Childhood asthma: pathogenesis and phenotypes

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Shareable abstract (@ERSpublications)
Complex interactions between viral infections, atopy, the microbiome, preterm birth, infant weight gain, environmental exposures and genetic susceptibility influence the development of wheezing illness and asthma in children


Abstract
In the pathogenesis of asthma in children there is a pivotal role for a type 2 inflammatory response to early life exposures or events. Interactions between infections, atopy, genetic susceptibility and environmental exposures (such as farmyard environment, air pollution and tobacco smoke exposure) influence the development of wheezing illness and the risk of progression to asthma. The immune system, lung function and the microbiome in gut and airways develop in parallel, and dysbiosis of the microbiome may be a critical factor in asthma development. Increased infant weight gain and preterm birth are other risk factors for development of asthma and reduced lung function. The complex interplay between these factors explains the heterogeneity of asthma in children. Subgroups of patients can be identified as phenotypes, based on clinical parameters, or endotypes, based on a specific pathophysiological mechanism. Paediatric asthma phenotypes and endotypes may ultimately help to improve diagnosis of asthma, prediction of asthma development and treatment of individual children, based on clinical, temporal, developmental or inflammatory characteristics. Unbiased, data-driven clustering, using a multidimensional or systems biology approach may be needed to better define phenotypes. The present knowledge on inflammatory phenotypes of childhood asthma has now been successfully applied in the treatment with biologicals of children with severe therapy-resistant asthma, and it is to be expected that more personalised treatment options may become available.

Introduction
Asthma is a multifactorial disease and although the underlying mechanisms are not fully understood, it has become clear that genetic vulnerability, atopy, respiratory infections, the lung and gut microbiome and environmental factors all play a role in asthma inception and pathogenesis. The complex interplay between all these factors explains the heterogeneity of asthma in children and supports a possible benefit of stratified precision medicine, in contrast to a “one size fits all” approach. Subgroups of patients can be identified based on clinical or biomarker criteria, often referred to as phenotypes. Clinical phenotypes may be helpful in diagnosis, prediction and treatment of children with wheezing illness or asthma. However, in real-life practice, there is a large heterogeneity and variability of phenotypic expression, meaning that phenotypes often overlap. The concept of “endotypes” has been introduced to understand how much each component of asthma pathophysiology contributes to the symptoms for each child in order to identify “treatable traits” and enable individualised therapy [1, 2]. Endotypic characterisation has been proven particularly useful in the treatment of children with severe therapy-resistant asthma [3].

Recently, unbiased, data-driven clustering, using a multidimensional or systems biology approach, has been used to define phenotypes. This combines different data domains that include symptoms, psychosocial aspects, lung function, inflammatory parameters, exposures, metabolomics, epigenomics, transcriptomics.
and fluctuation-based clustering [4–9]. By comparing several paediatric clustering studies and investigating phenotype stability during childhood, some consistent patterns in phenotypes have emerged [10]. In this review we first aim to unravel the interplay between pathophysiology, lung and immune development and early-life risk factors such as exposure to air pollution, viral infections, atopy, preterm birth, weight gain and the microbiome in the development of asthma in children. In a further step, we aim to disentangle the complexity of paediatric asthma phenotyping with a focus on clinical relevance.

**Early-life risk factors in asthma pathogenesis**

Childhood asthma is a complex disease, with a multitude of host and environmental factors which contribute to the evolution of the disease process. The relative contribution of each individual involved factors is typically small; however, their interactions during lung functional growth and the development of the immune system may eventually lead to different airway disease phenotypes. Here we summarise risk factors and proposed mechanisms related to the early origins of asthma in childhood (figure 1).

**Microbes, allergen sensitisation and asthma susceptibility**

Viral infections, in particular with human rhinovirus (HRV) and respiratory syncytial virus (RSV), and allergen sensitisation in early life are associated with asthma inception [11, 12]. 32% of infants that had been hospitalised with severe RSV infection had developed allergen sensitisation by 3 years of age, compared to only 9% of age- and sex-matched controls [12]. More severe illness induced by RSV (but also HRV) is associated with the development of asthma, and increased risk of atopy and asthma continued to 18 years of age [13]. Interestingly, despite the link between viral infections and asthma inception, immunoprophylaxis with palivizumab against RSV did not reduce asthma diagnoses at age 6 years, although wheezing symptoms in preschool children were reduced [14]. In addition, there is strong evidence that RSV-induced bronchiolitis can damage the airways to promote airway obstruction and recurrent wheezing [15]. Still, the direct causal link between early RSV infection and allergen sensitisation, and which of these comes first in the context of asthma inception, remain uncertain. For HRV, data from a high-risk birth cohort demonstrated that allergic sensitisation preceded HRV-induced wheezing [16]. However, the direction of causation when considering an unselected population is unclear. Studies using murine models and in vitro studies in humans are being undertaken to understand a causal link [17–20].

It is apparent that genetic susceptibility is important in determining asthma outcomes following viral infection. Data from two independent, high-risk birth cohorts (at least one atopic parent) have shown that children with the highest risk for early-onset asthma were those who had HRV-related wheezing illnesses in early life and were carriers of an at-risk allele in the ORMDL3 gene locus [21]. Important insights on the critical role of gene–environment interactions in determining outcome can be derived from farmyard studies. Children with at-risk alleles in the ORMDL3 gene locus had strong protection against asthma if

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**FIGURE 1** Overview of early-life factors that increase or decrease the risk of asthma development. Genetic susceptibility, viral infections and atopic sensitisation interact with environmental factors that may increase (living in an urban environment, exposure to cigarette smoke, air pollution, excess infant weight gain, preterm birth, disturbed airway/gut microbiome) or decrease (living in a rural environment, term birth, normal infant weight gain, protective airway/gut microbiome) the risk of development of wheezing and asthma. RSV: respiratory syncytial virus; HRV: human rhinovirus.
raised on animal farms [22]. The biological modifying mechanisms associated with the 17q21 locus are still incompletely understood. Interestingly, in addition to being raised on a farm, they modify the effect of a series of risk factors associated with recurrent airway disease, such as susceptibility to viral infections, breastfeeding or tobacco smoke exposure [22]. Additionally, these modifications are likely to involve several genes in the region, including ORMLD3 and GSDMB and several cell types, including immune and airway epithelial cells. This suggests that, in the absence of high levels of microbial exposure from the farmyard environment in early life, ORMLD3 enhances the clinical expression of wheezing associated with viral infection. In contrast, ORMLD3 risk alleles seem to provide protection from wheezing in the presence of favourable microbial exposures.

Undoubtedly, for both HRV and RSV, interactions between viral infection, genetic susceptibility and environmental exposures influence the development of wheezing illness and the risk for progression to asthma.

**Airway and gut microbiome and asthma onset**

The past decade many studies have shown that the airway and gut microbiome may be important in asthma development and that dysbiosis of gut and lung microbiome and delayed maturation of immune responses and airway microbial communities are related to the early development of asthma [23–26]. Asthma and preschool wheezing have been associated with a microbiota characterised by lower diversity and an abundance of *Moraxella*, and conversely, increased bacterial diversity has been positively associated with protection [24, 27].

The healthy lung microbiome is characterised by bacteria belonging to the phyla Bacteroidetes, Actinobacteria and Firmicutes [28]. Exogenous factors can affect the natural lung microbiota composition positively (farming environment) or negatively (allergens, air pollutants). The importance of environmental exposures within a critical window in early life, during which immune maturation occurs and the microbiome develops, is becoming increasingly apparent. In mice, the development of airway eosinophilia and hyperresponsiveness after house dust mite (HDM) exposure at a young age appeared to be dependent on the airway microbiome [29]. Additionally, in pups exposed to HDM, inhaled *Acinetobacter lwoffii* (a bacterium found in the protective farmyard environment) resulted in protection from airway eosinophilia and hyperresponsiveness [30]. The development and maturation of the respiratory microbiome in early life depends on exposures in the first few hours, including delivery mode, and the environment in the following 4–5 months [31–33]. The composition of indoor dust and bacterial exposure at 2 months of age have been associated with asthma development by 10 years [34]. In dust samples from the living rooms of infants at 2 months of age, bacterial richness was inversely associated with asthma. *Lactococcus* genus was a risk factor for asthma, while the abundance of 12 bacterial genera, predominantly from *Actinomyces* species, were associated with lower asthma risk [34]. The pattern of microbes that were associated with protection from asthma are similar to those found in the protective farmyard environment [35]. Farm studies have linked both the environmental and the host microbiome to asthma [24, 27]. Other than bacterial diversity, low fungal diversity in HDM was associated with development of asthma and increased exposure to dust yeast in early life may be protective against asthma and allergy [36, 37].

Dysbiosis of the gut microbiota results from several external influences including smoke exposure, antibiotics or diet, and this has been associated with altered systemic and local immune responses, including inflammatory changes in the lung [28, 38]. The exact mechanisms of communication in this gut–lung axis are not clear, but are partially mediated by bacterial metabolites, exerting immune responses in remote parts of the body such as the lungs [39]. The relationship between diversity in the gut microbiome and asthma development has been shown in several studies. Additionally, exposure to antibiotics in early life is associated with an increased risk of asthma development [40] and this effect might be explained by an effect of antibiotics on the gut microbiome.

The use of nonspecific immunomodulators derived from bacterial respiratory tract pathogens is gaining increasing attention [41]. In a retrospective study in children with recurrent respiratory tract infections, oral OM-85, which consists of alkaline lysis of 21 bacterial strains of respiratory tract pathogens, resulted in a significantly lower frequency of respiratory tract infections, wheezing episodes and intake of antibiotics [42]. A randomised controlled trial of sublingual MV130 (a mixture of six inactivated bacteria) has shown reduction in preschool wheeze attacks compared to placebo [43].

Thus, we have increasing evidence that the development and maturation of the lung and gut microbiome may affect the risk of asthma development. Whether early manipulation of the microbiome can reduce the risk of asthma remains to be shown.
Early-life nutrition and asthma onset
Several studies suggest that the onset of asthma may be influenced by early-life nutrition including breastfeeding. Systematic reviews have shown a consistent protective effect of ever being breastfed on later wheezing and asthma, which seemed to wane off in adolescents [44–47]. Most studies suggest that longer duration of breastfeeding lowers the risk of asthma compared to a shorter duration [44–47].

How breastfeeding exactly modifies the risk of asthma development is not fully clear, but effects on the developing immune system, microbial colonisation and the integrity of the gut mucosal barrier may all play a role [48].

There is a lack of evidence for partially or fully hydrolysed milk formula in preventing asthma, even in high-risk infants [49].

Vitamin D has been implicated as a protective factor for viral immunity in the lower airways, and may have favourable effects in asthma. Data on vitamin D status and vitamin D supplementation of the mother during pregnancy on asthma risk in the offspring are conflicting, with a majority of systematic reviews and meta-analyses suggesting that supplementation of vitamin D during pregnancy reduces the risk of wheezing and/or asthma [50–57]. One meta-analysis showed a U-shaped association between dose of vitamin D supplementation during pregnancy and risk of wheezing/asthma, suggesting that both low and high dosages of vitamin D may have negative effects [58]. The variable results of vitamin D supplementation may be explained by recent evidence that the maternal 17q21 genotype has an important influence on the protective effects of prenatal vitamin D supplementation against offspring asthma/recurrent wheeze [59]. Infant supplementation with vitamin D did not affect the risk of asthma at school age [60]. Omega-3 fatty acids have been assigned anti-inflammatory properties and supplementation of omega-3 fatty acids during pregnancy has shown a positive trend in reducing wheezing during the first years of life, but not asthma at school age [52, 61, 62]. Similarly, supplementation of omega-3 fatty acids during childhood did not reduce the risk of asthma [62].

Early-life exposure to pollutants and asthma onset
Epidemiological data support the link between even low-level exposure to air pollution during gestation and early life, and asthma development and impaired lung function growth [63–66]. The effects of weekly average exposure to particulate matter with an aerodynamic diameter <2.5 μm (PM2.5) during pregnancy and infancy on asthma development were investigated in a birth cohort of 184 604 children in Taiwan [67]. Increased exposure to PM2.5 during gestational weeks 6–22 and 9–46 weeks after birth were significantly associated with an increased incidence of childhood asthma. The effect of air pollution on lung function is dose dependent and is more pronounced when children are exposed during early lung development [64]. Data from three separate cohorts in the United States showed that declining levels of nitrogen dioxide (NO2), PM2.5 and PM10 were associated with improved lung function growth in children with and without asthma [68]. In central London (United Kingdom), a sequential annual cross-sectional study of 2164 children aged 8–9 years between 2009–10 and 2013–14 was undertaken following the introduction of London’s Low Emission Zone in 2008 [69]. The percentage of children living in areas exceeding the European Union limit value for annual NO2 exposure fell from 99% in 2009 to 34% in 2013. Forced vital capacity (FVC) was inversely correlated with annual NO2 and PM10 exposure, but there was no association between post-bronchodilator forced expiratory volume in 1 s (FEV1) and annual residential pollutant attributions. Although pollution exposure fell dramatically, there was no significant impact on FVC over the 5-year study, suggesting that the reduced lung volumes for age were a reflection of much longer term exposure and would fit with data from mechanistic models which highlight particular periods of vulnerability to even low-level exposures during pregnancy and immediately postnatally [64, 65, 67].

Observations in a mouse model suggested that postnatal concurrent exposure to both inhaled HDM and diesel exhaust particles (DEPs) result in more severe and less corticosteroid-sensitive airway disease [70]. Of note, murine models of maternal DEP exposure before and/or during pregnancy, with subsequent allergen and DEP exposure in early neonatal life, showed development of more severe allergic airway hyperresponsiveness in offspring compared to allergen exposure alone [71–73].

Obesity, early-life weight gain and asthma development
The relationship between obesity and asthma is a complex one, and is bidirectional, since asthma increases the relative risk of obesity by 1.5–1.7-fold, but obesity is also an independent risk factor for asthma [74–76]. A meta-analysis which included 18 prospective studies calculated a 20% risk increment for asthma in overweight children and a 40% risk increment in obese children [77].
Longitudinal assessments of birth weight and body mass index (BMI) to the age of 17 years were used to investigate associations of adiposity with asthma in >6000 children in the Taiwan Children Health Study [78]. Mendelian randomisation analysis revealed that the critical period during which adiposity predicted childhood asthma outcomes was before the age of 6 years. This suggests that the preschool years are a critical window to focus on healthy growth to influence later asthma. A similar analysis in the Avon Longitudinal Study of Parents and Children also showed that higher BMI in early life increased the risk of asthma by the age of 7 years [79]. Therefore, the rate of weight gain in the first few years of life may be an important factor for asthma development [80]. In a meta-analysis of almost 25,000 children, infant weight gain was associated with an increased risk of asthma and lower FEV1/FVC ratio and forced expiratory flow after exhaling 75% of vital capacity. Data from the Boston birth cohort have that shown extremely rapid weight gain during the first 4 and 24 months of life were each associated with increased risks of asthma, even after adjusting for birthweight and preterm birth [81]. Although epidemiological data increasingly point to the preschool years as the susceptible period in determining long-term asthma outcomes, the mechanisms underlying the effect of weight gain on asthma susceptibility are unknown. Of interest, a post hoc analysis of three randomised trials of inhaled corticosteroid (ICS) therapy in children aged 2–5 years with preschool wheezing has shown that overweight or obese children in the placebo arms had more exacerbations and symptoms compared to normal-weight children [82]. Overweight-obese children that received ICS were as responsive to therapy as normal-weight children, suggesting that the mechanisms of “steroid resistance” in obese children with asthma later in childhood may not apply during the preschool years.

**Prematurity and asthma development**

It is well known that preterm birth and low birthweight are important early-life risk factors for lower lung function later in life, and for the development of asthma [80]. In a meta-analysis of 20 studies, children born preterm had a mean 7.2% lower FEV1 % predicted compared to term-born controls, and in children diagnosed with bronchopulmonary dysplasia the mean FEV1 was 16.2% lower [83]. Associations between lung function and gestational age are present across the full range of gestational ages [80]. Even late preterms (born after 34–36 weeks gestational age) had a significantly decreased FEV1 compared to term-born controls. Recent work has shown that air pollution exposure during pregnancy had a more pronounced deteriorating effect on postnatal lung function in infants born prematurely, indicating that certain pre-morbid susceptible populations may react differently to environmental stimuli in early life [84]. The negative impact on lung function has also been shown for children born small for gestational age, although the effect is slightly different: children born with a younger gestational age had lower FEV1 and FEV1/FVC ratio, while children born small for gestational age had lower FEV1, but higher FEV1/FVC ratio [80]. This suggests smaller lungs with less obstruction in children born small for gestational age. After adjusting for lung function, preterm birth and low birthweight are also predictors of later asthma [80, 85]. Again, this effect has been shown for the full range of gestational age and even early-term-born children (37.0–38.6 weeks gestational age) had an increased risk of asthma with an adjusted OR 1.20 (95% CI 1.17–1.23) compared to full-term-born children [85]. This increased risk of asthma after preterm birth continues into middle-age [86]. Additionally, preterm-born children are at increased risk of severe bronchiolitis with RSV or rhinovirus, infections that may further increase the risk of subsequent asthma [87, 88]. The mechanisms underlying the increased risk on lower lung function and asthma development in premature-born children are not fully understood. Disrupted development of airways, together with adverse exposures such as mechanical ventilation, oxidative stress and inflammation have been suggested to cause structural damage and a decrease in airway calibre, fewer and simplified alveoli and increased lung fibrosis [89, 90]. In addition, adverse events in early life such as exposure to air pollution or tobacco smoke, and viral infections and preschool wheeze may lead to ongoing disease and reduced lung function growth [89]. Also, microbial dysbiosis in the gut microbiome, with a relative abundance of Proteobacteria and Firmicutes, and decreased *Lactobacilli* were reported with bronchopulmonary dysplasia (BPD) progression [91]. Delivery by caesarean section and postnatal antibiotic use influence this dysbiosis.

Data from Australia showed that the deficits in lung function in children with BPD increased between 4 and 12 years of age and that children with signs of inflammation on chest computed tomography scan, such as bronchial wall thickening, had the worst lung function trajectories [92]. This suggests that there is an ongoing inflammatory process in the lungs and airways of children with BPD. This ongoing disease is different from the typical eosinophilic inflammation as seen in asthmatic children as the fraction of exhaled nitric oxide (*F*eno), as a surrogate for eosinophilic inflammation, in children born preterm with or without BPD were similar to controls [93, 94]. Indeed, two studies showed evidence of neutrophilic inflammation and oxidative stress in the airways of preterm-born adolescents [95, 96]. Therefore, preterm-born children with or without BPD may display a separate “asthma” phenotype with various degrees of partly reversible,
obstructive and restrictive lung function abnormalities and signs of neutrophilic inflammation, which may not respond well to ICS.

In summary, immune responses in early life to viruses, allergens and/or pollution have a tendency towards exaggerated type 2 immunity, especially in susceptible children (figure 1). However, it remains to be seen whether this skewing can be “rescued” if the child is placed in a protective environment which favours a more diverse and mature airway and/or gut microbiome. The maturing immune system and airway microbiome appear to progress in parallel as there is a tight link between environmental exposures and microbial interactions and resulting immune responses. Obesity and rapid weight gain in the first few years of life may be other important factors that determine asthma outcomes. Last, preterm birth is a risk factor for later asthma and for reduced lung function.

**Phenotypes of childhood asthma**

The complex interplay between genetic background and early-life risk factors in asthma development leads to heterogeneity of asthma phenotypes in children. Therefore, the second aim of this review is to disentangle the complexity of paediatric asthma phenotypes, defined as one or more observable or measurable clinical properties [97], and endotypes defined by a specific mechanism. Clinical phenotypes are related to inflammatory endotypes (e.g. childhood-onset allergic asthma and T2-high inflammation), but there may be more endotypes within a phenotype [2, 98, 99]. Specific to paediatric wheezing disorders are the age-dependent and interacting relationships between clinical phenotypes (disease severity, temporal symptom pattern), type of inflammation, environmental triggers (e.g. viral infections, allergens, pollutants), response to treatment and comorbidities. In daily clinical practice, phenotypes are most useful in four domains: diagnosis, prediction, therapy and prevention, and the stability of disease and phenotype (figure 2).

**Diagnosis**

The most obvious phenotyping has been based on symptoms, where symptom severity (mild to moderate versus severe), the presence or absence of atopy, exacerbation rate, symptom pattern (episodic, intermittent, episodic, intermittent, recurrent/chronic), transient, remittent, unremitting/persistent, reversible/fixed AO, difficult asthma, STRA) controlled, partly controlled, uncontrolled brittle, stable/unstable) under control or therapy, exacerbations, adherence, dynamic functional biomarkers. In daily clinical practice, phenotypes are most useful in four domains: diagnosis, prediction, therapy and prevention, and the stability of disease and phenotype (figure 2).

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<th>Environmental context: societal, economic, family, pollutants, educational, allergens, infections</th>
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![FIGURE 2](https://doi.org/10.1183/13993003.00731-2021) Overview of phenotypes and endotypes in childhood asthma. In daily clinical practice phenotypes are most useful in four domains: diagnosis, prediction, therapy and prevention, and disease and phenotype stability. AO: airflow obstruction; STRA: severe therapy-resistant asthma; ACT: Asthma Control Test; PAQLQ: Pediatric Asthma Quality of Life Questionnaire.
recurrent/chronic) and triggers (infections, allergens, exercise) are distinct features [100–104]. Two archetypical groups have thus been identified: children with transient, often episodic symptoms, and those in whom recurrent wheezing persists beyond the first 6 years of life. Transient wheezing disorders are frequently observed in the first years of life, typically following viral infections and characterised by an episodic symptom pattern and symptom-free intercurrent intervals. This group often does not receive an asthma diagnosis. Children with typically recurrent or chronic wheeze have symptoms often triggered by multiple environmental factors (viruses, allergens, pollutants) in the first years of life, but tend to persist into later childhood and remain stable after the age of 6 years [105].

Prediction

For the purpose of prediction, research has focused on the prospective identification of temporal phenotypes (transient, remittent, persistent wheezing or asthma) (figure 2). Such temporal phenotypes have been identified using cohort studies, but unfortunately, temporal phenotypes can only be reliably assigned in retrospect, and this limits their clinical application [106–108]. In order to find ways to prevent the development of persistent asthma it is important to examine the development of pathophysiological endotypes. Although the mechanisms of transition into adulthood are still a matter of research, some underlying pathophysiological mechanisms such as traits associated with tracking of poor lung function after impaired lung development, or with the development of allergy, traits exhibiting features of metabolic syndrome with low-grade inflammation and oxidative stress (obesity, pollutants) or traits associated with microbial interactions (microbiome, viral infections) have been identified. Although ~30–50% of these recurrent asthma forms persist into adulthood, a significant proportion of children experience intermittent symptom patterns or symptom remission during adolescence, in particular male patients and children with milder symptoms and a low degree of atopy [109]. Nevertheless, some evidence suggests that despite clinical symptom remission, these patients may have persisting lung function impairment, bronchial hyperresponsiveness and airway inflammation and remodelling as an expression of a persistent underlying subclinical disease process in adolescence [110–112]. In order to reliably identify such trajectories, research in early endotype-specific risk factors and biomarkers is needed. Such traits and associated risk factors are increasingly better described. For example, environmental air pollution, tobacco smoke exposure, premature birth, nutritional effects and chronic airway inflammation have been shown to be related to impaired lung function growth and recurrent asthma symptoms [113]. Another such trait may be related to allergic pathways, whereby studies have shown trajectories with different types of sensitisation [114, 115]. However, allergic sensitisation and its relation to asthma progression is heterogeneous [115–118]. Some features have been shown to be clearly associated with asthma trajectories: these are multiple, high or early sensitisations, and also specific sensitisation to dog, cat or horse allergens, which are associated with later onset of asthma [119]. While such trajectories offer personalised options for prevention or treatment, early endotype-specific biomarkers or multi-omic profiles are needed. Ideally, these should be sensitive to the onset of asthma either early on or prior to the disease process.

Therapy and prevention

Asthma phenotyping has the potential to improve and personalise asthma management, either by better targeting of current treatments or by new treatment approaches [99, 120]. An important consideration here is that current paediatric asthma treatment largely relies on a simple regimen of first-line asthma drugs that have proven to be effective, safe and cheap [121]. Although these drugs do improve symptoms and lung function, ICS do not seem to influence lung function trajectories in children with asthma [122].

Personalised asthma treatment has been successfully applied to children with severe therapy-resistant asthma (STRA), a phenotype which does not respond to the standard high doses of ICS (>800 µg budesonide or equivalent) [123]. STRA needs to be separated from “difficult-to-treat” asthma, where poor asthma control is mainly a result of poor adherence, poor control of comorbidities (e.g. obesity, allergic rhinitis, psychosocial distress) or contextual circumstances (e.g. familial, educational, societal). Cohort studies have identified four subphenotypes in STRA: late-onset asthma with normal lung function, and three subphenotypes of early-onset atopic asthma with normal lung function, mild airflow limitation and severe airflow limitation [124]. If patients remain stable within such clusters over time, such pathological phenotypes may help guide add-on therapy. In STRA, a good example of endotype-specific treatment is the introduction of biologicals for the treatment of atopic asthma. At present, omalizumab (anti-IgE), mepolizumab (anti-interleukin (IL)5) and dupilumab (anti-IL4 and anti-IL13) are approved for use in children from the age of 6 years (omalizumab and mepolizumab) and 12 years (dupilumab), with omalizumab having the longest track record [3, 125]. As biologicals interfere with a specific component of the inflammatory cascade, patients are selected on the basis of their inflammatory phenotype, with quantitative cut-offs. Only children with the allergic, eosinophilic phenotype are eligible for such
treatment, with prescription algorithms depending on phenotype. Evidence for clinical effectiveness of
biologics in children aged >12 years has been summarised recently [123].

**Disease phenotype and stability**
The terms “controlled”, “partly controlled”, “uncontrolled” or “brittle” asthma describe clinical symptom
patterns, asthma control and exacerbation risks. In clinical practice, such terminology is largely used in a
qualitative or semiquantitative manner and often does not support precise treatment decisions. Efforts to
quantify asthma control in an observer-independent manner (e.g. by using asthma control tests or
questionnaires) have now become established tools for guiding asthma treatment. However, quantifying
asthma exacerbation risk or risks for phenotype stability and persistence of asthma remains a challenge in
childhood asthma. Recent studies have used observer-independent clustering methods to characterise
symptom patterns associated with asthma, with a potential use in telemonitoring screening tests [64]. It has
been hypothesised that the dynamics of weekly fluctuations of symptoms (i.e. how fast the lung recovers
from viral infection) in the first year of life are related to an asthma phenotype. The dynamics of symptom
fluctuations (and not the number of symptomatic weeks) could identify a cluster of infants with a higher
risk of subsequent persistent wheeze at preschool age [126].

Others have used biomarkers such as regular measurements of lung function or $F_{eNO}$ to identify clusters of
children with asthma in an observer-independent manner (dynamic phenotypes, fluctuation phenotypes) [9,
127]. Of particular interest are novel approaches using clustering methods that consider a time-series of
fluctuations, e.g. in daily adherence with inhaler treatment [128]. Although the techniques are all in their
infancy, data from adult asthmatics show that such fluctuation-based methods of telemonitoring using
novel machine-learning methods have the potential to characterise asthma stability and exacerbation risks
in an observer-independent manner [129–132]. Assessment of daily fluctuations of airway inflammation
have become feasible with $F_{eNO}$. $F_{eNO}$ shows a high degree of day-to-day fluctuation [133]. While single
values will not reflect the entire inflammatory disease process, recent evidence has shown that a series of
daily $F_{eNO}$ values is long-range correlated and related to exacerbation risks in children [127, 134].

**Inflammatory phenotypes**
Chronic inflammation of the airways plays a central role in the pathogenesis of asthma, and
anti-inflammatory treatment with ICS is the treatment of choice. The pattern of inflammation is determined
by several factors including age, aeroallergen sensitisation, airway infection (viral or bacterial) and disease
severity.

In preschool-aged children (<5 years) with recurrent wheezing, three recent unbiased analyses have shown
distinct clusters of inflammation in the lower airways with predominant eosinophilia associated with
aeroallergen sensitisation, or neutrophilia associated with bacterial and/or viral infection [135]. The
findings were independent of clinical phenotypes and symptom pattern [136]. Therefore, a significant
proportion of children in this age group does not have lower airway eosinophilia, and the inflammatory
heterogeneity helps to explain why many younger children with recurrent wheezing do not respond to ICS
[135]. We now have evidence to support the need for more objective inflammatory phenotyping in this age
group prior to making management decisions. In preschool children, blood eosinophils correlate with
airway eosinophils, and may be helpful to guide ICS treatment. The INFANT trial has supported this by
showing that preschool-aged children with recurrent wheezing and aeroallergen sensitisation with blood
eosinophils $>300$ cells·$\mu$L$^{-1}$ were differential responders to ICS [137]. However, noninvasive biomarkers
that will identify the neutrophilic/infection phenotype are still lacking. There are some observational data to
support targeted antibiotic therapy, including a recent study showing that low levels of tumour necrosis
factor (TNF)-$\alpha$ and IL-10 and high levels of CCL22 in nasal lining fluid of children with preschool
wheeze predicted favourable treatment response to azithromycin during acute episodes of asthma-like
symptoms [138–142]. However, definitive interventional trials are lacking.

The majority of school-aged children with mild to moderate asthma have allergic, eosinophilic airways
disease associated with type 2 immune responses, including elevated interleukin IL-5 and IL-13 [143].
This inflammatory phenotype is supported by indirect measures of inflammation, including exhaled nitric
oxide, a T2 biomarker, which is elevated in these patients [144]. Therefore, the majority of school-age
asthma is responsive to ICS and can be controlled. If there is persistent poor control with continuing
escalations in treatment, the most common explanation is failure to address the basics of management,
including adherence to ICS therapy and appropriate inhaler device or technique. Children with poor control
because of unresolved modifiable factors have difficult-to-treat asthma [3]. They commonly have a steroid
sensitive airway eosinophilia which improves when the basics are addressed, together with evidence of
improved lung function, reduction in ICS dose and fewer exacerbations up to 5 years later [145, 146].
Most evidence relating to airway inflammation in childhood asthma is biased towards severe disease, because invasive diagnostic techniques are often impossible in children with milder disease. Severe asthma in children is predominantly associated with persistent eosinophilic airway inflammation which may be relatively resistant to treatment with ICS [3, 145]. Interestingly, airway eosinophilia persisted despite reduced levels of interleukin IL-5 and IL-13, which are supposed to drive allergic asthma. The absence of these cytokines, together with persistence of eosinophilia in STRA has led to the hypothesis that innate mediators such as IL-33, which appear relatively steroid resistant, may dominate the immune response in STRA [147, 148]. Some studies have identified a “type-2-low” asthma endotype, associated with airway neutrophilia [149–153]. However, IL-4, -5 and -13, the signature type 2 cytokines, are very steroid sensitive, and thus steroid-treated patients are unlikely to have detectable levels. Hence, type-2-low asthma could be explained by suppression of type-2 cytokines by corticosteroids [154]. Although a neutrophilic phenotype seems uncommon in school-age asthma, analysis of cytokines in bronchoalveolar lavage fluid (BALF) from children with severe asthma has shown a mixed picture of type 2, type 1 (characterised by IL-12, TNF-α and interferon-γ) and T-helper-17 (characterised by IL-17 and granulocyte-colony stimulating factor), which are associated with BALF neutrophilia [153]. Children with neutrophilic inflammation were younger compared to those with eosinophilic or non-neutrophilic inflammation (median ages 6, 11 and 10 years, respectively) suggesting that neutrophilic disease is more common in preschool asthma [136, 153].

Therefore, it is unclear, especially in the context of STRA, whether or not type-2-low asthma is a distinct phenotype or merely represents concomitant bacterial infection or suppression of type 2 inflammation by corticosteroids [155]. However, some asthmatic children are nonatopic, and more mechanistic studies (characterisation of endotypes) are needed in this subgroup of children where therapeutic options are currently limited.

Little is known about the exact role of type 2 innate lymphoid cells (ILC2) in children with asthma. ILC2s in the airways are activated by cytokines derived from the epithelium, thymic stromal lymphopoietin, IL-25 and IL-33, and may recruit and activate eosinophils by IL-4, IL-5 and IL-13. Children with STRA had higher ILC2s compared to children with difficult-to-treat asthma, and it has been suggested that IL-33 contributes to the activation of ILC2 in STRA; ILC2s decreased after treatment with systemic corticosteroids [145, 148, 156]. There are no data on the role of ILC2s in children with mild to moderate asthma.

**Current limitations in the clinical application of phenotypes and endotypes as a basis for treatment**

Information on the stability of a phenotype is crucial before it can be considered as a guide to the management of asthma. Phenotypes should therefore be studied for reproducibility, feasibility and temporal stability. Such validation is often lacking, especially in children. With respect to viral wheeze (episodic, transient phenotype) versus multiple-trigger wheeze (recurrent, persistent phenotype), some years ago a European Respiratory Society taskforce concluded that, in the absence of evidence in favour of specific treatments, and the variability in time within subjects, the two phenotypes should be treated similarly, based on the severity and frequency of symptoms [10, 157–159].

Treatment guided by eosinophils in sputum has been shown to be beneficial in adults with asthma, but a single study in children with severe asthma showed no clear benefit [160, 161]. A study on sputum cytology in children with mild to severe asthma showed that 63% changed their inflammatory phenotype at least once a year, irrespective of asthma severity or treatment changes, which also limits the use of inflammatory phenotypes to guide asthma treatment [162]. Invasive diagnostic methods cannot be applied to most children with asthma, and there has been a keen interest in noninvasive biomarkers of specific biological processes, of which FeNO as a marker of eosinophilic inflammation is a prominent example [133]. The introduction of FeNO in clinical practice has been preceded by decades of research including basic and methodological studies and many clinical trials of FeNO-guided treatment and other applications. Finally, meta-analysis of FeNO-guided treatment in children resulted in an average significant reduction of 37% in exacerbation risk, without effects on other aspects of asthma control [163–165]. Presently, FeNO monitoring is not recommended for routine use in clinical asthma care, but considered useful in selected patients [166]. Many more biomarkers in exhaled air, breath condensate, induced sputum, blood and urine that might be used to define the inflammatory phenotype in children have been studied in past decades, often employing extremely sensitive assessments of substances of potential interest. Unfortunately, to date, none of these have proven feasible, and there is no evidence of benefit to clinical decision making. To better define phenotypes, an unbiased, data-driven clustering, using a multidimensional or systems biology approach may be needed. For example, in a cohort of 300 children within the Severe Asthma Research Program unsupervised clustering identified four clusters of children with severe asthma with differences in
clinical and pathophysiological characteristics [124]. Latent class analysis in a population-based cohort revealed four asthma trajectories, which may imply different treatment approaches [167]. Other groups used multilevel learning approaches for predicting asthma phenotypes using high-dimensional biomarker signatures including questionnaires, genotype, microarrays, real time quantitative PCR, flow cytometry and cytokine data [168]. Similar approaches may be used to predict asthma development in young children, better define asthma phenotypes and pave the way for personalised treatments. At present, such multidimensional strategies are hardly explored.

Conclusions
In the development of asthma, genes and gene–environment interactions play an important role, and protective environments such as farmyards may offer clues to the prevention of asthma development in susceptible children. In this respect, the airway microbiome and the lung–gut microbiome axis offer interesting insights, as dysbiosis of gut and lung microbiome seems to be involved in the development of later asthma. Possible preventive measures also include prevention of preterm birth (e.g. by smoking bans), reduction of adverse exposures such as air pollution and focus on healthy lifestyle and prevention of excessive weight gain in the first 2 years [169].

Paediatric asthma phenotypes may help to answer questions on the optimal treatment of individual children and may be based on clinical, temporal, developmental or inflammatory characteristics. Phenotypes may be helpful in prediction of persistent asthma, identifying personalised options for prevention and to personalise treatment or disease modification of asthma. At present, already, inflammatory phenotypes guide the use of biologicals. Multidimensional approaches integrating different high-dimensional biomarkers are hardly explored, but show promise for asthma prediction.

In recent years, much progress has been made in unravelling the many factors involved in asthma development and pathogenesis. The next challenge is to translate this knowledge in preventive and therapeutic strategies to reduce the burden and improve the prognosis of asthma in children.


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