

NEIGHBORHOOD HEALTH PLAN OF RHODE ISLAND

Section: Clinical Practice Guideline	Subject: Diagnosis and Management of Asthma
Effective: March 13, 1997	Updated: 2/99, 1/01, 10/02, 10/04, 10/06, 4/08, 3/10

RATIONALE

Asthma is one of the most common chronic diseases affecting the RIte Care population. Approximately 20.5% of the RIte Care population received some type of ambulatory diagnostic or therapeutic service related to asthma during state fiscal year 2002. In addition to the short- and long-term impact on individuals with asthma, asthma has a significant impact on the health care system and health care costs. There is overwhelming evidence that appropriate primary care can reduce morbidity and mortality from asthma-related illness as well as minimize asthma-associated limitations in activity.

Neighborhood Health Plan of Rhode Island (Neighborhood) bases these guidelines for the diagnosis and management of asthma on those created by the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report (EPR-3) *Guidelines for the Diagnosis and Management of Asthma – Full Report 2007* (US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute). NIH publication No. 08-4051, August 2007. Full report can be found on <http://www.nhlbi.nih.gov/guidelines/asthma/>.

DEFINITIONS

Asthma is a chronic complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. It is a chronic inflammatory disorder of the airways which, in susceptible individuals, causes recurrent episodes of coughing, wheezing, breathlessness, and chest tightness usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Asthma care is organized around the following four components of effective asthma management:

- **Measures of assessment and monitoring** to diagnose and assess the severity of asthma and to monitor whether asthma control is achieved and maintained
- **Education** for a partnership in asthma care
- **Control of environmental factors and comorbid conditions** that affect asthma.
- **Pharmacologic therapy**

Asthma assessment and monitoring determines:

- **Severity:** the intrinsic intensity of the disease process; severity is best measured in a newly-diagnosed patient not yet receiving long-term-control therapy.
- **Control:** the degree to which manifestations of asthma are minimized and goals of therapy are met.
- **Responsiveness:** the ease with which asthma control is achieved by therapy.

Assessment of both severity and control includes consideration both of

- **Impairment:** the frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced; and
- **Risk:** the likelihood of asthma exacerbations, progressive decline in lung function/lung growth, and/or adverse effects from medication.

The domains of impairment and risk may respond differentially to treatment (e.g. some patients can have adequate control of symptoms and minimal day-to-day impairment but still be at significant risk of exacerbations).

The **goal of asthma therapy** is **asthma control**:

- **Reduce impairment** (prevent chronic symptoms, require infrequent use of short-acting beta2-agonist (SABA), maintain (near) normal lung function and normal activity levels).
- **Reduce risk** (prevent exacerbations, minimize need for emergency care or hospitalization, prevent loss of lung function or reduced lung growth, have minimal/no adverse effects of therapy).

DIAGNOSIS OF ASTHMA

To establish a diagnosis of asthma, the practitioner should determine that

- symptoms of recurrent episodes of airflow obstruction or airway hyperresponsiveness are present;
- airflow obstruction is at least partially reversible; and
- alternative diagnoses are excluded.

Methods to Establish a Diagnosis of Asthma:

- **Detailed medical history**
 - History of any of the following:
 - cough (worse particularly at night)
 - recurrent wheeze
 - recurrent difficulty in breathing
 - recurrent chest tightness.
 - Symptoms occur or worsen in the presence of:
 - exercise
 - viral infection.
 - inhalant allergens (e.g., animals with fur or hair, house-dust mites, mold, pollen).
 - irritants (tobacco or wood smoke, airborne chemicals).
 - changes in weather.
 - strong emotional expression (laughing or crying hard).
 - stress.
 - menstrual cycles.
 - Symptoms occur or worsen at night, awakening the patient.
- **Physical exam** focusing on the upper respiratory tract, chest, and skin
 - increased nasal secretion, mucosal swelling, and/or nasal polyp.
 - wheezing during normal breathing or prolonged phase of forced exhalation, hyperexpansion of the thorax, use of accessory muscles, appearance of hunched shoulders, chest deformity;
 - atopic dermatitis, eczema.
- **Spirometry** to demonstrate obstruction and assess reversibility in adults and children ≥ 5 years of age. (Reversibility is determined by increase in FEV₁ \geq 12% from baseline or by increase \geq 10% of predicted FEV₁ after inhalation of short-acting bronchodilator.) If office spirometry shows severe abnormalities or there are questions regarding test accuracy or interpretation, patient should have further assessment in a specialized pulmonary function laboratory.

Differential Diagnosis of Asthma

Practitioners should consider alternative diagnoses, as appropriate. Additional studies are not routinely necessary but may be useful when considering alternative diagnoses.

- **Additional pulmonary function studies** (measurement of lung volumes, evaluation of inspiratory loops, diffusing capacity) if there are questions about

coexisting COPD, emphysema, a restrictive defect, vocal cord dysfunction (VCD), or possible central airway obstruction.

- **Bronchoprovocation** with, histamine, cold air, or exercise challenge, if asthma is suspected and spirometry is normal. A positive test indicates presence of airway hyperresponsiveness, which can also be present in other conditions (e.g. allergic rhinitis, cystic fibrosis, COPD). A negative test helps rule out asthma.
- **Chest x-ray** to exclude other diagnoses.
- **Biomarkers of inflammation** – usefulness of these measurements is currently being evaluated in clinical trials.

Recurrent episodes of cough and wheezing most often are due to asthma in both children and adults; underdiagnosis of asthma is frequent, especially in children who wheeze when they have respiratory infections.

Common diagnostic challenges include the following:

- **Cough variant asthma** – cough may be the principal – or only – manifestation of asthma, especially in young children. Diagnosis is confirmed by positive response to asthma medication.
- **Vocal cord dysfunction (VCD)** can mimic asthma, but is a distinct disorder and may coexist with asthma. Diagnosis comes from indirect or direct vocal cord visualization during an episode.
- **Conditions that may coexist with asthma and complicate diagnosis** – e.g.
 - gastroesophageal reflux disease/GERD (patients c/o frequent heartburn or pyrosis, often have episodes of nocturnal asthma)
 - allergic bronchopulmonary aspergillosis/ABPA (criteria for diagnosis include positive immediate skin test for *Aspergillus*, total serum IgE >417 IU, elevated serum IgE and/or immunoglobulin G to *Aspergillus*, central bronchiectasis)
 - obstructive sleep apnea/OSA (evaluate particularly in patients who are overweight or obese)
- **Children ages 0-4 years.** Diagnosis in infants and young children is challenging and is complicated by the difficulty in obtaining objective measurements of lung function in this age group. Caution is needed to avoid giving young children inappropriate prolonged asthma therapy. However it is important to avoid underdiagnosing asthma, and thereby missing the opportunity to treat a child, by using such labels as “wheezy bronchitis,” “recurrent pneumonia,” or “reactive airway disease”. The airway inflammatory response and structural changes that are characteristic of asthma can develop in the preschool years, and appropriate asthma treatment will reduce morbidity.

Consider referral to an asthma specialist

- if signs and symptoms are atypical,
- if signs of poor control with appropriate treatment
- if there are problems with a differential diagnosis, or
- if additional testing is indicated.

MANAGEMENT OF ASTHMA LONG TERM

Achieving and maintaining asthma control requires the four components of care. A stepwise approach to asthma management incorporates these four components. The stepwise approach incorporates all four components of care: assessment of severity to initiate therapy or assessment of control to monitor and adjust therapy; patient education; environmental control measures, and management of comorbid conditions at every step; and selection of medication (see pages 9 through 12 of this guidelines) .

(also see Appendix A – Key Clinical Activities for Diagnosis and Management of Asthma).

Assessment and Monitoring

- **Initial assessment before initiating therapy** - use information from the diagnostic evaluation to:
 - Classify asthma severity
 - Identify precipitating factors for episodic symptoms
 - Identify comorbid conditions that may impede asthma management
 - Assess the patient’s knowledge and skills for self-management.
- **Periodic monitoring of asthma control** to guide decisions for maintaining or adjusting therapy includes:
 - **Patient self-monitoring** of asthma control

- Either a record of symptoms or peak flow monitoring is appropriate
- Consider daily peak-flow monitoring for
 - patients with moderate or severe persistent asthma
 - patients who have history of severe exacerbations
 - patients who poorly perceive airway obstruction or worsening asthma.
- **Clinical visits** to monitor asthma control
 - Visit frequency
 - Visits at 2-6 week intervals for patients just starting therapy or who require a step up in therapy
 - Visits at 1-6 month intervals after control is achieved
 - Visits at 3-month intervals if a step down in therapy is anticipated.
 - Assess asthma control, medication technique, written asthma action plan, adherence, and patient concerns at every visit
 - Use spirometry to obtain objective measures of lung function
 - At the initial assessment
 - After treatment is initiated and symptoms and PEF have stabilized
 - During periods of progressive or prolonged loss of asthma control
 - At least every 1-2 years; more frequently depending on response to therapy.

Education

- **Develop an active partnership** with the patient and family by
 - Establishing open communications
 - Identifying and addressing patient and family concerns about asthma and its treatment
 - Developing treatment goals and selecting medications together with patient and family
 - Encouraging self-monitoring and self-management by regular reviews of patient's reports
- **Provide a written asthma action plan** for all patients
- **Encourage patients' adherence** to written asthma action plan
- **Integrate asthma self-management education** into all aspects of asthma care

Control of Environmental Factors and Comorbid Conditions

- **Evaluate the potential role of allergens and irritants**
 - Identify exposures
 - For patients with persistent asthma:
 - use skin testing or in vitro test to assess sensitivity to indoor allergens
 - assess significance of positive tests in context of person's history of symptoms when exposed to allergen
- **Advise patients to reduce exposure** to allergens and irritants to which they are sensitive
- **Consider subcutaneous allergen immunotherapy** for patients with persistent asthma in face of clear evidence of relation between symptoms and exposure to allergen
- **Consider inactivated influenza vaccination** for patients > 6 months of age who have asthma.
- **Identify and treat comorbid conditions** that may impede asthma management
 - ABPA – treat with prednisone, 0.5 mg/kg with gradual tapering; azole antifungal agents as adjunctive therapy may be helpful
 - GERD – treatment includes avoiding heavy meals, fried foods, caffeine, alcohol; avoiding food/drink with 3 hrs of retiring; elevating head of bed on 6-8 in. blocks; using proton pump inhibitor medication.

- Obesity or overweight – advise weight loss.
- OSA – treat with nasal continuous positive airway pressure (CPAP) if OSA definitively diagnosed.
- Rhinitis or sinusitis – treat rhinitis with intranasal corticosteroids, antihistamines, consider immunotherapy; treat sinusitis with intranasal corticosteroids and antibiotics.
- Stress and depression – additional education to improve self-management and coping skills may be helpful.

Medications

- **Quick-relief medications** are used to treat acute symptoms and exacerbations (**see Appendix C for dosages**)
 - **Anticholinergic** (Ipratropium bromide) provides additive benefit to SABA in moderate or severe exacerbations in the ED setting; may be used as alternative for patients who do not tolerate SABA.
 - **SABAs** (albuterol, levalbuterol, pirbuterol) – short-acting beta agonists are treatment of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm.
 - **Systemic corticosteroids** – not short-acting but used for moderate and severe exacerbations in addition to SABA
- **Long-term control medications** to achieve and maintain control of persistent asthma (**see Appendix B for usual dosages**)
 - **Corticosteroids**
 - Inhaled corticosteroids (ICSs) – most consistently effective long-term control medication at all steps of care for persistent asthma
 - Oral systemic corticosteroids
 - used in short course to gain prompt control of asthma
 - used long term for patients who require step 6 care
 - **Cromolyn sodium and nedocromil** used as alternative, but not preferred, medication for patients requiring step 2 care or as preventive treatment before exercise or exposure to known allergen.
 - **Immunomodulators/omalizumab (anti-IgE/Xolair®)** used as adjunctive therapy for patients ≥ 12 years of age who require step 5 or 6 care and have sensitivity to relevant allergens.
 - **Leukotriene modifiers** include LTRAs (montelukast and zafirlukast) and zileuton, a 5-lipoxygenase inhibitor; they are alternative but not preferred medication for patients requiring step 2 care or (not preferred) adjunctive therapy for patients ≥ 12 .
 - **LABAs** (salmeterol, formoterol)- long-acting beta agonists used in combination with ICSs for moderate or severe persistent asthma.
 - **Methylxanthines** – bronchodilator used as alternative, not preferred, therapy for step 2 care or as adjunctive therapy with ICS in patients ≥ 5
- **Complementary and alternative medications and interventions** generally have insufficient evidence to permit recommendations. Because as much as 1/3 of U.S. population uses these, it is important to explore/discuss their use with patients.
- **Delivery devices for inhaled medications (see Appendix D for list of devices)**
 - Patients should be instructed in the use of inhaled medications
 - Patients' technique in use of inhaled medications should be reviewed at every patient visit

CLASSIFYING ASTHMA SEVERITY AND INITIATING THERAPY IN CHILDREN

		Intermittent		Persistent					
				Mild		Moderate		Severe	
		Ages 0-4	Ages 5-11	Ages 0-4	Ages 5-11	Ages 0-4	Ages 5-11	Ages 0-4	Ages 5-11
Impairment	Symptoms	≤2 days/week		>2 days/week but not daily		Daily		Throughout the day	
	Nighttime awakenings	0	≤2 x/month	1-2x/month	3-4x/ month	3-4x/month	>1x/week but not nightly	> 1x/ week	Often 7x/week
	Short-acting beta ₂ -agonist use for symptom control	≤2 days/week		>2 days/week but not daily		Daily		Several times per day	
	Interference with normal activity	None		Minor limitation		Some limitation		Extremely limited	
	Lung Function ▪ FEV ₁ (predicted) or peak flow (personal best) ▪ FEV ₁ /FVC	N/A	Normal FEV ₁ between exacerbations >80% >85%	N/A	>80% >80%	N/A	60-80% 75-80%	N/A	<60% <75%
Risk	0-1/year (see notes)		≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma	≥2x/year (see notes) Relative annual risk may be related to FEV ₁					
Recommended Step for Initiating Therapy (See “Stepwise Approach for Managing Asthma” for treatment steps.) The stepwise approach is meant to assist, not replace, the clinical		Step 1 (for both age groups)		Step 2 (for both age groups)		Step 3 and consider short course of oral systemic corticosteroids	Step 3: medium-dose ICS and consider short course of oral systemic corticosteroids	Step 3 and consider short course of oral systemic corticosteroids	Step 3: medium-dose ICS OR step 4 and consider short course of oral systemic corticosteroids

decision-making required to meet individual patient needs.	<p>In 2-6 weeks, depending on severity, evaluate level of asthma control that is achieved.</p> <ul style="list-style-type: none"> ▪ Children 0-4 years old: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternative diagnoses or adjusting therapy. ▪ Children 5-11 years old: adjust therapy accordingly.
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Notes:

- The level of severity is determined by both impairment and risk.
- Assess impairment domain by caregiver’s recall of previous 2-4 weeks. Assign severity to the most severe category in which any feature occurs.
- Frequency and severity of exacerbations may fluctuate over time for patients in any severity category. At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity.
- In general, more frequent and severe exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity.
- For treatment purposes, patients with ≥ 2 exacerbations described above may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Key: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; ICU, intensive care unit; N/A, not applicable.

ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN

COMPONENTS OF CONTROL		Well Controlled		Not Well Controlled		Very Poorly Controlled		NOTES
		Ages 0-4	Ages 5-11	Ages 0-4	Ages 5-11	Ages 0-4	Ages 5-11	
Impairment	Symptoms	≤ 2 days/week, but not more than once on each day		> 2 days/week or multiple times on But not daily ≤ 2 days/week		Throughout the day		<ul style="list-style-type: none"> ▪ The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient’s or caregiver’s recall of previous 2-4 week. Symptom assessment for longer periods should reflect a global assessment, such as whether the patient’s asthma is better or worse since the last visit. ▪ At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control.
	Nighttime awakenings	≤ 1 x/month		1-2x/month	≥ 2 x/month	> 1 x/week	≥ 2 x/week	
	Interference with normal activity	None		Some limitation		Extremely limited		
	Short-acting beta ₂ -agonist use for symptom control (not prevention of EIB)	≤ 2 days/week		> 2 days/week		Several times per day		
	Lung Function	N/A	$> 80\%$	N/A	$60-80\%$	N/A	$< 60\%$	
▪ FEV ₁ (predicted) or peak flow (personal best)	$> 85\%$		$75-80\%$		$< 75\%$			
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year		2-3x/year	≥ 2 x/year	> 3 x/year	≥ 2 x/year	

	Reduction in lung growth	N/A	Requires long-term follow up	N/A	Requires long-term follow up	N/A	Requires long-term follow up	
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.						
<p>Recommended Action For Treatment</p> <p>(See “Stepwise Approach for Managing Asthma” for treatment steps.)</p> <p>The stepwise approach is meant to assist, not replace, clinical decision-making required to meet individual patient needs.</p>		<ul style="list-style-type: none"> ▪ Maintain current step. ▪ Regular follow up every 1-6 months. ▪ Consider step down if well controlled for at least 3 months. 	Step up 1 step	Step up at least 1 step	<ul style="list-style-type: none"> ▪ Consider short course of oral systemic corticosteroids ▪ Step up 1-2 steps 			
		<ul style="list-style-type: none"> ▪ Before step up: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. ▪ Reevaluate the level of asthma control in 2-6 weeks to achieve control; every 1-6 months to maintain control. Children 0-4 years old: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. Children 5-11 years old: Adjust therapy accordingly. ▪ For side effects, consider alternative treatment options. 						

Key: EIB, exercise-induced bronchospasm; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; ICU, intensive care unit; N/A, not applicable.

Stepwise Approach for Managing Asthma in Children 0-4 Years of Age *

Step up if needed (first check inhaler technique, adherence, environmental control, and comorbid conditions)

Assess Control: Step down if possible (and asthma is well controlled at least 3 months)

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
	Intermittent Asthma	Persistent Asthma: Daily Medication				
		Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2				
Preferred	SABA PRN	Low dose ICS	Medium dose ICS	Medium dose ICS + LABA or Montelukast	High dose ICS + LABA or Montelukast	High dose ICS + Oral Corticosteroids ICS + LABA or Montelukast
Alternative		Cromolyn or Montelukast				
	Each Step: Patient Education and Environmental Control					
Quick-Relief Medication	<ul style="list-style-type: none"> SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms. With viral respiratory symptoms: SABA q 4-6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations. <p>Caution: Frequent use of SABA may indicate the need to step up treatment. See text for recommendation on initiating daily long-term-control therapy.</p>					
	<p>Notes</p> <ul style="list-style-type: none"> The stepwise approach is meant to assist, not replace the clinical decision-making required to meet individual patient needs. If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up. If clear benefit is not observed within 4-6 weeks, and patient's/family's medication technique and adherence are satisfactory, consider adjusting therapy or an alternative diagnosis. Studies on children 0-4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur. 					

Key: Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy. ICS inhaled corticosteroid; LABA inhaled long-acting beta₂-agonist; LTRA leukotriene receptor antagonist, oral corticosteroids, oral systemic corticosteroids; SABA inhaled short-acting beta₂-agonist.

*See Appendix B and C for usual doses of medications recommended

Stepwise Approach for Managing Asthma in Children 5-11 Years of Age*

Step up if needed (first check inhaler technique, adherence, environmental control, and comorbid conditions)

Assess Control: Step down if possible (and asthma is well controlled at least 3 months)

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
	Intermittent Asthma	Persistent Asthma: Daily Medication				
		Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3				
Preferred	SABA PRN	Low dose ICS	Low dose ICS + LABA, LTRA or Theophylline OR Medium dose ICS	Medium dose ICS + LABA	High dose ICS + LABA	High dose ICS + LABA + Oral Corticosteroids
Alternative		Cromolyn, LTRA, Nedocromil, or Theophylline		Medium dose ICS + LTRA or Theophylline	High dose ICS + LTRA or Theophylline	High dose ICS + LTRA or Theophylline + Oral corticosteroids
	Each Step: Patient Education and Environmental Control, and Management of Comorbidities Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.					
Quick-Relief Medication	<ul style="list-style-type: none"> SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as need. Short course of oral systemic corticosteroids may be needed. Caution: Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment. 					
	<p>Notes</p> <ul style="list-style-type: none"> The stepwise approach is meant to assist, not replace the clinical decision-making required to meet individual patient needs. If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up. Theophylline is a less desirable alternative due to the need to monitor serum concentration levels. Steps 1 and 2 medications are based on Evidence A. Step 3 ICS and ICS plus adjunctive therapy are based on Evidence B for efficacy of each treatment and extrapolations from comparator trial in older children and adults-comparator trial are not available for this age group: steps 4-6 are based on expert opinion and extrapolation from studies in older children and adults. Immunotherapy for steps 2-4 is based on Evidence B for house dust mites, animal danders, and pollens: evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is great in children than adults. Clinicians who administer immunotherapy should be prepared equipped to identify and treat anaphylaxis that may occur. 					

Key: Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy. ICS inhaled corticosteroid; LABA inhaled long-acting beta₂-agonist; LTRA leukotriene receptor antagonist, SABA, inhaled short-acting beta₂-agonist.

* See Appendix B and C for usual doses of medications recommended

CLASSIFYING ASTHMA SEVERITY IN YOUTHS ≥ 12 YEARS OF AGE AND ADULTS

COMPONENTS OF SEVERITY		Intermittent	Persistent			
			Mild	Moderate	Severe	
Impairment Normal FEV ₁ /FVC: 8-19 yr >85% 20-39 yr >80% 40-59 yr >75% 60-80 yr >70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day	Notes: <ul style="list-style-type: none"> The stepwise approach is meant to assist, not replace the clinical decision making required to meet individual patient needs. Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs. At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥ 2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
	Nighttime awakenings	≤2 x/month	3-4x/ month	>1x/week but not nightly	Often 7x/week	
	Short-acting beta ₂ -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day	
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited	
	Lung Function	Normal FEV ₁ between exacerbations FEV ₁ >80% predicted FEV ₁ /FVC normal	FEV ₁ >80% predicted FEV ₁ /FVC normal	FEV ₁ >60% but <80% predicted FEV ₁ /FVC reduced 5%	FEV ₁ <60% predicted FEV ₁ /FVC reduced >5%	
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year (see notes)	≥ 2 x/year (see note)			
Recommended Step for Initiating Treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5 and consider short course of oral systemic corticosteroids	
In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.						

Key: EIB, exercise-induced bronchospasm; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; ICU, intensive care unit.

CLASSIFICATION ASTHMA CONTROL IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

COMPONENTS OF CONTROL		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2 x/month	1-3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta ₂ -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV ₁ or peak flow	>80% predicted/ personal best	60-80% predicted/ personal best	<60% predicted/ Personal best
	Validated questionnaires ATAQ ACQ ACT	0 ≤0.75* ≥20	1-2 ≥1-5 16-19	3-4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year	≥2x/year (see notes)	
	Progressive loss of lung function	Consider severity and interval since last exacerbation		
	Treatment-related adverse effects	Evaluation requires long-term follow up care.		
<p>Recommended Action For Treatment (See “Stepwise Approach for Managing Asthma” for treatment steps.)</p> <p>Before step up in therapy:</p> <ul style="list-style-type: none"> - Review adherence to medication, inhaler technique, environmental control, and comorbid conditions. - If any alternative treatment option was used in a step, discontinue and use the preferred treatment for that step. 		<ul style="list-style-type: none"> ▪ Maintain current step. ▪ Regular follow up every 1-6 months to maintain control. ▪ Consider step down if well controlled for at least 3 months. 	<ul style="list-style-type: none"> ▪ Step up 1 step. ▪ Reevaluate in 2-6 weeks. ▪ For side effects, consider alternative treatment options. 	<ul style="list-style-type: none"> ▪ Consider short course of oral systemic corticosteroids. ▪ Step up 1-2 steps. ▪ Reevaluate in 2 weeks. ▪ For side effects, consider alternative treatment options.

NOTES

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient’s recall of previous 2-4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as whether the patient’s asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with no-well-controlled asthma.

Key: EIB, exercise induced bronchospasm; ICU, intensive care unit.
ATAQ = Asthma Therapy Assessment Questionnaire[®]
ACQ = Asthma Control Questionnaire[®]
ACT = Asthma control Test[™]

Minimal important Difference: 1.0 for the ATAQ; 0.5 for the ACQ; not determined for the ACT.

*ACQ values of 0.76-1.4 are indeterminate regarding well-controlled asthma.

Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults*
 Step up if needed (first check inhaler technique, adherence, environmental control, and comorbid conditions)
Assess Control: Step down if possible (and asthma is well controlled at least 3 months)

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Notes
Intermittent Asthma	Persistent Asthma: Daily Medication Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.					
<i>Preferred:</i> SABA PRN (Evidence A)	<i>Preferred:</i> Low dose ICS (Evidence A) <i>Alternative:</i> Cromolyn, LTRA, Nedocromil, or Theophylline	<i>Preferred:</i> Low dose ICS + LABA OR Medium dose ICS (Evidence A) <i>Alternative:</i> Low dose ICS + either LTRA (A), Theophylline (B), or Zileuton (D)	<i>Preferred:</i> Medium dose ICS + LABA (Evidence B) <i>Alternative:</i> Medium dose ICS + either LTRA (B), Theophylline (B) or Zileuton (D)	<i>Preferred:</i> High dose ICS + LABA AND Consider Omalizumab for patients who have allergies (Evidence B)	<i>Preferred:</i> High dose ICS + LABA + Oral Corticosteroids (EPR-2 1997) AND Consider Omalizumab for patients who have allergies (Evidence B)	
Each Step: Patient Education and Environmental Control, and Management of Comorbidities. Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).						
Quick-Relief Medication for All Patients: <ul style="list-style-type: none"> SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed. Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment. 						

Key: Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy. ICS inhaled corticosteroid; LABA long-acting beta₂-agonist; LTRA leukotriene receptor antagonist; SABA, inhaled short-acting beta₂-agonist.

* See Appendix B and C for usual doses of medications recommended

MANAGEMENT OF ASTHMA EXACERBATIONS

Do not underestimate the severity of an exacerbation. Severe exacerbations can be life threatening and can occur in patients at any level of asthma severity.

Patients at high risk of asthma-related death require special attention; risk factors include:

- Previous severe exacerbation (intubation, ICU admission for asthma)
- ≥ 2 hospitalizations or >3 ED visits in past year for asthma
- Use of >2 canisters of SABA per month
- Difficulty perceiving airway obstruction or the severity of worsening asthma
- Low socioeconomic status or inner-city residence
- Illicit drug use
- Major psychosocial problems or psychiatric disease
- Comorbidities such as cardiovascular disease or other chronic lung disease.

Home Management – early treatment at home is the best strategy for managing asthma exacerbations:

- Use a written asthma action plan
- Recognize early signs, symptoms, peak expiratory flow (PEF) measures that indicate worsening asthma.
- Assess severity of asthma exacerbation – if PEF is below 50%, immediate medical care is usually required.
- Adjust medications (increase SABA and, in some cases, add oral systemic corticosteroids) and remove or withdraw from environmental factors contributing to the exacerbation.
- Monitor response and seek medical care if there is serious deterioration or lack of response to treatment.

Management in the Urgent or Emergency Care Setting

- Assess severity of asthma exacerbation:
 - Mild – dyspnea only with activity, $PEF \geq 70\%$ predicted or personal best, usually cared for at home (see above)
 - Moderate – dyspnea interferes with or limits usual activity; $PEF 40-69\%$ predicted or personal best; usually requires office or ED visit
 - Severe – dyspnea at rest interfering with conversation; $PEF 25-39\%$ predicted or personal best; usually requires ED visit and likely hospitalization
 - Life-threatening – too dyspneic to speak, perspiring; $PEF <25\%$ predicted or personal best; requires ED/hospitalization, possible ICU
- For moderate or severe exacerbations:
 - Supplemental oxygen.
 - Repetitive or continuous SABA.
 - Oral systemic corticosteroids
 - Monitor response with serial assessment of lung function measures, pulse oximetry, and symptoms.
 - Consider adjunctive treatments magnesium sulfate or heliox in severe exacerbations (e.g., forced expiratory volume in 1 second (FEV1) or $PEF <40$ percent predicted) unresponsive to initial treatment.
- Discharge with medication and patient education
 - Medications: SABA, oral systemic corticosteroids; consider initiating ICS.
 - Referral to followup care.: phone contact within 3-5 days, visit within 1-4 weeks
 - An emergency department asthma discharge plan.
 - Review of inhaler technique and, whenever possible, environmental control measures.

MANAGEMENT OF SPECIAL CIRCUMSTANCES

Pregnancy – maintain asthma control throughout pregnancy.

- Maintaining lung function is important to ensure oxygen supply to the fetus. It is safer to be treated with asthma medications than to have poorly controlled asthma.
- Monitor asthma control during all prenatal visits; asthma worsens in one-third of women during pregnancy and improves in one-third; medications should be adjusted accordingly.
- Albuterol is the preferred SABA.
- ICS is the preferred long-term control medication (Budesonide is preferred because more data are available on this medication during pregnancy).

Surgery – reduce risk for complications during and after surgery.

- Assess asthma control prior to surgery., including medication use (especially oral systemic corticosteroids in past 6 mo.) and pulmonary function
- Provide medication to improve lung function if lung function is not well controlled. A short course of oral systemic corticosteroids may be necessary.
- For patients receiving oral systemic corticosteroids during 6 months prior to surgery, and for selected patients on high dose ICS, give 100 mg hydrocortisone every 8 hours intravenously during the surgical period, and reduce the dose rapidly within 24 hours after surgery.

Exercise-Induced Bronchospasm (EIB) – Anticipate EIB in all asthma patients and act to prevent it.

- History of cough, shortness of breath, chest pain, or tightness, wheezing, or endurance problems during exercises suggests EIB. An exercise challenge will establish the diagnosis.
- Treatment strategies to prevent EIB include:
 - Long-term control therapy, if appropriate
 - Pretreatment before exercise with SABA, leukotriene receptor antagonists (LTRAs), cromolyn or nedocromil;
 - Frequent or chronic use of long acting beta₂-agonist (LABA) for pretreatment is discouraged, as it may disguise poorly controlled persistent asthma.
 - Warm up period before exercise
 - Mask or scarf over the mouth for cold-induced EIB.

Disparities – There is a higher rate of poorly controlled asthma and asthma deaths among Blacks and Latinos as compared to Whites.

- Contributing factors include
 - socioeconomic disparities in access to quality medical care,
 - under-prescription and underutilization of long term control medication,
 - environmental exposures,
 - cultural beliefs and practices about asthma management and
 - potentially biological and pathophysiological differences that affect the underlying severity and response to treatment.
- Clinicians should be aware of these barriers and strive to improve communication with their patients to ensure appropriate use of asthma medications.

REFERENCES

1. RIte Stats Analysis of RIte Care Utilization Data, RI Department of Human Services Center for Child and Family Health, vol. II, Issue 3, January 2003
2. NIH/NHLBI Publications, “Expert Panel Report (EPR-3): *Guidelines for the Diagnosis and Management of Asthma – Full Report 2007* (US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute). NIH publication No. 08-4051, August 2007.

KEY CLINICAL ACTIVITIES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA

Appendix A

FOUR COMPONENTS OF CARE

Clinical Issue	Key Clinical Activities	Action Steps
<p>Assessment and Monitoring</p>	<p>Assess asthma severity to initiate therapy.</p>	<p>Use severity classification chart, assessing both domains of impairment and risk, to determine initial treatment.</p>
	<p>Assess asthma control to monitor and adjust therapy.</p>	<p>Use asthma control chart, assessing both domains of impairment and risk, to determine if therapy should be maintained or adjusted (step up if necessary, step down if possible).</p> <p>Use multiple measures of impairment and risk: different measures assess different manifestations of asthma; they may not correlate with each other; and they may respond differently to therapy. Obtain lung function measures by spirometry at least every 1–2 years, more frequently for not-well-controlled asthma.</p>
	<p>Schedule follow up care.</p>	<p>Asthma is highly variable over time, and periodic monitoring is essential. In general, consider scheduling patients at 2 to 6 week intervals while gaining control; at 1–6 month intervals, depending on step of care required or duration of control, to monitor if sufficient control is maintained; at 3-month intervals if a step down in therapy is anticipated.</p> <p>Assess asthma control, medication technique, written asthma action plan, patient adherence and concerns at every visit.</p>

<p>Education</p>	<p>Provide self-management education.</p>	<p>Teach and reinforce:</p> <ul style="list-style-type: none"> -Self-monitoring to assess level of asthma control and signs of worsening asthma (either symptom or peak flow monitoring shows similar benefits for most patients). Peak flow monitoring may be particularly helpful for patients who have difficulty perceiving symptoms, a history of severe exacerbations, or moderate or severe asthma. -Using written asthma action plan (review differences between long-term control and quick-relief medication). -Taking medication correctly (inhaler technique and use of devices). -Avoiding environmental factors that worsen asthma. <p>Tailor education to literacy level of patient. Appreciate the potential role of a patient’s cultural beliefs and practices in asthma management.</p>
<p>Education (cont’d)</p>	<p>Develop a written asthma action plan in partnership with patient.</p> <p>Integrate education into all points of care where health professionals interact with patients.</p>	<p>Agree on treatment goals and address patient concerns.</p> <p>Provide instructions for (1) daily management (long-term control medication, if appropriate, and environmental control measures) and (2) managing worsening asthma (how to adjust medication, and know when to seek medical care).</p>
<p>Control Environmental Factors and Comorbid conditions</p>	<p>Recommend measures to control exposures to allergens and pollutants or irritants that make and asthma worse.</p>	<p>Determine exposures, history of symptoms in presence of exposures, and sensitivities (In patients who have persistent asthma, use skin or in vitro testing to assess sensitivity to perennial indoor allergens.)</p> <p>Advise patients on ways to reduce exposure to those allergens and pollutants, or irritants to which the patient is sensitive. Multifaceted approaches are beneficial; single steps alone are generally ineffective. Advise all patients and pregnant women to avoid exposure to tobacco smoke.</p> <p>Consider allergen immunotherapy, by specifically trained personnel, for patients who have persistent asthma and when there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive.</p>

	Treat comorbid conditions.	<p>Consider especially: allergic bronchopulmonary aspergillosis; gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis and sinusitis, and stress or depression. Recognition and treatment of these conditions may improve asthma control.</p> <p>Consider inactivated influenza vaccine for all patients over 6 months of age.</p>
Medications	Select medication and delivery devices to meet patient's needs and circumstances.	<p>Use stepwise approach to identify appropriate treatment options.</p> <p>Inhaled corticosteroids (ICSs) are the most effective long-term control therapy. When choosing among treatment options, consider domain of relevance to the patient (impairment, risk, or both), patient's history of response to the medication, and patient's willingness and ability to use the medication.</p>

FIGURE 17. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS*
Appendix B

Medication	0-4 Years of Age	5-11 Years of Age	≥12 Years of Age & Adults	Potential Adverse Effects	Comments (not all inclusive)
Inhaled Corticosteroids (See Figure 18, “Estimated Comparative Daily Dosages for ICSs.”)					
Oral Systemic Corticosteroids					(Apply to all three corticosteroids.)
Methylprednisolone 2, 4, 8, 16, 32 mg tablets Prednisolone 5 mg tablets, 5 mg/5 cc, 15 mg/5 cc Prednisone 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control Short-course “burst”: 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control Short-course “burst”: 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	7.5–60 mg daily in a single dose in a.m. or qod as needed for control Short-course “burst”: to achieve control, 40–60 mg per day as single or 2 divided doses for 3–10 days	*Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. *Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing’s syndrome, cataracts, muscle weakness, and—in rare instances —impaired immune function. *Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and Strongyloides	*For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). *Short courses or “bursts” are effective for establishing control when initiating therapy or during a period of gradual deterioration. *There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse. *Children receiving the lower dose (1 mg/kg/day) experience fewer behavioral side effects, and it appears to be equally efficacious. *For patients unable to tolerate the liquid preparations, dexamethasone syrup at 0.4 mg/kg/day may be an alternative. Studies are limited, however, and the longer duration of activity increases the risk of adrenal suppression.

Inhaled Long-Acting Beta2-Agonists (LABAs)					(Apply to both LABAs.)
Salmeterol -DPI 50 mcg/ blister	NA	1 blister q 12 hours	1 blister q 12 hours	*Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose.	<p>*Should not be used for acute symptom relief or exacerbations. Use only with ICSs.</p> <p>*Decreased duration of protection against EIB may occur with regular use.</p> <p>*Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.</p> <p>*Do not blow into inhaler after dose is activated.</p> <p>*Each capsule is for single use only; additional doses should not be administered for at least 12 hours.</p> <p>*Capsules should be used only with the inhaler and should not be taken orally.</p>
Formoterol -DPI 12 mcg/ single-use capsule	NA	1 capsule q 12 hours	1 capsule q 12 hours	<p>*A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established.</p> <p>*Potential risk of uncommon, severe, life-threatening or fatal exacerbation; see text for additional discussion regarding safety of LABAs.</p>	

Key: DPI, dry powder inhaler; EIB, exercise-induced broncospasm; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; IgE, immunoglobulin E; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group); SABA, short-acting beta2-agonist

*Note: Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

Cromolyn/Nedocromil					
Cromolyn MDI 0.8 mg/puff	NA	2 puffs qid	2 puffs qid	*Cough and irritation. *15–20 percent of patients complain of an unpleasant taste from nedocromil.	*One dose of cromolyn before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective as inhaled beta2-agonists for EIB as SABA.
Nebulizer 20 mg/ampule	1 ampule qid NA <2 years of age	1 ampule qid	1 ampule qid	*Safety is the primary advantage of these	*4- to 6-week trial of cromolyn or nedocromil may be needed to determine maximum benefit.
Nedocromil MDI 1.75 mg/puff	NA <6 years of age	2 puffs qid	2 puffs qid		*Dose by MDI may be inadequate to affect hyperresponsiveness. *Once control is achieved, the frequency of dosing may be reduced.
Immunomodulators					
Omalizumab (Anti IgE) Subcutaneous injection, 150 mg/1.2 mL following reconstitution with 1.4 mL sterile water for injection	N/A	N/A	150–375 mg SC q 2–4 weeks, depending on body weight and pretreatment serum IgE level	*Pain and bruising of injection sites in 5–20 percent of patients. *Anaphylaxis has been reported in 0.2% of treated patients. *Malignant neoplasms were reported in 0.5 percent of patients compared to 0.2 percent receiving placebo; relationship to drug is unclear.	*Do not administer more than 150 mg per injection site. *Monitor patients following injections; be prepared and equipped to identify and treat anaphylaxis that may occur. *Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.

Leukotriene Modifiers					
<p>Leukotriene Receptor Antagonists (LTRAs)</p> <p>Montelukast</p> <p>-4 mg or 5 mg chewable tablet</p> <p>-4 mg granule packets</p> <p>-10 mg tablet</p> <p>Zafirlukast</p> <p>-10 mg tablet</p> <p>-20 mg tablet</p> <p>5-Lipoxygenase Inhibitor</p> <p>Zileuton</p> <p>-600 mg tablet</p>	<p>4 mg qhs (1–5 years of age)</p> <p>NA</p> <p>N/A</p>	<p>5 mg qhs (6–14 years of age)</p> <p>10 mg bid (7–11 years of age)</p> <p>N/A</p>	<p>10 mg qhs</p> <p>40 mg daily (20 mg tablet bid)</p> <p>2,400 mg daily (give tablets qid)</p>	<p>*No specific adverse effects have been identified.</p> <p>*Rare cases of Churg-Strauss have occurred, but the association is unclear.</p> <p>*Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.</p> <p>*Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.</p>	<p>*Montelukast exhibits a flat dose-response curve. Doses >10 mg will not produce a greater response in adults.</p> <p>*No more efficacious than placebo in infants ages 6–24 months.</p> <p>*As long-term therapy may attenuate exercise-induced bronchospasm in some patients, but less effective than ICS therapy.</p> <p>*For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.</p> <p>*Zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. Doses of these drugs should be monitored accordingly.</p> <p>*Monitor hepatic enzymes (ALT). Warn patients to discontinue use if they experience signs and symptoms of liver dysfunction.</p> <p>*For zileuton, monitor hepatic enzymes (ALT).</p> <p>*Zileuton is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly.</p>

Methylxanthines					
<p>Theophylline</p> <p>Liquids, sustained-release tablets, and capsules</p>	<p>Starting dose 10 mg/kg/day; usual maximum:</p> <p>* <1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day</p> <p>* ≥1 year of age: 16 mg/kg/day</p>	<p>Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day</p>	<p>Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum: 800 mg/day</p>	<p>*Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia.</p> <p>*Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism.</p>	<p>*Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady state (at least 48 hours on same dosage).</p> <p>*Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential.</p> <p>*Patients should be told to discontinue if they experience toxicity.</p> <p>*Various factors (diet, food, febrile illness, age, smoking, and other medications) can affect serum concentrations. See EPR—3 Full Report 2007 and package inserts for details.</p>

FIGURE 18. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS
Appendix C

Drug	Low Daily Dose			Medium Daily Dose			High Daily Dose		
	Child 0–4 Years of Age	Child 5-11 Years of Age	≥12 Years of Age & Adult	Child 0–4 Years of Age	Child 5-11 Years of Age	≥12 Years of Age & Adult	Child 0–4 Years of Age	Child 5-11 Years of Age	≥12 Years of Age & Adult
Beclomethasone HFA 40 or 80 mcg/puff	NA	80–160 mcg	80-240 mcg	NA	>160–320 mcg	>240–480 mcg	NA	>320 mcg	>480 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	NA	180-400mcg	180-600 mcg	NA	>400–800 mcg	>600– 1,200 mcg	NA	>800 mcg	>1,200 mcg
Budesonide Inhaled Inhalation suspension for nebulization	0.25–0.5 mg	0.5 mg	NA	>0.5-1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
Flunisolide 250 mcg/puff	NA	500-750 mcg	500-1,000 mcg	NA	1000-1,250 mcg	>1,000-2,000 mcg	NA	>1,250 mcg	>2,000 mcg
Flunisolide HFA 80 mcg/puff	NA	160 mcg	320 mcg	NA	320 mcg	>320–640 mcg	NA	>640 mcg	>640 mcg
Fluticasone HFA/MDI: 44, 110, or 220 mcg/puff	176 mcg	88-176 mcg	88-264 mcg	>176-352 mcg	>176–352 mcg	>264–440 mcg	>352 mcg	>352 mcg	>440 mcg
DPI: 50, 100, or 250 mcg/inhalation	NA	100-200 mcg	100-300 mcg	NA	>200–400 mcg	>300–500 mcg	NA	>400 mcg	>500 mcg
Mometasone DPI 200 mcg/inhalation	NA	NA	200 mcg	NA	NA	400 mcg	NA	NA	>400 mcg

Triamcinolone acetonide 75 mcg/puff	NA	300-600 mcg	300-750 mcg	NA	>600–900 mcg	>750– 1,500 mcg	NA	>900 mcg	>1,500 mcg
<p>Key: DPI, dry power inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group)</p> <p><u>Therapeutic Issues:</u></p> <p>*The most important determinant of appropriate dosing is the clinician’s judgment of the patient’s response to therapy. The clinician must monitor the patient’s response on several clinical parameters and adjust the dose accordingly. Once control of asthma is achieved, the dose should be carefully titrated to the minimum dose required to maintain control.</p> <p>*Preparations are not interchangeable on a mcg or per puff basis. This figure presents estimated comparable daily doses. See EPR—3 Full Report 2007 for full discussion.</p> <p>*Some doses may be outside package labeling, especially in the high-dose range. Budesonide nebulizer suspension is the only inhaled corticosteroid (ICS) with FDA-approved labeling for children <4 years of age.</p> <p>*For children <4 years of age: The safety and efficacy of ICSs in children <1 year has not been established. Children <4 years of age generally require delivery of ICS (budesonide and fluticasone HFA) through a face mask that should fit snugly over nose and mouth and avoid nebulizing in the eyes. Wash face after each treatment to prevent local corticosteroid side effects. For budesonide, the dose may be administered 1–3 times daily. Budesonide suspension is compatible with albuterol, ipratropium, and levalbuterol nebulizer solutions in the same nebulizer. Use only jet nebulizers, as ultrasonic nebulizers are ineffective for suspensions. For fluticasone HFA, the dose should be divided 2 times daily; the low dose for children <4 years of age is higher than for children 5–11 years of age due to lower dose delivered with face mask and data on efficacy in young children.</p>									
<p><u>Potential Adverse Effects of Inhaled Corticosteroids:</u></p> <p>*Cough, dysphonia, oral thrush (candidiasis).</p> <p>*Spacer or valved holding chamber with non-breath-actuated MDIs and mouthwashing and spitting after inhalation decrease local side effects.</p> <p>*A number of the ICSs, including fluticasone, budesonide, and mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported.</p> <p>*In high doses, systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising). In low-to-medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established.</p>									

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Metered-dose inhaler (MDI) - Beta2-agonists - Corticosteroids - Cromolyn sodium - Anticholinergics	≥5 years old (<5 with spacer or valved holding chamber (VHC) or mask)	Actuation during a slow (30 L/min or 3–5 seconds) deep inhalation, followed by 10-second breathhold. Under laboratory conditions, open-mouth technique (holding MDI 2 inches away from open mouth) enhances delivery to the lung. This technique, however, has not been shown to enhance clinical benefit consistently compared to closed-mouth technique (inserting MDI mouthpiece between lips and teeth).	Slow inhalation and coordination of actuation during inhalation may be difficult, particularly in young children and elderly. Patients may incorrectly stop inhalation at actuation. Deposition of 50–80 percent of actuated dose in oropharynx. Mouth washing and spitting is effective in reducing the amount of drug swallowed and absorbed systemically. Lung delivery under ideal conditions varies significantly between MDIs due to differences in formulation (suspension versus solution), propellant (chlorofluorocarbon [CFC] versus hydrofluoralkane [HFA]), and valve design. For example, inhaled corticosteroid (ICS) delivery varies from 5–50 percent.
Breath-actuated MDI Beta2-agonist	≥5 years old	Tight seal around mouthpiece and slightly more rapid inhalation than standard MDI (see above) followed by 10-second breathhold.	May be particularly useful for patients unable to coordinate inhalation and actuation. May also be useful for elderly patients. Patients may incorrectly stop inhalation at actuation. Cannot be used with currently available spacer/valved holding chamber (VHC) devices.
Dry powder inhaler (DPI) Beta2-agonists Corticosteroids Anticholinergics	≥4 years old	Rapid (60 L/min or 1–2 seconds), deep inhalation. Minimally effective inspiratory flow is device dependent. Most children <4 years of age may not generate sufficient inspiratory flow to activate the inhaler.	Dose is lost if patient exhales through device after actuating. Delivery may be greater or lesser than MDI, depending on device and technique. Delivery is more flow dependent in devices with highest internal resistance. Rapid inhalation promotes greater deposition in larger central airways. Mouth washing and spitting is effective in reducing amount of drug swallowed and absorbed.

<p>Nebulizer</p> <ul style="list-style-type: none"> -Beta2-agonists -Corticosteroids -Cromolyn sodium -Anticholinergics 	<p>Patients of any age who cannot use MDI with VHC and face mask.</p>	<p>Slow tidal breathing with occasional deep breaths. Tightly fitting face mask for those unable to use mouthpiece.</p> <p>Using the “blow by” technique (i.e., holding the mask or open tube near the infant’s nose and mouth) is not appropriate.</p>	<p>Less dependent on patient’s coordination and cooperation.</p> <p>Delivery method of choice for cromolyn sodium in young children.</p> <p>May be expensive; time consuming; bulky; output is dependent on device and operating parameters (fill volume, driving gas flow); internebulizer and intranebulizer output variances are significant.</p> <p>Use of a face mask reduces delivery to lungs by 50 percent.</p> <p>Nebulizers are as effective as MDIs plus VHCs for delivering bronchodilators in the ED for mild to moderate exacerbations; data in severe exacerbations are limited. Choice of delivery system is dependent on resources, availability, and clinical judgment of the clinician caring for the patient.</p> <p>Potential for bacterial infections if not cleaned properly.</p>
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Key: ED, emergency department; SABAs, inhaled short-acting beta2-agonists

*See figures in component 2—Education for a Partnership in Asthma Care for description of MDI and DPI techniques.

FIGURE 10. AEROSOL DELIVERY DEVICES
Appendix D

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Metered-dose inhaler (MDI) - Beta2-agonists - Corticosteroids - Cromolyn sodium - Anticholinergics	≥5 years old (<5 with spacer or valved holding chamber (VHC) or mask)	Actuation during a slow (30 L/min or 3–5 seconds) deep inhalation, followed by 10-second breathhold. Under laboratory conditions, open-mouth technique (holding MDI 2 inches away from open mouth) enhances delivery to the lung. This technique, however, has not been shown to enhance clinical benefit consistently compared to closed-mouth technique (inserting MDI mouthpiece between lips and teeth).	Slow inhalation and coordination of actuation during inhalation may be difficult, particularly in young children and elderly. Patients may incorrectly stop inhalation at actuation. Deposition of 50–80 percent of actuated dose in oropharynx. Mouth washing and spitting is effective in reducing the amount of drug swallowed and absorbed systemically. Lung delivery under ideal conditions varies significantly between MDIs due to differences in formulation (suspension versus solution), propellant (chlorofluorocarbon [CFC] versus hydrofluoralkane [HFA]), and valve design. For example, inhaled corticosteroid (ICS) delivery varies from 5–50 percent.
Breath-actuated MDI Beta2-agonist	≥5 years old	Tight seal around mouthpiece and slightly more rapid inhalation than standard MDI (see above) followed by 10-second breathhold.	May be particularly useful for patients unable to coordinate inhalation and actuation. May also be useful for elderly patients. Patients may incorrectly stop inhalation at actuation. Cannot be used with currently available spacer/valved holding chamber (VHC) devices.
Dry powder inhaler (DPI) Beta2-agonists Corticosteroids Anticholinergics	≥4 years old	Rapid (60 L/min or 1–2 seconds), deep inhalation. Minimally effective inspiratory flow is device dependent. Most children <4 years of age may not generate sufficient inspiratory flow to activate the inhaler.	Dose is lost if patient exhales through device after actuating. Delivery may be greater or lesser than MDI, depending on device and technique. Delivery is more flow dependent in devices with highest internal resistance. Rapid inhalation promotes greater deposition in larger central airways. Mouth washing and spitting is effective in reducing amount of drug swallowed and absorbed.

<p>Nebulizer</p> <ul style="list-style-type: none"> -Beta2-agonists -Corticosteroids -Cromolyn sodium -Anticholinergics 	<p>Patients of any age who cannot use MDI with VHC and face mask.</p>	<p>Slow tidal breathing with occasional deep breaths. Tightly fitting face mask for those unable to use mouthpiece.</p> <p>Using the “blow by” technique (i.e., holding the mask or open tube near the infant’s nose and mouth) is not appropriate.</p>	<p>Less dependent on patient’s coordination and cooperation.</p> <p>Delivery method of choice for cromolyn sodium in young children.</p> <p>May be expensive; time consuming; bulky; output is dependent on device and operating parameters (fill volume, driving gas flow); internebulizer and intranebulizer output variances are significant.</p> <p>Use of a face mask reduces delivery to lungs by 50 percent.</p> <p>Nebulizers are as effective as MDIs plus VHCs for delivering bronchodilators in the ED for mild to moderate exacerbations; data in severe exacerbations are limited. Choice of delivery system is dependent on resources, availability, and clinical judgment of the clinician caring for the patient.</p> <p>Potential for bacterial infections if not cleaned properly.</p>
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Key: ED, emergency department; SABAs, inhaled short-acting beta2-agonists
 *See figures in component 2—Education for a Partnership in Asthma Care for description of MDI and DPI techniques.