QUICK REFERENCE

NAEPP Expert Panel Report Guidelines for the Diagnosis and Management of Asthma–Update on Selected Topics 2002*

The National Asthma Education and Prevention Program (NAEPP) keeps clinical practice guidelines up to date by identifying selected topics on asthma that warrant intensive review based on the level of research activity reflected in the published literature or the level of concern in clinical practice. The NAEPP Expert Panel identified key questions about asthma management and used a systematic review of the evidence, conducted by the Agency for Healthcare Research and Quality Evidence Practice Center, to prepare answers and update recommendations for clinical practice.

The NAEPP *Expert Panel Report: Guidelines for the Diagnosis and Managment of Asthma—Update on Selected Topics 2002* (EPR—Update 2002) presents up-to-date recommendations on:

Medications—long-term management of asthma in children with mild or moderate persistent asthma, combination therapy in moderate persistent asthma, and use of antibiotics to treat acute exacerbations of asthma

Monitoring—written action plans compared to medical management alone, and peak flow-based compared to symptom-based written action plans

Prevention—effects of early treatment on the progression of asthma

Medications

Long-Term Management of Asthma in Children

Question: Does chronic use of inhaled corticosteroids improve long-term outcomes for children with mild or moderate persistent asthma, compared to other asthma medications?

Answer: Strong evidence from clinical trials has established that inhaled corticosteroids improve control of asthma for children with mild or moderate persistent asthma compared to as-needed beta$_2$-agonists, as measured by prebronchodilator FEV$_1$, reduced airway hyperresponsiveness, improvements in symptom scores and symptom frequency, fewer courses of oral corticosteroids, and fewer urgent care visits or hospitalizations. Studies comparing inhaled corticosteroids to cromolyn, nedocromil, theophylline, or leukotriene receptor antagonists are limited, but available evidence shows that none of these long-term-control medications appears to be as effective as inhaled corticosteroids in improving asthma outcomes. Studies comparing medications in children younger than 5 years of age are not available; recommendations are based on expert opinion and extrapolation from studies in older children. The NAEPP EPR-2 recommendations for treating children with mild or moderate persistent asthma have been revised. (See charts for Stepwise Approach for Managing Asthma.)

*Updates the NAEPP *Expert Panel Report 2* (NIH Publication No. 97-4051).

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Based on observational studies, it is the opinion of the Expert Panel that the initiation of long-term-control therapy should be considered in infants and young children who have had more than three episodes of wheezing in the past year that lasted more than 1 day and affected sleep and who have risk factors for the development of asthma (parental history of asthma or physician-diagnosed atopic dermatitis or two of the following: physician-diagnosed allergic rhinitis, wheezing apart from colds, peripheral blood eosinophilia). This is in addition to previously recommended indications for starting long-term-control therapy—i.e., in infants and young children requiring symptomatic treatment more than two times per week or experiencing severe exacerbations less than 6 weeks apart.

Question: What are the long-term adverse effects of chronic inhaled corticosteroid use in children on the following outcomes: vertical growth, bone mineral density, ocular toxicity, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis?

Answer: Strong evidence from clinical trials following children for up to 6 years shows that the use of inhaled corticosteroids at recommended doses does not have frequent, clinically significant, or irreversible effects on any of the outcomes reviewed. The NAEPP EPR-2 statements have been updated but not changed: Inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma, and the potential but small risk of delayed growth is well balanced by their effectiveness.

Cumulative data in children suggest that low-to-medium doses of inhaled corticosteroids may have the potential of decreasing growth velocity (resulting in a small difference in height averaging 1 cm in the first year of treatment), but this effect on growth velocity is not sustained in subsequent years of treatment, is not progressive, and may be reversible. Cohort studies following children for more than 10 years suggest that final predicted height is attained. Physicians should monitor the growth of children and adolescents taking corticosteroids by any route of administration and, if growth appears slowed, weigh the benefits of asthma control against the possibility of growth suppression or delay.

Studies including 6 years of observation indicate that low-to-medium doses of inhaled corticosteroids have no adverse effects on bone mineral density in children and no significant effects on the incidence of subcapsular cataracts or glaucoma. Studies show that, on average, persons may have only clinically insignificant effects, if any, of inhaled corticosteroids on HPA axis function, although there may be rare individuals who are more susceptible.

Combination Therapy

Question: In patients with moderate persistent asthma who are receiving inhaled corticosteroids, does addition of another long-term-control agent improve outcomes?

Answer: Strong evidence from clinical trials consistently indicates that use of long-acting inhaled beta$_2$-agonists added to low-to-medium doses of inhaled corticosteroids leads to improvements in lung function and symptoms and reduced need for quick relief, short-acting beta$_2$-agonists. Adding a leukotriene modifier or theophylline to inhaled corticosteroids or doubling the dose of inhaled corticosteroids also improves outcomes, but the evidence is not as substantial. The NAEPP EPR-2 recommendations for moderate persistent asthma have been revised: The preferred treatment for adults and children over 5 years of age is the addition of long-acting inhaled beta$_2$-agonists to low-to-medium doses of inhaled corticosteroids. Adjunctive therapy combinations have not been studied in children younger than 5 years of age. For this age group, it is the opinion of the Expert Panel that there are two preferred options for treating moderate asthma: either the addition of long-acting inhaled beta$_2$-agonists to a low dose of inhaled corticosteroids or medium-dose inhaled corticosteroids as monotherapy.

Use of Antibiotics To Treat Acute Asthma Exacerbation

Question: Does adding antibiotics to standard care improve the outcomes of treatment for acute exacerbation of asthma?

Answer: Evidence from clinical trials suggests no benefit from antibiotic therapy for asthma exacerbations, whether administered routinely or when suspicion of bacterial infection is low. No studies have addressed the question of whether the addition of antibiotics to standard care improves the outcomes of treatment for asthma exacerbations when signs and symptoms suggest the possibility—but do not clearly indicate the presence—of bacterial infection. The NAEPP EPR-2 recommendation has not been changed: Antibiotics are not recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions—e.g., for those patients with fever and purulent sputum, evidence of pneumonia, or suspected bacterial sinusitis.

Monitoring

Written Action Plans Compared to Medical Management Alone

Question: Compared to medical management alone, does the use of a written asthma action plan improve outcomes?

Answer: Data are insufficient to support or refute the benefits of using written asthma action plans compared to medical management alone. Seven studies compared medical management with written action plans to medical management without action plans. Beyond including instructions on the action plan to the intervention groups, four of these studies did not include asthma education for either the intervention or control groups; three of the studies included similar but limited asthma education for both intervention and control groups. Only one study included children. Significant limitations in study designs and methods in these studies preclude conclusions. For example, the studies showing no benefits of written action plans did not have sufficient power for comparisons between treatment and control groups, and the two studies reporting significant improvements with action plans had potential biases in patient selection, withdrawals, data collection, or analysis.

However, a Cochrane review of 25 studies comparing asthma self-management education interventions for adults to medical care without such education also contrasted those studies with self-management interventions that included written action plans to those that did not. The self-management interventions with written action plans had the greatest benefits, including reduced emergency department visits and hospitalizations and improved lung function.

The NAEPP EPR-2 recommendations have not been changed: It is the opinion of the Expert Panel that use of written action plans as part of an overall effort to educate patients in self-management is recommended, especially for patients with moderate or severe persistent asthma and patients with a history of severe exacerbations.

Peak Flow-Based Compared to Symptom-Based Written Action Plans

Question: Compared to a written action plan based on symptoms, does use of a written action plan based on peak flow monitoring improve outcomes?

Answer: Evidence neither supports nor refutes the benefits of written action plans based on peak flow monitoring compared to symptom-based plans in improving health care utilization, symptoms, or lung function. Just four studies, one including children, were available, and these studies had limitations (e.g., inadequate sample sizes and power to detect differences or potential bias in patient selection). The evidence does not clearly show that a peak flow-based action plan is better, but equivalent benefits have been demonstrated. Patient preferences and circumstances (e.g., inability to recognize or report signs and symptoms of worsening asthma) may warrant choosing peak flow monitoring. The NAEPP EPR-2 recommendations have not been changed. It is the opinion of the Expert Panel that peak flow monitoring for patients with moderate or severe persistent asthma should be considered because it may enhance clinician-patient communication and may increase patient and caregiver awareness of the disease status and control.

Prevention

Effects of Early Treatment on Progression of Asthma

Question: For patients with mild or moderate persistent asthma, does early intervention with long-term-control therapy (i.e., inhaled corticosteroids) prevent progression of asthma as indicated by changes in lung function or severity of symptoms?

Answer: Evidence is insufficient to permit conclusions on the benefits of early treatment of asthma in preventing the progression of disease. The NAEPP EPR-2 statements on disease progression have been revised. The assumption that children ages 5 to 12 with mild or moderate persistent asthma have a progressive decline in lung function has not been supported by a large, randomized, controlled clinical trial. The trial found that although inhaled corticosteroids provided superior asthma control during treatment, symptoms and airway hyperresponsiveness returned when treatment was discontinued. This suggests that, for this age group, with mild or moderate asthma, treatment provides control but does not modify the underlying disease process. In contrast, prospective observational studies in other age groups suggest that a loss of lung function in children occurs in the first 3 to 5 years of life and can occur rapidly in adults with asthma. Adequate studies of whether treatment can prevent these declines in lung function have not yet been conducted.

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	Symptoms/Day Symptoms/Night	Medications Required To Maintain Long-Term Control Daily Medications
Step 4 Severe Persistent	Continual Frequent	■ Preferred treatment: – High-dose inhaled corticosteroids AND – Long-acting inhaled beta$_2$-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	■ Preferred treatments: – Low-dose inhaled corticosteroids and long-acting inhaled beta$_2$-agonists OR – Medium-dose inhaled corticosteroids. ■ Alternative treatment: – Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline. If needed (particularly in patients with recurring severe exacerbations): ■ Preferred treatment: – Medium-dose inhaled corticosteroids and long-acting beta$_2$-agonists. ■ Alternative treatment: – Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	■ Preferred treatment: – Low-dose inhaled corticosteroid (with nebulizer or MDI with holding chamber with or without face mask or DPI). ■ Alternative treatment (listed alphabetically): – Cromolyn (nebulizer is preferred or MDI with holding chamber) OR leukotriene receptor antagonist.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	■ No daily medication needed.

Quick Relief
All Patients

- Bronchodilator as needed for symptoms. Intensity of treatment will depend upon severity of exacerbation.
  - Preferred treatment: Short-acting inhaled beta$_2$-agonists by nebulizer or face mask and space/holding chamber
  - Alternative treatment: Oral beta$_2$-agonist
- 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 beta$_2$-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
If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

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 beta$_2$-agonist
- Minimal or no adverse effects from medications

Note

- The stepwise approach is intended to assist, not replace, the clinical decisionmaking 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 beta$_2$-agonists. Overreliance on short-acting inhaled beta$_2$-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.

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	Symptoms/Day Symptoms/Night	PEF or FEV_1 PEF Variability	Medications Required To Maintain Long-Term Control Daily Medications
Step 4 Severe Persistent	Continual Frequent	≤ 60% > 30%	■ Preferred treatment: – High-dose inhaled corticosteroids AND – Long-acting inhaled $beta_2$-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%	■ Preferred treatment: – Low-to-medium dose inhaled corticosteroids and long-acting inhaled $beta_2$-agonists. ■ Alternative treatment (listed alphabetically): – Increase inhaled corticosteroids within medium-dose range OR – Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. If needed (particularly in patients with recurring severe exacerbations): ■ Preferred treatment: – Increase inhaled corticosteroids within medium-dose range and add long-acting inhaled $beta_2$-agonists. ■ Alternative treatment (listed alphabetically): – 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%	■ Preferred treatment: – Low-dose inhaled corticosteroids. ■ Alternative treatment (listed alphabetically): 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	≥ 80% < 20%	■ 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 Relief
All Patients

- Short-acting bronchodilator: 2–4 puffs short-acting inhaled $beta_2$-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 $beta_2$-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
If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled $beta_2$-agonist
- Minimal or no adverse effects from medications

Note

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is % of personal best; FEV_1 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 $beta_2$-agonists. Overreliance on short-acting inhaled $beta_2$-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.

Usual Dosages for Long-Term-Control Medications

Medication	Dosage Form	Adult Dose	Child Dose*
Inhaled Corticosteroids *(See Estimated Comparative Daily Dosages for Inhaled Corticosteroids.)*			
Systemic Corticosteroids		*(Applies to all three corticosteroids.)*	
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	■ 7.5–60 mg daily in a single dose in a.m. or qod as needed for control	■ 0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	■ Short-course "burst" to achieve control: 40–60 mg per day as single or 2 divided doses for 3–10 days	■ Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc		
Long-Acting Inhaled Beta$_2$-Agonists *(Should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids.)*			
Salmeterol	MDI 21 mcg/puff	2 puffs q 12 hours	1–2 puffs q 12 hours
	DPI 50 mcg/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 mcg/50 mcg	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 *(Serum monitoring is important [serum concentration of 5–15 mcg/mL at steady state]).*			
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: ■ < 1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥ 1 year of age: 16 mg/kg/day

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