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Special Considerations for Infants and Young Children

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KEY POINTS

- The care of infants and small children with suspected asthma deserves special consideration because of the potential to modulate the disease process early on and alleviate the increased morbidity associated with uncontrolled asthma in this age group.
- After confounders and masqueraders of asthma have been excluded in the evaluation of children with suspected asthma, recurrent wheezing in infants and young children still comprises a heterogeneous group of conditions with different risk factors and prognoses.
- The diagnosis of asthma in infants and small children is often based on clinical grounds and complicated by the lack of clinically available tools that meet the criteria for the definition of asthma used in older children and adults such as airway inflammation, bronchial hyperresponsiveness and airflow limitation.
- Difficulties in the management of asthma include limited effective and convenient delivery devices, complete dependence on the caregivers to carry out the treatment regimen, and an inadequate selection of medications completely devoid of adverse effects.
- A partnership approach with emphasis on education, monitoring and training is key in the effective management of chronic cough or recurrent wheezing illnesses in very young children.
- Clinical trials using as needed treatment interventions have shown favorable efficacy outcomes, aimed at preventing severe exacerbations in young children with recurrent wheezing; however, trials aimed at primary prevention are still lacking.

The prevalence of asthma has increased even in the last decade but a better understanding of the mechanisms of asthma and the availability of more effective treatment may be responsible for the stabilization of the steady increase in asthma morbidity and mortality noted since the 1980s.¹ From data in the recent National Surveillance of Asthma,² current asthma was reported in 6% of children between 0 and 4 years old, with at least two thirds having at least one asthma attack in the previous year. The most important reason why asthma in infants and younger children deserves special consideration is the fact that healthcare utilization (ambulatory, emergency department visits and inpatient hospital admissions) for children under the

age of 4 years is greater than those of other age groups.² In addition, younger children with asthma are also more likely to be readmitted to the hospital for acute exacerbations.³ In a retrospective analysis of 49 asthmatic children whose mean age was 5.2 years (range 2 months to 16 years) admitted to a community-based pediatric intensive care unit over a 10-year period, as many as 75% were 6 years or younger.⁴ The public health consequences of dealing with asthma in children include the number of missed work days parents/guardians incur in order to care for an acutely ill child. Some studies have hinted that pulmonary development in infancy can be adversely affected by asthma, resulting in a decrease in lung function of approximately 20% by adulthood.⁵

Relevant clinical practice guidelines developed in recent years have addressed special challenges in the management of asthma in this age group.^{6,7} Many issues are unique to this age group: identifying very young children with recurrent episodes of cough and wheeze associated with viral illnesses who will develop persistent asthma later in life, presence of confounding factors or disease masqueraders, who needs controller therapy and when to start treatment, what medications to use, how best to deliver the medications and how to monitor the response to treatment.

Predicting Who is Likely to Develop Persistent Asthma

Recurrent wheezing in infants and young children comprises a heterogeneous group of conditions with different risk factors and prognoses. Viral infections (respiratory syncytial virus, rhinovirus, coronavirus, human metapneumovirus, adenovirus, parainfluenza and adenovirus) are common triggers of wheezing in preschool age children, even in those who will not develop persistent asthma later on. Factors or exposures early in life such as prematurity, fetal nutrition, duration of pregnancy, viral lower respiratory tract infections in the first years of life, cigarette smoke exposure, air pollution, postnatal nutrition, breastfeeding, family size, maternal age, socioeconomic status and allergen exposure have been implicated to varying degrees. Observational studies have also demonstrated an increased risk of asthma attributed to acetaminophen exposure during prenatal periods, infancy, childhood and even adulthood.⁸⁻¹¹ Genetics, atopy and prematurity appear to be the most important host risk factors in the development of asthma.

Several types of 'wheezers' in the young age group based on time of onset and outcome (transient or intermittent vs persistent) have been identified from longitudinal studies.^{12,13} The investigators from the Tucson Children's Respiratory Group

enrolled over 1,000 newborns served by a large health maintenance organization to evaluate factors involved in early-onset wheezing in relationship to persistent wheezing at 6 years of life.¹³ About half of the children had at least one episode of wheezing by 6 years of age. Nearly one third of the cohort had at least one episode of wheezing by 3 years of age. Only 40% of children who wheezed early had persistent wheezing at age 6 years. Of the total group, 20% had at least one episode of wheezing associated with a respiratory tract infection during the first 3 years of life but had no wheezing at 6 years ('transient wheezers'), 14% did not wheeze during the first 3 years of life but had wheezing at 6 years ('late-onset wheezers'), and 15% had wheezing at age 3 and 6 years ('persistent wheezers'). The 'transient wheezers' were more likely to have diminished airway function and a history of maternal smoking and were less likely to be atopic. The 'late-onset wheezers' had a similar percentage of atopic children to 'persistent wheezers' and were likely to have mothers with asthma. Hence, there seems to be a similar genetic predisposition for the asthma phenotype characterizing both 'persistent' and 'late-onset wheezers'. Essentially all of the current natural history studies have found that allergic disease and evidence of pro-allergic immune development are significant risk factors for persistent asthma.

An asthma predictive index (API) using a combination of clinical and easily obtainable laboratory data to help identify children age ≤ 3 years with a history of wheezing at risk of developing persistent asthma was developed from the Tucson cohort.¹⁴ Information on parental asthma diagnosis and prenatal maternal smoking status was obtained at enrollment, while the child's history of asthma and wheezing and physician-diagnosed allergic rhinitis or eczema, along with measurements of blood eosinophil count, were obtained at the follow-up visits. Two indices were used to classify the children. The stringent index required recurrent wheezing in the first 3 years plus one major (parental history of asthma or physician-diagnosed eczema) or two of three minor (eosinophilia, wheezing without colds, allergic rhinitis) risk factors, whereas the loose index required any episode of wheezing in the first 3 years plus one major or two of three minor risk factors. Children with a positive loose index were 2.6 to 5.5 times more likely to have active asthma sometime during the school years. In contrast, risk of asthma increased to 4.3 to 9.8 times when the stringent criteria were used. In addition, at least 90% of young children with a negative 'loose' or 'stringent' index will not develop 'active asthma' in the school age years.

A modified version of the API (mAPI) incorporates inhalant allergen sensitization as an additional major risk factor and food allergen sensitization as an additional minor risk factor to take into account important findings from other longitudinal natural history asthma studies.¹⁵ In the Berlin Multicentre Allergy Study, additional risk factors for asthma and bronchial hyperreactivity at age 7 years included persistent sensitization to foods (i.e. hen's egg, cow's milk, wheat and/or soy) and perennial inhalant allergens (i.e. dust mite, cat), especially in early life.^{16,17} In a prospective, randomized, controlled study of food allergen avoidance in infancy evaluating the development of atopy at age 7 years in a high-risk cohort, egg, milk and peanut allergen sensitization were risk factors for asthma.¹⁸ With these additional considerations, an mAPI has been used in an early intervention study for young children with recurrent wheezing.¹⁹ Henceforth, it has been adapted by the NAEPP EPR3 asthma guidelines as a requirement along with a history of four

wheezing episodes per year lasting more than 24 hours upon which initiation of controller therapy should be considered.⁶

These wheezing phenotypes derived from epidemiologic and longitudinal data are more helpful for prognostication and usually have limited clinical utility when a medical provider is faced with a child with recurrent wheezing or chronic cough. Hence, other phenotypes may have greater relevance when management decisions have to be made or clinical trials are undertaken. For example, a symptom-based classification, i.e. episodic (wheeze only in discrete time periods, mostly associated with upper respiratory infection) vs multi-trigger (symptom also occurs with activity, laughing, crying or even at night outside of an acute illness), was proposed by the European Task Force in 2008.²⁰ However its clinical applicability is limited as children can switch between the two categories at different times, and this classification does not consider the frequency, seasonality and severity of the episodes.²¹ A preschool child may have exercise-induced wheeze only when he/she is also having an acute episode or shortly after. During the late fall, winter and early spring in most areas in the northern hemisphere, preschool children who are in regular contact with other children can develop back to back viral respiratory illnesses that can each last up to 2 weeks or even longer. A child with a viral illness requiring a hospital admission is in the same classification as a child whose viral-induced wheezing illness is treated with a bronchodilator alone. Lastly, it is not known if there is a unique immunopathologic difference that can affect treatment between the two phenotypes. Therefore, clinical guidelines suggest starting treatment based on frequency of symptoms, severity of episodes and presence of risk factors.

Confounding Factors

The first practical consideration in approaching the wheezing child is to ensure that an alternative diagnosis is not present. In addition, infants and small children have a greater degree of bronchial hyperresponsiveness (BHR), which may predispose them to wheeze.²²

The differential diagnosis of wheezing in infants and young children includes conditions such as foreign body aspiration, structural airway anomalies, congenital lobar emphysema, abnormalities of the great vessels (e.g. vascular rings), congenital heart disease, cystic fibrosis, recurrent aspiration, immunodeficiency, infections, ciliary dyskinesia and mediastinal masses. Other clinical features, such as neonatal onset of symptoms, associated failure to thrive, diarrhea or vomiting, focal lung or cardiovascular findings, clubbing, constant wheezing, and hypoxemia outside of an acute illness, suggest an alternative diagnosis and require special investigations. Additional factors in addition to age at onset of symptoms that should be taken into consideration include triggers for the respiratory symptoms and aggravating conditions such as nighttime occurrences, environmental exposure, physical exertion, feeding, positioning and infections. Clearly, making the correct diagnosis is essential because the treatment for these conditions can vary substantially. For example, in children with significant gastroesophageal reflux, improvement in asthma symptoms with concomitant reduction in asthma medication use occurred after a prokinetic agent was instituted.²³ A practical approach that can be considered for a young child in whom asthma is strongly suspected is an empiric trial of asthma controller therapy while other evaluations are still being pursued (Figure 32-1).

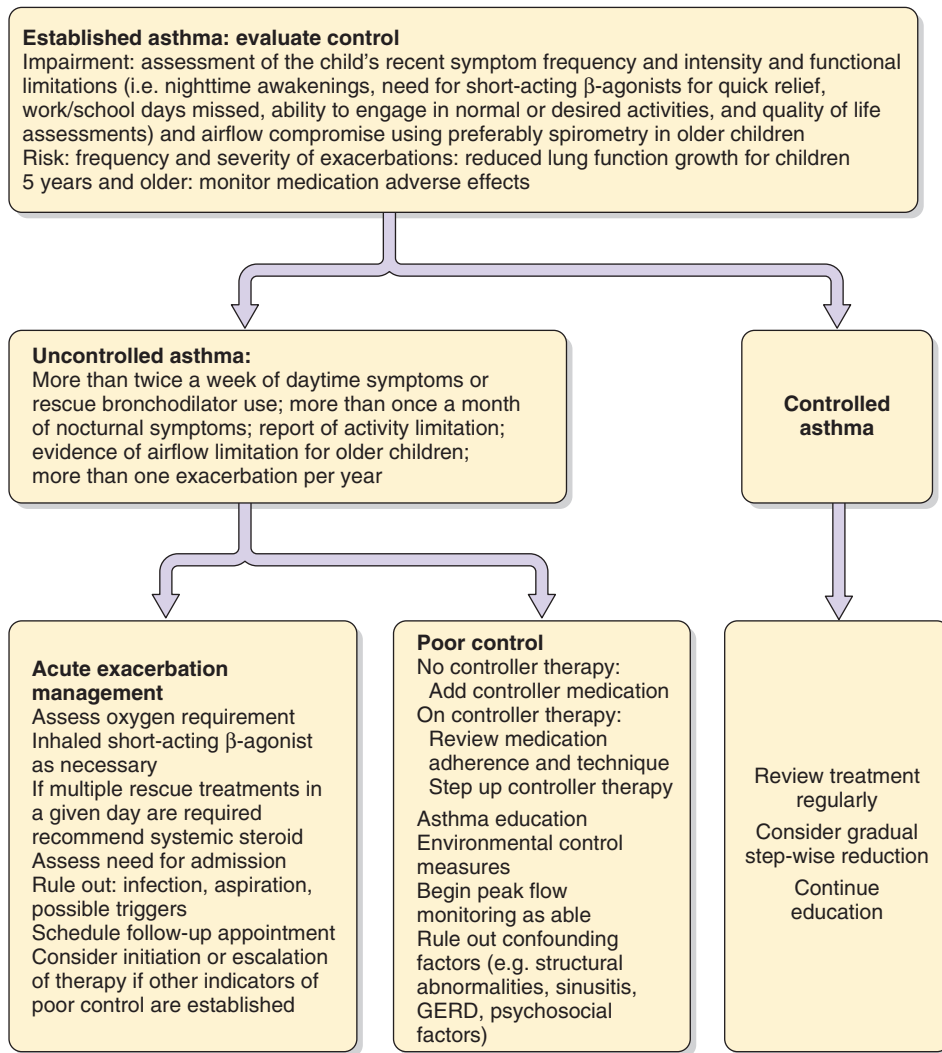
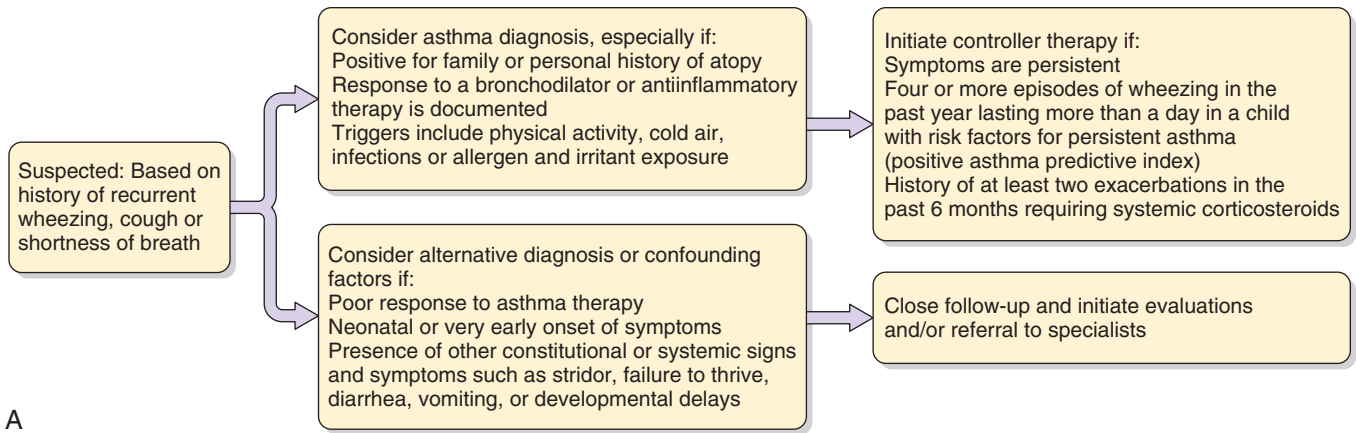


Figure 32-1 Algorithm for suggested management of infants and young children with suspected or established asthma. GERD – gastroesophageal reflux disease.

Diagnostic Tools to Evaluate Asthma in Young Children

Preschool children present some diagnostic challenges inherent to their young age such that a confirmation of a diagnosis can be difficult to make. Infants and young children are too young

to reliably perform objective measures of disease activity. Furthermore, they are unable to provide their own history so clinicians must depend on the parents'/caregivers' report. Werk et al sought to determine the factors primary care pediatricians believe are important in establishing an initial diagnosis of asthma.²⁴ Questionnaires on asthma diagnosis consisting of 20

factors obtained from the National Heart, Lung, and Blood Institute (NHLBI) National Asthma Education Prevention Program (NAEPP) Expert Panel Report 2 (EPR2) guidelines²⁵ and an expert local panel of subspecialists were sent to 862 active members of the Massachusetts American Academy of Pediatrics. Over 80% of the respondents rated five factors as necessary or important in establishing the diagnosis of asthma: recurrent wheezing, symptomatic improvement following bronchodilator use, presence of recurrent cough, exclusion of other diagnoses, and suggestive peak expiratory flow rate findings. Of note, 27% of the respondents indicated that a child had to be older than 2 years; 18% indicated that fever must be absent during an exacerbation.

The diagnosis of asthma in young children is based largely on clinical judgment and an assessment of symptoms and physical findings. The following characteristics are suggestive of asthma: wheezing or recurrent or persistent nonproductive cough or difficult breathing that may be worse at night or occurring with exercise, laughing, crying or exposure to tobacco smoke in the absence of a respiratory infection; reduced activity or interest in running or playing compared to other children with easy fatigability during walks; presence of other personal allergic diseases (atopic dermatitis or allergic rhinitis) or family history of asthma in first degree relatives; and response to either therapeutic trial of a corticosteroid or a short-acting bronchodilator as needed.⁷ Because lung function measurements in infants and small children are difficult to obtain, a trial of treatment is often a practical way to make a diagnosis of asthma in young children.

At present, for adults and older children, easily performed lung function measures and noninvasive markers of airway inflammation can be used to make the diagnosis of asthma, monitor asthma control or guide therapeutic decisions. The following section will highlight available procedures and techniques with the potential to measure lung function and airway inflammation in the young child.

FORCED OSCILLOMETRY

Forced oscillometry is a pulmonary function technique that measures respiratory system resistance (Rrs) and reactance (Xrs) at several frequencies. It involves the application of sine waves through a loudspeaker to the airway opening via a mouthpiece, through which the subject breathes normally for short periods of time. Measurements are carried out during tidal breathing over a 30-second interval with at least three efforts recorded. Given its relative ease of use, it is a reproducible and suitable measure of lung function in younger children.²⁶ Marotta et al performed pre- and post-bronchodilator spirometry and forced oscillometry in young children at risk for asthma and found no difference in baseline FEV₁ or resistance between children with asthma versus those without; the degree of bronchodilator response differentiated the two groups.²⁷ Some investigators believe that reactance at low frequencies is a reflection of peripheral airways function.²⁸

Using three different lung function measures, Nielsen and Bisgaard evaluated the bronchodilator response of 92 children 2 to 5 years old, 55 of whom had asthma.²⁹ Children with asthma had diminished lung function compared to nonasthmatic children using any of the following measures: specific airway resistance (sRaw) utilizing whole body plethysmography, or respiratory resistance utilizing either an interrupter

technique (Rint) or impulse oscillation technique at 5 Hz (Rrs5). Both asthmatic and nonasthmatic children responded to terbutaline, although children with asthma reversed to a greater extent than the nonasthmatic children. The investigators found that sRaw utilizing body plethysmography best distinguished asthmatics from nonasthmatics based on bronchodilator response. They concluded that assessment of bronchodilator responsiveness using sRaw may help define asthma in young children.

MEASUREMENT OF BRONCHIAL REACTIVITY

As with measurements of airflow limitation, procedures to assess BHR in infants and young children have distinctive challenges. Measurement of BHR using cold air (4 minutes of isocapnic hyperventilation) or dry air (6 minutes of eucapnic hyperventilation) challenge with sRaw as an outcome may be useful, practical alternatives to auscultatory pharmacologic or exercise bronchoprovocation challenges which are more difficult to standardize in young children.³⁰ Using a dry air challenge, magnitude of response was associated with a wheeze phenotype. Persistent wheezers had a larger increase in sRaw following eucapnic hyperventilation challenge compared with never wheezers, but no significant differences between never wheezers, late-onset or transient wheezers were seen.³¹

MEASURES OF INFLAMMATION

Exhaled nitric oxide (eNO) levels are elevated in patients with asthma³² and correlate positively with eosinophilic airway inflammation.³³ In addition, they rise during acute exacerbations³⁴ and fall following oral or inhaled corticosteroid (ICS) therapy.^{35,36}

Online³⁷ and offline³⁸ eNO measurements can be reliably obtained in very young children. Reference values using an offline tidal breathing method in healthy preschool children have recently been published.³⁹ Higher mean (\pm SEM) eNO concentrations (14.1 ± 1.8 ppb) were found in infants and young children (age 7 to 33 months) presenting with an acute wheeze and a history of at least three prior wheezing episodes compared to first-time viral wheezers (age 9 to 14 months) (8.3 ± 1.3 ppb, $P < .05$) and healthy matched controls (5.6 ± 0.5 ppb, $P < .001$). No differences in eNO measurements were seen between the last two groups. In addition, eNO levels were reduced by 52% after steroid therapy to a level comparable to those of the healthy controls and first-time wheezers.³⁸

Unlike sophisticated measures of lung function and BHR, eNO can be easily and quickly measured. An elevated eNO in preschool age children has been shown to predict asthma in school age.⁴⁰

In one of the few studies designed specifically to address the role of eosinophil cationic protein (ECP) in young children with recurrent wheezing, Carlsen et al⁴¹ found a strong correlation between serum ECP and response to albuterol/salbutamol using the tidal flow volume loop technique in children 0 to 2 years of age. These investigators suggested that ECP may be measuring airway inflammation and may have some prognostic value in diagnosing asthma in infants and toddlers with recurrent wheezing. The major drawback for ECP is its lack of sensitivity and blood sample collection.

Although direct investigation of the airway using bronchoscopy and biopsy is the gold standard for establishing airway

inflammation, it has limited clinical applicability, except when other pulmonary abnormalities are being considered. Understanding the underlying pathophysiology of the disease in children is critical in order to identify processes that can be impacted by interventions. Thickening of the bronchial epithelial reticular basement membrane (RBM) and eosinophilic airway inflammation are characteristic pathologic features of asthma found in children as young as 3 years old, but typically occurring between the ages of 6 to 16 years.⁴² It is unclear when airway thickening begins since routine biopsy studies are not performed in infants.⁴³ Studies on bronchoalveolar lavages obtained from wheezing infants and preschool children revealed an overall increase in airway inflammation, though it is rarely eosinophilic. In one study in which bronchial biopsies were performed on symptomatic infants, there was no consistent relationship between RBM thickening and inflammation, clinical symptoms and variable airflow obstruction,⁴⁴ similar to findings from biopsy studies in older school aged children with asthma.⁴⁵ The use of sensitive, noninvasive physiologic and biologic markers is very limited in the clinical evaluation of young children with asthma and recurrent wheezing.

Management

The goals of asthma management are not different between older children and preschool aged children – to attain good symptom control and allow normal activity levels, reduce exacerbations, optimize lung function and minimize medication side-effects. Available asthma guidelines such as the National Asthma Education Prevention Program Expert Panel Report 3 (NAEPP EPR3)⁶ and the Global Initiative for Asthma (GINA) update 2014 report⁷ acknowledge the special challenges unique to the management of asthma in preschool children; hence a specific approach and treatment recommendations for preschool children with asthma are presented. Both sets of guidelines emphasize maintenance of asthma control as the goal for asthma management and use of ICS as the preferred therapy for persistent asthma. A comprehensive management is outlined in several components and/or sections and generally includes: establishment of patient/doctor partnership and provision of education to enhance the patient's/family's knowledge and skills for self-management (appropriate use of devices and medications); identification and management of risk and precipitating factors and co-morbid conditions that may worsen asthma; adequate assessment and monitoring of disease activity (including symptom monitoring by parent/caregiver); appropriate selection of medications to address the patient's needs; and management of asthma exacerbations (with provision of a written asthma action plan). The details of each of these elements are discussed in Chapter 29.

Key differences between the two clinical guidelines are apparent. The approach implemented by the NAEPP EPR3 on starting controller therapy is based on the concept of asthma severity, which is the intrinsic intensity of disease and applicable for patients not receiving controller therapy. The guidelines have a separate set of criteria for various age groups and Table 32-1 summarizes the classification of asthma severity for children 0 to 4 years old. The classification of asthma severity is contingent upon the domains of impairment and risk and the level of severity is based on the most severe impairment or risk component. Impairment includes an assessment of the child's recent symptom frequency (daytime and nighttime), need for

short-acting β_2 -agonists for quick relief, and ability to engage in normal or desired activities. Risk refers to an evaluation of the child's likelihood of developing asthma exacerbations. Of note, in the absence of frequent symptoms, 'persistent' asthma should be considered and therefore long-term controller therapy initiated for infants or children who have risk factors for asthma (i.e. using the mAPI: any of parental history of asthma, physician-diagnosed atopic dermatitis, or sensitization to aeroallergens OR two of the following: wheezing apart from colds, sensitization to foods, or peripheral eosinophilia) AND four or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep OR two or more exacerbations within 6 months requiring systemic corticosteroids.

In the most recent iteration of the GINA global strategy,⁷ much emphasis is devoted to a 'shared-care approach' using an effective patient-healthcare provider partnership that has been shown to improve outcomes, and the process of 'assess, adjust treatment, and review response'. Eliciting specific goals of treatment from caregivers and providing education are key elements in this partnership. The process of assessing (diagnosis, symptom control, risk factors, inhaler technique, adherence and parent preference), adjusting treatment (medications, nonpharmacological strategies and treatment of modifiable risk factors), and reviewing response (medication effectiveness and side-effects) is recommended on an ongoing basis.

CONTROLLER THERAPY FOR SMALL CHILDREN WITH PERSISTENT ASTHMA

Based on the NAEPP EPR3 guidelines,⁶ upon establishing a diagnosis of asthma in young children, initiation of controller therapy is warranted for persistent asthma. The most important determinant of dosing is the clinician's judgment of the patient's presenting degree of severity. Initiation of long-term controller therapy should also be considered for infants and younger children who have risk factors for asthma (i.e. modified asthma predictive index: parental history of asthma, physician-diagnosed atopic dermatitis or sensitization to aeroallergens or two of the following: wheezing apart from colds, sensitization to foods or peripheral eosinophilia) and four or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep or two or more exacerbations in 6 months requiring systemic corticosteroids.

Medication dose adjustment is appropriate based on levels of asthma control, although dose-response relationships are not well studied. For preschool children already on a controller medication, management is tailored based on the child's level of control. As with the classification of asthma severity, assessment of asthma control is based on both impairment and risk (Table 32-2). The three levels of asthma control are 'well controlled', 'not well controlled' and 'very poorly controlled'. Children whose asthma is not well controlled have daytime symptoms or need for rescue albuterol >2 days/week, nighttime symptoms more than once a month but not more than once a week, 'some limitation' with normal activity, had two to three exacerbations in the past year, and an FEV₁ of 60–80% of predicted (or FEV₁/FVC ratio 75–80%) for children 5 years of age or older. Children with very poorly controlled asthma have symptoms 'throughout the day', nocturnal symptoms more than once weekly, need for rescue albuterol several times per day, 'extreme limitations' with normal activity, had ≥ 3 exacerbations in the past year, and for children at least aged 5 years, an

TABLE
32-1

Classifying Asthma Severity and Initiating Treatment in Children Aged 0 to 4 Years: Assessing Severity and Initiating Treatment for Patients Who are not Currently Taking Long-term Control Medications

Components of Severity		CLASSIFICATION OF ASTHMA SEVERITY (0–4 YR)			
		Intermittent	Mild	Moderate	Severe
Impairment	Daytime symptoms	≤2 d/wk	>2 d/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2×/mo	3–4×/mo	>1×/wk
	SABA use for symptoms (not EIB pretreatment)	≤2 d/wk	>2 d/wk but not daily and not more than once on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring systemic corticosteroids	0–1/yr	≥2 exacerbations in 6 months requiring systemic corticosteroids, or ≥4 wheezing episodes/1yr lasting >1 day and risk factors for persistent asthma		
		Consider severity and interval since last exacerbation Frequency and severity may fluctuate over time Exacerbations of any severity may occur in patients in any severity category			
Recommended step for initiating therapy		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed within 4–6 weeks, consider adjusting therapy or alternative diagnoses			

National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma – Summary Report 2007. *J Allergy Clin Immunol* 2007;120(Suppl):S94–138. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>.

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether a patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

EIB – Exercise-induced bronchospasm; SABA – short-acting β_2 -agonist use.

FEV₁ of <60% of predicted or FEV₁/FVC ratio <75%. Using a validated questionnaire to monitor quality of life for older children is recommended and perhaps the TRACK questionnaire⁴² discussed in a subsequent section may now be applied in younger children.

The NAEPP EPR3 provides an expanded stepwise treatment approach (Figure 32-2) even for young children. The choice of initial therapy is based on assessment of asthma severity. For patients who are already on controller therapy, modification of treatment is based on assessment of asthma control and responsiveness to therapy. A major objective of this approach is to identify and treat all 'persistent' and uncontrolled asthma with antiinflammatory controller medication. Management of intermittent asthma is short-acting inhaled β -agonist as needed for symptoms and for pre-treatment for those with exercise-induced bronchospasm (Step 1). The type(s) and amount(s) of daily controller medications to be used are determined by the asthma severity and control rating. Even for young children, the preferred treatment for 'persistent asthma' is daily ICS therapy, with or without an additional medication. Alternative medications for Step 2 include a leukotriene receptor antagonist (montelukast) or a nonsteroidal antiinflammatory agent (cromolyn). For young children (≤4 years of age) with moderate and severe persistent asthma, medium-dose ICS monotherapy is recommended and combination therapy of medium-dose ICS plus either a long-acting β -agonist (LABA) or montelukast is to be initiated only as a Step 4 treatment for uncontrolled asthma.

Children with severe persistent asthma (Treatment Steps 5 and 6) should receive high-dose ICS, a LABA or montelukast, and an oral corticosteroid, if required. A rescue course of systemic corticosteroids may be necessary at any step.

The 'step-up, step-down' approach initially introduced in the earlier versions of the NAEPP guidelines²¹ and slightly modified in the current iteration⁶ is discussed in further detail in Chapter 29. The NAEPP guidelines emphasize initiating higher-level controller therapy at the outset to establish prompt control, with measures to 'step down' therapy once good asthma control is achieved. Initially, airflow limitation and the pathology of asthma may limit the delivery and efficacy of ICS such that stepping up to higher doses and/or combination therapy may be needed to gain asthma control. Asthma therapy can be stepped down after good asthma control has been achieved and ICS has had time to achieve optimal efficacy, by determining the least number or dose of daily controller medications that can maintain good control, thereby reducing the potential for medication adverse effects. If step-up therapy is being considered at any point, it is important to check delivery device technique and adherence, implement environmental control measures and identify and treat co-morbid conditions.

The GINA 2014 global strategy also now offers a stepwise approach in the long-term management of asthma in very young children.⁷ However, if control is still inadequate despite 3 months of controller therapy, the following should be addressed before any step-up treatment is offered: that any

TABLE
32-2

Assessing Asthma Control and Adjusting Therapy in Children Aged 0 to 4 Years

Components of Control		CLASSIFICATION OF ASTHMA CONTROL (0–4 YR)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Daytime symptoms	≤2 d/wk but not more than once on each day	>2 d/wk	Throughout the day
	Nighttime awakenings	≤1×/mo	>1×/mo	>1×/wk
	SABA use for symptoms (not EIB pretreatment)	≤2 d/wk	>2 d/wk	Several times per day
	Interference or limitations with normal activity	None	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/yr	2–3/yr	>3 yr
	Treatment-related adverse effects	Medication side-effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		
Recommended action for treatment per NAEPP guidelines		Maintain current treatment Regular follow-up every 1–6 months Consider step down if well controlled for at least 3 months	Step up (1 step) and reevaluate in 2–6 weeks If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy For side-effects, consider alternative treatment options	Consider short course of oral systemic corticosteroids Step up (1–2 steps), and reevaluate in 2 weeks If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy For side-effects, consider alternative treatment options

National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma – Summary Report 2007. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>.

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2 to 4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g. requiring urgent, unscheduled care, hospitalization or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Before step-up therapy:
 - Review adherence to medications, inhaler technique and environmental control.
 - If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

other possible alternative or confounding condition is entertained; assessment of inhaler technique; adherence is acceptable; and exposure to allergens or tobacco smoke is avoided. The criteria for 'well controlled', 'partly controlled' and 'uncontrolled' asthma according to the GINA global strategy are summarized in Table 32-3, based on a 4-week recall. 'Well-controlled' asthma is characterized by at most daytime symptoms once a week, rescue/reliever treatment less than 2 times a week, absence of any activity limitation due to asthma, and no nocturnal cough or awakenings. 'Partly controlled' asthma has one to two of the following: ≥2 daytime symptoms a week, ≥2 rescue bronchodilator use, any nocturnal cough/awakenings, or limitations of activities. Lastly, 'uncontrolled' asthma is defined as presence of three or all features characteristic of 'partly controlled' asthma present in any week or exacerbation occurring once in any week.

The stepwise approach in the GINA 2014 global strategy has important differences from the NAEPP EPR3^{6,7} (Table 32-4). For Step 1 which recommends as needed short-acting β-agonist as the preferred controller choice for children with infrequent viral wheezing, with few or no interval symptoms, intermittent inhaled corticosteroid therapy is an alternative option if short-acting β-agonist treatment is not enough.^{46,47} Intermittent

high-dose ICS therapy given at the onset of a respiratory illness is further demonstrated to be as beneficial as maintenance therapy with ICS in children with recurrent wheezing and with risk factors for persistent asthma.⁴⁸ Because it has the potential to cause side-effects if given quite often during the year at higher doses, this should be considered for families who are able to use this intervention responsibly. Step 2 treatment is recommended for young children with symptom pattern consistent with asthma and not well controlled *or* with 3 or more exacerbations per year *or* with frequent wheezing episodes occurring every 6 to 8 weeks. Similar to the NAEPP EPR3 recommendation are the preferred medication using daily low-dose ICS (for at least 3 months trial) and the alternative option using a leukotriene receptor antagonist, but GINA 2014 global strategy now also includes intermittent ICS for Step 2 as an alternate option. The National Institute of Health sponsored AsthmaNet is currently undertaking a clinical trial comparing these three treatments in young children with persistent asthma. Preferred Step 3 treatment is double 'low-dose' ICS, indicated for children with established asthma not well controlled on low-dose ICS. The alternative option is low-dose ICS with a leukotriene receptor antagonist. The highest step (Step 4) basically proposes a referral to a specialist for expert advice. Additional options

TABLE 32-3 GINA Assessment of Asthma Control in Children 5 Years and Younger

A. Level of Symptom Control		
	In the past 4 weeks, has the child had:	Yes No
	Daytime asthma symptoms for more than a few minutes?	
	Any night waking or coughing due to asthma?	
	Reliever medication needed more than once a week (excludes reliever taken before exercise)?	
	Any activity limitation due to asthma? (Runs/plays less than other children, tires easily during walks/playing?)	
Controlled (none of the above)		
Partly controlled (1–2 of these)		
Uncontrolled (3–4 of these)		
B. Future Risk for Poor Asthma Outcomes		
Risk factors for asthma exacerbations		
<ul style="list-style-type: none"> • Uncontrolled asthma symptoms • One or more severe exacerbations in previous year • The start of the child’s usual ‘flare-up’ season (especially if autumn or fall) • Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens (e.g. house dust mite, cockroach, pets, mold), especially in combination with viral infection • Major psychological or socioeconomic problems for child or family • Poor adherence with controller medication, or incorrect inhaler technique 		
Risk factors for fixed airflow limitation		
<ul style="list-style-type: none"> • Severe asthma with several hospitalizations • History of bronchiolitis 		
Risk factors for medication side-effects		
<ul style="list-style-type: none"> • Systemic: frequent courses of oral corticosteroids; high-dose and/or potent inhaled corticosteroids • Local: moderate/high-dose or potent inhaled corticosteroids; incorrect inhaler technique; failure to protect skin or eyes when using inhaled corticosteroids by nebulizer or spacer with facemask 		

Adapted from the Global strategy for asthma management and prevention 2014. Available at: <http://www.ginasthma.org>.

TABLE 32-4 Stepwise Approach to Long-Term Management of Asthma in Children 5 Years and Younger (Global Initiative for Asthma 2014)

	Step 1	Step 2	Step 3	Step 4
PREFERRED CONTROLLER CHOICE		Daily low-dose ICS	Double ‘low-dose’ ICS	Continue controller and refer for specialist assessment
Other controller options		LTRA Intermittent ICS	Low-dose ICS + LTRA	Add LTRA Increase ICS frequency Add intermittent ICS
RELIEVER	As needed short-acting β ₂ -agonist			
CONSIDER THIS STEP FOR CHILDREN WITH	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern consistent with asthma and asthma symptoms not well controlled, or ≥3 exacerbations per year Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6–8 weeks Give diagnostic trial for 3 months	Asthma diagnosis, and not well controlled on low-dose ICS First check diagnosis, inhaler skills, adherence, exposures	Not well controlled on double ICS
KEY ISSUES	ALL CHILDREN <ul style="list-style-type: none"> • Assess symptom control, future risk, co-morbidities • Self-management: education, inhaler skills, written asthma action plan, adherence • Regular review: assess response, adverse events, establish minimal effective treatment • (Where relevant): environmental control for smoke, allergens, indoor/outdoor air pollution 			

Adapted from the Global strategy for asthma management and prevention 2014. Available at: <http://www.ginasthma.org>.
ICS – Inhaled corticosteroid; LTRA – leukotriene receptor antagonist.

diagnostic accuracy of 81% and 78%, respectively. Based on the highest area under the ROC curve, a score of less than 80 provided the best cut-off between sensitivity and specificity for uncontrolled asthma for this group. The pediatric version of the Asthma Control Test (cACT) has been validated for children as young as 4 years of age.

The GINA 2014 global strategy assessment of asthma control is discussed in an earlier section and summarized in Table 32-3.

Inhaled Corticosteroids

ICS are the preferred controller therapy for persistent asthma or asthma that is not controlled. Although there are six ICS available, nebulized budesonide is the only US Federal Drug Administration (FDA)-approved ICS for children less than 4 years of age. The initial studies with nebulized budesonide in young children with moderate to severe persistent asthma found it to be superior to placebo in improving symptoms, decreasing exacerbations, reducing chronic oral prednisone use or improving overall asthma control.^{52,53}

Studies have also evaluated the efficacy and safety of nebulized budesonide in children with mild to moderate persistent asthma.^{54–56} The efficacy of nebulized budesonide over placebo was consistently demonstrated with improvement in symptom scores, reduction in rescue medication use and improvement in morning peak expiratory flow rates in patients who could adequately perform the procedure. Improvement in symptom scores occurred as early as 2 weeks after starting budesonide.⁵⁶ Twice-daily dosing of 0.5 mg appeared to be somewhat more effective than 1 mg administered once daily. The investigators suggested that a dose of 0.25 mg/day may be sufficient for mild asthma, whereas subjects with moderate asthma should be treated with 0.5 to 1 mg/day and those with severe asthma dependent on oral steroids should be treated with 1–2 mg/day. No significant differences in basal cortisol levels or

ACTH-stimulated cortisol levels were found between any of the active treatment groups and placebo.

Pharmacokinetics of Nebulized Budesonide in Small Children. Little is known regarding the amount of drug delivered, by any inhaled device and with any drug, to infants and young children with asthma. ICS have the potential for adverse effects, so it is important to deliver the smallest amount of drug required for response. Agertoft et al evaluated the systemic availability and pharmacokinetics of nebulized budesonide in a group of preschool children (mean age 4.7 years) with chronic asthma.⁵⁷ Ten children underwent pharmacokinetic studies of both intravenously administered (125 µg) and inhaled budesonide (1 mg delivered by nebulization). The amount of nebulized budesonide delivered to the patient was calculated by subtracting the amount of drug remaining in the nebulizer, the amount emitted into the ambient air, and the amount found in the mouth after rinsing from the initial amount of budesonide in the nebulizer (the nominal dose). The mean dose to the subject was found to be 23% of the nominal dose (231 µg), while the systemic availability was only 6.1% of the nominal dose, or 61 µg. The clearance of budesonide was calculated to be 0.54 L/min with a $t_{1/2}$ of 2.3 hours, and V_{dss} of 55 L. The systemic availability in these small children was approximately half that seen in adults. In addition, the clearance of budesonide in these children was twice that of adults.

Recommended doses of different ICS formulations for children 5 years and younger according to low, medium and high doses in the NAEPP EPR3 and low-dose formulations in the GINA 2014 global strategy are shown in Table 32-5.^{6,7}

What type of patient will respond favorably to ICS in this age group is an important question that has yet to be answered. A study by Roorda et al using data from two large placebo-controlled studies evaluated the clinical features of preschool children likely to respond to fluticasone administered via a

TABLE 32-5 Estimated Comparative Inhaled Corticosteroid Doses

Drug	NAEPP EPR3 [†]			GINA 2014*
	Low	Medium	High	Low
Beclomethasone HFA, 40 or 80 µg/puff	NA	NA	NA	100 µg
Budesonide DPI 90, 80 or 200 µg/inhalation	NA	NA	NA	
Budesonide pMDI + spacer	NA	NA	NA	200 µg
Budesonide inhaled suspension for nebulization, 0.25-, 0.5- and 1.0-mg dose	0.25–0.5 mg	>0.5–1.0 mg	>1.0 mg	500 µg
Ciclesonide HFA/pMDI, 80 or 160 µg/puff				160
Flunisolide, 250 µg/puff	NA	NA	NA	
Flunisolide HFA/pMDI, 80 µg/puff	NA	NA	NA	
Fluticasone HFA/pMDI, 44, 110 or 220 µg/puff	176 µg	>176–352 µg	>352 µg	100
Fluticasone DPI, 50, 100 or 250 µg/inhalation	NA	NA	NA	
Mometasone DPI, 220 µg/inhalation	NA	NA	NA	Not studied below age 4 years
Triamcinolone acetonide, 75 µg/puff	NA	NA	NA	Not studied in this age group

*Only low doses are given. This is not a table of clinical equivalence. A low daily dose is defined as the dose that has not been associated with clinically adverse effects in trials that included measures of safety. Adapted from the GINA global strategy for asthma management and prevention 2014. Available at: <http://www.ginasthma.org>.

[†]Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma – Summary Report 2007. J Allergy Clin Immunol 2007;120(Suppl):S94–138. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>.

HFA – Hydrofluoroalkane propellant; pMDI – pressurized metered dose inhaler.

pressurized metered dose inhaler (pMDI) with holding chamber and facemask.⁵⁸ The investigators identified two clinical features that predicted a positive response to ICS therapy – frequent symptoms (≥ 3 days/week) and a family history of asthma. The presence of eczema and the number of previous acute exacerbations were not associated with response to fluticasone. Eczema predisposes a child with recurrent wheezing to subsequent asthma,¹⁴ but it does not appear to predict response to ICS therapy. It should be noted that a lack of response over a short course of treatment (12 weeks) does not necessarily mean that a response would not be seen over a much longer period of time (months to years). An NHLBI-sponsored AsthmaNet clinical trial which will be completed in 2015 is evaluating predictors of response to different interventions, specifically daily vs intermittent ICS therapy vs leukotriene receptor antagonist, in preschool aged children with persistent asthma.⁵⁹

The clinical efficacy and safety of intermittent ICS or systemic corticosteroid for young children with associated upper respiratory infection or viral induced wheeze remain controversial. A 2009 study which evaluated ‘as needed’ high-dose fluticasone propionate (750 μg twice daily) given at the onset of an upper respiratory tract illness found lower rescue oral corticosteroid use in those on active treatment compared to placebo (8% vs 18%, respectively); however this was accompanied by a statistically significant difference in height and weight gain.⁴⁶ In another 2009 study, oral prednisolone was found not to be superior to placebo with respect to duration of hospitalization, clinician and parent symptom severity assessment, and hospital readmission for preschool children presenting to a hospital with viral-induced mild to moderate wheezing.⁶⁰ A 2011 study which evaluated daily vs intermittent high-dose ICS therapy given at the onset of a respiratory illness in preschool aged children with recurrent wheezing and atopic risk factors found no difference between the two treatments with respect to prevention of severe exacerbations.⁴⁸

ICS and Growth in Small Children. Few published studies have evaluated the effects of ICS on the linear growth of preschool children. Reid et al, in an open-label study, measured linear growth velocity in 40 children (mean age 1.4 years) before and during treatment with nebulized budesonide.⁶¹ All of the children had ‘troublesome’ asthma despite treatment with an ICS administered with a pMDI with spacer and facemask or nebulized cromolyn before entry into the study. They were then administered 1 to 4 mg/day of nebulized budesonide depending on their level of asthma severity. The median intervals of time for linear growth determinations during the run-in period and nebulized budesonide treatments were 6 months and 1 year, respectively. The height standard deviation scores (SDSs) for the group during the run-in period were -0.21 , at baseline -0.46 , and after at least 6 months of nebulized budesonide -0.17 . Note that an SDS of less than 0 denotes impaired growth velocity. Thus the subjects were growing at less than an impaired rate before nebulized budesonide therapy, and the institution of nebulized budesonide did not result in further growth suppression. In fact, there was a trend toward improved growth velocity while on nebulized budesonide.

Skoner et al⁶² evaluated the growth of children enrolled in 52-week open-label extension studies of the three efficacy studies of budesonide.^{54–56} The dose of budesonide was either 0.5 mg once or twice daily with a taper to the lowest tolerated

dose, and conventional asthma therapy consisted of any available therapy including ICS in two of the studies; in total, 670 children participated. The investigators found a modest impairment in growth in only one of the three extension studies. The extension study where a decline in growth was noted consisted primarily of young children with milder asthma who had not been on ICS before entry into the initial study. In contrast, the two extension studies that did not find growth impairment consisted of children with more severe disease and had allowed for ICS use as part of the conventional asthma therapy algorithm. The Skoner study suggests that modest growth suppression can occur in young children receiving nebulized budesonide who have not required ICS therapy in the past and that children with milder asthma may be at greater risk for growth suppression secondary to increased intrapulmonary deposition. Alternatively, the findings may be attributable to the fact that over twice as many children randomized to the conventional asthma therapy arm withdrew from the study because of poor asthma control.

The PEAK and IFWIN studies which used ICS via MDI with a holding chamber and mask have also provided important findings on the adverse effects of long-term ICS on growth in preschool children at risk for persistent asthma.^{19,63,64} It is still uncertain if there is a potential for catch up or if the effects in very young children are cumulative. A follow-up study of PEAK participants 2 years after the clinical trial was completed showed no difference in growth between children who were on active ICS therapy compared to those who were randomized to placebo.⁶⁴ However, in a post hoc analysis, lower growth velocity was found among participants who were younger and weighed less, probably due to a relatively greater drug exposure. For young children with poor asthma control, the disease itself can negatively impact growth. The growth of 58 children (mean age 3.5 years for males, 4.4 years for females) with asthma was followed over a 5-year period.⁶⁵ Each child’s asthma was classified as being in good, moderate or poor control according to asthma symptoms during a 2-year observational period before the institution of ICS therapy. The group as a whole had diminished growth velocity to start the study, with a mean height velocity standard deviation (HVSD) score of -0.51 . Children whose asthma was in good control had the least evidence for growth suppression before ICS therapy was instituted and continued to grow at the same rate as when on therapy (HVSD score -0.01 pre- vs -0.07 during treatment). In contrast, the subjects whose asthma was poorly controlled grew poorly before and after institution of ICS therapy (HVSD score -1.50 pre- vs -1.55 during treatment). Of interest, those with moderately controlled asthma demonstrated improved growth velocity while on ICS therapy, with their HVSD score increasing from -0.83 to -0.49 . The investigators concluded that poor asthma control adversely impacts linear growth to a greater extent than ICS therapy.

Alternative and/or Adjunct Medications

The NHLBI NAEPP EPR3 guidelines recommend cromolyn or montelukast as alternative therapy for younger children with mild persistent asthma and combination therapy using ICS plus either LABA or montelukast for younger children with moderate to severe persistent asthma (Steps 4 and 5).⁶ GINA 2014 global strategy recommends leukotriene receptor antagonist or increased or intermittent ICS therapy as alternative options for Step 2 and add-on options for Steps 3 and 4.⁷

Cromolyn. Cromolyn (Intal) inhibits mediator release from mast cells. It inhibits both the early- and late-phase pulmonary components of the allergic response following inhalation of an allergen in sensitized subjects. A few studies have shown no added benefit with the use of cromolyn over placebo in young children with more severe disease.^{66–69} Several efficacy studies that have found cromolyn to have beneficial effects were short-term trials and employed small numbers.^{70,71} A meta-analysis of 22 control studies evaluating cromolyn in childhood asthma found it no better than placebo.⁷² A multicenter, randomized, parallel-group, 52-week, open-label study in preschool children found nebulized cromolyn (20 mg four times daily) ($N = 335$) to be inferior to nebulized budesonide suspension (0.5 mg daily) ($N = 168$) using several outcome parameters.⁷³ Children who received inhaled budesonide suspension had a reduced rate of asthma exacerbations per year, longer time to first asthma exacerbation and first use of additional long-term controller therapy; nearly doubled improvements in nighttime and daytime symptom scores by the second week of treatment; and lower use of rescue medications. Although there were no significant differences in the rates of hospitalization and emergency room visits between the two groups, significantly lower urgent care or unscheduled physician visits and oral corticosteroid use were found in children who received the ICS. However, mean height increases from baseline in children randomized to inhaled budesonide and inhaled cromolyn were 6.69 and 7.55 cm, respectively. This difference of 0.86 cm is similar to the difference in height measurements seen in other studies with ICS therapy after 1 year of treatment in both younger and older children.^{19,74,75}

Leukotriene Modifying Agents. Leukotrienes are potent pro-inflammatory mediators that induce bronchospasm, mucus secretion and airway edema. In addition, they may be involved in eosinophil recruitment into the asthmatic airway.⁷⁶ Leukotriene modifiers (synthesis inhibitor or receptor antagonist) have beneficial effects in terms of reducing asthma symptoms and supplemental β -agonist use while improving baseline pulmonary function.^{77–79} The leukotriene receptor antagonists (LTRA) prevent the binding of LTD₄ to its receptor. This class has a pediatric indication and includes both montelukast (given once daily; has been approved for treatment of chronic asthma for children age 1 year and older) and zafirlukast (administered twice daily; approved for children 7 years and older).

Safety and efficacy studies with the 4-mg chewable montelukast tablet in children aged 2 to 5 years with asthma have been published.^{80–82} Almost 700 children 2 to 5 years of age were enrolled to receive montelukast or placebo for 12 weeks in a double-blind, multicenter, multinational study at 93 centers worldwide.⁸⁰ Montelukast was well tolerated and was not associated with any significant adverse effects. Montelukast was superior to placebo in reducing daytime symptoms including improvements in cough, wheeze, difficulty breathing and activity level, and nighttime cough. In addition, montelukast therapy was associated with a reduction in rescue β -agonist use and reduced need for prednisone for acute severe exacerbations.

Studies have been done to evaluate the long-term effects of an LTRA (continuous⁸¹ and intermittent⁸²) on the occurrence of exacerbations in young children. In a 12-month, double-blind, parallel study which was designed to investigate the role of montelukast in the prevention of viral induced asthma exacerbations in children aged 2 to 5 years with a history of intermittent asthma symptoms, montelukast significantly reduced

the rate of asthma exacerbations by 31.9% compared with placebo. Montelukast delayed the median time to first exacerbation by approximately 2 months and the rate of ICS courses compared to placebo.⁸¹ In another study, 220 children aged 2 to 14 years were randomized to receive either intermittent montelukast or placebo at the onset of asthma or upper respiratory tract infection symptoms for a minimum of seven days.⁸² The montelukast group had 163 unscheduled health care resource utilizations for asthma compared with 228 in the placebo group (OR = 0.65, 95% CI 0.47–0.89). There was a nonsignificant reduction in specialist attendances and hospitalizations, duration of episode and β -agonist and prednisolone use. These studies suggest that intermittent or persistent therapy with montelukast for children with intermittent asthma symptoms is effective in reducing risk of exacerbations compared with placebo.

Long-acting Inhaled β -Agonists. LABAs are the alternative add-on therapy for children and adults with moderate and severe persistent asthma. The GINA 2014 global strategy does not include LABAs as controller therapy in any of their stepwise algorithms for very young children.⁷ They are not viewed as ‘rescue’ medications for acute episodes of bronchospasm, nor are they meant to replace inhaled anti-inflammatory agents. Salmeterol has a prolonged onset of action with maximal bronchodilation approximately 1 hour following administration; formoterol has an onset of effect within minutes. Both medications have a prolonged duration of action of at least 12 hours. As such, they are especially well suited for patients with nocturnal asthma⁸³ and for individuals who require frequent use of short-acting β -agonist inhalations during the day to prevent exercise-induced asthma.⁸⁴ There is an added advantage to the use of these alternative therapies for preschool children who may deserve an extended bronchodilatory coverage for exercise because they are constantly active. Salmeterol via the Diskus™ device is FDA approved for children as young as 4 years of age (50 μ g blister every 12 hours), whereas formoterol delivered via the Aerolizer™ is approved for use in children 6 years of age and older (12 μ g capsule every 12 hours). Both LABAs are also available as combination pMDI with an ICS (salmeterol and fluticasone [Advair], budesonide and formoterol [Symbicort], and mometasone and formoterol [Dulera]). Although LABAs combined with ICS are recommended for young children in Steps 4 to 6 of the NAEPP EPR3 guidelines (Figure 32-2), they have limited application.⁶ The Diskus™ combination product is FDA approved down to 4 years of age but its use requires adequate inspiratory effort to get an optimal delivery of the dry powder. While the pMDI can be used with a holding chamber, it is not currently approved for children younger than 12 years of age. The efficacy and safety of LABA or combination products in younger children with asthma are still uncertain due to lack of studies.

The FDA has requested the manufacturers of LABAs to update their product information warning sections regarding an increase in severe asthma episodes associated with these agents. This action is in response to data showing an increased number of asthma-related deaths in patients receiving LABA therapy in addition to their usual asthma care as compared with patients not receiving LABAs.

Treatment immediately prior to vigorous activity or exercise is usually effective. The combination of a SABA with either cromolyn or nedocromil is more effective than either drug

alone. Montelukast may be effective for up to 24 hours. Salmeterol and formoterol may block exercise-induced bronchospasm for up to 12 hours. There is one study that has evaluated single-dose bronchoprotective effects of salmeterol given through a Babyhaler spacer device using a methacholine provocation challenge in infants less than 4 years old with recurrent episodes of wheezing.⁸⁵ Originally 42 preschool children (age range 8 to 45 months) received one of the 25-, 50- or 100- μ g dose of salmeterol and a placebo dose 2 to 7 days apart in a double-blind, randomized fashion, but only 33 completed the study. The investigators found a dose-dependent bronchoprotective effect of salmeterol measured by treatment/placebo methacholine dose ratios. Significant improvements from placebo were found only for the 50 (2.5 fold) and 100 (fourfold) μ g doses.

ISSUES RELATED TO THE DELIVERY OF MEDICATIONS TO INFANTS AND SMALL CHILDREN

There are unique challenges relating to the delivery of medications (both oral and inhaled) to infants and young children with asthma. Obviously, liquid preparations are tolerated by infants but chewable tablets/pills can already be consumed by toddlers. Montelukast is available as oral granules or chewable tablet and prednisone/prednisolone comes in either liquid formulations or orally disintegrating tablet preparations. With regard to inhaled medications, certain anatomic and physiologic characteristics of children younger than 6 years are worth considering. First, because infants display preferential nasal breathing and have small airways, low tidal volume and high respiratory frequency, delivery of the drug to the lower airways is often inadequate.⁸⁶ Second, it is difficult if not impossible for young children to perform the maneuvers specified for optimal delivery of aerosol therapy such as slow inhalation through the mouth with a period of breath-holding for pMDIs or rapid and forceful inhalation required in the case of dry-powder inhalers (DPIs). Third, delivery devices appropriate for the young child are limited to those that require minimum cooperation from the child and must allow ease of administration for the caregivers. Although at present there are at least three inhaled aerosol delivery systems available for older children and adults, only two are used in this age group: the nebulizer and the pMDI with spacer/holding chamber and facemask. Because of the reliance on the subject's ability to generate a sufficient inspiratory flow and overcome the resistance required of DPIs, preschool age children are unable to use them.

Within these two general types of delivery systems there are numerous products available that vary widely in performance. The pMDI with spacer or holding chamber is portable and inexpensive, takes less time to administer and is likely to be better tolerated than delivery with a nebulizer. Dolovich et al⁸⁷ published a comprehensive systematic review to determine if device selection affects clinical efficacy and safety. Randomized placebo-controlled trials that involved various devices for the delivery of β -agonists, ICS and anticholinergic agents in different clinical settings (emergency department, inpatient, intensive care and outpatient) and patient populations (pediatric and adult asthma, and COPD) were included. Reports in which the same drug was delivered with different devices were analyzed. Their findings indicated that the drugs delivered via different formats are equally effective. Appropriate

technique, cooperation and convenience determine which delivery may be best.

Asthma clinical guidelines mention the use of inhaled short-acting β -agonist either by pMDI or nebulizer as an initial asthma exacerbation home intervention.^{6,7} The GINA global strategy recommends the use of short-acting inhaled β -agonist by pMDI (ideally with a spacer) for home management of mild, moderate and severe exacerbations. GINA also recommends nebulized treatments for severe exacerbations at home and for hospital-based management of acute asthma.⁷

Data in young children clearly support the use of β -agonists, at higher doses, administered via a pMDI with spacer for acute asthma.^{88,89} In a study of 60 children between 1 and 5 years of age hospitalized for an asthma exacerbation, Parkin et al found salbutamol (400 to 600 μ g, 4 to 6 puffs, based on weight) and ipratropium bromide (40 μ g, 2 puffs), both delivered via pMDI with an Aerochamber and mask, to be as effective as nebulized salbutamol (0.15 mg/kg) and ipratropium bromide (125 μ g) administered over 15 minutes by facemask.⁸⁸ However, nearly one third of the subjects randomized to MDI eventually required a nebulized β -agonist.

Two studies have evaluated lower respiratory tract deposition of a radiolabeled salbutamol/albuterol mixture administered to young children. Tal et al showed that on average, less than 2% of the nominal dose of the albuterol given by a pMDI with a spacer and mask to children less than 5 years old was deposited in the lower respiratory tract with most of the drug remaining in the spacer.⁹⁰ Wildhaber et al compared the lung deposition of radiolabeled salbutamol from a nebulizer and a pMDI and spacer in 17 asthmatic children aged 2 to 9 years.⁹¹ Both devices were delivering roughly 5% of the nominal dose to the lower airways. Because of the larger doses of salbutamol administered via the nebulizer (2,000 μ g vs 400 μ g) than the pMDI, a larger amount of drug was deposited in the airways using the nebulizer (108 μ g vs 22 μ g, respectively). In addition, both devices were approximately 50% less efficient in children less than 4 years old than in older children.

In general, β -agonist administration by nebulization is still probably a more practical delivery system for most infants and young children with severe acute asthma because it requires the simple technique of relaxed tidal breathing, particularly if it is difficult to use a tight fitting spacer and mask for a pMDI. In addition, oxygen can be used to power the nebulizer, providing β -agonist and supplemental oxygen simultaneously, and it does offer the capability to administer a controller agent and rescue β -agonist at the same time.

With respect to controller therapy, the only available inhaled drugs that are FDA approved for children under 4 years of age are cromolyn solution and budesonide suspension intended for nebulization. However, a pMDI with a spacer device is certainly more convenient and easier to administer. The GINA global strategy prefers the administration of ICS via a pressurized metered dose inhaler (pMDI) with a spacer and either a facemask (for 0 to 3 years of age) or a mouthpiece (for ≥ 4 years old) for young children with asthma but the dose delivered is variable between spacers.⁷ These guidelines mention the use of nebulizers as an alternative delivery system for children who are unable to use the spacer device effectively. Since young children are only expected to perform tidal breathing, the optimal number of breaths to empty the spacer device varies with the tidal volume, dead space and volume of the device. Important measures to maximize delivery of medication to very young

children include the following: enforcing a tight fitting mask around the child's mouth and nose, encouraging immediate inhalation after actuation, allowing 5 to 6 breaths per single pMDI actuation, making sure that the spacer valve is moving when the child is breathing through the spacer, shaking the inhaler in between actuations and using a lower volume spacer (<350 mL) in these very young children.

The Montreal Protocol, adopted in 1987, mandated a complete elimination of the chlorofluorocarbon (CFC) propellant due to concerns about its damaging effect on the ozone layer. Since 2008, pMDIs now contain hydrofluoroalkane (HFA). However, the pMDI HFAs (even rescue short-acting β -agonists) are approved for use only in children 4 years of age and older. There is no information available on the relationship between lung deposition from HFA pMDI and clinical efficacy or even long-term safety in small children. In addition, no studies exist comparing inhaled medications administered via nebulizer and HFA pMDI with spacer and mask.

Additional factors that should be considered are the costs to the patient (including use of spacer attachments which are not reimbursable) and the use of multiple delivery devices which requires more time for the clinician staff to educate families on proper techniques. To address both issues, perhaps the same type of device can be used for all inhaled drugs for an individual patient. The decision should also incorporate which device the clinician is capable of teaching properly and what the patient/parent prefers. When a child presents with uncontrolled asthma, the assessment should first focus on technique and adherence.

ADHERENCE

The issue of adherence in infants and small children is complicated because the child is entirely dependent on the caregiver to administer the medication. In an observational study of preschool children, Gibson et al sought to evaluate adherence with inhaled prophylactic medications delivered through a large volume spacer using an electronic timer device. Adherence was only 50% with a range of 0% to 94%.⁹² In addition, only 42% of the subjects received the prescribed medication on each study day, and reporting of symptoms in the diary cards did not correlate with good compliance with the prophylactic medication, nor was a correlation found between frequency of administration and adherence. In another study, parental reporting of symptom scores correlated with measured bronchodilator use in only 63% of preschool children.⁹³

A few studies have attempted to determine why caregivers are unable to administer medications as prescribed. Lim et al asked parents why they were reluctant to administer prophylactic medications (such as ICS) to their young children with asthma. Reasons cited included hesitancy to use medications for fear of dependence, side-effects and overdose.⁹⁴ Fortunately, patient education programs developed for parents of small children with asthma improve asthma morbidity and self-management outcome.^{95,96}

NONPHARMACOLOGIC INTERVENTION

Nonpharmacologic measures may be as important not only for young children with established respiratory symptoms, allergies and passive smoke exposure but also in the primary and

secondary prevention of asthma.⁹⁷⁻⁹⁹ The first and likely the most important step toward controlling asthma in sensitized children is to avoid or reduce the patient's exposure to the offending allergen. The environmental interventions that seem to hold the most promise are those that target reducing exposure to indoor allergens and tobacco smoke. Specific environmental control measures are covered in Chapter 21.

Yearly influenza immunization is also strongly recommended for children 6 months of age and older with chronic pulmonary diseases, including asthma. Kramarz et al evaluated the effectiveness of influenza vaccination in preventing influenza-related asthma exacerbations in children 1 to 6 years of age using a retrospective cohort study with the Vaccine Safety Datalink, which contains data on more than 1 million children enrolled in four large health maintenance organizations.¹⁰⁰ Of note, less than 10% of children with asthma were vaccinated against influenza in any of the years studied. Although the incidence rates of asthma exacerbation in those who were vaccinated were found to be higher in the vaccinated group than in those who were not vaccinated, the difference was thought to be largely confounded by asthma severity in the vaccinated group. Using a 'self-control' analysis to correct for this confounder, the risks of asthma exacerbation during each of the influenza seasons were reduced by 22% to 41% with influenza vaccination.

Management of Asthma Exacerbations in Young Children

Exacerbations, also commonly referred to as episodes or flare-ups, are acute deterioration of asthma control characterized by increased symptom severity, sudden change in child's activity or performance (lethargy or lack of interest or exercise intolerance), poor response to or sudden increased need for rescue medication, and breathing difficulty or respiratory distress at its worst. In this age group, these are often preceded by upper respiratory symptoms or viral syndrome. The most effective approach in managing asthma exacerbations involves early recognition of warning signs and early treatment. An action plan should be provided to the family members or caregivers which includes information about what medications to give, medical provider's contact information and when to seek urgent medical attention (such as signs of acute distress, symptoms unrelieved by bronchodilator, increased need for rescue treatment or repeated use of bronchodilator over several hours).⁷ A copy should also be given to daycare providers and school personnel.

HOME MANAGEMENT

Early treatment of asthma exacerbations may prevent a life-threatening event or a hospital admission. Initial treatment should be with a SABA (e.g. albuterol or levalbuterol): 2 puffs from an MDI via a spacer device with or without a facemask, which may be repeated every 20 minutes 2 more times, or a single treatment can be given by nebulizer (0.05 mg/kg [minimum dose, 1.25 mg; maximum, 2.5 mg] of 0.5% solution of albuterol in 2-3 mL saline; or 0.075 mg/kg [minimum dose, 1.25 mg; maximum, 5 mg] of levalbuterol).⁶ If the response is good as assessed by sustained symptom relief, the SABA can be continued every 3 to 4 hours for 24 to 48 hours. Patients should

be advised to seek medical care once excessive doses of bronchodilator therapy are used or for prolonged periods (e.g. >6 puffs of inhaled SABA are used within the first 2 hours, >12 puffs/day for >24 hours, or if the child has not recovered after 24 hours).^{6,7}

If the child does not completely improve with the initial therapy, the SABA should be continued and the caregiver should contact the physician urgently. If the child experiences marked distress, the caregiver should give the SABA immediately and bring the patient to the emergency department or call 9-1-1 or another emergency number for assistance. Intensification of acute treatment with an oral corticosteroid initiated by family members can be considered but evidence for its early use is debatable.¹⁰¹ Doubling the dose of inhaled corticosteroids is not proven sufficient to prevent worsening of exacerbations. However, recent studies in small children not on regular controller therapy have shown benefits from using high-dose ICS at the early onset of a respiratory illness in preventing the need for systemic corticosteroid.^{46,48} One study has shown the efficacy of starting a short course of montelukast at the onset of a respiratory tract illness in small children with episodic wheezing with respect to reducing symptom burden, healthcare utilization and time off work,⁸² but perhaps this benefit from a short course of leukotriene receptor antagonist at reducing symptom burden may only be expected in young children who have atopic risk factors.¹⁰²

MANAGEMENT IN THE EMERGENCY DEPARTMENT OR HOSPITAL

Clinical assessment is used, and scoring systems (e.g. Preschool Respiratory Assessment Measure [PRAM] and the Pediatric Asthma Severity Score [PASS]) have been developed to assess the severity of asthma exacerbations.¹⁰³ Severe exacerbations are characterized by any one of the following: altered mental state (agitated, confused or drowsy), oxygen saturation <92%; tachycardia (>200 beats/minute for 0 to 3 years old; >180 beats/minute for 4 to 5 years old); retractions; cyanosis; and 'silent' chest (wheeze inaudible).⁷ Functional assessment of a young child's degree of airflow limitation is impractical but oxygen saturation should be obtained. Chest radiographs are not recommended routinely but should be considered to rule out pneumothorax, pneumomediastinum, pneumonia or atelectasis.

Initial treatment can be with a SABA by inhaler (albuterol, 4–8 puffs) or nebulizer (0.15 mg/kg of albuterol 0.5% solution; minimum dose 2.5 mg), or nebulized high-dose SABA plus ipratropium bromide (0.25–0.5 mg), up to three doses in the first hour. Oxygen should be given to maintain oxygen saturation above 93%.^{6,7}

Systemic corticosteroids (oral prednisolone 1–2 mg/kg/day; maximum of 20 mg/day for <2 years of age, 30 mg for children 2 to 5 years of age, and 60 mg/day for older children or IV methylprednisolone 1 mg/kg every 6 hours)⁷ should be instituted if the child responds poorly to therapy at 1 hour or continues to deteriorate or if symptoms recur within 3 to 4 hours or symptoms persist beyond 1 day or if the child has recently been on oral corticosteroids. Sensitivity to adrenergic drugs may improve after initiation of corticosteroids.

If the child shows slow or poor response, continuous bronchodilator treatment for the first hour (0.5 mg/kg/h) can be administered. For older children and adults with severe exacerbation having no response to initial inhaled therapy, or for those

who cannot cooperate with or who resist inhalation therapy, adjunctive therapies include intravenous magnesium sulfate (25–75 mg/kg up to 2 g in children) and heliox driven albuterol nebulization, but their use in younger children is not as established. The use of isotonic magnesium sulfate by nebulization (150 mg, 3 doses in the first hour) as an add-on treatment for children as young as 2 years of age with severe exacerbation was found beneficial for those with more severe presentation in the presence of oxygen saturation <92% and with symptoms lasting less than 6 hours.¹⁰⁴

For impending or ongoing respiratory arrest, epinephrine 1:1,000 or terbutaline 1 mg/mL (both 0.01 mg/kg up to 0.3–0.5 mg) may be administered subcutaneously every 20 minutes for three doses, although the use of intravenous β_2 -agonists is still unproven. Children may need ventilatory support with 100% oxygen, intravenous corticosteroids and admission to an intensive care unit (ICU). Further treatment is based on clinical response and objective laboratory findings.

Hospitalization should be strongly considered for any child with a history of respiratory failure or significant psychosocial impediments to optimal acute asthma care. The decision to hospitalize should also be based on presence of risk factors for mortality from asthma, duration and severity of symptoms, course and severity of previous exacerbations, medication use at the time of the exacerbation, access to medical care, and home and psychosocial conditions. Maintenance fluids and electrolyte requirements (both corticosteroids and β_2 -agonists can cause potassium loss) should be provided, especially since these young children are likely to have poor oral intake secondary to respiratory distress or vomiting, but they require intensive monitoring as overhydration may contribute to pulmonary edema associated with high intrapleural pressures generated in severe asthma. Antibiotics may be necessary to treat co-existing bacterial infection.

Criteria for discharging young children home should include a sustained response of at least 1 hour to bronchodilator therapy. The child should also be ambulatory according to age expectation, comfortable, and able to keep food or drink down.⁷ Prior to discharge, the caregiver's ability to continue therapy and assess symptoms appropriately needs to be considered since children with a recent exacerbation are at risk of recurrent episodes. The caregiver should be given an action plan for management of recurrent symptoms or exacerbations, identification of triggers and how to avoid them, and instructions about rescue and controller medications and their use. Hospitalized patients should receive more intensive education prior to discharge. This is another opportunity to review inhaler technique. The inhaled SABA and oral corticosteroids should be continued, the latter for 3 to 7 days. Finally, the caregiver should be instructed about the follow-up visit, which typically takes place within 1 week. Referral to an asthma specialist should be considered for all children with severe exacerbations or multiple emergency department visits or hospitalizations.

Prevention of Asthma

Given the burden of asthma and recurrent wheezing illnesses in young children, with their associated morbidity and healthcare utilization due to risk of severe episodes, not to mention the high direct and indirect costs that go with them, preventive measures are indeed warranted. To have any chance for success,

early intervention will require identifying high-risk infants and establishing effectiveness of the intervention strategy in young children while minimizing the potential for adverse effects. This is discussed in more detail in Chapter 39. Primary prevention is ideal but the right intervention is lacking because of the heterogeneous nature of this condition.

Two studies have evaluated the effects of ketotifen and cetirizine, respectively, in preventing the onset of asthma in genetically prone children.^{105,106} In a double-blind, placebo-controlled, parallel study, children up to 2 years of age without a prior history of wheezing but with a family history of asthma or allergic rhinitis and presence of elevated serum IgE were randomized to receive either ketotifen (0.5–1 mg twice daily) ($N = 45$, mean age 11.5 months) or placebo ($N = 40$, mean age 10.8 months) for 3 years.⁴³ Only 9% of children on active treatment compared to 35% of the placebo group developed frequent episodes of wheezing during the study period ($P = .003$). The other study, called the Early Treatment of the Atopic Child, was a randomized, double-blind, parallel group trial that compared cetirizine (0.25 mg/kg twice daily) and placebo.¹⁰⁶ The medications were administered for 18 months to infants between 1 and 2 years of age with atopic dermatitis and a family history of atopy. The primary outcome, which was the time to onset of asthma in the next 18 months after discontinuation of treatment, was not different between the two groups. Half the children in both cetirizine and placebo groups developed asthma (defined as three episodes of wheezing during the 36 months of follow-up) ($P = .7$). However, in the cetirizine group, infants with evidence of dust mite or grass pollen sensitivity were less likely to have asthma over the 18 months of treatment with a sustained effect for grass-sensitized infants over the 36 months of follow-up compared with those treated with placebo. Furthermore, in the placebo group there was an increased risk of developing asthma in those with baseline sensitivity to egg, house dust mite, grass pollen or cat allergen. These two studies support the role of easily administered preventive measures in delaying or even preventing the development of asthma in genetically predisposed children.

Various other prevention modalities have shown promising potential to modulate asthma development. Given the relevance of environmental and allergen exposure in airway inflammation characteristic of asthma, interventions that can reduce these exposures (e.g. reducing tobacco smoke, dust mite or pet avoidance, and dietary modifications) have been undertaken, with modest overall results, and applicability may be limited by location and individual exposures.^{107–116} In addition, the success of interventions targeting reduction of exposure may be dependent on a multifaceted approach, and not just a single measure alone.¹¹⁷ Recognizing the role of airway infection (including serious respiratory syncytial virus [RSV] and rhinovirus infections in early life) in the development of recurrent wheezing and asthma susceptibility in childhood, perhaps prophylaxis against them might help reduce asthma development. A lower incidence of recurrent wheezing (and even physician-documented episodes) over a 2-year follow-up period was found among preterm infants without chronic lung disease who had received palivizumab (a humanized monoclonal antibody against the RSV fusion protein) compared with preterm infants who had not received palivizumab, prior to enrollment.¹¹⁸ There was also a significant difference in outcomes between palivizumab-treated and untreated children who were not hospitalized for RSV, suggesting that the effect of palivizumab was

not merely to prevent hospitalization but also to avert a lower respiratory tract illness from RSV. In addition, the protective effect of palivizumab appeared to be found in those children without a family history of asthma or atopy.¹¹⁹

A bacterial lysate, OM-85 BV, containing standardized lyophilized fractions per capsule from eight bacteria (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans* and *Neisseria*) is widely used in Europe to reduce acute respiratory tract infections. In a randomized, double-blind, placebo-controlled, parallel group study it has been found to be effective at reducing acute wheezing illnesses in children with a history of recurrent wheezing by 38% compared with placebo.¹²⁰ It remains to be evaluated in larger clinical trials if this can be an effective primary intervention modality that will prevent the development of asthma. Immunomodulators, including this immunostimulant, along with probiotics, prebiotics, anti-IgE and specific immunotherapy, are proposed as potential primary prevention interventions by a National Heart, Lung, and Blood Institute workshop committee.¹²¹

There has been a recent trend toward intervening early in the course of the disease with the hope of altering the natural history of asthma, and clinical trials of what can be considered secondary prevention measures have provided important observations. There have been studies that sought to determine if treatment with an ICS soon after the onset of early indicators of the disease would modify the course of asthma.^{19,47,63,102} The study designs varied with respect to the eligibility criteria, age at entry, frequency of past wheezing episodes and manner and duration of treatment (e.g. maintenance vs intermittent or as needed intervention).

The NHLBI Childhood Asthma Research and Education (CARE) network-sponsored Prevention of Early Asthma in Kids (PEAK) study enrolled approximately 300 2- to 3-year-old children with more than three episodes of wheezing and a positive mAPI to receive either fluticasone propionate 88 μg via pMDI or matching placebo twice daily for 2 years.¹⁹ During the third year observation period of interest, no difference in either the proportion of children with active wheezing or lung function measured using forced oscillometry between the two treatment groups was found. However, during the first two years while on treatment, symptom control was better and asthma exacerbations fewer for the active treatment group compared to placebo. A reduction in growth velocity during the first 8 months (6.6 ± 1.0 vs 7.3 ± 1.0 cm/yr between 1 and 8 months, $P = .005$) and a smaller mean increase in height between 4 and 12 months (4.5 ± 1.1 vs 4.9 ± 1.1 cm, $P = .001$) were observed in the ICS group. However, during the second year of treatment, the growth velocity in the ICS group was greater than that in the placebo group (7.0 ± 0.8 vs 6.4 ± 0.9 cm/yr, $P = .001$). Children in the ICS group had an average height percentile of 51.5 ± 29.2 compared to 56.4 ± 27.3 in the placebo group at the end of treatment ($P < .001$) and 54.4 ± 27.9 compared to 56.4 ± 26.9 at the end of observation ($P = .03$).

Another study (IFWIN; Inhaled Fluticasone propionate in Wheezy Infants) evaluated whether ICS therapy for infants with a history of wheezing could prevent active asthma and prevent loss of lung function in later childhood.⁶³ A total of 200 children (mean age at entry 1.2 years) from a birth study cohort with two documented episodes of wheeze or one prolonged episode, more than 1 month duration, and a parental history of atopy

were randomized to receive fluticasone propionate 100 µg or matching placebo twice daily. At age 5 years, no difference between the ICS and placebo groups in the proportion of children with current wheeze, physician-diagnosed asthma and use of supplemental open-label ICS (fluticasone 100 µg twice daily) was found. Furthermore, the number of exacerbations, lung function (using sRaw through plethysmography with dynamic lung volumes and expiratory flow) and bronchial hyperreactivity (using eucapnic voluntary hyperventilation) were also not different between the groups. Children who were on ICS, particularly after 6 to 12 months, had transient reduction in growth velocity; and those who received both masked and open-label ICS had a slower rate of growth, compared to either the 'masked treatment only' or 'open-label treatment only' groups.

While these two studies demonstrate that long-term treatment with ICS does not modify the course of asthma, they also raise the potential for systemic effects of this intervention which can limit its use for this purpose. Using ICS only for an acute illness and evaluating its long-term impact is attractive not only because it is less burdensome but also it may decrease the risk of growth retardation.

One study, the Prevention of Asthma in Childhood (PAC), sought to determine whether early intervention using intermittent administration of an ICS, when initiated at the first episode of wheezing and during subsequent episodes, could alter the development of asthma.⁴⁷ Of 411 infants born to mothers with asthma enrolled at one month of age, approximately 300 children received at least one 14-day course of budesonide 400 µg/day or matching placebo administered via pMDI and holding chamber (mean age at the first course of study medication was 10.7 months). For every acute illness, children were to start either treatment after 3 days of wheezing. Upon completion of this 3-year study, a similar percentage of symptom-free days between treatment groups (83% vs 82% for the budesonide and placebo groups, respectively) was found. In addition, 24% and 21% of children in the budesonide and placebo groups, respectively, had persistent wheezing. The mean duration of each acute wheezing episode was not reduced by budesonide therapy. Lung function using pre- and post-bronchodilator sRaw at age 3 years was comparable between the two treatment groups. Lastly, there was no difference in height between the groups. Thus, intermittent ICS did not alter the natural history of asthma in infants at risk for asthma nor did it change the duration of the acute wheezing episodes.

The NHLBI CARE Acute Intervention Management Strategies (AIMS) study¹⁰² randomized 238 children aged 12 to 59 months who had at least two episodes of moderate-to-severe wheezing requiring either an urgent care visit and/or systemic steroid course in the context of a respiratory tract illness within the past year. Participants were randomized to receive one of the following for 7 days at the onset of symptoms: budesonide inhalation suspension (1.0 mg twice daily) or montelukast group (4 mg once daily) or conventional rescue bronchodilator therapy. The primary outcome was the proportion of episode-free days (i.e. days free from cough, wheeze, trouble breathing, asthma-associated interference with daily activities or awakening from sleep, healthcare utilization due to wheezing, and use of asthma-related non-study medications) over the entire study period. Compared to conventional rescue bronchodilator therapy, neither budesonide nor montelukast initiated at early signs of illness increased the proportion of episode-free days over a 1-year period. In addition, no differential effect on oral

corticosteroid rescue, asthma healthcare utilization or quality of life was found. Nevertheless, both active study treatments demonstrated modest reductions in symptom severity score (such as wheezing, trouble breathing or activity limitation) relative to conventional therapy, particularly among children with positive API or prior oral corticosteroid use.

These studies provide important information regarding ICS therapy in young children with recurrent wheezing episodes although the overall results regarding prevention of progression to persistent asthma are not convincing. ICS can be indicated to improve asthma control but should not be expected to prevent the development of asthma or persistent wheezing, even for high-risk subjects.

Conclusion

Chronic cough and recurrent wheezing, typical manifestations of asthma, are quite common in young children, yet these symptoms render different long-term outcomes and, acutely, varying severity. For those with a more persistent pattern, controller therapy is indicated. A significant subset have a severe, intermittent course, and for these patients daily controller therapy may still be beneficial. However, recent studies have suggested the efficacy of 'as needed' high-dose inhaled corticosteroid started at the onset of a respiratory illness, particularly in very young children who have atopic risk factors. The development of persistent asthma and requirement for long-term controller therapy in a very young child can be predicted to a limited degree. Currently no clinically available objective and reliable measure of lung function, bronchial hyperreactivity or airway inflammation exists that is applicable to this age group, hence monitoring the effects of interventions or treatment on prevention of asthma inception, modulation of underlying inflammation, perhaps airway remodeling, prevention of deterioration in lung function over time and induction of physiologic or immunologic remission is not feasible. The need to evaluate objectively the efficiency and safety of the various delivery devices and HFA formulation available for inhaled therapies to infants and young children remains. Only a few medications have been approved for use in this population, and studies have demonstrated effects on asthma control using short-term parameters. Studies on prevention of asthma development are warranted, especially in those who are deemed susceptible. Yet these are the ultimate goals that may motivate patients and families, if indeed interventions can really alter the development and the natural history of their disease. These studies often require large sample size and monitoring over longer periods of time which require enormous resources and the use of practical, objective measures of disease activity which are still lacking.

Helpful Websites

The National Heart, Lung, and Blood Institute; website (<http://www.nhlbi.nih.gov/guidelines/asthma/asthgdl.htm>)

The Global Initiative for Asthma; website (<http://www.ginasthma.org/documents/4>)

The complete reference list can be found on the companion Expert Consult website at <http://www.expertconsult.inkling.com>.

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