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REVIEW

Preschool children with persistent asthmatic symptoms

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Abstract: Asthma is the most common chronic airway disease in children, with more than half the reported cases of persistent asthma starting in children below the age of 3 years. Asthma diagnosis in preschool children has proven to be challenging due to the heterogeneity of the disease, the continuing development of the immune system in such a young population, and lack of diagnostic options such as lung function measurement. Early diagnosis and treatment of asthmatic symptoms will improve patients' quality of life and help reduce disease morbidity. However, validated treatment options are scarce due to paucity of data and lack of conclusive studies in such a young patient population. Adjusting study design and endpoints to capture more reliable data with minimal risk of harm to patients is necessary. This thematic series review outlines the current position on preschool asthma, consolidates the current understanding of risk factors and diagnostic hurdles, and emphasizes the importance of early detection and management to help improve patients' quality of life, both present and future. Particular focus was given to anticholinergics and their emerging role in the treatment and control of asthma in pediatric patients.

Keywords: preschool children, asthmatic symptoms, tiotropium, anticholinergic

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Introduction

Asthma burden of disease

More than 300 million people worldwide are estimated to be affected by asthma.[1–3] The World Health Organization predicts that this number will increase by more than 100 million by 2025.[2] Asthma is one of the most frequent chronic diseases observed in children and adolescents, and the most prevalent airway disease in this age group.[4] Globally, approximately 14% of children experience asthma symptoms such as wheezing, shortness of breath and chest tightness.[4,5] In the USA, an estimated 7 million children and adolescents suffer from asthma,[6] and in the UK, approximately 10% of children receive treatment for asthma symptoms.[7] The majority of recorded persistent asthma cases begin before the age of 3 years, and up to 80% before the age of 6 years. Early symptoms are associated with increased disease severity and bronchial hyperresponsiveness.[8] Although most patients begin to display symptoms before the age of 5 or 6, the diagnosis of asthma in infants and preschoolers is more challenging than in older children and adults.[9]

Defining asthma

The International Consensus Report on the Diagnosis and Treatment of Asthma defines asthma as a chronic inflammatory disease displaying symptoms associated with variable airflow obstruction that is often reversible, either spontaneously or with

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treatment.[10] Wheezing has emerged as the most important symptom for the identification of asthma.[11] The Global Initiative for Asthma (GINA) report defines asthma as having a variable clinical spectrum, with wheezing, shortness of breath, chest tightness and cough.[4] The definitions of asthma in children <6 years are often poorly described and confusing, making the diagnosis of the disease in preschool children difficult. The European Respiratory Society task force proposed the use of terms "episodic (viral) wheeze" (for children with intermittent wheeze and who are fine between episodes) and "multiple-trigger wheeze" (for children who wheeze both during and after discrete episodes).[9] Other definitions have also been used to clarify the different phenotypes of preschool wheezing disorders; for example, the presence of transient early wheezing in children <3 years, non-atopic wheezing in children aged 3–6 years, and IgE-mediated wheeze in older children (Figure 1).[8] However, these definitions of preschool asthma-like symptoms may be considered too simplistic. More recent studies suggest these definitions reflect disease severity and that they are likely to vary with time.[12] A specific cause for the development of asthma has not been identified; however, interactions between the environment and genetic factors of each individual play a role.[13] These factors include viral infections, atopy, prematurity, exposure to tobacco smoke, exposure to elevated levels of air pollution, eczema or family history of asthma, or blood eosinophilia (Figure 2).[8,14,15]

By the time they reach school age, approximately half of preschool children diagnosed with wheeze become asymptomatic irrespective of treatment. However, in atopic and more severe cases, asthma symptoms have a higher probability of persisting for life.[16] While remission from

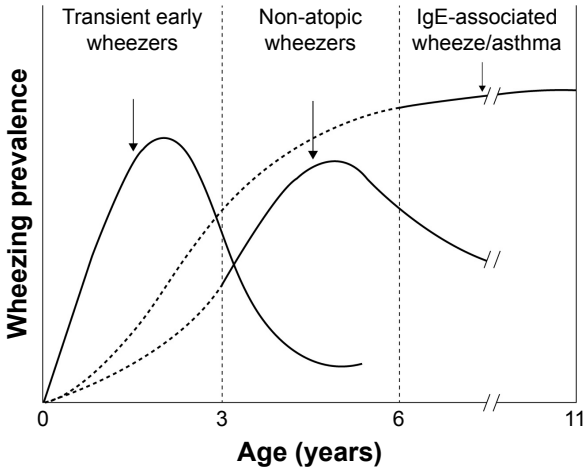

Figure 1 Proposed yearly peak prevalence of wheezing phenotypes in children.
Notes: Reproduced with permission from Martinez FD, Development of wheezing disorders and asthma in preschool children. *Pediatrics*, 109(2 Suppl): 362–367, Copyright © 2002 by the AAP.[8]

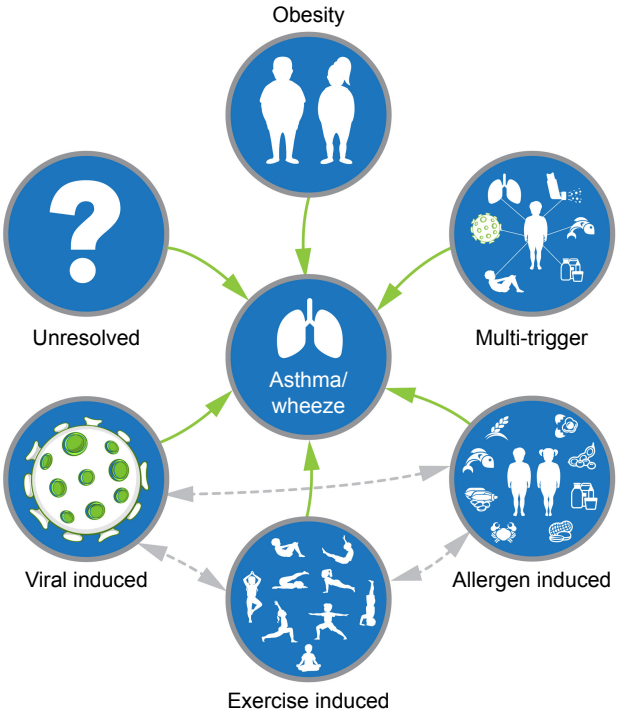

Figure 2 Pediatric asthma is a heterogeneous condition with multiple phenotypes arising from different underlying pathophysiologies.

childhood asthma is not uncommon, it becomes less likely with increasing severity of early symptoms. Currently, there is no primary prevention tactic; nevertheless, suggestions include avoiding exposure to tobacco smoke,[17] avoiding cesarean sections[18] and encouraging breastfeeding[18,19] to decrease the risk of future development of asthma. There is evidence indicating breastfeeding is protective against childhood asthma and wheezing disorders.[19] The impact of breastfeeding on respiratory health may vary across countries as culture and socioeconomic changes occur.[18,19]

This thematic series review discusses the challenges associated with diagnosing asthma in preschool children and identifies areas of research that are intended to improve the diagnostic process. We also make suggestions for timely and appropriate management of preschool asthma to improve the patient's quality of life, focusing on anticholinergics and their role in controlling the disease.

Challenges in diagnosis

The development of asthma-like symptoms and wheezing in preschool children can have a major impact on the quality of life of patients and their families, as well as public health if not correctly managed.[16] The first, and most important, step is to clearly identify which children are at risk of persistent asthma to allow the implementation of early management

strategies, resulting in reduced morbidity and mortality. Guidelines to date still do not clearly differentiate between the definition of asthma in adult and pediatric patients due to the complexity and diversity of the disease. Only after the 2014 revision of the GINA report was the concept that asthma manifests in children under 5 years of age acknowledged.[4]

The maturing of the respiratory and immune systems, the natural history of the disease, difficulty in diagnosis due to lack of reliable and reproducible tests, difficulty in delivering treatment and the unpredictable response to treatment are the most frequently cited causes of difficulties faced when diagnosing children.[16]

Asthma is the primary diagnosis for one-third of pediatric emergency department (ED) visits,[20] and is a frequent reason for preventable hospitalization[21,22] and absenteeism from school.[23,24] Nevertheless, it is estimated that asthma is still under-diagnosed in up to 75% of patients who present asthma-like symptoms, and approximately 11% of patients in primary care are erroneously prescribed inhaled corticosteroids (ICS).[20] This emphasizes the need for a standardized definition for the diagnosis of asthma in pediatric patients. Using a common systematic approach for asthma management can significantly improve outcomes. However, the dissemination and implementation of these recommendations are still a major challenge.[25]

Making a definite asthma diagnosis in children <5 years is difficult and can have important clinical consequences. Although FEV_1 is the preferred outcome variable of the U.S. Food and Drugs Administration (FDA) for asthma control in adults,[26] it is not the best measure for children with asthma. These patients often present normal lung function, and therefore normal FEV_1 values in the absence of symptoms; however, during acute exacerbations they develop severe airflow obstruction.[27] A study examining the relationship between FEV_1 and other clinical parameters used to diagnose asthma found that parent-reported symptoms, health care utilization, and functional health status measures are more helpful in characterizing asthma status than FEV_1.[27,28]

Treatment recommendations

The GINA report recommends a probability-based approach, using frequency and severity of symptoms to guide treatment decisions, with a therapeutic trial of a controller medication.[4,29] A large percentage of preschool children who present asthma-like symptoms are often treated with ICS to control inflammation. It was also suggested that early treatment with ICS could reduce the risk of developing irreversible airway obstruction. However, there are multiple studies emerging, with contradictory results as to the effect of ICS in such young patients. Two studies with ICS in wheezy infants and preschool children did not see any improvement.[30,31] This suboptimal response to medication is most likely due, in part, to variability of the natural history of the disease.

A serious challenge for the diagnosis of asthma is the underestimation of the severity of the disease by parents, guardians and patients.[32] It can be difficult to assess symptoms and the extent to which a child has adapted its lifestyle to avoid symptoms. This adaptation could mask distress or discomfort from parents/guardians, as many parents believe that if the child is not suffering from obvious symptoms, such as audible wheeze, there is no real problem.[33] Clear and open patient–physician communication to address patient-specific concerns can help the treating physician identify symptoms and make a more informed diagnosis, allowing the correct and appropriate treatment prescriptions and adaptations to be made.[34]

Sensitization and allergen-induced asthma

Sensitization to common atopic aeroallergens has been found to play a significant role in the development of asthma and should be assessed during diagnosis. An Australian study found a correlation between early allergic sensitization and the development of persistent asthma.[35] Other data suggest that approximately two-thirds of the German asthma patient population is sensitized to at least one allergen.[36] Among children, approximately 40% have been found to be sensitized to inhalant allergens by early school age, and more than a quarter of these will eventually develop asthma.[36] It is believed that increased exposure to other children, pets or farm animals in early life may protect children from future development of asthma. Other studies have demonstrated that children with older siblings, or those who attended day care within the first 6 months of life, were less likely to develop asthma.[8] However, sensitization to certain allergens, such as fungi or cockroaches, can increase the risk of development of asthma in children.[37]

Prediction models for the development of asthma in children may be used as tools to prevent delays in asthma diagnosis. Information provided by a predictive model can have a significant impact on the patient's present and future quality of life. To date, approximately 23 predictive models of asthma have been developed for children. However, none of the models developed for preschool children have high positive predictive value or high sensitivity. This lack of accuracy makes them unsuitable for routine clinical use.[20]

The accurate diagnosis of asthma in preschool children is a crucial step toward achieving control of the disease and optimizing the patient's quality of life.

Impact of early symptoms on future health

Asthma is a chronic inflammatory disease of the airways characterized by complete or partial airway obstruction reversibility.[4] This chronic inflammation can result in airway remodeling that can have a negative effect on exacerbations, lung function and response to treatment.[38] Childhood-onset asthma has been associated with reduced lung function and narrower airways later in life, increasing the severity of symptoms and the risk of exacerbations at later ages.[39] In adults, ED visits and hospitalizations caused by exacerbations have also been associated with an increased risk of repeated exacerbations, asthma severity and asthma control, which is also applicable to children.[38]

Asthma not only affects patients physically, but can have serious psychological repercussions if left uncontrolled or unrecognized. Data for mental health issues in children and adolescents with asthmatic symptoms are controversial. However, there are studies that suggest patients with asthma are more likely to suffer from a wide range of mental health problems compared with healthy counterparts, such as increased symptoms of mood and anxiety disorders. Negative situations and emotional distress can be associated with difficulty in breathing in many patients.[40] If young children are exposed to chronic levels of stress, they may develop coping mechanisms, such as behavioral and social adaptation. Patients who are able to adapt to the disease at an early age have been shown to experience less psychological morbidity and achieve better long-term management of the disease.[33]

Identifiable risk factors to aid early detection

The importance of identifying asthma and wheezing, and employing management strategies in preschool children start to become evident when children reach school age. Identifying risk factors for asthma could be a key factor in disease management. For example, rapid early weight gain in young children has been associated with symptomatic growth dysregulation, which precedes impaired airway development and clinical wheezing.[41] An association between high body mass index (BMI) and wheezing and asthma in children has been observed. Studies have shown that children with higher BMI are more likely to suffer from a more severe form of the disease compared with children with lower BMI values.[42] If the disease is not controlled early on, this can negatively affect many aspects of a child's development, including the learning process. Children with asthma have been found to have a higher school absence rate than their healthy peers.[43,44] This can have a significant impact on their future education and has been suggested to be a predictor of school dropout.[44,45]

What are the available reliable treatment options for preschool children?

Treatment of preschool children with cough and wheeze depends on the severity of the symptoms. For children with infrequent wheezing, guidelines recommend the use of short-acting beta$_2$-agonists as needed (Figure 3).[4] For children with more persistent symptoms, ICS are the mainstay prescribed therapy.[4] ICS are the most effective anti-inflammatory therapy available for patients with asthma and their regular use has been found to improve asthma control and quality of life, and decrease risk of exacerbations.[46,47] There is evidence to support the use of ICS in preschool children with asthma,[48,49] and GINA recommends a daily low dose of ICS for preschool children if the symptom pattern becomes consistent with that of asthma (Figure 3).[4] If symptoms worsen and are not well controlled, leukotriene receptor antagonists are suggested to be prescribed in conjunction with ICS, or the dose and frequency of ICS are to be increased (Figure 3). It is important to be aware that the continuous use of ICS has been linked to growth retardation and may not have an effect in all children whose symptoms are not well controlled.[50] More recent studies have highlighted that individual ICS therapies have differing safety profiles that are noticeably better than those of oral steroids. The risk of side effects is considerably reduced when the lowest effective dose is prescribed. Furthermore, systemic availability is reduced through appropriate inhaler device selection and monitoring concomitant medication use.[51]

These contraindications may deter patients/parents from the correct use of medication.

Available treatment options for preschool children with asthma are limited, with more options available for children over the age of 6 years.

There is evidence to support the use of long-acting muscarinic antagonists in older children, and tiotropium Respimat® has been approved as an add-on to ICS/long-acting β_2-agonists in patients with asthma in several countries. In the USA, it is approved for long-term, once-daily maintenance treatment of asthma in patients aged 6 years and older.[52] In the European Union, the indication for tiotropium Respimat has recently been updated for use as an add-on maintenance bronchodilator in patients aged 6 years and older with severe asthma who experienced one or more severe asthma exacerbation in the past year.[53] Recent clinical trials, spanning different age groups (6–11 years and 12–17 years), found improvements in lung function with tiotropium, and a safety and tolerability profile

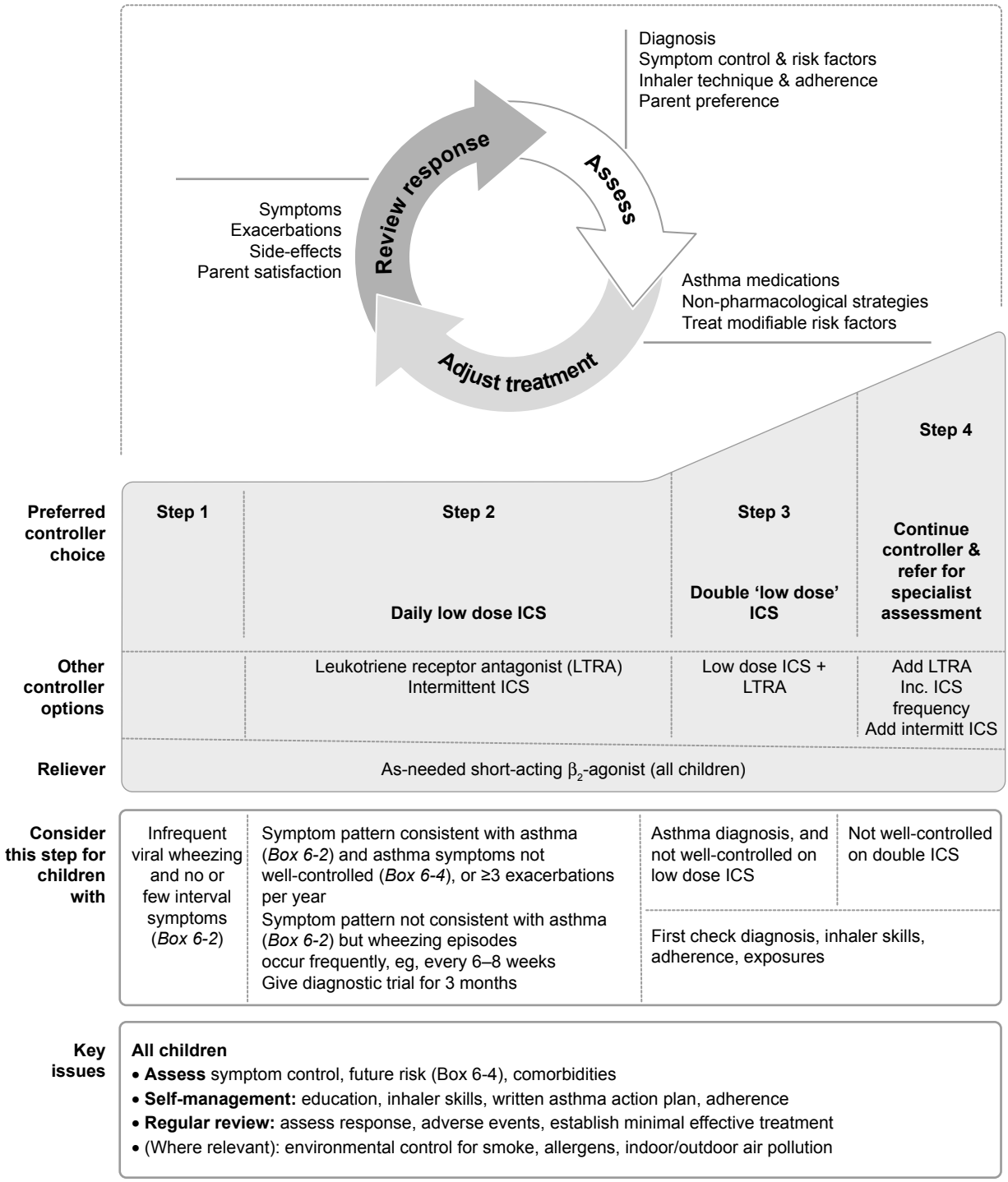

Figure 3 GINA-recommended treatment steps for preschool children with asthma.
Notes: Adapted with permission from the GINA 2018 Report.[4]
Abbreviations: GINA, The Global Initiative for Asthma; ICS, inhaled corticosteroid.

comparable with placebo.[54–61] There are very few trials investigating the efficacy of potential treatments in children under 6 years of age due to the previously discussed discrepancies in diagnosis criteria. However, a recent small study in preschool children with persistent asthmatic symptoms was the first to assess the safety and efficacy of tiotropium in children aged 1–5 years.[62] Tiotropium demonstrated a comparable safety and tolerability profile with placebo, in line with safety outcomes previously reported in patients over 6 years old.[54–61] However, the efficacy endpoints for this study were exploratory, even

though the endpoints were defined and were used for descriptive analyses only. While changes in daytime asthma symptom scores were not significant, the exploratory analysis recorded a smaller number of children reporting adverse events (AEs) related to asthma exacerbations and symptoms in children taking tiotropium compared with those taking placebo.[62] Further studies are needed to establish the efficacy of tiotropium in this very young patient population.

The importance of the correct device for therapy delivery

Ensuring that the patient is receiving the correct therapy is an important step in disease management. The selection of an appropriate device should be considered just as important as the therapy choice, as the correct handling of inhalers is essential to ensure patients receive the prescribed dose. Each device used for administration of aerosol therapy has different mechanisms of operation, performance characteristics and requirements for correct use. This means that patients and caregivers must be correctly instructed on the use of each different inhaler device they are prescribed; otherwise it will result in the incorrect use of the device and improper delivery of therapy to the lungs. Aerosol devices that are used by adults may not be appropriate for children because of the complex steps necessary for their correct use. Young children may also lack sufficient inspiratory strength to use a dry powder inhaler.[63] Breath-actuated inhalers are impractical for use in children as their erratic breathing patterns will make their use difficult for children under the age of 5 years. Inspiratory flows and lung volumes are largely size-dependent and increase with age and body mass; therefore, many children will not be capable of generating sufficient flow for correct inhaler device use until the ages of 5 or 6 years. Preschool children also lack the coordination between actuation and inhalation for the use of a metered-dose inhaler (MDI), whereas school-age children may have the hand-breath coordination but may lack the ability to determine when to use the device.[63] Other difficulties encountered with the use of inhalers in infants are that they breathe predominantly through their noses up to the age of 6 months, and toddlers are generally not able to use a mouth piece.[63] Consequently, aerosol administration in this very young patient population requires different mouth pieces such as an aerosol mask for patients up to the age of 3 or 4 years, or valved holding chambers and spacers for slightly older patients able to use a mouth piece (Table 1).[63] A commonly used delivery system in children under the age of 5 years is nebulizers. The advantage of nebulizers is that they do not require patient cooperation. Nevertheless, less than 10% of aerosolized therapy reaches the lungs when using nebulizers, and a large proportion of the treatment is deposited on the face, a large proportion on the apparatus and the remainder lost to the surroundings.[64] Pressurized MDIs (pMDIs) allow a higher proportion of the therapy to reach the lung, but require coordination between inhaling and activating the inhaler. The use of a spacer eliminates the need for coordination between actuation and inhalation of a pMDI. The valved holding chamber/spacer has a one-way valve that allows aerosol to move out of the chamber at inhalation and keeps particles in the chamber upon exhalation. Neonates and infants should not use these spacers without a face mask to aid therapy delivery[65] as they are unable to generate the inspiratory force required to open the one-way valve. The limitation encountered with face masks is that the delivery of therapy to the lungs is noticeably decreased.[64,66] Recently, a study used the Respimat and the AeroChamber Plus® Flow-Vu® anti-static valved holding chamber for the delivery of aerosol to preschool patients.[62]

Table 1 Choosing an aerosol device and interface for patients of different ages

	Device	Age	
		0–4 years	4–5 years
Aerosol device	Nebulizer	✓	✓
	pMDI with VHC	×	✓
	pMDI with VHC and face mask	✓	×
	DPI/breath-actuated pMDI	×	✓*
Interface	Mask	✓	✓
	Hood or high-flow nasal cannula	✓	×
	Mouth piece	×	✓

Notes: Adapted with permission from Ari A, Fink JB. Guidelines for aerosol devices in infants, children and adults: which to choose, why and how to achieve effective aerosol therapy. *Expert Rev Respir Med*. 2011;5(4):561–572, by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com).[63] *pMDI only at 5 years of age.

Abbreviations: DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler; VHC, valved holding chamber.

The challenges faced in the development and testing of new treatment options for this patient population

Most treatment options for asthma and respiratory diseases are not designed for use in preschool children. There is an unmet need for therapy options in this patient demography. A reason for this shortfall is that determining the effect of child growth and development on therapies, and vice versa, is a challenge in pediatric research.[67] It has long been recognized that different asthma symptom patterns in childhood may be associated with variations in the natural history of the disease. The changeability in disease phenotype and improbability of a homogeneous patient population make it problematic to

classify young patients or recruit them for trials. The various developmental stages of children at different ages will often require separate sub-analyses for infants, school-age children and adolescents to assess safety and efficacy of a treatment. This subdivision will inevitably increase the number of participants required per study.[67] As there is a scarcity of study participants, it will therefore increase the time needed to recruit enough participants for a study and require more effort to retain them. Once identified, it is likely that not all children with a disorder or condition will meet the eligibility criteria for a study.[67]

There are strict regulations that restrict the range of research that can be undertaken with children. Placebo-controlled trials for efficacy are more regulated when children participate, especially if the children receiving the placebo are exposed to more than the minimal amount of risk. Other ethical considerations include parents' reluctance to enroll their children in clinical trials due to concerns of safety and well-being for their child.[67]

Challenges faced with clinical outcome measures

Defining and measuring appropriate outcome variables for preschool populations is problematic as they are less able to perform lung function analyses.[68] Pediatric investigators and agencies, such as the FDA, often do not agree on what is considered an acceptable measure. Clinical endpoints must be appropriate for the target population. FEV_1 results are valuable for the diagnosis of asthma in adults; however, it is not always possible to ensure a preschool-age patient's cooperation, and therefore, reliable and reproducible results.[69] Young children are often not able to perform specific ventilation, reducing the role of lung function testing and other physiologic tests in the diagnosis of children under the age of 5 years.[37] The American Thoracic Society/ERS joint expert panel has acknowledged that the current repeatability criteria for adult spirometry are not appropriate for preschool children and there is a severe lack of objective measures for children.[70] With preschool children still developing, most will not have the chest wall strength to carry out spirometry at the required intensity to produce FEV_1 results. Forced expiratory volume in 0.5 seconds would be more physiologically appropriate for young children (<6 years) as their forced expiration is shorter than that of adults.[70] Changes in chest and lung anatomy, as well as the physiologic changes that occur during growth and development, affect lung function test results in very young patients.[71] Cooperation-free tests are the preferred method for screening of pediatric patients; however, these are generally available only in specialized centers due to the use of complex equipment.[69] Impulse oscillometry is a method that requires less patient cooperation compared with spirometry and may be useful in identifying children with lower airway obstruction in patients without obvious wheeze.[72]

Using questionnaires, such as the Childhood Asthma Control Test, which allows scoring by both children and parents, has shown that children tend to assess their asthma control significantly lower than parents do.[73] This can be because children are not able to fully complete questionnaires on their own, or often parents or guardians rely on observation, which can result in incomplete reporting. An alternative endpoint to use would be symptom-free days. This is a useful endpoint for pediatric asthma studies and easier to record than symptom scores.[74]

Identifying surrogate endpoints

With no tested reliable method for early detection of asthma currently available in the preschool-age demography, there is an urgent need to investigate this further. However, long placebo-controlled trials are considered unethical in such a young population and alternative endpoints need to be identified. Pharmacologic markers such as biomarkers, including measurement of fractional exhaled nitric oxide,[75] may serve as a surrogate endpoint.[76] The occurrence of AEs related to exacerbations and symptoms has, more recently, been proposed as a useful alternative endpoint in pediatric trials.[74] The FDA recognizes the use of surrogate endpoints as extremely promising for improving the efficiency in clinical research.[77] Incorporating surrogate endpoints could significantly accelerate the development of new therapies for infants, children and adolescents.[77] Surrogate endpoints may be used for early detection of safety issues that could point to toxicity problems of a new therapy.[77] Clinical trials designed to evaluate efficacy of a new drug are often too short and too small to detect rare AEs or events that occur after prolonged therapy.[78] Surrogate endpoints also do not directly measure clinical impact, but reflect therapeutic treatment effect, therefore their use can be controversial.[74,77] However, due to the unique requirements of pediatric research, careful and appropriate use of surrogate endpoints could allow more information to be gathered about therapeutic interventions during short clinical testing phases.[74]

Conclusion

With asthmatic symptoms present in young patients, and approximately 50% of patients with symptoms at 3 years of age likely to be later diagnosed with asthma, early detection and management of this chronic disease are essential to improve the patients' quality of life, not only in the present, but also in the future. There is a significant deficit in reliable

asthma identification measures and effective treatment strategies in preschool children. Further studies are needed to define pathogenesis, progression and outcomes of asthma in preschool children, as well as to identify efficacious interventions in this population.

Data sources and selection criteria

We based this review on the Global Initiative for Asthma guidelines published in 2018. We also included key publications by the World Health Organization. We searched for cited references in PubMed using the search terms "asthma," "cough," "wheezing," "breathlessness," "diagnosis," "management," "barriers," "primary care," "preschool" and "childhood." Our personal research article library was used to investigate and review relevant publications.

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