Chronic Care Model: Management of Asthma

November 2013

This Chronic Care Model was developed by AnewCare's Population Health Program with input and guidance from physicians and providers associated with our accountable care organization. This is a living document which draws from major expert organization guidelines, such as the National Heart, Lung, and Blood Institute's Expert Panel Report 3 and the American Academy of Allergy, Asthma & Immunology. This guideline is not meant to substitute for clinical expertise in treating the specific needs of an individual patient nor is it meant to serve as a standard of care. It serves as a resource on current best practices. Care needs to be individualized for each patient.

Goals of Chronic Care Model for Asthma

- Provide evidence-based care that is patient-centered and encompasses the full continuum of care, and serves to achieve the Triple Aim and the Blueprint goals.
- Improve outcomes and quality of care by:
  - Providing appropriate care (including patient/caregiver education) to improve asthma control, reduce asthma risk and improve quality of life.
  - Initiating or updating the patient's chronic care management plan and enhancing care coordination between ambulatory, acute care settings and the community (including school).
  - Improving patient and family experience.
  - Decreasing the risk of readmission to the ED and/or inpatient unit.
- Provide tools to achieve the quality measures relating to asthma as outlined in Accountable Care Organization 2013 Program Analysis: Quality Performance Standards Narrative Measure Specifications,[1] HEDIS 2013 Asthma Care[2] and the 2013 Physician Quality Reporting System Measures for Asthma.[3]

Measure Title	Agency	Measure Description
Ambulatory Sensitive Admission	ACO	All discharges with principal code for COPD or asthma in adults ≥ 40 YO (potentially avoidable admissions)
Appropriate Medication Use (ASM)	HEDIS	% Patients 5 – 64 YO (divided into subgroups: 5 – 11; 12 – 18; 19 – 50; 51 – 64; total) identified as having persistent asthma and appropriately dispensed medication
Medication Management (MMA)	HEDIS	• % Patients 5 – 64 YO (divided into subgroups: 5 – 11; 12 – 18; 19 – 50; 51 – 64; total) identified as having persistent asthma and who remain on asthma controller medication at least 50% treatment periods • % Patients 5 – 64 YO (divided into subgroups: 5 – 11; 12 – 18; 19 – 50; 51 – 64; total) identified as having persistent asthma and who remain on asthma controller medication at least 75% treatment periods
Asthma Medication Ratio (AMR)	HEDIS	% Patients 5 – 64 YO (divided into subgroups: 5 – 11; 12 – 18; 19 – 50; 51 – 64; total) identified as having persistent asthma and had a ratio of controller medications to total asthma medications of ≥ 0.50 during measurement year
Assessment of Asthma Control	PQRS	% Patients 5 – 50 YO with diagnosis asthma evaluated at least once for asthma control (impairment and risk) [Daytime symptoms AND nighttime awakenings AND interference with normal activity AND short-acting β2-agonist use AND number times oral systemic corticosteroids used in past 12 months]
Pharmacologic Therapy for Persistent Asthma	PQRS	% Patients 5 – 50 YO with diagnosis persistent asthma prescribed long-term controller medication
Tobacco Use: Screening	PQRS	% Patients 5 – 50 YO with diagnosis asthma (or 1° caregiver) who were queried about tobacco use and exposure to second-hand smoke in past 12 months
Tobacco Use: Intervention	PQRS	% Patients 5 – 50 YO with diagnosis asthma (or 1° caregiver) who currently smoke or are exposed to secondhand smoke in home environment who received tobacco cessation intervention in past 12 months

Asthma Clinical Practice Guidelines Summary
Derived from NAEPP-EPR-3

DIAGNOSIS	
Diagnosis of Asthma	• Recurrent, episodic symptoms: cough wheezing, difficulty breathing, chest tightness (often worse at night or with exercise), viral infections, exposure to allergens or irritants, changes in weather, hard laughing or crying, stress, other. • Airway obstruction at least partially reversible (by spirometry ≥ 5 YO) defined as an increase in FEV_1 of ≥ 12% and ≥ 200 ml after administration of a bronchodilator. • Other causes of airway obstruction considered and excluded. • (May consider history of improvement in symptoms or spirometry in response to trial of therapy.)

Assessment of Severity	• Assess severity to initiate therapy (refer to table 3).
	• Severity assessment is based on current impairment **(Evidence B)** and future risk **(Evidence C).**
	• Severity determination based on:
	  ○ Symptom frequency.
	  ○ Nighttime awakenings.
	  ○ Rescue inhaler use.
	  ○ Interference with normal activity.
	  ○ Lung function (spirometry ≥ 5 YO).
	  ○ Exacerbations requiring oral corticosteroids (OCS).
	• Choose severity category by the most severe response.
	• Categories are “intermittent,” “mild persistent,” “moderate persistent” and “severe persistent.”

TREATMENT PLANNING AND IMPLEMENTATION	

Goals of Therapy	• Reduce impairment **(Evidence A).**
	  ○ Prevent or reduce symptoms (goal ≤ 2 d/wk).
	  ○ Prevent or reduce nighttime awakenings (goal ≤ 1 -2 x/mo).
	  ○ Prevent or reduce interference with normal activity (goal no limitation).
	  ○ Prevent or reduce short acting β-agonist (SABA) use for symptom control [excluding prevention of exercise induced bronchospasm (EIB)] (goal ≤ 2 d/wk).
	  ○ Preserve lung function.
	• Reduce risk **(Evidence A).**
	  ○ Prevent or reduce asthma exacerbations requiring OCS (goal 0 – 1/yr).
	  ○ Preserve lung growth and function.
	  ○ Minimize treatment-related adverse effects.
	• Optimize health and function.
	  ○ Prevent or minimize need for emergency care or hospitalizations.
	  ○ Encourage full and active participation in activities.
	  ○ Maintain satisfaction with asthma care.

Assessment of Asthma Control	• Assess control to manage (step up, maintain, step down) therapy.
	• Control determination based on:
	  ○ Symptom frequency.
	  ○ Nighttime awakenings.
	  ○ Rescue inhaler use.
	  ○ Interference with normal activity.
	  ○ Lung function (spirometry ≥ 5 YO).
	  ○ Exacerbations requiring OCS.

- Reduction in lung growth (long-term follow-up required).
- Choose control category by the most severe response.
- Categories are "well controlled," "not well controlled" and "very poorly controlled."

Summary Table of Severity and Step Care					
Components		**Intermittent**	**Mild Persistent**	**Moderate Persistent**	**Severe Persistent**
Impairment	Symptoms	≤ 2 d/wk	> 2 d/wk	Daily	Throughout day
	Nighttime awakening	0 **(≤ 4 YO)** ≤ 2x/mo **(≥ 5 YO)**	1-2x/mo **(≤ 4 YO)** 3-4x/mo **(≥ 5 YO)**	3-4x/mo **(≤ 4 YO)** >1x/wk **(≥ 5 YO)**	>1x/wk **(≤ 4 YO)** Often 7x/wk**(≥ 5 YO)**
	Short acting β-agonist (SABA) use for symptoms	≤ 2 d/wk	> 2 d/wk	Daily	Several times per day
	Limitation of activity	None	Minor	Some	Extreme
	Lung function	FEV1 > 80% FEV1/FVC > 85% **(5 – 11 YO)** FEV1/FVC normal **(≥ 12 YO)**	FEV1 > 80% FEV1/FVC > 85% **(5 – 11 YO)** FEV1/FVC normal **(≥ 12 YO)**	FEV1 > 60% FEV1/FVC > 75% **(5 – 11 YO)** FEV1/FVC reduced by 5% **(≥ 12 YO)**	FEV1 < 60% FEV1/FVC < 75% **(5 – 11 YO)** FEV1/FVC reduced by > 5% **(≥ 12 YO)**
Rik	Exacerbations requiring oral corticosteroid (OCS)	0-1/yr	≥ 2/6 mo **(≤ 4 YO)** ≥ 2/yr **(≥ 5 YO)**		
Recommended step of care		**Step 1**	**Step 2**	**Step 3**	**Step 3** **(≤ 4 YO)** **Step 3 or 4** **(5 – 11 YO)** **Step 4 or 5** **(≥ 12 YO)**
Steps of care (preferred) Quick relief: SABA as needed. Note: SABA use more than 2x/wk (not EIB) indicates inadequate control. Proper inhalation technique, compliance with written asthma plan and management of environmental triggers is the foundation of asthma management.		**Step 1:** no control medication required. **Step 2:** low dose ICS (**≤ 4 YO** – consider referral). **Step 3 (≤ 4 YO):** medium dose inhaled corticosteroid (ICS) + referral **.** **Step 3 (> 5 YO):** low dose ICS + long acting beta-agonist (LABA) or leukotriene receptor antagonist (LRTA) **or** medium dose ICS (consider referral). **Step 4 (≤ 4 YO):** medium dose ICS + LABA or montelukast + referral. **Step 4 (> 5 YO):** medium dose ICS + LABA or LRTA + referral. **Step 5 (≤ 4 YO):** high dose ICS + LABA or montelukast + referral. **Step 5 (> 5 YO):** high dose ICS + LABA or LRTA + referral. **Step 5: (≥ 12 YO):** high dose ICS + LABA or LRTA + referral (consider omalizumab). **[Step 6** specialist care, high dose ICS + LABA or LTRA + OCS (**≥ 12 YO** consider omalizumab)].			

Step Care

- Initiate asthma medications according to the severity of disease initially; adjust medications to minimum dosage to achieve maximum control **(Evidence A)**.
- A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma for both impairment and risk **(Evidence A)**.
- Give specific training for the medication delivery device prescribed (nebulizer, dry powder inhaler (DPI), spacer, etc.).
- The most effective long-term management of the symptoms of persistent asthma is inhaled corticosteroids **(Evidence A)**. However, they do not modify the natural history of the disease.

	• Daily LABAs should be restricted to add-on therapy with ICS, if indicated, and not used as sole agents due to black box warning. Consider prescribing as a combination inhaler with ICS, if LABA needed.
	• Theophylline and oral β-2 agonists are not generally used in asthma due to side effect profile.
	• Chromones are currently not available as MDIs and only cromolyn is available for nebulized use.
	• LTRA's may be used in step-up care as alternative to LABA.
	• If OCSs are indicated, recommended dosage is 1 mg/kg/d, divided BID for 5 days.
	• Step care adjusts the number, frequency and types of medications required to achieve and maintain control, either by increasing as necessary **(Evidence A)** or decreasing **(Evidence C)** the medical regime as indicated by patient symptoms and/or objective measures.
	• If not well controlled, review history prior to increasing step of care.
	  ○ **I**nhalation technique to maximize effective dosage: if not already using, and if appropriate, add valved holding chamber (VHC)/spacer.
	  ○ **C**ompliance with control medication use.
	  ○ **E**nvironmental control strategies employed and review of triggers, including new triggers/changes in environment/seasonal changes, others.
	• If not well controlled, consider stepping up 1 step. If very poorly controlled, consider stepping up 2 steps and short course of OCS to gain control.
	• If patient is well controlled on current step of care for 3 months, consider stepping down 1 level, with the goal of finding the lowest step of care to maintain control.

Exercise Induced Broncho-constriction	• SABA, typically 2 puffs, 5 – 20 minutes prior to exercise will be effective for 2 – 4 hours to prevent EIB. • Regular, daily use will decrease the effectiveness. • EIB in a patient with chronic asthma suggests poor control of asthma and need for stepping up care. • LABAs should not be used as routinely as monotherapy for EIB and should only be added onto a patient already receiving ICSs. • LTRAs are effective in about half of patients and can be used daily or intermittently to attenuate EIB.
Follow-up	• 2 – 6 weeks while gaining control. • 1 – 6 months to monitor control. • 3 months, if anticipating step down. • Follow-up in 2 - 7 days after an ED visit or for a severe exacerbation. • Degree of asthma control should be routinely monitored to assess whether impairment and risk are reduced **(Evidence B).**
Rescue Therapy	• Inhaled short acting β2-agonists (SABA) should be prescribed for acute symptoms. • 2 - 8 puffs q 4 hr (<12 puff/24 hr) is recommended for an exacerbation. If preferred by patient, nebulizer may be used with dosage 2.5 – 5 mg (depending on patient weight). • Patient/family should have clear instructions (through Asthma Action Plan) about when to contact PCP or to proceed for urgent care. • Monitor the use of SABA as frequent use implies poor asthma control would require a re-evaluation (inhalation technique, compliance, and environmental control) and potential step-up in therapy.

Patient and Family Education	• There are 3 main components to education.
	  ○ Basic asthma facts.
	  ○ Role of medications, including long term control and short term relief, and potential side effects.

	○ Patient skills, including: ▪ Proper medication use (timing and technique). ▪ Self-monitoring and recognition of asthma exacerbation. ▪ Identification and avoidance of triggers/allergens. ▪ Use of action plan. ▪ Communication of action plan to others (school or coach). • Consider use of teach back method. • Use team-based approach to continuously reinforce messages, especially if exacerbation occurs. • Address fears and misconceptions. • Encourage patient to take responsibility for managing their asthma with guidance of written Asthma Action Plan **(Evidence B).** • Patients should be taught how to assess asthma control through symptoms or use of peak flow monitoring **(Evidence A).** • Patient education is essential to achieve optimal pharmacologic therapy **(Evidence A).**
Asthma Action Plan	• An individualized and explicit Asthma Action Plan needs to be developed for each patient with complete information about controller medications, clear understanding of points to increase or add medication and when to call for help, and when to proceed to for urgent care **(Evidence B).** • The plan should be reviewed at each visit. • The plan should be copied and shared with other care providers. • The plan may be driven by symptoms (cough, wheeze, shortness of breath, waking up at night, decreased ability to do normal activities) or by peak flow monitoring.
RISK FACTOR MODIFICATION	
Environmental Control	• Review exposure history to allergens and irritants to which the patient is sensitive, particularly indoor inhalant allergens **(Evidence A)** and tobacco smoke **(Evidence C).** • For an adult with new-onset asthma, access for occupational causes. • Evaluate exposure to places patient spends time (home, work, school, other caregivers, hobbies, etc.). • Allergy avoidance requires comprehensive focus to be effective **(Evidence A).**
Immunization	• Annual flu vaccination recommended. • Adults (19 – 64) with asthma should receive single dose of pneumonia vaccination (PPSV23).
Tobacco Use	• Ask at every visit about potential tobacco smoke exposure (personal and secondhand). • If patient smokes, strongly encourage and motivate patient to quit. • If patient is exposed to secondhand smoke, develop plan to minimize exposure (encourage parents or partner to quit or avoidance of situations where smoking occurs).
MONITORING	
Medication Reconciliation	• Accurately and completely reconcile all medications patient is taking at every visit (including supplements). • Review side effects, costs or other concerns. • Review correct technique with DPI, MDI, VHC/spacers and/or nebulizer – may have patient bring in inhaler and VHC/spacers (if used) to demonstrate. • Review compliance with medications (consider pharmacy records).
Self-Measured Goals and Home Monitoring	• If appropriate, review peak flow meter use through direct observation (have patient bring in their peak flow meter). • Peak flow monitoring may be appropriate for patients > 5 yo with: ○ Moderate of severe persistent asthma **(Evidence B).**

	○ History of severe exacerbation **(Evidence B).** ○ Poor perception of airflow obstruction **(Evidence D).** ○ Prefer this method **(Evidence D).** • If appropriate, review symptom-based monitoring diary **(Evidence B).** • Self-monitoring is important, whether through peak flow or symptom **(Evidence A).**
Pulmonary Function Test (≥ 5 YO)	• At time of diagnosis. • Every 1 – 2 years. • Consider if significant change in clinical status. • Consider after step-down to discover silent decline in lung function. • Consider after step-up to confirm response to changed therapy. • Airway hyperresponsiveness can be measured by the following ways: ○ Directly by methacholine chloride or histamine diphosphate. ○ Indirectly by hypertonic saline, adenosine monophosphate or mannitol. ○ Testing needs to be performed in a controlled environment by trained individuals, according to established guidelines and with appropriate emergency resources.
Referral	• Social Services may be needed if family resources are inadequate to provide medications or transportation to care. • Refer to specialist in asthma care (often allergist or pulmonologist): ○ Patient with life-threatening asthma exacerbation. ○ Patient not achieving goals of therapy after 3 – 6 months or sooner if patient is unresponsive to therapy. ○ Uncertainty as to the diagnosis. ○ Other comorbidities complicate diagnosis and/or treatment. ○ Additional testing is indicated, including allergy testing, bronchoscopy, provocative pulmonary testing. ○ Patient requires step 4 therapy or higher (step 3 for children 0 – 4 YO). May consider referral at step 3 (or step 2 for children 0 – 4 YO). ○ Patient has required ≥ 2 bursts OCS in 1 year or has been hospitalized due to asthma exacerbation. ○ Evaluation and possible mitigation of workplace induced asthma.
ACUTE EXACERBATION	
Assessment and Monitoring	• History and physical. • Frequent assessment of pulmonary index score (examines respiratory rate, wheezing, inspiratory/expiratory ratio, accessory muscle use, and pulse oximetry) – or comparable assessment tool. • Pulse oximetry (maintain oxygen saturation ≥ 92%). • Spirometry. • Note: Chest X-ray not routinely recommended unless suspected consolidation, pneumothorax, and failure to respond to treatment. Arterial blood gas not routinely recommended unless suspected progression to respiratory failure.
Medications	• High dose inhaled SABA's: ○ For more acute exacerbations, give through nebulizer with supplemental oxygen (mild to moderate may be treated with MDI and spacer). ○ May use intermittently or continuously. • Add nebulized ipratropium to SABA nebulizer for patients with severe or life-threatening exacerbation of who have poor initial response. • Give steroids early in the acute setting (oral route) [typical dosage 1 mg/kg/d (max 60 mg/d) qd x 5

	d].
	• Consider IV magnesium sulfate for adults with severe or life-threatening exacerbation of who have poor initial response.
	• Hospitalization is indicated for:
	  ○ Ventilator support.
	  ○ For severe or life-threatening exacerbation of who fail to respond to therapies.
	  ▪ Worsening FEV.
	  ▪ Worsening or persistently decreased hypoxia.
	  ▪ Hypercapnia.
	  ▪ Respiratory acidosis.
	  ▪ Exhaustion, confusion, altered mental state.
	  ▪ Respiratory arrest.
	• Routine use of antibiotics is not indicated for patients with acute asthma.

Discharge	• Reinforce education, discuss possible triggers, medication compliance and technique. • Review Asthma Action Plan and self-management skill. • Follow-up with PCP in 2 – 7 days.
DOCUMENTATION OF OUTCOME MEASURES	
Ambulatory Sensitive Admission	All discharges with principal code for COPD or asthma in adults ≥ 40 YO (potentially avoidable admissions).
Appropriate Medication Use (ASM)	% Patients 5 – 64 YO (divided into subgroups: 5 – 11; 12 – 18; 19 – 50; 51 – 64; total) identified as having persistent asthma and appropriately dispensed medication.
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Asthma Medication Ratio (AMR)	% Patients 5 – 64 YO (divided into subgroups: 5 – 11; 12 – 18; 19 – 50; 51 – 64; total) identified as having persistent asthma and had a ratio of controller medications to total asthma medications of ≥ 0.50 during measurement year.
Assessment of Asthma Control	% Patients 5 – 50 YO with diagnosis asthma evaluated at least once for asthma control (impairment and risk). [Daytime symptoms AND nighttime awakenings AND interference with normal activity AND short-acting β2-agonist use AND number times oral systemic corticosteroids used in past 12 months.]
Pharmacologic Therapy for Persistent Asthma	% Patients 5 – 50 YO with diagnosis persistent asthma prescribed long-term controller medication.
Tobacco Use: Screening	% Patients 5 – 50 YO with diagnosis asthma (or 1° caregiver) who were queried about tobacco use and exposure to secondhand smoke in past 12 months.
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Asthma Statistics

Sources used: CDC[4] and WHO[5]

- In 2010, about 25.7 million people in US had asthma (total prevalence 8.4%).
  - 18.7 million US adults had asthma (or 1 in 12 adults).
  - 7 million US children had asthma (or 1 in 11 children).
  - Asthma prevalence has increased nearly 15% in the past decade; in 2001, total prevalence was 7.3%.
- In 2009, asthma was associated with:
  - 8.9 million physician visits.
  - 1.9 million emergency department (ED) visits, ≈ 40% of those were under 15 YO.
  - 479,300 hospitalizations; asthma is the 3rd leading cause of hospitalizations under the age of 15.
  - 3,388 deaths, with a large percentage of deaths occurring in adults > 85 YO.
  - $56 billion in direct and indirect health care costs.
  - 10.5 million missed days of school.
  - 14.2 million missed days of work.
- US Demographics
  - Women are more likely to have asthma than men, but boys are more likely to have asthma than girls.
  - Asthma is more common in children than older adults.
  - African American children are 2 times more likely to have asthma than Caucasian children.
  - Ethnic distribution: Puerto Rican (16.1%), multi-race (14.1%), African American (11.2%), Native American (9.4%) Caucasian (7.7%) Mexican (5.4%) and Asian (5.2%).
  - Lower income (below poverty level) and lower education achievement are associated with a higher prevalence of asthma.
  - Smokers are more likely to have asthma than nonsmokers. Exposure to secondhand smoke has worsened the asthma symptoms of an estimated 400,000 – 1 million children[6].
  - Obese adults are more likely to have asthma than nonobese adults. Although, an examination of the 3rd National Health and Nutrition Examination Survey data revealed that obesity appears to be associated with dyspnea but not airflow obstruction. [7]
- An estimated 300 million people worldwide suffer from asthma, and 250,000 deaths annually are attributed to asthma. Globally, asthma is the leading cause of chronic disease in children.

Definition of Asthma

Source used: National Asthma Education and Prevention Program: Expert Panel Report 3 (NAEPP, 2007)[8]

- Asthma is a heterogeneous disorder, manifesting with variable degrees of symptoms between patients and within the same patient at different times.
- **NAEPP Working Definition of Asthma:**
  - Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, including mast cells, eosinophils, neutrophils, T-lymphocytes, macrophages and epithelial cells. Many different chemical mediators are involved, including cytokines, histamine, leukotrienes, thromboxanes, reactive oxygen species and chemokines.
  - In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness and chest tightness.
  - These episodes are usually associated with widespread but variable airflow obstruction that is often (but not always) reversible either spontaneously or with treatment. The episodes are

frequently provoked by triggers, including viral infections, exercise, indoor and outdoor allergens or irritants.

- **Airway Inflammation Leads to Airflow Limitation by:**
  - Bronchoconstriction – bronchial smooth muscle contraction to a variety of stimuli, including allergens or irritants. Both small airways and segmental and sub-segmental airways are involved.[9,10]
  - Airway hyperresponsiveness – exaggerated bronchoconstriction response to stimuli.
    - Airway hyperresponsiveness (AHR) is a central feature in the pathophysiology of asthma, but not all patients with AHR found by airway challenge have symptoms of asthma.[11]
    - AHR is a risk factor for developing asthma.[12]
  - Airway inflammation – edema, mucous hypersecretion and formation of mucous plugs in response to more persistent and progressive inflammation further limits airflow.
    - Inflammatory cells (neutrophils, eosinophils, mast cells, lymphocytes) are abundant in the lungs of patients with asthma.
    - Airway inflammation increases bronchial hyperresponsiveness.[13]
    - In severe asthma, an exaggerated inflammatory response is associated with impaired glutathione homeostasis, resulting in reduced antioxidant capacity and increased risk of airway injury.[14]
- **Genetics of Asthma**
  - Asthma occurs in a genetically susceptible individual exposed to environmental factors (especially indoor allergens) at a critical time in development of the immune system.[15]
  - The genetics is not fully understood, but it appears that there are different asthma genotypes.
  - A child with one parent with asthma is 2.6 times more likely to have asthma; a child with both parents with asthma is 5.2 times more likely to have asthma.[16]
  - In children, the immature immune system facilitates atopic responses.[17]
- **Pathophysiology of Asthma** [full description beyond the scope of this document]
  - Bronchoconstriction
    - Bronchoconstriction from allergens is an IgE dependent process that results in mast cells releasing histamine, tryptase, leukotrienes and prostaglandins.[18]
    - In patients sensitive to nonsteroidal anti-inflammatory drugs (NSAIDs), the mechanism does not appear to be IgE mediated.[19]
    - The mechanism for irritants is not as clearly defined, but may involve proinflammatory cytokines.
    - Exercise may induce bronchoconstriction through a change in osmolarity (due to loss of water in the airway from fast and deep breathing), which induces degranulation of mast cells.[20]
  - Early and late phase reactions
    - After initial exposure and immune response to an allergen, subsequent exposures lead to an allergen specific IgE binding on mast cells, followed by rapid degranulation. This is the early phase reaction.[21]
    - Late phase reaction may occur in some individuals several hours after exposure to the allergen. It is characterized by an influx of inflammatory and immune cells.[21] Release of mediators results in airway smooth muscle contraction, which may not completely resolve with β2-agonist use.
  - Airway inflammation
    - CD4 Lymphocytes: T-helper 1 cells, T-helper 2 cells (Th-1, Th-2), regulatory T cells (T_{reg}) and T-17 are involved.

        - An imbalance between Th-1 and Th-2 (favoring Th-2) contributes to the underlying etiology of allergies and asthma.
        - Th-1 cells drive cell-mediated responses [with interferon-gamma (IFN-Ɣ), tissue necrosis factor-alpha (TNF-α), and interleukin-2 (IL-2)], whereas Th-2 cells drive humoral responses (with IL-4, IL-5, IL-9, and IL-13).
        - Th-2 cytokines may contribute to the overproduction of immunoglobulin E (IgE), increased numbers of eosinophils and subsequent airway hyperresponsiveness.
        - Th-17 cells also are proinflammatory and may contribute to the host response to an allergen challenge.[22]
        - T_{reg} suppresses the Th-2 response. An imbalance in their functioning will result in an overexpression of Th-2.[23]
    - Eosinophils
        - Presence of eosinophils relates to asthma severity in many patients.[24]
        - Eosinophils release a variety of substances which may cause smooth muscle contraction, damage to airway epithelium, and airway remodeling and fibrosis.
    - Mast cells
        - Involved in early phase reaction.
        - Also release TNF which is important in recruiting inflammatory cells.[25]
    - Neutrophils are found in sudden-onset fatal asthma, occupational asthma, and in patients who smoke.[26]
    - Basophils produce histamine and leukotrienes, and produce more IL-4 and IL-5 than Th-2 cells.[27]
    - Structural cells, such as epithelial and endometrial cells, fibroblasts and smooth muscle cells may also contribute to the pathophysiological process.
- Airway remodeling
    - A subset of asthma patients have irreversible airflow obstruction caused by structural changes.[28]
    - Remodeling appears to be an early feature based on findings of epithelial loss and basement membrane thickening in bronchial biopsies of children with asthma.[29]
    - Severity of asthma seems to correlate with airway remodeling as opposed to disease duration.[30]
- It appears that there are different phenotypes of asthma with different cell lines and/or mediators being more prevalent in certain patients.[31] This difference may explain why some patients respond better to a therapy (such as anti-IgE monoclonal antibodies or leukotriene receptor blockers).

- **Proposed Hypotheses to Explain Increased Frequency of Asthma**
    - It is thought that energy efficient homes with better sealed windows and doors may be increasing the concentration of indoor allergens.[32]
    - The improved hygiene theory proposes that reduced exposure to infectious pathogens causes an imbalance in the immune response, triggering asthma.[33]
    - However, increased incidence of respiratory viral infections in infants has also been proposed as an explanation for increased frequency of asthma.[34]
    - Maternal smoking affects lung growth in the fetus which may affect the development of asthma in childhood.[35]
    - Increased awareness of asthma by providers and patients may increase the likelihood of a diagnosis.
    - Dietary factors, such as diets low in antioxidants and omega-3 fatty acids, have also been studied as possible contributing factors to the development of asthma.[43, 44]

- **Common Environmental Factors**
  - Airborne allergens (especially dust mites, cockroaches, and the mold Alternaria) and viral infections [especially respiratory syncytial virus (RSV) and rhinovirus] are very important triggers for asthma.[12,36]
  - Tobacco
    - Passive tobacco smoke is strongly associated with the development and persistence of recurrent coughing or wheezing during childhood.[37,38]
    - Tobacco smoke in utero is associated with an increased risk of wheezing, but it is unclear if this progresses to asthma.[39]
    - Smoking is associated with persistence of asthma.[35]
    - Almost half of older adults with asthma are current or former smokers.[40]
    - Cigarette smoke increases sputum inflammatory markers, IgE antibodies and bronchial responsiveness.[41]
  - Air pollution has been studied: A small, positive correlation was found between asthma symptoms and nitrogen dioxide and carbon monoxide, a marginal correlation was noted for sulfur dioxide; no relationship was noted for ozone and particulates.[42]
  - Occupations, such as nursing, cleaning and occupations which have exposure to chemical spills or fires, are associated with new onset asthma in adulthood.[45]
- **Asthma and Allergy**
  - Atopy is the presence of IgE antibodies to specific antigens, which results in an immediate hypersensitivity reaction when exposed to that antigen.
  - Atopic dermatitis, allergic rhinitis and asthma are related conditions. "Atopic March" refers to the presence of atopic dermatitis in infancy and early childhood, allergic rhinitis developing in childhood, and then asthma presenting in later childhood and adolescence.
  - The 3rd National Health and Nutrition Examination Survey found that about 50% of asthma cases were associated with atopy (defined as a positive skin test to an antigen).[46] 80% of children with atopic dermatitis develop asthma and/or allergic dermatitis.[47]
  - Other studies have also found strong associations between IgE levels and skin test reactivity.[48]
  - 30% of children with a food allergy have asthma and allergic rhinitis.[49] Food allergy is a risk factor for more severe asthma attacks with higher occurrences of asthma attacks requiring intubation.[50]
  - In infants, food allergies and atopic dermatitis are the most common manifestations of atopy; asthma and allergic rhinitis are the most common manifestations of atopy in older children.[51]

Diagnosis of Asthma: Algorithms 1; Tables 1 and 2

Sources used:
-NAEPP, 2007[8]
-Joint statement of the European Academy of Allergy and Clinical Immunology and the American Academy of Immunology (Practall), 2008[52]
-Canadian Thoracic Society (CTS), 2012[53]

- **Diagnosis of Asthma is Based on Three Factors:**
  - History reflecting episodic symptoms of airway hyperresponsiveness and/or airflow obstruction (including variable presentation of cough, recurrent wheezing, recurrent difficulty breathing, recurrent chest tightness) with symptoms that occur or worsen at night or with triggers.

- Note: A normal examination does not exclude the diagnosis of asthma, as the patient is often asymptomatic between episodes.
- Presence of multiple key indicators increases the likelihood of the diagnosis of asthma.
- Nighttime cough, seasonal cough, cough in response to specific trigger, or cough lasting longer than 3 weeks are suggestive for asthma.[54] In children, a dry hacking cough is frequently the only presenting complaint.[55]

Table 1: Key Indicators Suggestive of Asthma (History and Physical) (NAEPP[8])
History of any of the following
Cough, often worse at night or early morning
Recurrent (episodic) wheeze
Recurrent (episodic) difficulty breathing, shortness of breath
Recurrent (episodic) chest tightness
Symptoms occur or worsen at night and awaken patient
Symptoms occur or worsen with triggers:
Exercise
Viral infection
Inhalant allergens (animal dander, dust mites, mold, pollen)
Irritants (tobacco, wood smoke, airborne chemicals)
Changes in weather
Strong emotional expression (laughing or crying hard)
Stress
Menstrual cycle
Medications
Gastroesophageal Reflux Disease (GERD)
Food, food additives and preservatives (sulfites)
Physical: Presence of expiratory wheezing is a key indicator. Note: Due to episodic nature and reversibility, absence of findings does not rule out diagnosis.

- Airflow obstruction that is at least partially reversible on spirometry (with and without bronchodilators).
  - Because airway obstruction is by definition intermittent, spirometry may be normal if patient is not symptomatic. Repeat spirometry when the patient is symptomatic (may be required to confirm the diagnosis).
  - Airway obstruction: reduction in both forced expiratory volume in 1 second (FEV_1) and FEV_1/FVC (forced vital capacity) relative to reference or predicted values, based on age, height, sex and race.
  - Finding of airflow obstruction (reduction of FEV_1 /FVC on spirometry) has been shown to significantly predict future asthma risk.[56]
  - Reversibility is determined by an increase in FEV_1 of > 200 mL and ≥ 12 % (often 15 – 20% seen) from baseline measure after inhalation of short-acting β2-agonist (SABA).
  - Chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis and bronchiolitis will also have some degree of reversibility with bronchodilators, although typically “not significant.” There is not a clear cut off as to what is or isn’t “significant.”

Algorithm 1: Diagnosis of Asthma

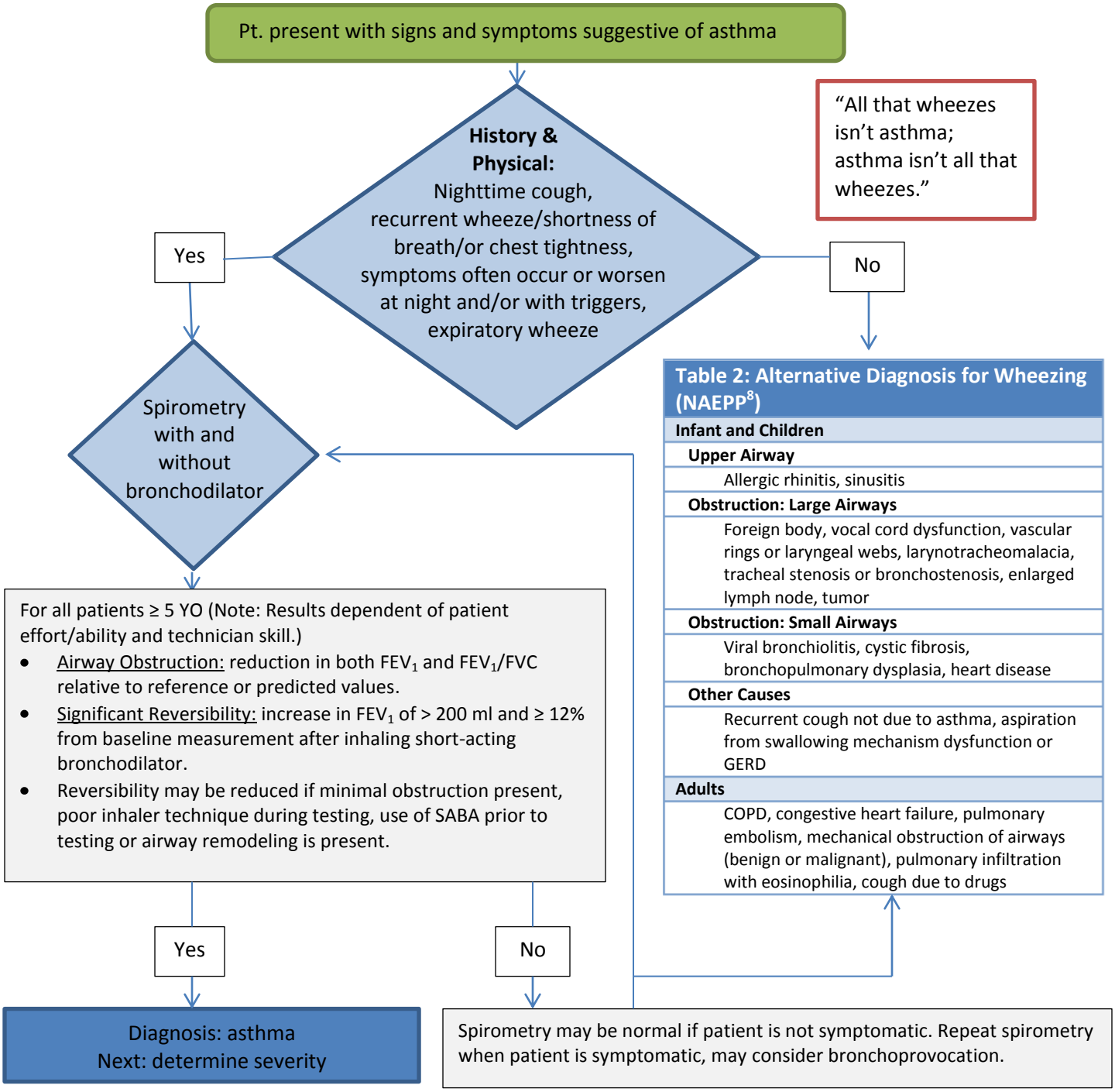


Table 2: Alternative Diagnosis for Wheezing (NAEPP[8])

Infant and Children
Upper Airway
Allergic rhinitis, sinusitis
Obstruction: Large Airways
Foreign body, vocal cord dysfunction, vascular rings or laryngeal webs, larynotracheomalacia, tracheal stenosis or bronchostenosis, enlarged lymph node, tumor
Obstruction: Small Airways
Viral bronchiolitis, cystic fibrosis, bronchopulmonary dysplasia, heart disease
Other Causes
Recurrent cough not due to asthma, aspiration from swallowing mechanism dysfunction or GERD
Adults
COPD, congestive heart failure, pulmonary embolism, mechanical obstruction of airways (benign or malignant), pulmonary infiltration with eosinophilia, cough due to drugs

- Patients with asthma may not show a significant response to bronchodilators on spirometry if they have no or minimal obstruction to begin with, have poor technique with the bronchodilator during the testing process, used a bronchodilator prior to testing, or have airway remodeling.

- Reversibility of airflow limitations may be incomplete in some individuals due to remodeling of airways from fibrosis, smooth muscle hypertrophy, angiogenesis, injury to epithelial cells, cellular hyperplasia, chronic inflammatory cell infiltration, collagen deposition, and/or thickening of the basement membrane.[57]
- For patients with severe persistent asthma or very poorly controlled asthma, it may be beneficial to give a 2 – 3 week trial of oral corticosteroids (OCS) to fully assess the degree of reversibility and establish a goal for ongoing controller therapy instead of relying on a predicted value.
- Follow American Thoracic Society Standards for performing spirometry.[58] Results are dependent on technician skill and patient effort and/or ability.
- Peak expiratory flow rate (PEFR) measurements are not an alternative to spirometry for diagnosis.
- Variability of FEV_1 or PEFR, either spontaneously or in response to therapy, is suggestive of asthma.[53]

- Alternative diagnoses excluded
  - Consider cough-variant asthma, especially in young children.
  - Vocal cord dysfunction (VCD) should be considered in difficult to treat, atypical asthma-like symptoms.
  - Other disorders that can be associated with wheezing may also be co-morbid conditions with asthma, such as VCD, GERD, allergic bronchopulmonary aspergillosis (ABPA).
  - Onset of symptoms after 50 YO may be from other diseases with overlapping symptoms, such as COPD, congestive heart failure, pulmonary embolism, lung cancer, GERD, bronchitis, bronchiectasis, bronchiolitis obliterans, sarcoidosis, anxiety disorder, others.
  - Additional studies are not usually necessary, but may aid if there is a suspicion of alternative diagnosis or failure to respond as expected to treatment.
    - Complete blood count to evaluate for significant anemia (which may cause dyspnea) and for eosinophilia, especially with presence of nasal polyposis or consideration for eosinophilic pneumonia or parasitic infection.
    - Additional pulmonary function tests may help. They include:
      - Diffusion capacity – reduced in COPD.
      - Lung volume measurement.
      - Evaluation inspiratory flow-volume loop - abnormality may suggest vocal cord defect.
    - Bronchoprovocation test with methacholine, histamine, cold air or exercise challenge may be useful if asthma is suggested but spirometry is (near) normal or symptoms are atypical.
      - Positive test suggestive of airway hyperresponsiveness which may be from asthma or other cause.
      - Negative test excludes asthma diagnosis.
    - Chest X-ray may be useful.
      - In patient with moderate to severe asthma AND with an onset when patient > 40 YO.
      - With presentation with other symptoms, such as fever, purulent sputum, hemoptysis, weight loss, significant hypoxia, nonreversible airflow obstruction, clubbing, peripheral edema, persistent localized wheezing, others.

        - Sweat-chloride test to evaluate for cystic fibrosis may be useful in child with respiratory complaints, diarrhea, recurrent pneumonia, failure to thrive, and/or edema.
        - Barium swallow may be useful in infant with recurrent asthma to evaluate for tracheoesophageal fistulas or compressive vascular anomaly. A barium swallow may also be useful for determining GERD, although a normal result does not exclude the diagnosis.
        - In adults who are never smokers with persistent airflow obstruction, a measurement of serum alpha-1 antitrypsin level is recommended.
    - There is no one test to establish or confirm the diagnosis of asthma. It is a diagnosis suggested by history and by spirometry, and by absence of other diagnoses. The diagnosis may be further reinforced by response to a trial of therapy. The British guideline on the management of asthma also includes history of a positive response to asthma therapy (either by symptoms or objective measurement) as a factor which increases the probability of asthma.[65]
- **Asthma Diagnosis in Children < 4 YO**
    - About 80% of children with asthma have symptoms before 5 YO, but the disease frequently has not been diagnosed correctly, especially in infants and toddlers.[66]
    - Common terms used for younger children include: reactive airway disease, asthmatic bronchitis, wheezy bronchitis, bronchiolitis, wheezing-associated respiratory illness and others.
    - "Reactive airways disease" is a nonspecific term implying a nonallergic airway hyperresponsiveness, which may be asthma. This term is generally not used for people older than 5 YO who can perform diagnostic spirometry.
    - Some asthma experts advocate that there are different phenotypes of asthma in children and describe patterns of childhood wheezing.[52]
        - Transient Wheezing
            - Infant who wheezes, but after 3 YO no longer wheezes.
            - (Retrospective diagnosis.)
        - Nonatopic Wheezing
            - Wheezing mainly triggered by viral infections, remits later in childhood.
            - (Retrospective diagnosis.)
        - Persistent Asthma
            - Atopy present (eczema, allergic rhinitis and conjunctivitis, food allergy) eosinophilia and/or elevated IgE.
            - IgE mediated sensitization to foods and inhaled allergens.
            - Parental history of asthma may be present.
        - Severe Intermittent Wheezing
            - Infrequent acute wheezing episodes with minimal morbidity between episodes.
            - Atopic characteristics (eczema, allergic sensitization, and eosinophilia).
            - Consider trigger.
                - Viral-induced.
                - Exercise-induced.
                - Allergen-induced.
                - Irritant-induced.
                - Other trigger
                - Note: Overlap common.
    - Diagnosis of asthma may be challenging due to difficulty obtaining objective measures of lung function in this age group; it is based on clinical features in the absence of an alternative diagnosis.

        - Caution against over-diagnosing with resultant, inappropriate, long-term medication usage.
        - Caution against under-diagnosing and resultant inappropriate under medication usage and resultant increase in morbidity.
        - Consider 4 – 6 week course of controller medication to confirm asthma diagnosis.[8] Marked clinical improvement during the trial of controller medication and deterioration with medication withdrawal support the diagnosis of asthma.
    - Natural history of asthma in young children
        - Younger children are more likely to wheeze with viral infections; 60% of these children will not persist with asthma by school age.[67]
        - Up to 50% of all children < 3 YO will have ≥ 1 episode of wheezing.[37] Atopic children are more likely to continue wheezing and those children ≤ 2 YO with more severe symptoms are more likely to have asthma later in life.[68]
        - In infancy, inhalant allergy is less common than food allergy; food allergy may manifest in the skin, gastrointestinal (GI) tract or respiratory tract.[69] Food allergies as an infant are a risk factor for the development of asthma later in childhood.[70]
    - **Asthma Predictive Index** may help predict which young children will (or will not) subsequently develop asthma. Risk is based on history of wheezing during first 3 years of life and 95% of children with a negative index will not develop asthma later in childhood.[71]
        - Either 1 of the following:
            - Parental history of asthma.
            - Physician diagnosis of atopic dermatitis.
            - Evidence of sensitization to aeroallergens.
        - Or 2 of the following:
            - Evidence of sensitization to foods.
            - > 4% eosinophilia.
            - Wheezing apart from viral respiratory infections.
- **Possible Future Biomarkers**
    - These tests are not yet routinely recommended for diagnosis of asthma.
    - It is noted that asthma is a heterogeneous disease. Instead of 1 biomarker being reflective of the current disease state, there will probably be a panel of markers required.[59]
        - Induced sputum for differential cell counts
            - Assumes that inflammatory infiltrate in sputum reflects inflammatory process in tissue.
            - Treating asthma based on the results of induced sputum eosinophilia may reduce severe eosinophilic asthma exacerbations in adults with moderate to severe asthma.[53]
            - However, normal sputum eosinophil count (< 1.9%) may reflect non-eosinophilic asthma phenotype (such as someone who has neutrophilic inflammation and will be steroid intolerant) [60] versus someone whose inflammation is well controlled with current steroid therapy.
            - Only performed in secondary care and specialist laboratories. Sputum is induced with nebulized hypertonic saline.
        - Fractional exhaled nitric oxide (FeNO)[61]
            - An exhaled biomarker which correlates with airway eosinophilia. An unclear mechanism results in increase in nitric oxide, which then affects vascular and pulmonary tone.

- FeNO levels rise with increasing airway inflammation and decrease with inhaled corticosteroid (ICS) use.[62]
- It had been suggested that by monitoring FeNO, patients were able to be controlled on lower ICS dosage. However, a Cochrane Review concluded that FeNO offers no benefit over adjusting ICS dose to control clinical symptoms.[63]
- It appears that there is a large variation of FeNO between individuals, perhaps reflecting the heterogeneous nature of asthma. There is overlap between patients with and without asthma and atopy cohorts. But FeNO levels are reproducible within an individual, so those changes within an individual may reflect true changes in their inflammatory state and response to therapy.[64]
- It is not clear if FeNO is a cause of airway inflammation or a marker for it.
- Cost currently restricts wide spread usage.

- Future biomarkers may include other exhaled breath condensate markers (such as pH and other markers of oxidative stress), serum proteins (such as eosinophil cationic protein levels and others) and urinary metabolites (such as urinary leukotriene-4).

Assessment and Monitoring: Asthma Severity and Control: Tables 3 - 5

Sources used:
-NAEPP, 2007[8]
-Global Initiative for Asthma (GINA), 2012[72]

- **Overview of Goals of Asthma Therapy**
  - Common goals of asthma treatment include:
    - Prevent (or minimize) symptoms.
    - Normalize (or prevent further deterioration) of pulmonary function.
    - Maintain normal activity levels (or improve current diminished activity level).
    - Prevent exacerbations (or reduce frequency and intensity).
    - Experience little to no medication side effects (or minimize toxicity).
  - Goals may need to be modified based on severity of asthma or degree of achievable control.
  - Treatment of asthma requires a multidisciplinary team with the patient or caregiver as an integral team member.
  - Patient education and self-management skills are key components.
  - Irritant and allergic trigger avoidance is important for many patients with asthma.
- **Complete History and Physical**
  - Identify any precipitating factors for episodic symptoms.
  - Identify any comorbid conditions which might confound treatment.
  - The presence or absence of wheezing does not indicate the severity of asthma.

Table 3: Medical History and Physical Examination (NAEPP[8])
Symptoms
Cough, wheezing, shortness of breath, chest tightness, sputum production.
Pattern of symptoms
Diurnal, seasonal, perennial, episodic, continuous.
Precipitating events
Viral respiratory infections, environmental allergens (mold, dust-mites, cockroaches, animal dander, pollen), smoking (primary or secondary), exercise, occupational exposure, irritants (strong odors, air pollutants, particulates, vapors, gases, aerosols, occupational chemicals), strong emotions, endocrine factors, drugs (aspirin, NSAIDs, others), changes to personal environment (remodeling, new office, weather changes), other.
Characteristics of spaces where spend time (home, work, school, family caregiver)

Location and age of home, heat and cooling system, wood-burning stove, dehumidifier, carpeting over concrete, mold and mildew, stuffed furniture or toys, pets with fur, other.
Family history
History of asthma, allergy, sinusitis, rhinitis, eczema, or nasal polyps in close relatives.
Development of disease and prior history
Age of onset and diagnosis.
History of early life injury to airways (bronchopulmonary dysplasia, pneumonia, parental smoking).
Progression of disease (better or worse).
Prior medication use and reason for discontinuation.
Present management strategies and response, including plan for managing exacerbation.
Frequency of use of SABA.
History of exacerbations
Usual prodromal signs and symptoms.
Rapidity, duration, frequency and severity.
Frequency of oral steroid use, ED visits, hospitalizations, ICU admissions, intubation.
Number and severity of exacerbations in past 12 months.
Usual patterns and management (what works).
Prior medications, including over-the-counter and complementary, reasons for discontinuing.
Social history
Daycare, workplace or school characteristics that might interfere with adherence to plan of care.
Social factors that might interfere with adherence to plan of care (in self or caregiver: substance abuse, financial constraints, transportation issues, other).
Social support.
Level of education.
Employment.
Impact of asthma on patient and family
Episodes of unscheduled care.
Number of days missed from school and/or work.
Limitation of activity – sports or physical work.
History of nocturnal wakening.
Effect on growth, development, behavior, school or work performance, and lifestyle.
Impact on family routines, activities or dynamics.
Economic impact.
Assessment of patients and families perceptions of disease
Patient's and patient's family: knowledge of asthma, its natural history, and effective controls.
Patient's beliefs regarding use and long-term effects of medications.
Ability of patient and patient's family to cope with disease and to recognize exacerbation.
Economic resources.
Sociocultural beliefs.
Physical examination – abnormalities that may be noted:
Vital signs
Growth retardation and obesity.
Tachypnea, tachycardia.
Anxious demeanor.
Upper respiratory tract
Increased nasal secretions, mucosal swelling, and/or nasal polyp.
Transverse crease on nose (from "allergic salute").
Halitosis (due to mouth breathing).
Chest

	Wheezing.
	Prolonged phase of forced exhalation.
	Hyper-expansion of thorax.
	Use of accessory muscles.
	Hunched shoulders.
Skin	
	Atopic dermatitis, eczema.

- **Asthma Severity**
  - In newly diagnosed (stable) patient, the next step is to assess asthma severity.
  - Severity reflects the intrinsic intensity of the disease process.
  - Severity is determined by symptom constellation, in a patient not receiving long term therapy, and measured lung function (≥ 5 years old – may be younger if able to comply with test).
    - There is some evidence that the pulmonary function values advocated for children do not adequately quantify asthma severity, and that symptoms and rescue medication usage may be more sensitive.[73]
    - However, percent predicted FEV_1 does predict future risk of asthma exacerbation.[74]
  - Assessment of severity guides the initiation of medical therapy.
  - Severity can be inferred in previously diagnosed asthma patient by the step of care (the amount and type of medication) required to maintain control.
  - Two tools used for estimating the risk of exacerbations and severity are the Asthma Exacerbation Clinical Score[75] and the Composite Asthma Severity Index (CASI).[76] Both are validated and take into account medication use, symptoms and exacerbations. CASI includes measured lung function, whereas the clinical score relies on self-reported history (see appendix).
- **Clarification**
  - The term "severe asthma" can have different meanings in the literature. The American Thoracic Society classifies severe or refractory asthma as requiring near or continuous OCS, or treatment with high dose ICS and 2 of the following: frequent requirement of rescue inhalers, requirement for other daily controller medication, near fatal asthma, 3 or more urgent care visits, persistent airflow limitation, 3 or more oral glucocorticoid bursts per year, prompt deterioration in weaning of OCS or ICS.[78]
  - The Joint Task Force of the American Thoracic Society and the European Respiratory Society recommend that asthma severity be defined as the degree of difficulty in achieving control for a patient on daily medication. Severity reflects the difficulty in achieving control based on underlying genetic factors, environmental factors and comorbidities.[79]
  - The NAEPP and GINA guidelines determine severity as baseline symptoms when not on controller medications. Severe persistent asthma is characterized by symptoms throughout the day, near nightly awakenings due to symptoms, significant interference with daily activities, and multiple daily use of rescue inhaler.[8,72]
  - NAEPP defines responsiveness as the ease to which asthma control is achieved by therapy.
  - Severe asthma, as defined by American Thoracic Society, corresponds to very poorly controlled asthma by NAEPP/GINA.
  - This document will use the NAEPP terminology.

Table 4: Classifying Asthma Severity (taken from Asthma Care Quick Reference[77]) (No controller medication)

Component of Severity		Intermittent			Persistent								
					Mild			Moderate			Severe		
Age (yrs)		0 – 4	4 - 11	> 12	0 – 4	4 - 11	> 12	0 – 4	4 - 11	> 12	0 – 4	4 - 11	> 12
Impairment	Symptoms	≤ 2 days/wk			> 2 days/wk but not daily			Daily			Throughout day		
	Nighttime awakenings	0	≤ 2 days/mo		1-2x / mo	3 – 4x/mo		3-4x /mo	> 1x/wk but not nightly		> 1x /wk	Often 7x/wk	
	SABA use for symptom control (not EIB)	≤ 2 days/wk			> 2 d/wk not daily	> 2 d/wk but not daily and no more than once any day		Daily			Several times per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
	Lung function		Normal between exacerbation										
	FVC_1 (% predicted)	NA	>80%	>80%	NA	>80%	>80%	NA	60-80%	60-80%	NA	<60%	<60%
	FEV_1/FVC		>85%	Nl		>85%	Nl		75-80%	↓5 %		<75%	↓>5%
Risk	Asthma Exac. requiring oral systemic steroids	0 – 1/yr			≥ 2/6 mo or ≥ 4x wheeze > 1 day / 12mo*	≥ 2/yr	More frequent and intense events indicate more severity						
		Consider severity and interval since last asthma exacerbation. Frequency and severity may fluctuate over time for patients in any category.											
Estimate of Severity: lowest Step of Therapy to Maintain Control		Step 1			Step 2			Step 3 or 4			Step 5 or 6		

*Children ≤ 4 YO: risk of 4 or more episodes of wheezing lasting longer than 1 day and affected sleep AND who have a positive Asthma Predictive Index (either 1 of the following: parental history of asthma, physician's diagnosis of atopic dermatitis or evidence of sensitization to aeroallergens or 2 of the following: evidence of sensitization to foods, > 4% eosinophilia, wheezing apart from colds).

- **Asthma Control**
  - In patient being treated for asthma, the next item to determine is degree of asthma control. The Joint Task Force of the American Thoracic Society and the European Respiratory Society recommends that asthma control be defined as the extent to which asthma treatment reduces (or eliminates) the signs and symptoms of asthma.[74]
  - NAEPP states that asthma control focuses on two domains:
    - Reducing impairment
      - (Impairment is the frequency and intensity of current or past symptoms and functional limitations from these symptoms.)
      - Reduce frequency, chronicity and intensity of symptoms.
      - Reduce requirement for SABA [≤ 2x per week – not including prevention of exercise induced bronchospasm (EIB)].

- Maintain (near) normal lung function and normal activity and performance levels (exercise, school and work).

- Reducing risk
  - [Risk is the future likelihood of exacerbations, progressive decline in lung function (or for children lung growth) or adverse effects from medications.]
  - Prevent exacerbations and minimize need to emergency care and hospitalizations.
  - Prevent progressive decline in lung function, reduced lung growth in children.
  - Minimize medication side effects.

Table 5: Classifying Asthma Control (taken from Asthma Care Quick Reference[77])

Component of Severity		Well Controlled			Not Well Controlled			Very Poorly Controlled		
Age (yrs)		0 – 4	4 - 11	> 12	0 – 4	4 - 11	> 12	0 – 4	4 - 11	> 12
Impairment	Symptoms	≤ 2 days/wk	≤ 2 days/wk but not more than 1 X /day	≤ 2 days/wk	> 2 days/wk (over 1 mo)	> 2 d/wk or multiple x ≤ 2 d/wk	> 2 days/wk	Throughout day		
	Nighttime awakenings	≤ 1/mo		≤ 2/mo	> 1x/mo	≥ 2x/mo	1-3x/wk	> 1x /wk	≥ 2x/wk	≥ 4x/wk
	Interference with normal activity	No limitation			Some limitation			Extremely limited		
	SABA use for symptom control (not EIB)	≤ 2x/wk			> 2x/wk			Several times per day		
	Lung function									
	FVC_1 (% predicted)	NA	> 80%	> 80%	NA	60-80%	60-80%	NA	< 60%	< 60%
	FEV_1/FVC		> 85%	Nl		75-80%	↓5%		< 75%	↓> 5%
	Validated questionnaire									
	ATAQ	NA		0	NA		1-2	NA		3-4
	ACQ			≤ 0.75			≥ 1.5			NA
	ACT			≥ 20			16-19			≤ 15
Risk	Asthma exac. requiring oral systemic steroids	0-1/yr			2-3/yr	≥ 2/yr		> 3/yr	≥ 2/yr	
		Consider severity and interval since last asthma exacerbation. Frequency and severity may fluctuate over time for patients in any category.								
	Reduction lung growth/ progressive loss lung function	NA	Evaluation requires long-term follow-up care.		NA	Evaluation requires long-term follow-up care.		NA	Evaluation requires long-term follow-up care.	
	Treatment related adverse effects	Medication side effects can vary in intensity from none to very troublesome.								
		The level of medication complexity does not correlate to specific levels of control, but should be considered in overall assessment of risk.								

- Classify level of asthma control, typically in preceding 2 – 4 weeks, by the most severe indicator of impairment or risk. Ratings are "well controlled," "not well controlled" and "very poorly controlled."
- Suboptimal asthma control is associated with underuse of controller medications, which may result from inability to afford medications, lack of understanding about the disease process and role of control medications, concerns about side effects of medication, competing concerns, poor inhalation technique, and others.[80]
- Asthma control requires a patient-centered team approach and includes the development of a comprehensive treatment plan with the patient and/or caregiver. The care plan includes:
  - Appropriate medications prescribed and appropriate usage of medication. In select patients, immunotherapy may be beneficial.
  - Avoiding environmental triggers associated with worsening symptoms.
  - Self-management skills, including proper use of medications, use of an action plan and self-monitoring (either by symptoms or peak flow measurement).
  - Long-term follow-up to assess,and adjust, and manage care.

- **Exacerbations**
  - Exacerbations are defined by the American Thoracic Society/European Respiratory Society statement as events that are different from the patient's previous state.[79]
  - Severe exacerbations require urgent action to prevent serious outcome, such as hospitalization or death. Change in baseline PEFR and SABA use is not a requirement as some patients may progress very quickly to requiring urgent or emergent care.
  - Moderate exacerbations require change in treatment to prevent progression to a more severe state. Increase in symptoms, decrease in PEFR, and increase SABA use for at least 2 days are components of moderate exacerbation.
  - "Mild" exacerbations were viewed as just outside the normal state and may just represent temporary loss of control.
- **Patient Ongoing Care: Assessment and Monitoring**
  - Patient follow-up (based on clinical judgment)
    - Every 2 – 6 weeks in patients just starting a therapy or stepping up therapy.
    - Once stable, visits can extend to 1 – 3 months, depending on the duration of asthma control, level of treatment required, and to evaluate for step-down in therapy.
    - Consider 3 – 6 month intervals in very stable patient.
    - Ongoing care is important as asthma control varies over time (seasonal variation, changes with development and growth, change in trigger exposures, etc.).
  - In-office assessment of asthma control can be achieved by use of validated questionnaires.
    - Sample validated questionnaires include:
      - ATAQ©: Asthma Therapy Assessment Questionnaire[81] http://www.asthmacontrolcheck.com/asthma_control/asthmacontrolcheck/hcp/index.jsp?WT.svl=1
      - ACQ©: Asthma Control Questionnaire[82] http://www.qoltech.co.uk/acq.html (note ACQ indeterminate if value between 0.75 (good control) – 1.5 (not well controlled)
      - ACT©: Asthma Control Test [83] http://www.asthma.com/resources/asthma-control-test.html
    - Typical questions address
      - Nighttime asthma symptoms.
      - Daytime asthma symptoms.
      - Quick-acting relief medication usage.

        - Participation in normal activities.
        - Perception of asthma control.
    - Perform spirometry
        - At time of diagnosis.
        - After patient has stabilized and is well controlled.
        - During periods of prolonged loss of control.
        - At least every 1 – 2 years.
        - Post bronchodilator FEV_1 may be used to follow lung growth over time.[84]
    - At each visit
        - Assess asthma control (recall of previous 2 – 4 week period).
        - Assess quality of life, including work/school absence and limitations in usual and valued activities.
        - Review medication technique and compliance. 30-60% of children have been found to not use their medications regularly.[85]
        - Review written action plan.
        - Therapeutic adherence (medication and trigger avoidance).
        - Patient concerns.
        - Consider step-down as good control of asthma has been achieved.

Education for Partnership in Care: Table 6

Sources used:
-NAEPP, 2007[8]
-GINA, 2012[72]

- **Partnership between Provider and Patient**
    - Partnership between provider and patient (and caregiver, if patient is a child) is required for effective asthma management.
    - Open conversation that is patient-centric and mindful of cultural factors, language barriers, and health literacy needs aides in compliance.
    - Identify and address patient and family concerns in an ongoing manner.
    - Emphasize patient's personal goals. Avoiding going to the emergency department may not be a patient-specific goal, but being able to go dancing at daughter's wedding (for an adult who won't quit smoking) or being able to stay in during the soccer game (for a teen who doesn't want to use her inhaler) might be powerful motivators.
    - Be mindful of psychosocial problems. Asthma may exacerbate psychosocial problems for the patient or family, and ongoing psychosocial problems may affect asthma symptoms.[86] Some stressors around asthma may include:
        - Fear of dying.
        - Anxiety about having an asthma attack.
        - Sleep deprivation due to nighttime symptoms.
        - Fear of "being different" or "being sick."
        - Concerns about long-term medication.
        - Insurance concerns.
        - Financial concerns.
        - Social isolation due to reduced participation in play or sports.
        - Discord due to limitation of potential triggers (e.g. can't visit home of family with smokers or friend with cat).
        - Altered family dynamics.

- **Self-Management Education**
  - Self-management education reduces emergency care, reduces functional limitations, minimizes costs and improves quality of life.[87]
  - Education should increase knowledge about asthma, the role of medications (including risks and benefits), proper use of medication, and should address any specific patient concerns through open communication. One goal of education is to increase patient's self-confidence in being a partner in care.
  - Self-management education should be an iterative process, and the messages need to be reinforced with each encounter.
  - Multiple educational strategies may be employed, including individual instruction, appropriate health literacy-level written materials, group programs, web-based learning, others.
  - All members of the health team can support and promote self-management education with consistent, evidence-based messages.
  - Patients who present for emergent care may need more intensive education, including (re)referral to an asthma educator, as well as a detailed examination of other barriers to care.
  - Patients should be taught how to monitor asthma control at home in an ongoing manner. This might include symptom recognition or PEFR, especially in patients with moderate or severe persistent asthma.
    - PEFR may be beneficial in patients with:
      - Moderate or severe persistent asthma.
      - History of severe exacerbation.
      - Poor perception of airflow obstruction.
      - Prefer this method.
    - PEFR monitoring may be useful to follow trends in an individual patient over time. The patient should establish a personal best. Readings below 80% of the best result indicate airway narrowing.
    - Obtaining PEFR is effort/technique dependent, and the patient needs to be instructed on proper technique and periodically refreshed on technique.
    - Monitoring asthma by use of a symptom diary can be equally effective to peak-flow monitoring.
  - The patient and provider should develop an individualized action plan.
    - An example of an action plan is from the American Academy of Allergy, Asthma and Immunology:[88] https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/NEW-WEBSITE-LOGO-asthma-action-plan_HI.pdf
    - Instructions should be clear.
      - As needed medications need to have clear instructions on how many puffs to administer, when to repeat and what is the maximum dose per day.
      - Clearly defined schedules for escalating care should be delineated, such as when to call the office and when to go to the ED.
      - Emergency contact information should be on the form, including physician office and family/friends contact.
      - Be clear that if a medicine is to be added or changed, state what is to occur with the other routine medications. For example, stepping up to a combined ICS/long-acting β-agonist (LABA) inhaler would involve discontinuing the prior ICS or if OCSs are to be started, all other medications are continued.
      - Consider using the teach-back approach (patient able to verbalize plan of care).

Table 6: Key Educational Components (NAEPP[8])
Basic asthma facts
The difference in airways between someone with asthma and someone without asthma.
The role of inflammation in the airway; hyperresponsiveness to triggers.
Episodic nature of asthma.
What happens during an asthma attack.
Review long-term asthma control goals.
Few to no daytime symptoms, no nighttime awakenings due to asthma symptoms, able to engage in normal activities, normal lung function.
Role of medications
Understanding the role of long-term control medications.
Prevent symptoms, must be taken daily, not for quick relief.
Understanding the role of quick-relief medication (SABA).
Do not provide long-term asthma control.
Use more than 2x per week (other than for EIB) indicate need to adjust controller medication.
Patient skills
Taking medications correctly.
Inhaler technique, including appropriate use of devises [valved holding chamber (VHC), spacer or nebulizer].
Taking medications as prescribed and outlined in action plan (controller daily, SABA if needed).
Identifying and avoiding environmental exposures that worsen patient's asthma symptoms.
Self-monitoring.
Assess level of asthma control, monitor peak expiratory flow rate (PEFR) (if appropriate), recognize and respond to early warning signs of worsening asthma control.
Use written Asthma Action Plan – developed and reviewed with patient.
Seek medical care as appropriate.
Communicate asthma plan with school and other caregivers.

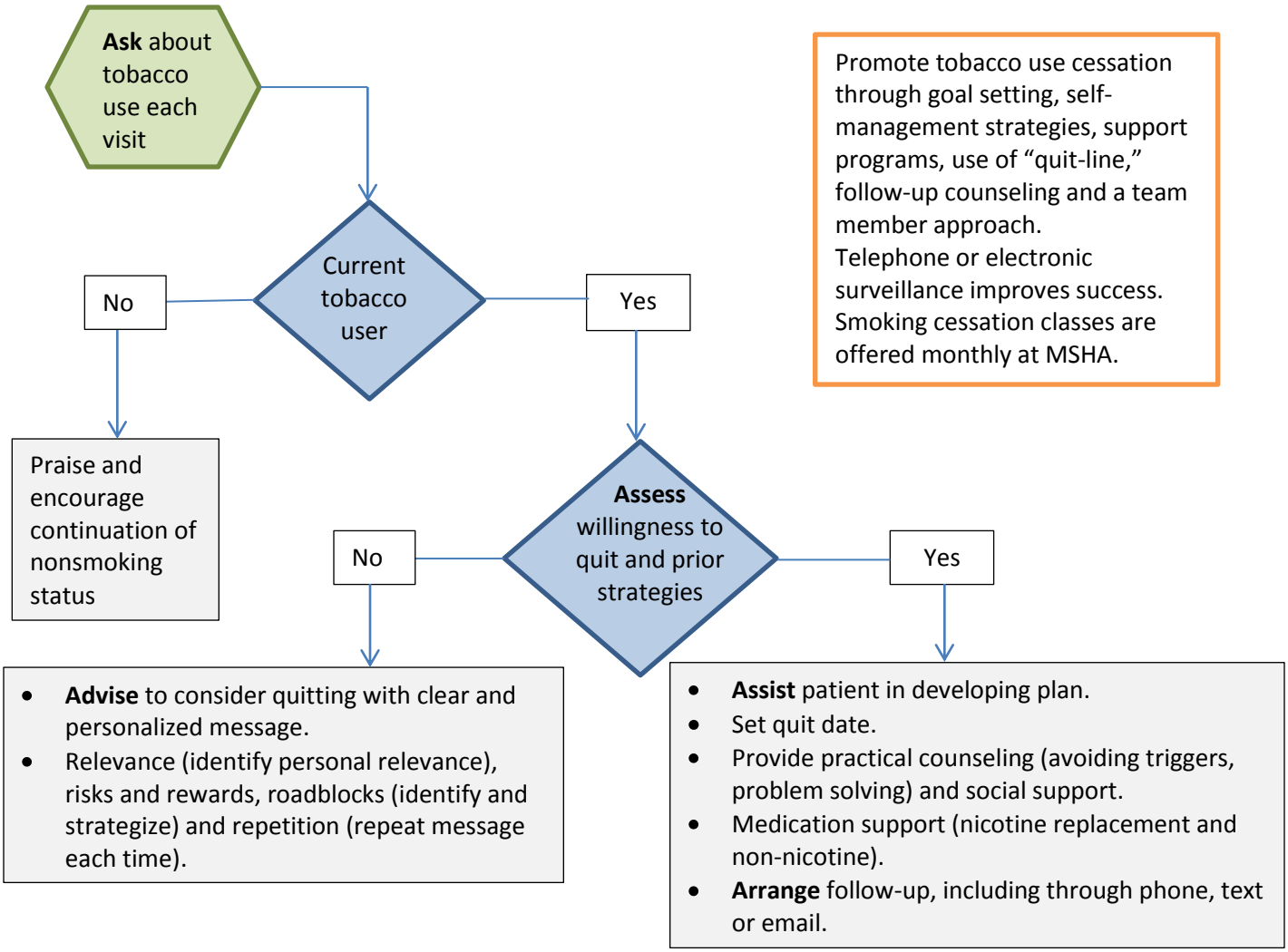
Control of Environmental Factors, Triggers and Comorbid Conditions; Algorithm 2

Sources used:
-NAEPP, 2007[8]
-GINA, 2012[72]
-Joint Task Force on Practice Parameters, 2010[89]

- **Evaluate Potential Role of Inhalant Allergens and Irritants**
  - Common indoor inhalant allergens include: dust mites, cockroaches, (furred) animal dander and molds.[12,36]
  - Common indoor inhalant irritants include: tobacco smoke, smoke from wood burning (stoves or fireplaces), strong perfumes or odors, chlorine-based cleaning products, particulate air pollution.[90]
  - Review history to attempt to identify triggers.
  - Support the patient and/or caregiver to stop smoking.
  - Advise patients to avoid or reduce exposure to triggers. This usually requires a multifaceted comprehensive approach. Reducing all triggers may be difficult to attain and sustain.
    - Clearing the Air of Asthma Triggers: 10 Steps to Making Your Home Asthma-Friendly. [91] http://www.epa.gov/asthma/pdfs/10_steps_en.pdf
    - The reverse side of the National Heart Lung and Blood Institute action plan is a plan to reduce asthma triggers.[92]

http://www.nhlbi.nih.gov/health/public/lung/asthma/asthma_actplan.pdf

Algorithm 2: Smoking Cessation



- For patients with persistent asthma, consider allergy testing; allergy immunotherapy may be indicated if there is a clear relationship between symptoms and exposure to allergen.
  - Measurement of total serum IgE is indicated if treatment with anti-IgE monoclonal antibody (omalizumab) is being considered.
  - Immunoassays of specific IgE allergens can be used for suspected allergens.
  - Allergy skin testing has a very high negative predictive value.
  - Patients with severe persistent asthma, nasal polyps, or history of sensitivity to aspirin and NSAIDs should avoid further exposure to these drugs as reexposure may lead to a severe and even fatal reaction (more common in adults).
  - High-efficiency particulate air (HEPA) and electrostatic precipitating filters do not substitute for more effective dust mite and cockroach control measures. They may reduce airborne animal dander, mold spores and particulate tobacco smoke, but have not been shown to have an effect on symptoms or lung function.[93]

        - Allergen avoidance is preferred to preexposure treatment.
        - Use of humidifiers and evaporative (swamp) coolers are not recommended in homes of patients who are sensitive to dust mites or mold.
        - Air ionizers are not recommended.
        - Food allergies rarely aggravate asthma symptoms. An exception is sulfites in foods (shrimp, beer and wine, dried food, processed potatoes).
- **Evaluate Potential Role of Other Triggers**
    - Medications may trigger asthma attacks, including aspirin and NSAIDS, as well as nonselective β-blockers (including topical ophthalmic solutions).
    - Respiratory tract infections, such as bronchitis, sinusitis, colds, influenza and other viral infections, are common asthma triggers in all ages. Yearly flu vaccines and pneumococcal vaccines are helpful and reduce respiratory infections.[94, 95]
        - Respiratory viral infections are the most frequent asthma trigger in childhood.
            - Respiratory syncytial virus, influenza virus, and rhinovirus (depending on season) are most common in children < 3 YO.
            - Rhinovirus is more common in older children.[96]
        - Respiratory infections tend to last longer in asthmatics. Airway hyperresponsiveness after a respiratory infection persists for an extended period of time.[97]
- **Exercise Induced Bronchoconstriction (EIB)**
    - May be the only presentation of asthma in children.[98]
    - EIB may occur in individuals without chronic asthma, but it is often the presenting sign of someone with asthma.
    - The Joint Task Force recommends not relying solely on history to determine EIB; physical and pulmonary function tests with and without bronchodilators, and possible provocative challenge testing may be required.
    - Symptoms.
        - Symptoms include shortness of breath, coughing, wheezing, tightness in chest developing about 15 minutes after start of exercise and typically resolving within an hour after resting, although some patients may experience symptoms only when cooling down from exercise. (Simple exertional dyspnea often abates within 5 minutes of stopping exercise.)
        - Often worse in cold, dry air. Other environments with allergens or pollutants may also enhance the development and severity of EIB.
        - Exercise is a trigger; it does not cause or worsen asthma.
    - Consider alternative diagnosis, especially if poor response to SABAs.
        - Exercise-induced laryngeal dysfunction may mimic as EIB.
        - Exercise-induced dyspnea may be related to obesity, other pulmonary process (such as interstitial pulmonary fibrosis) or cardiac cause.
    - Treatment.
        - A Cochrane Review concluded that 4 weeks of ICS usage attenuates EIB (as demonstrated by exercise testing) in most (but not all) patients with EIB and asthma.[99]
        - Frequent use of SABAs or long-acting bronchodilators (LABAs) for EIB can indicate poor asthma control. EIB occurs in 70 – 80% of children with asthma not receiving an asthma control medication.[100]
        - SABAs given shortly before exercise (5 – 20 minutes) can prevent EIB for 2 – 4 hours. However, prolonged regular use of SABAs can result in decreased bronchodilator effectiveness.[101]

        - Daily or frequent use of LABA to prevent EIB is not indicated as it may mask severity of asthma, and may be associated with increased morbidity and mortality (see black box warning). Occasional use for prolonged periods of exercise (> 3 hours) may be beneficial.
        - LTRA and cromolyn may also be beneficial to prevent EIB and do not appear to diminish in effectiveness with routine use. Montelukast has an onset of 2 hours and duration of 12 – 24 hours; however, effectiveness is highly variable amongst patients.
- **Identify and Treat Comorbid Conditions That May Impede Asthma Management**
    - COPD
    - Allergic bronchopulmonary aspergillosis – consider in patients who have asthma and history of pulmonary infiltrates, IgE sensitization to *Aspergillus*, and/or are corticosteroid-dependent.
    - GERD – consider especially in those with frequent nighttime asthma symptoms, even without typical GI symptoms.
    - Obese and overweight patients – asthma control may benefit from weight loss.[102]
    - Obstructive sleep apnea – consider in patients who are not well controlled.
        - The STOP-BANG questionnaire is a commonly used screening tool.[103]
        - http://sleepapnea.org/assets/files/pdf/STOP-BANG%20Questionnaire.pdf
    - Rhinitis/sinusitis – because of interrelationship of upper and lower airways, treatment of upper airway problems will improve asthma control.
    - Stress and depression – education to improve self-management skills may improve asthma.

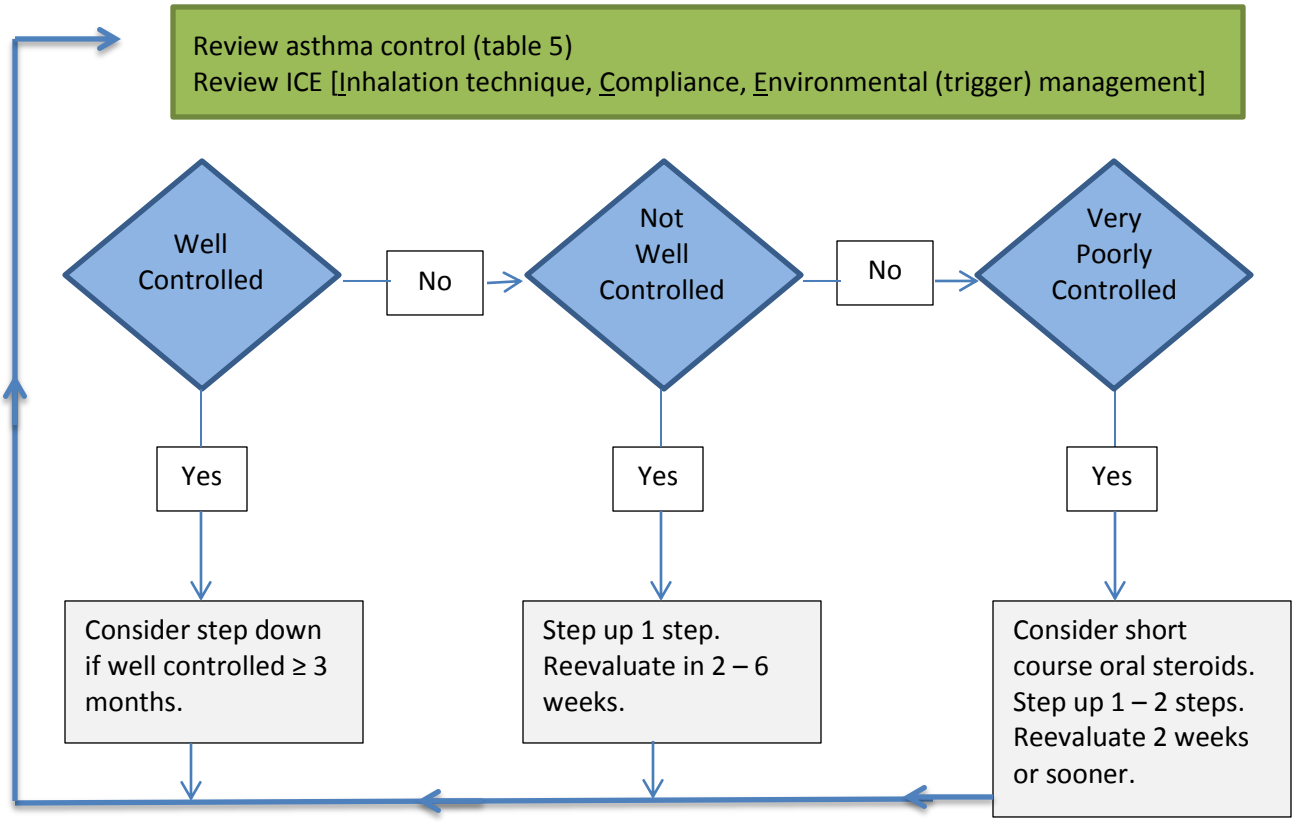
Medications: Algorithm 3, Tables 7 - 11

Sources used:
-NAEPP, 2007[8]
-Practall, 2008[52]

- **Introduction**
    - Medications are divided into 2 broad categories: Long-term control medications and quick-relief medications.
        - Long-term control medications: used daily to achieve and maintain control of persistent asthma.
        - Quick-relief medications: used to treat acute symptoms and exacerbations.
    - Different medication strategies target different aspects of asthma, including immune-mediated, inflammatory and smooth muscle tone changes.
    - The NAEPP and other expert guidelines present a stepped approach for asthma management. These guidelines are presented to support - not replace - clinical decision making.
    - The GOAL study is a prospective, randomized trial that examined the association between guideline-derived asthma control and health-related quality of life in approximately 1500 patients with varying degrees of asthma severity over 1 year. The study concluded that treatment aimed at controlling asthma normalizes health-related quality of life.[104]
    - For initiating therapy (newly diagnosed asthma) choose the step of therapy based on severity.

Algorithm 3: Ongoing Management of Asthma

Use a patient-centric team approach to reinforce asthma education and self-management. Review basic asthma facts, types of asthma medications and the importance of controller medications, proper inhalation techniques (including use of VHC/spacer), Asthma Action Plan, peak flow measurements (if requested), asthma symptoms (SABA use, nighttime awakening, frequency of symptoms, and activity impairment), trigger avoidance and environmental control measures, and any problems or questions.



Steps	Table 7: Preferred Treatment (See also table 8) [All steps have SABA PRN: use of SABA ≥ 2x week (not EIB) indicates inadequate control]
Step 1	No control medication required
Step 2	Low dose ICS
Step 3 (≤ 4 YO consult)	≤ 4 YO Medium dose ICS 5-11 YO Medium dose ICS OR low dose ICS + either LABA, LTRA or theophylline ≥ 12 YO Medium dose ICS OR low dose ICS + LABA
Step 4 (≥ 5 YO consult)	≤ 4 YO Medium dose ICS + either LABA or montelukast ≥ 5 YO Medium dose ICS + LABA
Step 5	≤ 4 YO High dose ICS + either LABA or montelukast 5-11 YO High dose ICS + LABA ≥ 12 YO High dose ICS + LABA AND consider omalizumab in patients with allergies
Step 6	≤ 4 YO High dose ICS + either LABA or montelukast + OCS 5-11 YO High dose ICS + LABA + OCS ≥ 12 YO High dose ICS + LABA + OCS AND consider omalizumab in patients with allergies
* Consult with asthma specialist recommended at this point.	

Table 8: Stepwise Approach for Asthma Management (NAEPP [8])					
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred: No daily controller	**Preferred:** Low-dose ICS	**Preferred:** Medium-dose ICS OR 5-11 YO: Low-dose ICS + either LABA, LTRA, or theophylline ≥ 12 YO: Low-dose ICS + LABA	**Preferred:** Medium-dose ICS + LABA OR ≤ 4 YO: Medium-dose ICS + LABA or montelukast	**Preferred:** High-dose ICS + LABA OR ≤ 4 YO: High-dose ICS + LABA or montelukast ≥ 12 YO: Consider adding omalizumab for patients with allergies	**Preferred:** High-dose ICS **+** LABA **+** OSC OR ≤ 4 YO: High-dose ICS **+**either LABA or montelukast **+** OSC ≥ 12 YO: Consider adding omalizumab for patients with allergies
Alternatives: NA	**Alternatives:** ≤ 4 YO: Cromolyn or montelukast ≥ 5 YO: Cromolyn, LTRA, or theophylline	**Alternatives:** ≥ 12 YO: Low-dose ICS + either LTRA, theophylline or zileuton	**Alternatives:** 5-11 YO: Medium-dose ICS + either LTRA or theophylline ≥ 12 YO: Medium-dose ICS + either LTRA, theophylline or zileuton	**Alternatives:** 5-11 YO: High-dose ICS + either LTRA or theophylline	**Alternatives:** 5-11 YO: High-dose ICS **+** either LTRA or theophylline **+** OSC
Quick Relief: SABA as needed for quick relief. Note: Use more than 2x/wk (not EIB) indicates inadequate control. Proper inhalation technique, compliance with written asthma plan and management of environmental triggers is the foundation of asthma management.					

  - A recent study examined step-up therapy with 182 children currently not controlled on 100 mcg fluticasone. The children were randomly assigned to each of the 3 different treatment arms for 16 week intervals. The treatment arms were 250 mcg fluticasone, 100 mcg fluticasone plus montelukast, and 100 mcg fluticasone plus 50 mcg salmeterol. The response to step-up with LABA was most likely to be the most effective than ICS or LTRA step-up. However, many children did have their best response to LTRA or ICS step-up, highlighting that treatment needs to be individualized with regular monitoring and adjusting to maximize results for each patient.[105]

- **Medication Technique**
  - Inhaled medications are available in a variety of devices that differ in technique. Also, spacers and VHC (preferred) can be used with certain devices to improve delivery of medication to the lungs.
  - For young children, masks can be used with the spacers/VHC or nebulizers. The seal of the mask with the face is very important as the medication can leak around the mask.
  - Patient preference is important to improve compliance.
  - Proper technique is very important and should be reviewed at each visit, including mouth care (rinse and spit after usage), nebulizer and spacer/VHC cleaning.

- A Cochrane Review has concluded that metered dose inhalers (MDIs) with spacers are at least equivalent to nebulizer delivery for β2-agonists for appropriately aged children to adults, including in emergency room settings.[107]
- If patient is not well controlled, consider stepping up 1 step; if patient is very poorly controlled, consider stepping up 2 steps.
- If patient is experiencing an acute exacerbation, consider a short course of oral systemic corticosteroids.
- If lack of control persists after stepping up (and patient is compliant with medications and environmental control), consider alternative diagnosis or other comorbid conditions.
- Consider stepping down if patient maintains good control for at least 3 months and is not anticipating change in triggers (seasonal variation, travel or other changes).

Table 9: Aerosol Technique (NAEPP)

Device	Technique	Discussion
Metered-Dose Inhaler (MDI)	○ Actuation during slow (3 – 5 sec) deep inhalation followed by 10-sec breath hold ○ Open-mouth technique (hold MDI 2 inches away from open mouth) enhances lung delivery in studies, but has not been shown to be clinically superior to closed mouth technique (MDI mouthpiece inserted between lips and teeth)	○ Slow inhalation and coordination of actuation during inhalation may be difficult ○ Patients may incorrectly stop inhalation with activation ○ Mouth washing and spitting effective in reducing amount of drug swallowed and absorbed systemically ○ Lung delivery (even under ideal conditions) varies significantly based on formulation, propellant and valve design
Breath-Activated MDI	Tight seal around mouthpiece and slightly more rapid inhalation than standard MDI, followed by 10-sec breath hold	○ May be useful for patients unable to coordinate inhalation and actuation ○ Patients may incorrectly stop inhalation with activation ○ Cannot be used with spacer/VHC
Dry Powder Inhaler (DPI)	Tight seal around mouthpiece and rapid (1 – 2 sec) deep inhalation followed by 10-sec breath hold	○ Most children < 4 YO may not generate sufficient inspiratory flow to activate inhaler ○ Delivery may be greater or less than MDI depending on device and technique ○ Rapid inhalation promotes greater deposition in large central airways ○ Mouth washing and spitting effective in reducing amount of drug swallowed and absorbed systemically
Spacer or Valved Holding Chamber (VHC)	Actuate only once into spacer/VHC per inhalation; slow (3 – 5 sec) deep inhalation followed by 10-sec breath hold For children < 4 YO face mask with VHC can be used; allow 3 – 5 inhalations per actuation Rinse plastic VHC once a month in soapy water and drip-dry	○ May be bulky ○ VHCs preferred over spacers as they do not need to coordinate actuation and inhalation ○ Indicated for patients who have difficulty performing MDI technique ○ Spacers and VHCs decrease oropharyngeal deposition ○ As effective as nebulizer for delivering SABA and anticholinergics in mild to moderate exacerbations; data in severe exacerbations limited
Nebulizer	Slow regular breathing with occasional deep breaths usually with mouthpiece, (may use tight fitting mask); blow-by technique not appropriate	○ Less dependent on patient's coordination and cooperation ○ May be expensive, time consuming, bulky, dependent on power source ○ Potential for bacterial infections if not cleaned properly

- For ongoing management, evaluate level of control (table 4) based on symptoms. May use validated questionnaire, such as ACT©, to assess nighttime awakenings, interference with normal activities, SABA use (not for EIB) and may monitor lung function by spirometry, if indicated. Also evaluate level of risk, including frequency of exacerbations requiring OSC and changes in lung growth/function over time.
- ICSs are the preferred first line of treatment for persistent asthma. They reduce impairment and risk, but do not alter underlying severity of asthma.
- If inadequate response to current level of care, prior to stepping up therapy:
  - Review ICE **very important** [106]
    - **I**nhaler (nebulizer) technique.
    - **C**ompliance with use of daily control medications (if prescribed) and Asthma Action Plan.
    - **E**nvironmental history and trigger management (including any new triggers).
  - Review for barriers, such as lack of consistent routine for medication administration, poor administration technique, poor parental understanding of asthma control, and parental concerns about medications.[80]
  - If poor response to therapy, especially in compliant younger child with severe symptoms, reconsider differential diagnosis.
  - Use preferred (not alternative) therapy at current step, if not already done.

- **Discussion Points**
  - Selection of treatment (or alternatives) is based on a patient-centric discussion, including expectations, prior experiences, concerns, willingness and ability to use medication. There are differences in the delivery devices, which may impact effective medication dosage. Trying a different formulation or adding an appropriate VHC/spacer may be an alternative to changing class of medication.
  - Referrals
    - Referral to asthma specialist.
      - ≤ 4 YO at step 3 care or higher (may consider at step 2).
      - ≥ 5 YO at step 4 care or higher (may consider at step 3).
      - Difficulty achieving or maintaining control of asthma or if symptoms are atypical.
      - Patient required > 2 bursts of oral systemic corticosteroids in 1 year.
      - Patient hospitalized due to asthma exacerbation.
      - Consideration of omalizumab.
      - Consider evaluation for allergy testing and possible allergy immunotherapy.
        - A Cochrane Review of 88 trials concluded that immunotherapy for asthma patients with proven sensitization to allergens improves bronchial hyperreactivity, reduces asthma symptoms, and reduces use of asthma medications.[109]
        - Immunotherapy should be given if asthma patient is currently stable, and should be given at a facility where emergency treatment can be given for a potential anaphylactic reaction and where patient can be observed for 30 minutes after therapy is administered.
      - Refer in additional testing is required, such as bronchoscopy.
    - Consider referral for asthma-specific education, including medication use and technique, trigger and allergen avoidance.
    - Consider referral for social services if cost or access to care is a barrier.

- Consider referral for mental health management if psychosocial barriers interfere with asthma control.

Table 10: Usual Dosages for Medications for Asthma (derived from NAEPP)

Medication	0 – 4 YO	5 – 11 YO	≥ 12 YO	Comments
Inhaled Corticosteroids (Control: Anti-inflammatory) [Low, Medium, or High dose]				
Beclomethasone HFA 40 or 80 mcg/puff Dose BID	NA	L: 80 – 160 M: > 160 – 320 H: > 320	L: 80 – 240 M: > 240 – 480 H: > 480	• Hydrofluoroalkane (HFA) propellant. • Mechanism of action (MOA): Reduces airway hyperresponsiveness, inhibits inflammatory cell migration and activation, blocks late phase reaction to allergens. • Preferred first line of treatment for persistent asthma: Reduces impairment and risk, but does not alter underlying severity. • For children < 4 YO. ○ < 1 YO: Safety and efficacy of ICS not yet been established. ○ Use face mask which fits snugly over nose and mouth; wash face afterwards. ○ Budesonide is compatible with albuterol, ipratropium and levalbuterol nebulizer solutions in the same treatment. ○ Use only jet nebulizers, as ultrasonic nebulizers are ineffective for solutions. ○ Budesonide may be administered 1 – 3x daily; fluticasone 2x daily. ○ Low dose fluticasone dosage higher than for 5 – 11 YO due to lower effective dosage delivered via mask. • Clinician's judgment of patient's response to therapy determines appropriate dosing. Monitor and adjust dosage. • Once asthma is controlled, titrate to the minimum dosage required to maintain control. • As the EPR states: These dosages are an estimate comparable daily dosage – refer to full packaging. Some dosages may be outside of the package labeling for the high-dose range. Consult with asthma specialist is recommended if patient requires high-dose ICS. • Potential side effect (S/E): cough, dysphonia, oral thrush. • In high dosages, systemic effects may occur. • Fluticasone, budesonide and mometasone are metabolized by the CYP 34A isoenzymes. Potent inhibitors of this isoenzyme include ritonavir and ketoconazole – effects include increased bioavailability and decreased clearance of the ICS. Clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported.
Budesonide DPI 90, 180 or 200 mcg/inhalation Dose BID	NA	L: 180 – 400 M: > 400 - 800 H: > 800	L: 180 – 600 M: > 600-1200 H: > 1200	
Budesonide Nebulizer (mg) QD-TID (severity)	L: 0.25 – 0.5 M: 0.5 – 1.0 H: > 1.0	L: 0.5 M: 1.0 H: > 1.0	NA	
Ciclesonide 80 or 160 mcg/puff QD-BID (severity)	NA	NA	L: 80 – 160 M: > 160 -320 H: > 320	
Flunisolide 250 mcg/puff Dose BID	NA	L: 500 – 750 M: 1,000-1250 H: > 1250	L: 500 – 1000 M: > 1000 – 2000 H: > 2000	
Flunisolide HFA 80 mcg/puff Dose BID	NA	L: 160 M: 320 H: ≥ 640	L: 320 M: > 320 – 640 H: > 640	
Fluticasone HFA/MDI 44, 110 or 220 mcg/puff Dose BID	L: 176 M: 176 – 352 H: > 352	L: 88 – 176 M: > 176 -352 H: > 352	L: 88 – 264 M: > 264 – 440 H: > 440	
Fluticasone DPI 50, 100 or 250 mg/inhalation Dose BID	NA	L: 100-200 M: > 200 - 400 H: > 400	L: 100 – 300 M: > 300 – 500 H: > 500	
Mometasone DPI 200 mcg/inhalation QD-BID (severity)	NA	NA	L: 200 M: 400 H: > 400	

Oral Systemic Steroids (Control: Anti-inflammatory)				
Methylprednisolone 2, 4, 8, 16, 32 mg Prednisolone 5 mg 5 mg/5 cc, 15 mg/5 cc Prednisone 1, 2.5, 5, 10, 20, 50 mg 5 mg/5 cc	0.25 – 1 mg/kg/d single dose AM or QOD as needed for control Burst to achieve control: 1 mg/kg/d; max 60 mg/d for 3 – 10 d (5 typical)	0.25 – 1 mg/kg/d single dose AM or QOD as needed for control Burst to achieve control: 1 mg/kg/d; max 60 mg/d for 3 – 10 d (5 typical)	7.5 – 60 mg/d single dose AM or QOD as needed for control Burst to achieve control: 40 – 60 mg/d for 3 – 10 d (5 typical)	• S/E short term use: reversible abnormalities in glucose, increased appetite, fluid retention, mood alteration, HTN, peptic ulcer, rarely – aseptic necrosis. • S/E long term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, DM, Cushing syndrome, cataracts, muscle weakness, rarely – impaired immune function. • Consider coexisting condition that could worsen with OSC, including herpes, varicella, TB, HTN, PUD, DM, osteoporosis, others. • Children receiving lower dosage (1.0 mg/kg/d) have fewer behavioral side effects and the dosage appears to be as efficacious as the higher dosage.
Inhaled Long-Acting β2-Agonists (LABAs) (Control: Long-acting Bronchodilator)				
Salmeterol DPI 50 mcg/blister	NA	1 blister q 12 hr	1 blister q 12 hr	• Preferred add-on for patient ≥ 12 YO on ICS. • Not indicated as monotherapy. • Should not be used for acute symptom relief or exacerbations. • LABAs are add-on therapy and not indicated for daily usage. Daily usage for EIB may mask severity of asthma control. • Decreased effectiveness for protection against EIB may occur with regular use. • S/E: tachycardia, tremor, hypokalemia, prolongation QTc interval in overdose. Potential of uncommon, severe, life-threatening or fatal exacerbation. • Formoterol has a faster onset of action than salmeterol, but not indicated as a rescue drug.
Formoterol DPI 12 mcg/capsule (for inhalation)	NA	1 capsule q 12 hr	1 capsule q 12 hr	
Combined (Control)				
Fluticasone / Salmeterol DPI: 100 mcg/50 mcg 250 mcg/50 mcg 500 mcg/50 mcg HFA: 45 mcg/21 mcg 115 mcg/21 mcg 230 mcg/21 mcg	NA	1 inhalation BID; dose depends on severity or control	1 inhalation BID; dose depends on severity or control	• Fluticasone/salmeterol: ○ 100/50DPI or 45/21HFA for patients stepping up from low to medium dose ICS. ○ 250/50 DPI or 115/21 HFA for patients stepping up from medium to high ICS. • Budesonide / formoterol: ○ Approved in youths ≥ 12 YO. NAEPP guidelines for dosage children 5 – 11 based on clinical trials using DPI. ○ 80/4.5 for patients stepping up from low to medium dose ICS. ○ 160/4.5 for patients stepping up from medium to high dose ICS.
Budesonide / Formoterol HFA: 80 mcg/4.5 mcg 160 mcg/4.5 mcg	NA	2 puff BID; dose depends on severity or control	2 puff BID; dose depends on severity or control	

				• Mometasone/formoterol: ○ 100/5 for patients stepping up from low to medium dose ICS. ○ 200/5 for patients stepping up from medium to high dose ICS.
Mometasone / Formoterol HFA 100 mcg/5 mcg 200 mcg/5 mcg	NA	NA	2 puff BID; dose depends on severity or control	
Cromolyn (Control: Mast Cell Stabilizer)				
Nebulizer 20 mg/ampule (MDIs not currently available due to propellant regulations.)	< 2 YO NA ≥2 YO 1 amp QID	1 amp QID	1 amp QID	• Alternative therapy for mild persistent asthma, although not widely used. • 4 – 6 week trial may be necessary to see maximum benefit. • Once control is achieved, dosing frequency may be decreased. • Can be used for EIB, but effect is shorter lived than SABA. • S/E cough and irritation. • Nedocromil MDI not currently available.
Immunomodulators (Control: Monoclonal Antibody)				
Omalizumab 150 mg/1.2 ml for subcutaneous injection	NA	NA	150 – 375 mg SC q 2 – 4 wks (depending on body weight and pretreatment IgE level)	• MOA: Anti-IgE – prevents IgE from binding to high affinity receptors on basophils and mast cells. • Don't administer more than 150 mg per injection site. • Be prepared and equipped to identify and treat anaphylaxis (0.2% patients). • Pain and bruising at injection site common (5 – 20% of patients experience). • Malignant neoplasms were reported in 0.5% of patients (vs. 0.2% of placebo). Relationship unknown.
Leukotriene Modifiers (Control)				
Leukotriene Receptor Antagonist				
Montelukast 4 mg or 5 mg chewable 4 mg granules 10 mg tablet	> 1– 6 YO 4 mg q HS	≥6 – 14 YO 5 mg q HS	10 mg q HS	• MOA: interfere with pathway of leukotriene mediators released from mast cells, eosinophils and basophils. • Alternative therapy for mild persistent asthma. Can be added to ICS as alternative to preferred LABA. • Dose-response curve is flat: no further benefit from higher dosages. • May attenuate EIB with long-term use – but less effectively than ICS. • No specific safety concerns.

Zafirlukast 10 mg or 20 mg tab	NA	7 – 11 YO 10 mg BID	20 mg BID	• Cases of reversible (and rarely irreversible) hepatic failure. • Taking with food decreases bioavailability. • Inhibits microsomal P450 metabolism: caution with other medications pathway, including warfarin and theophylline. • Monitor LFT and warn about liver dysfunction.
5-Lipoxygenase Inhibitor				
Zileuton 600 mg tab	NA	NA	600 mg QID	• Elevation liver enzymes has occurred and severe reversible hepatitis and hyperbilirubinemia. Monitor ALT. • Inhibits microsomal P450 metabolism: caution with other medications that use this pathway, including warfarin and theophylline.
Methylxanthines (Control – Mild – Moderate Bronchodilator) Note: Not Commonly Used				
Theophylline Liquid, SR tabs, capsules	Starting dose 10 mg/kg/d Maximum > 1 YO 16 mg/kg/d Maximum < 1 YO 0.2(age in wks) + 5 mg/kg/d	Starting dose 10 mg/kg/d Maximum 16 mg/kg/d	Starting dose 10 mg/kg/d up to 300 mg Usual maximum 800 mg/d	• Use uncommonly as alternative for mild persistent asthma or as adjunct with ICS in select patients ≥ 5 YO. • Adjust dosage to achieve serum concentration of 5 – 15 mcg/ml at steady state – routine monitoring essential. • Multiple factors (diet, febrile illness, age, smoking, other medications) can impact serum concentrations – see full package insert. • SE: insomnia. GI upset, PUD/GERD, hyperactivity in children, decreased urine flow in males with BPH. • Toxicity: tachycardia, SVT, N/V, CNS stimulation, HA, seizures, hematemesis, hyperglycemia, hypokalemia.
Inhaled Short-Acting β2 Agonists (SABAs) (Quick Relief)				
MDI				
Albuterol HFA 90 mcg/puff	*1-2 puffs 5 min before exercise *2 puff Q4-6 hr PRN	*2 puffs 5 min before exercise *2 puffs Q4-6 hr PRN *4 – 8 puffs q 20 min x 3, then q 1-4 hr for acute exac.	*2 puffs 5 min before exercise *2 puffs Q4-6 hr PRN *4 – 8 puffs q 20 min up to 4 hr, then q 1-4 hr for acute exac.	• MOA: relaxes smooth muscles. • SABAs are drug of choice for acute bronchospasm. • Increasing frequency of use or decreasing benefit from use indicated diminishing control of asthma. • Use more than 2 x /wk (other than for EIB prevention) indicated need for additional control. • May double usual dosage for mild exacerbations. • S/E: tachycardia, tremor, hypokalemia, headache, increased lactic acid, hyperglycemia.
Levalbuterol HFA 45 mcg/puff	NA	2 puffs 5 min before exercise 2 puffs Q4-6 hr PRN	2 puffs 5 min before exercise 2 puffs Q4-6 hr PRN	
Pirbuterol	NA	NA	2 puffs 5 min	• Patients with preexisting cardiovascular

200 mcg/puff			before exercise 2 puffs Q4-6 hr PRN	disease may have adverse cardiovascular effects with inhaled therapy. • Levalbuterol is more expensive.
Nebulizer				
Albuterol 063 mg/3 ml 1.25 mg/3 ml 2.5 mg/3 ml 5 mg/ml < 20 kg 2.5 mg/ml ≥ 20 kg 5 mg/ml	*0.63 – 2.5 mg in 3 ml saline q 4-6 hr PRN *2.5 – 5 mg q 20 min x 3, then 2.5-5mg q 1 – 4 hr for acute exac. *Or 0.5mg/kg/hr continuous nebulizer	*1.25 – 5 mg in 3 ml saline q 4-8 hr PRN *2.5 – 5 mg q 20 min x 3, then 2.5-10 mg q 1 – 4 hr for acute exac. *Or 10-15 mg/hr continuous nebulizer	*1.25 – 5 mg in 3 ml saline q 4-8 hr PRN *2.5 – 5 mg q 20 min x 3, then 2.5-10 mg q 1 – 4 hr for acute exac. *Or 10-15 mg/hr continuous nebulizer	• Nebulized SABA may be combined with cromolyn, budesonide or ipratropium solutions. • May double usual dosage for severe exacerbations.
Levalbuterol 0.31 mg/3 ml 0.63 mg/ 3 ml 1.25 mg/0.5 ml 1.25 mg/3 ml	0.31 – 1.25 mg in 3 ml saline q 4-6 hr PRN	0.31 – 0.63 mg q 8 hr PRN	0.63 – 1.25 mg Q 8 hr PRN	
Anticholinergic (Quick-Acting: Reduce Vagal Tone)				
Ipratropium MDI 17 mcg/puff	NA	NA	8 puff q 20 min up to 3 hr for acute exac	• MOA: inhibits muscarinic cholinergic receptors, which reduces vagal tone in airways. • Multiple doses in ED setting of ipratropium provide additional benefits to SABA for moderate to severe exacerbation. • Treatment of choice due to bronchospasm due to β-blocker medication. • May be alternative in patients unable to tolerate SABA. • S/E: drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed into eyes.
Ipratropium Nebulizer 0.25 mg/ml	NA	NA	0.25 mg q 6 hr	
Ipratropium + Albuterol MDI 18 mcg/ 90 mcg	NA	NA	2 - 3 puffs q 6 hr	
Ipratropium + Albuterol Nebulizer 0.5 mg/2.5 mg per 3 ml	1.5 ml q 20 min x 3 doses prn for acute exac	3 ml q 20 min x 3 doses prn for acute exac	3 ml q 20 min x 3 doses prn for acute exac	
Tiotropium	NA	NA	1 blister inhalation QD	• Tiotropium in not approved for asthma, but has been used for adults with severe asthma inadequately controlled on step 4 or 5 care (combined ICS/LABA).[108]

- **Special Considerations for Medications**
  - Glucocorticoids (ICS or OCS)
    - Glucocorticoids are potent anti-inflammatory agents and inhibit most steps in the cascade of the inflammatory response.[110] They reduce bronchial hyperresponsiveness, enhance lung function and prevent the late asthmatic response.
    - ICSs are the most effective anti-inflammatory therapy for all age groups across all degrees of persistent asthma, and at all steps of care.

- ICSs reduce symptom frequency and severity, functional limitations, and likelihood of asthma exacerbations.[111]
- ICSs vary in size of particle and in delivery mechanism (DPI versus MDI versus nebulizer). If the patient is not achieving full benefit, another formulation at a comparable potency (such as HFA-beclomethasone or budesonide DPI) may be indicated before stepping-up.
- While ICSs are the mainstay treatment for asthma and address airway inflammation, they do not appear to modify the course of disease after cessation of treatment.[112] Continued use of ICS is required to maintain asthma control and improved lung function.[113]
- Intermittent preventive use of ICS is being advocated by some for patients with mild persistent asthma, but the use still remains controversial. The TREXA trial, which was a randomized double-blind, placebo-controlled trial of 842 children and adolescents, found that daily ICS was the most effective strategy to prevent exacerbations (followed by initiating ICS and albuterol at the start of symptoms) with as needed albuterol as the least successful. They concluded that rescue ICS might be an effective step-down therapy for youth with mild persistent asthma.[114]
- A Cochrane Review of intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults found low-quality evidence that both strategies are similarly effective. Daily ICS use appears superior to intermittent use for improved lung function and airway inflammation, and for asthma control and reliever use. There did not appear to be a difference in FEV_1, quality of life, hospitalizations or ED visits. The intermittent strategy was associated with greater linear growth as opposed to daily ICS.[115]
- At this time, intermittent use of ICS is not generally recommended as it is not clear which patients might be appropriate candidates and when step-up to daily ICS needs to be imitated.
- Daily use of ICS is important in moderate to severe persistent asthma to reduce impairment and risk of uncontrolled asthma, including death.
- In general, ICSs are safe and well tolerated at the recommended dosages.
- To reduce potential for adverse effects from systemic absorption from the oropharynx:
  - Use VHC or spacer with non-breath activated MDI.
  - Rinse mouth and spit after usage.
- Use lowest dose of ICS that maintains asthma control. Consider adding LABA or alternative adjunctive therapy to low or medium dose of ICS rather that a higher dosage of ICS to maintain control.
- There is no established protocol for weaning ICS for patients with moderate to severe asthma. But it is reasonable to step down (25 – 50%, depending on clinical circumstances) with a clearly defined Asthma Action Plan and follow-up in place.[116]
- Rarely, there are patients who are resistant to OCS, and fail to show improvement in FEV_1 after a 2 week trial of OCS.
- Side effects of corticosteroids:
  - Linear Growth in Children
    - The effect of ICS on linear growth appears to be dose-dependent and the effect seems to occur in the first several months of treatment and is generally small (< 1 cm) and not progressive.[117]
    - As part of routine care, check children's height with a stadiometer. Remember that growth rates are variable and short-term evaluation may not predict final height.

- Bone density
  - High-dose ICS used for prolonged periods of time, especially with concurrent bursts of OCS, may be associated with the risk of reduced bone density.
  - Measure height yearly in adults. Consider bone densitometry, supplemental calcium and vitamin D.
  - In children, review age-appropriate dietary intake of calcium and vitamin D.
  - In children, long-term, low-dose ICS does not appear to effect bone density.[113]
- Hypothalamic-pituitary-adrenal (HPA) axis
  - Suppression of the HPA axis can occur with ICS, and increasing doses may cause adrenal suppression.[118]
  - Adrenal suppression cannot be ruled out by normal growth in children.[119]
- Ocular
  - Subcapsular cataract formation occurs more frequently in patients taking frequent oral systemic corticosteroids than chronic high-dose ICS. Routine slit-lamp examination is recommended. [120]

- Inhaled Long-Acting β2-Agonists (LABA)
  - LABAs have a black box warning by the FDA, as there was an increase in severe asthma exacerbations and slight increase in asthma-related deaths.
  - It is not clear if concurrent use of ICS or other controller medications modifies the risk.
  - A 2012 Cochrane Review examined 21 trials of 7474 children (from 4 – 17 YO) looking at LABA as monotherapy and in combination with ICS. They ascertained that 21 additional children experienced a significant adverse effect with LABAs alone and 3 additional children experienced a significant adverse effect with the combination of LABA and ICS. The review concluded that it was unclear if combination therapy alters the risk of dying with asthma, and that combination therapy is likely to be less risky than monotherapy with LABA. The risk of combination therapy has to be balanced by symptom relief in each child.[121]
  - Tolerance can occur with chronic use of LABAs.[122]
  - There appears to be a racial sensitivity to developing tolerance. African Americans were twice as likely to have treatment failure with LABAs as Caucasians, even though baseline symptoms and rescue inhaler use were lower prior to the study.[123]
  - LABA is a recommended by NAEPP as step-up therapy to patients who require more than low-dose ICS, as it reduces impairment and risk more than doubling ICS dosage. Practall recommends that LABAs are only used when high dose of ICSs are not effective or when patient has not responded to LTRA's.[52]
  - A Cochrane Review in 2009 examined 25 trials representing 5572 children and found that for children with persistent asthma, the addition of LABA to ICS improved lung function, but did not significantly reduce the rate of exacerbations requiring systemic steroids.[124]
  - LABAs:
    - Should not be used as monotherapy for long-term control; patients need to understand that LABAs are to be used in addition to ICS.
    - Should not be used for treatment of acute symptoms or exacerbations.
    - Should not be used daily to prevent EIB, as daily use will mask asthma control.

        - Daily dosage should not exceed 100 mcg salmeterol or 24 mcg formoterol.
    - Consider using combination ICS/LABA inhaler, as they might improve compliance and insure that the LABA cannot be used without the ICS.
    - Formoterol is considered a fast-acting β2- agonist (FABA), and the combination of budesonide/formoterol has been suggested to be a reliever and controller for patients > 12 YO with uncontrolled asthma and frequent exacerbations. More studying is required to determine the validity of this recommendation.[53]

- Inhaled Short-Acting β2- Agonists (SABA)
    - Bronchodilators with quick onset of action and lasting for 2 – 6 hours.
    - Recommended to be used as needed, rather than regular schedule.
    - Regular use is associated with desensitization, and with a loss of bronchoprotective effect, which is the ability to prevent against bronchoconstriction when exposed to an allergen, irritant or exercise. Observed changes to the bronchoprotective effect following allergen stimulation include release of eosinophil mediators, increased sputum eosinophils and enhancement of the late asthma response.[125]
    - Some patients require higher dosages of SABA to achieve bronchodilation in an asthma exacerbation.
- Leukotriene Receptor Antagonists (LTRAs)
    - LTRAs may be used as second-line monotherapy for mild asthma in children and as step-up therapy for persistent asthma in children. Note that montelukast can be used in children as young as 1 YO whereas zafirlukast is indicated for ≥ 7 YO.
    - They are not typically recommended for people > 12 YO.
    - A meta-analysis of adolescents and adults with mild to moderate asthma concludes that the benefits of ICS are generally greater than those seen with LTRA.[126]
    - One study of 6 – 17 YO children looking at montelukast versus low-dose fluticasone found:
        - 23% patients responded only to fluticasone.
        - 5% patients responded only to montelukast.
        - 17% patients responded to both medications.
        - 55% patients respond to neither.
        - Response to montelukast was associated with a younger age and shorter duration of asthma.
        - Response to fluticasone was associated with increased markers of allergies and decreased pulmonary function.
        - The study concluded by saying that children with markers of allergic inflammation (including higher eNO, total eosinophil counts, higher IgE) and reduced pulmonary function should preferentially be given ICS; other children could receive either ICSs or LTRAs.[127]
    - Montelukast has also been studied on an intermittent basis, initiated by the parent at the beginning of an URI. While early, intermittent use reduced time off from school and parental time off from work, but it did not significantly reduce duration of episode, SABA or OCS use.[128] Intermittent use of LRTA is not routinely recommended for children with intermittent asthma at this time.
    - If the LTRAs are not effective for adults after a 3 month trial, consider switching to zileuton, which has a different mechanism of action.[129]
- Chromones

- 4 – 6 weeks of use is typically needed to see an effect on chronic asthma symptoms. However, it is effective as a prophylactic for EIB or allergy exposure, and demonstrates a dose-response effect for prophylaxis.[130]
- A Cochrane Review comparing relative effectiveness of ICS and sodium cromoglycate in 17 trials with 1279 children and 8 trials of 321 adults concluded that ICSs were superior to cromoglycate for improvement of lung function and asthma controls with no difference in side effects. The studies were limited by short duration and did not report of quality of life or health care utilization rates.[131]
- The CAMP study compared nedocromil, budesonide, or placebo and found that budesonide provided better asthma control with reduced need for hospitalization, fewer missed school days and lower use of rescue medication.[113]
- There is no definitive evidence that chromones provide synergistic benefit with ICS, and may increase cost and medication complexity, especially as they are not currently available as an inhaler at this time.

- Anti-IgE Therapy
  - Approximately 30 – 50% of patients with severe asthma respond to omalizumab.[132]
  - The effect may take a minimum of 12 weeks to appear, so it may be reasonable to employ a 3 – 6 month trial to determine full effect.

- **Special Considerations by Populations**
  - ≤ 4 YO
    - Most children who develop asthma will have symptoms before their 5th birthday. Correct diagnosis and adequate treatment will reduce morbidity and mortality. However, not all wheeze and cough is due to asthma. Confounding the management decisions further is the fact that viral respiratory infections are the most common trigger of asthma symptoms in this age.
    - Young children who have exacerbations with viral infections often have a low level of impairment but a high level of risk; between exacerbations, there are no significant symptoms. However, exacerbations are often severe, requiring emergency care or hospitalization.
    - Many children who wheeze with viral respiratory infections will have remission of symptoms by 6 years of age.[67]
    - Montelukast is suggested as treatment for viral-induced wheeze in young children and has been shown to reduce frequency of exacerbations.[136]
    - Two thirds of children with frequent wheezing and a positive Asthma Predictive Index are likely to have asthma throughout childhood.[71] (See page 17.)

Table 11: Indications for Controller Medications in Children ≤ 4 YO [8, 71]
≥ 4 episode of wheezing that lasted more than 1 day in past year.
Positive Asthma Predictive Index.
Require quick-relief medications more than 2 days/week for period of more than 4 weeks.
Experience severe exacerbations < 6 weeks apart or ≥ 2 exacerbations requiring systemic glucocorticoids within 6 months.
Severe exacerbations associated with known triggers, such as seasonal allergens or respiratory viruses.

    - ICSs are the preferred long-term control medication, especially if atopy is present, and dosage should be titrated to the lowest dosage to maintain asthma control.
    - Budesonide is the only FDA-approved nebulized ICS for this age group. Avoidance of spray into the eyes is important because of concern of developing cataracts from topical exposure.

- Fluticasone with a face mask and MDI with VHC have also been studied and found to be effective in young children. [54]
- Close follow-up is important. If patient is not responding to care (and family is compliant with recommendations), consider alternative diagnosis or other comorbid conditions.

- Youth ≥ 5 YO
  - Encourage full and active participation in physical activities. If symptoms of exercise induced bronchospasm (EIB), consider pretreatment with SABA or other approved agent.
    - SABA prior to exercise may be helpful for 2 – 3 hours.
    - Occasional use of LABA may be needed if longer exercise time anticipated, but not indicated for daily use.
    - LTRAs can attenuate EIB in approximately half of patients, onset several hours after administration.
    - Cromolyn taken shortly before exercise is an alternative (although only available by nebulizer at this time).
    - A mask or scarf over the mouth may reduce cold-induced EIB.
  - Note: Frequent or severe EIB may indicate need to step up long-term control therapy.
  - Communicate Asthma Action Plan with school, camp and other care settings.
  - Involve the youth, as appropriate, in their Asthma Action Plan, medication usages, control and compliance, and environmental control. Address child's questions and concerns.
  - ICSs are the preferred long-term control medication, and dosage should be titrated to the lowest dosage to maintain asthma control.
  - Evaluate lung function with pulmonary function testing (if not already done) and periodically monitor as indicated.
  - Declines in lung function or repeated episodes of worsening asthma impairment may indicate a progressive worsening of the underlying severity of asthma.
- Adults
  - In general, adults with asthma can be divided into 2 subgroups:
    - Those who developed symptoms of asthma as children.
    - Those who had new-onset symptoms as adults.
  - Evaluate adults with new-onset asthma for occupational exposures.
  - Prevalence of asthma in those ≥ 65 YO is 4 – 8%.[134]
  - Asthma in older adults (≥ 65 YO) may be confounded by other chronic conditions, such as COPD and heart failure, and patients may have more respiratory symptoms. However, it does not appear that chronologic age is an independent risk for hospitalization for asthma.[135]
  - The asthma mortality rate increase seen between 1979 and 1996 occurred primarily in people ≥ 65 YO, with the subgroup of older African American women having the largest increase in mortality rate.[136]
  - Atopy, although less prevalent than in childhood, is still prevalent in adulthood. About ¾ of older patients with asthma are allergic to one or more common indoor allergens.[137]
  - Older patients with asthma may not be as perceptive of dyspnea due to asthma or they may complain less about symptoms, discounting shortness of breath as related to the aging process.[138]
  - If diagnosis is unclear or confounded with COPD or chronic bronchitis, consider short trial of oral systemic corticosteroids to establish reversibility and the potential benefit of asthma-specific therapy.

- Remember that asthma can occur concurrently with COPD or heart failure (or other cause of intermittent dyspnea and/or cough).
- Review medications for those which might exacerbate asthma, such as NSAIDs or β-blockers. ACE inhibitors may cause cough, which is not due to asthma.
- Review side effects of medications, including tremor and tachycardia.
- Review for potential drug interactions with theophylline (if patient is taking).
- Consider vitamin D and calcium supplementation for long term ICS use.
- Review proper medication technique, which may change with time due to coordination problems, arthritis causing trouble with actuating MDI, or confusion.

○ Pregnant women
- Uncontrolled asthma increases perinatal risk. Treat aggressively to avoid fetal hypoxemia.
- ICSs are preferred control medication and albuterol is the preferred quick-acting medication. Close perinatal follow-up is important.
- Generally speaking, 1/3 of pregnant women with asthma have worsening asthma symptoms, 1/3 have improved asthma symptoms, and 1/3 have no change.

○ Surgical patient
- Asthmatic patients may be at a higher risk with surgery due to:
  - Acute bronchoconstriction with intubation.
  - Hypoxemia and possibly hypercapnia.
  - Impaired, effective cough.
  - Atelectasis,
  - Respiratory infection,
- Prior to elective surgery, asthma management may need to be stepped up to improve lung function, if not well controlled.
- Use of OCS within 6 months of surgery or prolonged high-dose ICS requires special consideration.

- **Emerging Therapies**
  - Various immune modulators are being investigated, including anti-IL-5, anti-IL-13, anti-TNF-α, and TNF-receptor blocker, although preliminary results are not promising.
  - Also, longer acting ICSs are being developed, as are ultra-long-acting β-2 agonists.
  - Bronchial thermoplasty has just been approved for adults with poorly controlled, severe asthma. It is not widely available and long-term data is not available.

Managing Exacerbations: Algorithms 4-5, Tables 12-14

Sources used:
-NAEPP, 2007[8]
-GINA, 2012[72]
-Cincinnati Children's Hospital, 2010[160]
-Children's Hospital Colorado, 2011[161]

Definition

- Exacerbations are either acute or subacute periods of progressively worsening shortness of breath, chest tightness, cough and/or wheezing.
- Objective measures of diminished airflow (PEFR or spirometry) more reliably indicate severity as opposed to symptom history.
- Severe exacerbations can be life-threatening and can occur with any level of asthma severity (intermittent, mild, moderate or severe persistent asthma).

- Risk factors for asthma-related death include:
  - Previous severe exacerbation requiring intensive care unit (ICU) admission or intubation.
  - 2 or more hospitalizations, or 3 or more ED visits for asthma in past 2 years.
  - Use of > 2 canisters of SABA/month.
  - Difficulty perceiving airway obstruction or worsening symptoms.
  - Low socioeconomic status or inner-city residence.
  - Illicit drug use (patient or primary caregiver, if patient is child).
  - Major psychosocial problems or psychiatric disease (patient or primary caregiver, if patient is child).
  - Comorbidities, such as cardiovascular disease, other chronic lung disease, others.
  - Failure of patient, caregiver or clinician to recognize severity of disease and intensely manage.

- **Management Strategies**
  - The same 4 core management components apply to acute and chronic asthma care.
    - Assessment and monitoring:
      - Assess the severity of the current attack.
      - Review prior history of asthma exacerbations.
      - Frequently monitor response to therapy.
    - Patient education (once patient stable):
      - Inhalation technique, compliance and trigger avoidance.
      - Asthma Action Plan.
    - Environmental control (once patient stable):
      - Review if there was any precipitating trigger to emphasize specific avoidance.
      - Always discuss primary or secondary tobacco exposure and counsel if appropriate.
    - Medications:
      - SABAs - to address bronchoconstriction.
      - Systemic glucocorticoids (started very early in the exacerbation) - to address airway inflammation.
      - Supplemental oxygen, if indicated - to address hypoxia.
  - Detecting onset of exacerbations
    - Some patients are very sensitive to the change in asthma symptoms and can ascertain deterioration in their airflow.
    - Other patients are not as sensitive to determining changes in airflow based on symptoms, and benefit from determination of PEFR to detect deterioration.
    - Objective measures of airflow, either PEFR or spirometry, are the best method for ascertaining severity of an asthma attack in the office or ED.
    - Peak flow offers the benefit of being able to be completed at the bedside and can be repeated serially.
    - Normal ranges of PEFR depend on gender, height and age. If patient routinely checks PEFR at home, use their personal best as a comparator.
    - Proper technique includes having the patient stand, holding the zeroed meter (but not blocking the outflow), taking a deep breath, putting lips tightly around the mouthpiece, and blowing in as hard and fast as possible. Measurements should be repeated three times and the highest number recorded.
  - Brief history and focused physical
    - Review prior history of asthma exacerbations, including ED use, hospitalization, ICU admission, intubation, OCS use, and typical progression of exacerbation.

- Review time of onset and medication routinely and emergently employed, including last β2-agonist use (SABA or LABA).
- Review allergies and possible trigger.
- Review current symptoms.
- Examine vital signs, including pulse oximetry.
- Examine overall demeanor (anxiety, level of consciousness, agitation), breathlessness, accessory muscle use, work of breathing.
- Examine for airway exchange, wheezing, and work of breathing.
- Physical examination is not sensitive to determine severity of asthma attack. Up to 50% of patients will not manifest classic clinical findings.[139]
- Classic clinical finding may include:
  - Pulsus paradoxus (fall in systolic blood pressure during inspiration).
  - Accessory muscle use during inspiration.
  - Diaphoresis.
  - Inability to lay supine due to breathlessness.

Table 12: Classifying Severity of Asthma Exacerbation (derived from NAEPP[8])

Category	Signs and Symptoms	Initial PEFR (or FEV_1)	Clinical Course
Mild	Dyspnea only with activity (assess tachypnea in young child)	PEFR ≥ 70% predicted or personal best	• Usually managed at home • Usually have prompt relief with SABA • May require short course of OCS
Moderate	Dyspnea interferes with or limits normal activity	PEFT 40 – 69% predicted or personal best	• Usually required office or ED visit • Usually has relief from frequent SABA • Requires short course of OCS • Some symptoms may last 1 – 2 d after OCS begun
Severe	Dyspnea at rest, interferes with conversation	PEFR < 40% predicted or personal best May not be able to perform	• Usually required ED visit, likely to require hospitalization • Partial relief from frequent SABA • Requires OCS • Some symptoms may last > 3 days after OCS begun • Adjunctive therapies helpful (ipratropium, supplemental oxygen in ED)
Life Threatening	Too dyspneic to speak, diaphoretic	PEFR < 40% predicted or personal best May not be able to perform	• Requires ED/hospitalization; possibly ICU • Minimal or no relief from frequent SABA • IV corticosteroids • Adjunctive therapies helpful (ipratropium, supplemental oxygen, possibly others, in ED)

- **Acute Care: Home Management**
  Early symptom recognition and initiation of acute treatment at home is an effective strategy.
  - An educated and engaged patient or caregiver can recognize the signs of an exacerbation (by symptoms or PEFR) and can follow a prearranged written Asthma Action Plan.
  - The early treatment could include:
    - Removal from offending trigger.
    - Use of as-needed SABA for increased symptoms, or if PEFR falls below 80% predicted or personal best.
    - Increase SABA dosage (increase number of puffs per dosage or shorter interval between dosages; for example, 2 – 8 puffs or nebulized albuterol 2.5 – 5 mg, repeated in 20

minutes if incomplete relief) with close monitoring and contact with PCP if PEFR is between 50 – 79% of predicted or personal best. In select patients, initiation of a short burst of OCS may be considered as part of the action plan.
    - If PEFR < 50% of predicted or personal best, patient should proceed for immediate medical care.
    - Doubling ICS is ineffective at the start of an exacerbation.[8] One study has indicated that quadrupling the ICS dose may have an effect in mildly increased asthma symptoms.[140] Further study is suggested.
    - Alternative therapies, such as breathing warm, moist air, drinking a large volume of fluids, pursed lip breathing, or over-the-counter cold remedies, have not been shown to be effective and may delay beneficial treatment.
    - The Canadian Thoracic Society (CTS) has some specific recommendations based on clinical review regarding "yellow zone" care.[53]
        - Appropriate use of maintenance medications is important.
        - Evidence does not support starting or doubling the dosage of ICS at the start of an exacerbation or loss of control.
        - A 4-fold increase in the dose of ICS for 7 – 14 days may be effective in adults with a history of severe exacerbations (not children or adolescents).
        - There is no strong evidence for or against adjusting the dose of ICS/LABA combinations as part of a self-management plan. However, in people > 16 YO, increasing budesonide/formoterol to 4 puffs twice daily may be beneficial.
        - There is some question about not including OCS as part of the self-management strategy, and this decision should be individualized to the patient severity and history.

- **Acute Care: Urgent or ED Care**
    - The 3 primary goals of acute therapy are:
        - Rapid reversal of airway obstruction (with inhaled bronchodilators and early use of systemic glucocorticoids).
        - Correction of hypoxia.
        - Reducing likelihood of recurrence (by intensifying baseline therapy and close follow-up).
    - Serial monitoring of response to therapy
        - The pulmonary index score is a validated tool used to access severity and response to therapy.[141] It has been adopted by Niswonger Children's Hospital.
        - Monitoring is completed at initial presentation and periodically throughout the urgent care or ED stay. Frequency of monitoring may vary depending on the severity of the exacerbation and the frequency of the breathing treatments. Every 20 – 30 minutes may be appropriate for many patients.
        - No single measure is best for predicting need for hospitalization.
        - Lung function may be useful in children ≥ 5 YO (spirometry or PEFR), however, patients with a severe attack may not be able to perform.
        - Persistently reduced pulse oximetry and persistent signs and symptoms (including lung function if obtained) 1 hour after treatment have a greater risk of hospitalization.

Table 13: Pulmonary Index Score (PIS[141])

Score	Respiratory Rate (< 6 YO)	Respiratory Rate (≥ 6 YO)	Wheezing	Inspiratory / Expiratory ratio	Accessory Muscle Use	Oxygen Saturation

0	≤ 30	≤ 20	None	2 : 1	None	99 – 100
1	31 – 45	21 – 35	End Expiration	1 : 1	+	96 – 98
2	46 – 60	36 – 50	Entire Expiration	1 : 2	++	93 – 95
3	> 60	> 50	Inspiration & Expiration OR no wheeze heard due to minimal air movement	1 : 3	+++	< 93
In general: Score < 7 indicates a mild attack; score 7 – 11 indicates moderately severe attack; score ≥ 12 indicates a severe attack. However, PIS may underestimate the degree of illness in an older child.						

Algorithm 4: Acute Management of Asthma Exacerbation: Outpatient

Patient presents to outpatient clinic with exacerbation of asthma[160,161]

Assess History: current symptoms, triggers or illness, frequency SABA use, compliance with controller medications, prior asthma history (hospitalizations, ED visits, OCS use)
Physical Examination: Vital signs, oxygen saturation, distress, work of breathing, cough, wheezing, PIS
Monitoring: Vital signs, continuous pulse oximetry (if on supplemental O_2 to maintain SpO_2 > 92%), PIS before and after treatment, per protocol
Treatment: albuterol

- MDI with VCD: 4 - 8 puffs q 20 min; may repeat - total 3 x in 1 hour
- Intermittent Nebulized: 2.5 – 5 mg q 20; may repeat - total 3 x in 1 hour
- Continuous Nebulizer: 10 – 15 mg delivered over 1 hour

Treatment: Other:

- For moderate to severe exacerbations, can add ipratropium 0.5 mg to nebulized albuterol – total 3 x
- Oral prednisone (1 mg/kg max 60 mg/d) given if incomplete response after 1st treatment

Pediatric Dosage Albuterol
< 20 kg 2.5 mg/neb or 2 – 4 puffs /dose
≥20 kg 5 mg/neb or 4 – 8 puff/dose

Complete symptom resolution and stable for 1 – 2 hours after last treatment

Yes

Discharge home

- Asthma education and MDI technique review
- Written Asthma Action Plan
- OCS for 5 day, if needed
- Follow-up scheduled 3 – 7 days
- Assure patient has needed medications and supplies
- SABA q 4hr x 48hr

No

Proceed to ED

- Incomplete response to 3 treatments (1 continuous)
- Oxygen saturation <90% on room air
- PIS persists > 7

Algorithm 5: Acute Management of Asthma Exacerbation: ED

Patient presents to ED with exacerbation of asthma[160,161]

Assess History: current symptoms, triggers or illness, frequency of SABA use, compliance with controller medications, prior asthma history (hospitalizations, ED visits, OCS use), previous treatments (if transferred).
Physical Examination: vital signs, oxygen saturation, distress, work of breathing, cough, wheezing, pulmonary index score (PIS).
Monitoring: vital signs, continuous pulse oximetry (if on supplemental O_2 to maintain SpO_2 > 92%), PIS score before and after treatment, per protocol.
Treatment: Albuterol

- Intermittent nebulized: 2.5 – 5 mg q 20; may repeat for total of 3 x in 1 hour.
- Continuous nebulizer: 10 – 15 mg delivered over 1 hour [At Niswonger, higher dosages are used, up to 20 mg (for child > 20 kg)].

Pediatric Dosage Albuterol
< 20 kg 2.5 mg/neb
≥ 20 kg 5 mg/neb

Treatment: Other

- For moderate to severe exacerbations, can add ipratropium 0.5 mg to nebulized albuterol – total 3 x.
- Oral prednisone (1 mg/kg – max 60 mg/d) given if incomplete response after 1st.

Complete symptom resolution and stable for 1 – 2 hours after last treatment

Yes

Yes

Discharge home (PIS < 7 and SpO_2 > 92% on RA)

- Asthma education and MDI technique review
- Written Asthma Action Plan
- OCS for 5 days, if needed
- F/U scheduled 3 – 7 days
- Assure patient has needed medications and supplies
- SABA q 4 hr x 48 hr
- Initiate ICS if 1 prior ED/hospitalization in past 12 month

Incomplete Response (PIS 8 – 11) or Poor Response (PIS 12 – 15)

- Q2hr monitoring of VS (HR, RR, SpO_2)
- Albuterol continuous neb with oxygen
- Poor response if PIS maintains > 12 after 1 hour
  - Consider ABG, CXR
  - Consider adjunct therapies
  - Admission
- If PIS < 8 after 1 hour of continuous, hold and observe
- If PIS maintains < 8 after 2 hours, give 2 puff albuterol, and consider discharge (stable family with close follow-up)
- If PIS ≥ 8, resume continuous nebulizer and reevaluate after 1 hour; consider admission

- Protocols should be in place in urgent care setting to allow early initiation of SABA and supplemental oxygen to maintain pulse oximetry above 92%.
- Copies of the Niswonger ED and admission order sets are included in the appendix.
- Mainstays of therapy
  - Supplemental oxygen, if needed, to correct hypoxia.
    - Acute asthma exacerbation is associated with a ventilation–perfusion mismatch. β2-agonists may initially worsen the mismatch, as there may be increased blood flow to poorly ventilated areas of the lung. Oxygen saturation may decrease by ≥ 5% within 30 minutes after treatment with albuterol.[142]
    - Supplemental oxygen should be adjusted to maintain the oxygen saturation at ≥ 92%.[143] Continuous pulse oximetry monitoring is important.
    - Hypercapnia may be a concern with adults with COPD or in children with underlying lung disease, such as cystic fibrosis or bronchopulmonary dysplasia.

Table 14: Advantages and Disadvantages of Different Administration Modalities[8]

Modality	Advantage	Disadvantage
MDI with Spacer/VHC	• Full dose delivered quicker. • Less expensive. • Mask added allows use in young children. • Once stable, opportunity for patient reinforcement education about proper technique.	• Depending on VHC/spacer, may require more coordination. • Not appropriate for severe asthma. • Can't combine with ipratropium.
Intermittent Nebulizer	• Can combine with ipratropium. • Can use easily with supplemental oxygen. • Appropriate for all ages and severity of asthma.	
Continuous Nebulizer	• Can combine with ipratropium. • Can easily use with supplemental oxygen. • Appropriate for all ages. • For moderate to severe asthma, achieve goal of 3 nebulizer treatments within 1 hour.	• Young children may not tolerate the mask for long periods of time. • Associated with transient electrolyte abnormalities, including hypokalemia, hypophosphatemia and hypomagnesaemia. These are typically not clinically significant, but may require monitoring in hospitalized patient receiving continuous albuterol who has chronic diuretic use, cardiovascular disease, or previous history of electrolyte abnormalities.

  - Repetitive or continuous administrations of SABA with frequent monitoring
    - Patient may be able to be discharged home if complete resolution with first hour of therapy (and if stable for 1 – 2 hours after last treatment).
    - Different strategies include:
      - Albuterol: MDI with VHC/spacer
        - 2-4 puffs q 10 min x 2 or 4-8 puffs q 20 min for 3 total dosages (24 puffs total in 1 hour).

- May repeat every 1 to 4 hours, as needed (indicates need for hospitalization).
- (Pediatric: 1/4 – 1/3 puff/kg -maximum 8 puff q 20 min.)

- Albuterol: intermittent nebulized
  - 2.5 – 5 mg nebulizer q 20 min for 3 doses.
  - May repeat, then 2.5 – 10 mg q 1 – 4 hours, as needed (indicates need for hospitalization).
  - (Pediatric: 0.15 mg/kg maximum 5 mg q 20 min.)
- Albuterol: continuous nebulized
  - 10 – 15 mg albuterol over 1 hour (Niswonger and other pediatric EDs are using dosages of 20 mg for continuous nebulization).

- MDI versus nebulizer
  - Studies show that MDI with VHC/spacers are as effective as nebulized treatments.[144]
  - Although no precise comparison of effective dosage has been determined, 4 – 6 puffs of albuterol (observed by trained staff) appear to be comparable to a nebulizer treatment.[8]
- Albuterol (racemic) versus levalbuterol
  - It appears that levalbuterol (the L-isomer) is no more effective than racemic albuterol (the L- and S- isomers) for acute asthma treatment.[145]
  - Cost appears to be the differentiating factor, with levalbuterol being more expensive.

- Inhaled ipratropium is recommended in conjunction with SABAs for severe asthma in the ED.[8]
  - Typical adult dosing is 500 mcg by nebulizer q 20 min x 3, then as needed, or 8 puffs by MDI with VHC/spacer q 20 min, then as needed (Pediatric: 250 mcg/dose if ≤ 20 kg; 500 mcg/dose if > 20 kg).
  - Note: MDI should not be used in highly sensitive patients with peanut or soy allergy because the formulation contains soy lecithin.
  - A recent Cochrane Review of combined therapy of inhaled SABA and anticholinergic in children suggests that there is a benefit, noting improved lung function and lower hospital admission rates. It is not clear the patients who would benefit most from this therapy.[146]
  - Currently, it is reserved for patients with severe airflow obstruction who do not initially improve with SABA alone.[8]
  - Special circumstances where parasympatholytic therapy may be beneficial include patients taking monoamine oxidase inhibitors, patients whose asthma is triggered by a β-blocker therapy (oral or eye drops), or patients with COPD and asthma.[8]
- Early administration of systemic glucocorticoids
  - The NAEPP recommends systemic glucocorticoids for:
    - All patients with moderate to severe exacerbations (PEFR < 70% for moderate and < 40% of predicted or personal best for severe).
    - Patients who do not fully correct peak flow with SABA use.
    - Contraindications for systemic glucocorticoids may include hypersensitivity reaction, varicella infection, herpes simplex keratitis, tuberculosis, recent (< 2 weeks) or current systemic steroid use.

- Optimal dosage not known
  - Equivalent dosage of 40 – 60 mg prednisone is common for acute asthma exacerbations, given once daily.[8]
  - Oral route can be used as long as patient is not vomiting nor in impending respiratory arrest.
  - Prednisone and methylprednisolone are rapidly absorbed and have peak serum levels within 1 hour of oral administration, and efficacy is comparable to equivalent doses of IV glucocorticoids.
- Optimal timing of systemic glucocorticoids
  - Onset of clinical effect of systemic corticosteroids may take as long as 6 hours, so early administration is important (often defined as less than 1 hour after presentation to the ED or if incomplete response after 1st nebulizer treatment). One study found that hospitalization rate was inversely related to time of admission of corticosteroids in the ED.[147]
  - Another recent study looked at triage nursing initiation of glucocorticoids and found a reduced likelihood of admission and decreased time to clinical improvement and discharge.[148]

- Other diagnostic testing
  - Blood Gas
    - Respiratory drive increased in acute asthma, resulting in hyperventilation and decreased $PaCO_2$.
    - Normal or increased $PaCO_2$ found on ABG indicates severe airway narrowing and potential respiratory failure.
    - Hypercapnia only occurs if the peak flow is below 25% of normal. ABGs, therefore, are generally only indicated in patients with PEFR ≤ 25% predicted or personal best, or if too ill to complete PEFR.[149]
  - Chest X-ray
    - Generally unrevealing in an acute asthma attack except for those patients with focal findings on chest exam or suspected complications, including fever > 38.3°C, possible foreign body aspiration, unexplained chest pain, leukocytosis, hypoxemia or at high risk for complications, such as cancer, intravenous drug abuse, heart failure, other.[150]
- Alternative therapies, perhaps useful in select situations
  - IV magnesium sulfate
    - Bronchodilator effect of IV magnesium sulfate may be beneficial in patients with severe asthma exacerbation or for those who have not significantly improved after 1 hour of intensive conventional therapy, and are being considered for ICU admission.[151]
    - Inhaled magnesium sulfate offers no benefit as compared to placebo.[152]
    - Typical dosage in adults is 2 g infused over 20 minutes. It is contraindicated with renal insufficiency.
    - A meta-analysis found that magnesium sulfate is also effective for preventing hospitalizations in children with moderate to severe asthma when added to usual therapy.[153]

- Parenteral β2-Agonists
  - Epinephrine and terbutaline can be given subcutaneously or intramuscularly for severe asthma exacerbation or for very anxious, uncooperative patients who can't comply with inhaled route of β2-agonists.
  - In severely ill, poorly responsive patients, they can be given intravenously.
- Heliox
  - Helium – Oxygen mixtures have been administered in an attempt to improve ventilation. However, there is conflicting evidence from small, non-randomized studies that it is effective.[154]
  - The NAEPP suggests that heliox may be tried in life-threatening exacerbations in those who have not significantly improved after 1 hour of intensive conventional therapy.[8] However, a trial of heliox should not delay intubation in such a situation.
- Ketamine
  - Ketamine is a dissociative general anesthetic agent which also has bronchodilating properties. Observations and a few small trials have examined whether it has a clinically significant effect in acute asthma, but no consistent improvements over standard therapy have been observed.[155]
  - May be a good choice to use to sedate and provide analgesia to a child undergoing intubation.
- Leukotriene Receptor Antagonists
  - IV montelukast added to standard care improved FEV_1 up to 2 hours post-dose in a double-blind placebo control study of 583 adults. However, there was no significant difference in treatment failures (defined as decision to hospitalize or ED stay greater than 3 hours) between the treatment or placebo groups. This formulation is currently unavailable.[157]
  - A study of 641 adults with acute asthma suggests a role for zafirlukast. There were 3 treatment arms in the study in addition to routine care: placebo, high dose zafirlukast (160 mg one-time dose) and usual dose zafirlukast (20 mg). There were 2 arms post-discharge in addition to routine care: zafirlukast 20 mg BID for 28 days and placebo.[157]
    - There was an absolute reduction of 5% (relative reduction 34%) in extended ED stay or hospitalization for patients given high dose (but not usual dose) versus placebo.
    - Patients given zafirlukast post-discharge had a 5% absolute reduction (relative reduction 18%) in relapse rate versus placebo.
  - Studies have not found any significant benefit of adding LTRA to the standard therapy for acute asthma in children.[158]
  - This approach is currently not routinely recommended and more study is warranted.
- Alternative therapies not found to be useful
  - Methylxanthines - the risks versus benefits of theophylline to standard asthma care do not justify its use.[159]
  - Antibiotics – unless clearly indicated, or atypical infection (such as mycoplasma) is suggested.
  - Aggressive hydration - unless clinical dehydration present.
  - Chest physical therapy.
  - Mucolytics.

        - Anxiolytics or sedatives – as cause respiratory depression.

- **Disposition**
    - Hospitalization
        - Hospitalization allows close observation and the ability for timely, aggressive therapies.
        - Hospitalization may also allow removal away from the triggering environment.
        - Noninvasive ventilation [biphasic or continuous positive airway pressure (BiPAP or CPAP)] may decrease the work of breathing in an ICU setting.
        - The decision to hospitalize a patient is made from both objective and subjective measures and might include:
            - Prior history of severe exacerbations requiring ICU care or intubation.
            - Recent severe exacerbation.
            - Peak flow persisting less than 40% of predicted or patient's personal best after intensive therapy.
            - Patient not responding well to 4 – 6 hours of intensive therapy and has persistent cough, wheezing and shortness of breath, poor air movement, worsening or persistent hypoxia, hypercapnia, fatigue or mental status change.
            - PIS > 7.
            - Concerns about potential triggers in the home environment.
            - Concerns about access to timely follow-up, transportation to care or medication compliance.
        - Careful and complete communication across the transitions of care from the ED to the inpatient unit is important to avoid duplication or missed care.
        - Basic asthma understanding, medication usage, trigger avoidance and other asthma self-management approaches should be taught during the hospital stay.
        - Patients may be considered for discharge when:
            - Asthma signs and symptoms are considered mild.
            - PEFR > 70% predicted or personal best.
            - Patient tolerating SABA q 4 hr x 2.
            - Supplemental oxygen is no longer required (typically for 8 hours).
            - The treatment regimen can be performed at home, and the patient or caregiver has received asthma medication and is competent to use medications correctly.
            - Asthma Action Plan is complete, follow-up appointment with PCP is made, and patient or caregiver is clear on acute steps to take for worsening symptoms.
            - Access to medications has been confirmed (best if prescriptions are filled prior to discharge; this way, the patient can demonstrate correct usage prior to discharge).
    - Post-acute care (from ED or hospital)
        - Residual airway obstruction remains for several days following an acute exacerbation. OCSs are the preferred therapy to address airway inflammation in this setting and reduce relapse.[160]
        - Optimal duration of systemic glucocorticoids:
            - Return to baseline pulmonary function varies between patients and within the same patient depending on the severity of that asthma exacerbation. There is no precise duration of oral glucocorticoid usage.
            - In general, a hospitalized patient can be changed from IV to OCS as soon as they are able to eat and drink.
            - Typically, a hospitalized patient will complete a 5 day course of OCS.

- A patient discharged from the ED who showed a prompt response to β2-agonists may only require a 5 day course.
- Tapering dosage is not generally required for most patients.
- More individualized approaches are warranted for patients chronically maintained on OCS.

- ICS
  - Baseline ICS and other routine controller medications can be resumed as soon as tolerated while in hospital and should be taken concurrently with OCS.
  - Delaying initiation of ICS may lead to patient confusion.
  - ICS should be initiated in patients not previously on ICS but who have required emergent/urgent care per the NAEPP recommendations.
  - Patient education is a critical component to aide in compliance.
- If the patient does not have a clearly understood Asthma Action Plan, one should be developed prior to discharge from the ED or hospital.
- Timely follow-up with PCP is important (generally within 3 - 7 days); younger patients or those with more severe exacerbations may require closer follow-up.

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NAEPP-EPR 3: Ranking the Evidence	
Evidence A	Randomized controlled trials (RCTs), rich body of data. Category A requires substantial numbers of studies involving substantial numbers of participants.
Evidence B	RCTs, limited body of data. Category B pertains to when few randomized trials exist; they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
Evidence C	Nonrandomized trials and observational studies. Category C is derived from outcomes of uncontrolled or nonrandomized trials or from observational studies
Evidence D	Panel consensus judgment. Category D 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. The panel consensus is based on clinical experience or knowledge that does not meet the criteria for categories A through C.

ACT©	Asthma Control Test
AHR	Airway hyperresponsiveness
ATS	American Thoracic Society
BID	Twice daily dosing
BiPAP	Biphasic positive airway pressure
CAMP	Childhood Asthma Management Program
CASI	Composite Asthma Severity Index
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CTS	Canadian Thoracic Society
CTS	Canadian Thoracic Society
DM	Diabetes mellitus
DPI	Dry powder inhaler
ED	Emergency department
EIB	Exercise induced bronchospasm
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GINA	Global Initiative for Asthma
HEDIS	Healthcare effectiveness data and information set
HTN	Hypertension
ICE	Inhaler technique, Compliance, Environmental history
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IFN	Interferon
IgE	Immunoglobulin E
IL	Interleukin

LABA	Long-acting β-agonist
LTRA	Leukotriene receptor antagonist
MDI	Metered dose inhaler
MOA	Mechanism of action
NA	Not applicable
NAEPP	National Asthma Education & Prevention Program
NL	Normal
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCS	Oral corticosteroids
PCP	Primary care provider
PEFR	Peak expiratory flow rate
PIS	Pulmonary Index Score
PRN	As needed
PUD	Peptic ulcer disease
q HS	Every evening dosing
QD	Once daily dosing
QID	Four times daily dosing
QOD	Every other day dosing
RSV	Respiratory syncytial virus
S/E	Side effect
SABA	Short-acting β-agonist
SC	Subcutaneous
SOB	Shortness of breath
TB	Tuberculosis
Th	T-helper cell
TID	Three times daily dosing
TNK	Tissue necrosis factor
VHC	Valved holding chamber
YO	Years old

Appendix 1: Asthma Exacerbation Clinical Score [73]	
Reported asthma symptoms	✓
Symptoms for more than 3 months of year	
Symptoms precipitated by: **Colds**	
Symptoms precipitated by: **Cold air**	
Symptoms precipitated by: **Exercise**	
Symptoms precipitated by: **Dust**	
Current asthma medications	
Short-acting β2-agonist	
Inhaled steroids	
Leukotriene inhibitors	
Health care utilization	
Ever hospitalized for asthma	
Ever admitted to ICU for asthma	
≥ 2 Courses steroids in last year	
≥ 2 ED visits for asthma in last year	
≥ 3 Doctor visits last year	
≥ 6 Doctor visits last year (also mark ≥ 3 box)	
Medical history	
Personal history of eczema/hay fever	
Parental history of asthma or atopy	
Smoke exposure as infant or current	
Each item is worth 1 point	
Total score	
Low risk	≤ 5
High risk	≥ 9

Appendix 2: Composite Asthma Severity Index (CASI) Scorecard[78]	
Day symptoms and albuterol in the last 2 weeks	
0 – 3	0
4 – 9	1
10 – 13	2
14	3
Night symptoms and albuterol in the last 2 weeks	
0 –1	0
2	1
3 – 4	2
5 – 14	3
Lung function measures	
FEV1 % > 85	0
FEV1 % 80 – 84	1
FEV1% 70 – 79	2
FEV1% < 70	3
Controller treatment	

	No treatment	0
	Albuterol as needed	1
	Low-dose ICS (or montelukast)	2
	Low-dose ICS + LABA or medium-dose ICS	3
	Medium-dose ICS + LABA	4
	High-dose ICS	5
Exacerbations		
	Prednisone burst	2
	Prednisone burst plus hospitalization	4

Table: Predicted Average Peak Expiratory Flow Rate (PEFR in L/min) for Normal Males and Females (Lenier)

Age	**Males**					**Females**				
	60”	**65”**	**70”**	**75”**	**80”**	**55”**	**60”**	**65”**	**70”**	**75”**
20	554	602	649	696	740	390	423	460	496	529
25	543	590	636	679	725	385	418	454	490	523
30	532	577	622	664	710	380	413	448	483	516
35	521	565	609	651	695	375	408	442	476	509
40	509	552	596	636	680	370	402	436	470	502
45	498	540	583	622	665	365	397	430	464	495
50	486	527	569	607	649	360	391	424	457	488
55	475	515	556	593	634	355	386	418	451	482
60	463	502	542	578	618	350	380	412	445	475
65	452	490	529	564	603	345	375	406	439	468
70	440	477	515	550	587	340	369	400	432	461

Note: These values represent averages within 100 (male) - 80 (female) L/min.
African Americans and Hispanics tend to be ≈ 10% less.

Table: Predicted Average Peak Expiratory Flow Rate for Normal Children (Polger)

Height “	**PEFR L/min**	**Height “**	**PEFR L/min**	**Height “**	**PEFR L/min**
43	147	52	267	61	387
44	160	53	280	62	400
45	173	54	293	63	413
46	187	55	307	64	427
47	200	56	320	65	440
48	214	57	334	66	454
49	227	58	347	67	467
50	240	59	360		
51	254	60	373		