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RESPIRATORY DIGEST™

VOLUME 9

ISSUE 2

Special CME article jointly sponsored by the American Academy of Allergy, Asthma, and Immunology and MediCine Inc

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This publication series is supported by an educational grant from ALTANA Pharma US, Inc - a NYCOMED Company

Continuing Medical Education

Audience:
This program has been developed for allergists, pulmonologists, pediatricians, and primary care clinicians who treat respiratory disease.

Educational Objectives:
After reading this article, participants should be able to:

- Describe the predictors of asthma development in children and discuss the persistence of asthma into adulthood
- Describe the predictors of asthma development in adults
- Contrast the symptom patterns of asthma in children and adults
- Discuss the differences between children and adults with respect to asthma modification and treatment

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How Pediatric and Adult Asthma Differ, With Implications for Treatment

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The phenotypic expression of asthma throughout life reflects different susceptibilities, presentations, and triggers. The majority of asthma symptoms start in childhood; indeed, asthma is the most common chronic disease affecting children.[1,2] Approximately 60% of children who wheeze during the first 2 years of life stop wheezing after age 3; others—usually those with familial risk factors for allergy and asthma—continue to have symptoms and are eventually diagnosed with asthma.[2,3] However, despite recognition of these symptom patterns, much remains to be learned about how phenotype and genetic predisposition interact with environmental factors to cause full-blown asthma.

This article reviews the natural history of asthma with respect to the following:

- Predictors for the development and persistence of the disease in young children
- Predictors for the development of the disease in adults
- Phenotypic differences in symptom patterns for childhood and adult-onset disease
- Implications of potential phenotypic differences between children and adults for disease modification and treatment

Presentation of Asthma in Children and Adults

Diagnosis of asthma requires a careful medical history, physical examination, and, if possible, confirmation by objective measurements of pulmonary function. Several criteria are important in establishing the diagnosis:

- Evidence of episodic symptoms of airflow obstruction (eg, coughing, wheezing, shortness of breath, chest tightness)
- Demonstration of airflow limitation that is at least partially reversible
- Exclusion of alternative diagnoses
- Positive response to medication

The Medical History

The hallmark of asthma is the presence of characteristic symptoms including episodic breathlessness, wheezing, cough, and chest tightness. Children, especially young children, may express symptoms differently from adults. Fatigue and irritability may predominate. The young child may complain that "my chest hurts" or "my chest feels funny," while older children may avoid activities (eg, sports, sleepovers). It is difficult to diagnose asthma in infants, but rapid breathing, grunting during sucking, and difficulty feeding suggest asthma in a wheezing baby.[4]

A careful environmental history in relation to symptom expression is important; asthma symptoms may be provoked by incidental allergen exposure or induced by non-specific exposures, such as smoke, fumes, strong odors, cold air, and exercise. Exposure to environmental tobacco smoke is often associated with asthma in children.[4]

Variability, an essential component of the diagnosis of asthma, refers to the episodic nature of symptoms occurring over time. Some patients show a worsening of symptoms at night and in the early morning; seasonal variations are also common (eg, virus seasons, allergen seasons).[4] Diagnosis may also be complicated by symptoms that are intermittent, mild, and non-specific, particularly in children. Children show substantial intrinsic variability of asthma as evidenced in a review of five 12-week double-blind studies. A total of 276 placebo-treated children (4-11 years old) who had used only short-acting β_2-agonists prior to the study were evaluated. All showed >1 move between severity classifications (mild, moderate, and severe, based on peak flow measurements); >35% changed severity levels ≥15 times.[5]

Some key questions for the medical history are listed in **Table 1.** The diagnosis is strengthened by a history of allergy and/or a positive family history of asthma and/or atopic disease.[4]

The Physical Examination

Since asthma is frequently associated with allergic conditions (eg, allergic rhinitis, sinusitis, eczema), physical examination of the asthma patient focuses on the upper respiratory tract and skin in addition to the chest. The examination may be normal due to the episodic nature of asthma.[4]

Findings that support a diagnosis of asthma include[4]:

- Hyperexpansion of the thorax, especially in children
- Sounds of wheezing during normal breathing or during deep breathing (wheezing during forced exhalation is not a reliable indicator of airflow limitation, and may not be present)
- Signs and symptoms of allergic rhinitis and rhinosinusitis
- Atopic dermatitis/eczema

Objective Measurements

Whenever possible, the diagnosis of asthma should be confirmed with objective measures of pulmonary function, preferably spirometry and/or tidal flow-volume loop (the flow-volume curve

TABLE 1. SOME KEY QUESTIONS TO CONSIDER WHEN DIAGNOSING ASTHMA[3]

- Are there episodes of recurrent wheezing, coughing, chest tightness, or breathlessness?
- Does the patient have troublesome cough at night?
- Does the patient wheeze, feel breathless, or cough after exercise, or when exposed to environmental irritants or allergens?
- Do colds often "go to the chest" and/or take more than 10 days to clear up?
- Are symptoms improved by a trial of appropriate asthma treatment?

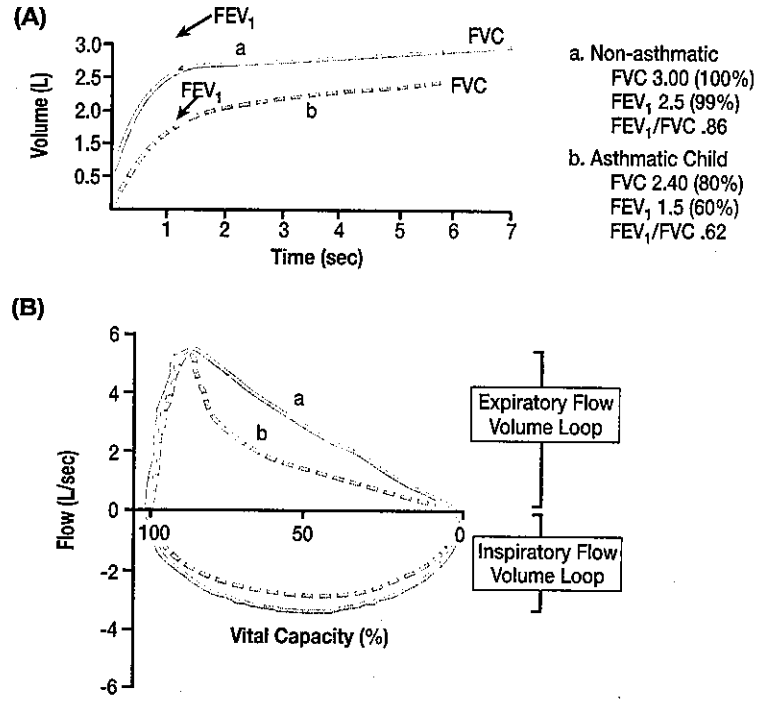

Figure. (A) Volume-time curves from a non-asthmatic and an asthmatic child showing decrease in FEV_1 in asthma. Expiratory times are adequate for both. (B) Flow-volume curves from same 2 children. Characteristic concave appearing flow volume loop shows airflow obstruction with asthma. Inspiratory flow volume loops are normal for both.[6]

during inspiration and expiration) (**Figure**).[6] Spirometry is recommended for diagnostic purposes due to its greater sensitivity in demonstrating airflow obstruction compared with peak expiratory flow (PEF). A decreased FEV_1/FVC ratio (generally <75%; <80% in children) demonstrates the presence of airflow obstruction; when obstruction is present, FEV_1 values >80%, 60% to 80%, and <60% predicted are consistent with mild, moderate, and severe persistent asthma, respectively.[4,6]

Reversibility in lung function is used to distinguish asthma from other obstructive airway disorders. Reversibility may be demonstrated by

- Rapid improvement in lung function (≥12% in FEV_1 or PEF) within minutes after using a short-acting bronchodilator
- Sustained improvement in lung function over a period of time (days, weeks) after starting appropriate controller therapy[4]

Lung function measurements do not always correlate with symptoms, and in patients with mild asthma, pulmonary function tests may be normal. Monitoring peak flow variability over 1-2 weeks

may be helpful to establish the diagnosis; it may also be useful for patients who cannot perform spirometry. PEF is generally lowest in the early morning (4 a.m. to 8 a.m.) and highest in the afternoon (around 4 p.m.).[4]

For young children and other patients who cannot perform spirometry or peak flow, a trial with an inhaled β_2-agonist and/or a short (3- to 7-day) course of oral corticosteroid may be helpful. A positive clinical response followed by deterioration when treatment is stopped supports a diagnosis of asthma.[4]

Special Considerations

Children ≤5 Years Old

Episodic wheezing and cough is very common in young children, even those who do not have asthma. In this age group, diagnostic factors suggestive of asthma include

- Frequent episodes of wheeze (>1/month)
- Activity-induced cough/wheeze
- Nocturnal cough in periods without viral infections
- Absence of seasonal variation in wheeze
- Symptoms persisting after age 3 years[4,7]

School-Age Children

In young school-age children, asthma continues to present most frequently as recurrent episodes of coughing or wheezing. Since most children cough throughout childhood, it is important to be able to distinguish cough indicative of asthma from other types of cough. Nocturnal coughing and exaggerated episodes of cough with exercise, cold air, or various exposures are suggestive, as is cough that improves following controller therapy. The presence of other allergic symptoms (eg, eczema, rhinitis) increases the likelihood of asthma. A careful review of family and environmental history is especially important.[7]

Adolescents

Asthma may be underdiagnosed in adolescents, who may be reluctant to acknowledge the condition. Adolescent children with a history of asthma may show increased disease severity associated with risk-taking behaviors, hormonal changes, and nonadherence to treatment (denial).[8]

Adults

Occupational asthma in adults is often misdiagnosed as chronic bronchitis or chronic obstructive pulmonary disease (COPD), resulting in inappropriate treatment. Thus, when interviewing an adult patient about onset of asthma or an unexplained increase in disease severity, it is important to inquire about work history and exposures at other locations.[4]

COPD is another inflammatory condition affecting the lungs that should be differentiated from asthma in adult patients. It is characterized by airflow limitation that is usually progressive and not fully reversible. Smokers with an allergic diathesis may be predisposed to develop severe and chronic airflow obstruction concomitant with an asthma-like eosinophilic airway inflammation.[4]

Other presentations seen in adults include aspirin-induced asthma and symptoms in women that are related to menses and hormonal changes.[4,9]

Classification of Disease Severity

Once diagnosed, asthma patients are classified as having mild intermittent or mild, moderate, or severe persistent disease based on symptom severity, frequency, and duration; degree of airflow obstruction; and interference with daily activities.[4] This categorization is largely used as a research tool, since disease control varies with treatment and over time. Any patient with asthma may have a severe exacerbation of symptoms due to viral infection or allergen exposure, or it may be idiopathic.[4]

Predictors of Childhood Asthma

Asthma is often first diagnosed in childhood, and estimates indicate that up to 80% of children with asthma develop symptoms, specifically recurrent wheeze (and/or cough), before age 5 years.[1-4] However, recurrent wheezing and coughing in infants and young children is common with many conditions.[1,2] Three questions are relevant in evaluating the onset and persistence of symptoms in relation to the development of asthma:

1. Can we identify different patterns of recurrent wheezing in young children? The answer is "yes" according to a large cohort study that followed 1,200 children in Tucson, Arizona, from birth to 6 years of age for history of wheezing and development of asthma.[2,3] Approximately 50% of the children had ≥1 wheezing episode by age 6 years, and these were then classified according to the pattern of recurrent wheezing by age. Transient wheezers (20%) had ≥1 episode of wheezing before age 3 years, but were no longer wheezing at age 6 years. Late-onset wheezers (15%) started wheezing between ages 3 and 6 years. Persistent wheezers (14%) had recurrent episodes of wheezing throughout the entire 6-year period.[2] Other population-based studies have reported similar heterogeneity of wheezing in young children.[10-12]

2. What causes recurrent wheezing in young children? Most wheezing in infancy and in young children is associated with viral respiratory tract infections, but the association between the specific infection and subsequent recurrent wheezing and development of asthma is complex.[2,13] Both respiratory syncytial virus (RSV) and rhinovirus (RV) have been associated with increased risk of recurrent wheezing and asthma; however, recent data suggest that RV infection may play a greater role in the development of infantile and early childhood wheezing.[13]

Twice as many preschool children at increased risk for allergies and asthma (ie, parental history of respiratory allergies and/or diagnosis of asthma) have been reported to wheeze during infection with RSV compared with RV (50% vs 25%). However, those who wheezed during RV season were more likely to continue to wheeze at age 3 years (RV, 63% vs RSV, 20%).[13] In adults, RV infection has been shown to increase lower airway inflammatory responses to allergen,

enhance bronchial hyperreactivity, and exacerbate asthma symptoms.[4] Whether RV infection in "at risk" infants and young children promotes the development of asthma is not definitively known.

3. Which factors contribute to the persistence of symptoms throughout childhood, ie, increase susceptibility to developing recurrent wheezing and asthma? A prospective study of 1,314 children followed from birth to age 13 years found that atopy, sensitization, and high level of exposures to common perennial allergens (house dust mite, animal dander) during the first 3-5 years of life were associated with reduced lung function and risk of bronchial hyperreactivity at school age, which showed a positive correlation with specific levels of allergen exposure.

In contrast, 90% of non-atopic children who wheezed in early life stopped wheezing and retained normal lung function.[11] Allergen sensitization after age 3 years was only weakly associated with asthma, suggesting that early exposure to allergens may alter the maturing immune system, resulting in aberrant inflammatory responses. Similar results were shown in another cohort study that evaluated the development of recurrent wheezing and asthma in relation to atopy in 1,456 children from birth to age 10 years.[12]

Thus, early allergen exposure in sensitive children appears to play an important role in the development of asthma, and the relationship is strong enough to be used as a predictive clinical index to identify young children (≤3 years old) who might be at high risk for developing asthma. **Table 2** presents the Modified Asthma Predictive Index (mAPI) developed using data from the Tucson Children's Respiratory Study.[3]

A positive mAPI has been demonstrated for preschool children with ≥4 severe wheezing episodes over 12 months requiring use of oral corticosteroids compared with children whose wheezing did not require oral corticosteroid treatment (P=0.007). The children with the positive mAPI also had more hospitalizations (P=0.0061) and urgent care visits (P=0.0048) related to their symptoms.[14] The findings suggest a childhood phenotype of severe, intermittent asthma that needs better definition and delineation of intervention strategies.

TABLE 2. MODIFIED ASTHMA PREDICTIVE INDEX (mAPI) FOR CHILDREN ≤3 YEARS OLD[3,13]

Child defined as a "frequent wheezer":
- Parents report ≥4 wheezing episodes, with at least 1 confirmed by a physician

1 major criterion:
- Parental history of asthma
- Physician-diagnosed atopic dermatitis
- Allergic sensitization to ≥1 aeroallergen

2 minor criteria:
- Allergic sensitization to milk, egg, or peanuts
- Wheezing unrelated to colds
- Blood eosinophils ≥4%

TABLE 3. SOME FACTORS INFLUENCING DEVELOPMENT AND EXPRESSION OF ASTHMA[4,10-12]

Host factors	**Increased risk of asthma**
Sex	Male
Airway size	Small airways in males
Gestation	Premature birth
Genetic background	Personal history of atopy and/or family history of atopy or asthma (particularly maternal)
Weight	Obesity, especially in females
Racial/ethnic background	African American, Puerto Rican
Environmental factors	**Increased risk of asthma**
Allergens	Exposure to food allergens and/or perennial allergens (eg, house dust mite, animal dander) in young children
Viruses	Chronic recurrent wheezing with viral infections in childhood
Tobacco smoke	Active smoking and/or passive exposure to tobacco smoke (particularly in young children)
Air pollution	Exposure to outdoor and/or indoor air pollutants
Inhaled irritants	Exposure of adults to occupational sensitizers
Diet	Increased use of processed foods; possibly, formula feeding as opposed to breast-feeding

Natural History of Asthma From Childhood to Adulthood

Most adult asthma begins in childhood and is mediated by multiple factors. In infants and young children, atopy is the strongest identifiable predisposing factor for asthma, and viral infections are the major cause of acute wheezing; other characteristics influence the expression of asthma over time.[4,11,12,15] Some of the individual and environmental factors associated with increased risk of asthma are listed in **Table 3**. The mechanisms by which these factors contribute to the development and expression of asthma are complex and interactive, and not all are causal in nature.

More study is needed to clarify the natural history of asthma. Again, three questions are relevant:

1. What are the risk factors for persistent asthma from childhood to adulthood? According to epidemiologic studies, the key independent factors associated with adult lung function and persistence of asthma are
   - Recurrent, persistent wheezing during childhood
   - A personal history of atopy and/or a family history of asthma and/or atopy
   - Female sex
   - Bronchial hyperreactivity
   - Exposure to tobacco smoke
   - Degree of symptom severity and lung function deficit[1,10]

2. What is the pattern for asthma from childhood to adulthood? The early acquisition of allergy is the most important driver for persistent symptoms in children

who have recurrent episodes of wheezing with viral infection.[2,4,11] These children are reported to have reduced lung function at school age without further impairment during adolescence and adulthood.[10,11]

Children with mild-to-moderate symptoms of asthma may experience clinical remission of their asthma symptoms as adolescents or adults. However, the limited data available suggest that these individuals retain some degree of lung function deficit, airway hyperreactivity, and airway inflammation.[1,8]

3. What are the risk factors for the development of asthma in adults who did not have asthma as children? Risk factors for the development of adult-onset asthma are not well delineated, but may include allergen exposure, obesity, hormonal changes, exposure to occupational sensitizers, tobacco smoking, and increased levels of air pollution. Whether these factors cause asthma in adults or exacerbate a "silent" condition is not clear.[4,9]

Several types of asthma are more likely to occur in adults. And adult-onset phenotypes are more likely to be associated with severe disease and less likely to show a well-defined relation to atopy. The three most common phenotypes are occupational asthma, aspirin-induced asthma, and menses-related asthma.[4,9]

Occupational asthma is estimated to account for ≤15% of adult-onset asthma. It may involve development of an immunologically mediated sensitization to an occupational agent and/or a rapid, but non-immunologic, response to high levels of irritant compounds.[4,9] Over 300 agents have been linked to occupational asthma; workers at greatest risk are those in farming, painting, cleaning, and plastic and chemical manufacturing.[4] The diagnosis of occupational asthma requires correlation between symptoms and the workplace. Once established, the pathophysiologic process may proceed independently of exposure. Thus, early recognition and control of exposure are important in managing this phenotype.[4,9]

Aspirin-induced asthma is frequently associated with severe asthma, severe rhinosinusitis with nasal polyps, little or no evidence of atopy, increased levels of airway leukotrienes, and increased circulating eosinophils.[4,9] The underlying pathophysiology probably involves alteration of the leukotriene pathways, and some (but not all) patients respond to treatment with leukotriene modifiers. These patients usually respond poorly to corticosteroids.[4,9]

Menses-related asthma involves exacerbations (often severe) associated with changes in sex hormones, usually before menstruation. This phenotype has been reported in a small proportion of women but is not well defined.[9]

Implications for Treatment

Asthma may be treated by disease modification and by pharmacotherapy.

Disease Modification

For most asthma patients, the disease begins in childhood, and early exposure to allergens predicts early development of symptoms.[11,15] The question then is whether minimizing (ideally, eliminating if possible) exposure to perennial allergens during maturation of the immune system might alter the development and/or course of the disease in susceptible children. Current data are limited and conflicting; more study is needed.

Another approach is use of allergen-specific immunotherapy. A 3-year course of immunotherapy in children with seasonal rhinoconjunctivitis who had no clinical asthma symptoms at the start of treatment reduced the risk of developing asthma, as indicated by fewer symptoms (odds ratio 2.52; $P<0.05$) and lower bronchial hyperreactivity to methacholine (odds ratio 2.78; $P<0.05$).[16]

Pharmacotherapy to Prevent Asthma

The Prevention of Early Asthma in Kids (PEAK) trial looked at 2 years of treatment with the inhaled corticosteroid (ICS) fluticasone or placebo followed by 12 months of additional observation in children (24-47 months old) who were identified, by a positive mAPI, as being at risk for asthma.[17] The primary outcome was the number of episode-free days during the third year of treatment. An episode-free day was defined as one with no cough or wheeze, no urgent care visits for asthma, and no use of asthma medications other than the ICS. At the end of the 2-year treatment period, children using ICS had significantly more episode-free days ($P<0.01$) with fewer asthma exacerbations and less use of additional controller medications ($P<0.001$ for both).[17] However, during the observation year, no significant between-group differences were observed. These data suggest that early intervention, even beginning in infancy, may reduce the morbidity of asthma but will not prevent development of asthma. Indeed, to date, no medication, including continual use of ICS, has been demonstrated to alter the natural history of asthma.[4,17]

Pharmacotherapy for Asthma Control

The principles of treating asthma are similar for children and adults. Treatment is directed toward both reducing the underlying chronic airway inflammation and minimizing symptom episodes. Thus, for most patients, pharmacotherapy requires both long-term controller therapy and a short-acting β_2-agonist for acute symptom exacerbations. The amount and frequency of the medications are dictated by age, activity level, and severity; a step-care approach is recommended by national and international guidelines.[4]

Controller Medications

For most asthma patients, regardless of age, ICS are the most potent and effective medications for treating the underlying airway inflammation. Currently available ICS are safe when used at recommended dosages, and the potential risks—even in children—are well balanced by their beneficial effects.[4] Data show that 90% of the efficacy of an ICS is achieved at relatively low dosages (eg, ≤250 µg fluticasone propionate; ≤500 µg beclomethasone dipropionate or budesonide).[18]

Long-acting β_2-agonists (LABA) are used as an add-on to ICS when additional control is necessary and/or to decrease the corticosteroid dosage.[4] These agents provide bronchodilation with a longer duration of action (≤12 hr) than short-acting β_2-agonists. There are no anti-inflammatory effects, but some complementary anti-inflammatory activity with ICS has been suggested. Data on LABA use in children are limited, although most formulations are approved for those as young as age 4 years based predominantly on safety evaluations. LABA should not be used as monotherapy. For patients with moderate-to-severe persistent asthma, who do best with a long-acting bronchodilator in addition to their ICS, combination therapy is now available in single devices, eliminating the need for multiple inhalers.[4]

Leukotriene modifiers (eg, montelukast, zafirlukast, zileuton) provide an alternative to low dosages of ICS for some patients with mild, persistent asthma (particularly, children), but are not as effective as ICS when used as monotherapy.[4] These medications also may be added to ICS when additional control is needed, but are not as effective as LABA in combination with ICS in adults (head-to-head comparisons in children are needed). Leukotriene modifiers are administered as tablets or sprinkles, which may be useful for young children and/or other patients who have difficulty managing inhaler devices. Montelukast may also be used prophylactically, prior to exercise or an anticipated exposure to allergens or cold air that exacerbates the patient's asthma.[4]

Adding leukotriene modifiers to ICS has been shown to be more effective in adults than in children.[4] In children with mild-to-moderate persistent asthma, a favorable response to monotherapy with montelukast was associated with younger age and shorter duration of asthma; in contrast, a better response to fluticasone was likely in children with decreased pulmonary function and/or increased levels of allergic inflammation.[19] In adults, leukotriene modifiers may be beneficial in aspirin-sensitive asthma, menses-related asthma, and "smoker's asthma."[9,20]

Other therapeutic approaches that may be used depending on the patient's specific needs include cromolyn sodium and nedocromil sodium, theophylline, and ipratropium bromide. Discussion is beyond the scope of this article, and the reader is referred to the Global Initiative for Asthma Report 2006[4] for more information.

CONCLUSIONS

Asthma involves complex interactions between the immune system and risk factors predisposing the individual to disease. Onset most frequently occurs in childhood, and specific patterns of symptoms in young children (wheezing with viral infection) have been described that may be associated with a phenotype for disease progression into adult years. Phenotypic expression is variable and associated with genetic predisposition to allergy and asthma along with early exposure to environmental allergens. The timing of environmental exposures appears to be critical, and an awareness of this timing may be essential for optimal clinical intervention.

Acknowledgments

I would like to thank Judith R. Farrar, PhD, FAAAI, for her editorial support in researching and compiling this article, and Robert Zeiger, MD, for his review and comments on the manuscript.

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CME Questions

1. Which of the following would not be indicative of a diagnosis of asthma?
a. Episodic symptoms of airflow obstruction
b. Irreversibility of airflow limitation
c. Exclusion of alternative diagnoses
d. Positive response to bronchodilators

2. FEV_1 measurements ranging from 71% to 79% predicted are consistent with which of the following diagnoses?
a. Mild intermittent asthma
b. Mild persistent asthma
c. Moderate persistent asthma
d. Severe persistent asthma

3. Which of the following risk factors is not associated with persistent asthma in adults?
a. Persistent childhood wheezing
b. History of atopy
c. Male sex
d. Bronchial hyperreactivity

4. Which of the following can be an alternative monotherapy to low-dose inhaled corticosteroids for mild persistent asthma, particularly in children?
a. Leukotriene modifiers
b. Long-acting β-agonists
c. Short-acting β-agonists
d. Antihistamines

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