

Childhood Asthma: Advances Using Machine Learning and Mechanistic Studies

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Abstract

A paradigm shift brought by the recognition that childhood asthma is an aggregated diagnosis that comprises several different endotypes underpinned by different pathophysiology, coupled with advances in understanding potentially important causal mechanisms, offers a real opportunity for a step change to reduce the burden of the disease on individual children, families, and society. Data-driven methodologies facilitate the discovery of “hidden” structures within “big healthcare data” to help generate new hypotheses. These findings can be translated into clinical practice by linking discovered “phenotypes” to specific mechanisms and clinical presentations. Epidemiological studies have provided important clues about mechanistic avenues that should be pursued to identify interventions to prevent the development or alter the natural history of asthma-related diseases. Findings from cohort studies followed by mechanistic studies in humans and in neonatal mouse models provided evidence that

environments such as traditional farming may offer protection by modulating innate immune responses and that impaired innate immunity may increase susceptibility. The key question of which component of these exposures can be translated into interventions requires confirmation. Increasing mechanistic evidence is demonstrating that shaping the microbiome in early life may modulate immune function to confer protection. Iterative dialogue and continuous interaction between experts with different but complementary skill sets, including data scientists who generate information about the hidden structures within “big data” assets, and medical professionals, epidemiologists, basic scientists, and geneticists who provide critical clinical and mechanistic insights about the mechanisms underpinning the architecture of the heterogeneity, are keys to delivering mechanism-based stratified treatments and prevention.

Keywords: machine learning; children; asthma mechanism

Asthma usually starts before school age and is responsible for a heavy burden of ill health, including premature death. Despite availability of effective drugs, a proportion of children with asthma have troublesome symptoms and frequent exacerbations. Not much has changed in asthma treatment; for most children, inhaled corticosteroids and leukotriene receptor antagonists remain controller medications of choice, but predicting response in individual patients continues to be a major clinical challenge (1–3). Up to 30% of children with asthma have only a partial improvement (or no improvement) when using currently

available antiinflammatory drugs (1, 2), and the delivery of personalized treatment, the cure, or the prevention appear as elusive as ever (4). A paradigm shift brought by the recognition that asthma is an aggregated diagnosis comprising different endotypes (4–6), coupled with recent breakthroughs in understanding important mechanisms leading to different clinical presentations, offers a real opportunity for a step change to reduce the disease burden on individual children, families, and the society. Asthma endotypes are defined as disease subtypes characterized by distinct pathophysiological mechanisms, and each endotype should

have a unique pathophysiology (5). However, common mechanisms may overlap different endotypes, which may in part explain the heterogeneity in treatment responses. For example, inhaled corticosteroids may target the common mechanism(s), and consequently patients belonging to several different endotypes will exhibit a range of responses (7). In contrast, a drug may target a unique pathway that underpins a specific endotype, and only patients belonging to that endotype will benefit (which may be the case for some of the novel biologics). One important issue going forward is to

(Received in original form October 17, 2018; accepted in final form December 19, 2018)

*A.C. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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CME will be available for this article at www.atsjournals.org.

Am J Respir Crit Care Med Vol 199, Iss 4, pp 414–422, Feb 15, 2019

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Originally Published in Press as DOI: 10.1164/rccm.201810-1956CI on December 20, 2018

Internet address: www.atsjournals.org

develop better ways to distinguish between meaningful asthma subtypes at a population and individual patient level. This would allow disaggregation of the primary outcome (asthma) into its constituent parts to facilitate the discovery of their underlying specific mechanisms, identify novel endotype-specific therapeutic targets for stratified treatment (8), and move away from symptom-based toward mechanism-based treatment.

Disaggregating Childhood Asthma: Can Data Science Facilitate Endotype Discovery?

One approach to identify asthma endotypes uses the advances in data-driven techniques, with the assumption that patterns of symptoms and/or biomarkers assessed either longitudinally (e.g., in birth cohorts) or cross-sectionally (e.g., in studies of patients with asthma) are a reflection of underlying mechanisms (7). However, this assumption is by no means certain. Such analyses range from univariate approaches that use a single symptom (usually wheeze) (9, 10), or measures of lung function (11–13) or various biomarkers (14–16) ascertained over time, to methods that model a number of variables together, either cross-sectionally (17, 18) or longitudinally (19, 20). Several recent articles have reviewed the use of data-driven methodologies for endotype discovery in childhood asthma (21–23) and have summarized how patterns “hidden” in large datasets can be uncovered using statistical and machine learning techniques, such as latent class analysis (LCA) (9, 10), principal component analysis (24, 25), cluster analysis (26), and exploratory factor analysis (27). Similar techniques have also been used in adult asthma (28, 29).

Although data-driven methods reveal a structure within “big healthcare data,” one has to be careful not to assume that derived classes (or clusters) exemplify “true” asthma endotypes. It has been shown that the choice of features used in machine learning algorithms, the use of different methods applied to the same dataset, or different data transformations in the same dataset using the same algorithm can drastically affect results (18). Furthermore, the optimal number of clusters identified in any analysis may be an artifact of the study design (30), and

there may be a considerable heterogeneity between individuals within supposedly homogeneous classes (23). Within-class heterogeneity, which has rarely been investigated or reported, may explain the discrepancies between different studies. This is exemplified by inconsistencies in risk factors associated with wheeze phenotypes reported in different studies that used the same methodology (longitudinal LCA) and the same feature (current wheeze) (23). Although phenotypes reported in different studies generally share the same nomenclature, classes/phenotypes with the same name often differ in the time of onset of symptoms, their longitudinal trajectories, and/or distribution in a study population (8, 23). The nomenclature that we currently use to describe patterns of childhood wheezing at a population level (e.g., “transient,” “persistent,” and “late-onset” wheezing) may not adequately convey the temporality of wheezing among individual children assigned to each of these classes (23). Furthermore, the same pattern of symptoms does not necessarily indicate the same underlying mechanism. For example, some patients assigned as persistent wheezers may wheeze at preschool age in association with virus infection (e.g., because of impaired antiviral responses) (31), but in the same child wheezing at school age may be caused by different mechanism (e.g., allergic sensitization and allergen exposure) (32). Finally, different mechanisms are not mutually exclusive (and may be synergistic), and it is possible that children in whom more than one mechanism is operating may have the most severe disease (32).

Findings from data-driven analyses may be translated into practice by linking “hidden” patterns discovered in clinical datasets with underlying pathology, with the ultimate aim to target therapies to pathophysiological mechanisms and deliver stratified treatment. Rapid advances in molecular methods that generate large amounts of data offer opportunities to use data-driven analyses to facilitate better understanding of mechanisms. Recent analysis using machine learning applied to multiple IFN-related, proinflammatory and regulatory cytokines and T-helper cell type 2 chemokines induced by rhinovirus-16 stimulation of blood mononuclear cells of children in a birth cohort study described six profiles (clusters, immunophenotypes)

of antiviral responses (32). Importantly, different immunophenotypes were linked to disease protection, early-onset troublesome asthma, and late-onset mild allergic asthma, providing pointers to potential mechanisms (32). A genome-wide association study using early-onset asthma with recurrent, severe exacerbations as an outcome identified a novel gene, CDHR3 (cadherin-related family member 3), that was associated only with this phenotype but not with physician-diagnosed asthma. Subsequent mechanistic studies have suggested that CDHR3 may be a receptor for rhinovirus C (33), identifying CDHR3 as a potential therapeutic target. This example demonstrates how information on asthma subtypes and relevant environmental exposures that interact with genes can be used to better understand pathophysiology (34). Geneticists can use asthma subtypes discovered by data-driven techniques as outcomes in future genome-wide association studies to offer further mechanistic insights.

Advances in Identifying Factors That Prevent or Propagate Childhood Asthma

Epidemiological studies have provided important clues into avenues that should be pursued to allow identification of interventions to prevent the development or change the natural history of childhood asthma. Two lines of investigation have been highlighted in recent years: first, the role of environments such as traditional farms, which offer protection from asthma (35); and second, the role of allergic sensitization and the interplay of allergens, microbes, and other environmental exposures in the development and exacerbation of asthma (36). Investigations of these paradigms provide examples of how to move from epidemiological observations to mechanistic studies and highlight the importance of the developing and maturing immune system.

Early-Life Immune Development and Asthma Onset

Evidence of the specific immune landscape in early life that results in increased propensity to exaggerated allergic inflammatory responses has been shown in neonatal mice, whereby shortly after birth, type 2 innate lymphoid cells, eosinophils, basophils, and mast cells accumulate in developing lungs in an IL-33-dependent

manner. These cells accumulated in naive mice without any external exposures (37). The immune responses were further exaggerated with allergen exposure. An exaggerated eosinophilia and airway hyperresponsiveness (AHR) are apparent in neonatal mice exposed to inhaled house dust mite (HDM) from 3 days of life compared with adult mice exposed to HDM from 8 weeks of life (38). The exaggerated type 2 immunity to allergen occurred despite high numbers of pulmonary natural Helios⁺ T regulatory cells. The difference in responses was explained by the developing airway microbiome, which increased in diversity during the first weeks of life and underwent a change from mainly Proteobacteria and Firmicutes phyla, toward Bacteroidetes. The change and increasing diversity in the airway microbiome with age was associated with less eosinophilia, AHR, and type-2 immune response and a parallel emergence of protective Helios⁺ T regulatory cells. This showed a direct relationship between the developing airway microbiome and induction of T regulatory cells needed for protection from allergen-induced inflammatory airways disease (38).

Microbial Exposures, Innate Immunity, and Asthma Prevention

The protective effect of the traditional farming was confirmed in the comparison of Amish and Hutterite children, with a striking fourfold lower asthma prevalence among the Amish (39, 40). These farming communities have similar genetic ancestry and exposures to most known risk factors for asthma, but with the key difference that Amish communities practice traditional farming and Hutterites use industrial agriculture (40). Circulating neutrophils with lower levels of CXCR4 (C-X-C chemokine receptor type 4) expression were higher in the Amish, and monocytes expressed a suppressive phenotype, suggesting differences in innate immunity were important in determining asthma susceptibility. In addition, in a murine model of allergic airways disease, intranasal administration of dust extracts from homes in the Amish community inhibited airway hyperreactivity and eosinophilia, and this protection was reversed in the absence of two molecules (MyD88 [myeloid differentiation primary response protein 88] and TRIF [TIR-domain-containing adapter-inducing IFN- β]), which are

critical in the development of innate immune signaling (40). These findings suggest that the mechanism by which the Amish environment provides protection is a modulation of innate immune responses (40, 41).

The key question of which component of the farmyard exposures is protective and can be translated into interventions requires confirmation. Numerous experimental studies have been undertaken in early-life models of allergen exposure to dissect the mechanisms and identify therapeutic targets. One of the components of the traditional farming environment that confers protection from asthma and allergies may be bacterial gram-negative LPS (endotoxin) exposure, which may also be an indirect marker of total microbial exposure (42). Interestingly, LPS exposure alone, at a high dose, results in significant airway inflammation characterized by neutrophilia and is used to recapitulate acute lung injury (43, 44). Smaller doses, when administered intranasally with allergen such as HDM, lead to allergic airways inflammation with eosinophilia and AHR (45). Yet, the key difference in the peripheral circulation between the protected Amish children and Hutterites was increased neutrophils and endotoxin levels in the Amish (40). It is likely that the type of endotoxin, exposure load (determined by the overall bacterial exposure), and duration are critical in determining disease protection or exacerbation. Among sensitized children, a combination of allergen and endotoxin exposure results in worse disease (46). In contrast, children who are protected from asthma have a continuous exposure to endotoxin from early life, and if exposure is removed (for example by migration from a rural to urban environment), the protection is lost (47–49). A murine model of chronic low-dose endotoxin exposure, followed by HDM exposure, has shown that prior endotoxin reduced the induction of dendritic cells by cytokines produced by bronchial epithelial cells, including IL-33, which in turn protected from the type-2 immune response development (50). Loss of the ubiquitin-modifying epithelial enzyme A20 resulted in a loss of the protection (50). This suggests that airway epithelial cell function may be central to the mechanism by which endotoxin confers protection in childhood asthma. However, this mechanistic link was investigated in an adult murine model, and mRNA levels of

the gene *TNFAIP3*, which encodes A20, were assessed after allergen exposure to bronchial epithelial cells from adults with asthma.

It is important to note that endotoxin load is often measured as an indirect representation of total microbial exposure, and the type and diversity of early-life bacterial exposure from a protective environment may shape the airway microbiome toward a phenotype that promotes immune responses that protect from allergic inflammation. The Finnish and Russian Karelia communities are another example of adjacent regions with contrasting socioeconomic demographics and lifestyles (51) and distinct asthma and allergy prevalence. Skin microbiota and bacterial microbes in nasal mucosa were strikingly different, with overall increased diversity and an abundance of *Acinetobacter* among Russian subjects who had 3- to 10-fold lower asthma prevalence (52). This causal link has recently been supported in a neonatal murine model of HDM exposure in which concomitant exposure of allergen and the inhaled lyophilized bacteria *Acinetobacter lwoffii*, from farm dust (53), conferred complete protection from the development of AHR in early life (54). This was associated with a significant reduction of pulmonary eosinophils and IL-5 and IL-13 (54). Increasing evidence from experimental models suggests that shaping the airway microbiome in early life modulates immune function to protect against the development of allergic airway inflammation and asthma. However, the optimal timing or duration of an intervention to achieve a “protective” airway microbiome in children remains unknown. Indeed, the constituents and route of administration of a protective intervention are also unclear. However, with evidence of cross-talk between the mucosal tissues and of the existence of a gut–lung axis (55), a pilot clinical trial of infantile oral bacterial lysates supplementation to prevent recurrent wheezing has shown benefit on both rate and duration of asthma attacks (56). The potential benefits of oral bacterial lysates in disease prevention among young children (6–18 mo old) at increased risk for asthma is currently being investigated in the ORBEX (Oral Bacterial Extract for the Prevention of Wheezing Lower Respiratory Tract Illness) trial (NCT02148796).

Acknowledging the limitations of murine studies and their applicability to children, increasing focus is being placed on investigating mechanisms using primary immune cells from children. The importance of interactions between allergens and infection in determining immune responses in childhood asthma is established (57), but specific mechanisms have been lacking. Longitudinal collection of peripheral blood cells from children at ages 2 and 3 years has shown differential expression of genes associated with natural killer cells among children who developed asthma by mid-school age (7 yr) (58). The gene response pattern was specific to children who were both sensitized and had asthma, thus identifying a potential molecular pathway for early intervention, before established disease (58).

Although peripheral blood remains an excellent source of inflammatory cells and mediators, the relationships between peripheral and pulmonary immune responses in childhood asthma are uncertain. Cohort studies are increasingly including longitudinal airway sample collection (59); although limited to the upper airway to ensure this is minimally invasive, such approaches are critically important if we are to understand mechanisms underlying asthma inception. Analysis of nasal epithelial cells by RNAseq and machine learning from adults has allowed identification of a 90-gene signature that classified asthma and provided a potential nasal diagnostic biomarker (60).

Viral and Bacterial Pathogens Contributing to Childhood Asthma

Neonatal hypopharyngeal colonization in the first 28 of days of life with *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* has been associated with increased risk of subsequent wheeze or asthma in childhood (61). Longitudinal nasopharyngeal sample collection for microbes has also shown that more than 80% of acute respiratory illnesses in preschool-aged children involve viruses, but they are accompanied by a change in the nasopharyngeal microbiome toward a dominance of a narrow range of pathogenic bacteria. The combination of the predominant bacterial genera associated with respiratory infections (*Moraxella*, *Streptococcus*, *Corynebacterium*, *Alloiococcus*, *Haemophilus*, and *Staphylococcus*)

and early-life allergic sensitization was associated with persistent wheeze and asthma by school age (62). In contrast, the presence of the same bacteria without sensitization was associated with transient wheezing illnesses until 3 years of age.

It is becoming increasingly apparent that viral pathogens alone are not the only trigger for symptoms and acute attacks. Bacterial pathogens and a dysbiotic airway microbiome may be as important for triggering symptoms and attacks as viruses (particularly for attacks of preschool wheeze) (63). The most common viruses that cause symptoms are rhinovirus and respiratory syncytial virus, and bacterial species that appear to be important include *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. A dysbiosis involving a predominance of these organisms contributes to recurrent symptoms and attacks (64). This suggests there are

phenotypes of preschool wheezers who may have a predominant infection-driven, neutrophilic airway inflammatory profile that does not respond to the usual therapeutic approach of inhaled corticosteroids (65, 66). However, the functional role and impact of airway bacteria detected during acute attacks on immune responses remains uncertain. Two trials have investigated the role of the macrolide antibiotic azithromycin for acute attacks of wheeze or troublesome lung symptoms in children younger than 5 years of age (67, 68). Although both showed benefit on symptom duration, neither showed improvement in severity of attacks, hospitalization, or time to next attack, and it is likely that the observed benefits were due to the immunomodulatory or antiinflammatory activity of azithromycin, rather than its antibacterial properties (69, 70). The potential antineutrophilic benefit of azithromycin is supported from separate

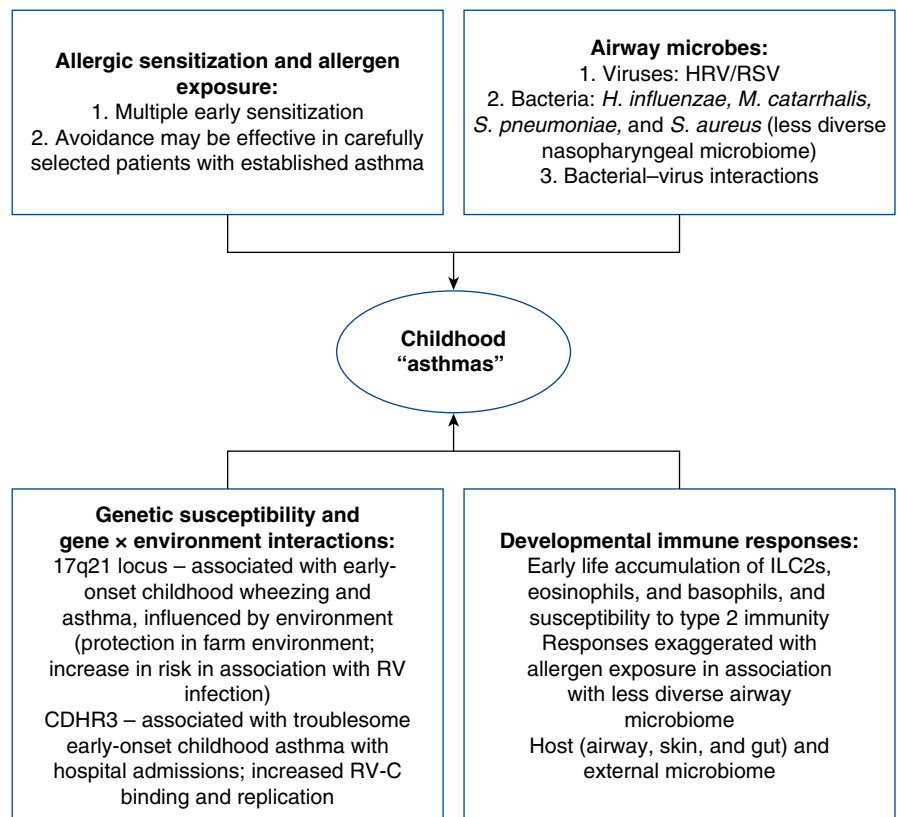


Figure 1. Host and environmental influences increasing susceptibility and severity: key influences that determine development of childhood “asthmas” identified from longitudinal cohorts and experimental investigations. CDHR3 = Cadherin Related Family Member 3; HRV = human rhinovirus; *H. influenzae* = *Haemophilus influenzae*; ILC2 = type 2 innate lymphoid cell; *M. catarrhalis* = *Moraxella catarrhalis*; RSV = respiratory syncytial virus; RV = rhinovirus; *S. aureus* = *Staphylococcus aureus*; *S. pneumoniae* = *Streptococcus pneumoniae*.

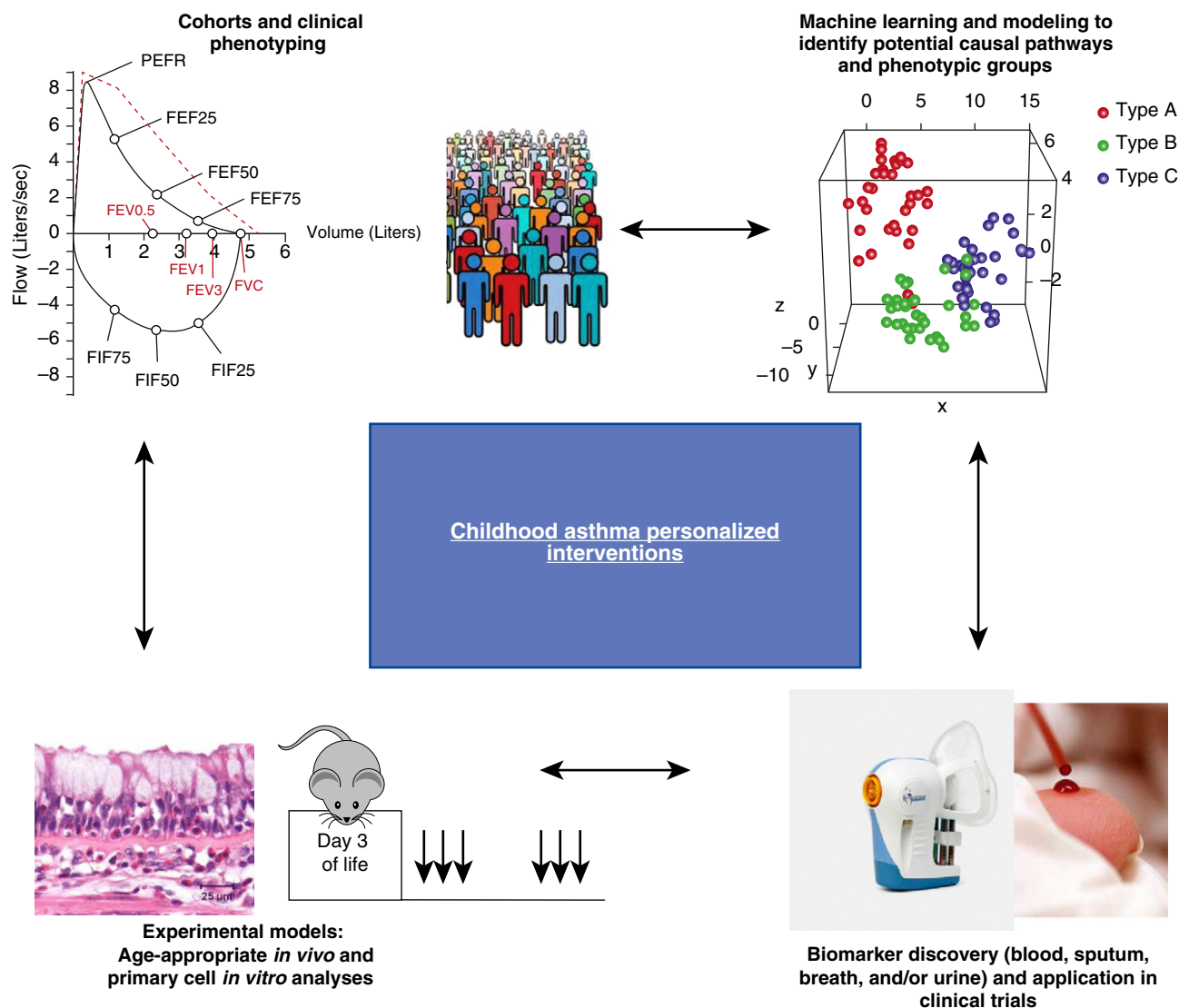


Figure 2. Integrated, multidisciplinary approach to enable discovery of interventions that allow prevention and disease modification in childhood asthma. Interpreting “big data” using clinical knowledge from patients and cohorts, mechanistic *in vitro* studies using human samples, and experimental animal model studies helps identify biomarkers and individualized interventions. Data scientists turn “big data” into useful information about the “hidden” structures using statistical and machine learning algorithms and help disaggregate asthma into “asthmas,” medical professionals and basic scientists provide critical clinical and mechanistic insights about the mechanisms underpinning the architecture of the heterogeneity, and geneticists use asthma subtypes discovered by data-driven techniques as outcomes in genetic studies to provide further mechanistic insights. Iterative decisions are made at each step to deliver mechanism-based stratified treatments and prevention. FEF = forced expiratory flow; FIF = forced inspiratory flow.

indirect evidence that lower airway inflammation in children with severe preschool wheeze reveals a phenotype with neutrophil predominance that is relatively insensitive to inhaled corticosteroid therapy (66). It is therefore not clear whether bacteria are causal or are present as “bystanders” as a result of mucosal immunosuppression by viral infection or corticosteroid therapy (71, 72). Future intervention studies for wheezing in preschool children and older children with established asthma therefore need to

investigate the downstream immunological consequences (whether beneficial or harmful) of manipulating of bacterial, viral, and fungal organisms (72).

Contribution of Allergic Sensitization to Preschool Wheeze and Asthma

The concomitant presence of infection and allergic sensitization is associated with a differential response to treatment with inhaled corticosteroids (73) and predicts the progression from preschool wheeze to later asthma (12, 74) and hospitalizations with

asthma attacks (75). A recent LCA of data from five clinical trials has revealed four classes that differed according to the presence of allergen sensitization and exposure (19). Only classes with multiple sensitization and persistent allergen exposure or sensitization with eczema were responsive to inhaled steroids (19). During school age, there appears to be a switch in the predominant driver of persistent symptoms from infection to allergic sensitization and allergen exposure, which results in a predominance of type 2

immunity with eosinophilic airway inflammation. Severe asthma in school-aged children is characterized by a steroid-insensitive eosinophilia, not neutrophilia (67, 76).

The PROSE (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations) trial, which demonstrated a significant reduction in seasonal exacerbations in autumn in children who received anti-IgE antibody omalizumab, has confirmed a close link between allergic sensitization and virus-induced asthma attacks (77); the patient subgroup who benefitted most had rhinovirus-induced exacerbations (78). However, although childhood asthma is closely associated with allergic sensitization (36, 79), most asthma guidelines do not advocate the assessment of sensitization for asthma diagnosis. Confirmation of sensitization does not prove that allergy is a cause of patients' symptoms (79), and in a proportion of sensitized children with asthma, presence of IgE antibodies ascertained by skin or blood tests is not related to either asthma presence or its severity (80). Similar to "asthma," "allergic sensitization" may be an agglomerate of several types of sensitization, some of which are benign and some pathologic (80), with only pathologic subtypes (such as multiple early sensitization) being associated with asthma (14, 74, 81). Several studies using machine learning identified cross-sectional (82) and longitudinal (15, 16) clusters of specific IgE responses to individual allergenic protein (allergen components), which were associated with different risks of asthma development (16), persistence (15, 83), and severity (14, 74, 82). However, these sensitization classes can only be identified by modeling of the large amounts of data collected longitudinally during childhood in hundreds of children (14, 74) and cannot as yet be differentiated or confirmed in a clinical situation. A recent study has shown that in a marked difference from IgE-mediated food allergy, in which sensitization to individual allergenic molecules predicts clinical reactivity (e.g., Ara h 2 in peanut allergy [84]), the key associate of asthma in children is not IgE response to any individual molecule but complex interaction patterns between allergen component-specific IgEs (85). Results from intervention studies such as Preventing Asthma in High Risk Kids (NCT02570984), which tests whether

2 years of treatment of high-risk children aged 2 to 3 years with omalizumab (anti-IgE) will prevent the progression to childhood asthma, will provide data that will allow triangulation to enable causal inference.

There is ongoing controversy as to whether allergen avoidance should be recommended in the treatment of childhood asthma, and several national and international guidelines conclude that allergen avoidance measures are ineffective and should not be used (86). Among children who are sensitized, virus infection and high allergen exposure act synergistically to increase the risk of hospitalizations with asthma attacks (75). The impact of mite avoidance on asthma exacerbations has been addressed in an intervention trial among mite-sensitized children with asthma aged 3 to 17 years randomized to receive either allergen-impermeable or placebo bed encasings; over the 1-year follow-up, the risk of hospital presentation due to asthma attacks was 45% lower in the active group (87). Future guidelines should take these results into account when making recommendations about nonpharmacological interventions.

Gaps in Knowledge and Future Directions

The gaps in our knowledge of the complexities of mechanisms and airway pathology in childhood "asthmas" (Figure 1) will only be filled with increasing assessments of lower airways and by application of novel technologies that enable significant amounts of mechanistic data to be generated from small and limited samples (88). The challenge of dissecting mechanisms driving endotypes in children and not extrapolating data from studies in adults is essential if we are to avoid inappropriate use of therapies. This is of particular importance as the novel biologics enter clinical practice, because the long-term effects of these treatments in children remain unknown. For example, both mepolizumab (anti-IL-5 monoclonal antibody) and benralizumab (an antibody to the receptor for IL-5) very successfully deplete circulating eosinophils (89). However, eosinophils may be essential for immune regulation and homeostasis (90, 91), and levels of circulating eosinophils in healthy children are higher than in adults (92) (and it is likely this is for a reason).

Therefore, a caution is needed before undertaking eosinophil depletion using systemic biologics in children without understanding mechanisms and potential consequences. To assume that cut-offs of peripheral eosinophils as a biomarker for antieosinophil biologics can be extrapolated from adults to children is another potential error.

One urgent direction for future research is to undertake interventional studies that incorporate mechanistic outcomes. We have embraced the challenge of assessing mechanisms in samples collected from children in observational cohorts and undertaken studies to investigate mechanisms underpinning pediatric severe asthma (76, 93, 94). However, interventional studies that assess only simple efficacy outcomes, such as symptoms or exacerbations, without consideration of mechanism of action of the intervention will not allow progress. Innovative technologies allow invaluable information to be generated from small-volume samples (transcriptomics, single-cell PCR, multiplex cytokine assays), and there are reliable techniques to assess airway pathology noninvasively (induced sputum, nasal epithelial brushings, breath tests), making it unacceptable to undertake interventional trials without mechanistic endpoints. We therefore propose that no pediatric interventional trial (including randomized controlled trials of novel and existing drugs) should be funded or approved by institutional boards without evidence of a parallel investigation of mechanisms. Together with birth cohorts and patient studies, and mechanistic studies in humans and animal models, this will generate invaluable "big data" assets to provide a foundation for a step change toward personalized medicine (Figure 2). To capitalize on this, we need to foster iterative dialogue and continuous interaction between experts with different but complementary skill sets. This may include (but should not be limited to) healthcare professionals, epidemiologists, basic scientists, biologists, geneticists, data scientists, computer scientists, and mathematicians. In such a team approach, methodologist and applied data scientists can turn "big data" coming from different sources into useful information to help disaggregate asthma into "asthmas" (4), with medical professionals and basic scientists providing critical clinical and

mechanistic insights about the mechanisms underpinning the architecture of the heterogeneity. Such a “team science” approach is key to delivering mechanism-based stratified treatments and prevention for common complex diseases (95).

The data-driven “revolution” to help clinical decision making will not be achieved by technology alone.

Technological advances have to be accompanied by a culture change in how we conduct research and by fundamental changes in the academic reward system that currently favors individuals over teams. Bringing together diverse disciplines in such a landscape is challenging, but childhood asthma may serve as an example of how a specific health problem can be

looked at from multiple perspectives. We need an equivalent of the Large Hadron Collider experimental program to bring together technological advances and human expertise across different domains to move a step closer toward a world without asthma. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, *et al.*; NIH/NHLBI AsthmaNet. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138:1608–1618, e12.
2. Szefer SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, *et al.* Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115:233–242.
3. Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, *et al.*; Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975–985.
4. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, *et al.* After asthma: redefining airways diseases. *Lancet* 2018;391:350–400.
5. Lotvall J, Akdis CA, Bacharier LB, Bjerner L, Casale TB, Custovic A, *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355–360.
6. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet* 2008;372:1107–1119.
7. Belgrave D, Henderson J, Simpson A, Buchan I, Bishop C, Custovic A. Disaggregating asthma: big investigation versus big data. *J Allergy Clin Immunol* 2017;139:400–407.
8. Belgrave DC, Custovic A, Simpson A. Characterizing wheeze phenotypes to identify endotypes of childhood asthma, and the implications for future management. *Expert Rev Clin Immunol* 2013;9:921–936.
9. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, *et al.* Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974–980.
10. Belgrave DCM, Simpson A, Semic-Jusufagic A, Murray CS, Buchan I, Pickles A, *et al.* Joint modeling of parentally reported and physician-confirmed wheeze identifies children with persistent troublesome wheezing. *J Allergy Clin Immunol* 2013;132:575–583, e12.
11. Belgrave DCM, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souef PN, *et al.* Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018;6:526–534.
12. Belgrave DC, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A. Trajectories of lung function during childhood. *Am J Respir Crit Care Med* 2014;189:1101–1109.
13. Berry CE, Billheimer D, Jenkins IC, Lu ZJ, Stern DA, Gerald LB, *et al.* A distinct low lung function trajectory from childhood to the fourth decade of life. *Am J Respir Crit Care Med* 2016;194:607–612.
14. Simpson A, Tan VY, Winn J, Svensen M, Bishop CM, Heckerman DE, *et al.* Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010;181:1200–1206.
15. Custovic A, Sonntag H-J, Buchan IE, Belgrave D, Simpson A, Prosperi MCF. Evolution pathways of IgE responses to grass and mite allergens throughout childhood. *J Allergy Clin Immunol* 2015;136:1645–1652, e8.
16. Howard R, Belgrave D, Papastamoulis P, Simpson A, Rattray M, Custovic A. Evolution of IgE responses to multiple allergen components throughout childhood. *J Allergy Clin Immunol* 2018;142:1322–1330.
17. Siroux V, Gonzalez JR, Bouzigon E, Curjuric I, Boudier A, Imboden M, *et al.* Genetic heterogeneity of asthma phenotypes identified by a clustering approach. *Eur Respir J* 2014;43:439–452.
18. Prosperi MC, Sahiner UM, Belgrave D, Sackesen C, Buchan IE, Simpson A, *et al.* Challenges in identifying asthma subgroups using unsupervised statistical learning techniques. *Am J Respir Crit Care Med* 2013;188:1303–1312.
19. Fitzpatrick AM, Bacharier LB, Guilbert TW, Jackson DJ, Szefer SJ, Beigelman A, *et al.*; NIH/NHLBI AsthmaNet. Phenotypes of recurrent wheezing in preschool children: identification by latent class analysis and utility in prediction of future exacerbation. *J Allergy Clin Immunol Pract* [online ahead of print] 26 Sep 2018; DOI: 10.1016/j.jaip.2018.09.016.
20. Belgrave DC, Granell R, Simpson A, Guiver J, Bishop C, Buchan I, *et al.* Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. *PLoS Med* 2014;11:e1001748.
21. Deliu M, Belgrave D, Sperrin M, Buchan I, Custovic A. Asthma phenotypes in childhood. *Expert Rev Clin Immunol* 2017;13:705–713.
22. Howard R, Rattray M, Prosperi M, Custovic A. Distinguishing asthma phenotypes using machine learning approaches. *Curr Allergy Asthma Rep* 2015;15:1–10.
23. Okseel C, Haider S, Fontanella S, Frainay C, Custovic A. Classification of pediatric asthma: from phenotype discovery to clinical practice. *Front Pediatr* 2018;6:258.
24. Smith JA, Drake R, Simpson A, Woodcock A, Pickles A, Custovic A. Dimensions of respiratory symptoms in preschool children. *Am J Respir Crit Care Med* 2008;177:1358–1363.
25. Hilvering B, Vijverberg S, Houben L, Schweizer R, Lammers J-W, Koenderman L. The identification of asthma phenotypes by categorical PCA: combinatorial analysis of clinical parameters and dysfunctional blood eosinophils. *Eur Respir J* 2014;44:P3006.
26. Deliu M, Yavuz TS, Sperrin M, Belgrave D, Sahiner UM, Sackesen C, *et al.* Features of asthma which provide meaningful insights for understanding the disease heterogeneity. *Clin Exp Allergy* 2018;48:39–47.
27. Pillai SG, Tang Y, Van Den Oord E, Klotzman M, Barnes K, Carlsen K, *et al.* Factor analysis in the Genetics of Asthma International Network family study identifies five major quantitative asthma phenotypes. *Clin Exp Allergy* 2008;38:421–429.
28. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–224.
29. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, *et al.* National Heart, Lung, and Blood Institute’s Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315–323.
30. Okseel C, Granell R, Mahmoud O, Custovic A, Henderson AJ; STELAR; Breathing Together Investigators. Causes of variability in latent phenotypes of childhood wheeze. *J Allergy Clin Immunol* [online ahead of print] 5 Dec 2018; DOI: 10.1016/j.jaci.2018.10.059.
31. Semic-Jusufagic A, Belgrave D, Pickles A, Telcian AG, Bakhsholiani E, Sykes A, *et al.* Assessing the association of early life antibiotic prescription with asthma exacerbations, impaired antiviral immunity,

- and genetic variants in 17q21: a population-based birth cohort study. *Lancet Respir Med* 2014;2:621–630.
32. Custovic A, Belgrave D, Lin L, Bakhsoliani E, Telcian AG, Solari R, *et al*. Cytokine responses to rhinovirus and development of asthma, allergic sensitization, and respiratory infections during childhood. *Am J Respir Crit Care Med* 2018;197:1265–1274.
 33. Bochkov YA, Watters K, Ashraf S, Griggs TF, Devries MK, Jackson DJ, *et al*. Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. *Proc Natl Acad Sci USA* 2015;112:5485–5490.
 34. Bonnelykke K, Ober C. Leveraging gene-environment interactions and endotypes for asthma gene discovery. *J Allergy Clin Immunol* 2016;137:667–679.
 35. Genuet J, von Mutius E. Do farm-grown lungs breathe better? *Thorax* 2017;72:202–203.
 36. Oksel C, Custovic A. Development of allergic sensitization and its relevance to paediatric asthma. *Curr Opin Allergy Clin Immunol* 2018;18:109–116.
 37. de Kleer IM, Kool M, de Bruijn MJ, Willart M, van Moorleghe J, Schuijs MJ, *et al*. Perinatal activation of the interleukin-33 pathway promotes type 2 immunity in the developing lung. *Immunity* 2016;45:1285–1298.
 38. Gollwitzer ES, Saglani S, Trompette A, Yadava K, Sherburn R, McCoy KD, *et al*. Lung microbiota promotes tolerance to allergens in neonates via PD-L1. *Nat Med* 2014;20:642–647.
 39. Holbreich M, Genuet J, Weber J, Braun-Fahrlander C, Waser M, von Mutius E. Amish children living in northern Indiana have a very low prevalence of allergic sensitization. *J Allergy Clin Immunol* 2012;129:1671–1673.
 40. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, *et al*. Innate immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med* 2016;375:411–421.
 41. Ober C, Sperling AI, von Mutius E, Vercelli D. Immune development and environment: lessons from Amish and Hutterite children. *Curr Opin Immunol* 2017;48:51–60.
 42. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, *et al*; Allergy and Endotoxin Study Team. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869–877.
 43. Proudfoot A, Bayliffe A, O’Kane CM, Wright T, Serone A, Bareille PJ, *et al*. Novel anti-tumour necrosis factor receptor-1 (TNFR1) domain antibody prevents pulmonary inflammation in experimental acute lung injury. *Thorax* 2018;73:723–730.
 44. Yokochi T. A new experimental murine model for lipopolysaccharide-mediated lethal shock with lung injury. *Innate Immun* 2012;18:364–370.
 45. Saglani S, Mathie SA, Gregory LG, Bell MJ, Bush A, Lloyd CM. Pathophysiological features of asthma develop in parallel in house dust mite-exposed neonatal mice. *Am J Respir Cell Mol Biol* 2009;41:281–289.
 46. Mendy A, Wilkerson J, Salo PM, Cohn RD, Zeldin DC, Thorne PS. Exposure and sensitization to pets modify endotoxin association with asthma and wheeze. *J Allergy Clin Immunol Pract* 2018;6:2006–2013, e4.
 47. Cabieses B, Uphoff E, Pinart M, Anto JM, Wright J. A systematic review on the development of asthma and allergic diseases in relation to international immigration: the leading role of the environment confirmed. *PLoS One* 2014;9:e105347.
 48. Garcia-Marcos L, Robertson CF, Ross Anderson H, Ellwood P, Williams HC, Wong GW. Does migration affect asthma, rhinoconjunctivitis and eczema prevalence? Global findings from the international study of asthma and allergies in childhood. *Int J Epidemiol* 2014;43:1846–1854.
 49. Rodriguez A, Vaca MG, Chico ME, Rodrigues LC, Barreto ML, Cooper PJ. Rural to urban migration is associated with increased prevalence of childhood wheeze in a Latin-American city. *BMJ Open Respir Res* 2017;4:e000205.
 50. Schuijs MJ, Willart MA, Vergote K, Gras D, Deswarte K, Ege MJ, *et al*. Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells. *Science* 2015;349:1106–1110.
 51. Ruokolainen L, Fyhrquist N, Haahtela T. The rich and the poor: environmental biodiversity protecting from allergy. *Curr Opin Allergy Clin Immunol* 2016;16:421–426.
 52. Ruokolainen L, Paalanen L, Karkman A, Laatikainen T, von Hertzen L, Vlasoff T, *et al*. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. *Clin Exp Allergy* 2017;47:665–674.
 53. Ege MJ, Mayer M, Normand AC, Genuet J, Cookson WO, Braun-Fahrlander C, *et al*. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011;364:701–709.
 54. Saglani S, Gregory LG, Manghera AK, Branchett WJ, Uwadiae F, Entwistle LJ, *et al*. Inception of early-life allergen-induced airway hyperresponsiveness is reliant on IL-13⁺CD4⁺ T cells. *Sci Immunol* 2018;3:eaan4128.
 55. Marsland BJ, Trompette A, Gollwitzer ES. The gut-lung axis in respiratory disease. *Ann Am Thorac Soc* 2015;12:S150–S156.
 56. Razi CH, Harmanci K, Abaci A, Ozdemir O, Hizli S, Renda R, *et al*. The immunostimulant OM-85 BV prevents wheezing attacks in preschool children. *J Allergy Clin Immunol* 2010;126:763–769.
 57. Jackson DJ, Gern JE, Lemanske RF Jr. The contributions of allergic sensitization and respiratory pathogens to asthma inception. *J Allergy Clin Immunol* 2016;137:659–665. [Quiz, p. 666.]
 58. Altman MC, Whalen E, Togias A, O’Connor GT, Bacharier LB, Bloomberg GR, *et al*. Allergen-induced activation of natural killer cells represents an early-life immune response in the development of allergic asthma. *J Allergy Clin Immunol* 2018;142:1856–1866.
 59. Turner S, Custovic A, Ghazal P, Grigg J, Gore M, Henderson J, *et al*. Pulmonary epithelial barrier and immunological functions at birth and in early life - key determinants of the development of asthma? A description of the protocol for the Breathing Together study. *Wellcome Open Res* 2018;3:60.
 60. Pandey G, Pandey OP, Rogers AJ, Ahsen ME, Hoffman GE, Raby BA, *et al*. A nasal brush-based classifier of asthma identified by machine learning analysis of nasal RNA sequence data. *Sci Rep* 2018;8:8826.
 61. Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bonnelykke K, *et al*. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med* 2007;357:1487–1495.
 62. Teo SM, Tang HHH, Mok D, Judd LM, Watts SC, Pham K, *et al*. Airway microbiota dynamics uncover a critical window for interplay of pathogenic bacteria and allergy in childhood respiratory disease. *Cell Host Microbe* 2018;24:341–352, e5.
 63. Kloepper KM, Lee WM, Pappas TE, Kang TJ, Vrtis RF, Evans MD, *et al*. Detection of pathogenic bacteria during rhinovirus infection is associated with increased respiratory symptoms and asthma exacerbations. *J Allergy Clin Immunol* 2014;133:1301–1307, 1307.e1–e3.
 64. Bisgaard H, Hermansen MN, Bonnelykke K, Stokholm J, Baty F, Skytt NL, *et al*. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. *BMJ* 2010;341:c4978.
 65. Beigelman A, Bacharier LB. Management of preschool recurrent wheezing and asthma: a phenotype-based approach. *Curr Opin Allergy Clin Immunol* 2017;17:131–138.
 66. Guiddir T, Saint-Pierre P, Purenne-Denis E, Lambert N, Laoudi Y, Couderc R, *et al*. Neutrophilic steroid-refractory recurrent wheeze and eosinophilic steroid-refractory asthma in children. *J Allergy Clin Immunol Pract* 2017;5:1351–1361, e2.
 67. Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, *et al*. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. *JAMA* 2015;314:2034–2044.
 68. Stokholm J, Chawes BL, Vissing NH, Bjarnadottir E, Pedersen TM, Vinding RK, *et al*. Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2016;4:19–26.
 69. Cohen RT, Pelton SI. Individual benefit vs societal effect of antibiotic prescribing for preschool children with recurrent wheeze. *JAMA* 2015;314:2027–2029.
 70. Grigg J. Antibiotics for preschool wheeze. *Lancet Respir Med* 2016;4:2–3.

71. Sabroe I, Postma D, Heijink I, Dockrell DH. The yin and the yang of immunosuppression with inhaled corticosteroids. *Thorax* 2013;68:1085–1087.
72. Smits HH, Hiemstra PS, Prazeres da Costa C, Ege M, Edwards M, Gam H, et al. Microbes and asthma: opportunities for intervention. *J Allergy Clin Immunol* 2016;137:690–697.
73. Fitzpatrick AM, Stephenson ST, Brown MR, Nguyen K, Douglas S, Brown LA. Systemic corticosteroid responses in children with severe asthma: phenotypic and endotypic features. *J Allergy Clin Immunol Pract* 2016;5:410–419, e4.
74. Lazic N, Roberts G, Custovic A, Belgrave D, Bishop C, Winn J, et al. Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts. *Allergy* 2013;68:764–770.
75. Murray CS, Poletti G, Keadze T, Morris J, Woodcock A, Johnston SL, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;61:376–382.
76. Andersson CK, Adams A, Nagakumar P, Bossley C, Gupta A, De Vries D, et al. Intraepithelial neutrophils in pediatric severe asthma are associated with better lung function. *J Allergy Clin Immunol* 2016;139:1819–1829, e11.
77. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136:1476–1485.
78. Esquivel A, Busse WW, Calatroni A, Togias AG, Grindle KG, Bochkov YA, et al. Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. *Am J Respir Crit Care Med* 2017;196:985–992.
79. Custovic A, Lazic N, Simpson A. Pediatric asthma and development of atopy. *Curr Opin Allergy Clin Immunol* 2013;13:173–180.
80. Holt PG, Strickland D, Bosco A, Belgrave D, Hales B, Simpson A, et al. Distinguishing benign from pathologic TH2 immunity in atopic children. *J Allergy Clin Immunol* 2016;137:379–387.
81. Tang HH, Teo SM, Belgrave DC, Evans MD, Jackson DJ, Brozynska M, et al. Trajectories of childhood immune development and respiratory health relevant to asthma and allergy. *eLife* 2018;7:e35856.
82. Simpson A, Lazic N, Belgrave DCM, Johnson P, Bishop C, Mills C, et al. Patterns of IgE responses to multiple allergen components and clinical symptoms at age 11 years. *J Allergy Clin Immunol* 2015;136:1224–1231.
83. Wickman M, Lupinek C, Andersson N, Belgrave D, Asarnoj A, Benet M, et al. Detection of IgE reactivity to a handful of allergen molecules in early childhood predicts respiratory allergy in adolescence. *EBioMedicine* 2017;26:91–99.
84. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125:191–197, e1–e13.
85. Fontanella S, Frainay C, Murray CS, Simpson A, Custovic A. Machine learning to identify pairwise interactions between specific IgE antibodies and their association with asthma: a cross-sectional analysis within a population-based birth cohort. *PLoS Med* 2018;15:e1002691.
86. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2018 [accessed 2019 Jan 17]. Available from: https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf.
87. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing severe asthma exacerbations in children: a randomized trial of mite-impermeable bedcovers. *Am J Respir Crit Care Med* 2017;196:150–158.
88. Farzan N, Vijverberg SJ, Kabesch M, Sterk PJ, Maitland-van der Zee AH. The use of pharmacogenomics, epigenomics, and transcriptomics to improve childhood asthma management: where do we stand? *Pediatr Pulmonol* 2018;53:836–845.
89. Bourdin A, Husereau D, Molinari N, Golam S, Siddiqui MK, Lindner L, et al. Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review. *Eur Respir J* 2018;52:1801393.
90. Yang BG, Seoh JY, Jang MH. Regulatory eosinophils in inflammation and metabolic disorders. *Immune Netw* 2017;17:41–47.
91. Mesnil C, Raulier S, Paulissen G, Xiao X, Birrell MA, Pirottin D, et al. Lung-resident eosinophils represent a distinct regulatory eosinophil subset. *J Clin Invest* 2016;126:3279–3295.
92. Aldrimer M, Ridefelt P, Rodoo P, Niklasson F, Gustafsson J, Hellberg D. Population-based pediatric reference intervals for hematology, iron and transferrin. *Scand J Clin Lab Invest* 2013;73:253–261.
93. Bossley CJ, Fleming L, Gupta A, Regamey N, Frith J, Oates T, et al. Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. *J Allergy Clin Immunol* 2012;129:974–982.
94. Gupta A, Sjoukes A, Richards D, Banya W, Hawrylowicz C, Bush A, et al. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *Am J Respir Crit Care Med* 2011;184:1342–1349.
95. Custovic A, Ainsworth J, Arshad H, Bishop C, Buchan I, Cullinan P, et al. The Study Team for Early Life Asthma Research (STELAR) consortium 'Asthma e-lab': team science bringing data, methods and investigators together. *Thorax* 2015;70:799–801.