



VA/DoD Clinical Practice Guideline for Management of Asthma in Children and Adults

STEP CARE Medication For Long-Term Control

Initial Severity	Use of Quick relief ^[b]	Activity limits	Symptoms		FEV1	Daily Medications ^[a]	
			Day	Night		Preferred	Alternative
Step 1 Intermittent	≤ 2 days/week	NONE	< 2 days/week	≤ 2x/month	> 80%	SABA PRN	--
Step 2 Mild	> 2 days/week not daily	Minor limitation	> 2 days/week not daily ^[c]	> 2x/month	> 80%	Low-dose ICS	--
Step 3 Moderate	Not more than once a day	Minor limitation	> 2 days/week not daily ^[c]	> 1x/week not nightly	60-80%	Age 0-4: Medium-dose ICS or Low-dose ICS +LTRA	--
						Age ≥ 5 to Adult: Low-dose ICS + LABA or Medium-dose ICS	Low-dose ICS + LTRA
Step 4 Severe	Daily	Some limitations	Daily ^[c]	Nightly	< 60%	Age 0-4: Medium-dose ICS + LTRA	Consider referral to specialist
						Age ≥ 5 to Adult: Medium-dose ICS + LABA	Medium-dose ICS + LTRA
Step 5 Severe	Several times a day	Extremely limited	Throughout the day ^[c]	Nightly	< 60%	Age 0-4: Medium-dose ICS + LABA + LTRA	Refer to specialist
						Age ≥ 5 to Adult: High-dose ICS + LABA Consider oral corticosteroids	Medium-dose ICS + LABA + LTRA Consider referral to specialist
Step 6 Severe	Several times a day	Extremely limited	Several times a day ^[c]	Nightly	< 60%	Age 0-4: High-dose ICS + LABA + LTRA (Consider 5-10 day course of oral corticosteroids)	Refer to specialist
						Age ≥ 5 to Adult: High-dose ICS + LABA + oral corticosteroids	High-dose ICS + LABA + LTRA Refer to specialist

[a] Every step: Patient education, environmental control, and management of co-morbidities.
 Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.
 Steps 4-6: Consider referral to specialist for evaluation and/or management.
 Steps 5-6: Consider Omalizumab for patients with allergies and elevated IgE.

[b] Quick-relief medications for all patients:
 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.

[c] More than 2 exacerbations per year (requiring oral systemic steroids) should prompt step up in therapy

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

Medication

Table 1: Drugs Used in Treatment of Asthma

Drug Class§	Uses	Cautions and Monitoring‡
<p><u>Inhaled Corticosteroids (ICS)</u></p> <p>Beclomethasone Budesonide Ciclesonide Flunisolide* Fluticasone Mometasone Triamcinolone*</p> <p>(See Table 2 for Dosage)</p> <p>*CFC MDIs are being phased out and will no longer be available in the near future</p>	<p>Considered first line agents for maintenance treatment of asthma</p>	<ul style="list-style-type: none"> • Local adverse effects include oral candidiasis, dysphonia, and reflex cough/bronchospasm <ul style="list-style-type: none"> ○ Use of a spacer or holding chamber (for non-breath activated inhalers) and rinsing mouth after inhalation can reduce the incidence of oral candidiasis ○ Use of a spacer or holding chamber (for non-breath activated inhalers) is used as a measure to prevent dysphonia. To treat dysphonia, temporarily reducing the dose of ICS, or rest for vocal stress has been used ○ Use of a spacer or holding chamber (for non-breath activated inhalers), slower inspiration, or pretreatment with a SABA may be tried for reflex cough/bronchospasm • Higher doses have been associated with adrenal suppression, glaucoma, cataracts, skin thinning, and bruising • High dose may increase the risk of developing osteoporosis • Smoking may decrease the effectiveness of ICS; regardless, patients with asthma should be encouraged to stop smoking
<p><u>Short-acting Beta-agonists (SABA)</u></p> <p>Albuterol Levalbuterol Pirbuterol</p> <p><u>Long-acting Beta-agonists (LABA)</u></p> <p>Formoterol Salmeterol</p> <p>Note: Formoterol and arformoterol are available in a nebulizer solution approved for maintenance therapy for COPD; at present, they are not approved for use in asthma.</p>	<p>Short-acting agents are used for acute relief of bronchospasm and prevention of exercise-induced bronchospasm</p> <p>Long-acting agents are used as the preferred add-on agents to inhaled corticosteroid</p>	<ul style="list-style-type: none"> • May cause palpitations, chest pain, rapid heart rate, increased blood pressure, tremor, nervousness • Decreases in potassium levels or hyperglycemia have occurred • Frequent use of SABA (>2 days/week) may indicate uncontrolled asthma and the need to intensify maintenance drug therapy • 2 to 6 puffs of SABA may be used in accordance with the asthma action plan. Patients who do not experience relief after 3 doses in a one hour period OR who need a dose more frequently than every 4 hours should seek medical care • Long-acting beta-agonists are CONTRAINDICATED AS MONOTHERAPY for maintenance treatment of asthma. If a long-acting beta-agonist is used, an inhaled steroid must also be prescribed and used by the patient on a daily basis • Long-acting beta-2 agonist are not to be used for the acute treatment of bronchospasm • Formoterol: Capsules are for oral inhalation only (capsules should not be swallowed). Administer using supplied inhalation device (Aerolizer) only

Drug Class§	Uses	Cautions and Monitoring‡
<p><u>Combination ICS/LABA</u></p> <p>Budesonide/formoterol</p> <p>Fluticasone/salmeterol</p>		<ul style="list-style-type: none"> • See comments for inhaled corticosteroids and beta-agonists
<p><u>Leukotriene Modifiers</u></p> <p>Montelukast</p> <p>Zafirlukast</p> <p>Zileuton extended-release</p>	<p>Monotherapy may be considered as an alternative (not preferred) to ICS for mild persistent asthma</p> <p>May be used as an alternative (not preferred) to a LABA for add on therapy to ICS</p> <p>Montelukast may be used for prevention of exercise-induced bronchospasm (zafirlukast and zileuton are not FDA approved)</p>	<ul style="list-style-type: none"> • Rare cases of Churg-Strauss have occurred with montelukast and zafirlukast; however, the association is unclear • Zafirlukast should be taken at least 1 hour before or 2 hours after meals due to decreased bioavailability when taken with meals. • Zafirlukast and zileuton can inhibit the metabolism of warfarin. INRs should be monitored during co-administration • Zileuton can inhibit the metabolism of theophylline; therefore, monitoring of theophylline levels is recommended • Zileuton is contraindicated in patients with active liver disease or persistent hepatic function enzyme elevation (> 3x ULN) • Assess hepatic function enzymes prior to initiation of zileuton, monthly for the first 3 months, every 2-3 months for the remainder of the first year, and periodically thereafter • Postmarketing surveillance of zafirlukast has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation. Consider periodic hepatic enzymes (ALT) monitoring • Patients and providers should be aware of the potential for neuropsychiatric events (e.g., suicidal ideation, depression, agitation, aggression, anxiousness, irritability, restlessness, dream abnormalities, hallucinations, and insomnia) with these medications. Patients should be told to contact their healthcare provider if these events occur. Consider discontinuing these medications if patients develop neuropsychiatric symptoms
<p><u>Mast cell stabilizer</u></p> <p>Cromolyn Nebulizer solution</p> <p>Note: Cromolyn is no longer available as a MDI</p>	<p>Monotherapy may be considered as an alternative (not preferred) to ICS for mild persistent asthma.</p> <p>May be used for prevention of exercise-induced bronchospasm; however, generally not as effective as SABA</p>	<ul style="list-style-type: none"> • Generally well tolerated although may cause coughing and wheezing • Improvement can occur in 1-2 weeks; however, maximal benefit may not be seen for 4-6 weeks • Needs to be dosed four times daily (may be reduced to three times daily once symptoms have stabilized) • Cromolyn is no longer available as a MDI; therefore, limiting the usefulness of this agent

Drug Class§	Uses	Cautions and Monitoring‡
<p><u>Methylxanthines</u></p> <p>Theophylline</p> <p>Aminophylline</p>	<p>May be considered as an alternative for maintenance of mild persistent asthma when other preferred options have not been successful</p> <p>May be considered as an adjunctive therapy with ICS for maintenance of moderate or persistent asthma.</p>	<ul style="list-style-type: none"> • Monitor theophylline levels. The usual therapeutic range is 5-15mcg/mL but some toxicity may be noted at the upper end of this range. • Adverse reactions include stomach upset, nausea, insomnia, tremors, palpitations, and irritability which may be lessened by initiating the dose low and increasing gradually • Serious adverse events including cardiac arrhythmias and seizures can occur at higher concentrations • Instruct patient not to take extra doses of theophylline for acute asthma attack. • Sustained-release products should not be crushed or chewed. • Scored tablets may be split without affecting absorption characteristics • Several drugs or other factors can influence theophylline concentration (list not intended to be inclusive of all interactions) <ul style="list-style-type: none"> ○ Drugs or factors decreasing theophylline clearance: cimetidine, ciprofloxacin, clarithromycin, disulfiram, enoxacin, erythromycin, mexiletine, pentoxifylline, propranolol, ticlopidine, troleandomycin, zileuton, allopurinol (≥ 600 mg/day), fluvoxamine, interferon, propafenone, tacrine, verapamil, congestive heart failure, cor pulmonale, elderly (> 60 yrs.), hepatic insufficiency (cirrhosis, acute hepatitis, cholestasis), fever (> 24 hrs.) ○ Drugs or factors increasing theophylline clearance: charcoal-broiled food; low carbohydrate, high protein diet; smoking (tobacco or marijuana); phenobarbital; phenytoin; rifampin, carbamazepine; isoniazid; moricizine
<p><u>Immunomodulators anti-IgE</u></p> <p>Omalizumab</p>	<p>Used as adjunctive therapy for severe persistent asthma (Step 5 or 6) who have a positive skin test or <i>in vitro</i> reactivity to a perennial aeroallergen</p>	<ul style="list-style-type: none"> • Not to be used in patients who have had a prior allergic reaction to omalizumab • Patient should have pre-treatment serum IgE 30-700IU/ml and positive skin test or <i>in vitro</i> reactivity to common aeroallergen (e.g., dust mites, pet dander, cockroach) • Give patient the omalizumab Medication Guide and instruct them to read it before each dose of omalizumab • Educate patient on signs and symptoms of severe hypersensitivity and anaphylaxis • Patients should carry and know how to initiate emergency self-treatment for anaphylaxis • Observe patients for an appropriate amount of time after each injection. In clinical trials, patients were observed for 2 hours after the 1st dose and 1 hour for subsequent doses. • Healthcare professionals should be prepared to manage life-threatening anaphylaxis • If a severe hypersensitivity reaction occurs, omalizumab should be discontinued

§ Refer to product package insert or other established resources for dosing recommendations and age specific use

‡ Table is not intended to be inclusive of all cautions and monitoring, but rather to highlight some of the major points

Table 2: Inhaled Steroids ^{a,b}

Inhaled steroid (dose/puff)	Dosage forms	Usual dosing interval	Low dose mcg/day ^c	Medium dose mcg/day ^c	High dose mcg/day ^c	PC
Beclomethasone 40mcg 80mcg	MDI (HFA)	12h	≥12 yrs 80-240 5-11yrs 80-160	≥12 yrs >240-480 5-11 yrs >160-320	≥12 yrs >480 5-11yrs >320	C
Budesonide 200mcg (delivered dose 160mcg) 90mcg (delivered dose 80mcg) 180mcg (delivered dose 160mcg) Budesonide suspension 0.25, 0.5, 1mg/2mL ampule Must use with PARI nebulizer or other high-efficiency nebulizer	DPI Nebulizer	12h 24h or 12h	≥12 yrs 200-600 5-11 yrs 180-400 5-11 yrs 0.5 0-4 yrs 0.25-0.5	≥12 yrs >600-1200 5-11 yrs >400-800 5-11 yrs 1.0 0-4 yrs >0.5-1.0	≥12 yrs >1200 5-11 yrs >800 5-11 yrs 2.0 0-4 yrs >1.0	B
Ciclesonide 80mcg 160mcg	MDI (HFA)	24h	≥12 yrs 80-160	≥12 yrs >160-320	≥12 yrs >320-1280	C
Flunisolide ^e 250mcg	MDI (CFC)	12h	≥12 yrs 500-1000 5-11 yrs 500-750	≥12 yrs >1000-2000 5-11 yrs >750-1250	≥12 yrs >2000 5-11 yrs >1250	C
Fluticasone (MDI/DPI) 44mcg /50mcg 110mcg /100mcg 220mcg/250mcg	MDI (HFA) DPI	12h	≥12 yrs 88-264 0-11 yrs 88-176	≥12 yrs >264-440 0-11 yrs >176-352	≥12 yrs >440 0-11 yrs >352	C
Mometasone 220mcg (delivered dose 200mcg) 110mcg (delivered dose 110mcg) ^d	DPI	24h or 12h	≥12 yrs 200	≥12 yrs 400	≥12 yrs >400	C
Triamcinolone ^e 100mcg (delivered dose 75mcg)	MDI with built-in spacer (CFC)	6-8h or 12h	≥12 yrs 300-750 5-11 yrs 300-600	≥12 yrs >750-1500 5-11 yrs >600-900	≥12 yrs >1500 5-11 yrs >900	C

PC = Pregnancy Category

^a Comparative daily doses adapted from the Global Initiative for Asthma 2007 and NHLBI Guidelines for the Diagnosis and Management of Asthma (EPR-3).^b For dosing recommendations, refer to the manufacturer's product package insert.^c Doses for budesonide suspension shown in mg.^d Dose of mometasone for children is 110mcg once daily.^e CFC MDIs are being phased out and will no longer be available in the near future.