

Guideline Update for the Diagnosis and Management of Asthma
National Asthma Education and Prevention Program
Expert Panel Report-3
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Introduction: According to the National Health Interview Survey conducted by the Centers for Disease Control and Prevention (CDC) in 2005, over 22 million persons are affected by asthma in the United States resulting in over 497,000 hospitalizations per year. Currently, it is one of the most common chronic diseases of childhood, with a prevalence of more than 6 million.¹ The National Asthma Education and Prevention Program (NAEPP) in collaboration with the National Heart Lung and Blood Institute (NHLBI) published the first Expert Panel Report (EPR-1) on the diagnosis and management of asthma in 1991.² The original report defined asthma as an inflammatory process with goals of minimizing symptoms, achieving normal lung function and activity levels, preventing exacerbations, as well as reducing the need for rescue agents.³ In 1997, EPR-2 was published followed by an update in 2002. The focus of these reports was the importance of early recognition and treatment of asthma in order to prevent loss of lung function over time.^{3,4} The revised guidelines (EPR-3) published in August 2007, reflect changes in clinical evidence regarding the pathophysiology and management of asthma since the previous guidelines were issued.

Key changes in EPR-3 include increased emphasis on assessing asthma control,

dividing pediatric treatment recommendations into two age groups, adjusting the role of long-acting beta₂-agonists (LABAs), and adding omalizumab (Xolair[®]) to some patient regimens.^{2,3,5}

Assessment of asthma severity and control: The EPR-1 defined asthma severity based on symptom frequency, limitations in activity, need for rescue therapy, and lung function. The severity classification was used to guide asthma treatment; however, it did not take into account the patient's response to the treatment or how well the recommended therapy controlled the patient's disease.³ The current guidelines emphasize the distinction between asthma severity and asthma control in assessment and treatment of patients.^{2,3} Severity according to EPR-3 is defined as "the intrinsic intensity of the disease process and the assessment used to initiate therapy".^{2,3} It is classified as intermittent or persistent. Persistent asthma is further classified into mild, moderate, or severe (refer to full EPR-3 Guidelines for differentiations). Control is defined as "the degree to which the manifestations of asthma severity (i.e., symptoms, functional impairments, and risks of untoward events) are minimized by treatment and the goals of therapy are met".^{2,3}

Table 1. Classification of Asthma Severity

Intermittent	Persistent		
	Mild	Moderate	Severe
Step 1	Step 2	Step 3 Or Step 4	Step 5 Or Step 6

Adapted from Expert Panel Report-3 2007.

Assessment of asthma severity and control (continued): Patients are classified as being well-controlled, not well-controlled, or very poorly-controlled (refer to full EPR-3 Guidelines for differentiations). Asthma severity and control can be divided further into two domains: current impairment of lung function and future longitudinal risks for exacerbations. Impairment is indicated by the frequency and intensity of symptoms and current or recent limitations in activity levels. Risk includes the likelihood of experiencing exacerbations or progressive lung dysfunction. Both impairment and risk must be considered when developing a treatment plan and when monitoring patient response.³

Pharmacologic management: Asthma progression is variable among patients and the disease course may change over time with age. As such the EPR-3, in contrast with the previous guidelines, divides asthma treatment recommendations into three age groups: 0-4 years, 5-11 years and ≥ 12 years.² These divisions are based on increased availability of clinical efficacy and safety data in children ≥ 5 years old, Food and Drug Administration (FDA)-approved age recommendations for appropriate medication use, age-related drug delivery issues, inability to obtain appropriate lung function measurements in younger age groups, and differences in wheezing phenotype based on age.^{3,5} In addition to dividing treatment recommendations into three age groups, other major pharmacotherapy changes in the EPR-3 include the expansion of treatment steps from four steps to six steps, giving equal weight to increasing to medium-dose inhaled corticosteroids (ICSs) or adding LABAs (e.g., formoterol [Foradil[®]] and salmeterol [Serevent[®]]) to low-dose ICSs in patients ≥ 5 years of age who are not adequately controlled on low-dose ICSs, and the addition of omalizumab therapy in allergic patients ≥ 12 years of age not controlled on high-dose ICSs in combination with LABAs.^{2,6,7}

A stepwise approach for the treatment of asthma has been implemented as in previous guidelines. Initial medication selection, doses, and frequencies are driven by asthma severity whereas adjustments in therapy should be based on asthma control and therapeutic response.² Previous guidelines contained four steps, with several progressive actions within each step. EPR-3 separates these actions and expands the management plan into six steps for simplicity. Step 1 is for those with intermittent asthma; Steps 2-6 are for those patients with persistent asthma requiring daily medications (See Table 1 and Figures 1-2). Regardless of age, the preferred first step of therapy is inhaled short-acting beta₂-agonists as needed and the preferred second step is low-dose ICSs. Inhaled corticosteroids are still the most potent and consistently effective long-term control agents.⁸ Step 3 includes increasing to medium-dose ICSs in all patients or using low-dose ICSs in combination with other agents such as LABAs in patients >4 years old. Patients categorized into Step 4 should receive medium doses of ICSs in combination with other agents. As one progresses into Steps 5-6, ICS doses are escalated and omalizumab should be administered in those patients ≥ 12 years old with allergies. Step 6 includes oral systemic corticosteroids for all age groups.^{2,7} In those who are poorly controlled, environmental exposures, inhaler technique and compliance, and comorbidities should be assessed prior to advancing to the next step of therapy.⁷ Patients not well controlled on their current daily long-term therapies should be advanced by one step. Clinicians should consider advancing patients who are very poorly controlled up two steps, administering a course of oral corticosteroids, or both.^{2,7} A short course of oral corticosteroids can help patients achieve quicker control, however, long-term corticosteroid therapy is warranted in those with severe persistent asthma.² Stepping down in order to determine the minimum number of medications needed to maintain asthma control may be considered in those patients who are well-controlled for at least 3 months.^{2,7} Even though steps and therapies have been delineated, regimens should be based on individual patient needs and responsiveness to therapy.⁷

The Step 3 debate – use of long-acting beta₂-agonists: In the 2002 EPR update, low-to-medium doses of ICSs in combination with LABAs were preferred in adults and children ≥ 5 years with moderate or severe persistent asthma as concomitant use results in improved lung function and asthma control compared to higher doses of ICSs alone. In children <5 years, recommendations included either the addition of LABAs to a low dose of ICSs or medium-dose ICSs as monotherapy.⁴ Since the publication of the 2002 EPR update safety issues with the use of LABAs have been raised. In the Salmeterol Multicenter Asthma Research Trial (SMART), the safety of salmeterol or placebo added to usual asthma care was evaluated. In an interim analysis there were small, but statistically significant higher rates of respiratory-related deaths (24 vs. 11, RR=2.16; CI 1.06-4.41), asthma-related deaths (13 vs. 3, RR=4.37, 95% CI 1.25-15.34) and combined asthma-related deaths or life-threatening experiences (37 vs. 22, RR=1.71; 95% CI 1.01-2.89) with salmeterol compared to placebo. These adversities were particularly high among African-American patients treated with salmeterol.⁹

Due to increased safety concerns with the use of these medications, the EPR-3 concludes that LABAs should not be used as monotherapy for long-term control in patients. However, LABAs should still be considered as adjunctive therapy in children ≥ 5 years old and adults with asthma inadequately controlled with low-dose ICSs. In these patients equal weight should be given to increasing the ICS dose as to the addition of LABA to a current ICS regimen. In patients with more severe persistent asthma (i.e., those requiring Step 4 management or higher), the EPR-3 still recommends the combination of LABAs and ICSs. Finally, it is noted that daily doses of LABAs should not exceed 100 mcg of salmeterol or 24 mcg of formoterol.²

The safety results from SMART and other LABA trials, resulted in black-box warnings and revisions to FDA-approved labeling for all products containing LABAs.^{5,10,11} In January 2008, the FDA requested manufacturers of all LABA-containing products submit controlled clinical trial data so that the safety of these agents in the treatment of asthma could be evaluated further.¹¹ Based on the data provided, at the time of this writing, FDA Advisors recommended formoterol and salmeterol no longer be used in the treatment of asthma. Advair[®], a combination of salmeterol and fluticasone, was still recommended since it is combined with an ICS to help reduce inflammation. A final recommendation from the FDA is pending.^{11,12}

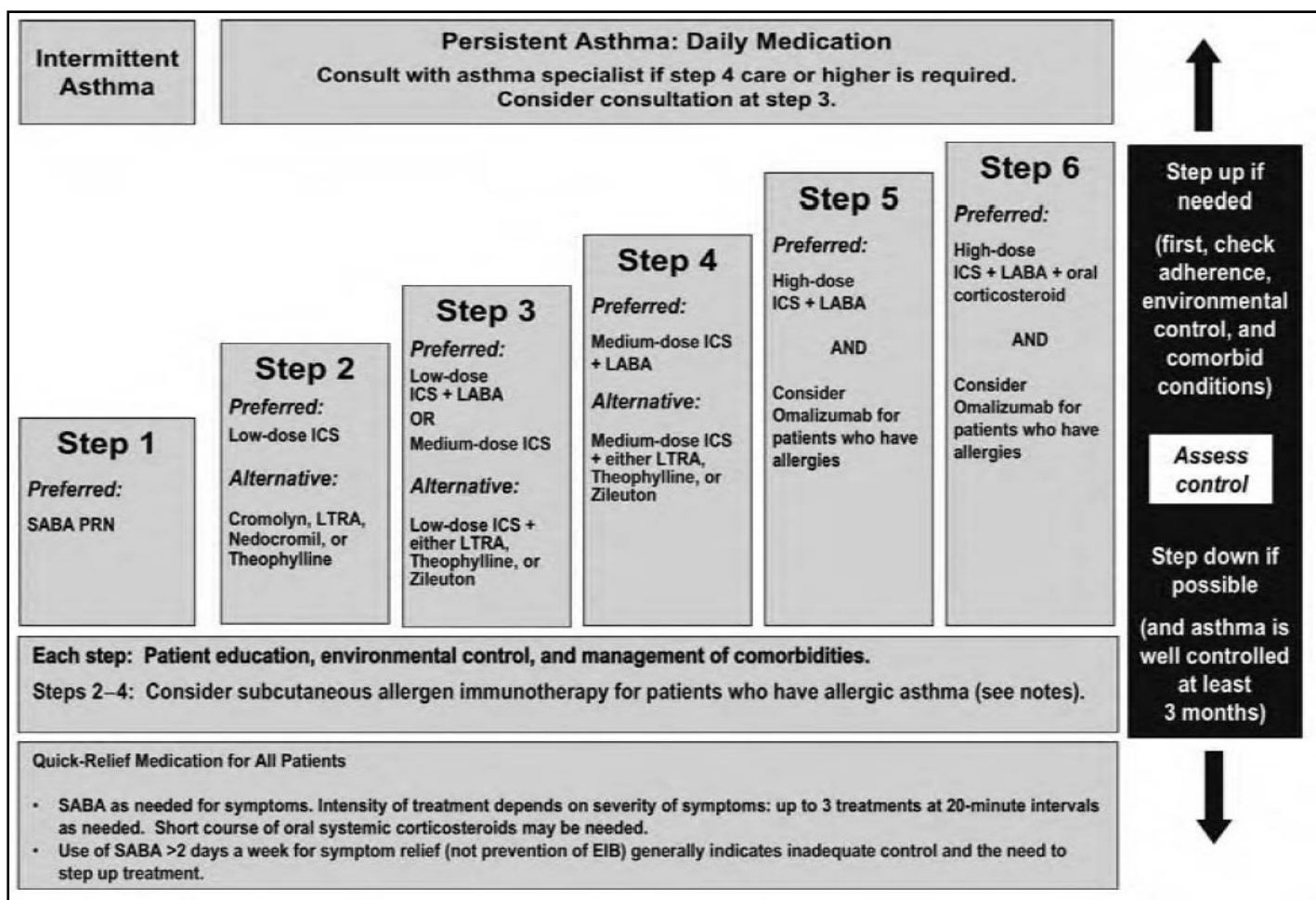
Figure 1: Stepwise Approach for Long-term Asthma Management in Children Aged 0-4 years and 5-11 years

		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Children 0-4 Years of Age		Intermittent Asthma	Persistent Asthma: Daily Medication				
			Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.				
	Preferred	SABA PRN	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + LABA or Montelukast	High-dose ICS + LABA or Montelukast	High-dose ICS + Oral corticosteroids + LABA or Montelukast
	Alternative		Cromolyn or Montelukast				
	Quick-Relief Medication	Each Step: Patient Education and Environmental Control <ul style="list-style-type: none"> SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms. With viral respiratory symptoms: SABA q 4-6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations. Caution: Frequent use of SABA may indicate the need to step up treatment. See text for recommendations on initiating daily long-term-control therapy.					
Children 5-11 Years of Age		Intermittent Asthma	Persistent Asthma: Daily Medication				
			Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
	Preferred	SABA PRN	Low-dose ICS	Low-dose ICS + LABA, LTRA, or Theophylline	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA + Oral corticosteroids
	Alternative		Cromolyn, LTRA, Nedocromil, or Theophylline	Medium-dose ICS	Medium-dose ICS + LTRA or Theophylline	High-dose ICS + LTRA or Theophylline	High-dose ICS + LTRA or Theophylline + oral corticosteroids
	Quick-Relief Medication	Each Step: Patient Education, Environmental Control, and Management of Comorbidities <p>Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.</p> <ul style="list-style-type: none"> SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed. Caution: Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.					

Adapted from Expert Panel Report-3 2007.

Omalizumab: The immunomodulator, omalizumab (Xolair[®]), is a recombinant, human monoclonal antibody which prevents IgE from binding to high-affinity IgE (FcεRI) receptors on mast cells and basophils, resulting in a decreased release of inflammatory mediators in response to allergens. It also decreases the number of IgE receptors on basophils and airway submucosal cells. It is FDA-approved for moderate-to-severe persistent asthma in adults and children ≥12 years old who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.^{5,13} The EPR-3 however recommends omalizumab as adjunctive therapy in Steps 5 or 6 for patients with allergies and severe persistent asthma uncontrolled with a combination of medium-dose ICSs and LABAs.^{2,5}

Figure 2: Stepwise Approach for Long-term Asthma Management in Patients Aged ≥12 years



Adapted from Expert Panel Report-3 2007.

Omalizumab (continued): This recommendation is based on data from two trials in patients with severe persistent asthma who were inadequately controlled with combination ICS and LABA therapy. The addition of omalizumab to these patients' regimens resulted in reduced asthma exacerbations and decreased emergency department visits.^{2,14,15} Omalizumab has not been compared to other adjunctive therapies (i.e., LABAs, leukotriene modifiers, and theophylline) in the treatment of moderate persistent asthma, however, all have been found to improve outcomes and permit reductions in doses of ICSs.² Furthermore, omalizumab is the only adjunctive therapy shown to have additive efficacy benefits when combined with high-dose ICSs plus LABAs in the treatment of severe persistent asthma.^{2,15} Omalizumab 150 mg to 375 mg should be administered subcutaneously every 2 or 4 weeks. Adjustments in dose and dosing frequency are based on baseline serum IgE levels and body weight. Anaphylaxis has been reported in 0.2% of patients who have received omalizumab, resulting in a black-box warning in product labeling. Most reactions occur within 2 hours of administration but have occurred several hours after administration. In addition, some reactions occurred after the first injection whereas others have occurred beyond 1 year of receiving regular doses of omalizumab. As such, clinicians should be prepared to treat anaphylaxis at any time and patients should be counseled on the signs and symptoms of anaphylaxis and the need to seek immediate medical attention if warranted. Omalizumab use has also been associated with an increased frequency of malignancies vs. placebo (0.5% vs. 0.2%, respectively).^{2,13}

Conclusion: EPR-3 continues to emphasize many concepts from EPR-1 and -2 and incorporates new recommendations based on the breadth of literature published about the pathophysiology of the disease and its pharmacologic management since the last update. By focusing on asthma control, clinicians are better able to tailor therapy based on an individual's needs. A better understanding of asthma processes in children and emerging data on the use and effects of varying asthma therapies in this patient population have resulted in the development of pediatric-specific treatment recommendations. New safety concerns with LABAs have resulted in alternative therapy recommendations. Finally, the availability of omalizumab, a new allergen immunotherapy, offers an additional option for those patients whose asthma is difficult to control. These new concepts in combination with increased assessment and monitoring, patient education, and control of environmental factors and other conditions that can affect asthma can help achieve the best possible management of asthma in both adults and children.²

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Did You Know...

Albuterol Hydrofluoroalkane (HFA)-Propelled Inhaler Transition

As part of the Montreal Protocol on Substances that Deplete the Ozone Layer the US has agreed to cease the production and importation of ozone-depleting substances such as chlorofluorocarbons (CFCs). As part of this commitment CFC-propelled albuterol metered-dose inhalers (MDIs) will no longer be produced, marketed, or sold in the US after December 31, 2008. All patients receiving albuterol CFC inhalers will need to be transitioned to ozone-safe hydrofluoroalkane (HFA)-propelled albuterol MDIs.

There are three HFA-propelled albuterol inhalers currently available on the market (See Table 1). Each actuation of an albuterol HFA inhaler delivers the same dose of albuterol (i.e., 90 mcg/actuation) as an albuterol CFC inhaler and is used in the same manner. Although each HFA inhaler comes in a different size, each contains 200 actuations. Patients should be counseled that HFA inhalers may taste differently and the force of the spray from an HFA-propelled inhaler may feel softer and less forceful than that of a CFC-propelled inhaler. Patients may need assurance these differences do not alter the HFA inhaler's effectiveness. In addition, patients should be advised to clean their albuterol HFA actuators under warm running water at least once a week to prevent clogging and follow each product's specific recommendations for appropriate priming methods.

Generic formulations of albuterol HFA inhalers are not currently available; therefore, these inhalers are more expensive than their generic albuterol CFC inhaler counterparts (See Table 1). Individual manufacturers may offer Patient Assistance Programs or discount coupons/cards for their HFA inhalers. Please refer to manufacturers' websites for current discount programs (see Table 1). In addition, Cleveland Clinic Pharmacies offer vouchers for one free Proventil® HFA MDI through their Virtual Samples Program (located at <http://pharmacy.ccf.org/virtualsamples/>).

Patients that purchased albuterol CFC inhalers prior to December 31, 2008, may continue using them until they are gone; however, new prescriptions and refills obtained after December 31, 2008, will be filled with albuterol HFA inhalers.

Table 1: Albuterol HFA Inhalers

Product	Manufacturer	Size	Average Wholesale Price
Generic Albuterol CFC MDI	N/A	17 g	\$29.00
Proventil® HFA MDI	Schering-Plough	6.7 g	\$42.20
Ventolin® HFA MDI	GlaxoSmithKline	18 g	\$37.60
ProAir® HFA MDI	Teva Specialty	8.5 g	\$36.70

Formulary Update

The CC Pharmacy and Therapeutics Committee met at the end of September 2008, and the following decisions were made:

Additions:

1. **Alvimopan (Entereg[®]):** It is FDA-approved to accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis. Alvimopan is a selective opioid antagonist with limited oral absorption and does not cross the blood brain barrier. The recommended dose is 12 mg orally 30 minutes to 5 hours prior to surgery followed by 12 mg orally twice a day beginning the day after surgery for a maximum of 7 days. Patients should receive no more than 15 doses. Alvimopan is for hospital use only. **Its use is restricted to Staff Physicians from the Department of Colorectal Surgery.**
2. **Regadenoson (Lexiscan[®]):** It is FDA-approved for radionuclide myocardial perfusion imaging in patients unable to undergo adequate exercise stress. It may be associated with less risk of AV block and bronchospasm compared to adenosine, but has demonstrated similar overall tolerability as adenosine. Regadenoson is administered as a rapid IV injection, rather than an IV infusion and a lack of weight-based dosing may simplify administration.
3. **Certolizumab (Cimzia[®]):** It is FDA-approved for patients with moderate-to-severe Crohn's Disease and is a TNF inhibitor. Prior to patients being initiated on certolizumab therapy, they must have a TB test. During therapy, patients should be monitored for signs and symptoms of infection, clinical response, and signs and symptoms of TB. The recommended initial adult dose is 400 mg (given as two subcutaneous injections of 200 mg), and then the 400 mg is repeated at Weeks 2 and 4. In patients who obtain a clinical response, the recommended maintenance dose is 400 mg subcutaneously every 4 weeks. **Its use is restricted to the Department of Gastroenterology for outpatient use only.**
4. **Tenofovir (Viread[®]):** It is on the Formulary, however, it now can be prescribed for chronic hepatitis B patients. For this indication, **its use is restricted to the Department of Gastroenterology/Hepatology for initiation of therapy only.**
5. **Adalimumab (Humira[®]):** It is added to the Formulary, but **its use is restricted to pediatric patients with refractory Crohn's disease.**

Changes for Formulary Restrictions:

1. **Eptifibatide (Integrilin[®]):** Staff Physicians from NeuroInterventional Radiology may prescribe eptifibatide for acute ischemic stroke. More specific guidelines will be developed for dosing and administration (e.g., guidelines for use).

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