



Asthma phenotypes in childhood

Monica B. Reddy^a and Ronina A. Covar^b

Purpose of review

This review describes the literature over the past 18 months that evaluated childhood asthma phenotypes, highlighting the key aspects of these studies, and comparing these studies to previous ones in this area.

Recent findings

Recent studies on asthma phenotypes have identified new phenotypes on the basis of statistical analyses (using cluster analysis and latent class analysis methodology) and have evaluated the outcomes and associated risk factors of previously established early childhood asthma phenotypes that are based on asthma onset and patterns of wheezing illness. There have also been investigations focusing on immunologic, physiologic, and genetic correlates of various phenotypes, as well as identification of subphenotypes of severe childhood asthma.

Summary

Childhood asthma remains a heterogeneous condition, and investigations these various presentations, risk factors, and outcomes are important since they can offer therapeutic and prognostic relevance. Further investigation into the immunopathology and genetic basis underlying childhood phenotypes is important so therapy can be tailored accordingly.

Keywords

asthma, childhood asthma phenotypes, pulmonary function test

INTRODUCTION

Investigating asthma phenotypes in children remains essential today for several reasons. Identification of a specific phenotype helps counsel the family as to what to expect with regard to outcome and prognosis in the child. A particular phenotype may potentially provide insight with regard to a tailored treatment regimen. External exposures and risk factors related to an asthma phenotype may be modifiable. Although we currently have algorithms to predict the likelihood of developing asthma [1], determining an asthma phenotype in a child remains a subjective effort. A limitation of current asthma phenotyping approaches is that these are largely based on the clinical presentation of the patient, and only recently do some studies provide some insight into the underlying immunopathology, as we will discuss later.

A landmark study, which investigated early childhood wheezing phenotypes, was from the Tucson Children's Respiratory Study [2]. These children were classified as never wheezers, early transient wheezers, persistent wheezers, and late-onset wheezers. Although each phenotype was associated with distinct risk factors and lung function, the phenotypic determinations were made at the age

of 6. This study [3] provided the basis for an important clinical trial in high-risk young children, which determined if long-term inhaled corticosteroid therapy could induce remission of asthma.

When discussing childhood asthma phenotypes, an important distinction must be made first between early wheezing phenotypes and childhood asthmatic phenotypes, as not all early wheezers progress to having a diagnosis of asthma. Guilbert *et al.* [4*] thoroughly reviewed various phenotypes from the historic birth cohorts (including the Tucson Children's Respiratory Study, the Italian Studies of Respiratory Disorders in Childhood and the Environment classification, and the Avon Longitudinal Study of Parents and Children classification), school-age population-based studies (including New Zealand Classification and the Melbourne classification), and symptomatic

^aNational Jewish Health and ^bDepartment of Pediatrics, University of Colorado Denver Health Sciences Center, Denver, Colorado, USA

Correspondence to Ronina A. Covar, MD, National Jewish Health, 1400 Jackson Street, J321, Denver, CO 80206, USA. . Tel: +1 303 398 1502; fax: +1 303 270 2170; e-mail: covarr@njhealth.org

Curr Opin Allergy Clin Immunol 2016, 16:000–000

DOI:10.1097/ACI.0000000000000252

KEY POINTS

- Childhood asthma phenotypes can be created using various statistical analyses, which account for onset and temporal patterns, and associated risk factors.
- Well defined outcomes of early childhood phenotypes are becoming more and more available in different settings across the world.
- Examining risk factors and studying the immunologic and genetic basis of phenotypes of childhood asthma may offer modifiable or preventive options.
- Further investigations into the basis underlying the various childhood phenotypes are important so therapy can be targeted, and failure of specific treatments can be predicted.

classification of wheeze (including episodic and multitrigger wheeze). This review also summarizes multiple risk factors, biomarkers, and predictive indices for asthma.

Historically, phenotypes have also been described based on both the patterns of wheeze (early wheeze, transient wheeze, persistent wheeze, and others) and based on the findings of the airway inflammatory phenotype (eosinophilic, neutrophilic, and paucicellular). In the last 2 years, there have been several important studies investigating childhood asthma phenotypes. These studies have identified new phenotypes on the basis of statistical analyses (using cluster analysis and latent class analysis methodology); evaluated the outcomes of previously established early childhood asthma phenotypes; investigated the risk factors of certain phenotypes; determined the immunologic, physiologic, and genetic correlates of various phenotypes; and identified subphenotypes of severe childhood asthma (Table 1) [5,6²²,7²³,8,9²⁴,10²⁵,11²⁶,12,13²⁷,14²⁸,15,16,17²⁹,18,19³⁰,20,21,22³¹].

DEFINING PHENOTYPES ON THE BASIS OF CLUSTER AND LATENT CLASS ANALYSES

Cluster analysis is the hypothesis-free technique of separating phenotypes on the basis of similar characteristics entered by the user. Just *et al.* [23] utilized cluster analysis to describe phenotypes of early childhood wheezing. They examined 551 children aged less than 36 months and identified three unique clusters: a mild episodic viral wheeze cluster characterized by mild disease and normal chest radiographic results, a nonatopic uncontrolled wheeze cluster characterized by severe disease

despite high doses of inhaled corticosteroids, and an atopic multitrigger wheeze cluster, which in addition to having multiple triggers also had eczema and evidence of atopy on serum-specific IgE testing.

On a larger level, the MeDALL project included children from seven European population-based cohorts [the Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic (BAMSE), Danish Allergy research center, Melbourne Atopy Cohort Study, GINIplus, LISApplus, Pollution and Asthma Risk: an Infant Study, and the Prevention and Incidence of Asthma and Mite Allergy cohorts; the total numbers of subjects studied were 17 209 children at age 4 and 14 585 children at age 8] and grouped these children using cluster analysis according to multiple variables, including a history of physician diagnosis of asthma, onset of asthma, asthma therapy, and IgE level, among others. They demonstrated that at 4 and 8 years, two clusters were identified; a reference group with low frequencies of asthma, rhinitis, and eczema and a second group with high frequencies of these diseases that was considered together as an allergic comorbidity cluster [5]. The patients in the allergic comorbidity cluster not only had high frequencies of asthma, rhinitis, and eczema but also had a higher prevalence of history of wheeze, additional nasooocular allergy symptoms (ocular pruritus and nasal congestion), urticaria, and food allergies.

A cluster analysis from the Childhood Asthma Management Program, which enrolled 1041 mild to moderate asthmatic patients aged 5–12 years, demonstrated five phenotypes from baseline characteristics defined on the basis of each factor grouping: atopic burden, airflow limitation, and baseline exacerbation history [6²²]. These phenotypes were defined as: ‘LLL: low atopy, obstruction, and exacerbation rate’; ‘HLL: atopic asthma with low levels of obstruction and medium rates of exacerbation’; ‘HHM: atopic asthma with high levels of obstruction and medium rates of exacerbation’; ‘MHH: moderately atopic asthma with high levels of obstruction and high exacerbation rates’; and ‘HHH: highly atopic asthma with high levels of obstruction and high exacerbation rates.’ The longitudinal stability or consistency of these clusters over the 4-year trial was demonstrated using measures of pulmonary function and exacerbation rates, with LLL having the best outcome over time. Another interesting observation was the heterogeneity in treatment responses between the groups. In terms of exacerbation during the trial phase, better response to an inhaled steroid compared with either placebo or nedocromil was found for LLL, HLL, and HHM. However, the MHH group responded better to either inhaled steroid or nedocromil compared

Table 1. Summary of recent findings on pediatric asthma phenotypes

Asthma phenotypes in children have recently been classified using cluster and latent analysis

MeDALL project [5]: reference group with low frequencies of asthma, rhinitis, and eczema versus an allergic comorbidity cluster (a group with high frequencies of asthma, rhinitis, eczema, prevalence of history of wheeze, nasooocular allergy symptoms, urticaria, and food allergies)

CAMP [6[■]]:

LLL: low atopy, obstruction, and exacerbation rate

HLL: atopic asthma with low levels of obstruction and medium rates of exacerbation

HHM: atopic asthma with high levels of obstruction and medium rates of exacerbation

MHH: moderately atopic asthma with high levels of obstruction and high exacerbation rates

HHH: highly atopic asthma with high levels of obstruction and high exacerbation rates

TENOR [7[■]] (subphenotypes of severe asthma):

A white, nonatopic female phenotype

An atopic phenotype

Male sex phenotype

A nonwhite race phenotype

An aspirin sensitivity phenotype

Latent class analysis from the PASTURE study compared five groups identified by cluster (persistent wheeze, late-onset wheeze, intermediate, transient, and no/infrequent wheeze) versus clinical phenotypes as determined by history and evaluation (phenotypes defined as frequent wheeze, asthma diagnosis, unremitting wheeze, recurrent unremitting wheeze, multitrigger wheeze, and episodic wheeze) [8]

Evaluating long-term outcomes of early childhood phenotypes

BAMSE prospective cohort study outcomes of phenotypes at age 8 and 16 years based on asthma onset [9[■]]: except for 'never asthma,' loss of pulmonary function at age 16 was seen; patients with active asthma also demonstrated impairment in small airways

Never asthma

Early transient asthma

Early persistent asthma

Late-onset asthma

Melbourne Atopy Cohort Study outcomes of phenotypes at age 12 and 18 years based on patterns of wheezing [10[■]]: persistent wheeze phenotype had a reduced growth in prebronchodilator FEV1 over time, and the intermediate-onset patients had irreversible airflow limitation at the age of 18 years

Never/infrequent wheezers

Early transient wheezers

Early persistent wheezers

Intermediate-onset wheezers

Late-onset wheezers

Investigating risk factors of various wheezing or asthma phenotypes

Antibiotic use in the first year of life was associated with transient wheezing (onset and resolution by age 3 years) and persistent asthma (wheezing before age 3 and continuing through 7 years) phenotypes, and not the late-onset phenotype (wheezing beginning after age 3) [11]

Children with lower socioeconomic positions were likely to have asthma alone and less likely to have atopy alone [12]

Socioeconomic status was also associated with persistent wheeze (and not never/infrequent wheeze, transient early wheeze, prolonged early wheeze, intermediate-onset wheeze, late-onset wheeze) [12]

Tobacco exposure from utero through childhood contributed to risk of having asthma alone, and not atopy alone nor both asthma and atopy [12]

Determining the immunologic, physiologic, and genetic correlates of various phenotypes

Immunologic

Allergic asthmatic patients in the German Clinical Asthma Research Association cohort have an increased number of T regulatory cells, compared with healthy controls. T regulatory cells of allergic asthmatic patients significantly suppressed IL-5, IL-13, and IFN γ with a decrease in innate immune regulators compared with nonallergic asthmatic patients [13[■]]

Obese asthmatic patients have a Th2 cytokine profile, and a higher expression of TLR2 and TLR9, compared with the nonobese asthmatic patients [14[■]]

Physiologic

Lung function impairment from birth through age 16 years was found in an asthma phenotype with atopic dermatitis and allergic rhinitis, and not in those with asthma only, an asthma and allergic rhinitis phenotype, or an asthma and atopic dermatitis phenotype [15]

Genetic

Nuclear factor I/A, a strong candidate gene associated with asthma and allergic rhinitis versus allergic rhinitis alone or asthma alone phenotypes [16]

Patient with eosinophilic asthma had higher levels of CLC, CPA3, and DNASE1L3 gene expression, whereas patients with neutrophilic asthma had increased gene expression of IL-1 β , ALPL, and CXCR2 [17[■]]

From the Copenhagen Prospective Studies on Asthma in Childhood, an SNP rs10063472 was associated with transient early symptoms, whereas the rs6888135 SNP was identified as having asthma at any point from birth until 7 years [18]

SNP (rs10044254) was recently defined, which is associated with an improved response to inhaled corticosteroids in pediatric cohorts [19[■]]

E. Identifying subphenotypes of severe childhood asthma

Severe asthma in children is different from severe asthma in adults [20]. Although both can have eosinophilic airway inflammation, children with severe asthma are predominantly male and severely atopic and adults with severe asthma have female predominance, aspirin sensitization, and nasal polyposis. Although both can exhibit evidence of airway remodeling, adults with severe asthma have fixed airway obstruction and more extensive airway remodeling changes

TENOR post hoc analysis showed five phenotypes using cluster analysis for adults and adolescents but not seen in the analysis for younger children [7[■]]

A white, nonatopic female phenotype

An atopic phenotype

Male sex phenotype

A nonwhite race phenotype

An aspirin sensitivity phenotype

Therapy-resistant asthma phenotype characterized by low FEV1 and high exhaled nitric oxide was defined in 20 of 36 children with severe asthma [21]

A phenotype of 'frequent exacerbators' in adults with severe asthma was also characterized by high exhaled nitric oxide and a history of smoking [22[■]]

ALPL, alkaline phosphatase, tissue-nonspecific isozyme; CLC, Charcot-Leyden crystal protein; CPA3, carboxypeptidase A3; CXCR2, chemokine (C-X-C motif) receptor 2; DNASE1L3, deoxyribonuclease I-like 3; PASTURE, Protection against Allergy – Study in Rural Environments.

with placebo; in contrast, the HHH group did not demonstrate differences in treatment responses. Although the sample size in the more severe clusters was small, this exemplifies the concept that phenotypes have the potential to provide direction with regard to treatment, such as those outlined in this study, and could provide the clinician with significant direction for patient-directed therapy.

A post hoc cluster analysis was performed on children, adolescents, and adults in the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study (a study of severe asthma); the post hoc analysis identified five phenotypes that could be determined for adult and adolescent asthmatic patients that correlated to outcomes (a white, nonatopic female phenotype; an atopic phenotype; a male sex phenotype; a nonwhite race phenotype; and an aspirin sensitivity phenotype) but these phenotypes could not be determined in children [7[■]].

Latent class analysis is increasingly utilized as an unsupervised, hypothesis-free statistical method that classifies patients on the basis of provided data. However, the clinical implications of defining phenotypes on the basis of statistical analysis of these epidemiologic studies are still not clear. The differences between assessing phenotype clinically versus using latent class analyses were compared

recently by Depner *et al.* using data from the Protection against Allergy – Study in Rural Environments (PASTURE) birth cohort. The five groups identified by cluster analysis (persistent wheeze, late-onset wheeze, intermediate, transient, and no/infrequent wheeze) also compared with clinical phenotypes as determined by history and evaluation (phenotypes defined as frequent wheeze, asthma diagnosis, unremitting wheeze, recurrent unremitting wheeze, multitrigger wheeze, and episodic wheeze), demonstrating support of analysis by the latent class analysis [8]. This study was unique in the two definitions of phenotypes as those identified by latent cluster analysis was only based on patterns of wheeze, whereas for the clinical phenotypes, an asthma diagnosis was assessed at the age of 6 with multiple other clinical characteristics included as well.

EVALUATING THE LONG-TERM OUTCOMES OF EARLY CHILDHOOD PHENOTYPES

Early asthma phenotypes were evaluated prospectively to determine symptom outcome and pulmonary function. We will outline some of the more recent larger analyses here. The BAMSE prospective birth cohort study followed children until the ages of 8 and 16 years, at which time points clinical

assessments, including spirometric data, were obtained. The children were stratified into four phenotypes on the basis of a questionnaire: 'never asthma,' 'early transient asthma,' 'early persistent asthma,' and 'late-onset asthma.' They demonstrated that for all phenotypes with asthma, there was a loss in pulmonary function and specifically a lower Forced expiratory volume in 1 second (FEV1) at the age of 16 [9[¶]]. They also demonstrated that for those patients with active asthma there was impairment in the small airways.

Another birth cohort study, the Melbourne Atopy Cohort Study, which followed children who were at high risk for allergy, assessed respiratory symptoms and spirometry at the age of 12 and 18. Early phenotypes were distinguished on the basis of wheeze (never/infrequent, early transient, early persistent, intermediate onset, and late onset). Transient wheezers did not have any respiratory sequelae at the age of 18, the persistent wheeze phenotype had a reduced growth in prebronchodilator FEV1 over time, and the intermediate-onset patients had irreversible airflow limitation at the age of 18 years [10^{¶¶}].

IDENTIFYING RISK FACTORS FOR WHEEZING PHENOTYPES

Investigations into the infant microbiome and the development of atopy have demonstrated a distinct relationship between early antibiotic use and not only the development of asthma but also certain wheezing phenotypes [11[¶]]. Ong *et al.* followed a cohort of children from birth, and evaluated for the development of asthma at age 7. They described three asthma phenotypes: the transient wheezing phenotype (defined as wheezing that began and resolved by 3 years of age); the late-onset asthma phenotype (which began after 3 years of age); and the persistent asthma phenotype (which began before 3 years of age and continued on through 4–7 years of age). Antibiotic use in the first year of life was associated with the development of transient wheezing and persistent asthma. In addition, the odds of persistent asthma doubled when five or more antibiotic courses had been used in early childhood.

A prospective study involving children in the Avon Longitudinal Study of Parents and Children identified socioenvironmental factors that were associated with certain phenotypes. The phenotypes were defined on the basis of reported MD-diagnosed asthma or atopy (based on environmental skin testing at age 7–8 years; no asthma or atopy, children with asthma alone, children with asthma and atopy, and children with atopy alone) and on the basis of temporal wheeze patterns using latent class analysis (never/infrequent wheeze, transient early

wheeze, prolonged early wheeze, intermediate-onset wheeze, late-onset wheeze, and persistent wheeze). Multiple socioeconomic factors and exposures (tobacco smoke, hygiene hypothesis variables, and breastfeeding, among others) were evaluated for each phenotype. Overall, children with lower socioeconomic positions were more likely to have asthma alone and less likely to have atopy alone. With respect to wheezing phenotypes, children with lower socioeconomic position were more likely to have persistent wheeze, but such association between socioeconomic status and other types of wheezing was not found. This study [12] also tried to determine the effects of various environmental exposures such as tobacco smoke. Tobacco smoke exposure throughout the life course, and not at specific time periods (*in utero* or childhood), contributed to the asthma alone, and in contrast with lower odds of atopy alone.

IMMUNOLOGIC, PHYSIOLOGIC, AND GENETIC CORRELATES OF VARIOUS ASTHMA PHENOTYPES

Immunologic

Taking a closer look at the basis of different phenotypes, Raedler *et al.* examined 275 steroid-naïve 4–15-year-old German children in the Clinical Asthma Research Association cohort. Quantitative and functional T regulatory and TH17 cell analyses were performed using peripheral blood mononuclear cells and then multiple cytokines and gene expression were assessed. Three phenotypes were identified on an immunologic basis: allergic asthma, nonallergic asthma, and healthy controls. Patients with allergic asthma demonstrated an increase in T regulatory cells compared with healthy controls but not nonallergic asthmatic patients [13[¶]]. They furthermore demonstrated that in the allergic asthmatic patients, the T regulatory cells significantly suppressed IL-5, IL-13, and IFN γ and there was a decrease in innate immune regulators compared with nonallergic asthmatic patients. The nonallergic asthmatic patients demonstrated an increase in IL-1 β , IL-17 shift, and neutrophilia and in addition expressed higher levels of anti-inflammatory IL-37, proline-serine-threonine phosphatase-interacting protein 2, and neutrophil receptor genes.

Obese childhood asthmatic patients demonstrate a Th2 cytokine profile compared with their nonobese counterparts [14[¶]]. An obese asthmatic phenotype was identified by Sanchez-Zauco *et al.*, which was not only identified by this increased Th2 profile but also in addition had a higher expression of Toll-like Receptor 2 and Toll-like receptor 9.

Physiologic

The effect of early allergic sensitization and atopy on the development of asthma has been described and is well accepted when considering environmental exposures contributing to asthma phenotypes. A more recent study [15] demonstrated that the long-term trajectory of lung function impairment beginning in childhood and continuing on may be secondary to disease onset *in utero*, rather than secondary allergic sensitization. In this study, Lodrup *et al.* studied children in the Environment and Childhood Asthma birth cohort study. A total of 329 study participants had lung function measured at birth, then again at ages 10 and 16 years. Asthma phenotypes were defined by the diagnosis of asthma at age 10 to 16 years combined with allergic rhinitis and/or atopic dermatitis, asthma only, an asthma and allergic rhinitis phenotype, an asthma and atopic dermatitis phenotype, and asthma with both allergic rhinitis and atopic dermatitis. In the phenotype of 'asthma, atopic dermatitis, and allergic rhinitis,' lung function impairment was seen from birth and lasting through age 16 years, implying that the disease onset was *in utero*.

Genetic

Multiple polymorphisms in genes regulating immune mechanisms and the development of recurrent wheezing in infants have been described [24[¶]]. The nuclear factor I/A gene was described as a strong candidate gene for asthma and allergic rhinitis [16] versus allergic rhinitis alone or asthma alone phenotypes.

Sputum analyses in adult patients have demonstrated more advanced findings, with sputum biomarkers that can identify the inflammatory phenotypes of asthma (eosinophilic versus neutrophilic) and in turn also predict inhaled corticosteroid response [17[¶]]. This study identified six gene biomarkers that could discriminate eosinophilic asthma from noneosinophilic asthma, paucigranulocytic asthma, or neutrophilic asthma. These genes were *Charcot-Leyden crystal protein* (CLC); *carboxypeptidase A3* (CPA3); *deoxyribonuclease I-like 3* (DNASE1L3); *IL-1 β* ; *alkaline phosphatase, tissue-nonspecific isozyme* (ALPL); and *chemokine (C-X-C motif) receptor 2* (CXCR2). Patient with eosinophilic asthma had higher levels of CLC, CPA3, and DNASE1L3 gene expression, whereas patients with neutrophilic asthma had increased gene expression of IL-1 β , ALPL, and CXCR2. In addition, inhaled corticosteroid treatment decreased the gene expression in eosinophilic asthmatic patients and this six-gene signature could predict inhaled corticosteroid response. Further pediatric studies that can

extensively analyze sputum biomarkers are needed at this time.

The protocadherin-1 gene (important in cell to cell adhesion) variants have been shown to increase the risk of development of asthma in early childhood [18]. This was done by the Copenhagen Prospective Studies on Asthma in Childhood, which is a prospective birth cohort study with the objective of finding the gene–environment phenotype relationship to the development of atopy. Children were enrolled at 1 year and then reassessed at intervals until the age of 7. The development of 'troublesome lung symptoms' as defined by symptoms of breathlessness, wheeze, and cough were also assessed and patients with recurrent symptoms were classified into transient early symptoms (with symptoms beginning and remitting in the first 3 years), late-onset symptoms (with symptoms beginning after 3 years), and persistent symptoms (symptoms beginning before 3 years and continuing after 3 years). An single nucleotide polymorphism (SNP) rs10063472 was associated with transient early symptoms. Furthermore, the rs6888135 SNP was identified as having asthma at any point from birth until 7 years.

It is known that variations in endotoxin response are associated with asthma and atopy in childhood, and multiple SNPs in genes involved in endotoxin signaling that appear to be associated with in-vitro IgE synthesis and in-vivo airway hyper-responsiveness were recently described [25]. Although genome studies have largely been focused on lung function and exacerbations, a novel SNP (rs10044254) was recently defined, which is associated with an improved response to inhaled corticosteroids in pediatric cohorts [19[¶]]. In the future, it is possible that we may be able to phenotype a young asthmatic patient at the genetic level, and this will ideally provide guidance in response to therapy and outcome.

SUBPHENOTYPES OF SEVERE ASTHMA

Fainardi and Saglani highlight the importance of differentiating the pediatric severe asthmatic patient from the adult severe asthmatic patient [20]. They describe that severe asthma in children is characterized by eosinophilic airway inflammation, male predominance and severe atopy with multiple aeroallergen sensitization and evidence of airway remodeling. Severe adult asthmatic patients are also predominantly eosinophilic, are female predominant, can have aspirin sensitization and nasal polyps, a fixed airway obstruction, and have more extensive airway remodeling (with increased smooth muscle mass, angiogenesis, and

increased thickness of the reticular basement membrane).

The TENOR post hoc analysis was discussed earlier [7[■]], which examined children 6–12 years and then adolescents older than 12 years who had severe asthma. Five clusters were identified with distinct phenotypes for adults/adolescents but not children (including a white, nonatopic female phenotype, an atopic phenotype, a male sex phenotype, a nonwhite race phenotype, and an aspirin sensitivity phenotype).

A prospective study in Brazil followed 61 children aged 6–18 years who had been diagnosed with severe uncontrolled asthma. Of those children, 10 had been misdiagnosed, 15 had moderate asthma, and 36 had severe asthma. Of the 36 children with severe asthma, 20 were treatment-resistant. When comparing on the baseline clinical characteristics obtained, children with low FEV1 and high exhaled nitric oxide distinguish a treatment-resistant phenotype [21].

Further studies have looked further to investigate exhaled nitric oxide with regard to asthma exacerbations and have found a correlation as well [22[■]]. Kupczyk *et al.* examined adult severe asthmatic patients and mild to moderate asthmatics and characterized a phenotype of ‘frequent exacerbators.’ This group of individuals was significantly more prone to exacerbations and was characterized by higher fractional exhaled nitric oxide and a history of smoking.

CONCLUSION

Childhood asthma phenotypes can be done in a number of ways. In early childhood when wheezing is quite common, the wheezing onset and pattern over time have remained a popular scheme of designating phenotypes and identifying risk factors, exposures, and outcome. In older children, incorporating multiple variables, such as atopic status, risks, lung function impairment, or exacerbation risks to create phenotypes can potentially predict treatment response or lack thereof. Other phenotypes of asthma, such as exercise-induced asthma and nocturnal asthma, are not discussed here but remain important considerations as well.

The ultimate goal for classification is to provide optimal treatment and to counsel families appropriately with regard to outcome. With personalized medicine on the forefront of treatment today, phenotyping becomes all the more critical; however, without linking these phenotypes to actual immunopathology and genetics does not give much insight into management of a patient seen frequently in the clinic setting. Easily measurable

biomarkers are important to determine phenotype and patient classification, and are more readily attainable than genetic evaluations at present. Serum, sputum, or other easily attainable biomarkers could ultimately be obtained and then used to stratify patients into phenotypes that could dictate disease outcome. Further investigation is needed in this area and until this time, the current literature presented will likely be utilized to describe childhood asthma phenotypes.

Acknowledgements

None.

Financial support and sponsorship

R.A.C.: Glaxo Smith Kline: manuscript author and Advisory Board and research grant; Roche: research grant; Astra Zeneca: research grant; Novartis: Advisory Board.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Castro-Rodriguez JA, Wright AL, Taussig LM, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Resp Crit Care Med* 2000; 162:1403–1406.
2. Martinez FD, Wright AL, Taussig LM. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332:133–138.
3. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *New Engl J Med* 2006; 354:1985–1997.
4. Guilbert TW, Mauger DT, Lemanske RF. Childhood asthma-predictive phenotype. *J Allergy Clin Immunol Pract* 2014; 2:664–670.

The article provides an excellent review of historical phenotyping studies and up-to-date information on comorbidities, biomarkers, and genetic polymorphisms.

5. Garcia-Aymerich J, Benet M, Saeys Y, *et al.* Phenotyping asthma, rhinitis and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster. *Allergy* 2015; 70:973–984.
6. Howrylak J, Fuhlbrigge A, Strunk R, *et al.* Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. *J Allergy Clin Immunol* 2014; 133:1289–130112.

The landmark study from the Childhood Asthma Management Program demonstrated that five cluster phenotypes could be defined on the basis of atopy, airflow limitation, and history of exacerbation.

7. Schatz M, Hsu, Jin-Wen, Zeiger R, *et al.* Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2014; 133:1549–1556.

The TENOR post hoc analysis examined children 6–12 years and then adolescents greater than 12 years. Five clusters were identified with distinct phenotypes for adults/adolescents but not children (including a white, nonatopic female phenotype, an atopic phenotype, a male sex phenotype, a nonwhite race phenotype, and an aspirin sensitivity phenotype).

8. Depner M, Fuchs O, Genuneit J, *et al.* Clinical and epidemiologic phenotypes of childhood asthma. *Am J Respir Crit Care Med* 2014; 189:129–138.
9. Hallberg J, Thunqvist P, Schultz ES, *et al.* Asthma phenotypes and lung function up to 16 years of age-the BAMSE cohort. *Allergy* 2015; 70:667–673.

The BAMSE cohort phenotyped patients into four groups: ‘never asthma,’ ‘early transient asthma,’ ‘early persistent asthma,’ and ‘late-onset asthma.’ For all phenotypes with asthma, there was a loss in pulmonary function and specifically FEV1 at the age of 16.

10. Lodge CJ, Lowe AJ, Allen KJ, *et al.* Childhood wheeze phenotypes show less ■ than expected growth in FEV1 across adolescence. *Am J Respir Crit Care Med* 2014; 189:1351–1358.

The Melbourne Atopy Cohort Study identified wheeze phenotypes of 'never wheeze,' 'early transient wheeze,' 'early persistent,' 'intermediate onset,' and 'late onset,' which were defined on the basis of a decrease in prebronchodilator FEV1. The persistent wheeze phenotypes in childhood were associated with reduced growth in prebronchodilator FEV1 over adolescence. The intermediate-onset wheezers showed irreversible airflow limitation by 18 years. The early transient wheeze group was defined as a benign condition with no sequelae for respiratory health by age 18.

11. Ong MS, Umetsu DT, Mandl KD. Consequences of antibiotics and infections ■ in infancy: bugs, drugs, and wheezing. *Ann Allergy Asthma Immunol* 2014; 112:441–445.

The article demonstrated that antibiotic use in the first year of life was associated with the development of transient wheezing and persistent asthma. A dose-response effect was observed. When five or more antibiotic courses were received, the odds of persistent asthma doubled. There is no association between antibiotic use and late-onset asthma.

12. Galobardes B, Granell R, Sterne J, *et al.* Childhood wheezing, asthma, allergy, atopy, and lung function: different socioeconomic patterns for different phenotypes. *Am J Epidemiol* 2015; 182:763–774.

13. Raedler D, Ballenberger N, Klucker E, *et al.* Identification of novel immune ■ phenotypes for allergic and nonallergic childhood asthma. *J Allergy Clin Immunol* 2015; 135:81–91.

The article demonstrated that patients with allergic asthma had increased T regulatory cells compared with healthy controls and those T regulatory cells from the allergic asthma patients significantly suppressed IL-5, IL-13, and IFN γ .

14. Sanchez-Zauco N, del Rio-Navarro B, Gallardo-Casas B, *et al.* High expression of Toll-like receptors 2 and 9 and Th1/Th2 cytokines profile in obese asthmatic children. *Allergy Asthma Proc* 2014; 35:34–41.

The study demonstrated that obese asthmatic children have a Th2 cytokine skew, and in addition have increased expression of TLR 2 and TLR 9 compared with the nonobese asthmatic children.

15. Lodrup Carlsen KC, Mowinckel P, Hovland V, *et al.* Lung function trajectories from birth through puberty reflect asthma phenotypes with allergic comorbidity. *J Allergy Clin Immunol* 2014; 134:917–923.

16. Dizier MH, Margaritte-Jeannin P, Madore AM, *et al.* The nuclear factor I/A (NFIA) gene is associated with the asthma plus rhinitis phenotype. *J Allergy Clin Immunol* 2014; 134:576–582.

17. Baines KJ, Simpson JL, Wood LG, *et al.* Sputum gene expression signature of ■ 6 biomarkers discriminates asthma inflammatory phenotypes. *J Allergy Clin Immunol* 2014; 133:997–1007.

The study identified six gene biomarkers that could discriminate eosinophilic asthma from noneosinophilic asthma, paucigranulocytic asthma, or neutrophilic asthma. These genes were CLC; CPA3; DNASE1L3; IL-1 β ; ALPL; and CXCR2.

18. Mortensen LJ, Kreiner-Moller E, Hakonarson H, *et al.* The PCDH1 gene and asthma in early childhood. *Eur Respir J* 2014; 43:792–800.

19. Park HW, Dahlin A, Tse S, *et al.* Genetic predictors associated with improvement of asthma symptoms in response to inhaled corticosteroids. *J Allergy Clin Immunol* 2014; 133:664–669.

Single nucleotide polymorphisms from children from the childhood asthma management program were analyzed. A novel SNP (rs10044254) was associated with an improved response to inhaled corticosteroids.

20. Fainardi V, Saglani S. The need to differentiate between adults and children when treating severe asthma. *Expert Rev Respir Med* 2015; 9:419–428.

21. de Andrade WC, Lasmar LM, Ricci Cde, *et al.* Phenotypes of severe asthma among children and adolescents in Brazil: a prospective study. *BMC Pulm Med* 2015; 15:36.

22. Kupczyk M, Brinke A, Sterk PJ, *et al.* Frequent exacerbators: a distinct ■ phenotype of severe asthma. *Clin Exp Allergy* 2015; 44:212–221.

The study defined frequent exacerbators as a subphenotype of asthma, which is particularly distinguished by an elevated FeNO and a history of smoking.

23. Just J, Gouvis-Echraghi R, Couderc R, *et al.* Novel severe wheezy young children phenotypes: boys atopic multiple-trigger and girls nonatopic uncontrolled wheeze. *J Allergy Clin Immunol* 2012; 130:103–110.

24. Esposito S, Ierardi V, Daleno C, *et al.* Genetic polymorphisms and risk of ■ recurrent wheezing in pediatric age. *BMC Pulm Med* 2014; 14:162.

The study examined infant wheezers at first presentation. They found 47 SNPs and 33 candidate genes associated with increased and decreased risks with regard to wheezing.

25. Sahiner UM, Semic-Jusufagic A, Curtin JA, *et al.* Polymorphisms of endotoxin pathway and endotoxin exposure: in vitro IgE synthesis and replication in a birth cohort. *Allergy* 2014; 69:1648–1658.