a global scale, for the health systems of individual countries, for the families of asthmatic children and for the asthmatic children themselves. At present, we have no cure for asthma, and paediatric asthma most often represents a lifelong problem, although modern and optimal treatment do offer good disease control; most children with asthma are able to have a "healthy" life, and participate in physical activities on an equal level with their healthy peers, with a normal development into adolescence and adulthood.

One major problem of paediatric asthma is the "lifelong" aspect. Recently, paediatric asthma has been reported as a major risk factor for chronic obstructive pulmonary disease (COPD) in adult life, thus underlining the need for early diagnosis, optimal treatment and monitoring of paediatric asthma.

This issue of the *European Respiratory Monograph* covers the different aspects of paediatric asthma. The many phenotypes of asthma with different clinical characteristics at different ages illustrate the heterogeneity of paediatric asthma. These include different levels of severity and, in particular, problematic severe asthma. Many different causative factors have a role in the pathogenesis of asthma and influence the clinical presentation. These include: food allergy; viral and bacterial infections; allergen exposure and exposure to indoor and outdoor pollutants; psychological factors; and physical activity and sports. The genetics of asthma is complicated, and epigenetics may help explain the increase in prevalence over recent decades.

The care and treatment of asthmatic children is one of the major tasks of paediatric respiratory medicine. There are different approaches to the treatment of asthma at different ages, and acute asthma requires particular concern and treatment strategies. Monitoring and follow-up of paediatric asthma remain important for optimal treatment.

All these aspects of handling paediatric asthma, as well as the many faces of paediatric asthma, are thoroughly discussed by distinguished paediatric pulmonologists in this issue of the *European Respiratory Monograph*. We hope that our young colleagues will find this Monograph useful in the clinical setting and that it will remain an inspiration in their future research.

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Chapter 1

Asthma in children: the road to individual asthma phenotypes

Karin C. Lødrup Carlsen[*,#] *and Kai-Håkon Carlsen*[*,#,¶]

SUMMARY: The childhood asthma prevalence increase, during recent decades, may represent a shift in distribution of asthma phenotypes. The lung meets the external environment directly through the airways, as well as indirectly, by way of circulatory, neural and immunological responses. However, it is not clear how, and to what extent, environmental factors together with constitutional and genetic factors co-act to result in asthma and define asthma severity. Despite decades of research there has not been a significant breakthrough in understanding the mechanisms, genetics, therapeutic interventions and possible preventive strategies of asthma. Thus, we still lack significant knowledge that could help target asthmatic children with optimal management or ultimately prevent asthma developing. These gaps in knowledge are likely to stem from our inability to identify relevant sub-groups of childhood asthma, or even to define asthma in a reasonably objective manner. The present chapter will briefly describe the importance of characterising childhood asthma phenotypes and approaches that have been and are currently undertaken to identify them.

KEYWORDS: Allergy, asthma, birth cohorts, child, phenotypes, statistics

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The childhood asthma disease spectrum is well recognised [1–3]. However, sub-groups are challenging to identify, define and use as a base for therapeutic considerations. At present we lack clear definitions for making an asthma diagnosis, particularly in the youngest children. Furthermore, it is challenging to identify early asthma from other wheezy disorders in preschool children, as well as defining optimal treatment options in this age group. These uncertainties probably reflect the current lack of understanding of the underlying pathophysiological mechanisms. Not only do we acknowledge that asthma is a heterogeneous disease [1, 4, 5], but even the relationship with other allergic diseases, as well as with allergic sensitisation, is unclear. This has resulted in an increasing number of papers approaching phenotype descriptions [6]. Thus, a need to rethink scientific approaches to understand these issues has led to new statistical approaches. Large collaborative research programmes, such as the MeDALL (Mechanisms of the

Development of ALLergy, Grant Agreement) [7], will use novel integrated approaches to answer some of these questions. However, what are the questions?

How many asthma types are there?

Clearly, nobody knows the answer to this at present. Several approaches have been attempted in the search for childhood asthma phenotypes. Starting with the traditional way of categorising, which is the presence or absence of allergic sensitisation (''allergic'' asthma), through to various time-presentations of ''wheezy'' phenotypes or a combination of these; severity of disease; intermediate phenotypic or asthmatic traits; and down to current statistical clustering methods [8]. The current focus is to free the analyses of information-bias imputed by the clinicians and scientists and thereby improve the chances of identifying a number of similar asthma cases identified by hitherto unknown characteristics.

The first classical dichotomous phenotypes were allergic *versus* nonallergic asthma. Later, four time-based, epidemiologically observed ''wheezing'' asthma phenotypes (transient, early onset, persistent and late onset) were proposed by the Tucson Children's Respiratory Study (TCRS), which studied infants from Tucson (Arizona, TX, USA) [8]. This was later followed-up by more recent, larger, birth cohort studies. In a recent collaborative study of the two birth cohorts Prevention and Incidence of Asthma and Mite Allergy (PIAMA) and Avon Longitudinal Study of Parents and Children (ALSPAC), remarkably similar clusters of five and six phenotypes, respectively, were identified, based upon the temporal pattern of reported wheezing [9]. These represented, in the ALSPAC study ''never/infrequent'' (59%), ''transient early'' (16%), ''prolonged early'' (9%), ''intermediate'' (3%), ''late'' (16%), and ''persistent'' (7%) wheeze determined in approximately 110,000 children [10], with similar objective correlates of asthma, atopy and lung function in accordance with the five-class model from the PIAMA study [9]. However, these ''wheeze'' phenotypes are not equivalent to asthma phenotypes, although ''asthma'' was more commonly defined in the intermediate, late and persistent wheezing phenotypes.

A recently published PRACTALL (PRACtical ALLergy) consensus reported criteria for defining asthma endotypes on the basis of their phenotypes and putative pathophysiology [11]. Some examples of phenotypes listed were eosinophilic asthma, exacerbation-prone asthma, obesity-related asthma, exercise-induced asthma (EIA), adult-onset asthma, fixed airflow limitation and poorly steroid-responsive asthma. However, they only partly overlap with the suggested endotypes, which were aspirin-sensitive asthma, allergic bronchopulmonary mycosis (ABPM), allergic asthma (adults), asthma predictive index (API) [12], positive preschool wheezer, severe late-onset hypereosinophilic asthma and asthma in cross-country skiers [11]. It is unclear if this relabelling will improve our current understanding of the underlying mechanisms and lead to a more targeted drug development.

Asthma as an allergic disease

There is no doubt that asthma is associated with allergic sensitisation [13–15], but with a significant variability in the strength of association between atopic sensitisation and asthma [16]. The fraction of wheeze attributable to atopy varies markedly, ranging from 0% in Turkey to 94% in China [16], as does the presence of allergic sensitisation in school-aged asthmatics (from 55–60% in Scandinavia [17, 18] and 95% in Australia [19]). Asthma has thus been regarded, predominantly, as an allergic disease. Furthermore, it is considered one of the clinical diseases expressed in a predominant temporal pattern within the ''atopic'' or ''allergic march'' from atopic dermatitis to allergic rhinitis and asthma [20, 21]. There is an emerging focus on the different asthma phenotypes throughout life, which are based upon observable traits, *e.g.* asthma with and without allergic sensitisation, eosinophilic or non-eosinophilic inflammation dominating the biopsy specimens [22, 23], and heterogeneity in response to treatment [24, 25]. This is seen in the context of trying to identify ''atopic'' genotypes to correlate with the asthma presentation; hitherto a relatively unsuccessful exercise.

Another issue of asthma as an allergic disease is that it is not clear to what extent eosinophilic inflammation is systemic or predominantly local [26]. Furthermore, most atopic subjects (*i.e.* those producing immunoglobulin (Ig)E antibodies towards common inhalant and food allergens) do not have asthma, and asthma-like clinical presentations (often referred to as "wheezy" disorders in children) are common prior to any signs or documentation of allergic markers [27].

Asthma in early childhood is difficult to diagnose, probably more so than in later childhood or in adults [28]. The clinical presentation of asthma varies throughout childhood, and the concept of diagnosing "asthma" distinct from other wheezy asthma-like presentations or phenotypes in early childhood is a debatable topic [29, 30]. One of the most problematic areas of understanding childhood asthma is probably related to "wheezy" disorders in the first few years of life. On one hand, asthma often debuts as wheezing within the first few years of life, on the other hand wheeze often appears early without clear signs of developing into asthma later in life.

The concept of phenotypes suggests a link to specific genotypes, whereby one individual should be distinguished from another by these characteristics. Clearly, this is not the case today for childhood asthma [1, 11, 31].

Is EIA a distinct phenotype?

EIA is common and sometimes the only manifestation of asthma in children and adolescents. Some 30 years ago it was stated that EIA occurred in 70–80% of asthmatic children that had not been treated with inhaled steroids, but this has been difficult to confirm in population studies [32]. Rather, in 10-year old children, exercise-induced bronchoconstriction (EIB) has been reported in approximately 8% of the normal population compared with almost 37% in the current asthma population [17]. Furthermore, many top performing athletes develop asthma and the mechanisms of their bronchial hyperresponsiveness (BHR) may differ from asthma presenting in early life. EIA is thought to be due to increased ventilation, caused by an increased in demand for oxygen, which is related to physical exercise through water loss and cooling of the airways. The cooling airways give rise to reflex parasympathetic nerve stimulation that results in bronchoconstriction [33–35]. Alternatively, water loss from the bronchial mucosa induces movement of water from inside the cell to the extracellular space [36], causing an intracellular increase in ion concentration [37] that possibly leads to mediator release mediators [36]. The possible epithelial barrier damage caused by extreme exercise may thus represent a specific phenotype, but this remains to be proven by further studies [38].

Classical phenotypes

The classical approach to childhood asthma has been to define asthma by various diagnostic criteria, and to add different allergic or atopic features to try and separate sub-groups of asthma. Thus, traits commonly appearing with, but not limited to, asthma (such as BHR or atopic sensitisation) are often added to "asthma" in order to try to distinguish one group of asthma from another. This may not be an optimal approach. There is a lack of common agreement for the diagnostic criteria of asthma to include all asthma and exclude all without asthma [28, 39–41]. The pragmatic asthma definitions, thereby, reflect a variety of asthma outcomes. The term "wheeze" is particularly problematic as it is not relevant to non-English speaking parts of the world. This symptom and sign of bronchial obstruction is a hallmark of early asthma, but may also have other pathophysiologic origins. A single episode, or few episodes, of wheeze is common in the first 1–2 years of life, usually occurring with a lower respiratory tract infection (LRTI), which often respond poorly to anti-asthmatic treatment [42, 43]; however, the wheeze is reportedly resolved in more than half of the children reported to have wheezed [29]. Although the term appears useful for objective correlates in many studies [9, 29, 44], it appears less useful in others [17, 45, 46]. However, the likelihood of asthma later in childhood increases with the number and severity of bronchiolitis obliterans (BO) episodes in the first few years of life [47], although predicting asthma

even by the presence of early BO, IgE antibodies or other atopy-related characteristics are difficult [48, 49].

Most asthma studies combine the presence of symptoms and reversible airflow obstruction, as well as a doctor's diagnosis of asthma, in their asthma definitions. However, a wide range of features have been proposed to subclassify asthma. These include: asthma symptoms, exacerbations, response to treatment, lung function, BHR, allergic sensitisation, allergic comorbidities, and triggers, as well as varying markers of inflammation [6, 10, 50, 51]. Adding markers of inflammation is probably necessary [7, 52], but has not yet proved valuable in subdividing classical phenotypes of childhood asthma. This may, in part, be because local inflammatory changes are less easily studied with the lack of local biological specimens. An obvious challenge in adding inflammatory and immunological markers to clinical characteristics is that very few subjects will eventually be classified within each phenotype. The likelihood of statistical power to detect meaningful risk factors and biological correlates is thereby reduced [6].

Development of approaches to define asthma phenotypes

Moving from the classical, clinically based phenotypes, the study undertaken on the infants in the TCRS study [8, 53] suggested that classification by temporal clinical presentation, when combined with allergic sensitisation, could propose phenotypes with potentially different underlying mechanisms as well as prognosis [8, 54]. This approach was later followed by more advanced statistical approaches to cluster groups of children with similar characteristics. One of these methods is latent class analysis [9, 10]. Although less biased than by a priori group comparisons performed by the researchers, a shortcoming is that the outcome was based upon "did the child wheeze within the last year". The (temporal) variable "wheeze" in the latest period resulted in remarkable similarities between the six ("never/infrequent", "transient early", "prolonged early", "intermediate", "late", and "persistent" wheeze) and five classes identified in the ALSPAC study and PIAMA study, respectively, as well as their correlates with traits such as allergic sensitisation, lung function and asthma [9].

Despite an improvement from researcher-driven hypotheses, there are, nevertheless, disadvantages to such an approach. Since the phenotypes are by nature retrospective, they are not helpful for the clinician. The time-points of definition are arbitrary, depending upon the time of follow-up investigations rather than biologically relevant events. The strength of interaction with risk factors may change and gene–environmental interactions are not accounted for [55]. The approach does not account for complex associations and interactions between the varying spectrums of factors likely to be involved in phenotype characteristics [6, 7, 9, 11, 56].

To reduce some of these shortcomings, SMITH *et al.* [57] described the use of data driven principal component analyses in a population-based cohort to identify groups of children with similar characteristics. Data from interviews, lung function (specific airway resistance), atopy and BHR at 3 and 5 years were used and five-group variants (components) were identified: wheeze, wheeze with irritants, wheeze with allergens, cough, and chest congestion with correlates to atopy and BHR.

A limitation with many of the approaches is the fact that most of the traits determining underlying pathophysiology are likely to be quantitative, rather than qualitative [58, 59]. This was shown by the quantitative measures of obstructive airways disease and specific IgE at 2 years being better predictors for later asthma than did the mere presence of these traits [48, 59].

Mathematical techniques, such as latent class analysis [10], principal component analysis [57], and de-trended fluctuation analysis (DFA) [60] have all been applied in asthma phenotyping and to identify children at risk for exacerbations [60]. Unsupervised cluster analyses were also used to identify severe childhood asthma phenotypes in a Paris (France) cohort [61]. Two distinct clusters of severe asthma were described. The "asthma with severe exacerbations and multiple allergies" cluster was characterised by more food allergies, more blood eosinophils, more basophils, more

uncontrolled asthma despite higher doses of inhaled corticosteroid, and an increase in hospitalisations. The second cluster "severe asthma with bronchial obstruction" represented older children with higher body mass index (BMI), lower lung function, more pronounced blood neutrophils and higher levels of all classes of immunoglobulin, apart from IgE [61]. A third cluster of mild asthma did not have distinct characteristics [61].

Rather than determining specific asthma phenotypes, it is increasingly likely that an approach identifying intermediate phenotypes may be of value. Thus, objective measures can be tested against clinical traits, as well as genotypes and gene–environment interactions [7, 62–65]. In the American Severe Asthma Research Program (SARP), intermediate phenotypes and various statistical models were used to identify predictors of bronchoalveolar lavage (BAL) cytokines for severe asthma [62]. This proof of principle study, to identify multidimensional BAL cytokine profiles, used intermediate quantitative asthma phenotypes in adults (determined by extreme values of BAL eosinophils and neutrophils, bronchodilator response and BHR), to test five different statistical prediction models. Their data suggested that logistic regression and multivariate adaptive regression splines produced the best methods to predict asthma phenotypes.

The optimal statistical approaches to identify the underlying pathophysiology in different phenotypes are not clear. New approaches like the integrative systems biology strategy rely on the applications of "omics" techniques (proteomics, metabolomics) with high-throughput measurement platforms integrated with biological and clinical data. These approaches may untangle phenotypic characteristics, reflecting underlying pathological mechanisms. Such understanding is essential in order to develop new biomarkers for early diagnosis, define phenotypes and disease severity, as well as predict response to therapy or drug toxicity [7]. Further studies are necessary to evaluate the application of these new tools to characterise and monitor the dynamic and complex nature of asthma.

Phenotypes and risk factors

An important feature of phenotype description is to identify relevant risk factors. The contradicting results found for the role of pet exposure and asthma, as well as other allergic diseases, may stem from our inability to distinguish relevant phenotypes [66]. Thus, such exposure may have an impact on a few subjects with certain genotype–phenotype characteristics compared with the (possible many) phenotypes, where pets do not matter. Other risk factors appear to exert a differential impact depending on when the outcome is determined; such as exposure to tobacco smoke, parental atopic disease, house dampness or reduced ventilation, allergic sensitisation, time of food allergen introduction and breastfeeding, to mention only a few. In the German Multicentre Asthma Study (MAS), it was found that the associations between risk factor (exposure) and wheeze or asthma were much stronger in early, rather than later, childhood [55]. This again raises the question as to whether or not phenotypes are stable or are altered over time. If the latter is true, then when and what are the underlying mechanisms that differentiate the changes in phenotypic expression?

Using new phenotypes in management approaches

Most recent guidelines suggest some sort of phenotypic classification to guide initial treatment [28, 43, 67, 68], stressing the need for a re-evaluation to assess treatment effect. However, trying to distinguish childhood asthma subgroups by symptoms, comorbidities, inflammatory markers, response to treatment or other features have, so far, not been very useful in the clinical settings [69]. In the search for individualised treatments, novel treatments are likely to depend upon our identification of relevant phenotypes.

Primary prevention of atopic diseases, which include asthma, has been remarkably unsuccessful so far. One aspect of this is our inability, with any level of certainty [70], in early childhood to

predict later childhood asthma [29. 47] or in childhood predict adult asthma [71]. Another aspect is to identify relevant-risk populations at an appropriate time when prevention is possible [70]. Childhood and even intra-uterine life [72, 73] represent a period in life in which immunology and pathophysiology undergoes decisive changes with life-long consequences [74, 75]. Thus, exposure to risk factors at certain time-points may differentially influence the developmental path [76]. This indicates that asthma-related outcomes may vary, not only according to early immunological and pathophysiological patterns, but may change course over time. The challenge is, therefore, to study if primary prevention of one ''atopic'' phenotype may reduce the development of another. For instance, loss-of-function in the filaggrin gene is involved in skin barrier defect and increases the risk of atopic eczema as well as asthma [77, 78]. Thus, if this triad constitutes a phenotype, is the asthma conferred through allergic sensitisation started off by allergens penetrating damaged skin? And what is the role of environmental exposure, in terms of asthma development, in the various phenotypes?

The numerous papers discussing asthma phenotypes, and the large number of suggested phenotypes (or even endotypes), are at present confusing. The overlap between the (novel) clusters (phenotypes) is often vast. No single phenotype, particularly in childhood, has, at present, significantly contributed to the individualised, targeted treatment or effective preventative strategies. Nevertheless, we need to improve our current understanding of the underlying mechanisms involved, in order to develop new drugs. And we may have to stratify primary or secondary preventive interventions in the future, based upon risk assessments and phenotypic characteristics at the start of life. But we are clearly not there at the moment.

Conclusions

Identification of ''true'' phenotypes for childhood asthma is likely to improve our understanding of the pathophysiology, increase our ability to find new treatment targets and enable us to individualise a patient's therapy. Thus, phenotype identification is likely to help us in the optimal secondary and tertiary prevention of asthma and other atopic disease; however, at present it is less likely to be useful for primary prevention. Novel data-driven statistical approaches could be essential in ascertaining the role of proteomics and with identifying new therapeutic targets, but are presently of limited usefulness for the clinician in preventing, predicting or treating childhood asthma.

Support Statement

K.C. Lødrup Carlsen is part of the MeDALL project.

Statement of Interest

One of K.C. Lødrup Carlsen's research projects, the ECA Study, has received funding from Phadia, as they supplied reagents for IgE measurements. She has also received a fee for giving a general talk on paediatric asthma from GSK. K-H. Carlsen has received fees for giving presentations from Nycomed Pharma, URIACH, MSD, Novartis. He has also received fees for consulting from MSD. These companies will not gain or lose from the present article.

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Chapter 2

Infantile and preschool asthma

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SUMMARY: In infants and preschool children the symptoms suggestive of asthma (*e.g.* wheeze) may be a clinical expression of a number of diseases with different aetiologies. If this is true, then it is unlikely that these different diseases would respond to the same treatment. Consequently, implementation of a management strategy which is effective for each individual patient is challenging, and controversies remain with respect to which patients should be given anti-asthma treatment, and when the treatment should be started and for how long. Whilst acknowledging these uncertainties, practicing physicians may use the Asthma Predictive Index (API) as a guide in clinical practice to identify young children with recurrent wheezing who are at risk of the subsequent development of persistent asthma, and who may benefit from preventative anti-asthma medication. We acknowledge that a number of questions on the most appropriate management strategy remain unanswered, including which type of medication is the best for individual patients (*e.g.* short-acting β-agonist *versus* inhaled corticosteroid (ICS) *versus* leukotriene receptor antagonist (LTRA)), dose (high *versus* low) and schedule (regular *versus* as needed).

KEYWORDS: Asthma, infants, predictive index, preschoolers, treatment, wheezing

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Even though almost 80% of asthmatics start having symptoms during the first 5 years of their life, asthma diagnosis in infants and preschool-aged (preschoolers) children is more challenging than in older children and adults [1]. Recurrent wheezing is frequently reported in preschoolers and is often association with upper respiratory tract infections (URTI), which in this age group occurs approximately six to eight times per year [2]; however, for many of these children wheezing does not recur later in life [3]. An additional challenge in this age group is that clinicians and practitioners often rely on parentally reported wheezing, which may be unreliable [4]. Furthermore, other conditions give rise to snoring, upper airway secretions, rattling sounds reflective of airway secretions or noisy breathing, all of which could be misinterpreted as a wheeze [5], and conventional pulmonary function testing is unavailable in most medical centres for children under the age of 5 years. Preschoolers are often diagnosed with asthma when a cough with wheezing or dyspnoea, which fluctuates over time, is reported in combination with the findings from a physical exam, family history and the presence of other clinical atopic diseases,

such as eczema or allergic rhinitis; response to treatment (either bronchodilator or continuously administered anti-inflammatory therapy) is also taken into account [6].

Phenotypes

Preschool wheezing is a highly heterogeneous condition and several birth cohort studies have proposed different phenotypes of childhood wheezing, based on its natural history [7]. The identification of the different phenotypes is important for studying the developmental pathways of asthma and the underlying disease mechanisms involved, the decision making process with regards the most appropriate treatment and the prediction of the clinical evolution [8]. A classic example of phenotyping, based on the temporal pattern of wheezing, was described in the well-known Tucson Children's Respiratory Study (TCRS), which identified three phenotypes based on the moment of onset and the resolution of wheezing. Symptoms with onset before 3 years of age were termed transient or persistent, depending on whether they had been resolved by the age of 6 years, while late-onset wheeze referred to symptoms that commenced after the age of 3 years and persisted thereafter [3]. This and other studies have suggested children with transient wheezing usually have no symptoms between colds and that this phenotype is related to a decreased lung function at birth, maternal smoking during pregnancy [9], male sex, presence of older siblings, attendance at a nursery [10–12], and the absence of atopy [13]. Alternatively, children with persistent wheezing may: have exacerbations caused by colds, allergens, or irritants; exhibit symptoms between major exacerbations; tend to have clinical atopic diseases, such as eczema or allergic rhinitis; often have first-degree relatives with atopy or asthma; and be born without any significant alteration of lung function [14]. In the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort study, using longitudinal latent class analysis, six different phenotypes were identified: never/infrequent wheeze, transient-early wheeze, prolonged-early wheeze, intermediate-onset wheeze, late-onset wheeze, and persistent wheeze [15]. A recent cross-cohort comparison of modelled phenotypes between ALSPAC and Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohorts has suggested that wheezing phenotypes identified by longitudinal latent class analysis were comparable in these births cohorts [16].

Recently, several publications have demonstrated the utility of an unbiased clustering approach in multidimensional data to identify different phenotypes of preschool asthma. In the Leicester cohort study, using a cluster analysis, three distinct wheeze phenotypes were identified: atopic persistent wheeze (patients with reduced levels of lung function and greater levels of bronchial hyperreactivity compared with healthy children), non-atopic persistent wheeze (patients who wheezed more commonly in winter and who were rarely atopic), and transient viral wheeze (patients with infrequent wheeze episodes triggered mostly by colds, which was resolved 2 to 4 years after the first survey) [17]. A principle component analysis using answers to multiple questions relating to wheeze and cough in Manchester Asthma and Allergy Study (MAAS) identified five distinct clinical phenotypes of coexisting symptoms amongst preschool children by the age of 5 years [18]. Similar phenotypic heterogeneity has been suggested for other secondary phenotypes often associated with preschool asthma (*e.g.* atopy) [19].

Although this body of work has improved the current understanding of the mechanisms and natural history of preschool wheezing disorders, the risk factors for the persistence and relapse of childhood asthma, as well as the outcome of pulmonary function, the phenotype allocation is very difficult (if not impossible) in a real-life clinical situation when a practicing paediatrician is assessing a young child with recurrent wheezing. Therefore, different wheeze phenotypes derived from the birth cohort studies are not particularly helpful for the management of patients in clinical practice [20]. Hence, a symptom-based classification has recently been proposed by the European Respiratory Society (ERS) Task Force on preschool wheeze as a treatment guide for clinicians in their everyday practice and for use in interventional studies that divide wheezing illnesses in preschool children into episodic (viral) wheeze (EVW) and multiple-trigger wheeze (MTW) phenotypes [21]. According to this classification, the term EVW refers to children with

exacerbations exclusively triggered by viral respiratory infections with no symptoms between episodes. Conversely, the term MTW refers to children who wheeze in response not only to viruses but also to other triggers, such as allergens, activity, weather, or cigarette smoke [21]. This has been considered a pragmatic and useful classification for preschoolers with recurrent wheezing, for everyday clinical practice, because some investigators believe it to be an important determinant of response to treatment: maintenance treatment with low to moderate continuous inhaled corticosteroids (ICS) is considered ineffective in patients with EVW [22, 23], while ICS maintenance works in patients with MTW [24]. Conversely, maintenance in addition to intermittent therapy with montelukast [25], as well as episodic high doses of ICS [22, 26], has a role in children with EVW. However, the proposed EVW/MTW classification has been recently criticised for several reasons. First, there is little evidence that these phenotypes are related to the longitudinal patterns of wheeze, or to different pathological processes [8]. Secondly, this symptom pattern of wheeze has not been objectively validated by pulmonary function tests or markers of airway inflammation, therefore, it is not clear if EVW and MTW represent distinct conditions with unique pathogenic mechanisms or are simply severity markers of the same disease [27]; however, SONNAPPA *et al.* [28] demonstrated lower levels of conductive airway ventilation inhomogeneity in patients that exhibit the MTW phenotype compared with EVW. Thirdly, this classification does not allow for differentiation between occurrences of wheeze of distinct severity and frequency from other respiratory symptoms, such as cough, colds, and chest congestion, and this is not taken into consideration [8]. Lastly, these two phenotypes do not appear to be stable over time; SCHULTZ *et al.* [29] recently demonstrated that children frequently change from exhibiting one type of clinically defined wheeze to the other in a course of only 1 year. Therefore, there is limited evidence to support the EVW/MTW classification and it is likely to change when additional evidence becomes available.

Prediction of wheeze persistence (clinical risk of asthma indices)

Identification of symptomatic preschoolers with recurrent wheezing who will go on to develop asthma enables an improvement in targeting secondary preventive actions and therapeutic strategies for those who are most likely to benefit [30]. To help in the early identification of preschoolers who wheeze and are at high risk of developing persistent asthma symptoms, a number of asthma predictive scores have been reported. By far the most widely used of these scores, in both the clinical and the research context, is the Asthma Predictive Index (API), developed about 10 years ago by using data from 1,246 children in the TCRS birth cohort [13]. This score combines simple and easily measurable clinical and laboratory parameters that can be obtained in any clinical setting. A positive API score requires recurrent episodes of wheezing during the first 3 years of life, as well as either one of two major criteria (physician-diagnosed eczema or parental asthma) or two of three minor criteria (physician-diagnosed allergic rhinitis, wheezing without colds, or peripheral eosinophilia greater than 4%). A loose index (fewer than three episodes per year and either one of the major or two of the minor criteria) and a stringent index (greater than three episodes per year and one of the major or two of the minor criteria) were created. Upon applying this algorithm, in the TCRS, children with a positive API were 2.6–13 times more likely to have active asthma between the ages of 6 and 13 years when compared with children who had a negative API [13]. A modified API (mAPI), which was used in a randomised trial of 285 subjects, incorporated allergic sensitisation to one or more aeroallergens as a major criterion and allergic sensitivity to milk, eggs or peanuts as a minor criterion, replacing physician-diagnosed allergic rhinitis in the original API [31].

Since the API was developed, some other asthma predictive scores have been devised, all including different factors predictive of wheeze persistence. In 2003, KURUKULAARATCHY *et al.* [32] developed a scoring system using data from 1,456 children in the Isle of Wight birth cohort. They found that a positive family history of asthma, a positive allergy skin-prick test at 4 years of age and recurrent chest infections at 2 years of age were associated with an increased risk of asthma at the age of 10 years [32]. More recently, in 2009 CAUDRI *et al.* [33], using data from 3,963 children from the

PIAMA birth cohort in the Netherlands, developed a predictive score called the PIAMA risk score, based on eight easily discernible clinical parameters (male sex, post-term delivery, parental education, inhaled medication used by parents, wheezing frequency, wheezing/dyspnoea apart from colds, number of respiratory tract infections, and diagnosis of eczema). Upon applying this predictive score to this birth cohort, children scoring 30 or higher had a risk factor >40% of having asthma at the age of 7–8 years [33].

Asthma predictive indices, especially the API, have been criticised because: they have been applied in clinical practice without a formal validation process having been performed in different populations *i.e.* external validation; they are not useful in predicting the long-term prognosis of preschool children with more severe or recurrent wheeze in clinical practice [34]; and they are relatively complex, whilst having no substantial benefit for predicting later asthma when compared with other simple prediction rules based on only frequency of wheeze [35]. However, those criticisms are not scientifically justifiable [36]. For example, the API and the PIAMA risk scores have recently been validated in independent populations [30, 35], and the API is an especially popular clinical prediction rule that combines simple and easily measurable clinical and laboratory parameters [13, 37] and that has been used for various purposes, such as recruiting children with high risk of developing persistent asthma symptoms for clinical trials [38, 39] and as a guide for treatment of preschoolers with recurrent wheezing in clinical practice [37]. The API was adopted in the most well-known asthma guidelines, Global Initiative for Asthma (GINA) [40] and National Institutes of Health (NIH) [41]. Finally, it is important to remark that the best parameter for determining the utility of any diagnostic test is the likelihood ratio, which in the case of the API is 7.3. This means that in places with a population at low, moderate, or high risk of having asthma at school age, *e.g.* 10%, 20% or 40%, for a child that goes to a paediatric clinic for recurrent wheezing episodes, the use of the API increases the probability of a prediction of asthma by four, three or two times, respectively (*e.g.* the pre-test probability of asthma moves from 10% to 42%, from 20% to 62%, or from 40% to 80%, respectively) (fig. 1). Additionally, the most useful property of the API is its ability to estimate the likelihood that preschoolers with recurrent wheezing will develop asthma by school age [42]. Therefore, we would argue that the use of the API and other asthma predictive scores are helpful in clinical situations and may help decrease morbidity in preschoolers with recurrent wheezing and who are at high risk of developing asthma, these scores would also help avoid the prescription of controller therapies to those children who probably have transient

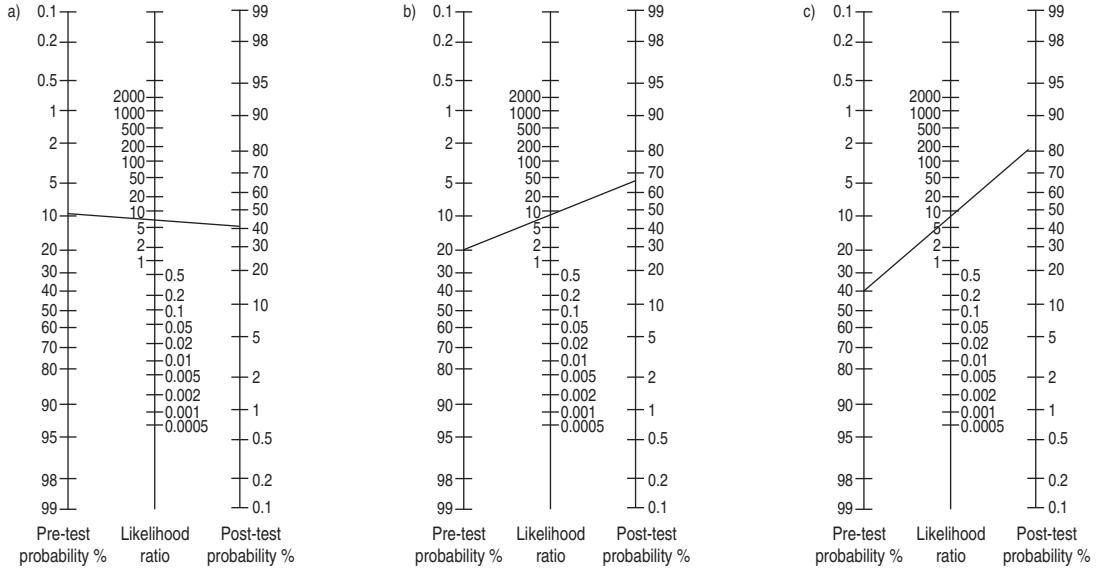

Figure 1. Application of the Asthma Predictive Index (API) at the likelihood ratio, which is 7.3, in hypothetical differing scenarios with a) a low, b) a moderate or c) a high-risk population of having asthma at school age.

wheeze rather than asthma. Moreover, there are three main reasons for diagnosing or labelling asthma in those infants/preschoolers who had recurrent wheezing and a positive API during their first 5 years of life. First, almost 80% of the asthma symptoms start during this period of life [1]. Secondly, the main decline in lung function occurs before the age of 5 years, as was shown in the TRCS [43]. Thirdly, even in developed countries the population of children with the worst asthma control is this age group [44]. Therefore, parents will be more prone to adhere to a prolonged treatment period with prevention drugs, *i.e.* ICS, if they know that the condition that causes the recurrent wheezing symptoms in their child is due to a chronic disease called asthma.

Treatment

In general, studies of therapy for preschool wheezing are often difficult to interpret, as they generally include heterogeneous groups of participants, with differences in age range, inclusion criteria, populations under study, severity of wheeze episodes, timing of initiation and form of administrating therapeutic strategies. Therefore, careful attention to all these aspects is important in the interpretation of the literature.

Short-acting β-agonists

These drugs, *i.e.* salbutamol, terbutaline, fenoterol and levalbuterol HFA, are the medications of choice to relieve bronchospasms during acute exacerbations of asthma/wheezing and for the treatment of exercise-induced bronchoconstriction (EIB). They should only be used on an as-needed basis at the lowest doses and frequency required; increased use, especially daily use, is a warning of deterioration of the disease and indicates the need to reassess treatment [40, 41].

Inhaled therapy constitutes the cornerstone of wheezing/asthma treatment in infants/preschoolers. A pressurised metered-dose inhaler (pMDI) with a valve spacer (with or without a face mask, depending on the child's age) is the preferred delivery system.

Inhaled corticosteroids

Preventing episodes of EVW have been shown to be difficult, with physicians often having no other option than to explain to parents how in a high proportion of cases the frequency and the severity of the exacerbations triggered by viral infections tend to diminish with the growth of the child [27]. Regular treatment with low-to-moderate ICS doses in children with EVW has been shown to be ineffective, and does not reduce the frequency or severity of the episodes. WILSON *et al.* [23] in a possibly underpowered study of 161 randomised patients with EVW, could not demonstrate significant differences in the use of rescue oral corticosteroids (OCS), admission to hospital, overall scores, number of symptom-free days, severity of symptoms, or duration of episodes between treatments when they compared budesonide (BD) 400 ug·day^{-1} *versus* placebo, administered over the course of a 4-month period [23]. A Cochrane review that tested if corticosteroid treatment, given episodically or daily, is beneficial to children with EVW concluded that there is no current evidence to favour maintenance, low-dose ICS for the prevention and management of episodic mild EVW [22].

In contrast, high-quality research evidence supports the use of ICS in preschoolers with MTW. BISGAARD *et al.* [45] gave either fluticasone propionate (FP) or sodium cromoglycate (SCG) for a 52-week period to a randomised group of 625 children aged from 1 to 3 years who had recurrent wheezing. Nearly half of the enrolled children had a history of atopic eczema or a family history of asthma, which is suggestive of the MTW phenotype in a great proportion of them. FP was associated with a significant reduction in symptoms, exacerbations, use of OCS and the use of rescue treatments compared with SCG [45]. WASSERMAN *et al.* [46] compared either FP twice daily *versus* placebo for 12 weeks in 332 children aged from 24 to 47 months with symptoms suggestive of MTW. When compared with placebo use FP significantly reduced asthma exacerbations, asthma symptoms and rescue albuterol use [46]. Similarly, CHAVASSE *et al.* [47] gave either FP

twice daily or a placebo during a 12-week period to a randomised group of 52 infants under the age of 1 year who had recurrent wheezing or cough and a personal or a first degree relative's history of atopy. FP was associated with significant improvement in mean daily symptoms and symptom-free days when compared with placebo treatment [47]. GUILBERT *et al.* [38] in the Prevention of Early Asthma in Kids (PEAK) study randomly assigned 285 children aged from 2 to 3 years with recurrent wheezing and a positive mAPI to treatment with either FP or a placebo for 2 years, followed by a 1-year period without medication. During the treatment period, use of FP was associated with a significantly greater proportion of episode-free days, a significant reduction in the use of rescue bronchodilators and a reduced rate of exacerbations that required the use of rescue OCS. However, there was no effect on asthma-related outcomes during the 1-year observational period after ICS was stopped, suggesting that the natural course of asthma in preschoolers, at high risk for subsequent asthma, is not modified by treatment with ICS. As a note of caution, it is important to mention that a reduction in the rate of growth was observed in the group assigned to ICS during the first year of treatment, suggesting that treatment with an ICS temporarily slows, but not progressively, the rate of growth in young children [40]. Finally, CASTRO-RODRIGUEZ and RODRIGO [48] conducted a meta-analysis on 29 randomised clinical trials (n=3,592) to compare the efficacy of ICS in infants and preschoolers with recurrent wheezing or asthma. They reported that patients who received ICS had significantly less wheezing/asthma exacerbations than those given a placebo (reduction by nearly 40% and with a number needed to treat of seven); *post hoc* subgroup analysis suggests that this effect was higher in those with a diagnosis of asthma than wheezing, but was independent of age (infants *versus* preschoolers), atopic condition, type of inhaled corticosteroid (BD *versus* FP), mode of delivery (metered-dose inhaler (MDI) *versus* nebuliser), and study quality and duration (less than 12 weeks *versus* equal to or greater than 12 weeks). In addition, children treated with ICS had significantly fewer withdrawals caused by wheezing/asthma exacerbations, reduced albuterol usage and more clinical and functional improvement than those on the placebo [48]. Consequently, regular treatment with ICS seems a reasonable strategy in children with moderate/severe recurrent wheezing, but therapy is only effective while being administered and cannot alter the natural history of the disease.

However, for young children with mild/moderate recurrent wheeze, perhaps the use of intermittent low-dose ICS with short-acting β_2-agonists (as required) will be enough, as was recently demonstrated in the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) study by ZEIGER *et al* [49]. They showed, in a random parallel study undertaken on 278 children aged from 12 to 53 months, that BD on a regular low-dose regimen (0.5 mg per night) was not superior to an intermittent high-dose regimen (1 mg twice a day for 7 days, starting early during a predefined respiratory tract illness) in reducing asthma exacerbations; however, daily administration led to a greater exposure to the drug during the year of the study [49]. If more studies confirm this finding, maybe intermittent therapy with high-dose ICS should be enough for controlling symptoms in infants/preschoolers with recurrent wheezing, avoiding secondary effects of daily chronic ICS use. Finally, taking the experience from the recent TReating Children to Prevent Exacerbations of Asthma (TREXA) study performed on 288 schoolchildren and adolescents (aged from 5 to 18 years) [50]. It was observed that ICS, when used as a rescue medication with short-acting β_2-agonists, might be an effective step-down strategy for young children with well-controlled mild asthma. This finding needs to be replicated in infants/preschoolers. Also, trials with regular low-dose regimen *versus* intermittent low-dose ICS with short-acting β_2-agonists should be studied, since a proportion of preschoolers with mild disease are overtreated, whilst those with severe disease are undertreated [50]. Perhaps, in the future, the use of intermittent low-dose ICS with short-acting β_2-agonists (*p.r.n.*) would be a good option for those young children with mild/moderate recurrent wheeze.

Alternatively, since children with EVW have exacerbations triggered solely by viral respiratory infections with no symptoms between episodes, their parents, in part because of concerns about secondary effects, usually prefer to provide treatments intermittently rather than continuously.

Consequently, various randomised clinical trials have tested if the intermittent use of ICS is beneficial for the acute management of preschoolers with EVW. Four studies have reported improved outcomes when ICS were used acutely for the management of EVW, specifically in the reduction of symptoms and OCS uses. DUCHARME *et al.* [51] reported a 50% reduction in the need for rescue OCS and a 20% reduction in other markers of severity and duration of exacerbations, through administering FP at a dose of 1,500 $\mu g \cdot day^{-1}$ to 129 children aged from 1 to 6 years of age, beginning at the onset of a URTI and continuing for a maximum of 10 days, over a period of 6–12 months. However, treatment with FP was associated with reduced height and weight gain [51]. SVEDMYR *et al.* [52] randomly assigned 55 children aged from 1 to 3 years with EVW to receive either BD or a placebo, beginning at the first sign of a URTI and continuing for 10 days. BD was administered at 1,600 $\mu g \cdot day^{-1}$ for the first 3 days and then at 800 $\mu g \cdot day^{-1}$ for the following 7 days. Asthma symptom scores were lower in children treated with BD than in those prescribed the placebo; however, the need for hospital care was not significantly different between the two groups [52]. WILSON and SILVERMAN [26] treated 24 preschoolers with episodic asthma, who were aged between 1–5 years, with either beclomethasone dipropionate (BDP) (2,250 $\mu g \cdot day^{-1}$) or a placebo, beginning at the first sign of an asthma attack and continuing for 5 days. Both daytime and night-time symptoms over the first week of the attack were significantly reduced with BDP treatment [26]. Likewise, CONNETT and LENNEY [53] reported that both mean daytime wheeze and mean night-time wheeze in the first week after infection were significantly lower in children with EVW treated with 1,600 $\mu \cdot day^{-1}$ of BD compared with the placebo, beginning at the onset of a URTI and continuing for 7 days or until symptoms had resolved for 24 hours [26]. A Cochrane review reported a non-significant trend towards a 50% reduction in requirement for OCS with improved symptoms and parental preference, concluding that episodic high-dose ICS provide a partially effective strategy for the treatment of mild EVW in childhood [22]. Given the occurrence of an average of six to eight URTI per year in children, the high doses of ICS used in these studies, and the reduced rate of growth in height and weight reported with this strategy, the benefits of ICS must be balanced against the potential side-effects of repeated short courses of high doses of ICS. Therefore, this strategy for treating preschoolers with EVW should not be routinely recommended for use in clinical practice.

Oral corticosteroids

Since children with EVW have episodic exacerbations triggered by viral respiratory infections, various studies have evaluated if OCS when administered during the acute wheezing episodes are beneficial in these patients. The evidence for this therapeutic strategy is conflicting. CSONKA *et al.* [54] performed a randomised, placebo-controlled study on 230 children with EVW, aged between 6 and 35 months, who were attended to in an emergency room and received either oral prednisolone (2 $mg \cdot kg^{-1} \cdot day^{-1}$) or a placebo for 3 days. Although the hospitalisation rates were similar between the two groups, the severity of the disease, the length of hospital stay, and the duration of symptoms were all reduced in children treated with prednisolone [54]. Likewise, DAUGBJERG *et al.* [55] compared different treatments for acute wheezing in 123 children aged from 1.5 to 18 months, and reported a significantly earlier discharge in infants receiving prednisolone compared with those receiving terbutaline alone. In contrast to these two studies, PANICKAR *et al.* [56] in a randomised, double-blind, placebo-controlled trial, undertaken on 687 children aged from 10 to 60 months who had been admitted to three hospitals in England suffering from an attack of wheezing associated with a viral respiratory infection, evaluated the efficacy of a 5-day course of oral prednisolone (10 mg once a day for children 10 to 24 months of age and 20 mg once a day for older children). As there was no significant difference in the duration of hospitalisation, the clinical score, albuterol use, the 7-day symptom score, or the number of adverse effects, the authors concluded that in preschoolers admitted to hospital with mild-to-moderate wheezing associated with a viral respiratory infection, oral prednisolone was not superior to a placebo [56]. One other therapeutic strategy that has been considered for treating children with EVW consists of keeping the OCS at home and asking parents to commence use at the first sign of symptoms, *i.e.* without waiting for a medical review, in an effort to abort the