SECTION 4, MANAGING ASTHMA LONG TERM IN CHILDREN 0–4 YEARS OF AGE AND 5–11 YEARS OF AGE

Diagnosis and Prognosis of Asthma in Children

Long-term management decisions begin with diagnosis and an appreciation for factors that may influence the prognosis for asthma in children.

DIAGNOSIS OF ASTHMA

0–4 Years of Age: **The Expert Panel recommends that essential elements in the evaluation include the history, symptoms, physical examination, and assessment of quality of life, as discussed in "Component 1: Measures of Asthma Assessment and Monitoring." A therapeutic trial with medications listed in figure 4–1a will also aid in the diagnosis.**

Several studies show that as many as 50–80 percent of children who have asthma develop symptoms before their fifth birthdays. Diagnosis can be difficult in this age group and has important implications. On the one hand, asthma in early childhood is frequently underdiagnosed (receiving such inappropriate labels as chronic bronchitis, wheezy bronchitis, reactive airway disease (RAD), recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract infections). Therefore, many infants and young children do not receive adequate therapy. On the other hand, not all wheeze and cough are caused by asthma, and caution is needed to avoid giving infants and young children inappropriate prolonged asthma therapy. Episodic or chronic wheeze, cough, and breathlessness also may be seen in other, less common, conditions, including cystic fibrosis, vascular ring, tracheomalacia, primary immunodeficiency, congenital heart disease, parasitic disease, and foreign-body aspiration.

Diagnosis is complicated by the difficulty in obtaining objective measurements of lung function in this age group.

5–11 Years of Age: **The Expert Panel recommends that the diagnosis in children 5 years of age and older should follow the same procedures recommended in "Component 1: Measures of Asthma Assessment and Monitoring."**

PROGNOSIS OF ASTHMA

Although asthma clearly has been demonstrated to be associated with airway inflammation and structural changes in adult patients, the age when these changes begin in asthma has not yet been defined precisely. Elevations in both inflammatory cells and mediators have been demonstrated in bronchoalveolar lavage specimens obtained from preschool children who have recurrent wheezing (Krawiec et al. 2001). Recently, endobronchial biopsy specimens from infants who have wheezing and documented airflow obstruction that was both reversible and nonreversible following the administration of bronchodilator were compared to four other groups of subjects: infants who had wheezing without airflow obstruction, school-aged children who had difficult-to-control asthma, and both school-aged children and adults who did not have asthma (Saglani et al. 2005). In the infants who had wheezing, regardless of bronchodilator reversibility or atopic status, the characteristic histopathologic features of thickening of the laminar reticularis and eosinophil inflammation were absent. Taken together, these data indicate that the airway inflammatory responses and structural changes that are characteristic of

asthma develop during the preschool years and may follow, and not precede, the physiologic changes associated with asthma.

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. Two general patterns of illness appear 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 absolute markers are available to predict the prognosis of an individual child; however, an asthma predictive index has been developed that identifies risk factors for developing persistent asthma. Children under 3 years of age who had four or more episodes of wheezing in the past year that lasted more than 1 day and affected sleep are significantly likely to have persistent asthma after the age of 5 years if they also have either (1) one of the following: parental history of asthma, a physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens, OR (2) two of the following: evidence of sensitization to foods, ≥4 percent peripheral blood eosinophilia, or wheezing apart from colds (See section 2, "Definition and Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma.").

PREVENTION OF ASTHMA PROGRESSION

The Expert Panel concludes that evidence to date does not support the previously hypothesized contention that early intervention with an ICS, either continuously (CAMP 2000; Guilbert et al. 2006) or intermittently (Bisgaard and Szefler 2006), may alter the underlying severity or progression of the disease. ICSs should be used to control asthma symptoms and to improve the child's quality of life, but their use should not be initiated or prolonged for the purpose of changing the natural history of the disease (i.e., the underlying severity or progression of asthma) (Evidence A).

Although a preliminary, retrospective study suggested 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 more recent long-term randomized controlled trial (RCT) in children 5–12 years of age (CAMP 2000) (Evidence A). The best available evidence does not support the assumption that children 5–12 years of age who have mild or moderate persistent asthma, on average, have a progressive decline in lung function. A followup analysis from the Childhood Asthma Management Program (CAMP) study indicates, however, that a subset of participants in both treatment and placebo groups experienced progressive reductions in lung growth compared to predicted measures (Covar et al. 2004). Further studies are needed to assess this risk fully.

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 early childhood asthma appears to occur during the first 3–5 years of life (Martinez et al. 1995; Morgan et al. 2005). A recent study enrolled children 2–3 years of age who were at high risk of developing persistent asthma and compared ICS therapy to placebo. The study demonstrated that this intervention clearly reduced symptom burden and the frequency of exacerbations while the ICS was administered daily for 2 years, but this therapy did not prevent the reappearance of persistent symptoms in the year of followup after discontinuing therapy (Guilbert et al. 2006).

MONITORING ASTHMA PROGRESSION

The Expert Panel recommends that the following measures be monitored over the course of children's followup visits, especially in those children who have moderate or severe persistent asthma (require Step 3 care or higher), to assess both impairment and risk domains for the development of progressive disease: course of medications, including increasing use of SABAs and escalation of long-term control medications; episodes of severe exacerbations requiring systemic corticosteroids, urgent care visits, or hospitalizations; pulmonary function measures including prebronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) and FEV_1 (percent predicted) and postbronchodilator FEV_1 (percent predicted) (Evidence B). If these measures so indicate, therapy should be stepped up to ensure adequate asthma control. See box 4–1 for a sample patient record for monitoring asthma progression in children.

BOX 4–1. SAMPLE RECORD FOR MONITORING THE RISK DOMAIN IN CHILDREN: RISK OF ASTHMA PROGRESSION (INCREASED EXACERBATIONS OR NEED FOR DAILY MEDICATION, OR LOSS OF LUNG FUNCTION), AND POTENTIAL ADVERSE EFFECTS OF CORTICOSTEROID THERAPY

Patient name:

Date					
Long-term control medication					
ICS daily dose*					
LTRA					
LABA					
Theophylline					
Other					
Significant exacerbations					
Exacerbations (number/month)					
Oral systemic corticosteroids (number/year)*					
Hospitalization (number/year)					
Pulmonary function					
Prebronchodilator FEV_1/FVC					
Prebronchodilator FEV_1 percent predicted					
Postbronchodilator FEV_1 percent predicted					
Percent bronchodilator reversibility					
Potential risk of adverse corticosteroid effects (as indicated by corticosteroid dose and duration of treatment)					
Height, cm					
Percentile Plots of growth velocity					

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; LTRA, leukotriene receptor antagonist

*Consider ophthalmologic exam and bone density measurement in children using high doses of ICS or multiple courses of oral corticosteroids.

Although there is no indication that treatment alters the progression of asthma severity in children, asthma is highly variable over time (see sections on "Natural History" and "Pathophysiology"), and treatment may have to be adjusted accordingly.

Treatment: Principles of Stepwise Therapy in Children

The Expert Panel recommends that the goal of asthma therapy is to maintain long-term control of asthma with the least amount of medication and hence minimal risk for adverse effects. Control of asthma may be viewed in the context of two domains—impairment and risk—and within these domains, defined as follows (Evidence A).

- **Reducing impairment**
  - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion)
  - Require infrequent use (≤2 days a week) of SABA for quick relief of symptoms (not including prevention of EIB)
  - Maintain (near) normal pulmonary function
  - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
  - Meet patients' and families' expectations of and satisfaction with asthma care
- **Reducing risk**
  - Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations
  - Prevent progressive loss of lung function; for children, prevent reduced lung growth
  - Provide optimal pharmacotherapy with minimal or no adverse effects

The Expert Panel recommends that the stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary (Evidence B, extrapolated from studies in older children and adults) and decreased when possible (Evidence D), is used to achieve and maintain this control.

The distinction between assessing impairment and risk to make treatment decisions draws attention to the multifaceted nature of asthma and the need to consider all manifestations of the disease. Assessing both domains emphasizes the need to consider separately asthma's effects on quality of life and functional capacity on an ongoing basis (i.e., at present) and the risks asthma presents for adverse events in the future, such as exacerbations or progressive reduction in lung growth. These domains may respond differentially to treatment. For example, a large study of children who had asthma revealed that 30 percent of the low-dose ICS treatment group, whose levels of impairment (symptoms, SABA use, lung function) improved, remained at risk of exacerbations requiring oral systemic corticosteroids (CAMP 2000).

The steps of care for managing asthma to achieve and maintain this control are presented in figures 4–1a and 4–1b. Deciding which step of care is appropriate for a patient depends on whether long-term control therapy is being initiated for the first time or whether therapy is being adjusted (i.e., stepped up to regain control or stepped down, for patients who have maintained control for a sufficient length of time, to determine the minimal amount of medication required to maintain control and/or reduce the risk of side effects). The classification of asthma severity, which considers the severity of both impairment and risk domains, provides a guide for initiating therapy for patients who are not currently taking long-term control medications. (See figures 4–2a and 4–2b for children 0–4 years of age and 5–11 years of age, respectively.) Once therapy is selected, or if the patient is already taking long-term control medication, the patient's response to therapy will guide decisions about adjusting therapy based on the level of control achieved in both the impairment and risk domains (figure 4–3a for children 0–4 years of age and figure 4–3b for children 5–11 years of age).

ACHIEVING CONTROL OF ASTHMA

Selecting Initial Therapy

0–4 Years of Age: Initiating Long-Term Control Therapy. **The Expert Panel concludes that initiating daily long-term control therapy:**

- **Is recommended for reducing impairment and risk of exacerbations in infants and young children who had four or more episodes of wheezing in the past year that lasted more than 1 day and affected sleep AND who have risk factors for developing persistent asthma: either (1) one of the following: parental history of asthma, a physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens OR (2) two of the following: evidence of sensitization to foods, ≥4 percent peripheral blood eosinophilia, or wheezing apart from colds (Evidence A).**

- **Should be considered for reducing impairment in infants and young children who consistently require symptomatic treatment more than 2 days per week for a period of more than 4 weeks (Evidence D).**

- **Should be considered for reducing risk in infants and young children who have a second asthma exacerbation requiring systemic corticosteroids within 6 months (Evidence D).** Recognition of these children and treatment with daily low-dose ICS therapy can significantly reduce overall symptom burden and the frequency of exacerbations, even though such treatment will not alter the underlying severity of asthma in later childhood (Guilbert et al. 2006).

- **May be considered for use only during periods of previously documented risk for a child (Evidence D). If daily long-term control therapy is discontinued after the season of increased risk, written asthma action plans indicating specific signs of worsening asthma and actions to take should be reviewed with the caregivers, and a clinic contact should be scheduled 2–6 weeks after discontinuation of therapy to ascertain whether adequate control is maintained satisfactorily (Evidence D).** Because of seasonal variations in exacerbations among children, such as during the seasons of increased upper respiratory infections (Johnston et al. 2006), it is possible, although not yet evaluated systematically, that some of the children described above may require daily therapy only during previously documented periods of increased risk of exacerbations for that individual.

5–11 Years of Age: Initiating Long-Term Control Therapy. **The Expert Panel recommends daily long-term control therapy for children who have persistent asthma (Evidence A).** In deciding when to initiate daily long-term control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma versus the possible adverse effects of medications given over prolonged periods. Long-term studies in children 5–12 years of age at the time of enrollment conclude that ICSs improve health outcomes for children who have mild or moderate persistent asthma, and that the potential albeit small risk of delayed growth from the use of ICSs is well balanced by their effectiveness (Evidence A) (CAMP 2000). Furthermore, available long-term data indicate that most children treated with recommended doses of ICSs achieve their predicted adult heights (Agertoft and Pedersen 2000). It is noted that the long-term prospective studies on growth involved budesonide, and retrospective analyses included studies on beclomethasone, but the results have been generalized to include all ICS preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of ICSs on growth is a drug-class effect.

Adjusting Therapy

The Expert Panel recommends that, if a child is already taking long-term control medication, treatment decisions are based on the level of asthma control that has been achieved: therapy should be stepped up if necessary to achieve control (Evidence B—extrapolated from studies in youths and adults) (See figures 4–3a and 4–3b.). After identifying the patient's treatment step, based on the patient's or parents' report of what medications the patient is currently taking, classify the level of control by measuring *impairment* based on symptoms, SABA use, and lung function (in children 5–11 years of age) and *risk* based on previous exacerbations and potential side effects. In general, the assessment leads to the following sequence of actions.

- **Address the *impairment* domain.** Consider factors related to the different age groups.

  - ***0–4 years of age:*** The level of impairment generally is judged on the most severe symptom. The risk domain is usually more strongly associated with asthma morbidity than the impairment domain, because children are often symptom free between exacerbations.

  - ***5–11 years of age:*** The level of impairment generally is judged on the most severe measure among symptom report, asthma control score (using validated tools if available), and pulmonary function measures. For patients at step 3 or higher care, if office spirometry is feasible and suggests poorer control than does the assessment of impairment based on other measures, consider fixed airway obstruction as the explanation and reassess the other measures of impairment. If fixed airway obstruction does not appear to be the explanation, consider a step up in therapy, because low FEV_1 is a predictor of risk for exacerbations in children. (See "Component 1: Measures of Asthma Assessment and Monitoring.")

  - **The Expert Panel recommends the following actions if control of the impairment domain is not achieved and maintained at any step of care:**

    - **Patient adherence and technique in using medications correctly should be assessed and addressed as appropriate (Evidence C).** See

"Component 2: Education for a Partnership in Asthma Care" for discussion on assessing adherence. Key questions to ask the child and parent include:

- Which medicines is your child currently taking? How often?
- Who is responsible for administering the child's medicine?
- Please show me how the child takes the medicine.
- How many times a week does the child miss taking the medication?
- What problems have you/your child had taking the medicine (cost, time, lack of perceived need)?
- What concerns do you have about your asthma medicines?

♦ **Other factors that diminish control of asthma impairment should be addressed as possible reasons for poor response to therapy and targets for intervention (Evidence C).** These factors include the presence of a coexisting condition (e.g., sinusitis), a new or increased exposure to allergens or irritants, or psychosocial problems. In some cases, alternative diagnoses, such as vocal cord dysfunction (VCD), should be considered.

♦ **If patient adherence, inhaler technique, and environmental control measures are adequate, and asthma is not well controlled, a step up in treatment may be needed (Evidence B—extrapolated).** For patients who have asthma that is not well controlled, in general step up one treatment step. For patients who have *very poor* asthma control, consider increasing treatment by two steps, a course of oral corticosteroids, or both (Evidence D).

■ **Address the *risk* domain.**

— **The Expert Panel recommends the following actions if control of the risk of exacerbations is not achieved or maintained (Evidence D):**

♦ ***0–4 years of age:*** If there is a history of one or more exacerbations, review adherence to medications and control of environmental exposures, review the patient's written asthma action plan to confirm that it includes oral prednisone for patients who have histories of severe exacerbations, and consider stepping up therapy to the next level (Evidence D).

♦ ***5–11 years of age:*** If the history of exacerbations suggests poorer control than does the assessment of impairment, the following actions are recommended: reassess the impairment domain, review adherence to medications and control of environmental exposures, review the patient's written asthma action plan to confirm that it includes oral prednisone for patients who have a history of severe exacerbations, and consider a step up in therapy, especially for children who have reduced lung function (Fuhlbrigge et al. 2001, 2006).

- **Address the *risk* domain with regard to side effects.**

  The Expert Panel recommends consideration of alternative and/or adjunctive therapies within the step of care the patient is receiving if the patient experiences troublesome or debilitating side effects. In addition, confirm efforts to control environmental exposures (Evidence D).

- **Consider referral to an asthma specialist. The Expert Panel *recommends* referral to an asthma specialist for consultation or comanagement of the patient if (Evidence D):**

  - **There are difficulties achieving or maintaining control of asthma.**

  - **A child 0–4 years of age requires step 3 care or higher (step 4 care or higher for children 5–11 years of age) to achieve and maintain control or if additional education is indicated to improve the patients' management skills or adherence. Referral may be *considered* if a child 0–4 years of age requires step 2 care or a child 5–11 years of age requires step 3 care.**

  - **The patient has had an exacerbation requiring hospitalization.**

  - **Immunotherapy or other immunomodulators are considered, or additional tests are indicated, to determine the role of allergy.**

MAINTAINING CONTROL OF ASTHMA

The Expert Panel recommends that regular followup contact is essential (Evidence B). Contact at 1- to 6-month intervals is recommended, depending on the level of control; consider a 3-month interval if a step down in therapy is anticipated (Evidence D). Clinicians need to assess whether control of asthma has been maintained and whether a step up or down in therapy is appropriate. Clinicians also need to monitor and review the written asthma action plan, which includes the medications, and the patient's self-management behaviors for daily management and handling worsening asthma (e.g., inhaler and peak flow monitoring techniques, actions to control factors that aggravate his or her asthma) (See "Component 2: Education for a Partnership in Asthma Care," figures 3–11 and 3–15, respectively.).

The Expert Panel recommends that once well-controlled asthma is achieved and maintained for at least 3 months, a reduction in pharmacologic therapy—a step down—can be considered helpful to identify the minimum therapy for maintaining well-controlled asthma (Evidence D). The opinion of the Expert Panel is that the dose of ICS may be reduced about 25–50 percent every 3 months to the lowest dose possible required to maintain control (Evidence D). Reduction in therapy should be gradual, because asthma control can deteriorate at a highly variable rate and intensity. The patient should be instructed to contact the clinician if and when asthma worsens. Guidelines for the rate of reduction and intervals for evaluation have not been validated, and clinical judgment of the individual patient's response to therapy is important. Patients may relapse when the ICS is completely discontinued (CAMP 2000; Guilbert et al. 2006; Waalkens et al. 1993); however, giving daily therapy only during periods of documented risk for a child (e.g., seasons of viral respiratory infections) may be considered (Evidence D).

KEY POINTS: INHALED CORTICOSTEROIDS IN CHILDREN

- ICSs are the preferred therapy for initiating long-term control therapy in children of all ages (Evidence A).
- ICSs, especially at low doses and even for extended periods of time, are generally safe (Evidence A).
- The potential for the adverse effect of low- to medium-dose ICS on linear growth is usually limited to a small reduction in growth velocity, approximately 1 cm in the first year of treatment, that is generally not progressive over time (Evidence A). Children receiving ICS should be monitored, by using a stadiometer, for changes in growth (Evidence D).
- The potential risks of ICSs are well balanced by their benefits.
- High doses of ICS administered for prolonged periods of time (for example, more than 1 year), particularly in combination with frequent courses of systemic corticosteroid therapy, may be associated with adverse growth effects and risk of posterior subcapsular cataracts or reduced bone density. Age-appropriate dietary intake of calcium and vitamin D should be reviewed with the child's caregivers (Evidence D). Slit-lamp eye exam and bone densitometry should be considered (Evidence D).
- See also section 3, component 4—Medications.

KEY POINTS: MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE

- Diagnosing asthma in infants is often difficult. Underdiagnosis and undertreatment are key problems in this age group. However, not all wheeze and cough are caused by asthma, and caution is needed to avoid giving inappropriate prolonged asthma therapy (EPR—2 1997). Thus, a diagnostic trial of asthma medications may be helpful.
- Treatment for young children, especially infants, who have asthma has not been studied adequately. Most recommendations for treatment are based on limited data and extrapolations from studies in older children and adults.
- The initiation of long-term control therapy:
  - Is recommended for reducing impairment and risk of exacerbations in infants and young children who had four or more episodes of wheezing in the past year that lasted more than 1 day and affected sleep AND who have either (1) one of the following: a parental history of asthma, a physician's diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens OR (2) two of the following: evidence of sensitization to foods, $\geq$4 percent peripheral blood eosinophilia, or wheezing apart from colds (Evidence A).

  - — Should be considered for reducing impairment in infants and young children who consistently require symptomatic treatment more than 2 days per week for a period of more than 4 weeks (Evidence D).
  - — Should be considered for reducing risk in infants and young children who have two exacerbations requiring systemic corticosteroids within 6 months (Evidence D).
  - — May be considered for use only during periods, or seasons, of previously documented risk for a child (Evidence D).

- When initiating daily long-term control therapy, daily ICS is the preferred treatment (Evidence A). Alternative treatment options (listed here in alphabetical order) include cromolyn (Evidence B—extrapolated from studies in older children) or leukotriene receptor antagonist (LTRA) (montelukast). The initial choice of long-term control medication includes consideration of treatment effectiveness, the domain of particular relevance for the individual patient (impairment, risk, or both), the patient's history of previous response to therapies, the ability of the patient and family to use the medication correctly, and anticipated patient and family adherence to the treatment regimen (Evidence D).
- Response to therapy should be carefully monitored. If there is a clear and positive response for at least 3 months, a careful step down in therapy should be attempted to identify the lowest dose required to maintain control. If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, the therapy should be discontinued and alternative therapies or diagnoses should be considered (Evidence D).
- Administration of an ICS early in the course of the disease will not alter the underlying progression of the disease (Evidence A). ICSs should be used to control symptoms, prevent exacerbations, and improve the child's quality of life, but their use should not be initiated or prolonged for the purpose of changing the progression or underlying severity of the disease.

The following recommendations for different steps of pharmacologic therapy to gain and maintain asthma control are intended to be general guidelines for making therapeutic decisions. They are not intended to be prescriptions for individual treatment. Specific therapy should be tailored to the needs and circumstances of individual patients. Pharmacologic therapy must be accompanied at every step by measures to control those environmental factors and comorbid conditions that can impede asthma control and by patient education (See section 3, "Component 2: Education for a Partnership in Asthma Care" and "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma.").

Treatment: Pharmacologic Issues for Children 0–4 Years of Age

The Expert Panel recommends that treatment of young children is often in the form of a therapeutic trial; therefore, it is essential to monitor the child's response to therapy. If there is no clear response within 4–6 weeks, the therapy should be discontinued and alternative therapies or alternative diagnoses considered (Evidence D). If there is a clear and positive response for at least 3 months, a step down in therapy should be undertaken to the lowest possible doses of medication required to maintain asthma control (Evidence D).

Treatment for young children, especially infants, has not been studied adequately. Recommendations are based on expert opinion, limited data, and extrapolations from studies in older children and adults (Baker et al. 1999; Kemp et al. 1999).

FDA APPROVAL

The following long-term control medications are approved by the FDA for young children:

- ICS budesonide nebulizer solution (approved for children 1–8 years of age)
- ICS fluticasone DPI (approved for children 4 years of age and older)
- Long-acting inhaled beta$_2$-agonist (LABA) salmeterol DPI and combination product (salmeterol + fluticasone) DPI (approved for children 4 years of age and older)
- LTRA montelukast, based on safety data rather than efficacy data, in a 4 mg chewable tablet (approved for children 2–6 years of age) and in 4 mg granules (approved down to 1 year of age)
- Cromolyn nebulizer (approved for children ≥2 years of age)

DELIVERY DEVICES

Several delivery devices are available for infants and young children. The dose received may vary considerably among devices and age groups. (See "Component 4: Medications," figure 3–24, for a summary of therapeutic issues regarding aerosol delivery devices.) In general, children less than 4 years of age will have less difficulty with an MDI plus valved holding chamber (VHC) with a face mask or a nebulizer with a face mask. The child's caregivers must be instructed in the proper use of nebulizers, appropriate size of face masks, and how to use VHCs with and without face masks for medication delivery to be effective and efficient. Using the "blow by" technique, holding the mask or open tube near the infant's nose and mouth, is not appropriate. For younger children, nebulizer therapy is an option for administering budesonide and cromolyn. Children between 3 and 5 years old may begin therapy with an MDI and spacer or VHC alone, but if the desired therapeutic effects are not achieved, they may require a nebulizer or an MDI plus spacer or VHC and face mask.

Treatment: Pharmacologic Steps for Children 0–4 Years of Age

Figure 4–1a presents treatment options within the stepwise approach to therapy. Selection of the step of care for a patient depends on whether long-term control therapy is being initiated for the first time or therapy is being adjusted. Classifying severity in patients not currently taking long-term control medication will guide decisions for initiating therapy (See figure 4–2a.). Assessing the level of asthma control in patients taking long-term control medication will guide decisions for adjusting therapy (See figure 4–3a.). Figures 4–4a, b, and c list usual dosages of asthma medications.

INTERMITTENT ASTHMA

Step 1 Care, Children 0–4 Years of Age

The Expert Panel recommends the following treatment for intermittent asthma:

- **SABA taken as needed to treat symptoms is usually sufficient therapy for intermittent asthma (EPR—2 1997).** If effective in relieving symptoms, intermittent use of SABA can continue on an as-needed basis. Increasing use, however, may indicate more severe or inadequately controlled asthma and thus a need to step up therapy.

- **The Expert Panel recommends the following actions for managing exacerbations due to viral respiratory infections, which are especially common in children (EPR—2 1997). These exacerbations may be intermittent yet severe.**

  — If the symptoms are mild, SABA (every 4–6 hours for 24 hours, longer with a physician consult) may be sufficient to control symptoms and improve lung function. If this therapy needs to be repeated more frequently than every 6 weeks, consider a step up in long-term care.

  — If the viral respiratory infection provokes a moderate-to-severe exacerbation, a short course of oral systemic corticosteroids should be considered (1 mg/kg/day prednisone or equivalent for 3–10 days).

  — For those patients who have a history of severe exacerbations with viral respiratory infections, consider initiating oral systemic corticosteroids at the first sign of the infection.

- **The Expert Panel recommends that a detailed written asthma action plan be developed for those patients who have intermittent asthma and a history of severe exacerbations (Evidence B)** (See “Component 2: Education for a Partnership in Asthma Care.”). Intermittent asthma—infrequent exacerbations separated by periods of no symptoms and normal pulmonary function—is often mild. Some patients, however, who have intermittent asthma experience sudden, severe, and life-threatening exacerbations. It is essential to treat these exacerbations accordingly. The patient’s written asthma action plan should include indicators of worsening asthma (specific symptoms) as well as specific recommendations for using SABAs, early administering of oral systemic corticosteroids, and seeking medical care.

  Furthermore, periodic monitoring (See “Component 1: Measures of Asthma Assessment and Monitoring.”) of the patient is appropriate to evaluate whether the patient’s asthma is indeed intermittent. The occurrence of two or more severe exacerbations within 6 months without symptoms in between them is an example of a child’s having minimal or intermittent impairment, but a persistent, high risk of exacerbation. In the opinion of the Expert Panel, this child should be considered to have persistent asthma (See figure 4–2a.). Such children can benefit from daily long-term control therapy (Bisgaard et al. 2004, 2005).

PERSISTENT ASTHMA

The Expert Panel recommends the following therapy for persistent asthma:

- **Daily long-term control medication at step 2 or above is recommended for children who had four or more wheezing episodes in 1 year and risk factors for persistent asthma (Evidence A). Consider daily therapy for children who have a second exacerbation requiring oral systemic corticosteroids in 6 months or children who consistently require symptomatic treatment >2 days a week for > 4 weeks (Evidence D).**

- **Quick-relief medication must be available. SABA should be taken as needed to relieve symptoms (EPR—2 1997).** The intensity of treatment will depend on the severity of the exacerbation (See section 5, "Managing Exacerbations of Asthma."). Use of SABA more than 2 days a week for symptom control (not prevention of EIB), or increasing use, indicates the need for additional long-term control therapy.

- **To gain more rapid control of asthma, a course of oral systemic corticosteroids may be necessary for the patient who has an exacerbation at the time long-term control therapy is started or in patients who have moderate or severe asthma with frequent interference with sleep or normal activity (EPR—2 1997).**

- **Close monitoring of the child's response to therapy is recommended (EPR—2 1997); treatment recommendations are based on limited data in this age group, and thus treatment is often in the form of a therapeutic trial. If no clear response occurs within 4–6 weeks and medication technique and adherence are satisfactory, the treatment should be discontinued and a change in therapy or alternative diagnoses should be considered. If there is a clear and positive response for at least 3 months, a step down in therapy should be undertaken to the lowest possible doses of medication required to maintain asthma control (Evidence D).**

- **Giving daily therapy only during specific periods of previously documented risk for a child may be considered (Evidence D).** Although this approach is not yet evaluated, it is possible that children who have specifically defined periods of increased risk for symptoms and exacerbations (e.g., during the seasons in which viral respiratory infections are common) may require daily long-term control therapy only during this historically documented period of risk. If long-term control therapy is discontinued, then written action plans for recognizing and handling signs of worsening asthma should be reviewed with the caregivers, and followup appointments 2–6 weeks later should be conducted to ensure that asthma control is maintained.

Step 2 Care, Children 0–4 Years of Age

- **Preferred treatment for step 2 care is daily ICS at a low dose (Evidence A based on studies of individual drug efficacy in this age group; comparator trials are not available).**

- **Alternative, but not preferred, treatments include (listed in alphabetical order) cromolyn (Evidence B—extrapolated from studies in older children) and montelukast (Evidence A). If an alternative treatment is selected and adequate asthma control is**

not achieved and maintained in 4–6 weeks, then discontinue that treatment and use the preferred medication before stepping up therapy.

- **Theophylline is not recommended as alternative treatment (EPR—2 1997)** because of its erratic metabolism during viral infections and febrile illness in children less than 5 years of age and the need to closely monitor and control serum concentrations.

At present, few studies of medications have been conducted in children younger than 3 years of age. ICSs have been shown to be effective in long-term clinical studies with infants and young children (Bisgaard et al. 2004; Guilbert et al. 2006). In contrast, cromolyn has demonstrated inconsistent symptom control in children younger than 5 years of age (Tasche et al. 2000). Montelukast has shown some effectiveness in children 2–5 years of age (Knorr et al. 2001) and, in young children who have a history of exacerbations, can reduce symptoms associated with exacerbations and the amount of ICSs used during exacerbations, although montelukast was not shown to reduce requirements for oral systemic corticosteroid to control exacerbations (Bisgaard et al. 2005).

Therefore, it is the opinion of the Expert Panel that low-dose ICS is the preferred daily long-term control therapy for infants and young children who have never before been treated with long-term control therapy. This medication should be prescribed in the form of a therapeutic trial, and response should be monitored carefully. Treatment should be stopped if a clear beneficial effect is not obvious within 4–6 weeks and the patient/family medication technique and adherence are satisfactory. If a clear and positive response exists for at least 3 months (and given the high rates of spontaneous remission of symptoms in this age group), the need for ICS therapy should be reevaluated. A step down to intermittent therapy, as needed for symptoms, may then be considered (Evidence D). If long-term control therapy is discontinued, then written asthma action plans for recognizing and handling signs of worsening asthma should be reviewed with the caregivers, and followup appointments should be conducted 2–6 weeks later to ensure that asthma control is maintained.

A trial of montelukast in children 2 years of age or older can be considered in situations in which inhaled medication delivery is suboptimal due to poor technique or adherence.

Step 3 Care, Children 0–4 Years of Age

- **Medium-dose ICS is the preferred step 3 treatment (Evidence D). The Expert Panel recommends increasing the dose of ICS, for children 0–4 years of age whose asthma is not well controlled on low doses of ICS, to ensure that an adequate dose is delivered (due to the inherent difficulty and variability of delivering aerosols) before adding adjunctive therapy (Evidence D).**

Only a few data are available to address step 3 care in children from 0 to 4 years of age in regard to the various options that have been studied in older children and adults (See the section on “Managing Asthma Long Term—Youths ≥12 Years of Age and Adults.”). The pivotal trials for budesonide nebulizer solution included children 6 months to 8 years of age and failed to detect a significant dose-dependent effect, from doses ranging from 0.25 mg twice daily to 1.0 mg twice daily, on either impairment or risk domains (Szefler and Eigen 2002). In children <5 years of age, ICS clearly reduced risk and impairment compared to placebo (Bisgaard 1999; Roorda et al. 2001; Szefler and Eigen 2002). One trial in 237 children 1–4 years of age suggested a dose-dependent decrease in exacerbations (risk domain), some symptoms, and as-needed albuterol use (impairment domain) from fluticasone propionate 100 mcg/day and

200 mcg/day by MDI plus VHC (Bisgaard 1999), although the 100 mcg/day did not lower exacerbations differently from placebo. Some trials comparing budesonide nebulizer solution 0.25 mg twice daily to 1.0 mg daily in infants 5–40 months old have shown improved symptom control with the higher dose; other trials show no difference (Szefler and Eigen 2002).

Few data are available on the addition of LABA in step 3 care in this age group. The only data are those involving 4 year olds who have asthma that is not well controlled on low-dose ICS; there are no data for children under 4 years of age. The LABA DPI preparation (either alone or as a combination product) currently available and approved for use in the United States has a delivery system that is difficult to administer correctly to the majority of children less than 4 years of age. Data from studies and clinical experience are needed to determine how conveniently the newly released LABA hydrofluoroalkane (HFA) preparation can be delivered to this age group. FDA approval for the combination of LABA and ICS in children 4–11 years of age is based primarily on safety data and extrapolation of efficacy data from adolescents and adults (Malone et al. 2005; Van den Berg et al. 2000). Two studies in children 4–11 years of age whose asthma was not completely controlled on ICS have demonstrated that the addition of LABA improved lung function and symptom control compared to placebo (Russell et al. 1995; Zimmerman et al. 2004). To date, studies have not shown a reduction in significant asthma exacerbations with the addition of LABA to ICS (Bisgaard 2003) in young children. Although 4-year-old children were included in these study populations, the small numbers enrolled preclude any accurate extrapolation from these findings to the larger population of children 0–4 years of age. No other studies have evaluated adjunctive therapies in this 0–4 years of age group.

In summary, few studies in this age group are available, and they have mixed findings. Some data show improvement in both the impairment and risk domains with increasing the dose of ICS in children 1–4 years of age. Data from studies including only small numbers of 4-year-old children show improvement in the impairment domain with the use of ICS plus LABA, but no studies show improvement in the risk domain with combination therapy.

Step 4 Care, Children 0–4 Years of Age

- **Medium-dose ICS AND either (listed in alphabetical order) LABA or montelukast is the preferred treatment for step 4 (Evidence D). Theophylline is not recommended as add-on therapy (EPR—2 1997).**

No data were found on add-on therapy in children 0–4 years of age whose asthma is not well controlled on medium-dose ICS. In the opinion of the Expert Panel, and extrapolating from studies in older children and adults, adding a noncorticosteroid long-term control medication to the medium dose of ICS may be considered before increasing the dose of ICS to high dose, to avoid the potential risk of side effects with high doses of medication. The LABA DPI preparation is difficult to administer correctly to the majority of children less than 4 years of age; studies are needed to determine if the recently released LABA HFA will be convenient to administer in this age group. Montelukast (an LTRA) in combination with lower doses of an ICS can be considered for add-on therapy in these children.

Theophylline is not recommended as add-on therapy due to the erratic metabolism of theophylline during viral infections and febrile illness (See figure 4–4a.), which are common in this age group, and the need for careful monitoring of serum concentration levels.

Step 5 Care, Children 0–4 Years of Age

- **High-dose ICS AND either LABA or montelukast is the preferred treatment (Evidence D).**

Step 6 Care, Children 0–4 Years of Age

- **High-dose ICS AND either LABA or montelukast AND oral systemic corticosteroids may be given for step 6 (Evidence D).**

Before oral systemic corticosteroids are given for prolonged periods as a long-term control medication, consider a 2-week course of oral systemic corticosteroids to confirm clinical reversibility and the possibility of an effective response to therapy or, in 4-year-old children, consider high-dose ICS in combination with both an LTRA and a LABA.

For patients who require long-term oral systemic corticosteroids:

- Use the lowest possible dose (single dose daily or on alternative days).
- Monitor patients closely for corticosteroid adverse effects (See component 4—Medications.).
- When control of asthma symptoms is achieved, make persistent attempts to reduce oral systemic corticosteroids. High doses of ICS are preferable because they have fewer side effects than oral systemic corticosteroids.
- Recommend consultation with an asthma specialist.

KEY POINTS: MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE

- Classification of severity, considering the new dimensions of both the impairment and risk domains, should guide decisions for initiating therapy in children not currently taking long-term control medications (EPR—2 1997).
- Assessment of asthma control, considering both the impairment and risk domains, should guide decisions for adjusting therapy—either stepping up (Evidence A) or stepping down (Evidence D).
- When initiating daily long-term control therapy for persistent asthma, daily ICS is the preferred treatment (Evidence A); alternative treatment options include cromolyn, LTRA, and theophylline (Evidence B). The choice of medication includes consideration of treatment effectiveness, the domain of particular relevance to the individual patient (impairment, risk, or both), the individual patient's history of previous response to therapies, the ability of the patient and family to use the medication correctly, and anticipated patient and family adherence with the treatment regime and cost (Evidence D).

- Administration of ICS early in the course of the disease will not alter the underlying progression of the disease. ICSs should be used to control symptoms, prevent exacerbations, and improve the child's quality of life, but their use should not be initiated or prolonged for the purpose of changing the progression or underlying severity of the disease (Evidence A).
- Children should be directly involved as much as possible in establishing goals for therapy and developing their written asthma action plans.
- Active participation in physical activities, exercise, and sports should be promoted (EPR—2 1997). Treatment immediately before vigorous activity or exercise usually prevents EIB. If symptoms occur during usual play activities, a step up in treatment is warranted (EPR—2 1997).
- A written asthma action plan should be prepared for the student's school, extended care, or camp, including the clinician's recommendation regarding self-administration of medication. Either encourage parents to take a copy to the child's school or obtain parental permission and send a copy to the school nurse or designee (Evidence C).

The following recommendations for pharmacologic therapy to gain and maintain asthma control (See figures 4–1b, 4–3b, 4–4a, b, and c.) are intended to be general guidelines for making therapeutic decisions. They are not intended to be prescriptions for individual treatment or to replace clinical judgment. Specific therapy should be tailored to the need and circumstances of individual patients. Pharmacologic therapy must be accompanied at every step by patient education and measures to control those environmental factors and comorbid conditions that can impede asthma control.

Treatment: Special Issues for Children 5–11 Years of Age

PHARMACOLOGIC ISSUES

The Expert Panel recommends that, when initiating daily long-term control therapy for mild or moderate persistent asthma, the choice of medication includes consideration of treatment effectiveness, the domain of particular relevance to the patient's asthma (impairment, risk, or both), the individual patient's history of previous response to therapies, the ability of the patient and family to use the medication correctly, anticipated patient and family adherence to the treatment regimen, and cost (Evidence D).

The Expert Panel recommends that children ≥10 years of age (and younger children as appropriate) be directly involved in developing their written asthma action plans (EPR—2 1997). Children entering puberty may experience more difficulties than younger children in adhering to a written asthma action plan because they may fail to recognize the danger of poorly controlled asthma (Strunk et al. 1985), they may not accept having a chronic illness, or they may view the plan as infringing upon their emerging independence and adulthood. In teaching these children the same asthma self-management techniques expected of adults, the clinician should address developmental issues, such as building a positive self-image and confidence, increasing personal responsibility, and gaining problem-solving skills. To accomplish this, it is often helpful to see the child initially without parents present and to involve

the child directly in setting goals for therapy, choosing the appropriate treatment, and reviewing the effectiveness of the written asthma action plan at repeated visits. The parents can be brought in at the end of the visit to review the plan together and to emphasize the parents' important role in supporting the child's efforts.

SCHOOL ISSUES

The Expert Panel recommends that the clinician prepare a written asthma action plan for the student's school or childcare setting. Either encourage parents to take a copy to the child's school or obtain parental permission and send a copy to the school nurse or designee (Evidence C). The written asthma action plan should include the following information (See "Component 2: Education for a Partnership in Asthma Care," figure 3–16.): instructions for handling exacerbations (including the clinician's recommendation regarding self-administration of medication); recommendations for long-term control medications and prevention of EIB, if appropriate; and identification of those factors that make the student's asthma worse, so the school may help the student avoid exposure. Nonrandomized studies and observational studies have demonstrated the usefulness of written asthma action plans and peak flow monitoring in schools (Barbot et al. 2006; Borgmeyer et al. 2005; Byrne et al. 2006; Erickson et al. 2006).

It is preferable to schedule daily, long-term medications so that they are not taken at school, even if this results in unequal dosing intervals throughout the day. In school districts that have more comprehensive school nurse coverage, however, children who would benefit from close supervision to promote adherence may be given medications at school. In this way, daily medication can be administered, and patient education can be supplemented most days of the week.

Students who have asthma often require medication during school to treat acute symptoms or to prevent EIB that may develop during physical education class, school recess, or organized sports. Reliable, prompt access to medication is essential, but it may be difficult because of school rules that preclude the child from carrying medications. The NAEPP and several member organizations have adopted resolutions that endorse allowing students to carry and self-administer medications when the physician and parent consider this appropriate. Many State governments have passed legislation that allows self-administration of asthma medication in schools. It may be helpful for some children to have a compressor-driven nebulizer and medication available at the school. See also "Component 2: Education for a Partnership in Asthma Care," for a discussion of school-based asthma programs that promote effective management of asthma in the school setting.

SPORTS AND EXERCISE ISSUES

The Expert Panel recommends that physical activity at play or in organized sports is an essential part of a child's life, and full participation in physical activities should be encouraged (EPR—2 1997). Many children who have asthma experience cough, wheeze, or excessive fatigue when they exercise. Treatment immediately before vigorous activity or exercise usually prevents EIB. If symptoms occur during usual play activities, a step up in long-term therapy is warranted. Poor endurance or EIB can be an indication of poorly controlled persistent asthma; appropriate use of long-term control medication can reduce EIB (See the section on "Managing Special Situations in Asthma—Exercise-Induced Bronchospasm."). Activity should be limited or curtailed only as a last resort.

Treatment: Pharmacologic Steps for Children 5–11 Years of Age

Figure 4–1b presents treatment options within the stepwise approach to therapy. Selection of the step of care for a patient depends on whether long-term control therapy is being initiated for the first time or whether therapy is being adjusted. Classifying severity in patients not currently taking long-term control medication is a guide for initiating therapy (See figure 4–2b.); assessing the level of asthma control in patients taking long-term control medication will guide decisions for adjusting therapy (See figure 4–3b.). Figures 4–4a, b, and c list usual dosages of asthma medications. Note that the recommendations in stepwise therapy are meant to assist, not replace, the clinical decisionmaking required to meet the individual patient's needs.

INTERMITTENT ASTHMA

Step 1 Care, Children 5–11 Years of Age

The Expert Panel recommends the following therapy for intermittent asthma (step 1 care):

- **SABA, taken as needed to treat symptoms, is usually sufficient therapy for intermittent asthma.**

  If a child requires increasing amounts of as-needed SABA, this may indicate more severe or poorly controlled asthma and thus the need to step up therapy (See figures 4–1b and 4–2b.).

- **Manage moderate or severe exacerbations due to viral respiratory infections, especially common in children, with a short course of oral systemic corticosteroids. Consider initiating systemic corticosteroids at the first sign of infection in children who have a history of severe exacerbations with viral respiratory infections (Evidence D).**

- **Provide a detailed written asthma action plan for those patients who have intermittent asthma and a history of severe exacerbations (Evidence B).** Intermittent asthma—infrequent exacerbations separated by periods of no symptoms and normal pulmonary function—is often mild. However, some patients who have intermittent asthma experience sudden, severe, and life-threatening exacerbations, and it is essential to treat these exacerbations accordingly. The patient's written asthma action plan should include indicators of worsening asthma (specific symptoms and peak expiratory flow (PEF) measurement), specific recommendations for using SABA, early administration of systemic corticosteroids, and seeking medical care. Recommendations regarding avoidance or control of allergies, irritants, or comorbid conditions that affect the child's asthma should also be included. Periodic monitoring is important to evaluate whether the patient's asthma is indeed intermittent. The occurrence of more than two exacerbations a year that require oral systemic corticosteroids, without symptoms between them, is an example of a child's having minimal or intermittent impairment, but a persistent risk of exacerbation. In the opinion of the Expert Panel, this child should be considered to have persistent asthma (See figure 4–2b.).

PERSISTENT ASTHMA

The Expert Panel recommends the following therapy for persistent asthma:

- **Use daily long-term control medication. The most effective long-term control medications are those with anti-inflammatory effects, that is, those that diminish chronic airway inflammation and airway hyperresponsiveness (Evidence A).**

- **Quick-relief medication must be available. SABA, taken as needed to relieve symptoms, is recommended (Evidence A).** The intensity of treatment will depend on the severity of the exacerbation (See section 5 on "Managing Exacerbations of Asthma."). Increasing use of SABA or use more than 2 days week for symptom control (not prevention of EIB) indicates the need to step up therapy.

- **To gain more rapid control of asthma, consider a course of oral systemic corticosteroids for the patient who has an exacerbation at the time long-term control therapy is started or in patients who have moderate or severe asthma with frequent interference with sleep or normal activity (EPR—2 1997).**

- **Giving daily therapy only during specific periods of previously documented risk for a child may be considered (Evidence D).** Although this approach is not yet evaluated, it is possible that children who have specifically defined periods of increased risk for symptoms and exacerbations (e.g., during the seasons in which viral respiratory infections are common) may require daily long-term control therapy only during this historically documented period of risk. If long-term control therapy is discontinued, then written action plans for recognizing and handling signs of worsening asthma should be reviewed with the caregivers, and followup appointments 2–6 weeks later should be conducted to ensure that asthma control is maintained.

- **Consider treating patients who had two or more exacerbations requiring oral systemic corticosteroids in the past year the same as patients who have persistent asthma, even in the absence of an impairment level consistent with persistent asthma (Evidence D).**

Step 2 Care, Children 5–11 Years of Age

- **Daily low-dose ICS is the preferred step 2 treatment (Evidence A).** High-quality evidence demonstrates the effectiveness of ICS as initial therapy for children who have persistent asthma (See "Component 4: Medications."). This approach is also the preferred treatment for stepping down treatment of patients who are well controlled on a higher treatment step.

- **Alternative treatments at this step include (listed in alphabetical order) cromolyn, LTRA, nedocromil, and theophylline (Evidence B).** Three comparator studies in children 5–17 years of age demonstrated that montelukast is not as efficacious as ICS on a range of asthma outcomes (Garcia-Garcia et al. 2005; Ostrom et al. 2005; Sorkness et al. 2007) (See "Component 4: Medications" and Evidence Table 14, Leukotriene Receptor Antagonist: Monotherapy/Effectiveness Studies.). One study that examined factors that might predict response to therapy found that children who had lower lung function (impairment domain) and/or higher levels of markers of allergic airway inflammation were more likely to respond favorably to ICS and not respond to montelukast in the impairment domain of FEV_1.

Children who did not have these characteristics may respond equally well to both medications (Szefler et al. 2005). Montelukast, then, is an appropriate treatment option. Of the LTRAs, montelukast may be more desirable, as it requires only once daily dosing; furthermore, zafirlukast has several potential drug interactions and a small risk for hepatotoxicity. Cromolyn and nedocromil, although having excellent safety profiles, require administration four times per day and have shown benefit inconsistently. Theophylline is less desirable because of its safety profile and the need to adjust dose based on diet, drug interactions, and variable metabolism with age (See figure 4–4a.). Theophylline may be considered, however, when cost and adherence to inhaled medications are concerns.

If an alternative treatment is selected and well-controlled asthma is not achieved and maintained, then discontinue that treatment and use the preferred medication before stepping up treatment.

Step 3 Care, Children 5–11 Years of Age

- **Low-dose ICS plus the addition of some form of adjunctive therapy or medium-dose ICS are equivalent options in step 3 care, based on extrapolation from studies in adults (Evidence B—extrapolation). Because of the lack of comparative data in this age group, however, the adjunctive therapies are listed in alphabetical order: LABA, LTRA, or, with appropriate monitoring, theophylline.**

  In adult patients whose asthma is not well controlled on low-dose ICS, the clinician has several options: (1) increasing the ICS dose, (2) adding a LABA, (3) adding a leukotriene modifier, or (4) adding theophylline. Based on considerable available evidence, the first two are preferred. In children, none of these options has been studied adequately or compared in the age range of 5–11 years, and the options have not been studied at all in those <5 years of age.

  — **Low-dose ICS plus the addition of adjunctive therapy (listed alphabetically):**

    - **Adding LABA to ICS:** Two trials demonstrated that children 4–11 years of age who had asthma not completely controlled by ICS achieved improved lung function and symptom control with the addition of LABA compared to placebo (Russell et al. 1995; Zimmerman et al. 2004). FDA approval for the combination in 4- to 11-year-old children, however, is based primarily on safety and extrapolation of efficacy from adolescents and adults (Malone et al. 2005; Van den Berg et al. 2000). To date, studies have not shown a reduction in significant asthma exacerbations from the addition of LABA to ICS treatment in children (Bisgaard 2003). One negative study of LABA in combination with ICS in children who had mild or moderate persistent asthma failed to establish a need in the study participants, at baseline, for more therapy than low-dose ICS, and thus did not sufficiently address the question of combination therapy with LABA (Verberne et al. 1998).

    - **Adding LTRA to ICS:** One trial of medications for children compared the addition of montelukast to budesonide, 400 mcg/day, and reported a slight increase in lung function (PEF, although not FEV_1) and a reduction in as-needed SABA use (Simons et al. 2001).

- **Adding theophylline:** A small trial in 36 children, 6–18 years of age, reported a small improvement in PEF, but not FEV_1 or bronchial reactivity, from the addition of theophylline to ICS (Suessmuth et al. 2003). Because of the risk of toxicity, multiple drug interactions, and the need to monitor serum concentrations regularly, with no significant beneficial effect over other adjunctive treatments, theophylline would be considered the less desirable option for adjunctive therapy.

— **Increasing the dose of ICS to medium dose:** A recent systematic review in children 4–16 years of age (Masoli et al. 2004) reported that the dose-response to fluticasone propionate for improvement in lung function and symptom control (in the impairment domain) appears to plateau between 100–200 mcg/day (low dose), although patients who have severe asthma may achieve additional response at 400 mcg/day (medium dose). A large prospective trial of budesonide in children 4–8 years of age who had moderate to severe asthma showed similar improvements in symptom control with low and high doses, with small improvements in lung function upon increasing the daily dose fourfold from 200 mcg/day to 800 mcg/day (medium dose) (Shapiro et al. 1998). None of these studies, however, evaluated whether patients not initially controlled on low-dose ICS had an improved response after increasing the dose. In adult studies, increasing the dose from 200 mcg budesonide further reduced exacerbations (Pauwels et al. 1997). The Expert Panel concludes that, while the benefits from ICS in the impairment domain may begin to plateau at low doses, increasing the dose for children who have asthma not well controlled at low dose ICS may benefit children who have more severe impairment and may also reduce the risk of exacerbations. Increasing the dose of ICS may increase the risk of systemic activity, although the clinical significance of the potential systemic effects is unclear (See component 4—Medications.).

In summary, based on the small amount of data available concerning asthma in children 5–11 years of age, as well as the lack of comparison studies for various long-term control regimens, it is not possible to recommend firmly whether administering higher doses of ICS or maintaining the low dose of ICS and adding adjunctive therapy is the best treatment approach for step 3 care. Thus, the Expert Panel considers increasing the dose of ICS to the medium-dose range or using lower doses of ICS plus adjunctive therapy to be equivalent options. Decisions at this juncture should consider which component of control (impairment or risk) is more affected. For the impairment domain, based on studies in older children and adults, children who have low lung function and >2 days/week impairment may be better served by adding LABA to a low-dose of ICS. One study in children suggests some benefit in the impairment domain with adding LTRA. Studies in children show that increasing the dose of ICS to medium dose can improve symptoms and lung function in those children who have greater levels of impairment. For the risk domain, studies have not demonstrated that adding LABA or LTRA reduces exacerbations in children. Adding LABA has the potential risk of rare life-threatening or fatal exacerbations. Studies in older children and adults show that increasing the dose of ICS can reduce the risk of exacerbations, but this may require up to a fourfold increase in the dose. This may increase the potential risk of systemic effects, although within the medium-dose range the risk is small.

Step 4 Care, Children 5–11 Years of Age

- **Medium-dose ICS AND LABA is the preferred step 4 treatment (Evidence B—extrapolated from studies in youths ≥12 years and adults).**

  Many children who have asthma that is not well controlled on step 3 therapy have low lung function contributing to their impairment; thus, extrapolating from studies on LABA as adjunctive therapy for older children and adults is particularly relevant, because the data show that a key benefit of adding LABA is improvement in lung function.

- **Alternative, but not preferred, treatment is medium-dose ICS AND either LTRA or theophylline (Evidence B—extrapolated from studies in youths ≥12 years of age and adults).**

  No data specifically address the comparative effects of the various choices of treatments to add on to ICS in children <11 years of age. Based on comparative studies in older children and adults (Evidence A), the preferred add-on treatment is LABA. If the physician has concerns regarding use of LABA, an LTRA can be given a therapeutic trial first. If a trial of LTRA is deemed ineffective, then the LTRA should be discontinued, and theophylline could be added. Theophylline is a less desirable option because of its safety profile and the need to monitor serum concentration levels. Cromolyn has not been demonstrated to be effective as add-on therapy.

- In the opinion of the Expert Panel, if the add-on therapy initially administered does not lead to improvement in asthma control, discontinue it and use a trial of a different add-on therapy before stepping up.

Step 5 Care, Children 5–11 Years of Age

- **High-dose ICS AND LABA is the preferred step 5 treatment based on extrapolation from studies in older children and adults (Evidence B—extrapolated).**

- **Alternative, but not preferred, add-on treatments include LTRA or theophylline (Evidence B—extrapolated).**

Step 6 Care, Children 5–11 Years of Age

- **High-dose ICS AND LABA AND oral systemic corticosteroids long term is the preferred treatment (Evidence D).**

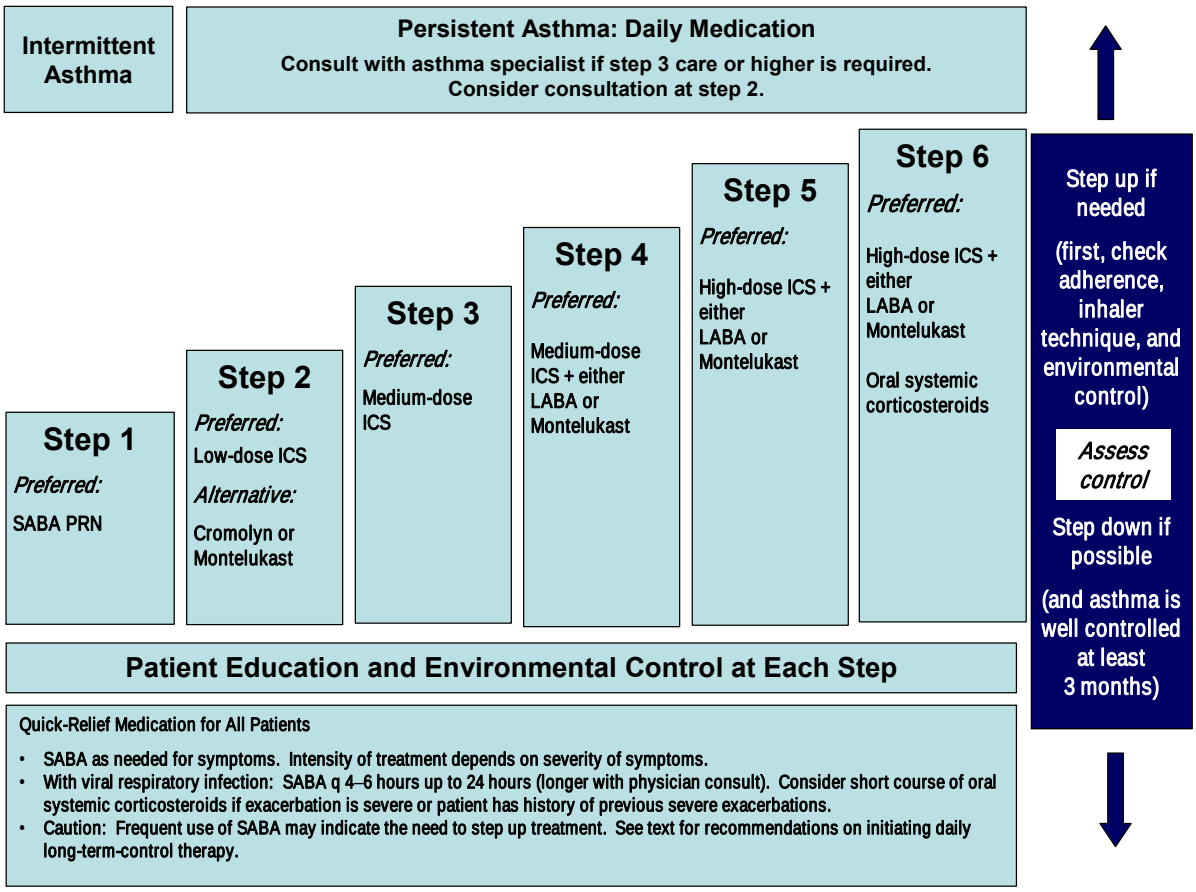
- **Alternative, but not preferred, add-on treatments are either an LTRA or theophylline AND oral systemic corticosteroids (Evidence D).**

Before maintenance prednisone therapy is initiated, consider a 2-week course of oral corticosteroids to confirm clinical reversibility and the possibility of effective response to therapy. At this level of treatment, it is strongly recommended to add measures of pulmonary function to assess response to oral corticosteroid therapy. If response is poor, a careful review for other pulmonary conditions or concomitant medical conditions should be conducted to ensure the primary diagnosis is indeed severe asthma.

For patients who require long-term oral systemic corticosteroids:

- Use the lowest possible dose (single dose daily or on alternate days).
- Monitor patients closely for corticosteroid adverse side effects (See box 4–1, “Patient Record: Monitoring Risk of Asthma Progression and Potential Adverse Effects of Corticosteroid Therapy.”).
- When well-controlled asthma is achieved, make persistent attempts to reduce oral systemic corticosteroids. High-dose ICS therapy is preferable to oral systemic corticosteroids.
- Recommend consultation with an asthma specialist.

FIGURE 4–1a. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE

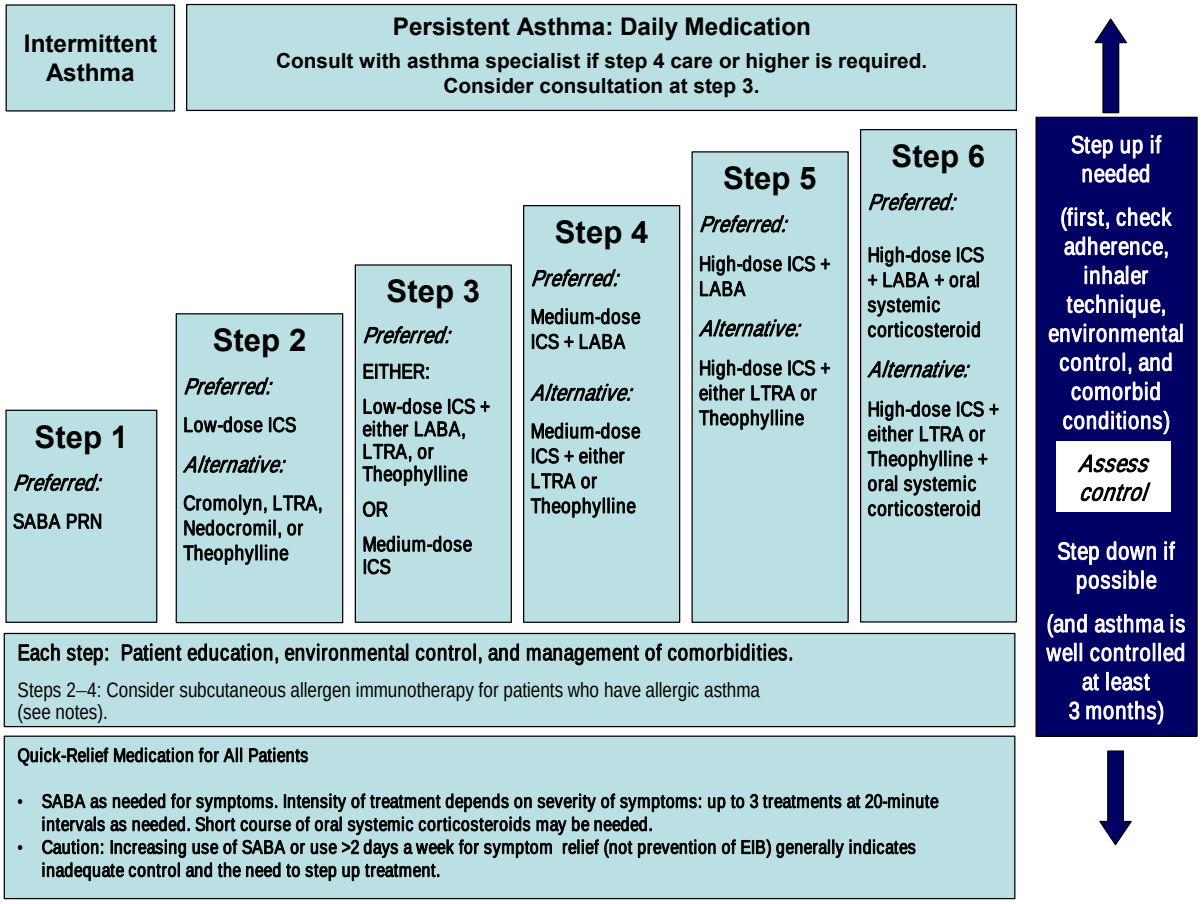


Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

FIGURE 4–1b. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 4–2a. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (0–4 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. → Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy (See figure 4–1a for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

Key: EIB, exercise-induced bronchospasm

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 4–2b. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 5–11 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. → Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy (See figure 4–1b for treatment steps.)		Step 1	Step 2	Step 3, medium-dose ICS option and consider short course of oral systemic corticosteroids	Step 3, medium-dose ICS option, or step 4 and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 4–3a. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 0–4 YEARS OF AGE

Components of Control		Classification of Asthma Control (0–4 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	>1x/month	>1x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year	>3/year
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See figure 4–1a for treatment steps.)		• Maintain current treatment. • Regular followup every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up (1 step) and • Reevaluate in 2–6 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up (1–2 steps), and • Reevaluate in 2 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.

Key: EIB, exercise-induced bronchospasm

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Before step up in therapy:
  - — Review adherence to medications, inhaler technique, and environmental control.
  - — If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FIGURE 4–3b. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 5–11 YEARS OF AGE

Components of Control		Classification of Asthma Control (5–11 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function • FEV_1 or peak flow • FEV_1/FVC	 >80% predicted/ personal best >80%	 60–80% predicted/ personal best 75–80%	 <60% predicted/ personal best <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term followup.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment **(See figure 4–1b for treatment steps.)**		• Maintain current step. • Regular followup every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up at least 1 step and • Reevaluate in 2–6 weeks. • For side effects: consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
- Before step up in therapy:
  - — Review adherence to medications, inhaler technique, environmental control, and comorbid conditions.
  - — If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN*

Medication	Dosage Form	0–4 years	5–11 years	Comments
Inhaled Corticosteroids (ICSs) ***(See figure 4–4b, Estimated Comparative Daily Dosages for ICSs in Children.)***				
Systemic Corticosteroids				***(Applies to all three corticosteroids)***
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	0.25–2 mg/kg daily in 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	■ 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). ■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ■ There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse. ■ Patients receiving the lower dose (1 mg/kg/day) experience fewer behavioral side effects (Kayani and Shannon 2002), and it appears to be equally efficacious (Rachelefsky 2003). ■ For patients unable to tolerate the liquid preparations, dexamethasone syrup at 0.4 mg/kg/day may be an alternative. Studies are limited, however, and the longer duration of activity increases the risk of adrenal suppression (Hendeles 2003).
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day 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 Beta$_2$-Agonists (LABAs)				■ **Should not be used for symptom relief or exacerbations. Use only with ICSs.**
Salmeterol	DPI 50 mcg/ blister	Safety and efficacy not established in children <4 years	1 blister q 12 hours	■ Decreased duration of protection against EIB may occur with regular use. ■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery. ■ Do not blow into inhaler after dose is activated.
Formoterol	DPI 12 mcg/ single-use capsule	Safety and efficacy not established in children <5 years	1 capsule q 12 hours	■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery. ■ 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 inhaler and should not be taken orally.

*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN* (CONTINUED)

Medication	Dosage Form	0–4 years	5–11 years	Comments
Combined Medication				
Fluticasone/ Salmeterol	DPI 100 mcg/ 50 mcg	Safety and efficacy not established in children <4 years	1 inhalation bid	■ There have been no clinical trials in children <4 years of age. ■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery. ■ Do not blow into inhaler after dose is activated.
Budesonide/ Formoterol	HFA MDI 80 mcg/4.5 mcg	Safety and efficacy not established	2 puffs bid	■ There have been no clinical trials in children <4 years of age. ■ Currently approved for use in youths ≥12. Dose for children 5–12 years of age based on clinical trials using DPI with slightly different delivery characteristics (Pohunek et al. 2006; Tal et al. 2002; Zimmerman et al. 2004).
Cromolyn/Nedocromil				
Cromolyn	MDI 0.8 mg/puff	Safety and efficacy not established	2 puffs qid	■ 4–6 week trial may be needed to determine maximum benefit. ■ Dose by MDI may be inadequate to affect hyperresponsiveness. ■ One dose before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective as inhaled $beta_2$-agonists for EIB. ■ Once control is achieved, the frequency of dosing may be reduced.
	Nebulizer 20 mg/ampule	1 ampule qid Safety and efficacy not established <2 years	1 ampule qid	
Nedocromil	MDI 1.75 mg/puff	Safety and efficacy not established <6 years	2 puffs qid	
Leukotriene Receptor Antagonists (LTRAs)				
Montelukast	4 mg or 5 mg chewable tablet 4 mg granule packets	4 mg qhs (1–5 years of age)	5 mg qhs (6–14 years of age)	■ Montelukast exhibits a flat dose-response curve. ■ No more efficacious than placebo in infants 6–24 months (van Adelsberg et al. 2005).
Zafirlukast	10 mg tablet	Safety and efficacy not established	10 mg bid (7–11 years of age)	■ For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Monitor for signs and symptoms of hepatic dysfunction.
Methylxanthines				
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual maximum: ■ <1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥1 year of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	■ Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage). ■ Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential. ■ See next page for factors that can affect theophylline levels.

Key: DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane (inhaler propellant); MDI, metered dose inhaler

FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN* (CONTINUED)

Factors Affecting Serum Theophylline Concentrations†

Factor	Decreases Theophylline Concentrations	Increases Theophylline Concentrations	Recommended Action
Food	↓ or delays absorption of some sustained-release theophylline (SRT) products	↑ rate of absorption (fatty foods)	Select theophylline preparation that is not affected by food.
Diet	↑ metabolism (high protein)	↓ metabolism (high carbohydrate)	Inform patients that major changes in diet are not recommended while taking theophylline.
Systemic, febrile viral illness (e.g., influenza)		↓ metabolism	Decrease theophylline dose according to serum concentration. Decrease dose by 50 percent if serum concentration measurement is not available.
Hypoxia, cor pulmonale, and decompensated congestive heart failure, cirrhosis		↓ metabolism	Decrease dose according to serum concentration.
Age	↑ metabolism (1–9 years)	↓ metabolism (<6 months, elderly)	Adjust dose according to serum concentration.
Phenobarbital, phenytoin, carbamazepine	↑ metabolism		Increase dose according to serum concentration.
Cimetidine		↓ metabolism	Use alternative H_2 blocker (e.g., famotidine or ranitidine).
Macrolides: erythromycin, clarithromycin, troleandomycin		↓ metabolism	Use alternative macrolide antibiotic, azithromycin, or alternative antibiotic or adjust theophylline dose.
Quinolones: ciprofloxacin, enoxacin, perfloxacin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose. Circumvent with ofloxacin if quinolone therapy is required.
Rifampin	↑ metabolism		Increase dose according to serum concentration.
Ticlopidine		↓ metabolism	Decrease dose according to serum concentration.
Smoking	↑ metabolism		Advise patient to stop smoking; increase dose according to serum concentration.

†This list is not all inclusive; for discussion of other factors, see package inserts.

FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Child 0–4	Child 5–11	Child 0–4	Child 5–11	Child 0–4	Child 5–11
Beclomethasone HFA						
40 or 80 mcg/puff	NA	80–160 mcg	NA	>160–320 mcg	NA	>320 mcg
Budesonide DPI						
90, 180, or 200 mcg/inhalation	NA	180–400 mcg	NA	>400–800 mcg	NA	>800 mcg
Budesonide inhaled						
Inhalation suspension for nebulization (child dose)	0.25–0.5 mg	0.5 mg	>0.5–1.0 mg	1.0 mg	>1.0 mg	2.0 mg
Flunisolide						
250 mcg/puff	NA	500–750 mcg	NA	1,000–1,250 mcg	NA	>1,250 mcg
Flunisolide HFA						
80 mcg/puff	NA	160 mcg	NA	320 mcg	NA	≥640 mcg
Fluticasone						
HFA/MDI: 44, 110, or 220 mcg/puff	176 mcg	88–176 mcg	>176–352 mcg	>176–352 mcg	>352 mcg	>352 mcg
DPI: 50, 100, or 250 mcg/inhalation	NA	100–200 mcg	NA	>200–400 mcg	NA	>400 mcg
Mometasone DPI						
200 mcg/inhalation	NA	NA	NA	NA	NA	NA
Triamcinolone acetonide						
75 mcg/puff	NA	300–600 mcg	NA	>600–900 mcg	NA	>900 mcg

Key: HFA, hydrofluoroalkane; NA, not approved and no data available for this age group

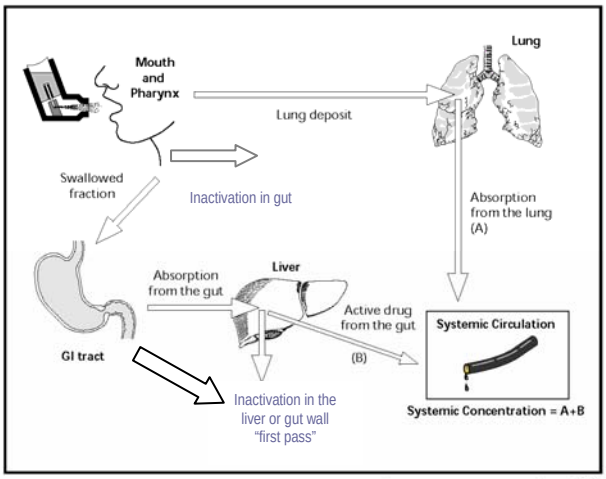
Notes:

- **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.
- Some doses may be outside package labeling, especially in the high-dose range. Budesonide nebulizer suspension is the only ICS with FDA approved labeling for children <4 years of age.
- Metered-dose inhaler (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. Dry powder inhaler (DPI) doses are expressed as the amount of drug in the inhaler following activation.
- For children <4 years of age: The safety and efficacy of ICSs in children <1 year has not been established. Children <4 years of age generally require delivery of ICS (budesonide and fluticasone HFA) through a face mask that should fit snugly over nose and mouth and avoid nebulizing in the eyes. Wash face after each treatment to prevent local corticosteroid side effects. For budesonide, the dose may be administered 1–3 times daily. Budesonide suspension is compatible with albuterol, ipratropium, and levalbuterol nebulizer solutions in the same nebulizer. Use only jet nebulizers, as ultrasonic nebulizers are ineffective for suspensions.
- For fluticasone HFA, the dose should be divided 2 times daily; the low dose for children <4 years is higher than for children 5–11 years of age due to lower dosedelivered with face mask and data on efficacy in young children.

FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN (CONTINUED)

- Comparative dosages are based on published comparative clinical trials (Adams et al. 2005; Barnes et al. 1998; Kelly 1998; Lasserson et al. 2005; Pedersen and O'Byrne 1997). The rationale for some key comparisons 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; Szefler et al. 2002).
  - The low- to medium-doses reflect 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 of high-dose range did not significantly increase efficacy but did increase systemic effect (Adams et al. 2001; Martin et al. 2002; Szefler et al. 2002).
  - The doses for budesonide and fluticasone MDI or DPI are based on recently available comparative data. These new data, including meta-analyses, show that fluticasone requires on-half the microgram dose of budesonide DPI to achieve comparable efficacy (Adams et al. 2005; Barnes et al. 1998; Nielsen and Dahl 2000).
  - The dose for beclomethasone in HFA inhaler should be approximately one-half the dose for beclomethasone chlorofluorocarbon (CFC) inhaler for adults and children, 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) and clinical trials demonstrating similar potency to fluticasone at 1:1 dose ratio (Boulet et al. 2004; Busse et al. 1999; Gross et al. 1999; Lasserson et al. 2005; Leach et al. 1998; Pedersen et al. 2002; Szefler et al. 2002; 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). 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 who had 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 a high dose of 2.0 mg budesonide compared to infants receiving lower doses, but this result was not statistically significant, perhaps due to the small study size (Scott and Skoner 1999).
  - The dose for flunisolide HFA is based on product information and current literature (Corren et al. 2001; Gillman et al. 2002; Richards et al. 2001).
  - The dose of budesonide/formoterol in children is based on product information and current literature (Pohunek et al. 2006; Tal et al. 2002; Zimmerman et al. 2004).
  - The dose for fluticasone HFA in children <5 years of age is based on clinical studies demonstrating efficacy at this dose of 176 mcg/day (Bisgaard et al. 2004; Guilbert et al. 2006).
- **Bioavailability**

  Both the relative potency and the relative bioavailability (systemic availability) determine the potential for systemic activity of an ICS preparation. As illustrated here, the bioavailability of an ICS is dependent on the absorption of the dose delivered to the lungs and the oral bioavailability of the swallowed portion of the dose received.
  - Absorption of the dose delivered to the lungs:
    - Approximately 10–50 percent of the dose from the MDI is delivered to the lungs. This amount varies among preparations and delivery devices.
    - Nearly all of the amount delivered to the lungs is bioavailable.



Adapted with permission from Barnes 1995.

FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN (CONTINUED)

— Oral bioavailability of the swallowed portion of the dose received:

- Approximately 50–80 percent of the dose from the MDI without a spacer or valved holding chamber is swallowed.
- The oral bioavailability of this amount varies:

  Either a high first-pass metabolism or the use of a spacer/holding chamber with an MDI can decrease oral bioavailability, thus enhancing safety (Lipworth 1995).

  The approximate oral bioavailability of ICS has been reported as: beclomethasone dipropionate, 20 percent; flunisolide, 21 percent; triamcinolone acetonide, 10.6 percent; budesonide, 11 percent; fluticasone propionate, 1 percent; mometasone, <1 percent (Affrime et al. 2000; Chaplin et al. 1980; Check and Kaliner 1990; Clissold and Heel 1984; Davies 1993; Harding 1990; Heald et al. 1995; Martin et al. 1974; Mollmann et al. 1985; Szefler 1991; Wurthwein and Rohdewald 1990).

Potential drug interactions

- A number of the ICSs, including fluticasone, budesonide, and mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported (Johnson et al. 2006; Samaras et al. 2005).

FIGURE 4–4c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS IN CHILDREN*

Medication	Dosage Form	0–4 Years	5–11 Years	Comments
Inhaled Short-Acting Beta$_2$-Agonists				
	MDI			
Albuterol CFC	90 mcg/puff, 200 puffs/canister	1–2 puffs 5 minutes before exercise	2 puffs 5 minutes before exercise	■ Differences in potencies exist, but all products are essentially comparable on a per puff basis. ■ An increasing use or lack of expected effect indicates diminished control of asthma. ■ Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need for additional long-term control therapy. ■ May double usual dose for mild exacerbations.
Albuterol HFA	90 mcg/puff, 200 puffs/canister	2 puffs every 4–6 hours as needed	2 puffs every 4–6 hours as needed	
Levalbuterol HFA	45 mcg/puff, 200 puffs/canister	Safety and efficacy not established in children <4 years	2 puffs every 4–6 hours as needed	■ Should prime the inhaler by releasing 4 actuations prior to use. ■ Periodically clean HFA actuator, as drug may plug orifice.
Pirbuterol CFC Autohaler	200 mcg/puff, 400 puffs/canister	Safety and efficacy not established	Safety and efficacy not established	■ Children <4 years may not generate sufficient inspiratory flow to activate an auto-inhaler. ■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.
	Nebulizer solution			
Albuterol	0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL (0.5%)	0.63–2.5 mg in 3 cc of saline q 4–6 hours, as needed	1.25–5 mg in 3 cc of saline q 4–8 hours, as needed	■ May mix with cromolyn solution, budesonide inhalant suspension, or ipratropium solution for nebulization. May double dose for severe exacerbations.
Levalbuterol (R-albuterol)	0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/0.5 mL 1.25 mg/3 mL	0.31–1.25 mg in 3 cc q 4–6 hours, as needed	0.31–0.63 mg, q 8 hours, as needed	■ Does not have FDA-approved labeling for children <6 years of age. ■ The product is a sterile-filled preservative-free unit dose vial. ■ Compatible with budesonide inhalant suspension.

FIGURE 4–4c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS IN CHILDREN* (CONTINUED)

Medication	Dosage Form	0–4 Years	5–11 Years	Comments
Anticholinergics				
	MDI			
Ipratropium HFA	17 mcg/puff, 200 puffs/ canister	Safety and efficacy not established	Safety and efficacy not established	■ Evidence is lacking for anticholinergics producing added benefit to beta$_2$-agonists in long-term control asthma therapy. ■ See "Management of Acute Asthma" for dosing in ED.
	Nebulizer solution			
	0.25 mg/mL (0.025%)	Safety and efficacy not established	Safety and efficacy not established	
Systemic Corticosteroids				***Applies to the first three corticosteroids***
Methylprednisolone	2, 4, 6, 8, 16, 32 mg tablets	Short course "burst": 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days	Short course "burst": 1-2 mg/kg/day maximum 60 mg/day for 3–10 days	■ 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			
	Repository injection			
(Methylprednisolone acetate)	40 mg/mL 80 mg/mL	7.5 mg/kg IM once	240 mg IM once	■ May be used in place of a short burst of oral steroids in patients who are vomiting or if adherence is a problem.

Key: CFC, chlorofluorocarbon; ED, emergency department; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow

*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

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