

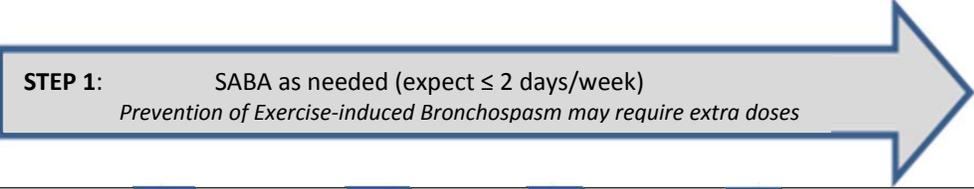
Montelukast's Role in the Treatment of Asthma

Asthma is a chronic condition characterized by long-term airway inflammation and respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough. The limitation on breathing due to the inflammation as well as symptoms can vary in intensity and change over time.² Symptomatic relief of an acute asthma exacerbation (flare-up) is usually managed with a rescue medication containing a short-acting beta-adrenergic agonist (SABA), such as albuterol, and, if needed, systemic steroid therapy. Increased use of a SABA or use more than twice a week, outside of preventing exercise-induced bronchospasm, indicates insufficient asthma control and need to intensify therapy. Controller medications used regularly are the key to managing persistent asthma. **Table 1** overviews the physiologic actions of currently available asthma medications.¹ Medications that are on the HFS Preferred Drug List are available at <http://ilpriorauth.com> or at <https://www.illinois.gov/hfs/MedicalProviders/Pharmacy/preferred>.

Category	Purpose	Medication class	Action
Quick-relief, Rescue medications for asthma exacerbation	Manage acute flare-up of symptoms (wheezing, shortness of breath, chest tightness, cough)	Short-acting beta-adrenergic agonist (SABA: e.g. albuterol)	<ul style="list-style-type: none"> Relax tight airway muscles/bronchodilate Prevent exercise-induced bronchospasm
		Anticholinergics (e.g. ipratropium)	<ul style="list-style-type: none"> Block muscarinic cholinergic receptors Reduce intrinsic vagal tone of the airway Additive to SABA in Emergency Room; Alternative to SABA
		Systemic corticosteroids (oral [e.g. prednisone] or injectable [e.g. methylprednisolone, if severe exacerbation])	<ul style="list-style-type: none"> Decrease inflammation Decrease airway hyper-responsiveness Block late-phase reaction to allergens
Controller medications	Control inflammatory and allergic responses that can decrease ability of air to flow through airways	Inhaled corticosteroid (ICS) (e.g. Flovent HFA)	<ul style="list-style-type: none"> Decrease inflammation Decrease airway hyper-responsiveness Block late-phase reaction to allergens
		Long-acting beta-adrenergic agonists (LABA) (e.g. salmeterol, formoterol)	<ul style="list-style-type: none"> Relax tight muscles around airways for at least 12 hours to help air flow (bronchodilation) Not monotherapy: Combine with ICS (e.g. Symbicort, Dulera) 12 years of age and older
		Leukotriene modifiers: leukotriene receptor antagonists (LTRAs: e.g. montelukast, zafirlukast)	<ul style="list-style-type: none"> Inhibit LTD₄ (montelukast) and LTE₄ (zafirlukast) receptor binding. LTD₄ causes smooth muscle contraction. LRTAs bronchodilate, decrease eosinophils and eosinophil-related inflammation. Adjunctive to ICS or alternative to ICS in select cases Work in exercise-induced bronchospasm
		Leukotriene modifiers: 5-lipoxygenase inhibitor (e.g. zileuton)	<ul style="list-style-type: none"> Inhibit 5-lipoxygenase and formation of leukotrienes (LTB₄, LTC₄, LTD₄, and LTE₄). The inhibition results in bronchodilation. Adjunctive to ICS or alternative to ICS in select cases
		Immunomodulators: monoclonal antibodies to IgE (e.g. omalizumab)	<ul style="list-style-type: none"> Prevent binding of IgE to receptors on basophils and mast cells Adjunctive- used if patient has sensitivity to allergens
		Mast cell stabilizers (e.g. cromolyn, nedocromil)	<ul style="list-style-type: none"> Stabilize cells; interfere w/ chloride channel function Alternative to preferred inhaled steroids Preventive therapy before exercise, unavoidable allergen exposure
		Xanthines (e.g. theophylline)	<ul style="list-style-type: none"> Relax airway muscles/bronchodilate Cause mild decrease in inflammation Adjunctive to ICS or alternative to ICS in select cases

Drug Utilization Review (DUR). The ongoing HFS DUR of asthma medications reveals overuse of rescue therapy and underutilization of first-line controller therapy (inhaled corticosteroids). In fiscal year 2013, pediatric HFS fee-for-service clients with asthma who frequented the Emergency Room more than once for asthma, used the following controller medications: 39% -inhaled corticosteroids alone, 17% - inhaled corticosteroid with a LABA, 42% - LTRA monotherapy, and the rest used only a xanthine, monoclonal antibody to IgE, 5-lipoxygenase inhibitor, or long-acting beta-agonist. Higher use of LTRAs (primarily montelukast) instead of first-line inhaled corticosteroids prompted DUR Board review of asthma guidelines and recently published literature for montelukast. Evidence-based clinical literature continues to support the use of inhaled corticosteroids as first-line controller therapy. The DUR Board recommended written provider education about the appropriate role of montelukast in the treatment of asthma based on guidelines.

Guidelines for managing asthma. Guidelines for the management of asthma have been published by the National Heart, Lung, and Blood Institute (NIH), and the Global Initiative for Asthma (GINA).^{1,2} A step-therapy approach is evident in both guidelines (**Table 2**). In the step therapy approach, treatments are added to current therapy if asthma remains uncontrolled. Guidelines advocate an inhaled corticosteroid as first line controller therapy for persistent asthma. Asthma control should be continuously assessed and after 6-12 weeks, step up therapy instituted if needed. After 3 months of stable asthma, step down to the lowest effective dose may be considered. The GINA guidelines provide step-down strategies.

Table 2. Asthma Treatment Guidelines from NIH and GINA ^{1,2}							
	AGE* (years)	Intermittent Asthma†	Persistent asthma: Daily controller medication‡ (Guideline recommendations are the same, except where NIH and GINA noted)				
Acute relief "rescue" Inhaler	All	SABA ≤ 2 days/ week or < 2 times/month					
			STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred First-line Controller Medication	NIH: 0-4 GINA: 0-5	If SABA for ≥3 wheezing episodes in a season or every 6-8 weeks. start controller medication ²	Low-dose ICS daily	ICS NIH: <i>Medium-dose</i> GINA: Double Low-dose (if budesonide or beclomethasone + formoterol, then low-dose ICS + formoterol)	NIH <i>Medium-dose</i> ICS AND LABA or LTRA	NIH <i>High-dose</i> ICS AND LABA or LTRA	NIH <i>High-dose</i> ICS AND LABA or LTRA AND OCS
	NIH: 5-11 GINA: 6-11	If SABA needed more than 2 times per week, or if risk of exacerbations, initiate controller medication ²		<i>Medium-dose</i> ICS NIH: OR <i>Low-dose</i> ICS AND LABA, LTRA, or Theophylline	<i>Medium-dose</i> ICS AND LABA	NIH: <i>High-dose</i> ICS AND LABA GINA: Refer for add-on omalizumab	NIH <i>High-dose</i> ICS AND LABA AND OCS
	12 and older	<i>Low-dose</i> ICS AND LABA NIH: OR <i>Medium-dose</i> ICS		GINA: OR <i>High-dose</i> ICS + LABA		NIH: <i>High-dose</i> ICS AND LABA AND omalizumab if allergies GINA: Refer for add-on anti-IgE therapy, or tiotropium (18+)	NIH <i>High-dose</i> ICS AND LABA AND OCS AND omalizumab if allergies
Alternative controller medication	NIH: 0-4 GINA: 0-5		LTRA OR NIH: Cromolyn GINA: <i>intermittent</i> ICS	GINA <i>Low-dose</i> ICS AND LTRA	GINA: higher ICS dose or frequency; Add LTRA, or <i>low-dose</i> OCS theophylline, intermit. ICS		
	NIH: 5-11 GINA: 6-11		LTRA OR <i>low-dose</i> theophylline NIH: OR Cromolyn, nedocromil	GINA: <i>Medium/high</i> dose ICS OR <i>low-dose</i> ICS AND LTRA	ICS dose: NIH <i>Medium</i> GINA: <i>High</i> AND LTRA or Theophylline	NIH: <i>High-dose</i> ICS AND LTRA or Theophylline GINA: add <i>low-dose</i> OCS	NIH <i>High-dose</i> ICS AND LTRA or Theophylline + OCS
	12 and older	GINA: Consider <i>low-dose</i> ICS		<i>Low-dose</i> ICS AND LTRA or theophylline OR NIH: Zileuton GINA: <i>medium-</i> or <i>high-dose</i> ICS instead	ICS dose: NIH <i>Medium</i> GINA: <i>High</i> AND LTRA or Theophylline OR NIH: Zileuton GINA: 18+yo: tiotropium	GINA: add <i>low-dose</i> OCS	

Abbreviations: *NIH=National Heart, Lung, and Blood Institute, GINA=Global Initiative for Asthma. † SABA=Short-acting beta-adrenergic agonist, EIB=Exercise-induced Bronchospasm, ICS= Inhaled corticosteroid. ‡ LTRA= leukotriene receptor antagonist, LABA= Long-acting beta-adrenergic agonists, OCS= oral corticosteroids; yo = years old, IgE=Immunoglobulin E.

A practice parameter to assist practitioners in managing the acute loss of asthma control in patients in the home setting was published by the Joint Task Force on Practice Parameters (JTF). Task Force members represent the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma, and Immunology.³ Patients with asthma are given Asthma Action Plans to help them manage their asthma between provider visits. Intermittent acute worsening of asthma is represented by the yellow zone on Asthma Action Plans signifying that asthma control is deteriorating and an intervention is needed. In terms of medication management, the yellow zone may be defined by symptoms that respond to one SABA treatment and recur in ≤ 4 hours. The intent of the Practice Parameter is to help manage deteriorating asthma in the yellow zone before the exacerbation progresses to the red zone in which urgent treatment with intravenous systemic corticosteroid therapy and nebulization in the Emergency Room, and/or, a hospitalization may be required. Of note, it may take 2 weeks of treatment to stabilize asthma after an acute worsening (yellow-zone episode). Recommendations for managing asthma exacerbations in the yellow zone from NIH and the JTF are noted in **Table 3**. Regular scheduled SABA use as the only treatment for yellow zone symptoms will not prevent progression to the red zone. This monotherapy may instead increase the risk of progression to the red zone. Each yellow zone episode may require a different amount of additional ICS to prevent progression to the red zone. The JTF practice parameter incorporates more current literature than the NIH guidelines to guide treatment choices in an evidence-based manner, even though some of their recommendations may be beyond FDA-approved package labeling (off-label). For example, the JTF recommendations for mild to moderate asthma are similar to the alternative Step 2 or 4 GINA guidelines, but the dynamic dosing and adjustable maintenance dosing regimens that incorporate the ICS-formoterol (LABA) combination inhalers may currently be considered off-label use in the United States.

Table 3. Managing Patients in the Yellow Zone of the Asthma Action Plan in the Home Setting[‡]		
Source*	Recommendation[†]	Recommendations for age or asthma severity
NIH Guideline¹	<ul style="list-style-type: none"> Increase SABA frequency Add short course of oral systemic corticosteroids Preliminary evidence: Quadruple ICS dose for 7 days	
Joint Task Force on Practice Parameters³	<ul style="list-style-type: none"> Activate yellow zone management of Asthma Action Plan at start of upper respiratory tract infection if this has been a trigger in the past. AND Use SABA 2 to 4 puffs every 4-6 hours during the exacerbation as needed <ul style="list-style-type: none"> If the SABA > 12 puffs per day: call provider Option: <ul style="list-style-type: none"> Increase low-moderate total daily dose of ICS over 24 hours to manage asthma control, for example, quadruple the total daily dose 	Child < 6 years old with recurrent wheezing and asthma risk factors
		High-dose ICS or LTRA at start of wheezing to decrease symptom intensity
		Mild to moderate asthma
		<ul style="list-style-type: none"> Symptom-driven use of ICS (dynamic dosing or adjustable maintenance dosing) SABA as needed
* NIH = National Heart, Lung, and Blood Institute. † SABA=Short-acting beta-adrenergic agonist, ICS= Inhaled corticosteroid. ‡ LTRA= leukotriene receptor antagonist.		

Role of montelukast, a LTRA. The first-line controller medication for all types of asthma is an inhaled corticosteroid (ICS). If consistent and dose-optimized use of first-line therapy is insufficient to control asthma, additional controller medications may be added. The role of LTRAs, including montelukast, appears limited to use in combination with or as an alternative to inhaled corticosteroids in certain patient age groups. Inhaled corticosteroids have demonstrated the most consistent efficacy in patients. Overall, unlike ICS, LTRA therapy has not demonstrated significant decreased frequency of hospitalizations, courses of prednisone, or number of asthma symptom-free days.²

What does the Department of Health and Family Services (HFS) expect for asthma care?

- Continuous asthma symptom evaluation to ensure appropriate step-up or step-down in therapy. Greater use of rescue therapy signals need to re-evaluate asthma type or severity.
- In addition to a rescue inhaler like albuterol, clients with persistent asthma should use step therapy.
- First-line ICS alone should be added and used regularly at an appropriate dose.
- If symptoms persist, despite optimal ICS dosing, consistent therapy adherence, and appropriate inhaler technique, higher doses and/or additional preferred controller medication may be added.
- Alternate therapies are less effective than ICS. On a case-by-case basis, HFS will consider LTRAs for asthma management after a sufficient therapeutic trial and adherence to preferred step therapy.

What can providers do for their patients with asthma?

- For patients with asthma, ask about asthma symptoms and rescue inhaler use at every visit, even if the patient presents for other complaints. All opportunities to reassess symptoms and progression to persistent asthma stages should be used. An Asthma Control Test or similar survey may aid in consistent symptom assessment.
- Ensure your patients have and understand the up-to-date Asthma Action Plan, so that they can help assess and manage their asthma symptoms before an exacerbation occurs resulting in Emergency room visits or hospitalizations. The Asthma Action Plan should be reviewed at every visit and adjusted as necessary. A sample Asthma Action Plan is available at <http://www.nhlbi.nih.gov/health/resources/lung/asthma-action-plan-html>.
- Educate your patient and their caregivers about their asthma, disease progression, preventive measures, and need to have a quick-relief medication with them at all times.
- Periodically check your patient's inhaler technique (with and without an inhalation spacer device if they are using one). HFS covers 2 spacer devices in a year if needed.
- Peak flow meters may be used at home for some patients to help assess their peak expiratory flow (PEF) and manage asthma symptoms. Meter results should correspond to green, yellow, and red zones in the patient's Asthma Action Plan. The peak flow meter may help patients correlate their symptoms with worsening or deteriorating asthma control. HFS covers peak flow meters.
- For maximal therapeutic effect, adhere to asthma guidelines' step therapy and treat underlying inflammation with ICS.
- Contact the patient's pharmacy and/or insurer to confirm therapy adherence before increasing doses or adding more controller medications (step-up therapy).
- Once asthma symptoms stabilize and are well controlled for at least 3 months, therapy should be adjusted (stepped down) to use the lowest effective medication doses of required therapy. For example, the ICS dose can be decreased 25% to 50% every 3 months if the patient's asthma remains stable. Step down therapy may help decrease adverse medication effects.

References:

1. National Heart, Lung, and Blood Institute (NHLBI). National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. 2007. Available at http://hp2010.nhlbihin.net/as_frameset.htm
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2016. Available at <http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention>
3. Dinakar C, Oppenheimer J, Portnoy J, et al. Management of acute loss of asthma control in the yellow zone: a practice parameter. Ann Allergy Asthma Immunology 2014 Aug; 113 (2):143-59. Available at http://aapdc.org/wp-content/uploads/2013/12/asthma-yellow-zone-parameter-8_2014-annals.pdf

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