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 physicians) 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 was the group's primary source 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. The following symbols, found in parentheses at the end of sentences, indicate the level of evidence for the statements as shown below (EPR-3, 2007):

(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).

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.

➢ Staging and use of appropriate medication(s)

- Classify initial asthma severity, based on impairment and risk, to select appropriate therapy.
- Provide a rescue inhaler for all patients with asthma 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 and/or improper inhaler technique before stepping up if asthma is not well controlled.
- Depending on the age, preferred step-up includes adding an inhaled long-acting beta$_2$-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 beta$_2$-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 all asthma devices 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.
- 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 Quitline 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 6 months if asthma is well controlled, 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.

ASTHMA

Prevalence

Asthma is primarily a chronic, lifelong inflammatory condition of the lungs that affects the lives of approximately 25 million people, and the number of individuals with asthma is continuing to grow. In 2009, an estimated 1 in 10 children (10%) had asthma. Most concerning is the large increase in prevalence among ethnic groups. From 2001 to 2009, the overall prevalence grew by 4.3 million with prevalence among African-American children climbing almost 50%. In 2009, non-hispanic blacks had the highest rates among racial/ethnic groups with about an 11% rate among all ages and 17% (1 in 6) rate among children (CDC Vital Signs, 2011). Among Hispanics, a disproportionate number of Puerto Ricans (16.6%) have asthma (CDC NCHS, 2012). Overall lifetime prevalence rates show more females (13.9%) than males (11.9%) affected by asthma. However, under the age of 18, boys (15.3%) are more likely to have asthma than girls (11.8%), while African-Americans (17.1%) are more likely than Caucasians (12.6%) (CDC NHIS, 2012 update).

Asthma is costly to manage and can lead to early deaths. Total costs, including medical expenses and lost workdays, have increased by $3 billion since 2002 reaching $56 billion in 2007. Of the 3,388 asthma deaths in 2009, fifty-seven were from South Carolina (CDC Vital Signs, 2011; SC DHEC, 2011).

In South Carolina, asthma is the most common chronic condition among children. More than 90,000 children are estimated to suffer from asthma which makes it a leading cause of school absences and disability[4] (SC DHEC 2011). There were 136,000 emergency room (ER) visits recorded due to asthma from 2008 to 2010, with more than 37,000 made by children (CDC Vital Signs, 2011; SC DHEC, 2011). Asthma and related conditions are the leading cause of hospital admissions for SC children (SC DHEC, 2010).

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 and 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 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. Age groups differ when measuring decline in lung function to follow progression of asthma. 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 aged 5–12 with mild to moderate persistent asthma will demonstrate progressive reductions in lung growth as measured by forced expiratory volume in 1 second (FEV_1); but, on average, lung function does not appear to decline for most of these children through 11–17 years of age. 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 chronic disease in 30-40% of patients, 30-70% of patients may experience substantial improvement in or resolution of symptoms by early adulthood. Atopy, school-age onset, and presence of bronchial hyperresponsiveness have been identified as predictors of persistent adult asthma (Kelly and Sorkness, 2011).

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, use of > 2 short-acting $beta_2$-agonist (SABA) canisters per month, cigarette smoking, and cardiovascular or psychiatric comorbidities (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).

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; 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 FEV_1 of ≥ 12 percent from baseline after inhalation of a SABA. Spirometry is generally recommended, rather than measurements by a peak flow meter, because of wide variability in peak flow meters and reference values. Peak flow meters are designed for monitoring, although they may also be used as an alternative to spirometry in the diagnostic evaluation if spirometry is not readily available (ATS/ERS, 2009). 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 FEV_1 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, thus 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, 2011 revised).

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 March 2012 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. 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 March 2012 available at: http://www.sccp.sc.edu/SCORxE).

Control of Environmental Factors and Comorbid Conditions

Asthma exacerbations may be caused by various triggers, including: allergens, viral infections, pollutants, and medications. Reducing exposure to some of these categories (e.g., avoiding active or passive exposure to cigarette smoke, and 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 asthma patients 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, 2010 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). 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, patients may try avoiding strenuous activity outdoors and remaining indoors (GINA, 2010 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 has 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 there is limited evidence of benefits on asthma symptoms in children (Evidence B) (BTS, 2011 revised; GINA, 2010 update; Gotzsche and Johansen, 2008). 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, dust mite, and rodent 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 March 2012 available at: http://www.sccp.sc.edu/SCORxE) (BTS, 2011 revised; Crocker et al, 2011; EPR-3, 2007; GINA, 2010 update; Roberts et al, 2005). However, patients/families living in multi-unit housing may have more difficulty eradicating cockroaches if there is a widespread infestation compared to others in single housing.

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) (BTS, 2011 revised; EPR-3, 2007). Immunotherapy reduces asthma symptoms, medication requirements and bronchial hyper-reactivity (BHR), with greater effect on allergen specific BHR than non-specific BHR (Abramson et al, 2010). Evidence is strongest for use of subcutaneous immunotherapy for single allergens, especially house dust mites, animal dander, and pollen (EPR-3, 2007). 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. 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, and those may persist for years after discontinuation. Evidence to date suggests that sublingual immunotherapy is less effective than subcutaneous immunotherapy, and more research is needed (BTS, 2011 revised; 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 B), obesity (Evidence B, limited studies), obstructive sleep apnea (Evidence D), rhinitis/sinusitis (Evidence B), and chronic stress/depression (Evidence D). (ALA, 2012; EPR-3 2007; Gibson et al, 2003; GINA, 2010 update; Taramarcaz and Gibson, 2003).

Consider inactivated influenza vaccination for children more than 6 months of age and adults who have asthma (Evidence A). Since asthma patients have a higher risk of complications from influenza, the Center for Disease Control recommends vaccination for all persons who have asthma as well as their household contacts and caregivers (Fiore et al, 2010). 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 as it has not been associated with an increase in asthma exacerbations immediately after vaccination (Cates et al, 2008). There is insufficient evidence to recommend routine pneumococcal vaccination in children and adolescents with asthma (Sheikh et al, 2002).

Medications

Medications for asthma are categorized into 2 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, 2010; Jonas et al, 2011 update; Lasserson et al, 2008). 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 March 2012 available at: http://www.sccp.sc.edu/SCORxE).

Long-term control medications include inhaled corticosteroids (ICS), long-acting inhaled beta$_2$-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 through anti-inflammatory mechanisms of action. 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). 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, 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, 2000a; Jonas et al, 2011). ICS should be initiated at a dose that is appropriate for the severity of the disease, with mild to moderate asthma responding to low to moderate ICS doses, and severe asthma benefiting from high ICS dose (Adams et al, 2000b, 2008a, 2008b, 2009; EPR-3, 2007; Lasserson et al, 2006). 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, 2000b, 2008a, 2009; BTS, 2011 revised; Powell and Gibson, 2003). 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). Attempts should be made to use an alternate-day regimen to minimize systemic side effects.

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 so they should not be used as monotherapy for asthma. Use of LABAs has been associated with an increased risk of asthma-related hospitalizations and death (Levenson, 2008). 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. LABAs carry a black box warning and should only be used as additional therapy for patients with

asthma who are inadequately controlled on an ICS (EPR-3, 2007). 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, 2011). 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).

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 a 5-lipoxygenase inhibitor (zileuton). Use of zileuton is limited because of hepatotoxicity and a potential for drug interactions. LTRAs are thus the leukotriene modifiers most frequently used in the management of asthma. Their main advantage is that they are taken orally once or twice daily. Two recent "pragmatic" trials suggest that LTRAs may be good options as first-line controller and step-up therapy. 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). Of note, study findings apply only to adults since very few patients younger than 25 years old were enrolled, despite eligibility criteria including children as young as 12 years of age. Overall, most of the 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 (Ducharme and di Salvio, 2004a; Ducharme et al, 2011a; EPR-3, 2007). Consequently, LTRAs are usually considered an alternative, non-preferred option for monotherapy or add-on therapy (EPR-3, 2007).

Other classes of medications are not commonly used for the treatment of asthma. **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 mainly used as adjunctive therapy to ICS to provide additional bronchodilation. They have minimal effect on airway reactivity and are significantly less effective than low-dose ICS (EPR-3, 2007; Seddon et al, 2006). Methylxanthines are rarely used due to their narrow therapeutic index requiring routine monitoring of serum concentrations. **Immunomodulators** such as omalizumab can be used for patients with allergic asthma. 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, 2010 update). Rare risks of severe anaphylactic reactions, malignancy, and cost typically limit the use of omalizumab for patients with severe persistent allergic asthma that is inadequately controlled with the combination of high-dose ICS and LABA (EPR-3, 2007; Walker et al, 2006).

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 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.

SABAs (e.g., albuterol, levalbuterol, pirbuterol) 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 beta$_2$-agonists, or theophylline (BTS, 2011 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, 2003). 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, 2011) 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; Welsh and Cates, 2010). Of note, oral administration of SABAs is not recommended in current guidelines as inhaled administration is more effective and safer than oral administration (BTS, 2011 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; Plotnick and Ducharme, 2000). 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).

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. 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 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 initial therapy, then the level of asthma control guides any follow-up treatment adjustments; selection and adjustment options for medication can include the type, 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).

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).

If asthma control is not achieved and maintained with initial therapy, consider non-adherence, poor inhaler technique, and lack of trigger control before stepping up therapy. Consider trials of other controller(s) in the same step before stepping up treatment (SCORxE Consensus), particularly if an alternative treatment option was initially selected (EPR-3, 2007).

Treatment Steps

	Evidence Level*		
AGE (years):	**< 5**	**5-11**	**≥ 12**
Step 1			
- SABAs prn are usually sufficient to manage symptoms for intermittent asthma (EPR-3, 2007).		B	A
- SABAs should be available and used as quick-relief therapy for ALL patients with persistent asthma (BTS, 2011 revised; EPR-3, 2007).		A	A
Step 2			
- ICSs are the most effective and preferred long-term control agent for initiating therapy for persistent asthma in children of all ages (BTS, 2011 revised; EPR-3, 2007). There are few head-to-head trials and less evidence in children compared with adults. ICSs improve asthma control in both children and adults 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
- Daily controller therapy is also recommended for preschool children with recurring wheezing and risk factors for persistent asthma (EPR-3, 2007).	A		
- Alternatively, intermittent treatment with short-course high-dose ICS at the beginning of respiratory tract infections may be effective, but more research is needed (Ducharme et al, 2009).	D		
- Low-dose ICS is the preferred therapy for mild persistent asthma (Adams et al, 2000b, 2008a, 2009; EPR-3, 2007)	A	A	A
- LABAs should be used with an ICS; LABAs have no anti-inflammatory activity and there is a rare, increased risk of severe asthma exacerbations and death (BTS, 2011 revised; EPR-3, 2007).			
- LTRAs are less effective than ICSs but may be a good alternative, particularly in young children requiring controller therapy and unable to use ICS (BTS, 2011 revised; Ducharme and di Salvio, 2004a; EPR-3, 2007).	A	B	A
Step 3			
- ICS increased to medium dose is a preferred therapy before adding another therapy, especially in children < 5 to ensure adequate dose delivery, since it is inherently difficult to administer aerosols (EPR-3, 2007; Lougheed et al, 2012). 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 those children with greater levels of impairment (Adams et al, 2000b, 2008a; EPR-3, 2007).	D	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 another preferred therapy in children ≥ 5 (EPR-3, 2007). Such add-on therapy may benefit many patients more than increasing ICS above low-dose (BTS, 2011 revised). There are studies reporting better benefit when adding a LABA to a low-dose of 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 (Ducharme et al, 2011a; Lougheed et al, 2010). In children < 12, 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 mixed, and some children do their best with an increased dose of ICS or the addition of an LTRA to a low-dose ICS (de Blic et al, 2009; EPR-3, 2007; Gappa et al, 2009; Lemanske et al, 2010; Ni et al, 2009; Ortega-Cisneros et al, 1998; Vaessen-Verbene et al, 2010; Verbene et al, 1998). Use of a LABA is associated with a potential risk of rare life-threatening or fatal exacerbations (EPR-3, 2007).		B**	A
- Addition of a LTRA to low-dose ICS is another preferred therapy in children ages 5-11, and an alternate option in children ≥ 12 years old that can provide some benefits on symptoms and impairment in children (Ducharme, 2004b; EPR-3, 2007).		B**	A

Step 4			
- Combination of medium-dose ICS AND LABA is the preferred treatment (EPR-3, 2007). A key benefit of adding LABA that has been shown in children > 12 is improved lung function (Ducharme et al, 2011a; EPR-3, 2007).	D	B**	A
- Addition of LTRA to medium-dose ICS is another preferred treatment in children < 5; but it is an alternate option in children ≥ 5 (EPR-3, 2007). Comparative studies in children ≥ 12 report that the addition of a LTRA is less effective than with a LABA, but a LTRA is an option if providers have safety concerns about using a LABA (Ducharme, 2004b; Ducharme et al, 2011a; EPR-3, 2007)).	D	B**	B
Step 5			
- Combination of high-dose ICS AND LABA is the preferred treatment (EPR-3, 2007).	D	B**	B
- Addition of LTRA to high-dose ICS is another preferred treatment in children < 5; but it is an alternate option in children aged 5-11 (EPR-3, 2007).	D	B**	
Step 6			
- Combination of high-dose ICS AND LABA AND oral corticosteroids is the preferred treatment (EPR-3, 2007). Consider a 2-week course of oral corticosteroids before beginning a maintenance regimen with oral corticosteroids to confirm the possibility of an effective therapeutic response and clinical reversibility.	D	D	D
- Addition of LTRA to high-dose ICS AND oral corticosteroids is another preferred treatment in children < 5; but it is an alternate option in children aged 5-11 (EPR-3, 2007).	D	D	D
- Consider combination of high-dose ICS AND LTRA AND LABA in 4-year-old children (EPR-3, 2007).			

* Evidence levels are provided for guideline-endorsed treatment options (EPR-3, 2007)
** Extrapolated from older children and adults

Step-Down

Once asthma is well controlled for at least 3-6 months, and the time of year is appropriate, 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, for example avoiding such an attempt during flu season or at the beginning of the school year (SCORxE consensus). There is no evidence to support specific recommendations on the rate of reduction and follow-up frequency; reduce medication therapy gradually to allow asthma control to be monitored. If on medium-high doses of ICS monotherapy, the ICS dose can be reduced by 25–50% every 3 months to the lowest dose that also maintains control (Evidence D) (EPR-3, 2007). If on low-dose ICS monotherapy, dosing can be switched from twice daily to once daily (GINA, 2010 update), although some ICSs may lose much of their efficacy with once daily dosing. If on a LABA and ICS combination, the caregiver can start by reducing the ICS dose by 50% until a low dose is reached, at which point the LABA can be discontinued (GINA, 2010 update). Alternatively, the combination LABA and ICS can be switched to once daily dosing, although some ICSs may lose much of their efficacy with once daily dosing. Another alternative is to first discontinue the LABA component, continue the ICS component at the same dose, then gradually taper down as suggested previously. Evidence in older adolescents and in adults suggests that this approach may be associated with a loss of asthma control (Brozek et al, 2012; GINA, 2010 update). If on a different combination (e.g., ICS and LTRA), the ICS dose can be decreased by 50% until a low dose is reached, at which point the other medication can be discontinued (GINA, 2010 update). It may not be possible to completely discontinue ICSs in all patients. Instruct patients how to contact their provider if and when asthma worsens. (Evidence D) (EPR-3, 2007). Some guidelines recommend that asthma remain well controlled for a year at the lowest dose of a controller medication before considering discontinuation of controller therapy (GINA, 2010 update).

Exercise-Induced Bronchospasm

Exercise-induced bronchospasm (EIB) should be anticipated in all asthma patients. 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).

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; and LTRAs (Evidence B) are also effective to prevent EIB when administered 2 hours prior to exercise (EPR-3, 2007; Kelly and Sorkness, 2011). Cromolyn or nedocromil taken shortly before exercise is another option, but it is not as effective as SABAs (Evidence B) (EPR-3, 2007). However, 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, 2011 revised; EPR-3, 2007). Adding a LTRA or a LABA can be considered for patients with EIB who are otherwise well controlled on ICS (BTS, 2011, 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; use of > 2 SABA canisters/month; difficulty perceiving airway obstruction or severity of worsening asthma; low socioeconomic status; illicit drug use; major psychosocial problems or psychiatric conditions; and medical comorbidities such as cardiovascular disease or other chronic lung disease (EPR-3, 2007).

Home management of asthma exacerbations. Asthma exacerbations are best managed with early recognition and treatment at home. Patients should be provided the following instructions as part of self-management education (EPR-3, 2007):

(1) how to use a written asthma action plan (AAP) with specific instructions on when and how to treat an exacerbation;

(2) how to identify early indicators of an exacerbation based on signs and symptoms, and PEF values, particularly in patients with moderate or severe asthma or a history of severe exacerbations, and in those who are poor symptom perceivers. A patient's PEF values of 50-79% of personal best/predicted signal 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. 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 (EPR-3, 2007; Rowe et al, 2007). Importantly, the guidelines no longer recommend doubling the ICS dose to treat acute exacerbations as it is not effective at reducing the severity or preventing the progression of exacerbations (EPR-3, 2007; Quon et al, 2010; Lougheed et al, 2012).

(5) how to avoid or minimize exposure to environmental triggers;

(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. Consideration should be given to initiating ICS for any patient treated in the emergency department for an asthma exacerbation (EPR-3, 2007).

Pharmacologic therapy for home management of asthma exacerbations.

Initial Treatment generally consists of SABA 2-6 puffs, up to two treatments 20 minutes apart. Further management varies depending on response to initial treatment. 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 ≥ 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 corticosteroid; 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.

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).

Viral respiratory infections, more common in children under 12, 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 different PEF values. A lower limit of 40% was selected for severe exacerbations (e.g., dyspnea at rest that interferes with conversation) since it is associated with exacerbation severity below which additional adjunctive therapies are beneficial, thus emergency department care is usually required, and maybe even hospitalization (EPR-3, 2007; Rowe et al, 2001). PEF < 25% personal best/predicted are associated with life-threatening exacerbations (e.g., too dyspneic to speak) that require hospitalization, possibly to intensive care unit (EPR-3, 2007; Smith et al, 2003).

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). 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 March 2012 available at: http://www.sccp.sc.edu/SCORxE). All

devices are equally efficacious if used with the proper technique. When selecting a device, the following should be considered: 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.

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) and infants can receive treatments through nebulizers, or MDIs with a spacer fitted with a facemask (Kelly and Sorkness, 2011; SCORxE consensus). In most cases, an MDI plus a spacer is as effective as a nebulizer (Cates, et al, 2006a, 2006b). 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). 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 March 2012 available at: http://www.sccp.sc.edu/SCORxE). Local side effects are most common, and include hoarseness and thrush. 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, 1999). 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).

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 aged 4-11, and in African-Americans. It is unknown at this time if this risk is obviated with the use of concomitant ICS (Cates et al, 2009a, Cates and Lasserton, 2009b, 2009c, 2010; Levenson 2008; Ni et al, 2009; Walters et al, 2007). LABAs should not be used as monotherapy for the treatment of asthma, and they carry a black box warning to that effect.

LTRAs are generally well tolerated. Postmarketing 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. If long-term therapy with oral corticosteroids is necessary, the lowest possible dose (single daily dose or alternate day dosing) should be used with close monitoring for adverse effects; persistent attempts to reduce oral corticosteroid use (high doses of ICS with LABA are preferable); and referral 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).

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 FEV_1, and is expressed as a percent of the predicted value or as a proportion of the forced vital capacity (FVC) or FEV_1/FVC.

Guidelines recommend that spirometry tests be performed: (1) during initial assessment (Evidence C), (2) after beginning treatment and stabilizing symptoms and PEF, (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).

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 as well as the evaluation of response to changes in treatment in addition to providing a quantitative measure of impairment. (Evidence B) Good candidates for peak flow monitoring include patients with moderate or severe persistent asthma, with a history of severe exacerbations (Evidence B), and with poor self-awareness of symptoms (Evidence D) (EPR-3, 2007).

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 fraction exhaled nitric oxide (FENO) concentrations (BTS, 2011 revised). Both are feasible and safe, and

may aid in the identification of corticosteroid responsiveness, but clinical experience is limited (ATS/ERS, 2009; Lougheed et al, 2012).

Visit Frequency

There is no evidence to support recommendations on monitoring frequency. Guidelines recommend that the first follow-up visit be in 2-6 weeks, and subsequent visits be scheduled every 1 to 6 months based on the level of asthma control (EPR-3, 2007). If asthma is well controlled, visits may be scheduled every 3-6 months (SCORxE consensus). If asthma is poorly controlled, a follow-up in 2-6 weeks is recommended. If asthma is very poorly controlled, a follow-up in 2 weeks is recommended.

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, 2011 revised; EPR-3, 2007; Lougheed et al, 2010; Wolf et al, 2002). Self-management education should focus on individual needs, be reinforced by a written personalized action plan, include regular review by a clinician, and be culture-specific (Bailey et al, 2009; BTS, 2011 revised; EPR-3, 2007). Key components of self-management education should be reviewed regularly and include the following (Evidence B): 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 to seek medical advice; and control of triggers (BTS, 2011 revised).

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 (Agrawal et al, 2005; Ducharme et al, 2011b; EPR-3, 2007; Sunshine et al, 2011; Zemek et al, 2008). 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). 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 (EPR-3, 2007). AAPs are a useful communication tool, particularly for parents or caregivers who have not accompanied the patient to the doctor.

Self-management education should be delivered 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).

Device Technique

Proper inhalation technique is essential to optimize medication delivery and therapeutic effect (Kelly and Sorkness, 2011) (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 March 2012 available at: http://www.sccp.sc.edu/SCORxE). Patients should be instructed on the proper use of their inhalers at each visit (EPR-3). 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 (by the provider and by the patient) and feedback on the patient's technique (Bosnic-Anticevich et al, 2010). Repeated instructions are needed to maintain correct technique over time (Bosnic-Anticevich et al, 2010; Munzenberger et al, 2007). Proper use of other devices such as peak flow meters and spacers should also be reviewed at every visit.

REFERRAL TO SPECIALIST

Consider patient referral to specialist (usually an allergist or pulmonologist) if:

- Difficulty achieving or maintaining control of asthma after 3-6 months of therapy (EPR-3, 2007)
- Uncontrolled on 2 controller ingredients (or one controller if < 5 years old)
- 2 bursts of oral steroids per year or exacerbation requiring hospitalization (EPR-3, 2007)
- High dose ICS is a consideration (EPR-3, 2007)
- Immunotherapy or omalizumab is a consideration (EPR-3, 2007)
- Additional testing is indicated (e.g., allergy skin testing, rhinoscopy, complete pulmonary function studies, provocative challenge, bronchoscopy) (EPR-3, 2007)
- Other conditions complicate asthma or its diagnosis (e.g., sinusitis, severe rhinitis, nasal polyps, vocal cord dysfunction) (EPR-3, 2007)
- Additional education and guidance on complications of therapy, nonadherence, or allergen avoidance are needed (EPR-3, 2007)

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