

The background features a collage of four photographs. The top-left photo shows a male doctor in a white coat writing on a notepad. The top-right photo shows a smiling family of three. The bottom-left photo shows a female doctor in a white coat looking at a laptop. The bottom-right photo shows a female doctor in a white coat holding a young child.

**Clinical Guidelines
For the
Management of Asthma**

Management of Asthma

SCOPE:

Schaller Anderson's guideline includes portions of the Stepwise key concepts listed in the Executive Summary of the National Asthma Education and Prevention Program (NAEPP) 2002 Update. A 2004 update on Asthma in Pregnancy is available, as well as the 2003 Guideline and Action Steps for providing quality asthma care.

Internet address: <http://www.nhlbi.nih.gov/health/prof/lung/asthma/asthmacare.pdf>

These guidelines are distributed under a quality improvement/utilization management program in order to identify criteria for appropriate and effective use of health care services and consistency in the care provided to plan enrollees. The guidelines are not intended to: (i) supplant the duty of a qualified health professional to provide treatment based on the individual needs of a patient; (ii) constitute procedures for or the practice of medicine by the party distributing the guidelines; or (iii) guarantee coverage or payment for the type or level of care proposed or provided.

DEFINITION:

Asthma is a chronic inflammatory disorder characterized by recurrent episodes of airway obstruction that are reversible either spontaneously or in response to treatment. Eosinophils, mast cells, epithelial cells, macrophages and T and B lymphocytes all play a key role. These cells secrete a wide variety of cell-derived mediators leading to airway inflammation, which can influence airway function. These mediators, irrespective of the age of onset, produce chronic inflammation that may, over time, result in airway remodeling, irreversible airflow obstruction and accelerated decline in lung function.

THERAPY:

Key to managing asthma is control of airway inflammation. This can be achieved by environmental measures such as avoidance of inflammatory triggers, including viral infections, airborne irritants (smoke, volatile fumes, dust) and, in allergic individuals, aeroallergens, as well as through use of anti-inflammatory agents, preferably via inhaled administration. Short acting bronchodilators are to be used on a short-term basis ONLY to control acute symptoms. Current therapy has been enhanced with the introduction of inhaled corticosteroids (ICS), long-acting beta agonists (LABA) and leukotriene receptor antagonists (LTRA) in recent years. Formulations of these drugs to treat young children, older children and adults have helped to successfully manage this chronic condition. Delays in managing the underlying chronic inflammatory processes are to be avoided.²

Evaluating and managing very young children poses significant challenges. While recurrent cough and/or wheezing are common among young children, pulmonary function testing is not generally available to the primary care provider. Distinguishing young children with wheezing primarily in response to viral infections from those destined to have continued wheezing and later develop asthma is extremely difficult. The Asthma Predictive Index (API)³ provides a means to assess such children for risk of wheezing under age six, and can help guide therapeutic decisions regarding institution of ICS in this challenging patient population. Major (physician diagnosis of asthma or allergic rhinitis) and minor criteria (physician diagnosis of eczema, eosinophilia and wheezing without a URI) predict future development of asthma. Such children may benefit from initiation of ICS therapy.⁴ This index has a positive predictive value of 59% and negative predictive value of 86-94%. (From Castro-Rodriguez et al. Am J Respir Crit Care Med 2000;162:1403-1406.)

When B-agonists or ICS are deemed appropriate for young children, administration via nebulizer and via metered dose inhaler with a holding chamber appear to be at least equally efficacious with perhaps better effect (for B-agonists at least) using the latter.⁵

Self-management interventions, including written action plans, have been found useful in adults, and have resulted in reduced emergency department visits, reduced hospitalization rates and improved lung function. These plans can be used with children as well, to assist families and treating physicians in coordination of care of this serious chronic process.

Evidence of the Effectiveness of Inhaled Corticosteroids

Inhaled corticosteroids are the most effective chronic anti-inflammatory therapy for asthma in both adults and children. This is especially true in children where this modality is the preferred treatment for all 3-severity levels (mild, moderate, and severe) of persistent asthma. With the availability of nebulized corticosteroids, these medications can now be safely used in young children. The longer asthma and its underlying chronic inflammation are left untreated the more negative the impact on pulmonary function. While effective in both improving lung function and reducing symptoms, and attractive because of once daily oral dosing, LTRAs are not as effective as ICS.⁶ For this reason, ICS are listed as preferred initial therapy in the NAEPP Guidelines.

As in any therapy, it is appropriate to use the lowest dose of ICS necessary to achieve adequate control of airway inflammation and symptoms. Fortunately for ICS, the greatest therapeutic effect is seen at lower doses (generally > 200 ng/day of either fluticasone or budesonide) while side effects remain low until higher doses (400-800 ug/day) are reached.^{7,8} For obvious reasons, concern over potential side effects has been particularly high regarding use of ICS in children. Fortunately, studies to date have shown that while there may be transient slowing of growth velocity in the first six months following institution of ICS therapy, there is little if any effect of ICS on final height attainment, no decrease in bone mineral density, and no significant adrenal suppression after prolonged use of ICS at doses below 400 ug/day.^{9,10} Regardless, any patient, child or adult, who seems to require daily doses of ICS, either as a single agent or in combination with LABA or LTRA, in excess of 400 ug/day should be evaluated by an asthma specialist.

Combination Therapy

For patients with moderate persistent or severe persistent asthma, combination therapy has been shown to provide superior control as compared to a simple increase in ICS dose.¹¹ NAEPP Guidelines list addition of LABA to ICS as preferred therapy; addition of an LTRA is an alternative. As with studies comparing ICS with LTRA, studies of combination therapy using ICS with LTRA versus ICS with LABA show efficacy for both, but greater efficacy for the ICS/LABA combination.¹² Efficacy has been shown for both fluticasone/salmeterol and budesonide/formoterol combinations, suggesting that the efficacy of ICS/LABA is a class effect and not specific to individual agents.

Omalizumab

Omalizumab (Xolair™) is a humanized murine monoclonal antibody directed against the high-affinity IgE receptor-binding region of the IgE molecule. It has been shown to reduce symptoms and improve quality of life in asthmatics with elevated levels of serum IgE. It also may allow a reduction in dose of ICS. It is currently FDA-approved for individuals > 12 years of age with total serum IgE levels of 30-700. Because of its cost and its administration by injection, use of omalizumab should be restricted to patients who fail to achieve adequate control while adherent to combination therapy or who require high dose ICS therapy and experience or are at increased risk for side effects.¹³

COMMENTS ON RECENT UPDATES FOR ADULTS WITH ASTHMA:

Long acting beta agonists such as salmeterol (Serevent®) are replacing older adjunctive therapies such as theophylline. In addition, the early introduction of inhaled corticosteroids for mild persistent asthma is emphasized. Controlled studies support written self-management plans based on respiratory symptoms or peak flow readings with the goal of reducing outpatient morbidity. Smoking cessation advice given in structured form has been useful in reducing smoking in adults.¹⁴

PREGNANCY AND ASTHMA:

Changes in peak flow readings or FEV₁ function in pregnant females are due to changes in asthmatic condition and not to the underlying pregnancy. Strict attention must be paid to proper levels of maternal PO₂, as a small decrease can lead to significant drops in fetal oxygenation. The use of inhaled short acting beta₂agonists, inhaled corticosteroids such as budesonide or fluticasone are of value and have not been associated with adverse pregnancy outcomes. Leukotriene inhibitors have been studied minimally in pregnancy. There is a somewhat higher risk for decreased fetal weight gain and preeclampsia in patients taking prednisone at doses in excess of 10 mg daily. Oral steroids can also have an adverse effect on gestational diabetes. Poorly controlled asthma can lead to increased incidence of cesarean delivery and is a greater risk to the fetus than are asthma medications.¹⁵

The Stepwise Concepts from the NAEPP expert panel are presented in the following pages.

1. Managing Infants and Young Children (5 years of age and Younger) with Acute or Chronic Asthma.
2. Managing Asthma in Adults and Children Older than 5 Years of Age
3. Usual Dosage for Long Term Control Medications

Stepwise Approach for Managing Asthma in Adults and Children ⁽¹⁾

Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) with Acute or Chronic Asthma

Classify Severity: Clinical Features Before Treatment or Adequate control		Medications Required to Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	Daily Medications
Step 4 Severe Persistent	Continual Frequent	<ul style="list-style-type: none"> Preferred treatment: <ul style="list-style-type: none"> - High-dose inhaled corticosteroids AND - Long-acting inhaled beta₂-agonists AND, if needed <ul style="list-style-type: none"> - Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids)
Step 3 Moderate Persistent	Daily > 1 night/week	<ul style="list-style-type: none"> Preferred treatments <ul style="list-style-type: none"> - Low-dose inhaled corticosteroids and long-acting inhaled beta₂-agonists OR - Medium-dose inhaled corticosteroids Alternative treatment: <ul style="list-style-type: none"> - Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline <p>If needed (particularly in patients with recurring severe exacerbations):</p> <ul style="list-style-type: none"> Preferred treatment: <ul style="list-style-type: none"> - Medium-dose inhaled corticosteroids and long-acting beta₂-agonists Alternative treatment: <ul style="list-style-type: none"> - Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline
Step 2 Mild Persistent	> 2/week but < 1x/day ≤ 2 nights/month	<ul style="list-style-type: none"> Preferred treatment <ul style="list-style-type: none"> - Low-dose inhaled corticosteroid (with nebulizer or MDI with holding chamber with or without face mask or DPI). Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> - Cromolyn (nebulizer is preferred or MDI with holding chamber) OR leukotriene receptor antagonist
Step 1 Mild Intermittent	> 2 days/week ≤ 2 nights/month	<ul style="list-style-type: none"> No daily medication needed

Quick Read
All Patients

- Bronchodilator as needed for symptoms. Intensity of treatment will depend upon severity of exacerbation.
 - Preferred treatment: Short-acting inhaled beta₂-agonists by nebulizer or face mask and spacer/holding chamber
 - Alternative treatment: Oral beta₂-agonists
- With viral respiratory infection
 - Bronchodilator q 4-6 hours up to 24 hours (longer with physician consult); in general, repeat no more than once every 6 weeks
 - Consider systemic corticosteroid if exacerbation is severe or patient has history of previous severe exacerbations
- Use of short-acting beta₂-agonists > 2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.



Step Down

Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.



Step Up

In control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Note:

- The stepwise approach is intended to assist, not replace, the clinical decision making required to meet individual patient needs.
- Classify severity; assign patient to most severe step in which any feature occurs.
- There are very few studies on asthma therapy for infants.
- Gain control as quickly as possible (a course of short systemic corticosteroids may be required); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled beta₂-agonists (e.g., use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy.
- Provide parent education on asthma management and controlling environmental factors that make asthma worse (e.g. allergies and irritants).
- Consultation with an asthma specialist is recommended for patients with moderate or severe persistent asthma. Consider consultation for patients with mild persistent asthma.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/parent's work missed
- Minimal use of short-acting inhaled beta₂-agonists
- Minimal or no adverse effects from medications

Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age: Treatment

Classify Severity: Clinical Features Before Treatment or Adequate control		Medications Required to Maintain Long-Term Control	
	Symptoms/Day Symptoms/Night	PEF or FEV, PEF Variability	Daily Medications
Step 4 Severe Persistent	Continual Frequent	≤ 60% > 30%	<ul style="list-style-type: none"> Preferred treatment: <ul style="list-style-type: none"> High-dose inhaled corticosteroids AND Long-acting inhaled beta₂-agonists AND, if needed Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids)
Step 3 Moderate Persistent	Daily > 1 night/week	> 60% - < 80% > 30%	<ul style="list-style-type: none"> Preferred treatments <ul style="list-style-type: none"> Low-dose inhaled corticosteroids and long-acting inhaled beta₂-agonists Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> Increase inhaled corticosteroids within medium-dose range OR Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. <p>If needed (particularly in patients with recurring severe exacerbations):</p> <ul style="list-style-type: none"> Preferred treatment: <ul style="list-style-type: none"> Increase inhaled corticosteroids within medium-dose range and add long-acting beta₂-agonists Alternative treatment (listed in alphabetically): <ul style="list-style-type: none"> Increase inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day ≤ 2 nights/month	≥ 80% 20-30%	<ul style="list-style-type: none"> Preferred treatment <ul style="list-style-type: none"> Low-dose inhaled corticosteroid Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> Cromolyn, leukotriene modifier, nedocromil, OR sustained-release theophylline to serum concentration of 5-15 mcg/mL.
Step 1 Mild Intermittent	> 2 days/week ≤ 2 nights/month		<ul style="list-style-type: none"> No daily medication needed Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.

Quick Read
All Patients

- Short-acting bronchodilator: 2-4 puffs short-acting inhaled beta₂-agonists as needed for symptoms.
- Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroids may be needed.
- Use of short-acting beta₂-agonists > 2 times a weeks in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.



Step Down

Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.



Step Up

If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Note:

- The stepwise approach is intended to assist, not replace, the clinical decision making required to meet individual patient needs.
- Classify severity; assign patient to most severe step in which any feature occurs (PEF is % of personal best; FEV₁ is % predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroids); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled beta₂-agonists. Over reliance on short-acting inhaled beta₂-agonists (e.g., use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy.
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if step 4 care is required. Referral may be considered if step 3 care is required.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/parent's work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled beta₂-agonists
- Minimal or not adverse effects from medications

Usual Dosage for Long-Term-Control Medications

Medication	Dosage Form	Adult Dose	Child Dose*
Inhaled Corticosteroids (See <i>Estimated Comparative Daily Dosages for Inhaled Corticosteroids</i>)			
Systemic Corticosteroids		<i>(Applies to all three corticosteroids)</i>	
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	<ul style="list-style-type: none"> 7.5 – 60 mg daily in a single dose in a.m. or qod as needed for control Short-course “burst” to achieve control: 40-60 mg per day as single or 2 divided doses for 3-10 days 	<ul style="list-style-type: none"> 0.25-2 mg/kg daily in single dose in a.m. or qod as needed for control Short-course “burst”: 1-2 mg/kg/day, maximum 60 mg/day for 3-10 days
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc		
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc		
Long-Acting Inhaled Beta2-Agonists (<i>Should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids</i>)			
Salmeterol	MDL 21 mcg/puff	2 puffs q 12 hours	1-2 puffs q 12 hours
	DPI 50 mg/blister	1 blister q 12 hours	1 blister q 12 hours
Formoterol	DPI 12 mcg/single-use capsule	1 capsule q 12 hours	1 capsule q 12 hours
Combined Medication			
Fluticasone/Salmeterol	DPI 100, 250, or 500 mg/50 mg	1 inhalation bid; dose depends on severity of asthma	1 inhalation bid; dose depends on severity of asthma
Cromolyn and Nedocromil			
Cromolyn	MDI 1 mg/puff	2-4 puffs tid-qid	1-2 puffs tid-qid
	Nebulizer 20 mg/ampule	1 ampule tid-qid	1 ampule tid-qid
Nedocromil	MDI 1.75 mg/puff	2-4 puffs bid-qid	1-2 puffs bid-qid
Leukotriene Modifiers			
Montelukast	4 or 5 mg chewable tablet	10 mg qhs	4 mg qhs (2-5 yrs)
	10 mg tablet		5 mg qhs (6-14 yrs) 10 mg qhs (> 14 yrs)
Zafirlukast	10 or 20 mg tablet	40 mg daily (20 mg tablet bid)	20 mg daily (7-11 yrs) (10 mg tablet bid)
Zileuton	300 or 600 mg tablet	2,400 mg daily (give tablets qid)	
Methylxanthines (<i>Serum monitoring is important [serum concentration of 5-15 mcg/ml at steady state]</i>).			
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day	Starting dose 10 mg/kg/day; usual max: <ul style="list-style-type: none"> < 1 year of age: 0.2 (age in weeks) + 5 + mg/kg/day ≥ 1 year of age: 16 mg/kg/day

*Children ≤ 12 years of age

Estimated Comparative Daily Dosages for Inhaled Corticosteroids

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Adult	Child*	Adult	Child	Adult	Child*
Beclomethasone CFC 42 or 84 mcg/puff	168-504 mcg	84-336 mcg	504 – 840 mcg	336-672 mcg	> 840 mcg	> 672 mcg
Beclomethasone HFA 40 or 80 mcg/puff	80-240 mcg	80-160 mcg	240-480 mcg	160-320 mcg	> 480 mcg	> 320 mcg
Budesonide DPI 200 mcg/inhalation	200-600 mcg	200-400 mcg	600-1,200 mcg	400-800 mcg	> 1,200 mcg	> 800 mcg
Inhalation suspension for nebulization (child dose)		0.5 mg		1.0 mg		2.0 mg
Flunisolide 250 mcg/puff	500 – 1,000 mcg	500-750 mcg	1,000 – 2,000 mcg	1,000-1,250 mcg	> 2,000 mcg	> 1,250 mcg
Fluticasone MDI: 44, 110, Or 220 mcg/puff	88-264 mcg	88-176 mcg	264-660 mcg	176-440 mcg	> 660 mcg	> 440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100-300 mcg	100-200 mcg	300-600 mcg	200-400 mcg	> 600 mcg	> 400 mcg
Triamcinolone acetonide 100 mcg/puff	400-1,000 mcg	400-800 mcg	1,000-2,000 mcg	800-1,200 mcg	> 2,000 mcg	> 1,200 mcg

*Children ≤ 12 years of age

1. Executive Summary of the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 2002. Published by National Heart, Lung, and Blood Institute. Web: <http://www.nhlbi.nih.gov>
2. Barriers to Effective Pediatric Asthma Care Swartz, MK, Banasiak NC, et al J Pediatric Health Care 2005; 19(2): 71-79.
3. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000; 162:1403-1406.
4. Teper AM, Kofman CD, Szulman GA, Vidaurreta SM, Maffey AF. Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma. Am J Respir Crit Care Med 2005; 171:587-590.
5. Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under five years of age: a systematic review with meta-analysis. J Pediatr 2004; 145(2):172-177.
6. Busse W, Raphael GD, Galant S, Kalberg C, Goode-Sellers S, Srebro S, Edwards L, Rickard K. Fluticasone Propionate Clinical Research Study Group. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. J Allergy Clin Immunol 2001; 107:461-468.
7. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. Am J Respir Crit Care Med 1998; 157:S1-S53.
8. Bisgaard H. Use of inhaled corticosteroids in pediatric asthma. Pediatric Pulmonol. 1997; (suppl);27-33.
9. Szeffler S, Weiss S, Tonascia J. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. N Engl J Med 2000; 343:1054-1063.
10. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 2000; 343:1064-1069.
11. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). Br Med J 2000; 320:1368-1373.
12. Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, Knobil K. Fluticasone propionate/sameterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. J Allergy Clin Immunol 2000; 106:1088-1095.
13. Rosenwasser LJ, Nash DB. Incorporating omalizumab into asthma treatment guidelines: consensus panel recommendations. Pharm & Therap 2003; 28:400-410.
14. Adult Asthma Consensus Guidelines Update LeMiere, C, Bai et.al. Can Resp J2004; 11(Supplement):9A-18A.
15. Pregnancy and Asthma: Recent Developments – Namazy JA, Schatz M. Curr Opin Pulm Med 11(1): 56-60, 2005
16. Managing Asthma during pregnancy – the Whys and how’s of aggressive control Blaiss, MS Postgrad Med 2004 115; (5): 55-64 and Postgraduate Medicine online. www.postgradmed.com/issues/2004/05_04/blaiss.htm

Additional Resources

PACE: Pediatrics Asthma Care Enrichment - an online CME Learning module sponsored by the Center for Health Care Education, LLC.

www.medscape.com/viewprogram/3613_pnt

Asthma Action Plan used with permission from the Institute for Clinical Systems Improvement (ICSI) asthma guideline March 2005.