

EVIDENCE-BASED BEST PRACTICES FOR THE MANAGEMENT OF ASTHMA IN PEDIATRIC PRIMARY CARE IN SOUTH CAROLINA

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Key Messages for Management of Asthma

Assess and document initial severity and follow-up control to select optimal medications.

Environmental control includes a smoke-free home and car and avoiding or minimizing exposure to triggers.

Develop a written asthma action plan (AAP) for patient self-management and provide copies for use at home, school and daycare.

Instruct patients and parents on the proper use of each of their inhalers.

BACKGROUND

A group of physicians (including a pulmonologist and primary care physician) and clinical pharmacists was created to develop this evidence-based best practices summary for the treatment of asthma in pediatric primary care. The National Institutes of Health, National Asthma Education and Prevention Program Expert Panel Report-3 (EPR-3) 2007 and Global Initiative for Asthma (GINA) 2015 Report were the group's main sources of information. This summary also utilized supplemental information from additional review of primary literature, clinical practice guidelines, and clinical consensus from the SCORxE writing group.

Treatment options recommended throughout this document are based on available data derived from various sources. When available, levels of evidence reported by the supportive citation can be found in parentheses at the end of selective sentences. Statements based on conflicting recommendations, lacking evidence, or in opposition to statements from publications were documented as SCORxE consensus, representing complete agreement amongst members of the writing panel. A representative sample of one set of evidence ratings (GINA, 2015 update) and SCORxE consensus are described below:

(Evidence A): Multiple well-designed randomized controlled trials (RCTs), directly relevant to the target population, that yielded a consistent pattern of findings. Evidence A requires substantial numbers of studies involving substantial numbers of participants.

(Evidence B): RCTs, limited body of data. Evidence is from end points of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the statement.

(Evidence C): Nonrandomized trials and observational studies. Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.

(Evidence D): Panel consensus judgment. This category is used only in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories.

(SCORxE Consensus): Consensus among the SCORxE asthma writing panel.

The information contained in this summary is intended to supplement the knowledge of clinicians regarding best practices and drug therapy to treat asthma in children and adolescents in a primary care setting. This information is advisory only and is not intended to replace sound clinical judgment, nor should it be regarded as a substitute for individualized diagnosis and treatment. Special considerations are needed when treating some populations with certain conditions (e.g., pregnancy/breast-feeding, cardiac disease, liver and renal impairment).

PEDIATRIC ASTHMA MANAGEMENT AT-A-GLANCE

➤➤ **Accurate diagnosis**

- Asthma diagnosis is based on clinical presentation of symptoms of **reversible** airflow obstruction and physical examination to rule out other conditions.
- Diagnosis should be confirmed with lung function tests. Spirometry before and after bronchodilator inhalation is the preferred objective measure for assessing lung function. Peak flow meters can be used as an alternative when spirometry is not available.
- Assess for triggers; e.g., cigarette smoke, viral infections, gastroesophageal reflux, odors, allergens.

➤➤ **Initial staging and use of appropriate medication(s) at baseline and follow-up**

- Classify initial asthma severity, based on impairment and risk, to select appropriate therapy.
- Provide a rescue inhaler for all patients with asthma (one for home and one for school/daycare) and a controller medication for those with persistent asthma.
- The controller of choice is an inhaled corticosteroid (ICS).
- Low-dose ICS is a more effective controller therapy than a leukotriene receptor antagonist (LTRA) for persistent asthma.
- Step medication treatment up or down as needed based on level of control.
- Consider using a validated questionnaire to facilitate and standardize the assessment of asthma control.
- Rule out non-adherence to asthma medications, improper inhaler technique, and/or lack of trigger control before stepping up if asthma is not well controlled.
- Depending on the age, preferred step-up includes adding an inhaled long-acting beta₂-agonist (LABA) or LTRA to ICS or increasing the ICS dose.
- Do not use a LABA without an ICS.
- If exercise-induced asthma is a specific problem, and asthma is otherwise well-controlled on ICS, consider adding LTRA or LABA.
- For allergic asthma, consider subcutaneous allergen immunotherapy when a clinically significant allergen cannot be avoided and there is clear evidence of a relationship between asthma symptoms and exposure to the allergen.

➤➤ **Goals of treatment: Achieve and maintain control of asthma**

- Eliminate impairment; e.g., symptoms, nighttime awakening, interference with normal activity, inhaled short-acting beta₂-agonist (SABA) use, and impaired lung function.
- Reduce future risk; e.g., exacerbations requiring oral corticosteroids, hospitalizations, progressive loss of lung function, reduction in lung growth, and side effects.

➤➤ Patient education

- Teach patients and parents basic facts about asthma and the purpose of each prescribed medication.
- Demonstrate proper administration technique of each asthma device the patient needs, and provide instruction sheets for future reference.
- Have patients demonstrate inhaler technique at each visit and provide them feedback.
- Develop a written asthma action plan (AAP) for patient self-management and provide copies for use at home, school and daycare.
- Engage patients and parents in the decision to monitor asthma control based on symptoms, peak flow readings or a combination of both.
- Educate families on how to monitor for overuse of rescue inhaler (> 1 canister/month) and why it is important.
- Discuss plan for management of acute exacerbations, including timely access to oral corticosteroids and detailed contact information.
- Review individualized AAP at every visit and modify as needed.

➤➤ Environmental control and trigger avoidance

- Ask parents, caregivers, and patients about tobacco use. Educate them about the importance of providing a smoke free home, car and environment. Advise smokers to quit and offer assistance (e.g., refer to the South Carolina Tobacco Quitline at 1-800-QUIT-NOW).
- Help patients recognize their own triggers and minimize exposure.
- Effective avoidance of allergens requires a multifaceted, comprehensive approach; single steps alone are generally ineffective.
- Consider involvement of a “lay parent coach” to visit the home and counsel the family to optimize care and improve the environment (e.g., refer to Family Connection Project Breathe Easy 1-800-578-8750).
- Educate families about how to appropriately manage the child’s asthma when exposure cannot be avoided (e.g., exercise, viral infections).
- Administer the inactivated flu vaccine annually.

➤➤ Follow-up on a regular basis to assess level of asthma control

- Follow-up every 3 to 12 months if asthma is well controlled (consider every 3 to 6 months for patients on a daily controller), and every 2 to 6 weeks if not under good control.
- Assess lung function tests periodically, preferably by spirometry. If peak flow meter is used, assess peak expiratory flow (PEF) against the patient’s personal best PEF.

PEDIATRIC ASTHMA

Prevalence

Asthma is primarily a chronic, lifelong inflammatory condition of the lungs affecting the lives of an estimated 29.6 million people in 2012, up more than triple from the estimated 6.7 million US asthma cases in 1980 (SC DHEC, 2015). In 2013, an estimated 8.3% of children had asthma (CDC NHIS, 2013, Table 4-1). Most concerning is the disparity among ethnic groups. From 2001 to 2009, the prevalence among African American children climbed almost 50% (CDC Vital Signs, 2011). In 2013, non-Hispanic blacks had the highest rates among racial/ethnic groups, with about a 10% rate among all ages and a 13.4% rate among children (CDC NHIS, 2013, Table 4.1). Among Hispanics, a disproportionate number of Puerto Ricans (14.6%) have asthma (CDC NCIS, 2013, Table 4-1). Overall lifetime prevalence rates show more females (12.7%) than males (11.9%) affected by asthma (CDC NCIS, 2013, Table 2-1). However, under the age of 18, boys (14.4%) are more likely to have asthma than girls (10.8%), while non-Hispanic blacks (18.2%) are more likely to have asthma than Caucasians (11.3%) (CDC NCIS, 2013, Table 2-1).

In South Carolina (SC), asthma is the most common chronic condition among children. More than 102,440 children are estimated to suffer from asthma, making it the most common chronic disease and leading cause of disability in children. The asthma prevalence rate is highest among those under 18 years old. An estimated 15 – 19% of SC high school students are estimated to suffer from asthma, and 22% of these students have missed school due to their asthma within the last year. Currently only about 1 in 4 SC high school students with asthma are estimated to have an asthma action or management plan from a doctor (SC DHEC, 2015).

Asthma is costly to manage and can lead to early deaths. More than \$110 million in hospitalization costs and more than \$59 million in Emergency Department (ED) costs were reported for SC in 2013. One percent (5,219) of all 2013 SC hospitalizations were for asthma, and 28% of those hospital admissions were children. Asthma and related conditions are the leading cause of hospital admissions for SC children. There were at least 73,000 ED visits due to asthma between 2011 – 2013, more than 28,000 (39%) of these visits by children. Of the 3,630 asthma deaths in the US in 2013, 61 were from SC (SC DHEC, 2015).

Etiology

Asthma is a common chronic disorder of the airways. Variable and recurring symptoms present due to an underlying inflammation can be complex and include airflow obstruction and bronchial hyperresponsiveness. The interactions of these symptoms are highly variable over time within each patient as well as between patients. How these clinical manifestations interact with an individual determines the severity of asthma at that point in time. Over time, airway remodeling involving an activation of many of the structural cells occurs and can result in permanent airway changes that increase airflow obstruction and airway responsiveness. Consequently, patients are less responsive to therapy; and some patients may only be able to achieve partial reversal of airway obstruction as airway remodeling progresses (EPR-3, 2007).

Current guidelines provide the following working definition for asthma: *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma (EPR-3, 2007).*

An established cause of the inflammatory process leading to asthma is still unknown but the timing of environmental exposures interplaying with a person's genetic make-up, as well as other host factors, appears to play an integral role. The strongest identifying predisposing genetic factor placing a person at risk to develop asthma is atopy, an immunoglobulin E (IgE)-mediated response to common aeroallergens. Specifically, viral respiratory infections and airborne allergens are two major environmental factors identified as most important

in the development, persistence, and possibly severity of asthma. These factors appear particularly influential in the susceptible host, especially at a critical time of development (e.g., immunological, physiological). Viral respiratory infections are already recognized as one of the most important triggers of asthma exacerbation. The interaction of respiratory infection along with exposure and sensitization to allergens should be considered together when determining what will lead to the future development of asthma. Though the association is less clearly established, an increased risk of an asthma diagnosis has also been reported with tobacco smoke, air pollution, occupations, and diet (EPR-3, 2007).

Course

Asthma is typically diagnosed in early childhood, but with varying symptoms and decline in lung function based on age. In general, infants and children from 0 to 4 years of age diagnosed with asthma usually have intermittent symptoms of wheezing associated with an infection, but are symptom-free in the interim. In contrast, children from ages 5 to 11 have symptoms associated with inflammation during normal day-to-day function and an increased rate of severe exacerbations compared with adults (Jackson DJ, 2014). Asthma begins early in life for most patients and early, recognizable risk factors for its persistence include atopic disease, maternal smoking during pregnancy, recurrent wheezing, and a parental history of asthma. The severity of symptoms and progression of asthma varies among individuals and will vary within individuals over time. By age 6, most of the decline in lung function occurs, and it occurs mostly in children whose asthma symptoms started before 3 years of age. A small percentage of children ages 5 – 12 with mild-to-moderate persistent asthma will demonstrate progressive reductions in lung growth as measured by forced expiratory volume in 1 second (FEV₁) (EPR-3, 2007). All children 0 – 11 years of age have a high risk of severe exacerbations; however, only children from 5 – 11 years old tend to have a high level of impairment associated with an asthma diagnosis (Jackson DJ, 2014). On average, lung function does not appear to decline for most of these children through 11 – 17 years of age.

Several exposures, including dust and pet allergens, maternal smoking during pregnancy, and outdoor pollutants have been associated with an increased risk of developing asthma. It has also been reported that antibiotic and/or acetaminophen use during pregnancy and infancy, and delivery by Caesarean section are associated with the risk of asthma development (GINA, 2015 update). In addition, current evidence indicates that the underlying severity of asthma is not affected by the long-term, daily use of control medication (EPR-3, 2007).

Whereas asthma is a life-long disease in 30 – 40% of patients, 30 – 70% of patients may experience substantial improvement in or resolution of symptoms by early adulthood. Atopy is known to be the principal risk factor for children to continue to have asthma (Kelly and Sorkness, 2014). A 2012 population study of 504,851 individuals of all ages (42.3% 0 – 17 years of age) in Canada with active asthma who were followed for 15 years found that asthma control and severity waxes and wanes over time (Gershon A, et al, 2012).

Some patients are at high risk of asthma-related death. Risk factors include: low socioeconomic status or inner city residence; prior severe exacerbations requiring intubation or ICU admission for asthma; recent hospitalization or emergency department visit for asthma; difficulty perceiving asthma symptoms or severity of exacerbations; poor adherence with asthma medications or asthma action plan; not using inhaled corticosteroids (ICS); use of > 1 short-acting beta₂-agonist (SABA) canister per month; current or recent use of oral corticosteroids; cigarette smoking; food allergies; and cardiovascular or psychiatric comorbidities (GINA, 2015 update; EPR-3, 2007).

Diagnosis

A diagnosis of asthma is based on: 1) episodic symptoms of airflow obstruction or airway hyperresponsiveness; 2) reversible airflow obstruction confirmed by spirometry; and 3) exclusion of alternative diagnoses (EPR-3, 2007). Depending on the clinical severity, diagnosis should preferably be made prior to starting controller treatment due to the increased difficulty in diagnosing asthma after treatment has been started (BTS, 2014).

A diagnosis of asthma should be considered in the presence of key symptoms or indicators. Although not diagnostic by themselves, the presence of multiple key indicators increases the probability of asthma: 1) wheezing (a high-pitched whistling sounds when exhaling), especially in children; 2) history of cough (worse particularly at night), recurrent wheeze, difficulty in breathing, or chest tightness; 3) symptoms occur or worsen in the presence of exercise, viral infection, animals with fur or hair, house dust mites (in mattresses, pillows, upholstered furniture, carpets), mold, smoke (tobacco, wood), pollen, changes in weather, strong emotional expression (laughing or crying hard), airborne chemicals or dusts, menstrual cycles; and 4) symptoms occur or worsen at night, awakening the patient (EPR-3, 2007). Viral infections that have extended duration and benefit from albuterol or oral steroids are also suggestive of asthma (SCORxE consensus). Of note, asthma is frequently underdiagnosed, particularly in children with viral-induced wheezing. Bronchitis, bronchiolitis, or pneumonia is often diagnosed in these children, despite signs and symptoms being most compatible with a diagnosis of asthma (EPR-3, 2007).

Physical findings that increase the probability of asthma include: hyperexpansion of the thorax, especially in children; use of accessory muscles; appearance of hunched shoulders; chest deformity; sounds of wheezing during normal breathing, or a prolonged phase of forced exhalation (typical of airflow obstruction); increased nasal secretions, mucosal swelling, and/or nasal polyps; and atopic dermatitis/eczema or any other manifestation of an allergic skin condition (EPR-3, 2007).

Spirometry is an essential objective measure to establish the diagnosis of asthma, because the medical history and physical examination are not reliable means of excluding other diagnoses or characterizing lung function. Spirometry can demonstrate obstruction and assess reversibility in patients 5 years of age and older. Reversibility is determined by an increase in FEV₁ of $\geq 12\%$ from baseline after inhalation of a SABA. Spirometry is preferred and generally recommended, rather than measurements by a peak flow meter, because of wide variability in peak flow meters and reference values. The following additional studies are not routinely necessary but may be useful when considering alternative diagnoses: additional pulmonary function studies; bronchoprovocation tests; chest x-ray; allergy testing; and biomarkers of inflammation (EPR-3, 2007).

Additional studies are not routinely performed but may be helpful to exclude alternative diagnoses (e.g., foreign body aspiration, vascular rings, tracheomalacia). Bronchoprovocation (e.g., with methacholine or exercise challenge) may be useful when asthma is suspected but spirometry is normal or almost normal. Bronchoprovocation is generally not recommended if FEV₁ is less than 65% of predicted; it should only be performed by a trained individual in an appropriate facility. Although a positive methacholine bronchoprovocation test is diagnostic for the presence of airway hyperresponsiveness, which is consistent with but not specific to asthma, a negative test has a high negative predictive value and is more helpful to rule out asthma (EPR-3, 2007). Similarly, a negative exercise challenge test is helpful in excluding asthma in patients with exercise-related shortness of breath (BTS, 2014 revised).

PEDIATRIC ASTHMA ALGORITHM

Use of Algorithm

The asthma algorithm provides sequenced medication recommendations based on best available evidence or consensus of the SCORxE writing group where evidence is lacking (for details, refer to the Algorithm for Treatment of Asthma (p. 2) of the SCORxE Evidence-Based Best Practices For the Management of Asthma in Pediatric Primary Care 8-page hand-out May 2015 available at: <http://www.sccp.sc.edu/SCORxE>). The algorithm's format and the approach of using algorithms to assist with optimal treatment decisions are based on the methods utilized by the Texas Medication Algorithm Project and the Texas Children's Medication Algorithm Project (Rush et al, 1999).

A thorough evaluation, detailed history, and comprehensive physical assessment should be performed to diagnose asthma prior to making treatment decisions. Patients may enter the algorithm at different stages depending on asthma severity and age. Each stage of the algorithm represents a trial of a different medication. Different formulations of a medication may be tried within a given stage to optimize response. Progression to

different stages should be considered when asthma is not well controlled after ruling out non-adherence, improper inhalation technique and lack of trigger control.

MANAGEMENT

Goals of Therapy

The goals of treatment are to eliminate impairment and reduce future risks associated with asthma. Impairment includes frequency and intensity of symptoms and functional limitations associated with asthma; future risks include recurrent asthma exacerbations, death, progressive decline in lung function (or reduced lung growth in children), and adverse effects from asthma medications. It is also important to assess and include the patient's goals in the individualized therapeutic plan. The ultimate goal of asthma management is to achieve and maintain control of the disease. (for well controlled asthma criteria, refer to the Classification table (p. 3) of the SCORxE Evidence-Based Best Practices For the Management of Asthma in Pediatric Primary Care 8-page hand-out May 2015 available at: <http://www.sccp.sc.edu/SCORxE>).

Control of Environmental Factors and Comorbid Conditions

Avoiding pre-natal and post-natal smoking is commonly recommended to minimize the development of asthma in children. Prenatal intake of vitamins D and E has been shown to lower the risk of wheezing. Other strategies reported include: recommending vaginal delivery when appropriate; providing an environment with decreased stress for both mother and child; avoiding broad spectrum antibiotics during pregnancy and the first year of life; and minimizing acetaminophen (Tylenol[®]) pediatric use which has been reported to increase the risk of asthma. Although not shown to have a direct effect on asthma risk, breastfeeding should be recommended for all infants for the associated positive benefits (Evidence A) (GINA, 2015 update).

Asthma exacerbations may be caused by various triggers, including allergens, viral infections, pollutants, irritants (e.g., strong smells, odiferous sprays), and medications. Reducing exposure to some of these categories (e.g., avoiding active or passive exposure to cigarette smoke, avoiding foods/additives/medications known to cause symptoms) improves asthma control and reduces medication needs. Whenever possible, reasonable measures should be taken to avoid or minimize exposure to other triggers such as viral infections, allergens, and pollutants. However, complete avoidance is usually difficult as many patients with asthma react to multiple triggers that are ubiquitous in the environment. Thus, medications to maintain asthma control have an important role since patients are often less sensitive to these triggers when their asthma is well controlled (GINA, 2015 update).

Direct or passive exposure to cigarette smoke, the most important indoor pollutant, adversely affects quality of life, lung function, need for rescue medications and long-term control with inhaled steroids. Parents, caregivers, and older children should be screened for tobacco use; smokers should be advised to quit and provided assistance. Parents and caregivers of children with asthma should be advised to provide a smoke free environment at home, in the car, and at daycare (EPR-3, 2007). While no direct evidence links e-cigarette exposure to asthma exacerbation risk, the inflammation caused by the nicotine in e-cigarettes could theoretically worsen asthma symptoms; second-hand e-cigarette smoke exposure is also a concern (Nickels et al, 2014). Avoidance of nicotine smoke exposure as first- or second-hand smoke via e-cigarettes is suggested (SCORxE Consensus). Asthma, especially if not well controlled, can be exacerbated by outdoor pollutants, which may have an additive effect with allergen exposure. In times of unfavorable outdoor conditions (e.g., cold temperatures, low humidity, high pollen and mold counts, air pollution), patients may try avoiding strenuous activity outdoors and remaining indoors (GINA, 2015 update).

Exposure of patients who have asthma to allergens (Evidence A) or irritants to which they are sensitized has been shown to increase asthma symptoms and precipitate asthma exacerbations. Assessment of the role of allergens, particularly indoor inhalant allergens, as contributing factors should be considered in patients with persistent asthma (Evidence A). The patient's medical history is usually sufficient to determine sensitivity to seasonal allergens; skin testing or *in vitro* testing is recommended to determine sensitivity to perennial indoor allergens (EPR-3, 2007). Minimizing exposure to allergens to which patients are sensitized is recommended; however, benefits of reducing allergen exposure on asthma morbidity and/or mortality have

limited data. Mites are the major allergen in house dust. Physical and chemical methods to decrease house dust mites have been shown to reduce numbers of house dust mites, but have not improved asthma symptoms (Evidence A). This lack of clinical benefit may be due to an inadequate reduction in number of house dust mites or to exposure in settings outside the patient's home (SCORxE Consensus). Effective allergen avoidance requires a multifaceted, comprehensive approach; individual steps alone are generally ineffective (Evidence A). Individualized, home-based, multi-trigger, multi-component interventions can effectively reduce exposures to cockroach, rodent, and dust mite allergens for patients sensitive to those allergens (Evidence A), and may improve asthma outcomes. (for environmental control measures, refer to the Environmental Control table [p. 7] of the SCORxE Evidence-Based Best Practices For the Management of Asthma in Pediatric Primary Care 8-page hand-out May 2015 available at: <http://www.sccp.sc.edu/SCORxE>) (BTS, 2014 revised; Crocker et al, 2011; EPR-3, 2007; GINA, 2015 update; Roberts et al, 2005). Patients and their families living in multi-unit housing may have more difficulty eradicating cockroaches if there is a widespread infestation compared to others in single housing.

Immunotherapy, whether subcutaneous or sublingual, may be used by an allergist in certain patients to reduce some asthma symptoms (BTS, 2014 revised; SCORxE Consensus). Immunotherapy can reduce asthma symptoms, medication requirements, and bronchial hyper-reactivity (BHR), with greater effect on allergen-specific BHR than non-specific BHR (Abramson et al, 2010). Use of either subcutaneous or sublingual immunotherapy must be compared with pharmacologic options (e.g., antihistamines) or the avoidance of the allergen while considering the risks of adverse effects, costs, and inconvenience of prolonged therapy (Evidence D) (GINA, 2015 update). Immunotherapy is generally reserved for patients whose asthma is difficult to control with medications because of the time commitment and the potential for serious side effects. Allergen subcutaneous immunotherapy can be considered when a clinically significant allergen cannot be avoided and there is clear evidence of a relationship between asthma symptoms and exposure to the allergen (Evidence B) (EPR-3, 2007). Evidence is strongest for use of subcutaneous immunotherapy for single allergens, especially house dust mites, animal dander, and pollen (EPR-3, 2007). A usual course of immunotherapy consists of weekly injections for 3 – 5 years. Side effects associated with immunotherapy include injection site reactions, rash, wheezing, breathlessness and very rarely life-threatening or fatal allergic reactions. Consequently, subcutaneous immunotherapy should only be administered in a physician's office where trained personnel and appropriate medical treatment are available (EPR-3, 2007). Interest has increased in the use of sublingual immunotherapy, which is associated with fewer side effects (particularly a lack of systemic reactions) than subcutaneous immunotherapy. Sublingual immunotherapy has shown beneficial effects on asthma control that may persist for years after discontinuation. Evidence to date suggests that sublingual immunotherapy is less effective than subcutaneous immunotherapy, and more research is needed (EPR-3, 2007).

Comorbid conditions that may impact asthma control should be evaluated and treated. Asthma control may improve when the following conditions are treated appropriately: allergic bronchopulmonary aspergillosis (Evidence A); symptomatic gastroesophageal reflux (Evidence A); obesity (Evidence B, limited studies); obstructive sleep apnea (Evidence D); rhinitis/sinusitis (Evidence B), and chronic stress/depression and anxiety (Evidence D). In patients with food allergies or known anaphylaxis, avoidance of the offending food plus training on anaphylaxis management are recommended for both the patient and the family/caregivers (ALA, 2012; EPR-3 2007; Gibson et al, 2009; GINA, 2015 update; Tamarcaz and Gibson, 2009).

The Centers for Disease Control and Prevention recommends annual influenza vaccination for all persons greater than 6 months of age (CDC, updated 2014). Patients with asthma have a higher risk of complications from influenza and therefore, should be advised to receive the influenza vaccine annually (Evidence D) (GINA, 2015 update). However, vaccination has not been shown to reduce the frequency or severity of asthma exacerbations during the influenza season (Evidence B) (EPR-3, 2007). Due to concerns of possible increased wheezing and hospital admissions in infants given live intranasal influenza vaccination, use of the inactivated influenza vaccine is recommended for patients with asthma as it has not been associated with an increase in asthma exacerbations immediately after vaccination (Cates and Rowe, 2013). There is insufficient evidence to recommend routine pneumococcal vaccination in children and adolescents with asthma (Sheikh et al, 2014; GINA, 2015 update).

In summary, a multifaceted approach to avoid triggers is likely necessary in order to improve asthma

outcomes. Interventions to help with asthma control include: avoiding tobacco exposure (Evidence A); eating a healthy diet with fruits and vegetables for general health benefits (Evidence A); reducing weight if obese (Evidence B); using non-polluting heating and cooking sources (Evidence B); employing relaxation strategies (Evidence B); identifying goals and strategies to deal with emotional stress (Evidence D); utilizing allergen immunotherapy after weighing the benefits against the risks (Evidence D); avoiding unfavorable outdoor conditions (cold, low humidity, high air pollution) and strenuous physical activity in these conditions (Evidence D); and avoiding foods causing a confirmed allergic reaction (Evidence D) (GINA, 2015 update).

Medications

Medications for asthma are categorized into two general classes: long-term controllers and rescue medications. Research reports that within the same class, one medication is not significantly more effective or harmful than any other medication (Cates and Lasserson, 2013a; Jonas et al, 2011 update; Lasserson et al, 2011). While medications are equally effective at equipotent doses, selection of a device that is appropriate for each patient (e.g., age, motor skills) is important to ensure adequate delivery of the medication to the lungs. (for asthma medication dosing information, refer to Dosing Guidelines [pp. 4 – 5] of the SCORxE Evidence-Based Best Practices For the Management of Asthma in Pediatric Primary Care 8-page hand-out May 2015 available at: <http://www.sccp.sc.edu/SCORxE>).

Long-term control medications include inhaled corticosteroids (ICSs), long-acting inhaled beta₂-agonists (LABAs), leukotriene modifiers, mast cell stabilizers, theophylline, and immunomodulators. The most effective long-term control medications are those that diminish the underlying inflammation characteristic of asthma (Level A) (EPR-3, 2007).

Corticosteroids reduce airway hyperresponsiveness, inhibit inflammatory cell migration and activation, and block late-phase reaction to allergen(s) through anti-inflammatory mechanisms of action. The underlying severity or progression of asthma is not altered by early intervention with continuously or intermittently administered ICSs. Although ICSs do not change the natural history of the disease, they do improve quality of life and should be used to control asthma symptoms (Evidence A) (EPR-3, 2007). The principal advantage of ICS over oral corticosteroids is their high local potency to reduce inflammation in the lung and their low systemic activity (EPR-3, 2007). Regular daily ICS use is the mainstay of controller therapy in patients of all ages with asthma (GINA, 2015 update; Chauhan et al, 2013a; Rodrigo and Castro-rodríguez, 2013). There is moderate strength of evidence that equipotent ICS doses administered through similar delivery devices are comparable in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication, as well as the overall incidence of adverse events or withdrawals due to adverse events (Adams et al, 2014; Jonas et al, 2011). ICS should be initiated at a dose that is appropriate for the severity of the disease, as there is some dose-response relationship. Patients with mild to moderate asthma are usually started on low to moderate ICS doses. There are limited data to guide dosing in severe asthma, but higher ICS doses are commonly associated with increased systemic side effects (Adams et al, 2008b, 2009a, 2009b, 2009c; EPR-3, 2007; BTS, 2014 revised; GINA, 2015 update). In mild to moderate asthma, regular treatment with higher dose ICS or initial treatment with higher dose ICS followed by a stepping down do not provide additional benefits (Adams et al, 2008b, 2009a, 2009c; BTS, 2014 update; Powell and Gibson, 2008). Titrate ICS to the lowest effective dose in order to minimize side effects. Oral corticosteroids can be used long-term for the treatment of severe asthma that is inadequately controlled with high-dose ICS in combination with another controller medication (EPR-3, 2007). Once control is achieved, make repeat attempts to gradually move to an alternate-day oral regimen to minimize systemic side effects (GINA, 2015 update).

LABAs include salmeterol and formoterol, and are defined as such because they provide bronchodilation for at least 12 hours after a single dose. LABAs are devoid of anti-inflammatory activity and carry a black box warning to only be used as add-on therapy for patients with asthma that is inadequately controlled on an ICS (EPR-3, 2007; GINA, 2015 update; BTS, 2014 update). Use of LABAs alone has been associated with an increased risk of asthma-related hospitalizations and death (Nelson, 2006). It is recommended that when added to ICS, a combination inhaler (ICS + LABA) be used to improve adherence and convenience (GINA, 2015 update; BTS, 2014 update), and to prevent inadvertent use of LABA alone (FDA

statement, 2010). Available data are inadequate to determine if concomitant use of ICS or other controller medications mitigates the increased risk of asthma-related death from LABAs, but there are trials occurring presently to evaluate this clinical question (Chowdhury et al, 2011; NCT01475721). Although bronchodilator response does not diminish with long-term use, chronic use of LABAs is associated with a partial loss of bronchoprotective effect against methacholine, histamine, and exercise challenge. For example, duration of protection against exercise-induced bronchospasm (EIB) is reduced from 9 hours after a single dose to less than 4 hours after chronic use (Kelly and Sorkness, 2014). LABAs may be used before exercise to prevent EIB, but frequent or chronic use before exercise is discouraged, as this may disguise poorly controlled persistent asthma (EPR-3, 2007). Although addition of LABAs to ICS have not been found to reduce exacerbations, an improvement in lung function parameters (e.g., FEV₁, peak expiratory flow) as well as increased short-term growth has been demonstrated compared with increased ICS dose (Castro-rodríguez et al, 2014). Therefore, addition of LABAs to ICS therapy is a consideration prior to increasing ICS dose (EPR-3, 2007; BTS, 2014; Kelly and Sorkness 2014).

Leukotriene modifiers interfere with the pathway of leukotriene mediators, which are released from mast cells, eosinophils, and basophils. These medications include the leukotriene receptor antagonists (**LTRAs**) montelukast and zafirlukast, and zileuton, a 5-lipoxygenase inhibitor. Use of zileuton is limited because of hepatotoxicity, drug-interaction potential, and four times daily dosing. LTRAs are thus the leukotriene modifiers most frequently used in the management of asthma, the main advantages being that they are taken orally once or twice daily. More specifically, montelukast is preferred because of advantages over zafirlukast, including once daily dosing, lack of pharmacokinetic interactions with food, and available dosage forms. Overall, most evidence from randomized clinical trials and meta-analyses show that LTRAs are less effective than low-dose ICS as monotherapy, or than add-on LABAs to ICS as combination therapy (EPR-3, 2007; Chauhan and Ducharme, 2012; Chauhan et al, 2013b; Chauhan and Ducharme, 2014; Castro-rodríguez et al, 2014). Consequently, LTRAs are usually considered an alternative, non-preferred option for monotherapy or add-on therapy (EPR-3, 2007; GINA, 2015 update). Two recent “pragmatic” trials, primarily in adults ≥ 25 years old (very few children enrolled, despite eligibility criteria including as young as 12 years of age), suggest that LTRAs may be options as first-line controller and step-up therapy since results showed an equivalent effect of LTRAs on asthma-related quality of life at two months when compared to ICS as first-line monotherapy and to LABAs as add-on therapy to an ICS. However, equivalence was not demonstrated at 2 years, despite better adherence in the LTRA treatment groups, which should have biased results in favor of equivalence (Price et al, 2011).

Other classes of medications are not routinely recommended or are rarely used for the treatment of asthma (EPR-3, 2007; GINA, 2015 update). **Mast cell stabilizers** (e.g., cromolyn and nedocromil) are considered safe but require four times daily dosing and have limited evidence of effectiveness. **Methylxanthines** (e.g., theophylline) are rarely used for adults and adolescents as adjunctive therapy to ICS to provide additional bronchodilation due to their narrow therapeutic index requiring routine monitoring of serum concentrations. They have minimal effect on airway reactivity and are significantly less effective than low-dose ICS (EPR-3, 2007; Seddon et al, 2009). **Immunomodulators** such as omalizumab are reserved for use later in a step-care approach. Omalizumab is the only adjunctive therapy demonstrated to provide additional benefits to high-dose ICS plus LABA in patients who have severe persistent allergic asthma (EPR-3, 2007; GINA, 2015 update). Compared with placebo, omalizumab has been shown, in certain subsets of patients with allergic triggers, to reduce the incidence of exacerbations, reduce ICS use, and improve quality of life measures in patients with moderate to severe disease (Lai et al, 2015; Normansell et al, 2014). Data up to one year of treatment duration has demonstrated a well-tolerated safety profile with the most common side effect reported being injection site reactions. Additionally, rare incidences of anaphylaxis have occurred (Lai et al, 2015; Normansell et al, 2014; Limb et al, 2007). While malignancy has been associated with omalizumab use, a causal relationship has not been established. High cost, patient age and characteristic limitations, and requirement that omalizumab must be administered in a healthcare facility equipped to treat potential anaphylaxis remain limitations to wide-spread use of this medication (Lai et al, 2015; Burch et al, 2012; Faria et al, 2014).

Rescue medications are used to provide prompt relief of bronchoconstriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing. These medications include short-acting beta₂-

agonists (SABAs) and anticholinergics. Although not as fast acting (onset > 4 hours), oral corticosteroids are also included in this section as they are used short-term for the treatment of moderate and severe exacerbations to prevent the progression and speed the recovery of exacerbations.

Inhaled SABAs (i.e., albuterol, levalbuterol) are the most effective bronchodilators. They have a quick onset (3–5 minutes) and fewer side effects compared with inhaled anticholinergics (e.g., ipratropium), oral beta₂-agonists, or theophylline (BTS, 2014 revised). Levalbuterol is the (R)-enantiomer of albuterol, which is a racemic mixture of (R)- and (S)-enantiomers; evidence of a clinically meaningful difference between albuterol and levalbuterol is inconclusive. SABAs are the treatment of choice for acute asthma symptoms and exacerbations and for prevention of EIB (Evidence A). Chronic, daily use of SABAs is not recommended as it offers no benefits, and may be associated with a small degree of tachyphylaxis of bronchoprotective effect and bronchodilator responsiveness, particularly without the use of concomitant ICS (EPR-3, 2007; Walters et al, 2009). SABAs are effective rescue medications, even in patients taking LABAs, but may require higher doses (approximately one extra puff) to compensate for a small degree of tachyphylaxis induced by chronic LABA therapy (Kelly and Sorkness, 2014) The LABA, formoterol, shows a similar onset of action and efficacy compared to SABAs when used as a rescue medication in adults, but it is not FDA-indicated for the treatment of acute exacerbations, nor is it recommended for that use by current US guidelines (EPR-3, 2007; GINA, 2015 update; Welsh and Cates, 2013). During an acute exacerbation, SABAs can be given via metered dose inhaler (MDI) with a spacer or nebulization (BTS, 2014 revised; GINA, 2015 update). Of note, current guidelines do not recommend oral administration of SABAs because inhaled administration is more effective and safer than oral administration (BTS, 2014 revised; EPR-3, 2007).

Inhaled anticholinergics such as ipratropium bromide can produce further bronchodilation when used in addition to SABAs, but clinical benefits of this approach have only been demonstrated in the emergency department management of severe asthma exacerbations (EPR-3, 2007; GINA, 2015 update; Griffiths and Ducharme, 2013). Anticholinergics can be used as an alternative to SABAs, but their efficacy has not been adequately compared to SABAs, and they are not FDA-indicated for the treatment of asthma (EPR-3, 2007; GINA, 2015 update).

Oral corticosteroids can be used in short courses to achieve prompt control of moderate to severe asthma upon initiation of therapy or to treat moderate or severe acute exacerbations. Oral steroids should be given early when treating asthma exacerbations in children (Evidence A) (BTS revised, 2014). ICS should not be substituted for oral steroids in acute asthma treatment (Evidence A) (BTS revised, 2014). Since side effects are dose and duration dependent, prompt reassessment of the asthma management plan is recommended if multiple short-courses (especially ≥ 4 per year) of oral corticosteroids are used (Evidence C) (EPR-3; 2007).

Stepwise Approach for Pediatric Asthma Management

The goal of treatment for all patients is to maintain long-term asthma control with the least amount of medication to minimize adverse effects. Evidence supports approaching pharmacologic therapy in a stepwise fashion to minimize impairment and risk while attaining and optimizing control of asthma (Evidence A). The level of asthma severity guides the initial therapy selected, then the level of asthma control guides any follow-up treatment adjustments. Selection and adjustment options for medication can include the type (including delivery method), amount, and administration schedule (Evidence A). Step-down therapy is helpful to pinpoint the minimum medication that still maintains control (Evidence D) (EPR-3, 2007).

If asthma control is not achieved and maintained with initial therapy, consider non-adherence (e.g., assess refill history, dose counter tallies, age appropriate self-care skills), poor inhaler technique, and lack of trigger control before stepping up therapy. Device pictures can be useful to assess adherence of pediatric patients and their families/caregivers. Consider trials of preferred controller(s) in the same step before stepping up treatment, particularly if an alternative treatment option was initially selected (EPR-3, 2007).

Treatment Steps

	Evidence Level*			
	AGE (years):	< 5	5-11	≥ 12
Step 1: SABA prn Rescue Inhaler				
- SABAs prn are usually sufficient to manage symptoms for intermittent asthma (EPR-3, 2007; BTS, 2014 revised).	D	A	A	
- SABAs should be available and used as quick-relief therapy for ALL patients with persistent asthma in all settings (BTS, 2014 revised; EPR-3, 2007).	D	A	A	
Step 2: Introduction of Controller Therapy (plus SABA prn rescue inhaler)				
- ICSs are the most effective and preferred long-term control agent for initiating therapy for persistent asthma in children of all ages (BTS, 2014 revised; EPR-3, 2007). There are few head-to-head trials and less evidence in children compared with adults. ICSs improve asthma control in children more effectively than LTRAs or any other single, long-term control medication. ICSs reduce impairment and risk of exacerbations, but they do not appear to alter the progression or underlying severity of the disease.	A	A	A	
- Low-dose ICS is the preferred therapy for mild persistent asthma (Adams et al, 2008b, 2009a, 2009c; BTS, 2014 revised; EPR-3, 2007; GINA, 2015 update).	A	A	A	
- Daily controller therapy is also recommended for preschool children with recurring wheezing and risk factors for persistent asthma (EPR-3, 2007).	A			
- LTRAs are less effective than ICSs but may be used as an alternative, particularly in young children requiring controller therapy and those patients unable/unwilling to use ICS (GINA, 2015 update; BTS, 2014 revised; Chauhan and Ducharme, 2012; EPR-3, 2007).	B	B	B	
Step 3: Medium-dose ICS or Two Controllers (plus SABA prn rescue inhaler)				
- ICS increased to medium dose is a preferred therapy before adding another controller in children < 5 in order to ensure adequate dose delivery, since lung deposition may be lower in this age group (EPR-3, 2007; Loughheed et al, 2012; GINA, 2015 update).	C			
- While the benefits from ICS in the impairment domain may begin to plateau at low doses, studies in children have demonstrated improved symptoms and lung function with increasing doses of ICS in children with greater levels of impairment (Adams et al, 2008b, 2009a; EPR-3, 2007).		B**	A	
- ICS dose increases can reduce the risk of exacerbations in older children and adults, but may require up to a four-fold dose increase (EPR-3, 2007).				
- Addition of a LABA to low-dose ICS is the preferred therapy in children ≥ 12 (GINA, 2015 update; Loughheed et al, 2012). Such add-on therapy may benefit these patients more than increasing ICS above low-dose (GINA, 2015 update). There are studies reporting better benefit when adding a LABA to low-dose ICS in older children and adults with low lung function and > 2 days/week impairment. For adolescents not fully controlled with low-dose ICS monotherapy, the addition of a LABA to ICS therapy has been demonstrated modestly more effective than use of a higher dose of ICS alone to improve lung function and symptom control as well as reduce use of SABAs and the risk of exacerbations requiring oral corticosteroids (Ducharme et al, 2010; EPR-3, 2007). Although combination of an ICS with a LABA has demonstrated a more effective improvement in lung function, its superiority remains modest compared with the combination of ICS and LTRA for improving symptoms, reducing the use of SABAs, and preventing exacerbations (Chauhan and Ducharme, 2014; Loughheed et al, 2010).				A
- In children 5 – 11, addition of a LABA to a low-dose ICS may be the best option for reducing asthma symptoms and improving asthma control, but data are limited and some children do their best with an increased dose of ICS or the addition of a LTRA to a low-dose ICS (BTS, 2014 revised; Chauhan et al, 2013a; de Blic et al, 2009; EPR-3, 2007; Gappa et al, 2009; Lemanske et al, 2010; Ni Chronin et al, 2010; Ortega-Cisneros et al, 1998; Vaessen-Verbene et al, 2010; Verberne et al, 1998).***			B	
- LABAs should only be used with an ICS; LABAs have no anti-inflammatory activity and there is a rare, increased risk of life-threatening or fatal exacerbations (BTS, 2014 revised; EPR-3, 2007; GINA, 2015 update). LTRA is an optional second controller if providers have safety concerns about using a LABA.				

Step 4: Medium-dose ICS and Second Controller (plus SABA prn rescue inhaler)		
- Combination of medium-dose ICS and LABA is the preferred treatment for ages 5 and older while an alternative is a medium-dose ICS and LTRA combination (EPR-3, 2007).**** A key benefit of adding a LABA that has been shown in children ≥ 12 is improved lung function (Chauhan and Ducharme, 2014; EPR-3, 2007).	B**	B
- Comparative studies in children ≥ 12 report that the addition of an LTRA is less effective than with a LABA, (GINA, 2015 update; Chauhan and Ducharme, 2014) but an LTRA is an optional second controller (see LABA precautions in Step 3).		A
- Due to the very limited data available in children < 5, available guidelines state the best treatment option has not been established. A treatment option to consider is medium-dose ICS and LTRA (GINA, 2015 update, EPR-3, 2007).	D	
Step 5: High-dose ICS and Second Controller (plus SABA prn rescue inhaler)		
- Combination of high-dose ICS and LABA is the preferred treatment for ages 12 and older (GINA, 2015 update).		A
- The addition of an LTRA is less effective than with a LABA, (GINA, 2015 update; Chauhan and Ducharme, 2014) but an LTRA is an optional second controller (see LABA precautions in Step 3).		A
- In children < 12, consider referral to a specialist (see higher level care) (GINA, 2015 update).	D	D**

* Evidence levels are provided for guideline-endorsed treatment options

** Extrapolated from older children and adults

*** ICS increased to moderate dose is the preferred therapy for children ages 6 – 11 (GINA, 2015 update).

**** Consider referral to a specialist in children ages 6 – 11 (GINA, 2015 update).

Higher Level of Care

Referral to a specialist is preferred for patients who are not controlled despite adherence and correct inhaler technique with controller regimens outlined above (Evidence D, GINA, 2015 update). A treatment option to consider, preferably with a specialist's advice, would be the combination of high-dose ICS and an LTRA for children < 5 years (GINA, 2015 update). For children 5–11 years, combination high-dose ICS and LABA would be preferred, with LTRA as an alternate second controller (EPR-3, 2007) (see LABA precautions in Step 3). If patients are still uncontrolled, oral corticosteroids may be added to high-dose ICS and second controller combination regimens ([Evidence D] GINA, 2015 update), (EPR-3, 2007). Before beginning a maintenance regimen with oral corticosteroids, consider a 2-week course to confirm a therapeutic response and reversibility of symptoms (EPR-3, 2007).

Consultation with a specialist is also recommended if considering a trial of omalizumab for patients 12 years of age and older with allergic asthma not controlled on high-dose ICS and LABA therapy (Evidence A),(GINA, 2015 update).

Step-Down

Once asthma is well controlled for at least 3 – 6 months, a step-down in asthma medications can be considered to identify the minimum therapy required to maintain good control (Evidence D) (EPR-3, 2007; SCORxE Consensus). Careful consideration should be given to the time of year before initiating a step-down (e.g., avoiding such an attempt during the fall season, flu season, or at the beginning of the school year) (Durrani, 2014; Rank et al, 2013a; SCORxE consensus). Step-down therapy should be conducted under close supervision in patients at risk for fixed airflow limitation (e.g., lack of ICS therapy, exposures to tobacco smoke or other inhaled irritants, and low FEV₁) or risk factors for exacerbations (e.g., past history of intensive care unit admission, continued exposure to smoke or allergens, comorbidities such as obesity, rhinosinusitis, and food allergy, and > 1 exacerbation in previous year) (GINA, 2015 update).

There is little evidence to support specific recommendations on the rate of reduction and follow-up frequency with guidelines primarily based on available research in adults. Reduce medication therapy gradually to allow asthma control to be monitored (BTS, 2014 revised; GINA, 2015 update, EPR-3, 2007). More rapid dose reductions during the season of better symptomatic control may be appropriate in children with milder asthma and a clear seasonal pattern to symptoms (BTS, 2014 revised). If on medium to high doses of ICS monotherapy, the ICS dose can be reduced by 25 – 50% every 3 months to the lowest dose that maintains control (Evidence B) (GINA, 2015 update) (Evidence D) (BTS, 2014 revised; EPR-3, 2007). If on low-dose ICS monotherapy, dosing can be switched from twice daily to once daily for budesonide, ciclesonide, and mometasone (GINA, 2015 update); other ICSs may lose much of their efficacy with once daily dosing. If on a medium to high dose ICS and LABA combination, the caregiver can start by reducing the ICS dose by 50% until a low dose is reached. Discontinuation of LABA therapy may be an option at this point, though evidence is insufficient in children to recommend this as a definitive course of action (SCORxE consensus). The FDA recommends discontinuing LABA first due to the risk of severe exacerbations and death, but evidence in older adolescents and adults suggests that discontinuation of LABA likely leads to loss of asthma control and increased asthma impairment (Brozek et al, 2012; GINA, 2015 update). If on a low-dose ICS and LABA combination, ICS dosing can be switched from twice daily to once daily for budesonide, ciclesonide, and mometasone; other ICSs may lose much of their efficacy with once daily dosing. There is less evidence for stepping down from a different combination (e.g., ICS and LTRA). Guidelines suggest decreasing the ICS dose by 50% until a low dose is reached and continuing the other controller medication (GINA, 2015 update). A complete cessation of ICS therapy is associated with an increased risk of exacerbations; therefore, ICS therapy should not be completely withdrawn without close supervision.

Most patients should be seen by their provider at least every 3 months during attempts to slow down therapy (Link, 2014) and instructed on how to contact their provider if and when asthma worsens (Evidence D) (GINA, 2015 update; EPR-3, 2007). Discontinuation of controller treatment may be considered in patients who are symptom-free for 6 to 12 months with no risk factors for exacerbations (GINA, 2015 update) and during a time of year when the individual patient is exposed to his/her fewest environmental triggers.

Exercise-Induced Bronchospasm

Exercise-induced bronchospasm (EIB) should be anticipated in all patients with asthma. During exercise, hyperventilation of drier and cooler air leads to a loss of heat and/or water from the lung, which can trigger EIB. Typically, EIB occurs during or within minutes of vigorous activity, peaking 5 – 10 minutes after the end of the activity, and resolving after another 20 – 30 minutes (EPR-3, 2007). Obesity or a lack of fitness may also cause shortness of breath and wheezing and should be differentiated from EIB.

Exercise may be the only trigger of asthma symptoms in some patients (EPR-3, 2007). EIB may

be attenuated by warming up prior to exercise, or by placing a mask or scarf over the mouth (for cold-induced EIB). Pre-treatment before exercise can effectively prevent EIB: SABAs (Evidence A) used within minutes of exercise can be helpful for 2 – 3 hours; LABAs (Evidence A) can be effective for up to 9 – 12 hours after a single dose, but only 4 hours after chronic daily use (Evidence A); and LTRAs (Evidence B) are effective to prevent EIB when administered 2 hours prior to exercise (Evidence A) (GINA, 2015 update; EPR-3, 2007;) and have not demonstrated the development of tolerance (BTS, 2014 revised). Cromolyn or nedocromil taken shortly before exercise is another option, but it is not as effective as SABAs (Evidence B) (EPR-3, 2007).

For most patients, exercise-induced asthma is a marker of inadequately controlled asthma, and is an indication for initiation or increase in controller medication, particularly ICS (BTS, 2014 revised; EPR-3, 2007). Adding an LTRA or a LABA can be considered for patients with EIB who are otherwise well controlled on ICS (BTS, 2014 revised).

Acute Exacerbations

Asthma exacerbations are subacute (over hours to days) or acute (over 1 – 2 hours) episodes of progressively worsening shortness of breath, cough, wheezing, and/or chest tightness, with characteristic reductions in expiratory airflow. Objective measures of lung function (spirometry or PEF), rather than symptoms, are more reliable indicators of severity. Good control of asthma with ICS reduces the risk of exacerbations. However, patients with any level of asthma severity may be susceptible to exacerbations, even severe ones that can be life threatening (EPR-3, 2007).

Patients at high risk of asthma-related death should receive intensive education and monitoring, and should seek medical care early during an exacerbation. Risk factors for asthma-related death include: history of severe exacerbations (e.g., requiring intubation or intensive care unit admission); ≥ 2 hospitalizations or ≥ 3 emergency department visits in the past year; poor adherence using asthma medication or following a written asthma action plan (AAP); use of > 1 SABA canister/month; current use or recent discontinuation of oral corticosteroids; difficulty perceiving airway obstruction or severity of worsening asthma; low socioeconomic status; illicit drug use; major psychosocial problems or psychiatric conditions; food allergies; and obesity. (GINA, 2015 update; EPR-3, 2007; Wechsler et al, 2007).

Home management of asthma exacerbations. Asthma exacerbations are best managed with early recognition and treatment at home. Self-management education of patients and their families/caregivers should be provided and includes (EPR-3, 2007):

- (1) How to use a written AAP with specific instructions on when and how to treat an exacerbation, including detailed provider contact information.
- (2) How to identify early indicators of an exacerbation based on signs and symptoms, and PEF values. PEF values are particularly useful in patients with moderate or severe asthma or a history of severe exacerbations, and in those who are poor symptom perceivers. A PEF value below 80% of personal best/predicted signals the need for SABA rescue medication; persisting values below 50% indicate the need for immediate medical care.
- (3) When to initiate treatment for an exacerbation based on symptoms and/or PEF values and when to contact the provider. If symptoms occur or PEF value falls below 80% of personal best/predicted, rescue SABA treatment should be initiated and response monitored; PEF values below 50% of personal best/predicted usually require immediate medical attention.
- (4) How to adjust medications in response to an exacerbation, such as briefly increasing SABA frequency and, possibly, adding a burst of oral corticosteroids (GINA, 2015 update; EPR-3, 2007; Rowe et al, 2008b). Importantly, guidelines do not recommend doubling the ICS dose to treat acute exacerbations as it is not effective at reducing the severity or preventing the progression of exacerbations (GINA, 2015 update; EPR-3, 2007; Quon et al, 2010; Loughheed et al, 2012).
- (5) How to avoid or minimize exposure to environmental trigger(s).

- (6) How to monitor response to treatment and access provider in a timely fashion if symptoms persist or deteriorate or response to SABA treatment decreases.

Pharmacologic therapy for home management of asthma exacerbations.

Initial Treatment generally consists of SABA 2 – 6 puffs via metered-dose inhaler or alternatively via nebulizer with up to two treatments administered 20 minutes apart (GINA, 2015 update; EPR-3, 2007). Further management varies depending on response to initial treatment. Children < 5 years of age should be monitored for at least 1 hour after start of SABA treatment (GINA, 2015 update). Determination of response is based on the worst sign or symptom (e.g., improved wheezing but persisting shortness of breath is not a good response):

Good Response: no wheezing or dyspnea (or tachypnea in young children), and PEF \geq 80% personal best/predicted; should contact provider for follow-up instructions; can continue SABA treatment every 3 – 4 hours for 24 – 48 hours; consider adding a burst of oral corticosteroids.

Incomplete Response: persistent wheezing or dyspnea (or tachypnea in young children), and PEF 50 – 79% personal best/predicted; add burst of oral corticosteroids; continue SABA treatment; should contact provider same day for further instruction.

Poor Response: marked wheezing or dyspnea, and PEF < 50% personal best/predicted; add burst of oral corticosteroids; repeat SABA treatment immediately. If distress is severe and nonresponsive to initial treatment, should contact provider immediately. If provider is unavailable, may consider proceeding to emergency department; call 911 for ambulance transport if needed (EPR-3, 2007). In children < 5 years, if inhaled SABA is needed for more than 6 puffs within the first 2 hours of the exacerbation or if recovery does not occur within 24 hours, patients should seek medical attention (GINA, 2015 update). If provider is unavailable, may consider proceeding to emergency department; call 911 for ambulance transport if needed.

Continue more intensive treatment for several days. SABA treatment should continue until symptoms improve and PEF is improving, although prolonged treatment with excessive doses (e.g., > 12 puffs/day for > 24 hours, unless per provider or AAP instructions) should prompt medical attention. Recovery from an exacerbation is often gradual and variable; symptoms may resolve in 1 – 2 days after moderate exacerbations, but may take 3 or more days after severe exacerbations. Airway inflammation may persist well beyond symptom resolution, up to 2 – 3 weeks (EPR-3, 2007). Patients need to follow up with their primary care provider within 1 – 2 weeks following self-managed exacerbations to have their written AAP reviewed, symptoms assessed, and cause of exacerbation potentially identified (GINA, 2015 update), including the need for more patient education.

Viral respiratory infections, more common in children under 12 years of age, may cause intermittent but severe exacerbations. Management recommendations are based on exacerbation severity (EPR-3, 2007):

Mild: SABA every 4 – 6 hours for 24 hours (or longer per clinician instructions) may be sufficient to control symptoms and improve lung function. If this therapy is required more often than every 6 weeks, a step up in long-term asthma therapy should be considered.

Moderate to severe: consider a short course of oral corticosteroids.

History of severe exacerbations: consider initiating oral corticosteroids at the first sign of a viral respiratory infection.

In the urgent or emergency care setting, classification of exacerbation severity and its management are based on severity of signs and symptoms, and PEF values. Severe exacerbations (e.g., dyspnea at rest that interferes with conversation and a PEF < 40% personal best/predicted) benefit from additional adjunctive therapies and usually require emergency department care, and maybe even hospitalization (EPR-3, 2007; Rowe et al, 2008a). Life-threatening exacerbations (e.g., too dyspneic to speak and PEF values < 25% personal best/predicted) require hospitalization, possibly to intensive care unit (GINA, 2015 update; EPR-3, 2007; Smith et al, 2008). Arterial oxygen saturation (SpO₂) level < 92% is another objective measure used to determine the need for hospitalization (BTS, 2014 revised; GINA, 2015

update; SAMH, 2013 update).

Inhaler Devices and Spacers

Inhaled asthma medications are available in a variety of devices that differ in the technique required; they include nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs). Dose counters on MDIs and DPIs can be a useful tool to assess adherence and help the patient know when to replace the inhaler. Each type of device has advantages and disadvantages (for details, refer to Tips for Optimal Selection and Use of Inhalers [p. 8] of the SCORxE Evidence-Based Best Practices For the Management of Asthma in Pediatric Primary Care 8-page hand-out May 2015 available at: <http://www.sccp.sc.edu/SCORxE>). All devices are equally efficacious if used with the proper technique. An efficient and evidence-based technique for selecting an inhaler is to use the 3W-H approach, asking “Who? What? Where? and How?” (Dekhuijzen et al, 2013). Specific things to consider when selecting a device include: device/drug availability; patient age and the ability to use the selected device correctly; device use with multiple medications; cost and reimbursement; drug administration time; convenience; and patient preference (Dolovich et al, 2005). The most important consideration in device choice is how effectively the individual patient and caregiver can use it and whether they will continue to do so as long as prescribed. For any device, a crying or screaming child can greatly reduce lung deposition (Kwok and Chan, 2014).

Children under 4 years of age usually cannot generate sufficient inspiratory flow to use DPIs. Although some DPI products are approved for use in children as young as 4 years of age, proper DPI technique is not likely to be achieved until children are over 8 years old (SCORxE consensus). Young children (≤ 4 years of age) and infants can receive treatments through nebulizers, or MDIs utilizing a spacer fitted with a facemask (Kelly and Sorkness, 2014). The tightness of the facemask is a crucial factor for drug delivery (Kwok and Chan, 2014). In most cases, an MDI plus a spacer is as effective as a nebulizer (Cates et al, 2009, 2014). Volume of a spacer should not be much larger than a patient’s tidal volume, as it can decrease drug delivery (Kwok and Chan, 2014). Children as young as 6 years of age may be able to use an MDI alone, however proper MDI technique is not likely to be achieved until they are older than 8 years of age (Dolovich et al, 2005; SCORxE consensus). Use of a spacer with an MDI is often preferred well into teenage years due to difficulties in mastering the MDI technique (SCORxE consensus). It has been shown that MDIs with a spacer compared with MDI alone showed less wheezing, less cough after an asthma attack, and shorter school absences (Kwok and Chan, 2014). Use of a spacer is also beneficial in reducing local side effects of ICS such as thrush and hoarseness, particularly in patients with poor inhaler technique (Dolovich et al, 2005; Irwin and Richardson, 2006).

Side Effects

ICS medications are generally well tolerated and safe at recommended doses (for details, refer to Select Asthma Medication Side Effects table [p. 6] of the SCORxE Evidence-Based Best Practices For the Management of Asthma in Pediatric Primary Care 8-page hand-out May 2015 available at: <http://www.sccp.sc.edu/SCORxE>). Local side effects are most common, and include hoarseness, thrush, and less commonly, steroid rash. Patients should be instructed to brush teeth, rinse mouth and spit after each use to minimize the risk of local side effects; those using a spacer with a facemask should also wash the skin covered by the facemask after each use. The use of a spacer with an MDI reduces the incidence and severity of local side effects. Systemic side effects can occur with any ICS given for prolonged periods, albeit the risk is much lower than with oral corticosteroids (EPR-3, 2007). Low to medium doses of ICS therapy may be associated with a small (approximately 1 cm), dose-related height deficit within the first 1-2 years of therapy, primarily in children who initiate therapy before puberty. The most recent evidence suggests that this height deficit may persist into adulthood but is not progressive or cumulative (EPR-3, 2007; Kelly et al, 2012; Sharek et al, 2011). Monitor height and weight using a growth chart on an annual basis (BTS, 2014 revised). High-dose ICS therapy is associated with alterations in glucose metabolism, and rarely with dermal thinning, easy bruising, and adrenal suppression (EPR-3, 2007). Other systemic side effects such as reduced bone mineral density and ocular effects (i.e., cataracts and glaucoma) have only been reported in adults with a high lifetime cumulative exposure to

ICS (EPR-3, 2007). To minimize adverse effects in patients using ICS, use the lowest dose for controlling symptoms. If higher doses are needed, the use of add-on agents (e.g., LABAs) should be considered (BTS, 2014 revised).

LABAs have been associated with a small increased risk of severe, life-threatening asthma exacerbations and asthma-related death compared to non-LABA treatment. The risk appears greatest in children ages 4 – 11 (no data available < 4 years of age), and in African-Americans (Nelson, 2006). It is unknown at this time if this risk is obviated with the use of concomitant ICS (Cates et al, 2013; Cates and Karner, 2013; Cates and Lasserson 2013a, 2013b; Ni Chroinin et al, 2010). LABAs carry a black box warning never to be used as monotherapy for the treatment of asthma (Walters et al, 2014).

LTRAs are generally well tolerated. Post-marketing cases of behavior and mood-related changes have been reported with LTRAs, as well as rare cases of fatal hepatic failure with zafirlukast (EPR-3, 2007).

SABAs administered at usual doses have reported side effects that include tachycardia, skeletal muscle tremor, headache, and irritability; use of very high doses may be associated with hyperglycemia and hypokalemia (EPR-3, 2007).

Oral corticosteroids used in frequent (4 or more per year) short-term courses ('bursts') are associated with similar systemic side effects as chronic, daily use of oral corticosteroids. For patients receiving oral steroid bursts of 14 days or less, no taper is needed (SAMJ, 2013). If long-term therapy with oral corticosteroids is necessary, administer the lowest possible dose in the morning (single daily dose or alternate day dosing) and monitor closely for adverse effects; make persistent attempts to reduce oral corticosteroid use (high doses of ICS with LABA are preferable); and refer to an asthma specialist (EPR-3, 2007).

EVALUATION OF PATIENT RESPONSE

Use of Measurement-Based Care

Measurement-based care (MBC) promotes the use of rating scales or questionnaires at every visit to measure impairment, risk, side effects, and patient adherence as well as guide tactics to modify dosage and treatment duration. Examples of standardized questionnaires include the Asthma Control Test™ (ACT), the Childhood Asthma Control Test, the Asthma Control Questionnaire, and the Asthma Therapy Assessment Questionnaire (ATAQ) control index. These questionnaires measure elements of the impairment domain such as daytime and nighttime symptoms, use of rescue medications, and interference with usual activities. Assessment of the risk criteria is more difficult. Some assessment of the risk of exacerbations can be inferred from the medical history such as a history of exacerbations requiring emergency department (ED) visits, hospitalization, or intensive care unit admission. However, there are patients who have few symptoms or impairment of quality of life but are still at high risk of severe, even life-threatening exacerbations. Finally, little is known about the prevalence of a heightened risk of progressive loss of pulmonary function among patients who have asthma or whether any current treatment can prevent it (EPR-3, 2007; BTS, 2014 revised; GINA, 2015 update).

Lung Function Tests

Spirometry is the most often used lung function test to assess the risk of future adverse events. Lung function is usually measured as the FEV₁, (forced expiratory volume in one second after a deep breath) and is expressed as a percent of the predicted value or as a proportion of the forced vital capacity (FVC) or FEV₁/FVC.

Of note, in patients aged 5 years and younger, spirometry may not be reliably performed. Many children with uncontrolled asthma will have normal lung function between exacerbations (BTS, 2014 revised; GINA, 2015 update).

Guidelines recommend that spirometry tests be performed: (1) during initial assessment (Evidence C); (2) 3 – 6 months after beginning treatment and stabilizing symptoms and PEF (EPR-3, 2007; GINA, 2015 update); (3) during times of progressive or prolonged loss of asthma control; and (4) at least every 1 – 2 years (Evidence D) (EPR-3, 2007). Depending on clinical severity and response to treatment, spirometry may be needed more frequently (Evidence D). To detect the potential for decline and rate of decline of pulmonary function, it is useful to follow spirometry measures over the patient's lifetime (Evidence C). Consider using an experienced coach to conduct spirometry tests to help optimize patient performance.

The use of handheld mechanical or electronic metered devices to obtain quantitative and reproducible PEF measurements provides a simple way to assess the presence and severity of airflow obstruction. Daily long-term PEF monitoring can aid in the early detection of changes in asthma control that require treatment adjustment, the evaluation of response to changes in treatment, and providing a quantitative measure of impairment (Evidence B) (EPR-3, 2007). Once ICS has been initiated, personal best PEF readings are typically attained within 2 weeks. The average and diurnal PEF values usually continue to improve for 3 months (GINA, 2015 update). Good candidates for long-term peak flow monitoring include patients with severe persistent asthma, a history of severe exacerbations (Evidence B), exercise intolerance, and/or poor self-awareness of symptoms (Evidence D) (EPR-3, 2007, GINA, 2015 update).

Biomarkers of airway inflammation may have a role in assessing severity of disease or response to treatment. Eosinophilic inflammation in children can be assessed with induced sputum analysis or fractional exhaled nitric oxide (FENO) concentrations (BTS, 2014 revised). Both are feasible and safe, and may aid in the identification of corticosteroid responsiveness, but are not routinely recommended due to limited clinical experience and uncertain benefit. (Lougheed et al, 2012). Specifically in patients with severe asthma, eosinophils found in the sputum may help dictate adjustments of ICS dose and correlate with a reduction of exacerbation frequency (BTS, 2014 revised; GINA, 2015 update).

Visit Frequency

There is no evidence to support recommendations on monitoring frequency. It is recommended to base the frequency of visits on the patient's initial level of control, their response to treatment, and their level of engagement with self-management. Guidelines recommend a range of 2 – 12 weeks for the first follow-up visit (GINA, 2015 update, EPR-3, 2007, SCORxE Consensus), and subsequent visits every 3 – 12 months based on the level of asthma control (GINA, 2015 update). Consider follow-up every 3 – 6 months for patients on a daily controller (SCORxE Consensus). If asthma is poorly controlled, a follow-up in 2 – 6 weeks is recommended (EPR-3, 2007). Additionally, a visit should occur within 1 week of an exacerbation event (BTS, 2014 revised; GINA, 2015 update).

PATIENT EDUCATION

Self-Management and Asthma Action Plan (AAP)

Self-management education programs have been shown to improve a wide range of asthma outcomes (BTS, 2014 revised; EPR-3, 2007; Lougheed et al, 2010; Wolf et al, 2008). Use written, personalized AAPs reviewed on a regular basis to reinforce self-management education and focus on individual needs, taking into consideration the patient's cultural background, health literacy and autonomy (Bailey et al, 2009; BTS, 2014 revised; EPR-3, 2007; GINA, 2015 update; Gardner A et al, 2015). Review key components of self-management education regularly (Evidence A) and include: basic information about asthma; patient's current level of control; what well-controlled asthma looks like; types and roles of medications; inhaler technique; how to recognize and handle worsening asthma; when and how to seek medical advice (e.g., detailed emergency contact information for home/caregivers, school, afterschool); strategies to control triggers, and importance of adherence to medications and appointments (BTS, 2014 revised). Set educational targets according to the patient's age that include

participation of older children in self-management (ICON, 2012).

Self-management education that includes a written AAP appears to be more effective than other forms of self-management education, although more research is needed to confirm the independent contribution of AAP to the overall effect on asthma outcomes. Additionally, computer-based and internet-based educational methods may be useful, especially for older children and adolescents (Evidence B) (Agrawal et al, 2005; Ducharme et al, 2011; EPR-3, 2007; Sunshine et al, 2011; Zemek et al, 2008, ICON, 2012). For recommended resources, refer to Selected Features of Suggested Asthma Resources table [p. 7] of the SCORxE Evidence-Based Best Practices For the Management of Asthma in Pediatric Primary Care 8-page hand-out May 2015 available at: <http://www.sccp.sc.edu/SCORxE>. All patients, especially those with moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma, should be provided a written AAP that includes instructions for both daily management and recognition and management of worsening asthma (EPR-3, 2007). Either peak flow-based or symptom-based self-monitoring can be effective if taught and followed correctly (Evidence B) (EPR-3, 2007). Overall, symptom-based plans were found to be superior to peak flow-based plans in children and adolescents (Zemek et al, 2008), yet peak flow-based plans may be particularly useful for patients who are poor symptom perceivers or have a history of severe exacerbations. When using a peak-flow-based plan, personal best is preferred to percent predicted peak (Evidence A) (EPR-3, 2007; GINA, 2015 update). AAPs are a useful communication tool, particularly for parents or caregivers who have not accompanied the patient to the doctor. It is important to provide an individualized AAP to schools/care facilities along with ensuring availability of a rescue inhaler.

It is important to deliver self-management education at an appropriate reading and health literacy level. Health literacy is the ability to obtain, process, and understand health information in order to make informed decisions about health care. More than one-third of adults have limited health literacy, which is associated with medication errors and nonadherence, higher health care costs, poor chronic disease management, increased hospitalizations, and poor health outcomes. Since it is difficult to identify which patients may have limited health literacy, a Health Literacy Universal Precautions Toolkit has been developed to help adult and pediatric practices ensure that systems are in place to promote better understanding by all patients (AHRQ, 2010).

Patients unable to undertake guided self-management due to low health literacy can still achieve benefit through a structured program of regular medical review. Efficacy of self-management education does not differ whether the patients adjust their medication using written AAP or according to their health care providers (Evidence A) (GINA, 2015 update).

Device Technique

Proper inhalation technique is essential to optimize medication delivery and therapeutic effect (Kelly and Sorkness, 2014) (for details, refer to Basic Steps for Use of Inhalers [p. 8] of the SCORxE Evidence-Based Best Practices For the Management of Asthma in Pediatric Primary Care 8-page hand-out May 2015 available at: <http://www.sccp.sc.edu/SCORxE>). Using a device-specific checklist, instruct patients on the proper inhaler use at each visit (EPR-3, 2007; GINA, 2015 update). Proper use and technique may: increase adherence; decrease the need for step-up therapy; decrease the need for ED visits and hospitalizations; and decrease asthma exacerbations. Group education, video instruction, and personal instruction are all effective methods of education about inhaler technique. The most effective approach includes written and verbal instructions, physical demonstrations with each device (by provider/experienced coach and by the patient) and feedback on the patient's technique (Bosnic-Anticevich et al, 2010). Errors often recur within 4-6 weeks after initial training; repeated instructions are needed to maintain correct technique over time (Bosnic-Anticevich et al, 2010; Munzenberger et al, 2007; GINA, 2015 update). Proper use of other devices such as peak flow meters and spacers should also be reviewed at every visit.

REFERRAL TO SPECIALIST

Considerations for referral to a specialist (usually an allergist or pulmonologist) include:

- Difficulty confirming a diagnosis (BTS, 2014 revised; GINA, 2015 update)
- Symptoms present from or near birth (BTS, 2014 revised)
- Difficulty achieving or maintaining control of asthma after 3 – 6 months of therapy (EPR-3, 2007; BTS, 2014 revised; GINA, 2015 update)
- Risk factors for asthma-related death (e.g., near-fatal attack in the past, anaphylaxis in a patient with asthma (GINA, 2015 update)
- Other conditions complicating asthma or its diagnosis (e.g., sinusitis, severe rhinitis, nasal polyps, vocal cord dysfunction, aspirin-exacerbated disease, allergic bronchopulmonary aspergillosis) (EPR-3, 2007; BTS, 2014 revised; GINA, 2015 update)
- Uncontrolled on 2 controller medications (or one controller if < 5 years old)
- 2 bursts of oral steroids per year or exacerbation requiring hospitalization (EPR-3, 2007; GINA, 2015 update)
- High dose ICS as a consideration (EPR-3, 2007)
- Indication for immunotherapy or omalizumab (EPR-3, 2007)
- Indication for additional testing (e.g., allergy skin testing, rhinoscopy, complete pulmonary function studies, provocative challenge, bronchoscopy) (EPR-3, 2007)

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