132 Pediatric Asthma

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Introduction

A mother brings in her 3-year-old son because he has recurrent respiratory symptoms.

He coughs at night, when he laughs or cries, or runs outside. He has had post-tussive emesis on occasion. Colds settle into his chest and he has been diagnosed with bronchitis, croup, and pneumonia several times.

He is usually treated with antibiotics and has been given albuterol breathing treatments on several occasions which helped his symptoms. The last time he was sick he received 5 days of oral steroids, which was very beneficial. He is nasally congested on most days. His mother states he seems to be susceptible to colds and he is sick more frequently than he is well.

He was full term and his immunizations are up to date. He has not been hospitalized nor has he had surgical procedures. When he was an infant he had hives and vomiting with cow's milk formula and scrambled eggs. He tolerates dairy and eggs now.

He is an only child and he attends day care 5 days a week.

His mother has allergies and his father had asthma when he was a child. His maternal cousin has eczema and peanut allergy.

He is not presently on medications.

Physical exam reveals a well nourished happy 3 year old with height and weight at the 75%.

He has pale swollen nasal turbinates with clear discharge bilaterally. He has mild scarring of the tympanic membranes and shotty posterior cervical lymph nodes bilaterally. Cardiovascular exam is normal. His chest has normal configuration and his lungs are clear to auscultation; however, after running in the exam room he begins to cough.

The skin demonstrates dry, erythematous patches in the antecubital and popliteal fossae.

He does not have clubbing or cyanosis or edema of the extremities.

Does this child have asthma? Does he have risk factors for asthma? What is the differential diagnosis of a child with these recurrent respiratory symptoms? What is the severity classification? What is appropriate workup and treatment plan for this child?

Will his symptoms remit or persist over time?

Definition/Classification

The Global Initiative for Asthma (GINA) guidelines define asthma descriptively as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night or in early morning. These episodes are usually associated with widespread but variable airflow obstruction which often is reversible either spontaneously or with treatment."

Asthma is a syndrome. A syndrome is defined as "an aggregate or set of concurrent symptoms indicating the presence and nature of a disease." Such an aggregate can be recognized only if it is associated with clear criteria for doing so. Asthma is a syndrome because there is no readily available genetic, blood, or pulmonary function test that can be used to objectively diagnose it, particularly in young children in whom it usually starts. Consequently, it is not surprising that a variety of underlying physiologic disorders may result in the constellation of symptoms that are consistent with asthma.

The diagnosis of asthma is usually made clinically based upon the history and response to asthma medications. In older children and adults, pulmonary function studies (spirometry) may be done before and after bronchodilator; however, many patients particularly those with cough variant asthma do not demonstrate obstruction on spirometry. To assist in making the diagnosis, the GINA guidelines recommend that the following questions be asked with positive responses increasing the likelihood that the patient has asthma.

- Has the patient had an attack or recurrent attacks of wheezing?
- Does the patient have a troublesome cough at night?
- Does the patient wheeze or cough after exercise?

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- Does the patient experience wheezing, chest tightness, or cough after exposure to airborne allergens or pollutants?
- Do the patient's colds "go to the chest" or take more than 10 days to clear up?
- Are symptoms improved by appropriate asthma treatment?

Etiology

Atopy

Many studies such as the Tucson study and the PEAK trial have shown that allergy plays an important role in the development of asthma. In addition, total IgE is a strongly heritable trait. In a genome-wide association study, functional variants in the gene encoding the alpha chain of the high affinity receptor for IgE (FCER1A) on chromosome 1q23 (rs2251746 and rs2427837) were strongly associated with total IgE. The most significant single nucleotide polymorphism (SNP) influenced the cell surface expression of FCER1A on basophiles, and genome-wide expression profiles indicated an interesting novel regulatory mechanism of FCER1A expression via GATA-2. Polymorphisms within the RAD50 gene on chromosome 5q31 were consistently associated with IgE levels and increased the risk for atopic eczema and asthma and STAT6 was confirmed as susceptibility locus modulating IgE levels.

Obesity

Obesity has been shown to be a risk factor for the development of asthma. Infant weight gain has been shown to be associated with the development of asthma later in childhood. Though weight gain is not associated with daily asthma symptoms or lung function it is associated with an increased need for prednisone and urgent care visits. Conversely, smaller weight gain is associated with fewer exacerbations.

Obese patients with asthma are more likely to report continuous symptoms, miss more work days, use short acting beta agonists, use inhaled corticosteroids (ICS), and use controller medication than matched nonobese asthmatics. They also are less likely to be in asthma remission and are more likely to have severe persistent asthma.

Environmental Factors

Environmental tobacco smoke (ETS) is the best understood and likely the most significant indoor air pollutant. It not only confers a significant increase in risk of developing asthma, it also causes an increase in IgE sensitization as well as an increase in asthma severity. Asthma is more severe in former smokers both before and after treatment than in those who have never smoked. Though smoking cessation is an important goal in treatment of asthmatic patients, smoking initiation needs to be reduced, especially in teenagers. This is because cigarette smoking has a persistent, dose-dependent, negative impact on the response to treatment in patients with uncontrolled asthma even after smoking cessation.

Outdoor air pollutants with significant impact on asthma include nitrogen oxides (NO_x), sulfur oxides (SO_x), and ozone along with particulates. Sensitivity to these exposures does vary and has a genetic component. For example, arginases (encoded by ARG1 and ARG2 genes) have an important effect on asthma pathogenesis through effects on nitrosative stress. Arginase expression is upregulated in asthma and varies with TH2 cytokine levels and oxidative stress. Both ARG1 and ARG2 genetic loci are significantly associated with asthma. Within each locus, the ARG1 haplotype is associated with reduced risk and the ARG2 haplotype is associated with increased risk of asthma. The effect of the ARG1 haplotype is associated with the presence of atopy and ambient ozone. Atopic children living in high-ozone communities with the ARG1 haplotype have a reduced asthma risk.

Infections

Many common respiratory viruses have been linked to recurrent wheezing in infancy and early childhood, including rhinovirus and respiratory syncytial virus. In addition, some of these viruses are linked to as high as a 40% increase in risk for asthma later in childhood. The "hygiene hypothesis" suggests, however, that infections during early childhood influence the immune system in such a way that the risk of developing asthma is reduced.

In the childhood origins of asthma study (COAST), 289 newborns were followed prospectively. The investigators found that even one moderate to severe rhinovirus infection during infancy drastically increases the risk of recurrent wheezing and possibly of the subsequent development of asthma. Apparently, healthy infants who experience repetitive severe viral respiratory infections develop recurrent wheezing, possibly as a consequence of lung damage and/or airway remodeling. It also seems that infants born with poor antiviral responses and/or airway hyperresponsiveness (AHR) are prone to have repetitive severe illnesses which may increase their risk of

developing asthma. This effect is most pronounced if the infants wheeze with rhinovirus infections as opposed to infections with RSV which is less specific for development of asthma.

Epidemiology

The world wide prevalence of asthma is increasing. Epidemiological studies based upon symptom questionnaires of parents of young children (6–7 years old) and older children (13–14 years old) in the ISAAC study Phase I (International Study of Asthma and Allergies in Children) show variability between countries with highest prevalence rates of asthma symptoms in 12 months in UK, Ireland, New Zealand, and Australia followed by South, Central, and North America, Kuwait, and South Africa. The lowest rates were reported in several Eastern European countries (Romania, Georgia, Albania, Uzbekistan), Greece, China, India, and Ethiopia. In Southeast Asia the lowest prevalence of symptoms was in Malaysia and China and the highest in Japan, Thailand, Philippines, and Hong Kong.

Studies show patterns of increasing prevalence of asthma worldwide especially in Western countries and as communities become more urbanized. Asthma symptoms in Chinese adolescents was lowest among residents of mainland China and greater for those in Hong Kong and for those who immigrated to Canada and was highest for those born in Canada. A significant increase in the prevalence of asthma in the Kingdom of Saudia Arabia was noted from 8% in 1985 to 23% in 1995 in a questionnaire of children between 8 and 16 years which was hypothesized to be related to changes in environmental factors of increased tobacco smoke and indoor animal exposure. Although the prevalence of asthma symptoms tends to be more common in affluent countries, the symptoms are more severe in less affluent countries.

According to data from the US National Center for Health Statistics, the burden from childhood asthma seems to have leveled off after many years of increasing. Asthma prevalence in the USA increased by an average of 4.3% per year (from 3.6% to 6.2%) between 1980 and 1996. Asthma attack prevalence remained constant between 1997 and 2000. After a decrease between 1980 and 1989, the asthma office visit rate increased by an average of 3.8% per year from 1989 to 1999. The asthma hospitalization rate grew by 1.4% per year from 1980 to 1999. Although childhood asthma deaths are rare, the asthma death rate increased by 3.4% per year from 1980 to 1998. Children aged 0–4 years had the largest increase in prevalence and had greater health care use, but adolescents had the highest mortality.

Unfortunately, racial and ethnic disparities remain large for asthma utilization and mortality. The asthma burden is borne disproportionately by black children. Racial disparities were largest for asthma hospitalizations and mortality: compared with white children. In 1998–1999, black children were more than three times as likely to be hospitalized, and in 1997–1998 they were more than four times as likely to die from asthma.

In the USA, the Centers for Disease Control and Surveillance published data from surveys of 2001–2003 reporting higher rates for current asthma for children (8.5%) than for adults (6.7%), for blacks (9.2%) than whites (6.9%) and for those of Puerto Rican descent (14.5%) than those of Mexican descent (3.9%) and the rates of asthma deaths in the USA increased during 1980–1990, but have decreased each year since 2000. In the2007 report of The National Health Interview Survey, the greater prevalence of asthma in minority populations occurred in non-Hispanic black children more likely to have ever been diagnosed with asthma (20%) than Hispanic children (13%) or non-Hispanic white children 11%).

In early childhood, asthma is twice as prevalent among boys as girls. As the asthma rate among young girls increases, however, the gap in prevalence of asthma in early childhood between boys and girls decreases. The ratio reverses in adolescence and early adulthood with asthma becoming more common in women though the reasons for this gender-related difference is unclear.

In a survey of randomly chosen adult patients and parents of children with current asthma in the USA, surveyors asked about short-term symptoms (4-week recall), long-term symptoms (past year), and activity limitation. The surveyors found that 10.7% had mild intermittent disease while 77.3% had moderate to severe persistent disease suggesting that a majority of the US population with asthma experiences persistent rather than intermittent asthma.

Pathogenesis: Including Genetics

Asthma is known to be an inheritable condition. Whole genome screens are beginning to identify gene-rich regions that are of special relevance to the development of asthma and atopy. Candidate genes for the development of asthma include the many genes that regulate IgE production, the proliferation and maturation of eosinophils and mast cells, and epithelial barrier function. Some

of the better defined genes contributing to the development of asthma, include Arg/Gly, 17q12–21, ADAM-33, and the filaggrin (FLG) gene. In addition, several genes have been identified that effect patient response to medications. These genes include Arg/Gly alleles of the beta2 receptor as well as components of the leukotriene pathway. The identification of novel genes for asthma suggests that many genes with small effects rather than few genes with strong effects contribute to the development of asthma. These genetic effects are modified interactions with a person's environmental exposures, though some genetic influences also operate independently of environmental factors. A number of important gene–environment interactions have been identified which may aid in the identification of individuals who are particularly susceptible to environmental hazards.

Since asthma is an inflammatory airway disease that is associated with upregulation of TH2-type cytokines, genes encoded in the corresponding cluster on chromosome 5q on T cells and inflammatory cells are of particular interest. This upregulation along with local airway susceptibility factors leads to airways hyperresponsiveness, variable airflow obstruction, and in some cases to airways remodeling. Two examples are polymorphisms involving IL-4 receptors and the enzymes controlling cysteinyl leukotriene production.

In addition to inflammation of the airways caused by atopy, interactions between the respiratory epithelium and other environmental factors such as virus infections, ETS, and pollutants also contribute to tissue damage and abnormal repair responses that can lead to remodeling. Previously unknown genes involved in this interaction have recently been identified. Dipeptidyl peptidase 10 (DPP10) and disintegrin and metalloproteinase-33 (ADAM-33) are examples of newly identified genes that are associated with asthma that are preferentially expressed in the airway epithelium and underlying mesenchyme.

Leukotrienes contribute to the inflammatory process in asthma, to the extent that leukotriene modifiers are mainstays in the therapy of asthma. Leukotriene pathway genes have been shown to be involved in the pathogenesis of and treatment response in asthma. Certain genetic variants in these pathway genes also appear to be associated with the development of aspirin-exacerbated respiratory disease, and pharmacogenetic response. Those specific variants include two variants in the 5-lipoxygenase gene that are both associated with response to 5-lipoxygenase inhibition and to leukotriene receptor antagonists (LTRA), variants in genes encoding the two cysteinyl LTRA, and a leukotriene C4 synthase promoter polymorphism that has been associated with the risk of asthma exacerbations.

Transcription factors control the development of TH1 and TH2 T-cells. Two of these, the T-box transcription factor and GATA3, appear to be involved in the development of asthma and atopic diseases. Another homeobox transcription factor H.20-like homeobox 1 (HLX1) interacts closely with the T-box transcription factor. Nineteen polymorphisms have been identified in this gene, and seven of these are associated with increased likelihood of developing childhood asthma. These appear to work by decreasing promoter transactivation disrupting specificity protein-transcription factor binding.

Another T cell-specific T-box transcription factor (TBX21) induces the differentiation of T-cells to a TH1 phenotype and prevents the formation of TH2 cells in combination with the homeobox transcription factor HLX1. Three SNPs in this gene increased the risk of developing childhood asthma significantly. In addition, two polymorphisms in the promoter region influence TBX21 promoter activity. A specific combination of TBX21 and HLX1 polymorphisms increases the asthma risk by more than threefold, which demonstrates a synergistic effect on asthma risk.

Null mutations in the FLG gene have been shown to be major risk factor for. A meta-analysis of 24 studies on FLG mutations, eczema, and asthma showed strong associations with eczema and also that certain mutations are significantly associated with asthma though the strongest effects were for the combination of asthma and eczema. No association between FLG mutations and asthma in the absence of eczema. The two common FLG-null mutations R501X and 2282del4 and three recently identified rare FLG variants (R2447X, S3247X, 3702delG) increased the risk for eczema more than threefold, conferred a substantial risk for allergic rhinitis, and increased the risk of asthma occurring in the context of eczema but not of asthma alone.

In addition to pathogenesis, genetic factors also may explain ethnic disparities not explained otherwise by environmental, social, cultural, or economic factors. In particular, differences in susceptibility allele frequencies have been observed that increase the risk of asthma in certain populations. A meta-analysis of African-ancestry populations yielded three SNPs in genes of potential biologic relevance to asthma and allergic disease: rs10515807, mapping to the alpha-1B-adrenergic receptor (ADRA1B) gene on chromosome 5q33; rs6052761, mapping to the prion-related protein (PRNP) gene on chromosome 20; and rs1435879, mapping to the DPP10 gene on chromosome 2q12.3–q14.2. Though certain forms of these SNPs are associated with minority populations in the USA, their

significance with respect to disparities remains to be determined.

Bronchial hyperresponsiveness (BHR) and asthma are linked to chromosome 5q31–q33 with some evidence that the protocadherin 1 gene (PCDH1) has several novel sequence variants. In seven out of eight populations from The Netherlands, UK, and USA, PCHD1 gene variants were significantly associated with BHR both in families with asthma and in general populations. PCDH1 mRNA and protein are expressed in airway epithelial cells and in macrophages.

Several studies have suggested that chromosome 19q13.1–3 contains asthma susceptibility genes. In particular, support has been found for an asthma/lung function susceptibility locus (48.9–49.1 Mbps) which apparently is localized to the plasma urokinase plasminogen activator receptor (PLAUR) gene. PLAUR SNPs in the 5′ region, intron 3, and 3′ region are associated with asthma and BHR susceptibility and predict FEV_1 and plasma PLAUR concentrations. SNPs in the 5′ region showed an association with asthma, FEV_1, and BHR. These same were associated with plasma PLAUR levels as well as with FEV_1 decline in subjects with asthma. The association of PLAUR with lung function decline appears to support a role for PLAUR in airway remodeling in asthma.

Pathology

The GINA guidelines first recommend that asthma severity be classified as intermittent, or as mild, moderate, or severe persistent based on specific criteria (Table 132.1). This classification is determined with the assumption that the patient has yet been treated since once treatment is initiated the symptoms are expected to improve. The NHLBI guidelines have similar criteria for the four categories of asthma severity.

Once treatment is initiated, both guidelines recommend that the degree of asthma control should be monitored to determine whether treatment needs to be increased, remains the same, or even decreases. The criteria for asthma control outlined in the GINA guidelines are shown in Table 132.2. In clinical practice, the need for simple methods to assess asthma control has led to investigation of a variety of candidate measures. The method that is most effective depends on the outcome that is to be achieved. If the goal is to minimize symptoms and exacerbations, then the measurement should utilize standardized measures of symptoms such as the Asthma Control Test (ACT). On the other hand, if reduction of eosinophilic pulmonary inflammation is the goal, then measures such as eosinophilic cationic protein (ECP) should be used. The question is how the various measures relate to each other and how well they lead to the ultimate asthma outcome, which is a reduction in long-term morbidity and mortality while maximizing the patient's quality of life.

Both the NHBLI guidelines and the GINA guidelines emphasize the need to monitor and maximize asthma control as a major goal of treatment. The main reason for this new emphasis on control is due to the recognition that the adverse effects of taking medications when they are not necessary may offset the advantage of complete medical control. It may be easy to prescribe all of the medicine all of the time; however, it is not as easy to prescribe just the right amount of treatment to reach a balance between the benefits of medical control and the

Table 132.1
Classification of asthma before treatment * (Gina Guidelines 2008, P23)

Intermittent Asthma
Symptoms less than once a week
Brief exacerbations
Nocturnal symptoms not more than twice a month
FEV1 or PEF >80% predicted
PEF or FEV1 variability <20%
Mild Persistent
Symptoms more than once a week but less than once a day
Exacerbations may affect activity and sleep
Nocturnal symptoms more than twice a month
FEV1 or PEF >80% predicted
PEF or FEV1 variability <20–30%
Moderate Persistent
Symptoms daily
Exacerbations may affect activity and sleep
Nocturnal symptoms more than once a week
Daily use of inhaled short-acting B2-agonist
FEV1 or PEF 60–80% predicted
PEF or FEV1 variability >30%
Severe Persistent
Symptoms daily
Frequent exacerbations
Frequent nocturnal asthma symptoms
Limitation of physical activities
FEV1 or PEF <60% predicted
PEF or FEV1 variability >30%

*The worst feature determines the severity classification

Table 132.2
Levels of asthma control (Gina Guidelines 2008, Chapter 2 Diagnosis and Classification P 23)

Characteristic	Controlled	Partly Controlled	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/ awakenings	None	Any	
Need for reliever/ Rescue treatment	None (twice or less/week)	More than twice/week	
Lung Functions (FEV or FEV1)	Normal	<80% predicted or personal best (if known)	
Exacerbations	None One or more/ year*	One in any week+	

*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate

+By definition, an exacerbation in any week makes that an uncontrolled asthma week

Lung function is not a reliable test for children 5 years and younger

There are several validated questionnaires which may be used to access asthma control including the Asthma Control Test (ACT) and Childhood Asthma Control Test (C-ACT) (http://www.asthmacontrol.com), the Asthma Therapy Assessment Questionnaire (ATAQ) (http://www.ataqinstrument.com), the Asthma Control Questionnaire (ACQ) (http://www.goltech.co.uk/Asthma1.htm).1 The questionnaires may be used by researchers and clinicians in the assessment of patient asthma control at follow up visits

harms of treatment. Patients have been asserting their desire to take less medicine for a long time by choosing to be nonadherent to recommendations made by their physicians. Their volitional decisions to take less medicine while physicians prescribe more medicine leads to a question of what the best method is for measuring asthma control and what effect such measurements could have on outcomes. For this reason, it is essential that any treatment of asthma consider both the reduced burden of disease while at the same time recognized reduction in the burden of treatment.

The measures of asthma control that will be considered in this chapter include validated measures of symptoms (e.g., ACT), pulmonary function testing (PFT), airway hyperresponsiveness (AHR), exhaled nitric oxide (eNO), induced sputum for eosinophils, ECP and exhaled breath condensates (EBC). Though other measures such as bronchial alveolar lavage and bronchial biopsy may provide a more definitive assessment of airways inflammation, they are not appropriate for routine clinical use in an outpatient setting.

Clinical Manifestations: Symptoms, Signs

The NHBLI guidelines emphasize the need for assessment of daytime and nighttime asthma symptoms as a measure of control. Symptoms of asthma generally consist of recurrent cough, wheeze, and difficulty breathing that vary in intensity spontaneously, or in response to bronchodilators or to provoking agents. To facilitate quantification of asthma symptoms as a measure of control, the five-item ACT was developed. As a screening tool, the ACT shows good agreement with specialist's rating of asthma control. The test has been validated for identifying patients with poorly controlled asthma. It also has been found to be a useful tool for helping physicians to identify patients with uncontrolled asthma and to help them follow patients' progress. It has been found to be internally consistent, repeatable, and sensitive to changes in asthma control. It correlates well with specialists' ratings of asthma control, pulmonary function tests, and with treatment recommendations. An ACT score of 19 or less provides an optimum balance of sensitivity and specificity for detecting uncontrolled asthma.

Pulmonary Function Testing

Asthma is a condition that is manifested by airways obstruction due to cellular infiltration and edema leading to narrowing. Since it is not practical to directly measure the degree of narrowing in a patient's airways, it is necessary to use surrogate measures of airflow resistance such as FEV_1 and FEV_1/FVC. Even so, there is some debate about the utility of measures of airflow limitation in patients with asthma. The NHLBI recommends that objective measures of airflow limitation be obtained at regular intervals and has included them as a component of asthma severity and control. The measurements are easy to perform, noninvasive, and relatively inexpensive. For these reasons, PFT has become the standard test used in clinical trials and it has achieved widespread use in clinical

practice. Use of PFT does have its limitations, however. Though patients with decreased FEV_1 have been shown to have an increased risk of having an asthma exacerbation, even patients with an $FEV_1 > 80\%$ predicted have a 20% of having an exacerbation.

Airway Hyperresponsiveness

AHR is defined as the concentration of a provoking agent that is required to reduce FEV_1 by 20% from baseline. This can be expressed either as the provocation concentration (PC20) or the provocation dose (PD20), which is the concentration multiplied by the volume delivered. AHR is used to measure the sensitivity of airways to provoking agents and also to define underlying mechanisms of drug action and bronchoconstriction. The most common agents used for AHR include methacholine, histamine, AMP, exercise, cold air, and dry air (eucapnic hyperpnea). Recently, hyperosmolar mannitol also has been used. Allergens can also be used to determine the sensitivity of an allergic individual over time in response to a new treatment.

In general, methacholine, an agent that directly activates smooth muscle cells in the lung, is used for making the diagnosis of asthma by identifying AHR and to guide treatment. Exercise is used as a model of exercise-induced asthma, though eucapnic hyperpnea also is being tested as a surrogate to identify exercise-induced asthma. These techniques indirectly cause AHR by enhancing the release of prostaglandins, leukotrienes, and histamine. There is increasing interest in agents that act indirectly to release mediators to better define the underlying mechanisms of inflammation.

To determine predictors for failed reduction of ICS in patients with well-controlled asthma taking a stable dose of an ICS, the ICS was halved every 8 weeks in a clinical trial. The significant predictors of a failure of ICS reduction were AHR to both histamine and mannitol at baseline and during the dose-reduction phase. Response to mannitol and percent sputum eosinophils were significantly greater before a failed ICS reduction than before the last successful ICS reduction, whereas there were no significant differences in symptoms, spirometry, or eNO.

Tests of AHR are well suited to monitor the success of a treatment strategy. In one study comparing AHR-guided treatment using methacholine with recommendations from the NHLBI guidelines, investigators found that the AHR-guided strategy led to more effective asthma control and greater improvement of airways inflammation. In particular, patients treated according to the AHR strategy had a 1.8-fold lower rate of mild exacerbations than did patients treated with the reference strategy. In addition, FEV_1 improved more and there was a greater reduction in thickness of the subepithelial reticular layer in the AHR strategy group.

Eosinophil Cationic Protein

Eosinophil cationic protein (ECP) is another measure that has been studied as a potential biomarker of eosinophilic airway inflammation. ECP has been measured in serum, plasma, sputum, saliva, and bronchoalveolar lavage (BAL) fluid; however, serum and sputum are the most common sources. The concentration of ECP correlates well with airway inflammation but not with AHR. Since it can be elevated in other atopic diseases, measurement of ECP is not diagnostic for asthma, though it has been shown to be useful for assessing asthma severity and compliance with anti-inflammatory medications. ECP also has the potential to be used as a guide for managing ICS therapy.

Serum concentrations of ECP are significantly higher during acute asthma exacerbations than during clinical remissions. In addition, patients with an FEV_1 less than 75% predicted have higher ECP concentrations than those with a higher FEV_1. ECP also is higher in children with chronic asthma symptoms compared with non-asthmatic, non-atopic children.

Induced Sputum

The value of sputum induction in pediatric asthma lies in its potential to directly and noninvasively assess airway inflammation in children. Induced sputum is one way to determine which types of cells (neutrophils or eosinophils) are predominant in the airways of a patient with asthma. The challenge is to get a good sample that is reflective of the pulmonary cellularity and that is not too contaminated by saliva. For adults, this is relatively straight forward though it is less easy in children due to their lack of cooperation in the maneuver and to their tendency to swallow sputum rather than spit it out. In one study using induced sputum neutrophil and eosinophil counts as markers of inflammation, the presence of sputum neutrophils but not eosinophils was associated with lower postbronchodilator FEV_1 suggesting that neutrophilic airway inflammation is associated with poorer response to treatment.

Since exacerbations of asthma are likely to be due to an increase in airway inflammation, an increase in the number of cells in induced sputum may prove to be a marker of an impending exacerbation. Both increases in sputum eosinophils and eNO correlate with decreased morning peak flows and FEV1. In addition, higher sputum percentage eosinophils are associated with atopy, increased bronchodilator reversibility, lower FEV_1/FVC ratio, higher eNO levels, circulating eosinophils, sputum and serum eosinophil cationic protein, and greater asthma severity. Tailored asthma interventions based on sputum eosinophils are beneficial in reducing the frequency of asthma exacerbations in patients with asthma.

Exhaled Breath Analysis

International asthma guidelines recommend that a variety of clinical tests be used to monitor asthma control. These have focused largely on identifying variable airflow obstruction and responses to provoking agents, bronchodilator, or corticosteroids. A growing interest has recently been directed toward identifying noninvasive markers of airway inflammation including gases such as nitric oxide and EBC collection. Exhaled breath analysis is used to measure inflammation and oxidative stress in the respiratory tract, to make a diagnosis of airway disease and as a guide to monitor and adjust therapy. EBC is obtained by cooling exhaled air. Its composition is believed to mirror that of the fluid lining the airways. While EBC is still considered to be a research tool, other exhaled components such as eNO measurement are closer to clinical practice.

Exhaled Nitric Oxide

Fractional eNO (FeNO) is a gas that is increased in atopic asthma, correlates with various inflammatory markers, and is reduced by treatment with corticosteroids and antileukotrienes but not by beta2-agonists. Since NO is a gas at room temperature, it does not liquefy on cooling and therefore it is not an EBC. FeNO is a reliable marker of eosinophilic airway inflammation that can be measured using standardized techniques in children as young as 4 years. FeNO is believed to be another surrogate marker of inflammation. Until recently, measurement of FeNO was limited to research facilities and secondary care institutions. With the development of portable nitric oxide analyzers (MINO; Aerocrine AB; Smidesvagen, Sweden) routine measurement of FeNO is more available for clinical practice without the need for the more expensive units (NIOX; Aerocrine) without losing any accuracy in measurement.

FeNO appears to represent a distinct parameter from other, more clinically based measurements. The concentration of FeNO is significantly elevated in uncontrolled asthma and decreases after anti-inflammatory therapy. A low eNO appears to be predictive of not having an exacerbation of asthma in the near term. An elevated FeNO in preschool-aged children with moderate-to-severe intermittent wheezing also is associated with an increased risk of respiratory tract infections and with aeroallergen sensitization.

Current asthma guidelines recommend adjusting treatment on the basis of lung function tests and symptoms. Unfortunately, neither of these has been shown to be closely associated with airway inflammation. This leads to the question of whether FeNO can be used to manage asthma as effectively as the more standard measurements. FeNO concentrations do seem to change more rapidly in response to administration of ICS than FEV_1 or AHR suggesting that it is more sensitive to changes in inflammation than these other measures. By using it to guide step-down treatment, FeNO measurement seems to reduce the use of ICS without compromising asthma control. There have been studies with different results. Clearly, further research is needed to fully define the value of FeNO measurements as a guide to asthma treatment.

Exhaled Breath Condensates

Collection of EBC is a noninvasive method for obtaining samples from the lungs to assess airway inflammation and oxidative stress and may be useful in the assessment of childhood asthma. EBC contains large number of mediators including adenosine, ammonia, hydrogen peroxide, isoprostanes, leukotrienes, nitrogen oxides, peptides, and cytokines. Concentrations of these mediators are affected by lung diseases and can be altered by therapeutic interventions. In addition, the pH of EBC changes in response to the presence of respiratory diseases. Recently, the American Thoracic Society/European Respiratory Society Task Force on EBC provided recommendations for the collection and measurement of EBC. The recommendations included instructions to "collect EBC during tidal breathing using a noseclip and a saliva trap; define

cooling temperature and collection time (10 min is generally sufficient to obtain 1–2 mL of sample and well tolerated by patients); use inert material for condenser; do not use resistor and do not use filter between the subject and the condenser."

Increased concentrations of 8-isoprostane, hydrogen peroxide, nitrite, and 3-nitrotyrosine are found in EBC in inflammatory lung diseases. Increased levels of lipid mediators are found in these diseases, with a differential pattern depending on the nature of the disease process. With the development of smaller, less expensive, and more sensitive analyzers, exhaled breath analysis may become available for diagnosis and monitoring of asthma in the routine clinical practice.

Exhaled 8-isoprostane is a stable marker of oxidative stress. Mean exhaled 8-isoprostane concentrations are significantly higher in steroid-naive asthmatic children than in healthy children. Children with asthma who take ICS also have higher 8-isoprostane levels than normal children suggesting that it is not normalized by inhaled steroid therapy. Exhaled 8-isoprostane also does not correlate with duration of asthma, dose of inhaled steroids, or FeNO.

Aldehydes and glutathione are additional biomarkers of oxidant and antioxidant status in asthma, respectively. Children with exacerbations had higher concentrations of malondialdehyde (an oxidant), that decreased after steroid therapy, than healthy controls. Conversely, glutathione (an antioxidant) concentrations are decreased during exacerbations and increased with steroid therapy.

Cysteinyl leukotrienes (Cys-LT) and isoprostanes are inflammatory metabolites derived from arachidonic acid whose levels are increased in the airways of asthmatic patients. Isoprostanes are relatively stable and specific for lipid peroxidation, which makes them potentially reliable biomarkers for oxidative stress found during asthma exacerbations. Both substances decrease with prednisone treatment but not as much as FeNO suggesting that corticosteroids may not be fully effective in reducing oxidative stress in children who are having an exacerbation of asthma.

EBC pH and ammonia concentrations have been used as a noninvasive method to measure acid-base status in the airways of asthmatics. Both pH and ammonia are lower in patients with asthma than in healthy control groups. In addition, both values increase with ICS-treatment. At low pH values found in the airways, nitrite, which is an endogenous airway compound, is converted to nitric oxide (NO) in quantities that may be sufficient to account for the concentrations of NO found in the expired air of asthmatics.

Diagnosis

2007 NHLBI Guidelines

In 2007, the NHLBI published the third complete update of its guidelines for the diagnosis and treatment of asthma. Though previous versions emphasized careful diagnosis of asthma, categorization of severity and treatment based on that severity, little emphasis was placed on long-term assessment of asthma control. The third update corrected that oversight with its emphasis on ongoing measurement of asthma control with corresponding modification of treatment. There are a number of reasons for this including a growing recognition that maintaining asthma control is an important component of prevention of adverse outcomes such as emergency department (ED) visits, hospitalizations, and death.

Since asthma is a heterogeneous syndrome with some phenotypes responding better to certain treatments than others, identification of markers that can help to predict asthma exacerbations is an important component of control, particularly since asthma severity changes frequently over time. This heterogeneity includes variability in clinical, physiologic, and pathologic parameters. Children with asthma frequently move between severity categories, particularly if they start with inadequate asthma control to begin with.

To achieve the best control, asthma severity needs to be determined repeatedly using assessments of lung function, albuterol use, and asthma symptoms along with new markers of eosinophilic airway inflammation. There is increasing evidence that management guided by measures of inflammation is superior to other measures leading to a reduction in exacerbation frequency and a reduction of inhaled corticosteroid dosage.

International GINA Guidelines

In addition to the NHLBI guidelines in the USA, the GINA guidelines have been accepted as an international set of asthma guidelines. Since it was formed in 1993, the GINA, a network of individuals, organizations, and public health officials, has played a leading role in disseminating information about the care of patients with asthma based on a process of continuous review of published scientific investigations. A comprehensive workshop report entitled "A Global Strategy for Asthma Management and Prevention," first published in 1995, has been widely adopted, translated, and reproduced, and forms the basis for many national guidelines. The 2006 report contains important

new themes. First, it asserts that "it is reasonable to expect that in most patients with asthma, control of the disease can and should be achieved and maintained," and recommends a change in approach to asthma management, with asthma control, rather than asthma severity, being the focus of treatment decisions. The importance of the patient–care giver partnership and guided self-management, along with setting goals for treatment, are also emphasized. Management of asthma according to the GINA guidelines has been shown to be associated with a decrease in asthma morbidity and mortality.

Differential Diagnosis

Since asthma is a heterogeneous syndrome that is defined clinically, a number of related diseases can have similar symptoms. It is important to distinguish between alternative diagnoses and conditions that trigger underlying asthma. For example, Respiratory Syncytial Virus and Rhinovirus are common triggers of asthma in young children. Though it is possible for a child with RSV to wheeze, it is more common for a patient with asthma to wheeze when infected with these viruses than for a nonasthmatic person. These viruses therefore are triggers of asthma and not alternative conditions. Similarly, Gastroesophageal Reflux Disease (GERD) is a trigger for asthma as opposed to an alternative disease since most children with this condition do not wheeze.

The most common alternative disorders in children include Cystic Fibrosis which often manifests as a chronic obstructive lung disease, Vocal cord dysfunction (VCD), congenital abnormalities of the lower airways (bronchogenic cysts, abnormal blood vessels, TE fistulae, etc.), Cardiac asthma which is actually congestive heart failure manifesting with wheezing, immotile cilia syndrome (Kartagener's syndrome if associated with situs inversus), and immunodeficiency. Other conditions such as foreign body aspiration must be considered along with various conditions associated with chronic cough such as post-viral cough, habit cough, and exposure to irritants. Children with alpha-1-antitrypsin deficiency usually present with liver disease, and COPD in a child is very rare.

Since most of these alternative diagnoses can be excluded either by history or simple diagnostic tests and most obstructive wheezing lung disorders in children actually are manifestations of asthma, it is not necessary to perform exhaustive testing in every child to rule out alternative conditions. Instead it is reasonable to prescribe a short trial of asthma treatment and evaluate the response to it. If the patient fails to improve significantly after a reasonable treatment trial, alternative conditions should then be considered.

Treatment

General Care

Trigger Avoidance

Allergen exposure in children with asthma with known sensitivity not only can increase asthma symptoms but can also trigger an asthma exacerbation. Therefore, patients with persistent asthma should be evaluated for atopy for potential of allergen exposure. This should be done by taking a careful allergy history and with either skin prick testing or in vitro testing for allergen-specific IgE. Sensitized patients should be encouraged to limit their allergen exposure.

The most common indoor allergens are dust mite, fungi, and animal dander. When indoor allergens are suspected to be present, consideration should be given to requesting an environmental home or school assessment by an environmental hygienist. Such assessments may help to identify the types and amount of exposure and can help guide avoidance recommendations.

Dust mites are considered to be an important trigger of asthma. These acarids are found in upholstered furniture, bedding, and carpeting and they feed on shed skin cells, fungi, and each other. They produce 5 μm fecal pellets that contain dust mite allergens and that become airborne when disturbed. Suggested methods for reducing exposure to dust mites include air filtration, reduction of humidity, chemical acaracides, and use of dust-mite impermeable mattress covers. Because the fecal pellets settle out of the air relatively quickly, air filtration has not been shown to be very effective for reducing dust mite exposure. Reduction of humidity to 35% can reduce dust mite populations but is hard to consistently achieve in microenvironments such as a bed because of respiration and perspiration by its human occupants. There is limited evidence that these simple interventions such as dust mite covers and chemical acaracides are effective for treating asthma. Instead, a comprehensive set of environmental control measures is likely to be required.

Exposure to pet dander from furry animals is another important trigger of asthma. There is some evidence that individuals born into houses with cats can become desensitized; however, once sensitization has occurred it is important to avoid exposure. While

avoidance would seem to be easily accomplished for sensitized individuals, the reality is that most households consider their pet to be a member of the family that they are very reluctant to part with. For that reason, a number of strategies have been evaluated for reducing pet allergen while retaining the dog or cat. The most effective has been to simply wash the dog or cat regularly to remove most of the allergen. Denaturants such as tannic acid and dilute bleach also have been proposed as ways to reduce allergen exposure. Regular use of a high-efficiency vacuum such as a HEPA or cyclonic vacuum also has been proposed as a way to reduce pet allergen exposure. Ultimately, it is likely that a combination of these approaches will be necessary to sufficiently reduce exposure so that the pet can remain in the home without triggering asthma.

Irritants trigger asthma symptoms by non-immunologic mechanisms. ETS is one of the most important indoor irritants. For that reason, all patients with asthma should be evaluated for exposure to ETS and referrals to smoking cessation programs should be offered when appropriate. Avoidance of smoke from wood burning stoves, fireplaces, and grills should be advised, as well as avoidance of strong odors, volatile organic compounds, and other respiratory irritants. Adolescents should also be screened for possible occupational exposures, particularly those who have new onset asthma.

Finally, a detailed history should be taken to identify possible, treatable comorbid conditions that may cause increased symptoms. Examples of these conditions include gastrointestinal reflux disease, aspirin sensitivity, rhinosinusitis, obesity, sleep apnea, and stress. If identified as a contributing factor, comorbid conditions should be aggressively treated.

Vaccinations

Patients with asthma are more likely to have serious health problems as the result of many infections. As a result, immunizations should be kept up-to-date with current recommendations. In particular, inactivated influenza vaccinations should be offered to all children greater than 6 months of age with asthma every fall. Children with asthma should not receive the live attenuated influenza vaccine. The 23-valent pneumococcal polysaccharide vaccine is currently only routinely recommended for adults with asthma. Children should continue to receive the 7-valent pneumococcal vaccine as part of their routine immunization schedule but it is not considered to be part of asthma treatment.

Asthma Self-management

Asthma education is an essential component of asthma management. Asthma care providers should teach patients and families the basics of asthma and medication techniques in simple language. Patients should be taught about asthma and step-down treatment. In addition, clinicians should provide written asthma action plans that include the patient's daily controller medications as well as how to recognize and handle worsening asthma symptoms. Action plans based on peak flow meter readings are no more effective than plans based on symptoms.

The Acute Intervention Management Strategies (AIMS) trial attempted to determine what management strategies are effective by following children with a variety of allergy, asthma, environmental, and quality of life assessments. They found that episodic use both of ICS and LTRA led to reductions in trouble breathing and interference with activity during episodes. This suggests that parents can use symptoms to guide the need for controller medications for long-term management of asthma.

The question of what intervention would be effective for treating an exacerbation of asthma has been extensively reviewed. There is limited evidence for the addition of a long acting beta-agonist (LABA) during an episode of asthma to prevent the need for oral steroids. Addition of or doubling the dose of an inhaled corticosteroid has not been shown to be effective. The one intervention that has been shown to be effective is to quadruple the dose of the inhaled corticosteroid at the onset of respiratory symptoms. If needed for an exacerbation, a short course of oral steroids has been found to effectively prevent relapses of asthma.

Spacers

Spacers should be considered for use with all metered dose inhalers (MDIs) when the patient is unable to coordinate an inhalation and actuation. In particular, spacers should be considered for infants and very young children. Though there does not appear to be a significant difference between the different types of spacer, it is important that it be fitted to the patient so that it can be used properly. Holding chambers, when used correctly, are as effective for

delivering an aerosol as is nebulizer delivery and they may be more effective for treating acute episodes of asthma.

The Future of Asthma

While asthma continues to be a significant global health problem, the future of asthma management appears to be bright. Over the next decade it is likely that genetic tests will identify individuals who are at high risk for developing asthma and that new treatments will be developed based on those new insights. Treatment will be personalized based on knowledge of a person's genetic makeup eliminating the "one size fits all" approach that is used today. In addition, asthma control will be monitored using sensitive biomarkers that relate to outcomes that are important. And finally, it is possible that preventative approaches to asthma will be developed so that the prevalence of this troublesome disease will decline.

Specific Treatment

The 2007 NHLBI guidelines for the diagnosis and management of asthma outline a stepwise approach to initiating various pharmacologic treatments. While initiation of treatment is based on the severity of asthma, long-term management is based on control. The recommendations are for patients to step-up treatment if control is inadequate and to maintain or step-down treatment when control is achieved to determine the least amount of treatment necessary to maintain optimal control. The specific medications recommended for each step are shown in *Table 132.3*.

Table 132.3
Stepwise approach for managing asthma

Stepwise approach for managing asthma in children 0–4 years of age	
	Preferred medications
Step 1	SABA PRN
Step 2	Low-dose ICS
Step 3	Medium-dose ICS
Step 4	Medium-dose ICS and either LABA or montelukast
Step 5	High-dose ICS and either LABA or montelukast
Step 6	High-dose ICS and either LABA or montelukast and oral systemic corticosteroid
Stepwise approach for managing asthma in children 5–11 years of age	
	Preferred medications
Step 1	SABA PRN
Step 2	Low-dose ICS
Step 3	Low-dose ICS and either LABA, LTRA, or theophylline or medium-dose ICS
Step 4	Medium-dose ICS and LABA
Step 5	High-dose ICS and LABA
Step 6	High-dose ICS and LABA and oral systemic corticosteroid
Stepwise approach for managing asthma in children >12 years of age	
	Preferred medications
Step 1	SABA PRN
Step 2	Low-dose ICS
Step 3	Low-dose ICS and LABA or medium-dose ICS
Step 4	Medium-dose ICS and LABA
Step 5	High-dose ICS and LABA and consider omalizumab
Step 6	High-dose ICS and LABA and oral systemic corticosteroid and consider omalizumab

Source: Reproduced from the NHLBI Asthma Guidelines 2007

Relievers

Short acting beta-agonists (SABAs) include albuterol, levalbuterol, and pirbuterol. These medications quickly relax bronchial smooth muscles leading to bronchodilation. These drugs are also beneficial for prevention of exercise-induced bronchospasm when used 15–20 min before exercise. The mechanism of action involves activation of adenlycyclase resulting in an increase in cAMP which in turn leads to activation of protein Kinase A which inhibits phosphorylation of myosin and lowers intracellular calcium resulting in relaxation of bronchial smooth muscle. Other benefits include reduced vascular permeability and edema and increased cillary beat frequency. Side effects include tremor, increase in heart rate, prolongation of QT interval and hypokalemia and hyperglycemia especially with frequent use.

Asthma mortality epidemics occurred in 6 countries in the early 1960s associated with the introduction of isoprenaline forte and in the 1970s in New Zealand with the introduction of fenoterol. Both of these beta adrenergic agents are nonselective with enhanced cardiovascular side effects especially in high doses and with frequent administration in persons with hypoxemia from asthma. Selective beta adrenergic agents currently in the market such as albuterol, salbuterol, and levalbuterol have not been associated with epidemics of asthma mortality.

In patients with mild asthma, scheduled use of albuterol does not provide either beneficial or deleterious effects on asthma control. Consequently, SABAs should be used as rescue medication and ideally should be necessary infrequently if the asthma is under good control. An increased need for SABA use should be viewed as a marker for increased inflammation and to signify the need to increase daily controller medications. A patient who requires frequent SABA use and is not controlled should receive stepped-up therapy with an inhaled corticosteroid and/or systemic corticosteroids because beta adrenergic agents do not provide the needed anti-inflammatory activity.

Inhaled Corticosteroids

ICS are the most potent and effective maintenance treatment of asthma and should be used in all patients who require more than infrequent use of SABA. ICS reduce airway inflammation and hyperresponsiveness. There are a large number of ICS currently available for the treatment of asthma. These medications can be increased in a stepwise fashion to obtain improved asthma control though most have a limited dose-response range. The NHBLI recommendations for the comparative daily doses of various ICS are shown in *Table 132.4*.

Table 132.4
Estimated comparative daily doses of inhaled corticosteroids

Drug	Low dose (mcg per day)			Medium dose (mcg per day)			High dose (mcg per day)		
	Age 0–4	Age 5–11	Age ≥ 12	Age 0–4	Age 5–11	Age ≥ 12	Age 0–4	Age 5–11	Age ≥ 12
Beclomethasone HFA 40 or 80 mcg/puff	N/A	80–160	80–240	N/A	>160–320	>240–480	N/A	>320	>480
Budesonide 90, 180, or 200 mcg/DPI	N/A	180–400	180–600	N/A	>400–800	>600–1,200	N/A	>800	>1,200
Budesonide inhalation suspension	250–500	500	N/A	>500–1,000	1,000	N/A	>1,000	2,000	N/A
Flunisolide 250 mcg/puff	N/A	500–750	500–1,000	N/A	1,000–1,250	1,000–2,000	N/A	>1,250	2,000
Fluticasone HFA 44, 110, or 220 mcg/puff	176	88–176	88–264	>176–352	>176–352	>264–440	>352	>352	>440
Mometasone 110 or 220 mcg/DPI	N/A	110	220	N/A	110	440	N/A	110	>440
Triamcinolone acetonide 75 mcg/puff	N/A	300–600	300–750	N/A	>600–900	>75–1,500	N/A	>900	>1,500

Source: Reproduced from the NHLBI Asthma Guidelines 2007

Though ICSs are the most commonly used asthma controller medications, responses to corticosteroids vary widely between individuals. Though it is difficult to predict who will respond and who will not, a genetic cause in the form of variations in corticotropin-releasing hormone receptor 1 (CRHR1) has been shown to be associated with enhanced response with individuals homozygous for the variants showing increased lung function response to corticosteroids.

Long Acting Beta-Agonists

LABAs are defined as beta-agonists whose half-lives are at least 12 h duration. LABAs are more lipophilic secondary to their extended side chain which leads to a longer duration of action. Medications in this class include salmeterol and formoterol. Formoterol has an onset of action within 15 min and salmeterol within 30 min. LABAs are used in combination with ICS in the maintenance of asthma and are not recommended for use as monotherapy. In the USA, packaging of LABA includes a black box warning from the Food and Drug Administration in which practitioners are advised to weigh the risks and benefits of this medication prior to use.

The GINA guidelines recommend increasing inhaled corticosteroid doses in all children with asthma not controlled on low-dose ICS before adding a long-acting beta2-adrenergic agonist, whereas NHLBI guidelines have different age-based recommendations for children. In patients younger than 5 years, NHLBI guidelines recommend increasing the inhaled corticosteroid dose before adding a LABA; in children aged 5–11 years, equal weight is given to increasing the inhaled corticosteroid dose or including add-on therapy to low-dose ICS. In adults and adolescents aged 12 years and older, GINA recommends adding a LABA to low-dose ICS in preference to increasing the dose of inhaled corticosteroid. The NHLBI guidelines give equal weight to these choices, with alternative, although not preferred, therapies including the addition of theophylline, zileuton, or LTRA to low-dose ICS.

A number of concerns were voiced in 2006 regarding the safety of the use of LABAs for treatment of asthma. These concerns included whether use of this class of drug increases the risk for hospitalization, near death, or death due to asthma, whether the increased risk was greater in African Americans, and whether individuals who are homozygous for arginine at the 16th codon of the beta2-adrenergic receptor have a poorer response or even deteriorate when prescribed LABAs. Subsequent studies addressed each of these concerns and have been consistently reassuring.

Leukotriene Modifiers

This class of medications include both LTRA (montelukast and zafirlukast) as well as a 5-lipoxygenase inhibitor (5-LO; zileuton). The NHLBI guidelines consider LTRAs to be an alternative, but not preferred monotherapy for the treatment of mild persistent asthma. They also are considered to be effective for adjunct therapy in children <12 years; however, LABAs are the preferred adjunct therapy in adults and children >12. Finally, LTRAs are indicated for treatment of exercise-induced bronchospasm. Zileuton is less preferred to LTRAs in children >12 years because of the need for liver function monitoring. LTRAs and Zileuton also may attenuate bronchoconstriction in aspirin sensitive individuals.

Oral Corticosteroids

Oral corticosteroids are potent anti-inflammatory agents whose efficacy in the treatment of asthma is well documented. Because of the many side effects, however, every consideration must be given to administering the lowest dose of oral corticosteroids for the shortest amount of time. Before prescribing oral corticosteroids for maintenance therapy it is important that the use of all other conventional asthma medications be maximized.

Short courses of oral corticosteroids have been shown to be effective for treatment of acute asthma exacerbations. In particular, when taken at the onset of a respiratory infection, a 3–5 days course of an oral steroid can reduce the risk of an ED visit or hospitalization for asthma. Once an asthma exacerbation has taken place, oral steroids are effective for treatment in the ED to reduce the likelihood of hospitalization, though they need to be given as early as possible.

Other Agents

Cromolyn sodium and nedocromil are similar but distinct medications whose anti-inflammatory properties are felt to occur via mast cell stabilization. They may be used as an alternative, but are not preferred treatment in mild persistent asthma. They also may be useful as preventative treatments prior to exercise and when a predictable

exposure to an allergen is unavoidable. Both of these agents are considered to have relatively weak anti-inflammatory effects that take time to become apparent. Their main benefit is their extremely low side effect profile.

Theophylline is a nonselective phophodiesterase inhibitor that provides some bronchodilation. Sustained-release theophylline is an alternative, but not preferred treatment of mild persistent asthma in children >5 years old. Theophylline was widely prescribed for treatment of asthma in the 1980s but fell into disuse in favor of ICS. The main drawback to theophylline is its relatively narrow therapeutic index and well-known side effects that include tachycardia, arrhythmias, nausea, hyperactivity and at higher concentrations, seizures. If theophylline is used it is necessary to monitor serum theophylline concentrations to ensure that the levels are therapeutic without becoming toxic. A number of medications interact with theophylline metabolism including cimetadine, ketaconazole, and many macrolide antibiotics.

Omalizumab

Omalizumab is a recombinant, humanized, monoclonal antibody directed to the portion of the IgE molecule that binds to mast cells and basophiles, thus preventing binding of IgE and subsequent degranulation of these cells. Omalizumab is considered to be an effective adjunct therapy in asthma patients >12 years old with moderate to severe persistent asthma and allergies documented by skin prick testing or in vitro testing. The safety and efficacy of omalizumab in children of ages 6–11 is currently under investigation.

Combinations

Given the extensive list of treatment options for controlling asthma, the question is how to determine which treatment is most appropriate for a particular individual. Both ICSs and LTRAs lead to improvement in most measures of asthma control. However, clinical outcomes, pulmonary responses, and inflammatory biomarkers such as exhaled nitric oxide eNO improve significantly more with ICS treatment than with LTRAs treatment. In addition, elevated FeNO seems to be a predictor of better response to ICS compared with an LTRA.

For moderate persistent asthma, ICSs are more effective. This was confirmed by the Pediatric Asthma Controller Trial (PACT) which found that fluticasone monotherapy and combination fluticasone/salmeterol combination provided greater improvements in asthma control days than montelukast alone. These results are not surprising given the greater anti-inflammatory effects of ICS; however, there is limited information comparing the two agents for patients with mild asthma where the anti-inflammatory effect required for control may be less.

For mild asthma it is possible that both ICS and LTRA would provide sufficient control assuming that patients respond to them equally. To determine how frequently children with asthma do respond to ICS or LTRA, a comparison study was performed in children 6–17 years of age with mild-to-moderate persistent asthma. While 17% responded to both medications, 23% responded only to fluticasone, 5% responded only to montelukast alone and surprisingly, 55% responded to neither medication. Since most patients with asthma improve with treatment, this result suggests that there is more going on than simple anti-inflammatory treatment with medications.

The GINA guidelines are similar to the NHLBI guidelines with an important difference. In the GINA and NHLBI guidelines, patients with moderate to severe asthma are advised to use ICS or an ICS/LABA combination with a SABA as reliever. Because some patients still fail to achieve guideline-defined asthma control leading to overuse of SABA reliever medication at the expense of ICS, the GINA guidelines recommend that such patients use an ICS/LABA combination for both maintenance and reliever therapy. This clearly is contrary to recommendations from the NHLBI guidelines. The GINA treatment strategy has been shown to significantly reduce the rate of severe asthma exacerbations compared with ICS/LABA plus SABA while achieving equivalent daily symptom control with a lower overall steroid load.

Finally, there has been controversy over whether ICS can modify the subsequent development of asthma in children at high risk for asthma. This is important because if ICS does modify subsequent disease development and severity, a stronger case can be made for more aggressive ICS use in young children even when they are asymptomatic. On the other hand, if disease progression is not affected by regular ICS use, it is hard to recommend that asymptomatic children receive aggressive treatment given the potential harms, both physiologic and psychological, that are associated with such treatment. In the one study that addressed this question in preschool children at high risk for asthma, 2 years of inhaled-corticosteroid therapy did not change the development of asthma symptoms or lung function during a third, treatment-free year. These findings suggest that ICS treatment does not lead to a subsequent disease-modifying effect after ICS treatment is discontinued.

Allergen Immunotherapy

Patients who do not respond adequately to pharmacotherapy or who wish to avoid long-term use of medications should be considered for allergen immunotherapy. Injection immunotherapy has been shown to be effective for the treatment of asthma in children in a meta-analysis of clinical trials In addition, sublingual immunotherapy has also shown substantial efficacy for treatment of asthma in children and may be as effective as an inhaled corticosteorid for mild persistent asthma.

Prognosis

Although many children wheeze within the first 3 years of life with viral infections, not all of these children continue to have asthma symptoms as they age. A prospective study of 6-year-old children in Tucson, Arizona found that 51% never wheezed, 19.9% wheezed at least once with viral illness during the first 3 years of life but not at 6 years (transient wheezing), 15% did not wheeze at 3 years but had wheezing at 6 years (late onset), and 13.7% had wheezing both at 3 and 6 years (persistent). Smoking by mother, lack of history of maternal atopy, and lower lung function of the child in the first 3 years of life were risk factors for transient wheezing whereas children who continued to wheeze at 6 years were more likely to have mothers with allergy and to have elevated serum IgE levels. In addition, young children were more likely to continue to wheeze at 6 and 13 years of age if they had risk factors including parental history of asthma or eczema, eosinophilia, wheezing apart from colds, and allergic rhinitis, and over 95% of children without these criteria never wheezed actively between 6 and 13 years.

Patterns of wheezing prevalence and levels of lung function appear to be established by age 6 years and do not change much after that. In a follow-up report, the prevalence of atopy and wheeze by age 16 years was similar for never and transient wheezers and for persistent and late-onset wheezers. Both transient early, and persistent wheezers had significantly lower FEF(25–75), FEV_1, and FEV_1:FVC ratio, respectively when compared to never wheezers.

The natural history of asthma is one of periods of remission followed by reemergence of symptoms in some individuals. A New Zealand cohort study of children with asthma followed into adulthood found that 14.5% continued to wheeze to age 26 years, 27.4% had remission at age 26 years, and 12.4% had a remission but relapsed by age 26 years. Risk factors for persistence and relapse of asthma were earlier onset of wheezing, sensitivity to dust mites, BHR, female sex, and smoking.

Another cohort study of babies at risk for atopy in the UK in which most of the children who wheezed before the age of 2 years and did not wheeze at 11 years did not develop allergies or bronchial hyperresponsiveness whereas 20 of 23 children who wheezed at 11 years had atopy and increased bronchial hyperresponsiveness. Those with positive skin test to egg and milk as infants correlated with asthma at 22 years of age.

Persistence of childhood asthma correlated with severity of asthma in a Canadian study. Children who were hospitalized during the first year after the diagnosis of asthma had a threefold risk of persistent asthma and those with at least four physician visits for asthma had a 2.6-fold increased risk of persistent asthma at age 12 years.

As to the long-term natural history, 30–80% of asthma patients seem to develop symptoms again later in life. This is because some patients who outgrow their asthma continue to have persistent airway eosinophilic inflammation, AHR and airway narrowing. In summary, family history of allergies, personal history of allergic rhinitis, wheezing apart from colds, more severe asthma symptoms in childhood, and lower lung function in childhood tends to be associated with persistence or relapse of asthma as adults.

Prevention

According to the NHLBI guidelines as outlined in *Table 132.5*, the goal for asthma treatment is to control asthma by reducing impairment and risk. This can be done using a stepwise approach to medications in which treatment increases as symptoms increase and decreases when symptoms decrease. To do this it is essential that patients be taught to monitor their degree of asthma control. Because asthma is a chronic disease, it is likely that the relationship between a patient and the asthma provider will be long-term necessitating that the two approach management of the asthma as partners. Referral to an asthma specialist should be considered for patients with persistent asthma for possible comanagement. Patients should receive information about identifying and avoiding asthma triggers including testing for specific IgE, environmental control and when indicated specific allergen immunotherapy. And finally, all patients with asthma should receive a written action plan so that they can control their asthma if and when it flares to reduce the likelihood of an ED visit, hospitalization, and most importantly, avoidance of death. By following these steps it

Table 132.5
Managing asthma long-term

• The goal for therapy is to control asthma by reducing impairment and risk (Evidence A).
• A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma in both the impairment and risk domains (Evidence A).
• Monitoring and follow-up is essential (Evidence B).
• Because asthma is a chronic inflammatory disorder of the airway, persistent asthma is most effectively controlled with daily long-term control medication directed toward suppression of airway inflammation (Evidence A).
• Therapeutic strategies should be considered in concert with clinician–patient partnership strategies; education of patients is essential for achieving optimal pharmacologic therapy (Evidence A).
• At each step, patients should be advised to avoid or control allergens (Evidence A), irritants, or comorbid conditions that make the patient's asthma worse (Evidence B).
• A written asthma action plan detailing for the individual patient the daily management (medications and environmental control strategies) and how to recognize and handle worsening asthma is recommended for all patients; it is particularly recommended for patients who have moderate or severe asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B). The written asthma action plan can be either symptom-based or peak-flow-based; evidence shows similar benefits for each (Evidence B).
• Referral to an asthma specialist for consultation or comanagement of the patient is recommended if there are difficulties achieving or maintaining control of asthma; if additional education is needed to improve adherence; if the patient requires step 4 care or higher (step 3 care or higher for children 0–4 years of age); or if the patient has had an exacerbation requiring hospitalization. Consider referral if a patient requires step 3 care (step 2 care for children 0–4 years of age) or if additional testing for the role of allergy is indicated (Evidence D).

Source: Reproduced from the NHLBI Asthma Guidelines 2007

should be possible for all patients with asthma to have well-controlled disease with little or no impairment.

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