

Special considerations—asthma in children

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Background: Asthma is among the most common chronic diseases of childhood. Management of pediatric asthma requires an understanding of the issues that uniquely effect children. This review provides the reader with the current state and future directions of pediatric asthma.

Methods: Review of the pediatric asthma literature was undertaken with emphasis on randomized controlled trials and systematic reviews.

Results: The prevalence of pediatric asthma remains elevated and is increasingly being appreciated in select global regions. Effective treatment in any setting begins with a focused medical history that queries key asthma features that inform both diagnostic and monitoring strategies. A thorough medical history may yield comorbid upper airway disorders and allergic triggers that could potentially exacerbate airway inflammation. Pre-bronchodilator and post-bronchodilator lung function testing is a preferable diagnostic strategy to quantitatively assess obstructive pulmonary disease among children capable of performing the testing maneuvers. Pediatric asthmatics who continue to have poor disease control require monitoring of medica-

tion adherence and drug delivery techniques, because both are often linked with disease outcomes. Therapeutic strategies in children are notably distinct from adults due to the possible effects of inhaled corticosteroids on reduced bone mineral density and growth. Adolescents may also require more time to address the psychosocial complexities that may complicate the required daily usage of asthma medicines.

Conclusion: Asthmatic children are distinct from their adult counterparts due to limitations inherent in the pediatric age group. A unified and evidence-based approach to pediatric asthma may improve clinical outcomes. © 2015 ARS-AAOA, LLC.

Key Words:

child; pulmonary medicine; lung diseases; obstructive; review; wheezing; cough

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Despite the advancements of pediatric asthma care in the past 20 years, disease symptoms appear to be persistent and impactful on multiple societal outcomes globally.^{1,2} Complex healthcare systems, as seen in the United States, attribute a large percentage of total healthcare costs to pediatric asthma.^{3,4} An estimated \$10 billion of the \$62.8 billion that the United States spent on asthma in 2009 was ascribed to pediatric asthma.⁵ The U.S. Office of Disease Prevention and Health Promotion has developed a 2020 target of reducing hospitalizations and emergency rooms visits attributed to asthma among children less than

5 years of age by 56% and 28%, respectively.⁶ This goal, along with the global effort to reduce non-communicable diseases by 25% in 2025, will likely not be achieved without a more concerted effort to more effectively diagnose and treat the disease process.⁷

Pediatric asthma care does not differentiate itself from adult-based approaches in that it involves a multidimensional approach that requires jointly addressing clinical, environmental and socioeconomic variables.⁸ Care for children is made more challenging due to limitations inherent in applying age-appropriate strategies that take into account developmental and family barriers. This review focuses on the current state of pediatric asthma as it pertains to epidemiology, pathogenesis, clinical assessment, and treatment. At the conclusion of the review, the reader should have a better understanding of the current state and future challenges that are unique to pediatric asthma.

Materials and methods

Data for this review were identified by searching PubMed, EMBASE, and CINAHL databases. Particular emphasis

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was placed on randomized controlled trials (RCTs) and systematic reviews. RCTs were chosen to provide more reliable recommendations; however, they may have been limited by a lack of diversity in the demographic characteristics of participants. This limitation was addressed by the inclusion of studies implemented in various global settings to enhance the translatability of the recommendation to a global readership. Systematic reviews were also used because they provide the strongest evidence from summarizing RCTs; however, they are inherently limited by the methodology and execution of the summarized RCTs. Inclusion criteria included literature that pertained directly to asthma among children less than 18 years of age. Only articles published in the English language were reviewed, without date restrictions. Selected articles were also searched for relevant references.

Definition

Asthma is defined as a chronic inflammatory disorder associated with airflow obstruction and bronchial hyperresponsiveness.⁸ This descriptive definition is applied to both pediatric and adult populations but is often not as easily applicable in preschool-aged children. Young children in particular may have overlapping clinical presentations among differing respiratory diseases processes.⁹ For example, bronchiolitis is often diagnosed in those less than the age of 2 years and is frequently treated with medications typically prescribed for asthma exacerbations.¹⁰ For pediatric asthmatics, a reasonable working definition is recurrent diagnoses of wheezing, cough, shortness of breath, and/or chest tightness.¹¹ Ideally, responsiveness to these symptoms to beta₂ (B₂)-agonists (eg, albuterol or salbutamol) therapies or medications targeting inflammatory pathways further enhance the likelihood of the diagnosis.^{12,13}

Epidemiology

Asthma is among the most common noncommunicable chronic diseases of childhood. Approximately 14% of the estimated 2.2 billion children worldwide are likely to have disease symptoms.^{14,15} Based on The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires applied in 128 nations, continued high asthma prevalence was seen in English-language countries and Latin America.² ISAAC questionnaires have relied on reported wheezing episodes as a proxy measure for asthma. Although wheezing may have multiple etiologies in children and may not directly correlate with a diagnosis of asthma, its presence serves as a sensitive tool to estimate asthma prevalence in varied global settings with limited access to diagnostic technologies or respiratory therapies.^{16,17} Active wheezing symptoms were in children aged 6 to 7 years in 19.1% and 17.3% in North America and South America, respectively; this may be compared to the approximately 9% of reported wheezing in the same age group in both the Asia-Pacific and Eastern Mediterranean regions, respectively.² Time trends in the United States among children <18 years

of age had confirmed these findings by noting an increase in current asthma prevalence with 6.5 million and 6.8 million reporting “still having asthma” in 2005 and 2012, respectively.^{18,19} However, prevalence of wheezing symptoms did appear to be decreasing in adolescents in Western Europe. Within the minimum 5-year time frame that the first and third ISAAC questionnaires were applied in Western Europe, children reporting current wheezing decreased by 0.07% per year in those aged 13 to 14 years but increased by 0.20% per year in those aged 6 to 7 years.²

The rising usage and cost of accessing healthcare services for active pediatric asthma symptoms are of increasing importance in high-income countries in Europe and North America.¹⁵ Over the time period from the first and third ISAAC questionnaires (approximately 1995 to 2002), hospital admission rates had declined in most such countries, with the exception of Hong Kong and Poland.² Children immigrating to these high-income regions also appear to have a higher prevalence of symptoms and presumed usage of healthcare services, which is important given shifting population trends. This trend is predicated though on the time spent in the new country of origin.^{20,21} In a survey among 29,305 children in Italy, 7.7% of migrant children residing in the country for greater than 5 years had asthma symptoms, compared to only 3.3% of children living in the country less than 3 years ($p < .005$).²² Despite the decreasing global trends in hospitalizations, emergency department visits appear to be increasing in regions with complex healthcare systems, as seen in the United States and United Kingdom.^{23,24} This trend is significantly more notable among children of African descent in the United States and in those residing in low-income households.²³

The global prevalence of asthma appears to be on the rise, notably in rapidly industrializing countries, as evidenced by the findings of the third ISAAC questionnaire.² In parts of Africa, where the disease is often underdiagnosed, asthma appeared to have more severe presentations. Latin America had seen a rise in asthma symptoms in both age groups whereby a 0.32% and 0.07% increase was seen in children aged 6 to 7 years and 13 to 14 years, respectively. Symptoms appear to be increasingly recognized in young children in Asia, which may be more significant given the rising population trends in the region. The Indian subcontinent had an increase of 0.2% and 0.06% in symptoms in both those aged 6 to 7 years and 13 to 14 years, respectively. Nationwide surveys in China from 1990 to 2000 in 27 cities noted pediatric asthma prevalence increasing from 0.9% in 1990 to 1.5% in 2000.²⁵ Detailed healthcare utilization data is not as widely obtainable in lower-income countries, but one can surmise that the rising recognition of asthma trends in these regions will ultimately translate to higher usage of healthcare services.

Pathophysiology

The pathophysiology of asthma is explained in detail elsewhere in the Asthma Primer. In brief, the major

physiological event resulting in asthma symptoms is airflow limitation secondary to bronchoconstriction.⁸ The acute bronchoconstriction is largely the result of an allergen-induced release of inflammatory mediators via an immunoglobulin E (IgE)-dependent pathway.²⁶ However, a recent prospective study among 16,147 children in 12 European birth cohorts has suggested that IgE sensitization may not be the dominant causal mechanism for atopic diseases.²⁷ Non-IgE dependent pathways (eg, exercise, inhaled irritants, stress, etc.) may be result in bronchoconstriction of varying degrees, but the mechanism by which this occurs in children is not as well defined.^{28,29} Given the magnitude of clinical management focused on IgE-mediated asthma pathways, this review will predominantly describe pediatric-specific diagnostic, assessment, and therapeutic strategies in the context of the more classical immune presentation.

Diagnosis

Given the limited ability to use diagnostic technologies available in the adult population, a thorough medical history is critical in the diagnosis of asthma—particularly in preschool-aged children. Young children are not capable of performing the coordinated forced expiratory maneuvers required for diagnostic spirometry testing. The Global Initiative for Asthma (GINA) 2014 Global Strategy for Asthma Management and Prevention (GSAMP) suggests as an alternative modality the identification of the following key features that are consistent with a diagnosis of asthma in preschool-aged children: recurrent cough, wheezing, dyspnea, reduced activity levels, family history of disease, and empiric response to asthma therapies.³⁰

Children at approximately 4 to 5 years of age may be capable of performing office-based spirometry, which could provide a more reliable diagnostic approach, mirroring older-aged populations.^{31,32} Spirometry captures both effort-dependent and effort-independent lung function. Obstructive lung disease consistent with a diagnosis of asthma may be observed in those with a disproportionate reduction in forced expiratory volume in 1 second (FEV1) in relation to the forced vital capacity (FVC).³³ A ratio of FEV1/FVC <80% is considered to be a sensitive marker for poor asthma control.⁸ This major variable is different than adults, because of the higher elastic chest recoil in children, whereby the ratio of FEV1/FVC <70% is indicative of obstructive lung disease.³⁴ The information gleaned from the lung mechanics at baseline may be further enhanced with spirometry performed pre-bronchodilator and post-bronchodilator administration.^{35,36} Bronchodilators include B2-agonists that dilate smooth muscles and provide diagnostic insight into the reversibility of airway bronchoconstriction. Data is interpreted based on predicted pediatric values that rely on age, gender, height, and ethnic background. FEV1 values that increase by greater than 12% after administration of a B2-agonist is consistent with bronchodilator-responsive reversibility of

airway constriction.³³ Further concerns regarding obstructive and restrictive lung patterns may be discerned with the use of lung plethysmography.³⁷ Peak flow measurements often have been used as a proxy measure for spirometry given that they can be quickly obtained in the home and outpatient office settings. However, individual variability is quite high on peak flow meters given that it is entirely effort-dependent and therefore limits their utility.³⁸ Peak flow meters are largely beneficial only in motivated children with a known ability to accurately reproduce their results in conditions of well-being and during asthma exacerbations.

Bronchoprovocation with methacholine challenge testing (MCT) is more often used as a diagnostic tool in the adult population, because the reference values are predominantly based on adult literature.³⁹ MCT can be performed in school-aged children capable of performing reliable, reproducible lung function values. Inhaled methacholine is a potent bronchoconstrictor and positive testing is diagnostic for bronchial hyperresponsiveness. A positive test is determined by the provocative dose that results in a 20% change in the large airway lung function. The limited MCT studies conducted in children indicate the cutoff value for a provocative concentration of inhaled methacholine that causes a decrease in FEV1 of 20% is 4.0 mg/mL; therefore, similar to the adult population.^{40,41} However, positive MCT results may be found in pediatric pathologies other than asthma (eg, allergic rhinitis, cystic fibrosis), though negative testing is helpful to rule out a diagnosis of asthma.⁴²

Allergy testing may be undertaken to determine potential environmental triggers. Greater details into the role of allergy testing in asthma can be found elsewhere in the Asthma Primer. Of particular note for children is the use of the medical history obtained from pediatric caregivers, which usually is sufficient to determine the possibility of sensitivity to seasonal allergens.⁴³ However, history alone is often not an adequate tool to determine sensitivity to perennial indoor allergens. Skin or in vitro testing may be used to determine specific IgE antibodies to potential indoor or outdoor allergens. Positive testing may be indicative of a potential trigger for asthma symptoms and also a therapeutic approach in terms of immunotherapy or remediation of the inciting agent.^{44,45}

Allergy-induced asthma may also have increased airway and serum eosinophils whose numbers correlate with the intensity of airway inflammation.^{46,47} Sputum may be collected for measurement of airway eosinophils in the adult population given the ease in obtaining, but this is more challenging to acquire in the young pediatric population. For children not capable of providing an induced sputum sample, bronchoscopy with saline lavage may be an alternative method for specimen acquisition.⁴⁸ Assessment of fractional exhaled nitric oxide (FeNO) may be an alternative proxy measure in children for determining the level of eosinophilic inflammation in the bronchial mucosa.⁴⁹ Cutoff points for significantly high FeNO levels in children are

notably lower than adults; levels greater than 35 parts per billion (ppb) in children, as compared to >50 ppb in adults, is indicative of eosinophilic inflammation.⁵⁰

Chest X-rays should be obtained in all pediatric asthmatics with poorly controlled symptoms or if the history is indicative of an alternative pulmonary morbidity. Chest imaging may assist with disease processes that present with asthma-like symptoms (eg, pneumonia, allergic bronchopulmonary aspergillosis, foreign body obstruction, or interstitial lung diseases).^{9,51–53} Moreover, consideration for diagnostic strategies specific for gastroesophageal reflux disease (GERD), which is beyond the scope of this review, should also be considered in the young pediatric population. GERD may underlie or exacerbate airway inflammation that often is ascribed solely to pulmonary-based asthma pathology.^{8,54}

Assessment and monitoring

The 2014 GINA GSAMP base pediatric disease control on the prevalence of asthma symptoms and requirements for B₂-agonist therapies (Table 1).³⁰ Criteria for control require parental recall over a 4-week time period of the frequency of daytime symptoms, nighttime awakenings, usage of B₂-agonists and interference with normal activity. Severity classification is determined by the number of fulfilled symptoms criteria and should be measured prior to the initiation of asthma therapies and at each healthcare encounter in which asthma is the primary issue of concern.

Validated questionnaires can be obtained for determination of the impairment domain and assessment of disease control after therapies have been initiated. These tools require minimal time commitment for application, though are limited by the lack of incorporation of quantitative spirometry measurements. Two commonly utilized instruments include the Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT).^{55,56} Both are validated for self-administration for children >11 years of age. Assessment of asthma control and therapeutic efficacy may be determined in children as young as 4 to 11 years of age using the Childhood ACT (cACT)—though insufficient data is available to show its responsiveness over time.⁵⁷ Asthma control may be monitored in preschool-aged children using the validated Test for Respiratory and Asthma Control in Kids (TRACK).⁵⁸ Encompassing both impairment and risk domains, TRACK is, however, limited by insufficient research to document its responsiveness over time in varied clinical scenarios and population subgroups. The ISAAC questionnaire, mentioned earlier in the Epidemiology section, is another instrument that has been designed to assess not only prevalence but also the severity of key asthma symptoms in school-aged children. A beneficial feature of this tool is that it has been validated in over 2 million children worldwide, uses written and video components, available in >40 languages and assesses other atopic comorbidities (rhinitis and eczema).⁵⁹

Treatment

GINA recommends stepwise pharmaceutical-based treatment based on the classification of asthma severity.³⁰ The goal is to maintain long-term control with the least amount of medications and thus minimize the risk of adverse events. Classification of intermittent asthma requires treatment with solely B₂-agonist therapy (eg, albuterol or salbutamol) as needed. Worsening severity of persistent asthma requires a stepwise approach of increasing dosages of inhaled corticosteroid (ICS) therapies, with the possible addition of a leukotriene receptor antagonist (LTRA) (eg, montelukast). Long-acting B₂-agonists (LABA) (eg, salmeterol or formoterol), used jointly with ICS therapies, may be considered in those with moderate to severe persistent asthma. ICS therapies are the preferred drug therapy for long-term asthma control in the pediatric population.

If no benefit is observed within a 4-week to 6-week time frame on a daily controller medication, review of drug adherence, delivery technique, and environmental exposures should be undertaken prior to modifying the therapy or considering alternative diagnoses.^{60–63} Poor asthma control should prompt a thorough examination of medication adherence because this is among the most common causes of poor response to therapies.^{8,64} Although beyond the scope of this review, adherence can be maximized with targeted and engaging asthma education strategies focused on both children and their caregivers. A recent systematic review of the role of adherence in asthma exacerbations in the pediatric and adult population noted that appropriate adherence was significantly associated with fewer severe asthma exacerbations.⁶⁵ Adherence among adolescents is particularly difficult given psychosocial factors, but recent work has indicated that improved mental health screening, peer support, and social media-based strategies may be particularly helpful in this age group.^{66–68} Drug delivery technique is also important in the assessment of asthma control. Metered dose inhalers (MDIs) used with valved holding chambers (VHCs) are equally as effective as nebulized therapies in children of all ages when given appropriately.^{69,70} MDI+VHCs are preferred over nebulizer therapies given the reduced length of time to receive the treatment dosage, therefore minimizing the often seen difficulties in maintaining a tight seal of the facemask around the lips of children who have difficulties remaining in a fixed position for the duration of a 5-minute to 15-minute nebulizer treatment.⁷¹ Moreover, effective distribution of particle deposition from a nebulizer requires either a tight-fitting mask or mouthpiece—both difficult to achieve in noncompliant young children. The use of suboptimal nebulized therapy methods may result in increased oropharyngeal deposition of the drug, as opposed to the desired lung deposition.^{71–73}

As mentioned earlier, ICS therapies are the recommended therapy for persistent asthma.⁸ Multiple ICS therapies are approved in the pediatric age group but a major

TABLE 1. GINA assessment of asthma control in children delineated by age cutoff³⁰

Asthma symptom control in children ≤5 years of age ^a	Level of asthma symptom control		
In the past 4 weeks, has the patient	Well controlled	Partly controlled	Uncontrolled
Daytime asthma symptoms for more than a few minutes, more than 1 ×/week	None of these	1 to 2 of the 4 asthma control criteria are present	3 to 4 of the 4 asthma control criteria are present
Night waking or night coughing due to asthma			
Reliever medication needed more than 1 ×/week			
Activity limitation due to asthma (eg, runs/plays less than other children, tires easily during walks/playing)			
Asthma symptom control in children ≥6 years of age ^a			
Daytime asthma symptoms more than 2 ×/week	None of these	1 to 2 of the 4 asthma control criteria are present	3 to 4 of the 4 asthma control criteria are present
Night waking due to asthma			
Reliever needed for symptoms more than 2 ×/week			
Activity limitation due to asthma			

^aPatient symptoms in the past 4 weeks.

GINA = Global Initiative for Asthma.

drawback has been the need for administration of medications that require twice-daily dosing. Medication adherence is difficult particularly in the adolescent population and is further compounded by employed caregivers with little time to properly supervise medication delivery.^{74,75} Adherence and subsequent treatment response may improve with the increased availability of once-daily formulations. For example, inhaled ciclesonide and mometasone are approved for once-daily administrations in select geographic regions.^{76,77} Though noted to result in improvement in lung function in adult-based studies, a systematic review of studies children aged 4 to 17 years of age could not demonstrate a significant improvement in asthma symptoms using once-daily ciclesonide compared to twice-daily budesonide administration (risk ratio [RR] 2.20; 95% confidence interval [CI], 0.75 to 6.43).⁷⁸ Moreover, concerns have arisen for dose- and duration-dependent adverse effects of daily ICS therapies on linear growth and bone mineral density.⁷⁹ Select studies have explored the use of as needed ICS therapies to minimize these concerns. However, the limited studies in the pediatric population have not shown equal or improved effectiveness using as-needed ICS therapies, as compared to daily administration.^{80,81} Another treatment strategy may be to add a LABA in those not responding to moderate or high dosages of ICS therapies. A systematic review among children with chronic asthma, ICS+LABA therapies were noted to yield significantly greater improvement in FEV1 (0.08 L; 95% CI, 0.06 to 0.11 L); however, no statistically significant group differences in symptom-free days, hospital admission, quality of life, use of reliever medication, and adverse events were noted.⁸² Ultimately, the goal of treatment of persistent asthma in the pediatric population should focus on determining the lowest effective ICS dose that results in disease control.⁸

Montelukast and zafirlukast are LTRA therapies that may be recommended as an additive component to the medication regimens of mild to moderate persistent asthmatics. Zafirlukast is approved in the United States for children older than 5 years of age, but close monitoring of liver enzymes should occur because of its association with hepatic dysfunction.⁸³ Montelukast is a more often prescribed LTRA therapy because its limited side effect profile is more preferable and is approved for use in children as young as 6 months. It is an attractive therapy to provide to children because its oral preparation and once-daily administration is easier to administer. Montelukast has shown a benefit among preschool-aged children with intermittent asthma, whereby it delayed median time to first exacerbation by approximately 2 months ($p = 0.024$) and decreased the requirement of inhaled corticosteroid courses ($p = 0.027$) compared with placebo.⁸⁴ However, a systematic review of children greater than 6 years of age with mild to moderate asthma noted no significant reduction in systemic steroid requirements or hospital admissions when taking combined LTRA+ICS therapies.⁸⁵ Intermittent usage of montelukast for wheezing in children aged 10 months to 5 years also showed no benefit in reducing unscheduled healthcare visits for respiratory symptoms.⁸⁶ Pediatric and adult-based literature does indicate that montelukast may have a significant benefit in improving nasal symptoms and lung function in those with comorbid allergic rhinitis and asthma.^{87,88}

Biologic therapies are increasingly being recognized as a potential treatment for moderate to severe persistent asthmatics who do not respond to conventional asthma therapies. Omalizumab is a monoclonal antibody that selectively binds to IgE and is indicated in patients as young as 6 years of age in Europe and >12 years of age in the

United States. It is indicated in those with IgE-mediated asthma who have a positive skin test or in vitro reactivity to a perennial allergen that cannot be controlled with ICS therapies alone.⁸⁹ A randomized study among 576 children aged 6 to 12 years of age noted a 43% reduction in annual asthma exacerbations in those receiving omalizumab vs placebo ($p < 0.001$).⁹⁰ A recent systematic review in adults and children with moderate to severe asthma receiving omalizumab (compared to placebo) noted a 10% reduction in asthma exacerbations (odds ratio [OR], 0.55; 95% CI, 0.42 to 0.60), 2.5% reduction in hospital admissions (OR, 0.16; 95% CI, 0.06 to 0.42) and withdrawal of daily ICS therapies (OR, 2.50; 95% CI, 2.00 to 3.13) over 16 to 60 weeks of treatment.⁹¹ Despite the benefits, the therapy is constrained by its high cost and time commitment to receive the bimonthly/monthly subcutaneous treatments.⁹² Other potential future biologic therapies include mepolizumab (anti-interleukin-5 [IL-5]) and lebrikizumab (anti-IL-13).^{93,94} These therapies have yet to be routinely studied in the pediatric population, but a multicenter placebo-controlled trial conducted among patients 12 to 74 years of age reported that the rate of clin-

ically significant exacerbations was 2.40 per patient per year in the placebo group vs 1.15 in the mepolizumab group (52% reduction, $p < 0.0001$).⁹⁵ Lebrikizumab has yet to be studied in children but research in adults indicates improvement in biomarkers of IgE-mediated airway inflammation.⁹⁶

Conclusion

Pediatric asthma is increasingly being appreciated globally secondary to improved diagnostic strategies and enhanced recognition of environmental triggers. With increasing awareness comes the need for aggressive and individualized therapies that require a coordinated response by primary and specialty healthcare providers. Specialty providers are needed to jointly address notable comorbidities, including allergies and upper airway pathologies, for the enhancement of patient outcomes and quality of life. Given the prevalence of asthma, effective disease control in the pediatric population requires a comprehension of key concepts in disease management that this review has provided. ☯

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