

AND

- The treatment group was treated immediately following diagnosis of asthma compared to a control group that received the same treatment after a delay

OR

- The population was stratified by the duration of asthma prior to the initiation of long-term-control medication and outcomes compared across the different strata.
- Treatment duration was at least 1 year.
- At the start of the study, no more than 10 percent of the population was currently being treated with or had been continuously (more than 1 month) treated in the past with the long-term-control medication being studied.

I Summary of Findings

Studies

Although the objective was to review the literature on the effects of any long-term-control medications (e.g., inhaled corticosteroids, leukotriene modifiers, cromolyn, nedocromil, theophylline), the available studies were limited to research on inhaled corticosteroids. (See the key evidence tables in this section for a summary description of the eligible studies.)

Four studies reporting on a total of 475 asthma patients met the inclusion criteria for this key question: two randomized controlled trials (RCTs) (Haahtela et al. 1994; Overbeek et al. 1996) and two single-arm studies (Selroos et al. 1995; Agertoft and Pedersen 1994). Just one of the studies enrolled children who were 3 to 11 years of age (Agertoft and Pedersen 1994). According to EPR-2 classification of severity, two studies involved mild asthma (baseline FEV₁ greater than 80 percent predicted) (Haahtela et al. 1994; Agertoft and Pedersen 1994), and two involved moderate asthma (Overbeek et al. 1996; Selroos et al. 1995). Each of the two RCTs (Haahtela et al. 1994; Overbeek et al. 1996) was an open-label extension of an RCT originally intended to evaluate the efficacy of inhaled corticosteroids. In these studies, the patients who were initially assigned to the noncorticosteroid-treated control group were subsequently administered inhaled

corticosteroids at the conclusion of the original RCT. Each of the single-arm studies (Selroos et al. 1995; Agertoft and Pedersen 1994) analyzed a cohort of patients treated in a hospital-based clinic, where the patients were stratified by the individual's duration of asthma prior to initiating inhaled corticosteroids treatment, and outcomes were compared across the strata.

The duration of the followup was 3 years in the randomized trials and 2 and 3.7 years, respectively, in the single-arm studies. Haahtela et al. (1994) treated one group with inhaled corticosteroids for 24 months, then treated the delayed inhaled corticosteroid group for 12 months. Overbeek et al. (1996) treated one group with inhaled corticosteroids for 30 months, initiated treatment with inhaled corticosteroids in the delayed group, and followed both groups for an additional 6 months. In the single-arm studies, patients starting on inhaled corticosteroids were followed for 2 years in one study (Selroos et al. 1995) and for 2 to 6 years (mean: 3.7 years) in the final study (Agertoft and Pedersen 1994).

All four trials reported lung function outcomes, but no two studies used the same measure to report change in lung function from baseline. Neither of the two RCTs (Haahtela et al.; Overbeek et al. 1996) met the SRE criteria that define higher quality studies. Neither study maintained blinding to treatment throughout the course of the study. For both, the rate of dropouts/withdrawals exceeded the established threshold. Analyses were not done by intent to treat or in a manner to minimize dropout bias. With respect to SRE asthma-specific indicators of study quality, both randomized trials established reversibility on lung function measurements and controlled for use of other asthma medications, but neither study reported power calculations for outcomes, adequately accounted for excluded patients, specified a priori which were primary outcomes for analysis, reported compliance, or controlled for the effects of seasonality on outcomes.

A major limitation of the single-arm studies is that patients entered the study at varying time points in the duration of their disease, making it impossible to compare outcome data at a uniform time point. A second limitation in such studies is the high

potential for selection bias. It is likely that patients who have had asthma longer will have more severe disease, both because of disease progression and because asthma is more likely to remit in milder cases.

Finally, the SRE literature search found no prospective studies to address this key question in the specific population of interest. As a result, the available evidence from studies that compared early with delayed inhaled corticosteroid treatment has notable limitations with respect to the study population, time frames for study entry and followup, clarity of reporting with respect to details of interest to the question, and the use of appropriate control groups. For some trials, it was impossible to accurately calculate the number of enrolled or evaluable patients of interest, because reporting of one or the other number was combined with other patient groups (e.g., patients who have COPD or individuals with severe asthma).

The SRE also included consideration of results from CAMP 2000, although the research was not published until after the SRE literature search, and the study design does not address the question of intervention timing (early vs. delayed treatment). The study is considered in the SRE because it evaluates the long-term (4 to 6 years) effect of treatment on lung growth and asthma symptoms in more than 1,000 children with mild or moderate asthma. The RCT comparing inhaled corticosteroids and nedocromil with placebo (all groups received as-needed beta₂-agonists) met SRE criteria for high quality. Thus, the study provides robust evidence on the course of childhood asthma.

Results of Studies

Of the four studies identified by the SRE literature search, the randomized trial by Haahtela, although small (52 evaluable study participants), is the most relevant in terms of study design and population. The design includes comparisons that directly address the key question of interest, and the population is limited to individuals with mild asthma who were enrolled in the study at a similar point in the history of their disease—i.e., a diagnosis within the 12 months prior to enrollment. The first phase of the study was a randomized control comparison of a group treated daily with inhaled corticosteroids and

a group treated with daily beta₂-agonists, and followed for 24 months. The second phase of the study was an open-label study in which 67 percent of the original beta₂-agonist treatment group was given inhaled corticosteroids and followed for 12 more months; the original inhaled corticosteroid treatment group was either continued on a reduced dose of steroid or given a placebo. Outcomes at the end of 3 years indicated improvements in lung function measures and symptom scores in both groups, with larger increases occurring in the immediate inhaled corticosteroid group compared to the delayed inhaled corticosteroid group (FEV₁ 0.15 L vs. 0.02 L; PEF 42 L/min vs. 15 L/min; PC15 5.0 vs. 4.22 DD histamine; symptom score change of 0.8 vs. 0.4 from a mean baseline of 2.2 on a 1 to 10 point scale). Although these findings appear to support the hypotheses that an irreversible decline in lung function can occur in asthma not treated with an anti-inflammatory medication and that treatment with inhaled corticosteroids may have an impact on decline, methodologic features of the study limit the conclusions that can be reached. No statistical tests of significance were performed comparing baseline and 3-year outcomes between the immediate and the delayed treatment groups, and the differences are of unknown clinical significance because the magnitude is of a size that could be explained by bias. Bias may have occurred due to the lack of strict comparability between the double-blind and open-label phases of the trial, lack of controls for doses of inhaled corticosteroids, and a high rate of withdrawal from the study during the open-label phase (36 of 53 patients in the delayed treatment group and 16 of 50 in the immediate treatment group were available for analysis at 3 years), with no tests of comparability between withdrawals and continuing patients.

The second randomized trial identified in the SRE is also an open-label extension of a double-blind RCT designed to evaluate the efficacy of inhaled corticosteroids. The study had three treatment groups: one received inhaled corticosteroids, a second received inhaled ipratropium, and a third received placebo, but all groups received an inhaled beta₂-agonist four times a day (Overbeek et al. 1996). After 30 months of treatment, the asthma patients in the groups not receiving inhaled corticosteroids were given that agent and followed 6 additional

months in an open-label observation. This allows comparison of a group (49 patients) receiving immediate vs. a group (53 patients) receiving delayed inhaled corticosteroids for asthma. Results reported a greater but not statistically significant rise in FEV₁ during the initial 3 months of inhaled corticosteroid therapy for the immediate treatment group (13.8 percent increase vs. 8.5 percent increase; $p = 0.13$), and a statistically significant rise in PC15 values for the initial 6 months of inhaled corticosteroids in the immediate treatment group (1.77 doubling dose vs. 0.79, $p = 0.03$), and no differences in symptom score values. The study suggests the possibility of some benefit for immediate treatment, but conclusions are severely limited by several methodologic problems. For example, it is not clear at what point in the individual patient's disease process the treatment was started; the study populations include a mix of patients with severe asthma and COPD, and there were no comparisons made relevant to the key question—i.e., comparison of baseline and final lung function measured at the end of the trial. Further, there was a high dropout rate (less than half the eligible patients participated in the extended open-label phase) with no analysis of the withdrawals, which may introduce bias.

For the single-arm studies, one study enrolled 105 consecutive patients started on inhaled corticosteroids and observed them for 2 years (Selroos 1995). Changes in lung function outcomes (FEV₁ percent predicted and PEF percent predicted) were compared among the patients, according to groups stratified by duration of asthma at the onset of treatment (0 to 6 months, 14 patients; 6 to 12 months, 35 patients; 12 to 14 months, 13 patients; 24 to 60 months, 19 patients; 60 to 120 months, 15 patients). All strata were compared to the 0- to 6-month duration group; no comparison among strata was reported. The greatest increase in lung function measures occurred in the group with the shortest (0 to 6 months) duration of asthma (17 percent increase in FEV₁ percent predicted); and the least increase occurred in the group with the longest (60 to 120 months) duration of asthma (0 percent increase, $p < 0.01$). All other strata except the 24- to 60-month group had significantly less degree of lung function improvement than the 0- to 6-month group, but of varying magnitude.

For PEF, the 0- to 6-month group had a 21 percent increase in percent predicted values, compared with a 2 percent increase in the 60- to 120-month group ($p < 0.05$), but differences among the other strata varied in magnitude and significance. Although the stratification accounted for differences in duration of disease, it is impossible to compare outcome data at a uniform time point in the disease. Further, baseline differences in lung function and asthma severity indicate some selection bias. Finally, approximately one-third of the study participants were current or exsmokers, and the proportion of current smokers varied from 0 percent to 29 percent in the different groups. Thus, study design features, variance in final outcome measures among the strata, and the confounding factors of asthma severity and smoking limit interpretation of the results.

The second single-arm study identified by the SRE is a nonrandomized, prospective controlled trial of long-term outcomes in 216 children treated with inhaled corticosteroids for a mean of 3.7 years compared to 62 children who declined recommendations for inhaled corticosteroid treatment (Agertoft and Pedersen, 1994). In a supplemental cohort analysis, patients in the inhaled corticosteroid group were stratified by prior duration of asthma (0 to 2 years, 2 to 3 years, 3 to 5 years, and more than 5 years). This allowed a comparison relevant to the key SRE question. The main reported outcome was annual change in percent predicted FEV₁, calculated by linear regression. Results showed a mean change in FEV₁ per year of 8.2 percent for the 0- to 2-year group, 6.7 percent for the 2- to 3-year group, 3 percent for the 3- to 5-year group, and 2.4 percent for the more than 5-year group. A statistically significant correlation existed between the duration of asthma and the estimated change in FEV₁ per year; however, the differences were not significant between every group (e.g., the less than 2 vs. the 2- to 3-year strata or the 3- to 5-year vs. the more than 5-year strata). A major difficulty in interpreting these results is that the linear regression assumes a linear change in outcomes over the entire course of the study. However, it is well documented in the literature that there is a pattern of a sharp initial rise in FEV₁ during the first 3 months of inhaled corticosteroid treatment that is then followed by a plateau. Indeed, the final difference in FEV₁ percent predicted between the less than 2-year strata

(101 percent) and the more than 5-year strata (96.2 percent) was 4.8 percent after a mean of 3.7 years of treatment. This is considerably less than the 5.8 percent per year difference estimated by the linear regression model applied to the data.

The results of the CAMP 2000 study influence the conclusions derived from the SRE (CAMP 2000). This study is a three-arm, RCT evaluating the outcome effects of inhaled corticosteroids or nedocromil sodium compared to placebo in 1,041 children over a mean followup period of 4.3 years. The primary outcome measure was postbronchodilator FEV₁. Although the design of CAMP does not address the question of early versus delayed intervention (the average duration of asthma was 5 years for the study population), it does address the question of the effect of intervention with two treatments on disease progression as defined by loss in FEV₁ percent predicted.

CAMP researchers found an initial, highly statistically significant difference between treatment and control groups for change in postbronchodilator FEV₁ in the first year of the study, but no difference in change from baseline to the end of the 4- to 6-year followup period. This outcome measure was chosen to minimize the effects of reversible airway constriction and individual variability over time that are observed with prebronchodilator FEV₁. The finding of no difference in postbronchodilator FEV₁ and minimal change overall in lung function over 4 to 6 years for the entire study population does not support the hypothesis that treatment with inhaled corticosteroids improves lung growth in children with mild or moderate persistent asthma. It is of particular interest that CAMP does not document progressive decline in lung function in the placebo group, or significant improvement from baseline in the treatment groups (CAMP 2000). Similar to the findings related to lung function outcomes, no progressive decline in symptoms with the placebo groups was noted. Symptom scores and night-awakening scores improved over the course of the study in both the inhaled corticosteroid and placebo groups, with greater improvement throughout the study period shown in the inhaled corticosteroid group. The improvements in the placebo group may have been a result of the close medical supervision and patient education given to all study participants,

but the greater improvements in symptom scores and airway hyperresponsiveness indicate superior effectiveness of inhaled corticosteroid treatment. However, after inhaled corticosteroid treatment was withdrawn, symptom scores and airway hyperresponsiveness values were no different between groups. This finding indicates that the inhaled corticosteroids provided superior control and prevention of symptoms, but did not modify underlying disease. The finding that the placebo group did not experience a decline in lung function does not support the assumption of such a decline in children with mild or moderate asthma in this age group.

As noted in the Background Information section, it is likely that a progressive decline in lung function occurs in younger children and in adults. It is also possible it occurs in individuals with more severe asthma.

The studies identified by the SRE most relevant to addressing the question of whether early intervention with inhaled corticosteroids can prevent progression of disease were suggestive of benefit, but methodologic issues severely limit the conclusions that may be drawn. Additional consideration of the CAMP study supports cautious interpretation of the studies identified in the SRE. Although none of these studies was designed specifically to compare immediate versus delayed treatment in preventing progression of disease, the results provide critical insights for future research. At this time, the Expert Panel concludes that the evidence is insufficient to permit conclusions regarding the use of early intervention vs. long-term-control medication to prevent progression of disease.

Recommendations for EPR Update

Modifications in the EPR-2 are necessary to reflect the current understanding of natural history of persistent asthma, based on the SRE and review of additional, recently published studies that provide insights on the progression of asthma. It is clear that further research is needed to define the benefits of early intervention, the appropriate time of intervention, the nature of asthma as a progressive disease, and the effect of medications on preventing

progression. Until this information is available, the Expert Panel recommends the following revisions to EPR-2 (the blue text indicates new text), based on the SRE.

Introduction: Pharmacologic Therapy
(page 4, column 2, final paragraph in EPR-2)

Observations into the basic mechanisms of asthma have had a tremendous influence on therapy. Because inflammation is considered an early and persistent component of asthma, therapy for persistent asthma must be directed toward long-term suppression of the inflammation. Thus, EPR-2 continues to emphasize that the most effective medications for long-term-control are those shown to have anti-inflammatory effects. For example, early intervention with inhaled corticosteroids can improve asthma control and normalize lung function. However, it remains to be determined whether intervention with inhaled corticosteroids or any other long-term-control therapy can prevent irreversible airway obstruction that may be associated with asthma (Evidence D).

Pathogenesis and Definition: Child Onset Asthma
(page 10, column 1, paragraph 2 in EPR-2)

Asthma often begins in childhood, and when it does, it is frequently found in association with atopy, which is the genetic susceptibility to produce IgE directed toward common environmental allergens, including house-dust mites, animal proteins, and fungi (Larsen 1992). With the production of IgE antibodies, mast cells and possibly other airway cells (e.g., lymphocytes) are sensitized and become activated when they encounter specific antigens. Although atopy has been found in 30 to 50 percent of the general population, it is frequently found in the absence of asthma. Nevertheless, atopy is one of the strongest predisposing factors in the development of asthma (Sporik et al., 1990). Furthermore, a large epidemiologic study shows that among children who have recurrent episodes of wheezing during the first 3 years of life and have either one of two major risk factors (parental history of asthma or physician diagnosis of atopic dermatitis) or two of three minor risk factors (wheezing apart from colds,

peripheral blood eosinophilia, or physician diagnosis of allergic rhinitis) have a 76 percent probability of developing asthma during the school years (Evidence C) (Castro-Rodriguez et al. 2000).

Pathogenesis and Definition. Airway Remodeling
(page 11, column 2, paragraph 3 in EPR-2)

Airway remodeling. In some patients with asthma, airflow limitation may be persistent and nonresponsive to treatment. This nonresponsiveness may be caused by changes in the structure of airways. These changes include wall thickening, subepithelial fibrosis, goblet cell hypermetaplasia, myofibroblast hyperplasia, myocyte hyperplasia and hypertrophy, vascular neogenesis, and epithelial hypertrophy (Elias 1999). Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response. Although yet to be fully explored, the importance of airway remodeling as a possible cause of persistent airflow limitation and the possible role of chronic inflammation as a cause of remodeling suggest a rationale for early intervention with anti-inflammatory therapy. This hypothesis must be confirmed with specific, prospective, controlled studies.

Component 1: Measures of Assessment and Monitoring. Spirometry
(page 28, column 1 in EPR-2)

The Expert Panel recommends that spirometry tests be done (1) at the time of initial assessment; (2) after treatment is initiated and symptoms and PEF have stabilized, to document attainment of (near) "normal" airway function; and (3) at least every 1 to 2 years to assess the maintenance of airway function. These spirometry measures should be followed over the patient's lifetime to detect potential for decline and rate of decline of pulmonary function over time (Evidence D).

Component 3: Pharmacologic Therapy.
Key Points: The Medications, Inhaled Corticosteroids (page 58 in EPR-2)

Increased understanding of inhaled corticosteroids notes that:

- Early intervention with inhaled steroids likely will improve overall asthma management, but its effect on preventing irreversible airway injury remains to be determined (SRE-Evidence A, B).

Component 3: Pharmacologic Therapy.
Special Considerations for Managing Asthma in Different Age Groups. Infants and Young Children, Diagnosis (page 95, column 1, paragraph 2 in EPR-2)

Among children 5 years of age and younger the most common cause of asthma symptoms is viral respiratory infection. At present, the relative contributions of airway inflammation, bronchial smooth muscle abnormalities, or other structural factors in producing wheeze with acute viral upper respiratory infections are unknown. There appear to be two general patterns of illness in infants and children who have wheezing with acute viral upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood.

No clear markers to predict the prognosis for an individual child exist. However, epidemiologic studies suggest that for children less than 3 years of age who have more than three episodes of wheezing in a year (that last more than 1 day and affect sleep), the following predictive index identifies the risk associated with persistent asthma after 6 years of age. If a child has either (a) a physician diagnosis of atopic dermatitis or a parental history of asthma OR (b) two of the following: physician-diagnosed allergic rhinitis, greater than 4 percent peripheral blood eosinophilia, or wheezing apart from colds, then the child has a high likelihood (76 percent probability) of developing persistent asthma (Evidence C) (Martinez 1995; Castro-Rodriguez 2000). It is conceivable that early recognition and treatment of these high-risk children could result in secondary prevention of persistent asthma, although this is not yet established by clinical trials.

Component 3: Pharmacologic Therapy,
Special Considerations for Managing Asthma in Different Age Groups. Infants and Young Children, Treatment (page 95, column 2 in EPR-2)

In deciding when to initiate daily long-term-control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma vs. the possible adverse effects of medications given over prolonged periods. There is evidence that anti-inflammatory treatment can reduce morbidity from wheezing in early childhood (Connett et al. 1993). Long-term studies in children 5 to 12 years of age at the time of enrollment conclude that inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma and that the potential albeit small risk of delayed growth from the use of inhaled corticosteroids is well balanced by their effectiveness (SRE-Evidence A) (CAMP 2000). Further, available long-term data indicate that most children treated with inhaled corticosteroids achieve their predicted adult heights (Agertoft and Pedersen 2000). It is noted that the long-term prospective studies on growth involved budesonide and that the retrospective analyses included studies on beclomethasone, but the results have been generalized to include all inhaled corticosteroid preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies of numerous preparations suggest that the potential effect of inhaled corticosteroids on growth is a drug class effect. In children with demonstrable adverse effects related to inhaled corticosteroid therapy, other options (cromolyn, LTRA, nedocromil, or theophylline) for initiating or maintaining long-term-control therapy are available.

Based on high-quality evidence, the Expert Panel recommends long-term-control therapy for children with mild or moderate persistent asthma because it controls and prevents asthma symptoms (SRE Evidence A). However, evidence to date is insufficient to permit conclusions regarding whether early vs. delayed intervention with daily long-term-control medication will alter the underlying course of the disease. Although a preliminary study suggests that

appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a recent long-term RCT in children 5 to 12 years of age (CAMP 2000) (SRE-Evidence A, B). The best available evidence does not support the assumption that children 5 to 12 years of age with mild or moderate persistent asthma have a progressive decline in lung function that can be prevented by early initiation of long-term-control medications. Observational prospective data from other large groups of children suggest that the timing of the CAMP intervention was too late, as most loss of lung function in childhood asthma appears to occur in the first 3 to 5 years of life (Martinez et al. 1995). However, it has not yet been determined whether early recognition of children at high risk of developing persistent asthma coupled with early therapeutic intervention will either prevent the loss of lung function or prevent the development of persistent disease. Currently, critical prospective studies to address these issues are in progress. Similarly, to date no studies have evaluated whether intervention with inhaled corticosteroids can prevent the more rapid decline in lung function that can occur in adults with asthma.

Recommendations for Future Research

The SRE revealed methodological problems in most of the studies that evaluated the effect of inhaled corticosteroids on the progression of asthma. RCTs designed explicitly to address the research question are urgently needed. Further, new opportunities are now available to treat children younger than 5 years of age in whom the incidence of asthma onset is highest (Yuninger et al. 1992) and the risk for declines in lung function growth is high (Stern 2000; Castro-Rodriguez 2000). For example, LTRA is available for children as young as 2 years of age and inhaled corticosteroid nebulizing suspension for children as young as 1 year of age. In addition, new classes of medication that may be feasible for young children currently are being evaluated for their potential to modify disease: e.g., anti-IgE agents, cytokine antagonists, and cytokine receptor antagonists.

Because disease onset is high in children younger than 5 years of age and because these children are initially evaluated and managed by primary care physicians, it is important to establish firm diagnostic criteria for persistent asthma. Further, a refinement in the definition of disease progression must occur and methods to monitor progression should be designed and evaluated for use in clinical practice.

Specifically, more information in the following areas is needed to enhance our knowledge about the natural progression of asthma in children and adults, as well as appropriate interventions to alter it:

- Additional long-term studies, lasting a minimum of 2 years, of each medication class (e.g., inhaled corticosteroids, LTRAs, anti-IgE) in order to define the impact of treatment on the progression of asthma. Studies should:
 - In young children, be designed to assess for effect on measures including pulmonary function
 - In adults, be designed to examine whether loss of pulmonary function may be a unique feature of adult asthma, especially adult-onset asthma.
- Studies to determine the significance of declines in lung function and its relevance to other long-term events, including quality of life and severity of symptoms (acute exacerbations, symptoms, nighttime awakenings). Identification of the most appropriate pulmonary function measure to use for monitoring lung function growth in children and lung function declines in adults.
- Studies to identify the prevalence of airway remodeling and whether it can be predicted by asthma phenotype and genotype.
- Studies to identify methods for reliably and easily measuring and interpreting pulmonary function in young children. Forced oscillation could improve the feasibility of pulmonary function testing in young children, but these tests must be verified.
- Validation of a profile to predict persistent asthma and levels of asthma severity.

- Studies to identify and compare relevant outcomes that define disease progression and measure the effects of interventions to alter it. Pulmonary function, airway hyperresponsiveness, markers of inflammation, symptoms, medication use, and disease severity classifications are some outcomes of interest.
- Studies to design and evaluate methods for use in primary clinical practice to monitor individuals for progression of their disease. Serial measures of pulmonary function, assessments of medication requirements and urgent care visits over time, and, for infants, application of the asthma predictive index are possible approaches.
- Studies to evaluate when long-term-control therapy might be discontinued.
- Studies to evaluate the effectiveness of early use of environmental control measures, with or without pharmacologic therapy, alter the progression of disease.

Key Evidence Tables

Table 3-1. Study Characteristics

Citation	Study Design	Study Setting	Asthma Severity	Eligibility
Overbeek, Huib, Kerstjens et al. 1996	Open label extension of randomized parallel arm, double-blinded, placebo controlled trial	Country: Netherlands Funding: Pharmacologic + government grant Tx Setting: Unknown/Other; Multicenter	Stated: Not specified Estimated: Unable to estimate	Patient eligibility based on lung function only. (1) FEV ₁ (type not specified) minimum 1.2 L and 1.64 to 4.5 residual SDs below predicted, or FEV ₁ /inspiratory vital capacity ratio >1.64 residual SDs below predicted. (2) Histamine PC20 maximum 8 mg/mL. Exclusions: Patients with medication use or conditions likely to interfere with the purpose of the study.
Haahtela, Jarvinen, Kava et al. 1994	Open label extension of randomized parallel arm, double-blinded, controlled trial	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other; Multicenter	Stated: Mild Estimated: Mild	Patient eligibility based on lung function and symptoms. FEV ₁ (postdose) minimum 80% of predicted; increase of more than 15% after inhalation of beta ₂ -agonist or decrease of more than 15% after exercise tolerance test. Maximum duration of symptoms 12 months. Exclusions: History of smoking within 6 months, regular asthma treatment, prior treatment with corticosteroids or cromolyn.
Agertoft and Pedersen 1994	Prospective cohort analysis within parallel, controlled trial; patients stratified by prior duration of asthma	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other	Stated: Mild-moderate Estimated: Mild-Severe	Patient eligibility based on utilization and stated severity. Minimum of three prior visits to clinic within past year, with mild or moderate persistent asthma. Exclusions: Prior use of inhaled corticosteroids for more than 2 weeks per year; other chronic diseases.
Selroos, Pietinalho, Lofroos et al. 1995	Prospective cohort study; patients stratified by prior duration of asthma	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other	Stated: Mild-moderate Estimated: Mild-Severe	Patient eligibility based on lung function and symptoms. FEV ₁ (type not specified) maximum 75% of predicted or PEF (a.m. clinic) maximum 75% of predicted; and/or use of inhaled bronchodilators >3x/week, and/or regular asthma symptoms during day or night, and/or reduced exercise tolerance. Exclusions: Prior use of inhaled corticosteroids; irreversible airway obstruction.

Source:

Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01-EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 3-2. Study Parameters

Citation	Pretreatment	Study Arm	Number Enrolled	Corticosteroid Delay	Treatment
Overbeek, Huib, Kerstjens et al. 1996	None	Inhaled corticosteroid—immediate		Corticosteroids delayed 0 months, then administered for 36 months	All patients received 200 mcg beclomethasone dipropionate 4x daily; all patients received 500 mcg terbutaline 4x daily.
		Inhaled corticosteroid—delayed		Corticosteroids delayed 30 months, then administered for 6 months	All patients received 500 mcg terbutaline 4x daily for entire study. Some patients received 40 mcg ipratropium bromide 4x daily for first 30 months of study. All patients received 200 mcg beclomethasone dipropionate 4x daily for final 6 months of study.
Haahtela, Jarvinen, Kava et al. 1994	Run-in 2 weeks to establish patient eligibility	Inhaled corticosteroid—immediate		Corticosteroids delayed 0 months, then administered for 36 months	All patients received 600 mcg budesonide 2x daily for first 24 months, then reduced to 200 mcg 2x daily for final 12 months of study.
		Inhaled corticosteroid—delayed		Corticosteroids delayed 24 months, then administered for 12 months	All patients received 600 mcg budesonide 2x daily for final 12 months of study.
Agertoft and Pedersen 1994	Run-in 52 weeks to establish patient eligibility	Inhaled corticosteroid—immediate		Prior duration of asthma 0–12 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
		Inhaled corticosteroid—delayed 1		Prior duration of asthma 12–24 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
		Inhaled corticosteroid—delayed 2		Prior duration of asthma 24–36 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
		Inhaled corticosteroid—delayed 3		Prior duration of asthma 12–24 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
Selroos, Pietinalho, Lofroos et al. 1995	None	Inhaled corticosteroid—immediate		Prior duration of asthma 0–6 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 1		Prior duration of asthma 6–12 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 2		Prior duration of asthma 12–24 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 3		Prior duration of asthma 24–60 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 4		Prior duration of asthma 60–120 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 5		Prior duration of asthma >120 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.

Source:

Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Key Evidence Tables

Table 3-3. Lung Function Outcomes: FEV₁

Citation	Study Arm	Number Enrolled	Number Evaluable	Study Duration (years)	
Overbeek, Huib, Kerstjens et al. 1996	Inhaled corticosteroid—immediate	91	49	3.0	
	Inhaled corticosteroid—delayed	183	53	3.0	
Haahtela, Jarvinen, Kava et al. 1994	Inhaled corticosteroid—immediate	50	16	3.0	
	Inhaled corticosteroid—delayed	53	36	3.0	
Agertoft and Pedersen 1994	Inhaled corticosteroid—immediate			3.7	
	Inhaled corticosteroid—delayed 1			3.7	
	Inhaled corticosteroid—delayed 2			3.7	
	Inhaled corticosteroid—delayed 3			3.7	
Selroos, Pietinalho, Lofroos et al. 1995	Inhaled corticosteroid—immediate	14		2.0	
	Inhaled corticosteroid—delayed 1	35		2.0	
	Inhaled corticosteroid—delayed 2	13		2.0	
	Inhaled corticosteroid—delayed 3	19		2.0	
	Inhaled corticosteroid—delayed 4	15		2.0	
	Inhaled corticosteroid—delayed 5	9		2.0	

	FEV ₁ Baseline	FEV ₁ Final	FEV ₁ P-Value	Comments
	64.6 +/- 14.1% predicted	13.8% pred (change, 95% CI, 7.7-18.7)		Number of patients enrolled includes both COPD and asthma patients; number evaluable includes only asthma patients.
	61.2 +/- 15.6% predicted	8.5% pred (change, 95% CI, 3.3-15.9)	NS	Comparison only made of rise in FEV ₁ during initial 3 months' treatment with inhaled corticosteroids in both groups.
	3.17 +/- 0.8 L	3.32 L		Values represent FEV ₁ at start of initial study and final FEV ₁ after 3 years.
	3.05 +/- 0.7 L	3.07 L		No statistical comparison performed on change in FEV ₁ from start of study until final end-point.
	NR	8.2% pred/yr (change, 95% CI, 6.1, 10.3)		Final FEV ₁ % predicted 101 +/- 13.6% Calculation of % increase/yr in FEV ₁ by linear regression probably not appropriate.
	NR	6.7% pred/yr (change, 95% CI, 5.0, 8.4)		
	NR	3% pred/yr (change, 95% CI, 1.8, 4.2)		
	NR	2.4% pred/yr (95% CI, 1.1, 3.7)		Final FEV ₁ % predicted 96.2 +/- 9.5%, p <0.05 as compared to inhaled corticosteroid-immEDIATE group.
	70 +/- 21% predicted	87 +/- 18.7% predicted		
	70 +/- 21% predicted	75 +/- 17.7% predicted	0.100	Comparison of change in FEV ₁ vs. Ctl
	78 +/- 18% predicted	85 +/- 18.0% predicted	<.0500	Comparison of change in FEV ₁ vs. Ctl
	60 +/- 16% predicted	68 +/- 21.8% predicted	NS	Comparison of change in FEV ₁ vs. Ctl
	62 +/- 18% predicted	66 +/- 19.4% predicted	<.0500	Comparison of change in FEV ₁ vs. Ctl
	67 +/- 30.0% predicted	67 +/- 30.0% predicted	<.0100	Comparison of change in FEV ₁ vs. Ctl

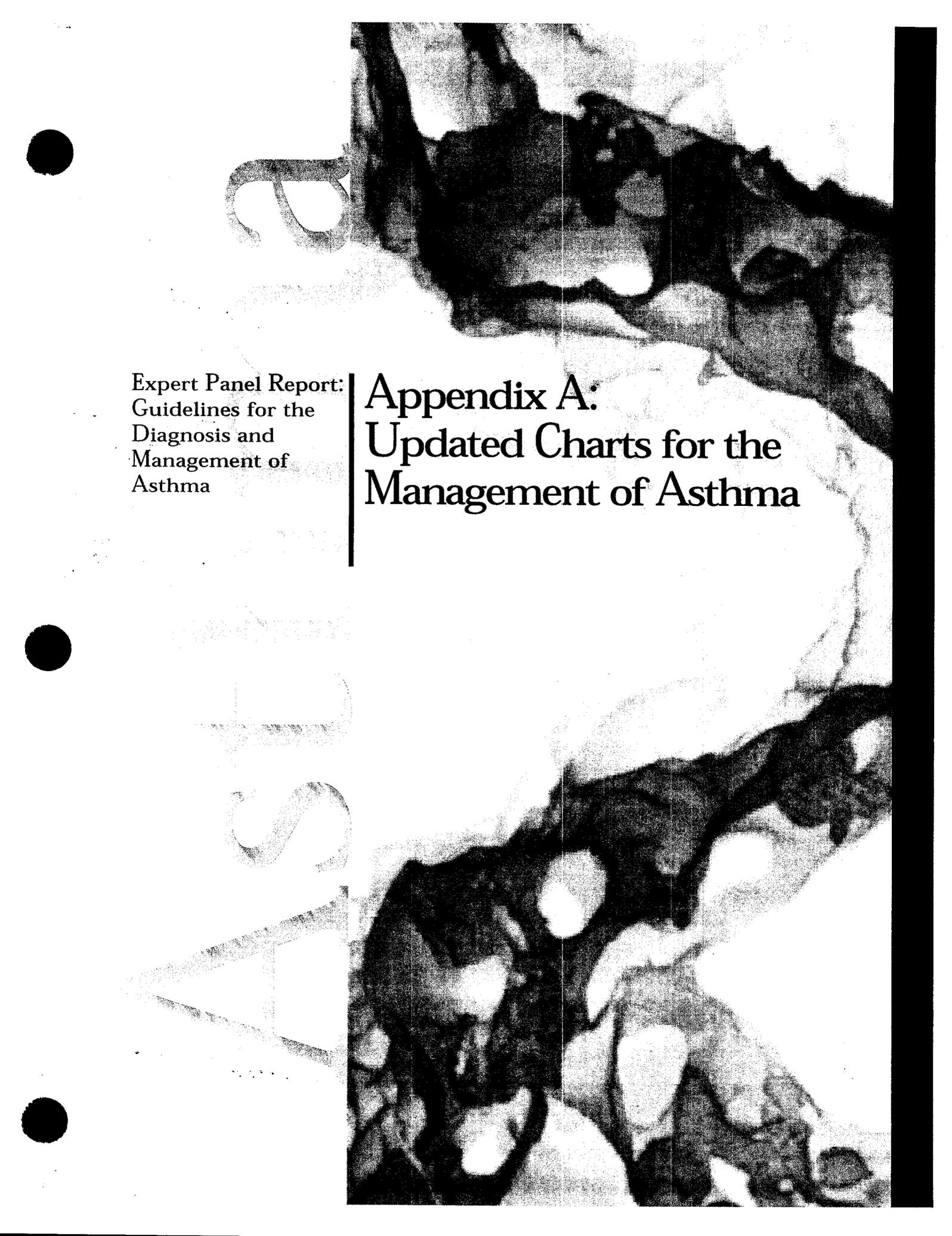
Source:

Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

References

- Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88(5):373-81.
- Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01-EO44. Rockville, MD: Agency for Healthcare Research and Quality, September 2001.
- 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(4 Pt 1):1403-6.
- Childhood Asthma Management Program (CAMP) Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054-63.
- Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1-3 years. *Arch Dis Child* 1993;69(3):351-5.
- Elias JA, Zhu Z, Chupp G, Homer RJ. Airway remodeling in asthma. *J Clin Invest* 1999;104(8):1001-6.
- Finucane KE, Greville HW, Brown PJ. Irreversible airflow obstruction: Evolution in asthma. *Med J Aust* 1985;142(11):602-4.
- Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikander K, Persson T, Selroos O, Sovijarvi A, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331(11):700-5.
- Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339(17):1194-200.
- Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, Wahn U. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. *Lancet* 2000;356(9239):1392-7.
- Martinez FD. Viral infections and the development of asthma. *Am J Respir Crit Care Med* 1995;151(5):1644-7.

- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. The Group Health Medical Associates. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332(3):133-8.
- Overbeek SE, Kerstjens HA, Bogaard JM, Mulder PG, Postma DS. The Dutch Chronic Nonspecific Lung Disease Study Groups. Is delayed introduction of inhaled corticosteroids harmful in patients with obstructive airways disease (asthma and COPD)? The Dutch CNSLD Study Group. *Chest* 1996;110(1):35-41.
- Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987;70(3):171-9.
- Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J* 1982;284(6330):1665-9.
- Selroos O, Pietinalho A, Lofroos AB, Riska H. Effect of early vs. late intervention with inhaled corticosteroids in asthma. *Chest* 1995;108(5):1228-34.
- Stern DA, Burrows B, Halonen M, Wright AL, Martinez FD. Increased prevalence of asthma in Anglo children living in Tucson Arizona. *Am J Respir Crit Care Med* 2000;161:A795.
- Xuan W, Peat JK, Toelle BG, Marks GB, Berry G, Woolcock AJ. Lung function growth and its relation to airway hyperresponsiveness and recent wheeze. Results from a longitudinal population study. *Am J Respir Crit Care Med* 2000;161(6):1820-4.
- Yunginger J, Reed CE, O'Connell EJ, Melton LJ 3rd, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates, 1964-1983. *Am Rev Respir Dis* 1992;146(4):888-94.
- Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). *J Allergy Clin Immunol* 1999;103 (3 Pt 1):376-87.



Expert Panel Report:
Guidelines for the
Diagnosis and
Management of
Asthma

Appendix A: Updated Charts for the Management of Asthma

Appendix A-1. STEPWISE APPROACH FOR MANAGING ASTHMA

Figure 1. Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) With Acute or Chronic Asthma (Updates EPR-2 Figures 3-4a and 3-6)

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, - 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>.....</p> <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 corticosteroids (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 Relief All Patients	<ul style="list-style-type: none"> ■ Bronchodilator as needed for symptoms. Intensity of treatment will depend upon severity of exacerbation. <ul style="list-style-type: none"> - Preferred treatment: Short-acting inhaled beta₂-agonists by nebulizer or face mask and space/holding chamber - Alternative treatment: Oral beta₂-agonists ■ With viral respiratory infection <ul style="list-style-type: none"> - 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 If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control	
<ul style="list-style-type: none"> ■ Minimal or no chronic symptoms day or night ■ Minimal or no exacerbations ■ No limitations on activities; no school/parent's work missed 	<ul style="list-style-type: none"> ■ Minimal use of short-acting inhaled beta₂-agonist ■ Minimal or no adverse effects from medications

- 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. Overreliance on short-acting inhaled beta₂-agonists (e.g., use of short-acting inhaled beta₂-agonist every day, increasing use or lack of expected effect, or 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., allergens 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.

APPENDIX A-1. STEPWISE APPROACH FOR MANAGING ASTHMA (continued)

Figure 2. Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age: Treatment (Updates EPR-2 Figures 3-4a and 3-4b)

Classify Severity: Clinical Features Before Treatment or Adequate Control		Medications Required To Maintain Long-Term Control	
	Symptoms/Day Symptoms/Night	PEF or FEV ₁ 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 treatment: <ul style="list-style-type: none"> - Low-to-medium 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 inhaled beta₂-agonists. ■ Alternative treatment: <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 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%	<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 Relief
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 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.

- 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; 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. Overreliance on short-acting inhaled beta₂-agonists (e.g., use of short-acting inhaled beta₂-agonist every day, increasing use or lack of expected effect, or 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/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled beta₂-agonist
- Minimal or no adverse effects from medications

APPENDIX A-2. USUAL DOSAGES FOR ASTHMA MEDICATIONS

Figure 1. Usual Dosages for Long-Term-Control Medications (Updates EPR-2 Figure 3-5a)

Medication	Dosage Form	Adult Dose	Child Dose*	Comments
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	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	<ul style="list-style-type: none"> ■ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). If daily doses are required, one study suggests improved efficiency and no increase in adrenal suppression when administered at 3 p.m. (Beam et al. 1992). ■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ■ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
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 Beta₂-Agonists				
Salmeterol	MDI 21 mcg/puff	2 puffs q 12 hours	1-2 puffs q 12 hours	<ul style="list-style-type: none"> ■ Should not be used for symptom relief or exacerbations. Use with corticosteroids. ■ May use one dose nightly for symptoms.
	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	<ul style="list-style-type: none"> ■ Efficacy and safety have not been studied in children <5 years of age. ■ Each capsule is for single use only; additional doses should not be administered for at least 12 hours. ■ Capsules should be used only with the Aerolizer™ inhaler and should not be taken orally.

APPENDIX A-2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 1. Usual Dosages for Long-Term-Control Medications (Updates EPR-2 Figure 3-5a)

Medication	Dosage Form	Adult Dose	Child Dose*	Comments
Combined Medication				
Fluticasone/Salmeterol	DPI 100 mcg, 250 mcg, or 500 mcg/50 mcg	1 inhalation bid; dose depends on severity of asthma	1 inhalation bid; dose depends on severity of asthma	<ul style="list-style-type: none"> Not FDA approved in children <12 years of age. 100/50 for patient not controlled on low-to-medium dose inhaled corticosteroids. 250/50 for patients not controlled on medium-to-high dose inhaled corticosteroids.
Cromolyn and Nedocromil				
Cromolyn	MDI 1 mg/puff Nebulizer 20 mg/ampule	2-4 puffs tid-qid 1 ampule tid-qid	1-2 puffs tid-qid 1 ampule tid-qid	<ul style="list-style-type: none"> One dose prior to exercise or allergen exposure provides effective prophylaxis for 1-2 hours.
Nedocromil	MDI 1.75 mg/puff	2-4 puffs bid-qid	1-2 puffs bid-qid	<ul style="list-style-type: none"> See cromolyn above.
Leukotriene Modifiers				
Montelukast	4 mg or 5 mg chewable tablet 10 mg tablet	10 mg qhs	<ul style="list-style-type: none"> 4 mg qhs (2-5 years of age) 5 mg qhs (6-14 years of age) 10 mg qhs (>14 years of age) 	<ul style="list-style-type: none"> Montelukast exhibits a flat dose-response curve. Doses >10 mg will not produce a greater response in adults.
Zafirlukast	10 or 20 mg tablet	40 mg daily (20 mg tablet bid)	<ul style="list-style-type: none"> 20 mg daily (7-11 years of age) 10 mg tablet bid 	<ul style="list-style-type: none"> For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.
Zileuton	300 or 600 mg tablet	2,400 mg daily (give tablets qid)		<ul style="list-style-type: none"> For zileuton, monitor hepatic enzymes (ALT).
Methylxanthines				
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 	<ul style="list-style-type: none"> Adjust dosage to achieve serum concentration of 5-15 mcg/mL at steady-state (at least 48 hours on same dosage). Due to wide inter-patient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important. See figure 3-5a, page 87, EPR-2 for factors that can affect theophylline levels.

*Children ≤ 12 years of age

APPENDIX A-2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 2. Estimated Comparative Daily Dosages for Inhaled Corticosteroids
(Updates EPR-2 Figure 3-5b)

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 DPI: 50, 100, or 250 mcg/ inhalation	88-264 mcg 100-300 mcg	88-176 mcg 100-200 mcg	264-660 mcg 300-600 mcg	176-440 mcg 200-400 mcg	> 660 mcg > 600 mcg	> 440 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

Note

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effect.
- Comparative dosages in the EPR-2 were based on a limited number of published comparative clinical trials and extrapolation of differences in topical potency and lung delivery. This updated comparative dosage chart is based on review of recently published clinical trials involving more than 5,000 patients and published reviews (Barnes PJ et al. 1998; Kelly 1998; Pedersen 1997). The key differences from the EPR-2 include a higher dosage of budesonide and recommendations for two newly available medications: beclomethasone HFA and budesonide suspension for nebulization. The rationale for these changes is summarized as follows:
 - The high dose is the dose that appears likely to be the threshold beyond which significant hypothalamic-pituitary-adrenal (HPA) axis suppression is produced, and, by extrapolation, the risk is increased for other clinically significant systemic effects if used for prolonged periods of time (Martin et al. 2002; Szeffler et al. 2002).
 - The low and medium dose reflects findings from dose-ranging studies in which incremental efficacy within the low-to-medium dose ranges was established without increased systemic effect as measured by overnight cortisol excretion. The studies demonstrated a relatively flat dose-response curve for efficacy at the medium-dose range; that is, increasing the dose to high-dose range did not significantly increase efficacy but did increase systemic effect (Martin et al. 2002; Szeffler et al. 2002).
 - The dose for budesonide dry powder inhaler (DPI) is based on recently available comparative data with other medications, rather than the comparison to budesonide metered-dose inhaler (MDI) that was used in the EPR-2. These new data, including a meta-analysis of seven studies, show that budesonide DPI is comparable to approximately one-half the microgram dose of fluticasone (Barnes NC et al. 1998; Nielsen and Dahl 2000).
 - The dose for beclomethasone HFA is one-half the dose for beclomethasone CFC, based on studies demonstrating that the different pharmaceutical properties of the medications result in enhanced lung delivery for the HFA (a less forceful spray from the HFA propellant and a reengineered nozzle that allows a smaller particle size) (Leach et al. 1998; Busse et al. 1999; Gross et al. 1999; Thompson et al. 1998).
 - The dose for budesonide nebulizer suspension is based on efficacy and safety studies (Baker et al. 1999; Kemp et al. 1999; Shapiro et al. 1998), but no comparative studies with other inhaled corticosteroids are available. It is noted that the efficacy studies did not demonstrate a clear or consistent dose-response, although the high dose of 2.0 mg was effective in a placebo-controlled study in 40 infants with severe asthma (de Blic et al. 1996). In a small open-label long-term safety study, the ACTH stimulated cortisols appeared lower in the 13 infants receiving the high dose of 2.0 mg budesonide compared to infants receiving lower doses, but this was not statistically significant due, perhaps, to the small study size (Scott and Skoner 1999).
- Some doses may be outside package labeling, especially in the high-dose range.
- MDI dosages are expressed as the actuator dose (the amount of the drug leaving the actuator and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, not all of which is available to the patient), which is used in many European countries and in some scientific literature. DPI doses are expressed as the amount of drug in the inhaler following activation.

APPENDIX A-2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 3. Usual Dosages for Quick-Relief Medications (Updates EPR-2 Figure 3-5d)

Medication	Dosage Form	Adult Dose	Child Dose*	Comments
Short-Acting Inhaled Beta₂-Agonists				
<i>MDI</i>				
Albuterol	90 mcg/puff, 200 puffs	<ul style="list-style-type: none"> ■ 2 puffs 5 minutes prior to exercise 	<ul style="list-style-type: none"> ■ 1-2 puffs 5 minutes prior to exercise 	<ul style="list-style-type: none"> ■ An increasing use or lack of expected effect indicates diminished control of asthma. ■ Not generally recommended for long-term treatment. Regular use on a daily basis indicates the need for additional long-term-control therapy. ■ Differences in potency exist, but all products are essentially comparable on a per puff basis. ■ May double usual dose for mild exacerbations. ■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.
Albuterol HFA	90 mcg/puff, 200 puffs	<ul style="list-style-type: none"> ■ 2 puffs tid-qid prn 	<ul style="list-style-type: none"> ■ 2 puffs tid-qid prn 	
Pirbuterol	200 mcg/puff, 400 puffs			
<i>DPI</i>				
Albuterol Rotahaler	200 mcg/capsule	1-2 capsules q 4-6 hours as needed and prior to exercise	1 capsule q 4-6 hours as needed and prior to exercise	
<i>Nebulizer solution</i>				
Albuterol	5 mg/mL (0.5%) 2.5 mg/3 mL 1.25 mg/3 mL 0.63 mg/3 mL	1.25-5 mg in 3 cc of saline q 4-8 hours	0.05 mg/kg (min 1.25 mg, max 2.5 mg) in 3 cc of saline q 4-6 hours	<ul style="list-style-type: none"> ■ May mix with cromolyn or ipratropium nebulizer solutions. May double dose for severe exacerbations.
<i>Nebulizer solution</i>				
Bitolterol	2 mg/mL (0.2%)	0.5-3.5 mg (0.25-1 cc) in 2-3 cc of saline q 4-8 hours	Not established	<ul style="list-style-type: none"> ■ May not mix with other nebulizer solutions.
<i>Nebulizer solution</i>				
Levalbuterol (R-albuterol)	0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/3 mL	0.63 mg-2.5 mg q 4-8 hours	0.025 mg/kg (min. 0.63 mg, max. 1.25 mg) q 4-8 hours	<ul style="list-style-type: none"> ■ 0.63 mg of levalbuterol is equivalent in efficacy and side effects to 1.25 mg of racemic albuterol. The product is a sterile-filled preservative-free unit dose vial.

APPENDIX A-2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 3. Usual Dosages for Quick-Relief Medications (Updates EPR-2 Figure 3-5d)

Medication	Dosage Form	Adult Dose	Child Dose*	Comments
Anticholinergics				
Ipratropium	<i>MDI</i>			<ul style="list-style-type: none"> Evidence is lacking for anticholinergics producing added benefit to beta₂-agonists in long-term-control asthma therapy.
	18 mcg/puff, 200 puffs	2-3 puffs q 6 hours	1-2 puffs q 6 hours	
<i>Nebulizer solution</i>				
0.25 mg/mL (0.025%)	0.25 mg q 6 hours	0.25-0.5 mg q 6 hours		
Ipratropium with albuterol	<i>MDI</i>			<ul style="list-style-type: none"> Contains EDTA to prevent discoloration of the solution. This additive does not induce bronchospasm.
	18 mcg/puff of ipratropium bromide and 90 mcg/puff of albuterol.	2-3 puffs q 6 hours	1-2 puffs q 8 hours	
	200 puffs/canister			
<i>Nebulizer solution</i>				
0.5 mg/3 mL ipratropium bromide and 2.5 mg/3 mL albuterol	3 mL q 4-6 hours	1.5-3 mL q 8 hours		
Systemic Corticosteroids				
<i>(Applies to the first three corticosteroids)</i>				
Methylprednisolone	2, 4, 6, 8, 16, 32 mg tablets	<ul style="list-style-type: none"> Short course "burst": 40-60 mg/day as single or 2 divided doses for 3-10 days 	<ul style="list-style-type: none"> Short course "burst" 1-2 mg/kg/day, maximum 60 mg/day, for 3-10 days 	<ul style="list-style-type: none"> Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
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			
(Methylprednisolone acetate)	<i>Repository injection</i> 40 mg/mL 80 mg/mL	240 mg IM once	7.5 mg/kg IM once	<ul style="list-style-type: none"> May be used in place of a short burst of oral steroids in patients who are vomiting or if adherence is a problem.

* Children ≤12 years of age

APPENDIX A-2. USUAL DOSAGES FOR ASTHMA MEDICATIONS

Figure 4. Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital (Updates EPR-2 Figure 3-10)

Medication	Dosages		Comments
	Adult Dose	Child Dose*	
Short-Acting Inhaled Beta₂-Agonists			
Albuterol			
Nebulizer solution (5.0 mg/mL, 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization	Only selective beta ₂ -agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min.
MDI (90 mcg/puff)	4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed	4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver. Use spacer/holding chamber	As effective as nebulized therapy if patient is able to coordinate.
Bitolterol			
Nebulizer solution (2 mg/mL)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a mg basis	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI (370 mcg/puff)	See albuterol dose	See albuterol dose	Has not been studied in severe asthma exacerbations.
Levalbuterol (R-albuterol)			
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL)	1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed, or 5–7.5 mg/hour continuously	0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed, or 0.25 mg/kg/hour by continuous nebulization	0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects.
Pirbuterol			
MDI (200 mcg/puff)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a mg basis	Has not been studied in severe asthma exacerbations.
Systemic (Injected) Beta₂-Agonists			
Epinephrine 1:1000 (1 mg/mL)	0.3–0.5 mg every 20 minutes for 3 doses sq	0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for 3 doses sq	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/mL)	0.25 mg every 20 minutes for 3 doses sq	0.01 mg/kg every 20 minutes for 3 doses then every 2–6 hours as needed sq	No proven advantage of systemic therapy over aerosol.

APPENDIX A-2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 4. Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital
(Updates EPR-2 Figure 3-10)

Medication	Dosages		Comments
	Adult Dose	Child Dose*	
Anticholinergics			
Ipratropium bromide			
Nebulizer solution (0.25 mg/mL)	0.5 mg every 30 minutes for 3 doses then every 2-4 hours as needed	0.25 mg every 20 minutes for 3 doses, then every 2 to 4 hours	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to beta ₂ -agonist therapy.
MDI (18 mcg/puff)	4-8 puffs as needed	4-8 puffs as needed	Dose delivered from MDI is low and has not been studied in asthma exacerbations.
Ipratropium with albuterol			
Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol.)	3 mL every 30 minutes for 3 doses, then every 2-4 hours as needed	1.5 mL every 20 minutes for 3 doses, then every 2-4 hours	Contains EDTA to prevent discoloration. This additive does not induce bronchospasm.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg of albuterol.)	4-8 puffs as needed	4-8 puffs as needed	
Systemic Corticosteroids			
<i>(Dosages and comments apply to all three corticosteroids)</i>			
Prednisone	120-180 mg/day in 3 or 4 divided doses for 48 hours, then	1 mg/kg every 6 hours for 48 hours then 1-2 mg/kg/day	For outpatient "burst" use 40-60 mg in single or 2 divided doses for adults (children: 1-2 mg/kg/day, maximum 60 mg/day) for 3-10 days.
Methylprednisolone	60-80 mg/day until PEF reaches	(maximum = 60 mg/day) in 2	
Prednisolone	70% of predicted or personal best	divided doses until PEF 70% of predicted or personal best	

* Children ≤12 years of age

Note

No advantage has been found for higher dose corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy provided gastrointestinal transit time or absorption is not impaired. The usual regimen is to continue the frequent multiple daily dose until the patient achieves an FEV₁ or PEF of 50 percent of predicted or personal best and then lower the dose to twice daily. This usually occurs within 48 hours. Therapy following a hospitalization or emergency department visit may last from 3 to 10 days. If patients are then started on inhaled corticosteroids, studies indicate there is no need to taper the systemic corticosteroid dose. If the followup systemic corticosteroid therapy is to be given once daily, one study indicates that it may be more clinically effective to give the dose in the afternoon at 3 p.m., with no increase in adrenal suppression (Beam et al. 1992).

References

- Baker JW, Mellon M, Wald J, Weich M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999;102(2):414-21.
- Barnes NC, Hallett C, Harris TA. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;92(1):95-104.
- Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med* 1998;157(suppl):S1-S53.
- Beam WR, Weiner DE, Martin RJ. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. *Am Rev Respir Dis* 1992;146(6):1524-30.
- Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burt J, Donnell D, Hannon S, Colice GL et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104(6):1215-22.
- de Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, Scheinmann P. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol* 1996;98(1):14-20.
- Gross G, Thompson PJ, Chervinsky P, Vanden Burt J. Hydrofluoroalkane-134a beclomethasone dipropionate, 400 µg, is as effective as chlorofluorocarbon beclomethasone dipropionate, 800 µg, for the treatment of moderate asthma. *Chest* 1999;115(2):343-51.
- Kelly HW. Comparison of inhaled corticosteroids. *Ann Pharmacother* 1998;32(2):220-32.
- Kemp JP, Skoner D, Szefer SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999;83(3):231-9.

Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12(6):1346-53.

Martin RJ, Szeffler SJ, Chinchilli VM, Kraft M, Dolovich M, Boushey HA, Cherniack RM, Craig TJ, Drazen JM, Fagan JK et al. Systemic effect comparisons of six inhaled corticosteroid preparations. *Am J Respir Crit Care Med* 2002;165:1377-83.

National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. *Guidelines for the diagnosis and management of asthma*. Expert Panel Report 2, Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; 1997.

Nielsen LP, Dahl R. Therapeutic ratio of inhaled corticosteroids in adult asthma: A dose-range comparison between fluticasone propionate and budesonide, measuring their effect on bronchial hyper-responsiveness and adrenal cortex function. *Am J Respir Crit Care Med* 2000;162(6):2053-7.

Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997;52(39 suppl):1-34.

Scott MB, Skoner DP. Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma. *J Allergy Clin Immunol* 1999;104(4 Pt 2):200-9.

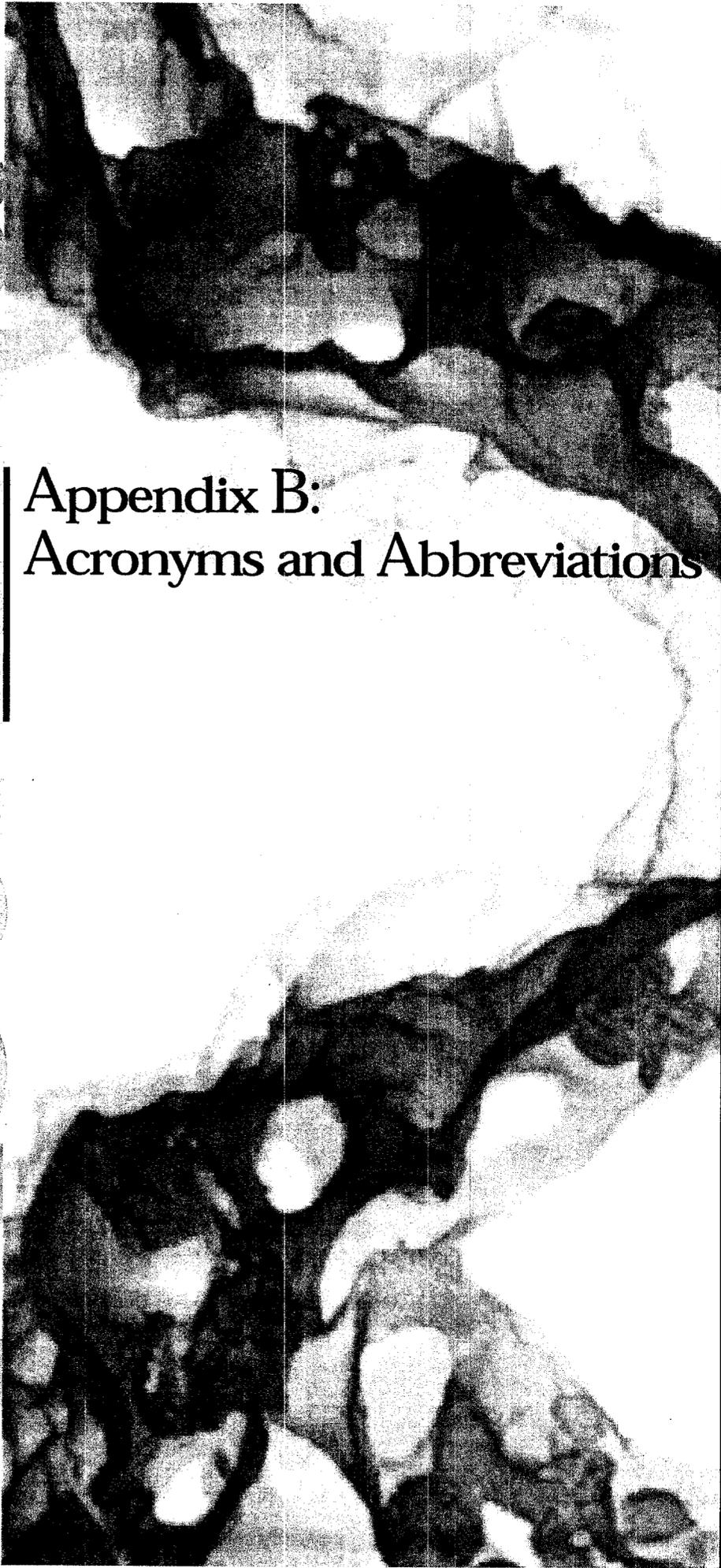
Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol* 1998;102(5):789-96.

Szeffler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, Craig TJ, Dolovich M, Drazen JM, Fagan JK et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109(3):410-8.

Thompson PJ, Davies RJ, Young WF, Grossman AB, Donnell D. Safety of hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol. *Respir Med* 1998;92(suppl):33-39.

Expert Panel Report:
Guidelines for the
Diagnosis and
Management of
Asthma

Appendix B: Acronyms and Abbreviations



**Appendix B:
Acronyms and
Abbreviations**

ACTH	adrenocorticotrophic hormone
AHRQ	Agency for Healthcare Research and Quality
BDP	beclomethasone dipropionate
BMD	bone mineral density
BUD	budesonide
CAMP	Childhood Asthma Management Program
CI	confidence interval
COPD	chronic obstructive pulmonary disease
ctl	control arm
DPI	dry powder inhaler
EIB	exercise-induced bronchospasm
EPR—Update2002	Expert Panel Report-2
EPR-2	Federal Drug Administration
FDA	forced expiratory volume in 1 second
FEV ₁	fluticasone propionate
FP	hypothalamic-pituitary-adrenal
HPA	interferon
IFN	interleukin
IL	kilogram
kg	leukotriene receptor antagonist
LTRA	metered-dose inhaler
MDI	Medical Subject Heading
MeSH	milligram
mg	milliliter
mL	not available
NA	National Asthma Education and Prevention Program
NAEPP	National Heart, Lung, and Blood Institute
NHLBI	not reported
NR	peak expiratory flow
PEF	pharmaceutical industry
pharm. ind.	predicted
Pred	randomized controlled trial
RCT	standard deviation
SD	systematic review of the evidence
SRE	symptoms
sx	Technology Evaluation Center
TEC	T-helper
Th	treatment
tx	

For More Information

The NHLBI Health Information Center is a service of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. The NHLBI Health Information Center provides information to health professionals, patients, and the public about the treatment, diagnosis, and prevention of heart, lung, and blood diseases. For more information, contact:

NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Phone: 301-592-8573
TTY: 240-629-3255
Fax: 301-592-8563
Web site: <http://www.nhlbi.nih.gov>

Discrimination Prohibited: Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the National Heart, Lung, and Blood Institute must be operated in compliance with these laws and Executive Orders.



U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES



National Institutes of Health



National Heart, Lung,
and Blood Institute

NIH Publication No. 02-5074
June 2003

spine

Expert Panel Report:
Guidelines for the Diagnosis and Management of Asthma

Update on Selected Topics 2002

National Heart, Lung,
and Blood Institute