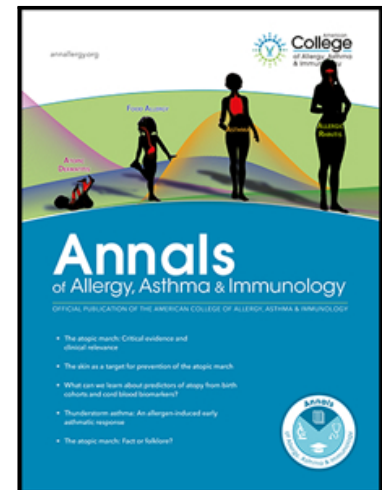


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Mfonobong Udoko MD , Heather De Keyser MD, MS ,
Stanley J. Szeffler MD , For Annals of Allergy, Asthma and
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Should Asthmatic Children Simply be Treated as Little Adults?

Mfonobong Udoko, MD, Heather De Keyser, MD, MS, Stanley J. Szeffler, MD, For Annals of Allergy, Asthma and Immunology

The Breathing Institute, Children's Hospital Colorado and Department of Pediatrics, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO

*Corresponding author at: 13123 East 16th Avenue, Box 395, Aurora, CO 80045

Stanley.Szeffler@childrenscolorado.org

Mfonobong.Udoko@childrenscolorado.org

Heather.DeKeyser@childrenscolorado.org

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Introduction

Asthma is the most common chronic disease in children, affecting approximately 8.3% of children in the United States with significant impact including school absenteeism, loss of parental workdays, and high health care utilization. Asthma remains common in adulthood, affecting approximately 7.7% of adults in the United States with continued mortality, morbidity and financial implications. Asthma is a heterogenous disease that warrants distinct approaches between children and adults. First, we will discuss age-variant asthma phenotypes which drive the varying clinical presentations of asthma. Next, we will discuss the importance of parental and community engagement to overcome the unique challenges in managing children with asthma. Finally, we will discuss considerations for future asthma care for children, which is now directed toward early intervention and primary prevention of asthma, and ideally for disease remission to prevent adverse respiratory outcomes in adults.

Age-variant Asthma Phenotypes

Clustering studies of adult asthma have identified early vs late onset asthma clusters with unique clinical characteristics attributed to distinct underlying biological mechanisms. With this degree of variation, it is clear that children with asthma should not simply be treated as little adults. Several large clustering studies, including subjects >age 6 years, have identified the following primary asthma phenotypes: (1) early onset mild allergic asthma, (2) early onset moderate-severe allergic asthma, (3) late onset non-allergic eosinophilic asthma, and (4) late onset non-allergic, non-eosinophilic asthma [1]. In early childhood, wheezing phenotypes (atopic vs non-atopic wheeze), better characterize the heterogeneity of symptoms with atopic wheezing, being more likely to have persistent symptoms into late childhood with impairment in lung function [2].

Overall, the classic pediatric phenotypes (typically clusters 1 and 2) are driven by aeroallergen sensitization with IgE antibody production and type 2 inflammation (T2), in contrast to adult-onset asthma phenotypes which are driven by non-allergic T2-low or non-T2 inflammation. In children, aeroallergen sensitization is an established risk factor for viral wheezing and may predict persistence of wheezing and asthma risk [3]. IgE pathways may impair innate viral immune responses which likely contributes to increased viral infections in early childhood and contribute to the wheezing phenotypes in this age group [3]. Additionally, the diagnosis of asthma in young children can be challenging with non-specific symptoms, such as cough and wheezing, which overlap with frequent viral respiratory tract infections (Table 1).

Parental education and engagement are vital, particularly in early and late childhood, to identify symptom patterns and clinical history consistent with the diagnosis of asthma since young children are unable to reliably perform spirometry to confirm airflow limitation and/or bronchodilator response.

Asthma triggers shift with age, from viral triggered to allergen triggered, with the emergence of respiratory symptoms such as exercise induced symptoms, chest tightness and dyspnea, becoming more prevalent in late childhood and adolescence, supporting the diagnosis of asthma [4]. Also, with increasing age, the diagnosis of asthma becomes more easily supported with objective testing, including pulmonary function and other markers of T2 inflammation, such as exhaled nitric oxide, IgE and blood eosinophils, along with aeroallergen testing, confirming the diagnosis of allergic asthma. Thus, asthma has a developmental pattern in children that, unlike adult asthma, can be left undiagnosed for a period of time due to the lack of objective testing and a slowly emerging pattern of the disease.

For pharmacologic treatment in children, there is a greater prevalence of T2-high disease which is more responsive to steroid therapy compared to T2-low or non-T2 disease, which is prevalent in adults who are less responsive to steroid therapy (Table 1). Once non-biologic therapies are optimized for patients with difficult to control severe asthma, it is important to identify an asthma phenotype associated with targeted T2 therapy response. Severe asthma includes both allergic and non-allergic phenotypes as candidates for biologic therapy with T2 targets including IgE, interleukin (IL)-5, IL4R and thymic stromal lymphopoietin (TSLP). There are no current biologic therapies targeted towards non-T2 disease. The 2021 Global Initiative for Asthma report (<https://ginasthma.org/gina-reports/>) provides recommendations for targeted T2 therapies, stratified by pediatric age including: (1) ≥ 6 years: omalizumab (anti-IgE) for severe allergic asthma and mepolizumab (anti-IL5) for severe eosinophilic asthma; (2) ≥ 12 years: benralizumab (anti-IL5) for severe eosinophilic asthma and duplimumab (anti-IL4/anti-IL13) for severe eosinophilic asthma/oral corticosteroid dependent asthma.

Adults with asthma have additional options for biologic therapies with much of the evidence for therapeutic effect and safety for biologics remains in the adult population with limited evidence in the pediatric population. Omalizumab is the most studied biologic for severe childhood asthma and a

significant gap remains in studying the efficacy and safety of the newer biologics in children. Therefore, in children with asthma, treatment is individualized and altered with increasing age based on symptom presentation, ability to monitor pulmonary function and administer medications. There are age-specific approvals for certain asthma medications, especially for asthma biologics, as compared to more extensive approvals for adults with asthma.

Parental and Community Engagement

Beyond diagnosis, non-pharmacologic asthma management in childhood presents unique challenges that are not present in adulthood. In children, parental support for the treatment plan and willingness to reduce allergen exposure and follow age-appropriate management plans including medication administration is essential. Education for patients and parents must remain a priority for medication adherence, correct administration technique and overall care. School based asthma programs and/or home visit programs provide an opportunity for continued education, supervised asthma care and establishing age-appropriate expectations for self-monitoring [4].

Looking to the Future

Future studies should be directed at identifying biomarkers for early diagnosis, identification of phenotype (clusters based on clinical characteristics and lung function) and endotype (clusters based on underlying pathophysiology), and for predicting and monitoring treatment response [1]. This signals a gradual change in treatment goals from symptom control and risk reduction to the goal of altering the natural history of asthma, including prevention and remission. Proposed frameworks for remission

include clinical remission (based on symptom control and medication reduction) and complete remission (based on clinical remission + objective reduction in asthma-related inflammation) [5]. We now have an opportunity to examine the effects of asthma biologic therapy on preventing the progression of asthma in children as well as inducing remission. Therefore, attention must now be directed to the early diagnosis of asthma even before symptoms emerge. Once that is possible, we could develop management strategies for primary prevention. Of great interest, The Preventing Asthma in High Risk Kids (PARK) study is in progress and that will shed light on whether omalizumab can prevent or reduce asthma severity in atopic children ages 2 to 4 years with recurrent wheezing and selected risk factors for asthma [3]. If successful, omalizumab and perhaps other biologics could be considered for earlier application with the goal of altering the natural history of asthma.

Conclusions

In summary, given the heterogenous nature of asthma, we must identify emerging phenotypes associated with defined endotypes and design individualized approaches based on endotypes for managing children with asthma. Perhaps with increasing knowledge, it may be possible to apply treatment strategies often withheld until asthma is at a moderate or severe level in adolescents and adults, to an application in early childhood to more effectively prevent the progression of asthma in children. This strategy would play an important role in preventing adverse respiratory outcomes in adults.

Disclosure statement:

MU has no conflicts to declare.

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Table 1: Key Differences Between Asthma in Pediatric and Adult Populations

Diagnosis of Asthma	- Diagnosis can be more challenging in children due to non-specific symptoms and inability to obtain objective testing - <i>Allergic, T2-high inflammation</i> is predominant in pediatrics compared to <i>non-allergy, T2-low or non-T2 inflammation</i> in adults. Asthma phenotypes can be utilized to identify disease markers to aid in diagnosis
Asthma Management	- Children are more steroid-responsive compared due to more T2 high disease compared to adults with more T2-low or non-T2 disease - Biologics are studied initially and more extensively in adults, offering increased therapeutic options in adults with moderate to severe asthma compared to children with moderate to severe asthma - Parents and caregivers must be involved in treatment plans, which introduces challenges related to recognizing symptoms and education in children, as compared to adults where optimal self-care is essential for management. - Effective intervention strategies targeted to early childhood provides an opportunity to prevent the progression of asthma and induce remission, as compared to adults where established disease components are irreversible.