Pediatric Asthma: Current Concepts

Case Study and Commentary, Kristen K. Volkman, MD, and Michael C. Zacharisen, MD

Asthma is a chronic inflammatory disease of the airways that is characterized by reversible airway obstruction, airway hyperresponsiveness to stimuli, variable airway resistance and flow rates, and transient increases in lung volume. Classic symptoms include cough, wheezing, dyspnea, and chest tightness [1]. Worldwide, asthma prevalence is increasing, with generally higher prevalence rates in westernized societies, English-speaking countries, and developing countries as they become urbanized [2]. In 2002, over 30 million people in the United States had ever been diagnosed with asthma during their lifetime [3]. Asthma is the most common chronic disease in children, affecting 9 million patients younger than 18 years in 2002 [4]. Sixty percent of people who have asthma experienced an exacerbation in the previous year; 4 million of these patients were children [3]. While death due to asthma is rare in children, 187 patients younger than 18 years died from asthma in 2002 [3].

These statistics have equally significant socioeconomic correlates. In the United States, the total cost of asthma in 2002 was $14 billion, $9.4 billion attributed to direct costs (expenses generated in the disease’s prevention, treatment, and rehabilitation) and $4.6 billion to indirect costs (value of resources lost as a result of time absent from work or other usual daily activity as a result of illness) [5]. Medications are now the largest component of direct costs, surpassing costs of inpatient hospitalization [6]. However, children had close to 200,000 hospitalizations in 2002 for asthma, mostly in those younger than 5 years [3]. On average, children with asthma miss more days of school per year compared to their classmates without asthma, with 14.6 million missed days in 2002 at a cost of $1.4 billion [5]. Children were seen in 13.9 million outpatient visits and over 700,000 emergency department (ED) visits for asthma [3]. The ED visit rate for asthma was highest among children younger than 5 years [3]. Societal differences among children with asthma exist as well, with children of poor families more likely to have ever been diagnosed with asthma and more non-Hispanic black children diagnosed with asthma versus non-Hispanic whites and Hispanics [4].

Prior to 1980, asthma was considered a disease of airway...
obstruction and the concept of inflammation was lacking. We now understand that asthma is a complex clinical syndrome with multicellular inflammation and injury even in those with mild persistent disease. Guidelines for the diagnosis and management of asthma from international organizations and professional societies [7–10] define asthma as a “chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli” [7]. These guidelines use expert opinion and systematic review of the literature to establish management recommendations.

The increasing prevalence and socioeconomic impact of pediatric asthma make recognition and proper treatment by primary care physicians crucial. Advances in understanding the complex pathophysiology of asthma, the risk factors for development of persistent asthma, and effective treatment options have led to earlier and more aggressive treatment in younger patients with milder disease. This case-based review reinforces established guidelines for the diagnosis and treatment of pediatric asthma and explores controversial issues.

**CASE STUDY**

**Initial Presentation**

A 6-year-old Caucasian girl with a 3-year history of intermittent cough that occurs with exercise and is relieved with inhaled albuterol is brought by her mother to the patient’s family medicine physician.

- What is the approach to diagnostic evaluation in a patient with asthma symptoms?

**Diagnostic Workup**

The diagnosis of asthma is not based on a single test or measure but rather comes from the synthesis of information gathered through various evaluations [7]. As with any medical evaluation, the diagnosis of asthma begins with a thorough history and complete physical examination (Table 1). A history of recurrent symptoms of cough, wheeze, dyspnea, chest tightness, and chronic cough lasting more than 6 weeks or persisting after upper respiratory infections or diagnoses of recurrent bronchiolitis, pneumonia, “chronic or wheezy bronchitis,” and reactive airway disease should arouse suspicion for asthma. Nocturnal or early morning cough or lower respiratory symptoms with exertion similarly should arouse suspicion, and further questions should be posed [7–10]. Key information obtained from the interview includes onset, duration, frequency, and severity of wheezing, cough, dyspnea, and chest tightness; allergic and nonallergic precipitating and/or

<table>
<thead>
<tr>
<th>Table 1. Diagnosis of Asthma</th>
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<tbody>
<tr>
<td>History</td>
</tr>
<tr>
<td>Symptoms: cough, wheeze, dyspnea, chest tightness</td>
</tr>
<tr>
<td>Timing: frequency of day/night symptoms</td>
</tr>
<tr>
<td>Triggers: allergens (indoor, outdoor), exercise, cold air, outdoor air pollution, tobacco smoke, irritants, infections (viral, sinusitis, atypical bacteria), psychological stress, gastroesophageal reflux disease, food allergy</td>
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<tr>
<td>Severity: emergency department visits, hospitalizations with/without intubation, oral steroids</td>
</tr>
<tr>
<td>Response to treatment</td>
</tr>
<tr>
<td>Personal history of atopy: eczema</td>
</tr>
<tr>
<td>Family history of atopy</td>
</tr>
<tr>
<td>Environment: daycare, pets, smoke/irritants, roaches</td>
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<tr>
<td>Physical examination</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
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<tr>
<td>Skin (eczema)</td>
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<tr>
<td>Objective measures of pulmonary function</td>
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<tr>
<td>Spirometry</td>
</tr>
<tr>
<td>Peak expiratory flow rate</td>
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<tr>
<td>Complete pulmonary function tests</td>
</tr>
<tr>
<td>Other testing</td>
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<tr>
<td>Complete blood count, peripheral eosinophilia</td>
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<tr>
<td>Total serum IgE level</td>
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<tr>
<td>Measures of specific IgE</td>
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<tr>
<td>Allergy skin testing</td>
</tr>
<tr>
<td>In vitro testing: radioallergosorbent test, enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>Chest x-ray</td>
</tr>
<tr>
<td>Bronchial provocation</td>
</tr>
<tr>
<td>Methacholine, histamine, exercise, cold air</td>
</tr>
<tr>
<td>Testing to exclude other disease entities</td>
</tr>
<tr>
<td>Initial</td>
</tr>
<tr>
<td>Sinus or chest computed tomography scan</td>
</tr>
<tr>
<td>Neck x-ray</td>
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<tr>
<td>Upper gastrointestinal series and/or 24-hour pH probe</td>
</tr>
<tr>
<td>Viral or bacterial cultures</td>
</tr>
<tr>
<td>Sweat chloride</td>
</tr>
<tr>
<td>Advanced</td>
</tr>
<tr>
<td>Laryngoscopy and/or bronchoscopy</td>
</tr>
<tr>
<td>Cilia biopsy</td>
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<tr>
<td>Quantitative immunoglobulins</td>
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<td>α1-Antitrypsin level</td>
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aggravating factors; pattern of symptoms (either seasonal or perennial, continual or episodic); and diurnal variation such as nocturnal or morning awakening. Particular attention should also be paid to need for and frequency of oral corticosteroids, current and past treatment and response, unscheduled visits to the primary care physician, ED, or urgent care, history of hospitalizations with or without intensive care admissions and intubations, and impact on quality of life (eg, missed days from school, limitation of activity, and family life). In addition, any past history of early-life airway injury (eg, bronchopulmonary dysplasia) and personal or family history of atopy should be established. Details regarding the home environment, parents’ work, school, and daycare should be determined along with the presence of furred pets and exposure to second-hand tobacco smoke [7–9]. This information will help identify the symptoms likely due to asthma, help determine the likelihood of asthma, assess the severity of asthma, and identify possible precipitating factors [7].

During the physical examination, attention should be given to the upper and lower respiratory tract and skin evaluation [7,9]. The presence of wheezing, hyperexpanded thorax, prolonged expiratory phase, or evidence of atopy (rhinitis, atopic eczema) supports the diagnosis [7]. However, due to the variability of asthma, the physical examination may be normal [8,10]. The finding of digital clubbing suggests an alternative diagnosis.

Spirometry is essential to the evaluation and diagnosis of asthma in older children because it provides objective measurement of lung function and can determine the presence of airway obstruction, reversibility, and variability [8]. Correlation between a patient’s recognition or physician’s assessment of symptom severity and degree of airflow obstruction may be poor. However, even children with symptoms and medication use consistent with severe persistent asthma may have normal lung function on spirometry [11]. The spirometric predicted values for each patient are based on age, sex, weight, height, and race. Asthma is characterized by a reduction in the volume of air exhaled during the first second (FEV₁) and the ratio of FEV₁ to forced vital capacity [7–9]. Peak expiratory flow rate (PEFR) less than 80% predicted and forced expiratory flow (FEF₂₅–₇₅) less than 65% predicted also indicate obstructed airways, but these measures are less reliable [9]. Variation of more than 20% of PEFR in the morning versus in the late afternoon also indicates asthma [7–9]. The spirometric hallmark of asthma is improvement of FEV₁ by at least 12% after administration of a bronchodilator [7,8]. Both spirometry and PEFR are effort-dependent and require cooperation from the patient in order to achieve proper technique and reliable results. A developmental and maturity level that is achieved between 6 and 7 years for spirometry and between 4 and 5 years for PEFR [8,9] makes these tests less useful in younger children. Newer forms of lung function testing, such as forced oscillation, are being evaluated for clinical utility in infants and young children. Compared with spirometry, lung function determined by oscillometry recently was found to correlate better with asthma in 4-year-old asthma-prone children [12]. While forced oscillation has the benefits of being noninvasive, well tolerated, and effort independent, selection of reference values and interpretive strategies confounds current clinical use.

When spirometry is normal or symptoms atypical but asthma is still suspected, a provocation challenge with methacholine or histamine may be performed [7–9]. However, bronchial provocation, while sensitive for a diagnosis of asthma, has low specificity and should be undertaken in a trained facility [8,9]. Further studies may help to establish the diagnosis of asthma and rule out other diseases in the differential diagnosis (Table 1 and Table 2) [7,9,13]. A chest radiograph should be obtained at some point in patients of all ages who have symptoms suggestive of asthma to rule out other causes.

### How is asthma diagnosed in young children?

Objective measurement of lung function in toddlers is difficult at this time, making diagnosis in this age-group challenging. In addition, wheezing and cough are common symptoms in other childhood illnesses such as bronchiolitis [7,8]. Therefore, the diagnosis is clinical and based on history, physical examination, and response to treatment. Asthma in toddlers is “underrecognized, underdiagnosed, and undertreated” [9] and is frequently diagnosed as chronic bronchitis, recurrent pneumonia, or reactive airways disease. The younger the child who wheezes or the more atypical the history, the more likely that recurrent wheezing is due to a disease process other than asthma (Table 2). These other entities must be ruled out. Once this is done and if symptoms persist, asthma treatment should be initiated; response to therapy supports the diagnosis of asthma [8,9]. Conversely, poor response to therapy indicates the possibility of diagnoses other than asthma or a concomitant condition perpetuating symptoms [7,9]. Wheezing in the first year of life is not a prognostic factor for asthma or for more severe asthma later in life [8].

### What is the role of allergy testing?

The association of asthma and atopy is well known, with 60% of children with asthma having at least one positive skin test to an aeroallergen [14]. Assessment of allergic status, while not being of diagnostic value for asthma, can help
identify allergic triggers of asthma that the patient should subsequently avoid. The National Asthma Education and Prevention Program (NAEPP) guidelines recommend that patients with persistent asthma requiring daily therapy be evaluated for allergies [7]. The preferred method of allergy identification is skin puncture tests as opposed to measurement of serum-specific IgE using the radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA) [8,9]. Allergy skin testing by a trained specialist is safe, accurate, and clinically relevant, and a wide range of allergen extracts are available.

• What are risk factors for the development of asthma?

For most children with asthma, the disease starts early in life, with 75% having symptoms before age 3 years [14]. Asthma clusters in families, suggesting that it is a heritable disease, although no particular gene or group of genes has been identified with certainty [8]. Likely, the combination of a genetic predisposition for asthma with certain environmental exposures leads to the development of asthma. Numerous epidemiologic studies have been undertaken to investigate risk factors for the development of asthma so that effective treatment or prevention can be initiated in children at high risk.

The main risk factors for the development of childhood asthma are personal history of atopy, family history (especially maternal) of asthma, and male gender [14]. Other risk factors considered to be significant include exposure to environmental tobacco smoke (ie, second-hand tobacco smoke) prenatally and postnatally, lower respiratory tract infection with respiratory syncytial virus (RSV), and sensitization to the fungus Alternaria [14]. Many other risk factors for the development of asthma have been evaluated, such as daycare attendance, lack of breast-feeding, immunizations, prematurity, diet, non-RSV respiratory infections, exposure to pets, dust mites, and cockroach, indoor and outdoor pollution, obesity, and low birth weight [8,14–16]. The “hygiene hypothesis” suggests that lack of environmental exposure to endotoxins in early life can influence subsequent development of the immune system, resulting in a TH2 bias where the cytokine milieu is skewed toward the development of allergies and asthma [17]. Evidence implicating some of these potential risk factors for asthma is conflicting, and their true effects remain unclear.

Like the number of asthma risk factors currently being investigated, strategies for asthma prevention are numerous. They include breast-feeding, dietary interventions, and decreasing exposure to aerallergens, tobacco smoke, and infections [8,18–20]. Until asthma risk factors are definitively proven and their interaction with genetic host factors and

### Table 2. Differential Diagnosis of Cough and Wheeze in Children

<table>
<thead>
<tr>
<th>Location</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Upper respiratory tract</td>
<td>Allergic rhinitis</td>
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<td></td>
<td>Infectious rhinitis</td>
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<tr>
<td></td>
<td>Rhinosinusitis</td>
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<td></td>
<td>Adenoidal or tonsillar hypertrophy</td>
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<td>Foreign body</td>
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<td>Middle respiratory tract</td>
<td>Laryngeal web</td>
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<td></td>
<td>Laryngotracheomalacia</td>
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<td></td>
<td>Esophageal foreign body</td>
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<td></td>
<td>Tracheoesophageal fistula</td>
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<tr>
<td></td>
<td>Tracheal or bronchial stenosis</td>
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<tr>
<td></td>
<td>Tumor</td>
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<tr>
<td></td>
<td>Respiratory papillomatosis</td>
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<tr>
<td></td>
<td>Croup</td>
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<tr>
<td></td>
<td>Pertussis</td>
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<tr>
<td></td>
<td>Epiglottitis</td>
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<td></td>
<td>Laryngotracheobronchitis</td>
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<td></td>
<td>Toxic inhalation</td>
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<td></td>
<td>Vocal cord dysfunction</td>
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<tr>
<td></td>
<td>Vascular ring</td>
</tr>
<tr>
<td></td>
<td>Foreign body</td>
</tr>
<tr>
<td></td>
<td>Laryngeal nerve palsy</td>
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<tr>
<td>Lower respiratory tract</td>
<td>Asthma</td>
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<tr>
<td></td>
<td>Viral bronchiolitis</td>
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<td></td>
<td>Cystic fibrosis</td>
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<td></td>
<td>Cilia dyskinesia</td>
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<td>Bronchopulmonary dysplasia</td>
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<td></td>
<td>Foreign body</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td></td>
<td>Chronic aspiration</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hemosiderosis</td>
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<tr>
<td></td>
<td><em>Chlamydia trachomatis</em> infection</td>
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<tr>
<td></td>
<td>Obliterative bronchiolitis</td>
</tr>
<tr>
<td></td>
<td>Toxic inhalation</td>
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<td></td>
<td>Tumor</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation syndrome</td>
</tr>
<tr>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td>Congenital cardiac disease</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>α1-Antitrypsin deficiency</td>
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</tbody>
</table>
environmental exposures established, primary prevention of asthma cannot be specifically and aggressively pursued.

**History**

Over the past 8 months, the patient’s cough has become more frequent, occurring daily for the past month such that she uses albuterol 3 times per day. She denies chest tightness, shortness of breath, and wheezing. Nocturnal symptoms have not been noted. She was seen by her physician 2 weeks ago, who recognized that her asthma was not controlled and prescribed montelukast 5 mg daily and budesonide dry powder inhaler 1 inhalation twice daily. The patient tried this regimen for 1 week, but there was no noticeable improvement in her symptoms, likely because of the short duration of use and suboptimal inhaler technique as she forgot to hold her breath after inhalation. She has been hospitalized for respiratory distress with wheezing twice in the past 8 months and 2 additional times in her lifetime. She has not required endotracheal intubation or admission to the intensive care unit. She was prescribed two 5-day courses of oral corticosteroids during these hospitalizations, which significantly relieved her symptoms. She has perennial clear rhinorrhea with occasional sneezing and nasal congestion. Evaluation for sinusitis, gastroesophageal reflux disease (GERD), and pertussis are negative.

Past medical history is significant for eczema. Family history is negative for atopy and asthma. Environmental history reveals that she lives in a 60-year-old house with radiator heat but no air conditioning, 2 cats, and wall-to-wall carpeting, and exposure to second-hand tobacco smoke are also significant. Pertinent physical examination findings are obesity, allergic-appearing nasal mucosa, and atopic dermatitis. Risk factors for persistent asthma in the case patient include personal history of atopy, environmental tobacco smoke exposure, and possibly, obesity and pet exposure.

Asthma can present with only chronic cough (ie, cough-variant asthma). This type is seen especially in young children, and because the cough usually occurs at night (between 2 and 4 AM), evaluation during the day is normal [7,8]. In addition, the cough often occurs after exercise, an upper respiratory infection, or exposure to allergic and nonallergic triggers and is usually not responsive to antitussives or antibiotics [1]. Helpful clues in the diagnosis are PEFR variability and response to inhaled anti-inflammatory or bronchodilator medications [7]. Entities that can mimic cough-variant asthma are GERD, postnasal drip, sinusitis, habit cough, or use of angiotensin-converting enzyme inhibitors [8].

- **When is consultation with an asthma specialist recommended?**

Consultation by asthma specialists is cost-effective [21] and should be considered for patients who have experienced life-threatening asthma exacerbations; have not met goals of asthma therapy (see below); have atypical signs and symptoms; have complicating diagnoses (eg, vocal cord dysfunction, GERD, sinusitis); require additional diagnostic testing (eg, allergy skin testing); require additional education and guidance; may be candidates for specific allergen immunotherapy; have severe persistent asthma; required continuous oral corticosteroid therapy or high-dose inhaled corticosteroids (ICS) or required 2 or more bursts of oral corticosteroids in a year; are less than 3 years of age with moderate or severe persistent asthma; or have a history suggesting an occupational or environmental exposure as the source of asthma [7]. The guidelines [9] developed by the Joint Task Force on Practice Parameters offer additional reasons to consult an asthma specialist.

- **How is asthma severity determined?**
Asthma severity is based on the combination of subjective and objective findings (eg, frequency of daytime and nocturnal symptoms and lung function) before treatment [8,22] (Table 3). However, the asthma severity index described in the Global Initiative for Asthma (GINA) guidelines provides 2 strategies for classifying asthma severity based on whether the patient is currently on therapy or naive to treatment. In addition, while very similar to the NAEPP guidelines, the GINA guidelines have a different daytime symptom frequency for mild intermittent and persistent asthma and also classify asthma severity using frequency and extent of exacerbations, physical activity limitations, and use of a short-acting β₂-agonist (SABA) [8]. Patients should be given the highest classification in which any one of their features appears. These criteria are not static: as patients achieve control of their asthma for a period of time, treatment can be stepped down, and if control continues patients should be reclassified. The converse is also true [8,22]. In our experience, some patients with asthma do not fit neatly into severity classification guidelines. For instance, patients who classify as mild intermittent asthma but have severe exacerbations are difficult to classify and can be challenging to treat. Such obstacles remind us that guidelines describe a broad approach to management and that treatment plans must be individualized to the patient.

### Diagnosis

The allergist informs the patient’s mother that her daughter’s symptoms are consistent with moderate persistent asthma. Given the positive allergy skin testing to multiple aeroallergens, the physician also makes a diagnosis of allergic rhinitis. Further history reveals that the girl’s cough began when the cats were adopted 3 years ago and is worse during the late summer and early fall months. This information in conjunction with her positive allergy skin tests to cat and ragweed suggests that allergic asthma triggers are present. In addition, her cough worsens when her father smokes cigarettes in her presence and with upper respiratory infections, indicating nonallergic triggers for her asthma.

- **What are the goals of asthma therapy?**

Current treatment guidelines are designed to achieve the following goals of therapy: prevent chronic and troublesome asthma symptoms; maintain normal or near normal pulmonary function; maintain normal activity levels; prevent recurrent asthma exacerbations; minimize the need for ED visits or hospitalizations; provide optimal pharmacotherapy with minimal or no adverse effects; and meet patients’ and families’ expectations of and satisfaction with asthma care.

### Table 3. Asthma Severity Based on Criteria Prior to Therapy

<table>
<thead>
<tr>
<th>Severity</th>
<th>Days with Symptoms</th>
<th>Nights with Symptoms</th>
<th>PEFR or FEV₁ (% predicted)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe persistent</td>
<td>Continual</td>
<td>Frequent</td>
<td>≤ 60</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Daily</td>
<td>&gt; 1 night/week</td>
<td>&gt; 60 but &lt; 80</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>&gt; 2 days/week but &lt; 1 time/day</td>
<td>&gt; 2 nights/month</td>
<td>≥ 80</td>
</tr>
<tr>
<td>Mild intermittent</td>
<td>≤ 2 days/week</td>
<td>≤ 2 nights/month</td>
<td>≥ 80</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in the first second of expiration; PEFR = peak expiratory flow rate. (Adapted from reference 22.)

*Patients older than 5 years.

The NAEPP and GINA guidelines recommend using a stepwise approach to treating asthma in order to gain and maintain control of asthma; that is, medications are increased or decreased in response to level of asthma control. The treatment regimen is determined by asthma severity. The preferred approach is to treat aggressively at a level higher than the patient’s severity in order to achieve prompt control [7]. Once control is achieved and sustained, therapy can be stepped down cautiously, reducing the dose of ICS by 25% every 2 to 3 months. Stepping down therapy is also useful in determining the minimum amount of therapy needed to maintain control. Conversely, if asthma control is not reached on therapy within 4 to 6 weeks, stepping up treatment can be considered after reviewing patient compliance, technique with devices, avoidance measures, and evaluation for comorbid conditions that can alter asthma control [7,8]. The stepwise approach for managing asthma as recommended by the NAEPP and GINA guidelines is not meant to
replace clinical judgment. Treatment plans should be individualized to the specific needs and circumstances of the patient and developed as a collaborative effort between the patient and clinician.

Pharmacotherapy

The medications used to treat asthma are divided into 2 general classes: long-term-control and quick-relief medications [7]. Long-term-control medications (also known as “controllers” in the GINA guidelines [8]) are taken on a daily basis and include anti-inflammatory agents, long-acting bronchodilators, and leukotriene modifiers (LTM) [7]. According to the NAEPP’s 2002 update, the initial preferred long-term-control medication for children of all ages with persistent asthma is ICS, not LTMs, cromolyn, or nedocromil [22]. The report’s review of randomized controlled trials shows that compared with as-needed β₂-agonists, ICS improved long-term outcomes, including fewer courses of oral corticosteroids, urgent care visits, and hospitalizations. The report also found limited data from studies comparing ICS with cromolyn, nedocromil, theophylline, or LTM that suggest ICS therapy is more effective in improving asthma outcomes. Based on these data, the NAEPP recommends ICS as the preferred long-term-control medication for children older than 5 years [22] (Table 4). Because similar data for children younger than 5 years is lacking, current recommendations for this age-group are based on expert opinion and extrapolation from studies in older children [22] (Table 5). The report further recommends that LTM be used as alternative therapy, not preferred treatment. At least 50% of patients appear to not respond to either LTM or ICS [23].

The GINA guidelines differ from the NAEPP guidelines in regard to alternative therapy in moderate persistent asthma and the addition of theophylline, LTM, and long-acting oral β₂-agonists in severe persistent asthma for all children. Likewise, for children younger than 5 years, the GINA guidelines recommend medium-dose ICS therapy alone for moderate persistent asthma versus the combination therapy recommended in the NAEPP guidelines [8]. In regard to infants and young children, long-term-control therapy should be strongly considered for (1) patients who have experienced more than 3 episodes of wheezing that lasted more than 1 day and affected sleep and who have identifiable risk factors for the development of asthma and (2) patients who require symptomatic treatment more than twice weekly and who have severe exacerbations as frequently as every 6 weeks [22]. Even though ICS have been shown to improve outcomes in asthma, review of the literature reveals that there is insufficient data to determine if early treatment with these medications prevents disease progression [22]. In addition, despite proper dosing of these medications, some patients require daily or every other day oral corticosteroids to control their asthma.

Inhaled long-acting β₂-agonists (LABA) relax airway smooth muscle to antagonize bronchoconstriction. These agents should not be used for relief of acute exacerbations since tolerance to their effects develops [24] and they do not address the inflammatory processes in asthma. LABA can be used to prevent exercise-induced bronchospasm and as an adjunct to anti-inflammatory medications for persistent asthma [7]. In the NAEPP’s 2002 update, review of the literature showed that the addition of inhaled LABA to low-to-medium doses of ICS in the treatment of moderate persistent asthma improves lung function, decreases symptoms, and decreases use of SABA [22]. As a result, the treatment guidelines recommend this therapy as an element of preferred treatment and theophylline or LTM as alternative therapy [22] (Tables 4 and 5). Again, the recommendation to use combination therapy applies to patients older than 5 years, and the data on which this recommendation is based have been extrapolated to children younger than 5 years [22]. While low- or medium-dose LABA plus LTM or medium-dose ICS alone can be used in this age-group, LABA preparations for children younger than 5 years are not available, another reminder that some patients do not neatly fit into the guidelines.

Quick-relief medications, or “ relievers,” include SABA

Table 4. Recommended Treatment for Adults and Children Older Than 5 Years

<table>
<thead>
<tr>
<th>Severity</th>
<th>Daily Medication</th>
<th>Preferred Quick-Relief Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe persistent</td>
<td>High-dose ICS and inhaled LABA</td>
<td>Inhaled SABA</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Low- or medium-dose ICS and inhaled LABA</td>
<td>Inhaled SABA</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>Low-dose ICS</td>
<td>Inhaled SABA</td>
</tr>
<tr>
<td>Mild intermittent</td>
<td>No daily medication needed</td>
<td>Inhaled SABA</td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroids; LABA = long-acting β₂-agonist; LTM = leukotriene modifier; SABA = short-acting β₂-agonist. (Adapted from reference 22.)
and anticholinergics (ie, ipratropium bromide). They provide rapid relief of bronchoconstriction and associated symptoms of cough, chest tightness, wheezing, and dyspnea. Systemic corticosteroids are considered a quick-relief medication due to their effects in treating asthma exacerbations by preventing progression, aiding recovery time, preventing relapses, decreasing need for ED visits or hospitalizations, and reducing morbidity [7,8]. Other therapies have been used to treat acute asthma exacerbations such as heliox, intravenous magnesium, and inhaled heparin, but data on their use are limited.

Inhaled SABA used on an as-needed basis for acute symptoms is the mainstay of therapy for mild intermittent asthma and must be available for all patients with persistent asthma (Tables 4 and 5). However, if quick-relief medication is being used on a daily basis or is increased, then long-term-control medication should be initiated or supplemented [7,8]. SABA have been shown to have predictable, dose-related, potency-related adverse effects and may increase airway hyperresponsiveness [25].

**Are the recommended asthma medications safe?**

Much of the concern over medication safety in the treatment of childhood asthma centers on corticosteroids. Generally, ICS are well tolerated and safe at the recommended doses. Local adverse effects are well known and include oral candidiasis, dysphonia, and reflex cough. Bronchospasm is rare. Thrush is one of the most common side effects, occurring more frequently in adults than children. Thrush can be prevented by using a spacer device, by rinsing the mouth with water after inhalation, by administering doses on a less frequent dosing schedule, and by using the lowest possible dose to achieve asthma control. Dysphonia is usually associated with increasing doses of ICS and vocal stress and can be prevented by using a spacer device, temporarily reducing dose, and vocal rest. Reflex cough and bronchospasm can be diminished by employing slower rates of inhalation, use of a spacer device, and pretreatment with inhaled SABA [7].

Systemic adverse effects of asthma therapy have been identified, especially with high doses of ICS or in individuals sensitive to lower doses. The systemic effects in children likely have gained more attention because ICS are used for longer periods of time, perhaps a lifetime, and are often initiated during periods of rapid growth. The widely accepted conclusions based on current group data regarding growth reveals that growth velocity is decreased in the first year in children receiving ICS but final adult height is unaffected [26,27]. In the 2002 NAEPP update, the long-term effects of chronic ICS on children’s vertical growth, bone mineral density, ocular toxicity, and suppression of the hypothalamic-pituitary axis were examined. Systematic review of the literature suggested that use of ICS at recommended doses does not have long-term clinically significant or irreversible effects on these 4 parameters [22]. As with any medical therapy, the potential development of adverse effects must be weighed against the risks of uncontrolled disease.

**What nonpharmacologic interventions should be part of the treatment plan?**

Education

Asthma education is central to effective asthma management. A Cochrane review and systematic review and meta-analysis of the literature showed that education can reduce morbidity associated with the disease [28,29]. Likewise, a controlled clinical trial found asthma education to be cost-effective in children [30]. Education includes individualized instruction to the caretaker or child on the proper tools and knowledge to manage complex medication regimens, to initiate avoidance measures, to recognize and treat exacerbations, and to effectively communicate with health care providers [7,8].
With education, patients and their families eventually gain the confidence and skills to manage their asthma.

The NAEPP guidelines recommend that patient education begin at the time of diagnosis and continue through each clinician-patient interaction [7]. Patients must understand the basic pathophysiology of asthma so that the rationale for treatment is clear. They also should understand how to self-monitor symptoms and peak flows with use of a written, individualized daily self-management plan and action plan for acute exacerbations and how to keep an asthma diary to track symptoms, peak flows, and use of quick-relief medication. Particular attention should be given to instructing patients how to use different inhaler devices, including dry powder and metered dose inhalers, since technique differs between devices. Metered dose and dry powder inhalers are practical and generally preferred for children older than 4 years, while nebulizer therapy is often used for infants and young children. The clinician should encourage compliance with treatment and avoidance measures for environmental triggers [7,8,10]. It is important to highlight the role of different arms of therapy (eg, long-term-control medications versus quick-relief medications) as well as indications for use. Patient education should be tailored to the individual needs of the patient, taking into consideration cultural or ethnic beliefs [7–10]. Finally, a partnership should be established between patients/families and health care providers, including ancillary staff such as nurses and respiratory therapists. This partnership allows patient and clinician goals to be integrated into the treatment plan. Patient education is a continual process that includes review and revision of treatment goals, daily self-management plans, action plans for exacerbations, review of inhaler technique, and promotion of communication between patient, family, and health care provider over time [7].

Avoidance of Triggers

Avoidance of allergic and nonallergic triggers is an important component of asthma management. As discussed, allergic triggers can be investigated by skin puncture tests or the less sensitive in vitro specific IgE testing (RAST, ELISA). Once allergens are identified, specific environmental control measures to reduce exposure in the home, school, or daycare environment can be implemented. Common inhaled allergens include but are not limited to animal dander, dust mite, cockroach, molds, and pollens. The best animal dander control measure is removal of the animal from the home; however, if this is not possible, keeping the animal out of the patient’s bedroom, bathing the pet weekly, and adding filters on air ducts are other alternatives. Dust mite avoidance focuses on encasing pillows and the mattress and box spring with impermeable covers, washing bedding weekly in hot water, reducing humidity to less than 50%, and removing carpeting. Using poison bait or traps as well as discarding garbage and exposed food helps decrease cockroach exposure. To reduce mold growth, eliminate water sources such as humidifiers and clean moldy surfaces. To reduce pollen exposure, patients should remain indoors with air conditioning and windows closed during the season in which the patient is affected, and outdoor clothes drying should be avoided [7–10]. Single interventions are less effective than broad, sweeping measures. Patients with asthma should also receive the influenza vaccine yearly.

Although testing for nonallergic triggers of asthma is not possible, avoidance measures still can be undertaken to reduce exposure and effects on asthma. Environmental tobacco smoke is a significant irritant leading to asthma exacerbations and is considered a risk factor for the development of childhood asthma. Avoidance of environmental tobacco smoke may require cessation of smoking in the home, work, or daycare environment. Other nonallergic triggers that should be avoided include air pollution, fumes, and strong odors [7–10].

Monitoring and Self-Management

Periodic assessment and monitoring of asthma by clinicians and patients provides the opportunity to continue asthma education and allows health care providers to readily follow asthma signs and symptoms, pulmonary function, level of function, recent history of exacerbations, and patient’s and family’s level of satisfaction. Physicians also can monitor different aspects of pharmacotherapy such as side effects, changes in dosages, adherence, inhaler technique, and use of oral corticosteroids and quick-relief medication [7,10]. Whether stepping therapy down or up, periodic assessments are essential to determine if the goals of therapy are being met. While the frequency of follow-up visits is based on clinical judgment, some patients may need evaluation on a more frequent basis [7]. Patients on oral steroids should be seen every month, while most patients with well-controlled asthma can be seen every 3 to 6 months.

A cornerstone of asthma management is self-management. Skills to facilitate self-management include PEFR monitoring and a written individualized self-management plan [7–10]. These 2 tools are commonly employed in both adults and children with asthma, but whether they improve outcomes remains controversial. Systematic reviews of the effectiveness of PEFR monitoring and written action plans [31–36] and randomized studies of PEFR monitoring and written self-management plans in children have had conflicting results [31,36–38]. Personal experience suggests that certain individuals can benefit from using peak flow data, while others obtained no apparent benefit and the data did not predict exacerbations or control. In the NAEPP 2002 update, review of the literature showed that data neither support nor discredit the benefits of using written action plans when compared to medical management alone [22].
Cochrane review concluded that self-management education in adults that included written action plans reduced ED visits and hospitalizations and improved lung function [33]. Therefore, the report recommends the incorporation of written action plans for asthma self-management in patients with moderate or severe persistent asthma and patients with a history of severe exacerbations [22]. The report also addressed whether written action plans should be based on symptoms or PEFR monitoring. The systematic review of the literature again neither supports nor refutes the conclusion that PEFR-based action plans are superior to symptom-based plans. As a result, the NAEPP recommendations are unchanged; PEFR monitoring should be considered in patients with moderate or severe persistent asthma [22].

**Initiation of Therapy**

After consultation with the allergist, the family medicine physician prescribes a dry powder combination therapy with low- to medium-dose ICS (fluticasone) and an inhaled LABA (salmeterol) (medium-dose budesonide or fluticasone by metered dose inhaler with or without LTM would also have been appropriate) for long-term control and a SABA via metered dose inhaler as a quick-relief medication. The family medicine physician reviews the role of each of the medications and explains inhaler technique. A topical nasal steroid spray and nonsedating oral antihistamine for allergic rhinitis is also prescribed, which should improve control of her asthma as well. The family medicine physician reinforces the importance of eliminating or at least minimizing the patient’s exposure to dust mite, cat, ragweed, and environmental tobacco smoke and suggests ways to avoid these triggers as initially discussed by the allergist. Finally, both physicians recommend that the patient pursue a weight management program coordinated with an after-school activity of aerobics/stretching/meditation, peer discussion, and nutrition, participate in exercise and sports, and receive the influenza vaccine annually. The patient is instructed to follow-up in 6 weeks with the family medicine physician and thereafter every 3 to 6 months. Follow-up with the allergist in 6 months is encouraged.

**Follow-up**

At the follow-up visit, the patient and her mother report that they have been able to properly monitor PEFR and incorporate these measurements into her written action plan for asthma self-management. Likewise, she is able to reliably perform spirometry on follow-up visits. The patient is able to prevent the development of oral candidiasis by rinsing her mouth after administration of ICS. Over the course of 3 months, the family medicine physician steps down her therapy to the lowest possible dose as her asthma becomes controlled. The patient’s mother expresses satisfaction with the management of her daughter’s asthma but is also concerned about whether the asthma will be a problem beyond her childhood years.

At the 6-month follow-up with the allergist, asthma education topics are reviewed and questions from the patient and her mother are addressed.

- **What is the patient’s prognosis?**

The natural history of childhood asthma is a frequent concern of patients and their families. A commonly asked question is, Will my child outgrow asthma? A study by Martinez et al [39] helps clarify the natural history of childhood asthma and suggests that prognosis for this disease may depend on phenotype. In this prospective cohort study, newborns were followed through age 6 years and assessed for wheezing. The children were divided into 4 phenotypes: 1) those who never developed wheezing; 2) those who had wheezed in the first 3 years of life but not at 6 years (transient early wheeze); 3) those who did not wheeze in the first year of life but did wheeze at age 6 (late onset wheeze) and; 4) those who wheezed at 3 and 6 years (persistent wheeze). Further analysis determined that those with transient early wheeze were more likely to have mothers who smoked tobacco and had lower lung function at birth. This group likely represents patients with congenitally smaller airways that predispose them to wheezing early. Children with late-onset and persistent wheezing were more likely to have mothers with asthma, to be male, and to be atopic. However, children with persistent wheezing were also more likely to have reduced lung function at age 6 years, to have higher serum IgE levels at age 9 months, to have eczema, and to have mothers who smoked [39]. It is likely that asthma will be a lifelong illness for this patient. However, with proper therapy, education, avoidance measures, adherence, and medical follow-up, her asthma can be successfully managed.

**Conclusion**

In recent decades, the medical community’s knowledge and understanding of the complexities of asthma have increased substantially. Indeed, elucidating the pathophysiology of asthma has led to great advances in diagnosis and management. Despite this, some aspects of asthma remain to be clarified, and numerous investigations are underway to achieve this goal (see Sidebar, page 168). In the meantime, the current available treatment guidelines provide clinicians with the tools to effectively treat patients with asthma in an individualized fashion.
Pediatric Asthma

New Developments in Asthma Management

Although asthma is an inflammatory lung disease, current diagnostic and monitoring methods do not directly measure lung inflammation. Well-known procedures such as bronchoscopy (the diagnostic gold standard) with either biopsy, bronchial brushings, or lavage and specific allergen provocation testing have been proposed as methods to evaluate asthma, but these invasive procedures pose an element of risk and their use largely remains experimental [9,40,41]. Bronchial provocation with methacholine, histamine, exercise, or cold air is an established technique that aids in the diagnosis of asthma if the patient’s history is suggestive but the physical examination and spirometry are normal [9]. Recently, adenosine 5’-monophosphate and mannitol have been investigated as potentially superior bronchoprovocative agents [42,43]. A less invasive method of direct measurement of airway inflammation being investigated entails inducing sputum production with nebulized hypertonic saline. Cells and inflammatory mediators in the sputum samples are determined, specifically evaluating for eosinophils and their proteins. Induced sputum analysis may assist in the diagnosis and treatment of asthma, titration of ICS to the minimal effective dose, and determination of asthma exacerbations [40]. This method yields comparable results to the more invasive gold standard bronchoscopy. However, inducing sputum with hypertonic saline can induce bronchospasm, and the induction procedure, processing of samples, and cell counting is time-consuming, limiting this technique for routine clinical situations [40,44]. In addition, this method has not been well studied in children.

Assessment of eosinophilic inflammation by measuring serum and urinary eosinophil markers has been proposed. However, 2 randomized studies have shown that these markers are not as useful as individual tools as initially hoped [45,46].

Exhaled nitric oxide (NO) has been studied extensively and appears to be the most useful marker of airway inflammation. Moreover, measurement of exhaled NO is noninvasive and provides readily available and reproducible results. NO is a free radical synthesized by the oxidation of l-arginine to NO and l-citrulline by NO synthases. Exhaled NO is increased in patients with asthma and decreases with administration of ICS [40]. The gold standard technique to measure exhaled NO can be performed by patients as young as age 4 years, and alternative methods for measurement in younger children and infants have been described [41,47]. Despite standardization of the method, no reference values for children have been established. Exhaled NO correlates with sputum eosinophil counts, but extensive studies comparing exhaled NO to bronchoscopy results have not been performed. Studies suggest that exhaled NO may serve as a method to diagnose asthma, monitor treatment response and compliance, and assess for asthma exacerbations [40,41,47]. Current problems with utilizing exhaled NO in a clinical setting include the high cost of chemiluminescence analyzers (method of NO measurement) and confounding sources of NO such as the nasopharynx and NO in ambient air [48].

In 2003, omalizumab was approved for the treatment of moderate to severe persistent asthma in patients aged 12 years and older. Omalizumab is a humanized monoclonal antibody targeted to IgE. Randomized, double-blind, placebo-controlled trials showed that omalizumab improved asthma symptom scores, reduced exacerbations, improved lung function, reduced the use of quick-relief medications, and improved quality of life; it also was associated with fewer emergency department visits and hospitalizations and lower ICS doses [49–52]. Potential disadvantages include the high cost of treatment and need for subcutaneous injections every 2 to 4 weeks. Dosing is based on total serum IgE and weight. Other therapies being explored include allergen vaccination with immunostimulatory DNA, anti-interleukin therapies, sublingual and oral immunotherapy, cytokines, and cytokine inhibitors. Moreover, as the genetics of asthma becomes more clear and specific genes are identified, pharmacotherapy research may be targeted to particular genes, allowing treatment to be individualized according to genotype. For example, measuring exhaled NO and urinary leukotriene levels may be helpful in predicting who will respond to ICS and LTMss, respectively [53].
CASE-BASED REVIEW

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Pediatric Asthma: Current Concepts

DIRECTIONS: Each of the questions below is followed by 4 possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. A 7-year-old child with asthma has daytime symptoms 3 times per week, symptoms 1 night per month, and normal FEV₁ on spirometry. The asthma severity classification in this patient is
   (A) Mild intermittent
   (B) Mild persistent
   (C) Moderate persistent
   (D) Severe persistent

2. Preferred “controller” (daily) treatment for a 5-year-old patient with moderate persistent asthma is
   (A) Cromolyn
   (B) Leukotriene modifier
   (C) Medium-dose inhaled corticosteroid
   (D) Low-dose alternate-day oral steroids

3. Diseases of the middle respiratory tract that should be excluded when assessing for asthma in the pediatric population include all of the following EXCEPT
   (A) Congenital cardiac disease
   (B) Foreign body
   (C) Vocal cord dysfunction
   (D) Pertussis

4. Diagnoses that complicate asthma include all of the following EXCEPT
   (A) Gastroesophageal reflux disease
   (B) Sinusitis
   (C) Allergy
   (D) Streptococcal pharyngitis

5. All asthma treatment plans should include
   (A) Avoidance, pharmacotherapy, patient education, immunotherapy
   (B) Avoidance, pharmacotherapy, periodic assessment and monitoring, patient education
   (C) Avoidance, self-management, periodic assessment and monitoring, anti-IgE therapy
   (D) Pharmacotherapy, aromatherapy, patient education, self-management
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