

New Directions in Pediatric Asthma



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KEYWORDS

• Asthma • Adherence • Adolescent • Antibacterial agents • Biologics
• Environmental exposures • Inner-city • Lung function

KEY POINTS

- Respiratory viral infections in early life and the development of early allergic sensitization are strongly associated with the inception and persistence of early onset asthma.
- Important areas of prevention investigation include the potential diversification of microbiota through use of pharmaceutical products containing protective bacteria and the use of an asthma biological therapy in early life by reducing or blocking immunoglobulin E or cytokine responses and potentially the response to viral exposure.
- Preschool-aged children with a history of recurrent wheezing, with an increased risk to develop asthma show reduction of disease morbidity with the use of a daily inhaled corticosteroid.
- Further characterization of phenotypes/endotypes and discovery of new biomarkers would allow personalization of therapy and development of new treatment strategies in the future.
- Treatment with high-dose inhaled corticosteroid plus a long-acting beta-agonist, leukotriene modifier, theophylline, anticholinergics, biological therapies, and/or prolonged use of oral corticosteroids are used to achieve control in children with severe asthma.

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Childhood asthma affects an estimated 6.8 million children in the United States,¹ which places them at significant risk for hospitalizations, emergency room visits, and school absences.^{2–4} Management of pediatric asthma is challenging, given the heterogeneous phenotypes that evolve as the child ages. Disease management centers around reducing or eliminating exposure to factors that contribute to disease causation and/or worsen symptoms, such as the reduction of environmental exposure to allergens, pollutants and other environmental factors, the appropriate use of asthma medications, and the effective delivery of education of children and their families and caregivers. However, it is not yet clear how to optimize these approaches, potentially including the customization of therapy by asthma phenotype, and thus several future unmet needs exist.

CHILDHOOD ASTHMA INCEPTION AND PROGRESSION

Asthma is clearly a disorder with both genetic and environmental determinants. Data from longitudinal birth cohorts suggest that infections with, and inappropriate responses to, respiratory viruses, particularly human rhinovirus (HRV) and respiratory syncytial virus,^{1–4} as well as the development of early allergic sensitization,^{5–7} are strongly associated with the inception and persistence of early onset asthma. The most highly replicated genetic region linked to asthma development is the *ORMDL3* locus on chromosome 17q,⁸ which seems to be associated with increased susceptibility to human rhinovirus-induced wheezing in early life.⁹ Several studies have confirmed that being raised in close proximity to animals in a farm setting is highly protective against the development of asthma,^{10,11} blocking the increased susceptibility to early onset asthma conferred by variants in the *ORMDL3* locus and reducing the incidence of both atopic and nonatopic wheezing in early life. Most evidence supports the protective effect of farm animals as being mediated by exposure to diverse environmental microbes.¹² Of greater importance was that the same 17q alleles that conferred asthma risk in children with wheezing illnesses in early life also conferred strong protection against early onset asthma in children raised on animal farms.¹³ Thus, pharmaceutical products containing protective bacteria, or their products, could prevent early onset asthma by simulating exposure to more diverse microbiota. Moreover, asthma biological therapy may have the potential prevent the development of asthma in susceptible children by reducing or blocking immunoglobulin E (IgE) or cytokine responses related to the allergic immune response and potentially the response to viral exposure. Understanding the effectiveness, safety, and underlying mechanisms of these interventions remains important.

PREVENTION OF PEDIATRIC ASTHMA

Identification of potentially modifiable environmental and host risk factors for asthma development has heralded a shift from disease treatment to primary asthma prevention through alteration of these factors. Recently, a systematic review revealed that smoke exposure at any age is associated with decreased lung function, persistent wheeze, and asthma.¹⁴ Thus, interventions to effectively and substantively reduce exposure to pre- and postnatal smoke may reduce asthma incidence and improve lung function in children. In the westernized lifestyle, increased consumption of a diet dominated by processed foods typically deficient in vitamins and minerals may make growing children more susceptible to atopic disease.¹⁵ This raises the possibility that improving the maternal diet is a low-cost and potentially effective intervention for primary prevention for numerous inflammatory diseases.¹⁶ Maternal prenatal dietary supplementation with vitamin D^{17–22} or fish oil^{23–25} supplementation have been studied and demonstrate their potential to prevent recurrent wheeze or asthma.

Influence of the gut microbiome on immune development and the manifestations of atopic disease is an ongoing area of study, with evidence that intestinal dysbiosis in early infancy may alter human immune development and that early exposure to a diverse microbial environment is likely protective.²⁶ These data suggest that modification of environmental bacterial exposures in early life may decrease a child's risk of asthma development through alteration of the child's gastrointestinal and airway microbiomes.

Viral respiratory tract infections are an established risk factor for asthma, suggesting that prevention and modification of these infections may protect children from developing recurrent wheezing and asthma. Prophylactic vaccination,^{27,28} antiinflammatory therapies,^{29–31} and immunostimulatory agents^{32–34} have been studied (with inconsistent results) to assess their effect on prevention or modulation of acute respiratory tract illnesses that may lead to long-term protection from recurrent wheezing and asthma. Further research into modification of the risk and severity of early life infections is essential if asthma prevention is to become a reality.

Immunostimulatory agents, such as bacterial extracts (Ref the RAZI paper), may also have a role in enhancing innate and adaptive immune response to infection by targeting the gut-lung immune axis. It is hoped that ongoing trials and longitudinal birth cohort studies will help identify additional protective strategies, because effective asthma prevention is most likely to require multifactorial approaches.

PRESCHOOL ASTHMA AND ASTHMALIKE SYMPTOMS

For preschool-aged children with a history of recurrent wheezing, but who do not yet meet the definition of persistent disease, and demonstrate increased risk to develop asthma (positive modified asthma predictive index), evidence favors the use of a daily inhaled corticosteroid (ICS)^{6,10–12} to reduce disease morbidity. A recent study comparing daily ICS, leukotriene receptor antagonists (LTRA), or intermittent use of ICS used with a short-acting beta-agonist as needed for symptoms in preschool-aged children with mild persistent asthma, daily ICS treatment was found to be the most likely effective therapy in controlling asthma control, particularly in children with aeroallergen sensitization or blood eosinophil counts of at least 300 cells/ μ L.¹⁴ Alternatively, preschool-aged children who were not sensitized to aeroallergens and had blood eosinophil levels less than 300 cells/ μ L demonstrated relatively low exacerbation rates with ICS, LTRA, or intermittent ICS treatment. Moreover, therapeutic options beyond Step 2 GINA recommendations in the preschool population have little supporting evidence to date. Treatment of preschool asthma would be advanced with better understanding of the mechanisms of asthmalike symptoms in these children and investigation of alternative therapies. Studies in this age group are needed to determine the efficacy of ICS in combination with other asthma medications (long-acting beta-agonists [LABA], LTRA, and/or long-acting antimuscarinic antagonists) and moderate- to high-dose ICS apart from budesonide. Two large clinical trials that studied the use of azithromycin early in a lower respiratory tract infection (LRTI) have shown efficacy in decreasing the severity or duration of the episode in preschool-aged children with history of recurrent severe LRTIs but not yet persistent disease or receiving controller therapy.^{28,29} Further research is needed to establish if children treated with repeated azithromycin treatment are at risk for the development of antibiotic-resistant organisms. Also, the effectiveness of biological therapy in preschool-aged children with significant atopic disease has not yet been studied and may represent an opportunity for early treatment and disease prevention or modification.

OBJECTIVE MEASURES OF LUNG FUNCTION IN PRESCHOOL-AGED CHILDREN

Objective measures of lung function are important in the diagnosis and management of asthma. Spirometry, the pulmonary function testing modality most widely used in asthma, may be difficult for some preschoolers. However, with appropriate coaching and technician training, substantial proportions of 3- and 4-year-old children can complete spirometry.³⁵ Impulse oscillometry (IOS) is a noninvasive method of measuring lung function during tidal breathing that many preschoolers can perform. Fractional exhaled nitric oxide (FeNO) levels correspond to eosinophilic inflammation and predict responsiveness to corticosteroids. In the future, the degree of bronchodilator response that corresponds to early life asthma should be determined, along with expanding the reference values for key parameters in IOS (eg, area of reactance). Further evidence is needed to understand how elevated FeNO levels distinguish among wheezing phenotypes in infancy and school-aged children and the best clinical use of FeNO.

SCHOOL-AGED CHILDREN WITH ASTHMA

Asthma management encompasses the day-to-day treatment of the disease itself, in addition to management of comorbidities and education of patient and family. The lack of effect of treatment of asymptomatic gastroesophageal reflux on asthma control in children with persistent asthma (REF: Teague WG JAMA) demonstrates the importance of robust clinical trials in examining the effects of treatment of comorbidities in achieving improved asthma outcomes. As mentioned earlier, a child's specific disease phenotype may affect the response to pharmacologic treatment.

Children with an allergic or T2-high phenotype (elevated FeNO, peripheral eosinophilia, elevated allergen-specific IgE or positive skin tests) are more likely to respond to daily ICS than LTRAs. For patients who do not achieve an adequate response to ICS or LTRA, particularly those with a neutrophilic or nonatopic phenotype, treatment with macrolide antibiotics (largely azithromycin) may be considered.³⁶ However, additional studies are needed to determine the efficacy of, and phenotype responsive to, macrolide treatment for asthma.³⁷

For children uncontrolled on low-dose ICSs, evidence supports increasing the ICS dose to the moderate range or adding a second controller medication and continuing low-dose ICS.^{38,39} In 161 children, a comparison of 3 step-up strategies (medium-dose ICS, low-dose ICS + LABA, low-dose ICS + LTRA) showed a greater likelihood of a better response to LABA step-up than to LTRA or medium-dose ICS dose.⁴⁰ Future topics of exploration should include further refinement of asthma phenotypic differences and underlying comorbid conditions, which may affect response to pharmacologic treatment and the underlying mechanisms that drive this response. This is particularly important for those who do not respond to ICS therapy or do not have underlying atopy.

CHILDREN WITH SEVERE ASTHMA

Severe asthma in childhood is a heterogeneous condition, typically defined as asthma that requires a high level of therapy to achieve control or that may remain uncontrolled despite this level of therapy. Factors that drive this need for increased therapy include poor access to care, underrecognition of symptoms, high exposures to irritants and/or allergens, suboptimal medication adherence, challenging environmental exposures, comorbid conditions, and treatment refractory severe asthma.^{8,41,42} Some of these children may have other conditions that mimic the symptoms of asthma. A thorough

evaluation and treatment of the most modifiable of these potential contributors is important. If symptoms continue to be uncontrolled despite addressing this assessment, treatment with high-dose ICS plus an LABA, leukotriene modifier, theophylline, biological therapies, and/or prolonged use of oral corticosteroids are used to achieve control.^{4,43,44} Anticholinergic and biological therapy could be used to help minimize the adverse effects from steroid use.^{4,41,45} Children with severe asthma often benefit from frequent disease monitoring and a multidisciplinary approach.

Further research should include validation of phenotype/endotype clusters in longitudinal studies with exploration of mechanisms that would allow personalization of therapy and development of new treatment strategies. Discovery of new phenotypic biomarkers will allow for improved asthma phenotype identification and improved management in the future.

PERSONALIZED MEDICINE AND PEDIATRIC ASTHMA

Environmental Exposures

Understanding key factors and relationships of biological, physical, and psychosocial environmental characteristics and the impact on asthma control is important. Multiple studies have shown that a child's home and school environments expose them to multiple indoor allergens (eg, mouse, cockroach, and pets), biological matter (eg, endotoxin), and pollutants (eg, nitrogen dioxide), and these exposures are associated with increased asthma morbidity.^{46–49} Furthermore, some environmental exposures can either be protective or be a risk factor for asthma depending on exposure timing. Currently, there is a lack of high-quality evidence demonstrating that single component interventions for indoor allergen exposure reduction can improve asthma outcomes.⁵⁰ Higher domestic endotoxin levels are also linked to increased asthma prevalence, severity, and exacerbations.^{51–55} In contrast, there are data supporting that early endotoxin exposure is associated with a decreased risk of childhood asthma.^{43,56,57}

As mentioned previously, the microbiome in early infancy can influence asthma risk and asthma.⁵⁸ Environmental microbiome diversity in the school is linked to increased asthma symptom days.⁵⁹ Exposure to high levels of pollutants such as ozone, SO₂, NO₂, PM_{2.5} (aerodynamic diameter of 2.5 microns or less), and CO is associated with asthma exacerbations, symptoms, and hospitalizations.^{41,60–63} The psychosocial environment, a child's neighborhood socioeconomic status, family relationships, housing quality, and social networks are also significant contributors to asthma morbidity.^{42,44,45,64–67}

Moving forward, investigation should focus on critical exposure windows in pregnancy and childhood through cohort studies and randomized trials. Additional evidence is needed to determine the efficacy of specific allergen and other exposure remediation interventions in order to design multifaceted interventions with the best synergistic effects. Law and policy reform are also needed to reduce environmental and social disparities that lead to poor asthma outcomes.

Addressing Poor Adherence to Treatment

Treatment adherence in young children involves several factors, including the child, family, community, and health care system. Although effective asthma control medications exist,^{68–71} patient adherence to these medications is low with adherence rates frequently less than 50%.^{71–73} Asthma management recommendations are complex, including difficulty following inhalation device instructions, need for daily medication use and monthly refills, identification and avoidance of triggers, recognition of increase

symptoms, and need for action.⁷⁴ As a result, many children experience uncontrolled symptoms and potentially preventable exacerbations with consequent decreases in their quality of life.⁷⁵⁻⁷⁷

Effective interventions to promote treatment adherence involve multiple components, including monitoring, feedback, education, and cognitive/behavioral interventions. Education content usually includes discussion of asthma, triggers, medications, peak flows, inhalation technique, and review of a written asthma action plan. Behavioral techniques include self-management strategies, feedback, and incentive plans.⁷⁸ Health care system navigators or community health care workers reinforce to families the importance of following their treatment plan resulting in improvements in adherence and asthma control.⁷⁹⁻⁸¹ Treatment adherence monitoring and providing feedback to the child and family may lead to improvement in treatment adherence in children,⁸²⁻⁸⁷ ideally leading to improved asthma outcomes.

Additional research is needed to determine the key intervention components and to establish how to implement and sustain these interventions in at-risk communities and families, particularly young children. More investigation is essential to elucidate the impact of child development on treatment effectiveness and treatment adherence.

Inner-City Asthma

The inner city is a well-established and well-studied location that includes children at high risk for high asthma prevalence, severity, and morbidity. Several risk factors contribute to asthma in inner-city populations including black race and Puerto Rican Hispanic ethnicity,^{87,88} prematurity,⁸⁹⁻⁹¹ obesity,⁹²⁻⁹⁴ specific aeroallergen⁹⁵⁻⁹⁹ and pollutant exposure,^{57,100-103} socioeconomic status,^{87,104,105} and psychosocial factors.¹⁰⁶⁻¹⁰⁸ Environmental¹⁰⁹⁻¹¹² trigger remediation of dust mite, cockroach, and mouse allergens and medical interventions such as guideline-based asthma care and biological therapy have improved outcomes in the inner-city children with asthma.^{113,114} Future work targeting the identification and modification of risk factors and the use of novel interventions will be essential to reduce disparities in this high-risk group of children with asthma.

Community-Based and School Partnerships

Reducing the disparity of health outcomes between children with asthma and healthy children will require extending pediatric asthma care beyond traditional medical settings and engaging in successful health partnerships with the community and schools. School-based asthma programs such as SAMPRO have been demonstrated to improve communication and the dissemination of asthma action plans and medications to schools and the children that attend them.¹¹⁵⁻¹²⁰

Future directions include determining which intervention components are the most effective in improving asthma outcomes and establishment of a system of standardized data collection to assess health and educational for children with asthma. In order to be sustainable, legislation is needed to support government funding and financial incentives to disseminate and maintain school-based asthma care.

SUMMARY

Several new developments have occurred over the last 5 years relevant to the field of pediatric asthma. Despite these substantial advances, there is much more to learn. Multiple essential areas for further exploration and research have been identified in order to continue the quest to improve pediatric asthma outcomes, particularly in vulnerable, high-risk populations.

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