Pediatric asthma phenotypes
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Purpose of review
There is currently limited ability to identify which infants and young children with recurrent wheezing will ultimately develop persistent asthma. In addition, it is not clear how risk factors influence the development of asthma in later childhood and adulthood. This review will discuss efforts to categorize these children with recurrent wheezing and develop asthma-predictive tools.

Recent findings
Transient and persistent wheezing phenotypes have been identified with atopy, reduced lung function, and viral and bacterial respiratory infection as major risk factors for persistence of asthma. Children with severe asthma tend to have greater magnitude of atopy and lower lung function than those with mild–moderate asthma. These phenotypes and risk factors have been described in previous studies and are supported by the recent literature.

Summary
Heterogeneity of wheezing phenotypes may account for different responses to treatment and varied outcomes. Overlap in phenotypes and instability over time also add additional challenges to defining discrete groups of children with specific outcomes. Further studies are needed to determine combinations of variables that may improve phenotype designation with the goal of improving asthma prevention and treatment as well as predicting outcomes and understanding the pathogenesis of asthma.

Keywords
asthma, children, phenotype, wheezing

INTRODUCTION
Although nearly 50% of children have wheezing with respiratory illnesses in their first year of life, only 20% will have continued wheezing in later childhood [1]. Because of the heterogeneity of the disorder, there is limited ability to identify infants and young children with recurrent wheezing who are at increased risk of developing persistent asthma. In addition, it is not clear how risk factors influence the development of asthma in later childhood and adulthood. Efforts have been made to categorize these children with recurrent wheezing and develop predictive tools to determine who will ultimately develop persistent asthma [2*,3,4,5*].

WHEEZING PHENOTYPES
Both epidemiologic and symptom-based phenotypes have been used to describe patterns of wheezing in young children and identify associated risk factors.

Epidemiologic phenotypes: transient and persistent wheezing
The Tucson Children’s Respiratory Study (TCRS) has generated the most well-known wheezing classification. In this prospective longitudinal study of 1246 newborns followed for lower respiratory tract infections, four wheezing phenotypes were identified (Table 1) [1].

(1) Never wheezing (51%) – children who never wheezed
(2) Early transient wheezing (20%) – onset of wheezing before age 3 years with resolution by age 6 years
Phenotypes with increased risk of persistent asthma into adolescence and adulthood:
(1) Persistent wheezing (14%) – onset of wheezing before age 3 years with continued wheezing at age 6 years

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Late-onset wheezing (15%) – children who developed wheezing between 3 and 6 years of age

These groups were further characterized into transient infant wheezing, nonatopic persistent wheezing, and IgE-associated/atopic persistent wheezing [6–8]. Transient wheezing begins in the first year of life, resolves by preschool age, and is associated with decreased lung function, smaller airways (low flow rates by lung function testing), maternal tobacco use during pregnancy, having siblings, and daycare attendance. Nonatopic persistent wheezing (lack of allergic sensitization and methacholine hyper-responsiveness) begins in infancy and resolves in mid-childhood. Although IgE-associated/atopic persistent wheezing can begin early in life, it increases in prevalence with age. It is associated with personal and family history of allergic disease, methacholine hyper-responsiveness, and decreased lung function. Children in the IgE-associated/atopic persistent wheezing and late-onset wheezing groups are at increased risk of persistent asthma-like symptoms into adolescence and adulthood. Conversely, the children in the nonatopic persistent wheezing phenotype group experience a decrease in wheezing episodes by early adolescence [9].

On the basis of a study of 16 333 school-age children, the Italian Studies of Respiratory Disorders in Childhood and the Environment (SIDRIA) classification scheme is similar to the TCRS (Table 1). Two exceptions were an upper age limit for transient early wheezing of 2 years and the frequency of the wheezing phenotypes. In this study, 83% had never wheezed, 7% had transient early wheezing, 4% had persistent wheezing, and 6% had late-onset wheezing [10].

The Avon Longitudinal Study of Parents and Children (ALSPAC) prospective examined maternal report of wheezing in 6265 children [11] using sophisticated statistical methods. With the use of more time points at shorter intervals than the Tucson study combined with objective measures (e.g. lung function and allergen sensitization), two additional phenotypes were identified (Table 1) [12]:

1. Never/infrequent wheeze (59%)
2. Transient early wheeze (16%) – wheezing common from 6 to 18 months, but rare to never after 42 months
3. Prolonged early wheeze (9%) – wheezing common from 6 to 54 months, but rare to never after 69 months
4. Intermediate-onset wheeze (3%) – wheezing rare to never from 6 to 18 months, but common thereafter
5. Late-onset wheeze (6%) – infrequent wheezing from 6 to 42 months, but common thereafter
6. Persistent wheeze (7%) – wheezing common from 6 months onward

Risk factors in all groups included a parental history of asthma (especially maternal) and personal allergic disease. Transient infant wheezing was associated with maternal smoking during pregnancy and having older siblings. Persistent wheezing was associated with prematurity and lower socioeconomic status.

The Netherlands Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study is a longitudinal birth cohort study which demonstrated similar wheezing phenotypes in 2810 children (never, infrequent wheeze, transient early wheeze, intermediate-onset wheeze, late-onset wheeze, and persistent wheeze) [13**] as well as similar associations with asthma, allergic disease, bronchial hyper-responsiveness and lung function (Table 1).

Across these epidemiologic studies there are some variations in the age range for phenotypes as well as inconsistencies in associated risk factors. Furthermore, there are also concerns about their usefulness in clinical practice, prospective validity, and potential investigator bias in categorization.

### Episodic and multitrigger wheezing

The European Respiratory Society defined two symptom-based phenotypes: episodic and multitrigger wheeze [14]. Children with episodic (viral) wheeze do so only during discrete periods. Children
with multitrigger (including viruses, allergens, exercise, and cigarette smoke) wheeze have wheezing both during exacerbations and between episodes and have lower airway function compared with the episodic wheezing phenotype [15]. Adding an additional layer of complexity, these phenotypes may not be stable over time. In one study, over half of the children classified into either episodic or multitrigger wheezing phenotypes switched to the other phenotype in the subsequent year [16].

**SEVERE ASTHMA PHENOTYPE**

Severe asthma can be differentiated from mild–moderate asthma by greater symptom burden, more frequent exacerbations, greater allergic sensitization, more airflow obstruction, and increased fractional exhaled nitric oxide (FeNO) despite higher doses of corticosteroids [17,18]. Symptoms may also be identifiable in early life. Historical data from children enrolled in the National Institutes of Health (NIH) Heart, Lung, and Blood Institute Severe Asthma Research Program (NHLBI SARP) showed that children with severe asthma had onset of symptoms in the first 24 months of life compared with 60 months in mild–moderate asthma [17]. In addition, children with severe asthma had higher prevalence of atopic dermatitis and positive skin prick testing to aeroallergens by early childhood [17]. Even before the onset of symptoms, asthma may be present. This is illustrated by studies showing that infants with the lowest pulmonary function are those who will go on to have persistent asthma [19,20] and severe bronchial hyper-responsiveness in childhood [19].

In an NHLBI SARP cluster analysis of children with asthma, four clusters were identified, all with varying degrees of allergic disease and a trend of increasing severity [21]: late-onset symptomatic asthma with normal lung function, early-onset atopic asthma with normal lung function, early-onset atopic asthma with mild airflow limitation, and early-onset atopic asthma with advanced airflow limitation. Duration of asthma, number of controller medications, and baseline lung function were major predictors of cluster assignment. Allergic disease, FeNO concentrations, and age of asthma onset were also factors.
Differences in lower airway inflammatory response in severe asthma may also distinguish severe asthma from moderate asthma. In a unique study, by applying a linear discriminant analysis and a supervised method of high-dimensional data reduction to measurements of cytokines and chemokines in bronchoalveolar lavage (BAL) fluid and alveolar macrophage lysate in children with severe asthma, there was a unique molecular phenotype with increased markers of BAL inflammation and alveolar macrophage activation [22**]. Children with moderate and severe asthma were phenotypically distinct without a clear T(H)1 or T(H)2 pattern.

Although neutrophilic, eosinophilic, and mixed airway inflammatory phenotypes have been reported based on BAL and sputum samples from children with severe asthma [23–25], the role of these cells and whether treatment is beneficial in children is unclear. Airway eosinophilia may be present prior to the onset of asthma [26**]. A study of children who had nonbronchoscopic BAL during elective surgery showed that the BAL eosinophil percentage was significantly increased in children who later developed late-onset childhood wheeze compared with those who never wheezed. Patterns of inflammation are complex and there are likely interactions between cell types, and symptom patterns may not correlate with a particular inflammatory picture. For example, some young adults with asthma in clinical remission have as much eosinophilic inflammation as those with symptomatic asthma [27]. Although the significance of airway neutrophilia remains to be determined, there may be a relevant cause, such as an underlying bacterial infection, and potential benefit from treatment [28**].

The clinical utility of both epidemiologic and symptom-based phenotypes may be limited due to variability in symptoms and risk factors over time, and overlap of phenotypes. Furthermore, there are no specific therapies targeted to particular phenotypes. Thus, it is unclear if identification of phenotypes and treatment by these phenotypes can modify the course of disease or ultimate outcome.

**ASTHMA RISK FACTORS**

The major risk factors for development and persistence of asthma are allergic disease, reduced lung function, and viral and bacterial infections [28**,29,30**]. In addition, numerous genetic, environmental, and developmental factors interact to determine the natural history of asthma in an individual.

**Allergic disease**

Numerous phenotype studies have illustrated the relationship between allergic disease and asthma [12,31–33]. For example, in the Tucson cohort, allergic disease was the main risk factor for development of persistent asthma [1]. Children with late-onset and persistent wheezing had a significantly higher rate of allergen sensitization at age 6 years, and alternaria sensitization was associated with a higher rate of asthma at age 22 years [31]. In addition, the intermediate-onset, late-onset, and persistent wheezing phenotypes in the Avon cohort were most strongly associated with allergic disease and childhood asthma [12].

**Reduced lung function**

Children with persistent wheezing phenotypes have a greater degree of lung function impairment compared with other phenotypes [12,32–34,35*]. In the Avon cohort, phenotypes with prolonged early, intermediate-onset, and persistent wheezing had lowest lung function, and intermediate and late-onset phenotypes had the greatest airway hyperresponsiveness [12].

Different studies have shown abnormal lung function at various ages [1,31,32,35*,36–38]. In children who developed persistent wheezing at 6 years of age in the Tucson cohort, lung function was normal in infancy but reduced at 6 years and into adolescence [1]. Also in the Tucson cohort, persistent wheezing in early life and airway hyperresponsiveness and low airway function at 6 years were associated with both chronic and newly diagnosed asthma at 22 years of age [31]. Studies of cohorts from Norway and Australia showed abnormal lung function as young as 1 month of age in children who developed persistent wheeze in later childhood [36,37]. There is also an association with exposure to high levels of perennial allergens early in life and lower lung function during the school years in children with atopic persistent wheezing [39].

**Viral infections and bacterial colonization**

It is unclear whether certain viral respiratory infections cause asthma or if those who wheeze with these illnesses are already predisposed to the development of asthma [40*]. Nevertheless, viral respiratory infections in infancy (especially with human rhinovirus) are predictive of the development of asthma in later childhood [41]. These infections may amplify the asthma risk with allergic disease and reduced lung function during early childhood [42,43]. A recent study by Bisgaard et al. [30**] demonstrated that neonates colonized in the hypopharyngeal region with
Streptococcus pneumonia, Haemophilus influenza, or Moraxella catarrhalis, or with a combination of these organisms, are at increased risk of recurrent preschool wheezing and asthma at age 5. In a recent study by Schwerk et al. [28***], 42 preschool-aged children with severe persistent wheezing were examined by bronchoscopy and BAL. Eighty-one percent had neutrophilic inflammation and 59% of these had elevated bacterial counts of S. pneumonia, H. influenza, or M. catarrhalis. After 2–6 weeks of antibiotic treatment, 92% of these children demonstrated a marked improvement of symptoms [28***]. Another possible mechanism for these associations may be that a person with immune function that is biased toward atopy may have altered host defenses that both increase susceptibility to bacterial and viral infections and increase risk of developing asthma [44–48].

**ASTHMA-PREDICTIVE TOOLS**

Various attempts have been made to develop clinical scoring tools to identify children who will continue to wheeze.

**Asthma-predictive index**

The most commonly used asthma-predictive scoring system is the asthma-predictive index (API) derived from the Tucson cohort study (Table 2) [4,5*,49] to predict future wheezing in children 3 years of age with at least one previous episode of wheezing.

Major criteria were clinician-diagnosed eczema and parental asthma. Minor criteria were clinician-diagnosed allergic rhinitis, wheezing apart from colds, and eosinophilia at least 4%. Children with wheezing and either one major or two minor criteria at 3 years of age were four to seven times more likely to have asthma during later childhood. The API was validated in a population-based birth cohort of 1954 children in Leicester, UK [51*], with similar results. In addition, results were comparable using a simpler definition.

The value of the API may lie in the identification of children who are unlikely to develop persistent asthma. With low sensitivity (15–57%), the API is a poor predictor of development of asthma [4,5*,49,51*,52*]. However, with a high negative predictive value, the API can identify children with a low likelihood of developing later asthma when their API is negative [4,5*,31]. The US National Asthma Education and Prevention Program Expert Panel Report 3 supports use of a modified API (allergic skin testing replaces clinician-diagnosed allergic rhinitis) in the diagnosis of asthma (Table 1), although the sensitivity and specificity have yet to be determined [53]. The API may help identify preschoolers who respond to inhaled corticosteroids [54,55**]. For example, in a study of preschool children with recurrent wheeze and a positive API, ciclesonide modestly reduced wheeze exacerbation rates and improved lung function [55**].

Other asthma risk scores have also been developed [56–58]. Using these scoring systems, combinations of risk factors including recurrent chest infections at 2 years of age, family history of asthma, positive skin prick test to at least one food or inhalant allergen at 4 years of age, and recurrent nasal symptoms at 1 year of age [56], greater severity of obstructive airway disease during the first 2 years of life [57], male sex, post-term delivery, medium/low parental education, wheezing frequency, wheezing/dyspnea apart from colds, parental report of serious infections, and presence of doctor-diagnosed eczema [58] confer significantly greater risk for a preschooler with wheeze to have persistent asthma in later childhood. In one study, for example, children with high scores had 46% risk of later persistent asthma compared with 3%.

<p>| Table 2. Modified API versus original API |</p>
<table>
<thead>
<tr>
<th>Modified asthma predictive index</th>
<th>Original asthma predictive index</th>
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</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Parental history of asthma</td>
<td>Parental history of asthma</td>
</tr>
<tr>
<td>MD-diagnosed atopic dermatitis</td>
<td>MD-diagnosed atopic dermatitis</td>
</tr>
<tr>
<td>Allergic sensitization to at least one aeroallergen</td>
<td></td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Allergic sensitization to milk, egg, or peanuts</td>
<td>MD-diagnosed allergic rhinitis</td>
</tr>
<tr>
<td>Wheezing unrelated to colds</td>
<td>Wheezing unrelated to colds</td>
</tr>
<tr>
<td>Blood eosinophils ≥4%</td>
<td>Blood eosinophils ≥4%</td>
</tr>
</tbody>
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A history of four or more wheezing episodes with at least one physician diagnosed. In addition, the child must meet at least one of the above major conditions or at least two of the following minor conditions. * Differences in indices are made bold. Modified with permission from [50].
risk of later asthma [58]. The API and other predictive scores have not been validated in diverse populations.

**Fractional exhaled nitric oxide and specific IgE in prediction of future wheezing**

In preschool children from the PIAMA study with symptoms suggestive of asthma, higher FeNO and inhalant allergen sensitization (specific IgE) were positively associated with asthma in later childhood, independent of the preschool clinical history. The combination of FeNO, specific IgE, and clinical history improved the prediction of future wheezing [59**].

**Clinical relevance**

There are many challenges in providing clinical care for young children with recurrent wheezing, especially due to the heterogeneity of asthma in this population. Parents often want to know if their young child will continue to have asthma when they are older. In order to counsel parents as well as aid in management decisions, assessment of risk factors for ongoing persistent asthma in an individual child is useful. This assessment would include a detailed history and physical testing for allergic sensitization and pulmonary function. In contrast to school-aged children and adolescents, preschool-aged children with asthma tend to be exacerbation-prone with limited impairment. It is not clear how to apply phenotypes to manage childhood asthma, particularly with nonatopic wheezing. In recent trials, treatment with either daily inhaled corticosteroids [60] or leukotriene receptor antagonists [61] has shown efficacy in preschool-aged children with intermittent wheezing. In addition, intermittent high-dose inhaled corticosteroid therapy is comparable in efficacy to daily low-dose inhaled corticosteroid therapy in high-risk children in this population [62,63**,64]. However, there are relatively limited high-quality trials of asthma therapy in preschool-aged children. Therefore, management of these children is largely guided by expert opinion and studies in older children. In older children with persistent asthma, several studies support the use of inhaled corticosteroids, particularly for those with allergic sensitization [65].

**CONCLUSION**

Transient and persistent wheezing phenotypes have been identified, with allergic disease, reduced lung function, and viral respiratory infection in infancy, as major risk factors for persistence of asthma. Refining clinical phenotypes of asthma using a combination of variables, such as inflammatory biomarkers [66**,67–71,72**], cellular and molecular characteristics [22**], lung imaging [73**,74], genetics [75–78], other factors such as medication exposures, nutritional deficiency, and obesity [79–81], and statistical techniques [21**,22**] may ultimately help predict outcomes, improve prevention and treatment, and better understand the pathogenesis of asthma.

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**Conflicts of interest**

Theresa Guilbert: Payment for development of educational presentations: Peerpoint Medical Education Institute (2009 – CME course on RSV); Teva (reviewed educational slide deck – 2011).

Consultancy: Medimmune (2010 – research advisor); Teva (2011 – research advisor); MAP Pharmaceuticals (2010 – research advisor); Glaxo-Smith-Kline (2011 – research advisor and DSMB); Astra-Zeneca (2009 – research advisor); Merck-Schering-Plough (2009 – research advisor); Genetech/Novartis (2009 – research advisor).

**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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 431–432).

2. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? Clin Exp Allergy 2010; 40:1130–1141. This review discusses research related to childhood asthma phenotypes and highlights the need for a multidimensional approach to refine classical phenotypes.
5. Castro-Rodriguez JA. The Asthma Predictive Index: early diagnosis of asthma [review]. Curr Opin Allergy Clin Immunol 2011; 11:157–161. This study reviews the importance of determining risk of persistent asthma in young children with wheezing and discusses the utility of the API.
Pulmonology


17. This study highlights the instability of wheezing phenotypes.


19. This study highlights the contribution of bacterial infections to persistent wheezing in preschool children.


23. This study was unique in that it examined the association between pre- and post-bronchodilator lung function and the wheezing phenotype in preschool children.


27. This review highlights recent insights into severe asthma in children derived from the National Heart, Lung, and Blood Institute’s Severe Asthma Research Program (SARP).


36. This study was unique in that it examined the association between pre- and post-bronchodilator lung function and the wheezing phenotype in preschool children.


42. This review discusses the link between viral lower respiratory infections and later asthma.


49. Hartert TV. Are persons with asthma at increased risk of pneumococcal infections, and can we prevent them? J Allergy Clin Immunol 2008; 122:724–725.


54. This study validated the API developed in the Tucson cohort in children from the population-based Leicester Respiratory Cohort, and also showed that a similar prediction could be made using simpler rules.


56. This article discusses the low sensitivity of the API in identifying those who will develop persistent asthma, and the challenges of applying this to clinical practice.

57. The majority of children with severe persistent wheezing and bacterial infection had improvement in symptoms after antibiotics.
This study explores the role of periostin in airway hyper-responsiveness in mice. Both FeNO and specific IgE measured at 4 years of age improved the prediction of asthma symptoms until the age of 8 years, independent of clinical history. Evaluation studies in children from the PIAMA birth cohort with preschool wheezing. This study examined pulmonary function and serum cytokines and showed that this study assessed the relationship between airflow limitation and airway dimensions assessed by multidetector CT in asthma. This study examined whether IgE levels and asthma might differ in their relation to early life cytokine production. This study examined the relationship between airflow limitation and airway dimensions in asthma using multidetector-row computed tomography. This review examines the current literature related to vitamin D supplementation for pediatric obesity-associated asthma differed from atopic asthma and was characterized by Th1 polarization.


56. Kurukulasuriyage RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent wheezing in very young children who had a positive modified API, recurrent wheezing episodes, and at least one exacerbation in the previous year. Eur Respir J 2008; 638:13.


73. This study examined whether IgE levels and asthma might differ in their relation to early life cytokine production. This study assessed the relationship between airflow limitation and airway dimensions assessed by multidetector CT in asthma. This review examines the current literature related to vitamin D supplementation for pediatric obesity-associated asthma differed from atopic asthma and was characterized by Th1 polarization.


81. This review examines the current literature related to vitamin D supplementation for asthma treatment or prevention.


This study examined pulmonary function and serum cytokines and showed that pediatric obesity-associated asthma differed from atopic asthma and was characterized by Th1 polarization.