SECTION 4, MANAGING ASTHMA LONG TERM IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

KEY POINTS: MANAGING ASTHMA LONG TERM IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

■ The goal for therapy is to control asthma by (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

♦ 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 youths, prevent reduced lung growth

♦ Provide optimal pharmacotherapy with minimal or no adverse effects

■ A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma in both the impairment and risk domains (Evidence A):

— The type, amount, and frequency of medication is determined by asthma severity for initiating therapy and by the level of asthma control for adjusting therapy (Evidence A).

— Step-down therapy is essential to identify the minimum medication necessary to maintain control (Evidence D).

■ Monitoring and followup is essential (Evidence B).

— When initiating therapy, monitor at 2- to 6-week intervals to ensure that asthma control is achieved (Evidence D).

— Regular followup contacts at 1- to 6-month intervals, depending on the level of control, are recommended to ensure that control is maintained and appropriate adjustments in therapy are made—step up if necessary and step down if possible. Consider 3-month intervals if a step down in therapy is anticipated (Evidence D).

- Because asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations, persistent asthma is most effectively controlled with daily long-term control medication, specifically, anti-inflammatory therapy (Evidence A).

  — ICSs are the preferred treatment option for initiating long-term control therapy (Evidence A).

  — Selection of an alternative treatment option includes consideration of treatment effectiveness, the domain of particular relevance to the 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's and family's adherence to the treatment regime (Evidence D).

- Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal pharmacologic therapy (Evidence A).

- At each step, patients should be advised to avoid or control allergens (Evidence A), irritants, or comorbid conditions that make the patient's asthma worse (Evidence B).

- A written asthma action plan detailing for the individual patient daily management (medications and environmental control strategies) and how to recognize and handle worsening asthma is recommended for all patients; written asthma action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B). The written asthma action plan can be either symptom or peak-flow based; evidence shows similar benefits for each (Evidence B).

- Referral to an asthma specialist for consultation or comanagement is recommended if there are difficulties achieving or maintaining control of asthma; if the patient requires step 4 care or higher; if immunotherapy or omalizumab are considered; or if the patient has had an exacerbation requiring hospitalization. Consider referral if the patient requires step 3 care (Evidence D).

- Special considerations for youths (EPR—2 1997):

  — Pulmonary function testing should use appropriate reference populations. Adolescents compare better to childhood than to adult predicted norms.

  — Adolescents (and younger children as appropriate) should be directly involved in establishing goals for therapy and developing their asthma management plans.

  — Active participation in physical activities, exercise, and sports should be promoted.

  — A written asthma management plan should be prepared for the student's school, including plans to ensure reliable, prompt access to medications. 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.

■ Special considerations for older adults (EPR⸺2 1997):

  — Chronic bronchitis/emphysema may coexist with asthma. A trial of systemic corticosteroids will determine the presence of reversibility and the extent of therapeutic benefit.

  — Asthma medications may aggravate coexisting medical conditions (e.g., cardiac disease, osteoporosis); adjustments in the medication plan may be necessary.

  — Be aware of increased potential for adverse drug/disease interaction (e.g., aspirin, beta-blockers).

  — Review of patient technique in using medications and devices is essential; physical (e.g., arthritis or visual) or cognitive impairments may make proper technique difficult.

■

SECTION 4, STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Treatment: Principles of Stepwise Therapy in Youths ≥12 Years of Age and Adults

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

■ 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

  — 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 youths, prevent reduced lung growth

  — Provide optimal pharmacotherapy with minimal or no adverse effects

The stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible, is used to achieve and maintain this control. This approach is illustrated in figure 4–5. Because asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations, therapy for persistent asthma must emphasize efforts to suppress inflammation over the long term and to prevent exacerbations. Recommendations in the stepwise approach to therapy are based on the Expert Panel's review of the literature (See "Component 4: Medications.") and the Expert Panel's experience.

The steps of care for managing asthma are presented in figure 4–5. 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. Care is stepped up to regain control, and it is 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 (figure 4–6), 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. 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 (See figure 4–7.).

ACHIEVING CONTROL OF ASTHMA

Selecting Initial Therapy for Patients Not Currently Taking Long-Term Control Medications

The Expert Panel recommends the following actions to achieve asthma control in patients who are not currently taking long-term control medications.

- **Assess asthma severity (EPR—2 1997).** Asthma severity is based on measurements of impairment and risk; see figure 4–6 and the discussion in "Component 1: Measures of Asthma Assessment and Monitoring."

- **Select treatment that corresponds to the patient's level of asthma severity (EPR—2 1997).** See figure 4–6 for the recommended step of care at different levels of severity, and see figure 4–5 for treatment options at each step of care. See figures 4–8 a, b, and c for usual dosages of medications. However, the clinician must also judge the individual patient's needs and circumstances to determine at what step to initiate therapy. For example, patients who have moderate or severe asthma that frequently interferes with sleep or normal activity often benefit from a course of oral corticosteroids to gain control of asthma more rapidly. Each patient's response to treatment must also be assessed.

- **If at a followup visit in 2–6 weeks after starting treatment, depending on severity, asthma is not well controlled (see below), then treatment should be advanced to the next step. If uncontrolled asthma persists, then the diagnosis should be reevaluated, and, if confirmed, treatment should be advanced another step (Evidence D).**

Adjusting Therapy

The Expert Panel recommends that, once therapy is selected, or if the clinician sees a patient for the first time who is already taking a long-term control medication, treatment

decisions are based on the level of the patient's asthma control (See figure 4–7.) (Evidence A).

■   **Assess asthma control.** As in assessment of asthma severity, asthma control can be considered in terms of impairment and risk domains (Evidence C). Both domains should be addressed to select appropriate therapy; the level of control is generally judged on the most severe indicator of impairment or risk (Evidence D).

Impairment Domain

This domain is multifactorial because the different manifestations of asthma do not necessarily correlate with each other, and each factor should be assessed if possible (Evidence C).

Symptoms. Three types of symptom assessments each appear to provide unique information regarding asthma control: symptom frequency, nighttime awakening, and activity limitation (Fuhlbrigge et al. 2002; Nathan et al. 2004; Vollmer et al. 1999). Frequency of shortness of breath appears to be particularly related to asthma control (Nathan et al. 2004) and quality of life (Moy et al. 2001).

SABA use. Frequency of SABA use is a good measure of short-term (past month) (Nathan et al. 2004; Vollmer et al. 1999) and long-term (past year) asthma control (Schatz et al. 2006). Frequent use of SABA before exercise may confound these measures unless quick relief and prophylactic use can be separated.

Pulmonary function. Office spirometry (prebronchodilator) or home peak flow measures reflect control in treated patients (Bateman et al. 2004; Juniper et al. 1999, 2001). Pulmonary function measures may be poorly correlated with asthma symptoms (Shingo et al. 2001; Stahl 2000).

Validated questionnaires. Several validated tools have been developed to measure asthma control (Juniper et al. 1999; Nathan et al. 2004; Vollmer et al. 1999) and can be used to classify asthma control. (See "Component 1: Measures of Asthma Assessment and Monitoring," figure 3–8.)

Risk Domain

The risk domain includes frequency and severity of exacerbations and the occurrence of treatment-related adverse effects. Patients at any level of control of impairment may experience severe exacerbations. A history of previous exacerbations, especially exacerbations leading to ED visits or hospitalizations in the previous year, significantly increases the risk of subsequent exacerbations (Adams et al. 2000; Cowie et al. 2001; Eisner et al. 2001; Lieu et al. 1998; Schatz et al. 2004; Yurk et al. 2004). This highlights the need to obtain a history of previous exacerbations requiring hospitalization (including need for intensive care unit (ICU) admission or intubation), ED visits, and other unscheduled physician visits. In addition, increasing exacerbation rates are noted with decreasing FEV_1 categories >80 percent, 60–79 percent, and <60 percent predicted (Fuhlbrigge et al. 2001, 2006; Kitch et al. 2004).

It is generally hoped that control of *impairment* will reduce the risk of exacerbations (Schatz et al. 2005; Vollmer et al. 1999), but there may be a disassociation between the two. It has been demonstrated that control based on bronchial hyperreactivity (Sont et al. 1999), sputum eosinophilia (Green et al. 2002), or possibly fractional exhaled nitric oxide (FeNO) (Smith et al.

2005) is more effective in reducing exacerbations than control based on clinical markers alone, but more studies are needed, and only FeNO monitoring may become practical enough to be used clinically for this purpose.

■ **Adjust therapy based on level of asthma control (Evidence A).** The following considerations will guide selection of therapy based on level of asthma control. Classify current level of asthma control, generally, by the most severe indicator of impairment or risk (figure 4–7) (Evidence D).

— If the patient's asthma is not well controlled:

♦ Identify the patient's current treatment step (figure 4–5), based on what he or she is actually taking. In general, step up one step for patients whose asthma is not well controlled. For patients who have very poorly controlled asthma, consider increasing by two steps, a course of oral corticosteroids, or both. Before increasing pharmacologic therapy, consider poor inhaler technique, adverse environmental exposures, poor adherence, or comorbidities as targets for intervention.

♦ If the office spirometry suggests worse control than does the assessment of impairment based on other measures, (1) consider fixed airway obstruction as the explanation (Aburuz et al. 2005) (See "Component 1: Measures of Asthma Assessment and Monitoring".), and use changes from percent personal best rather than percent predicted to guide therapy; (2) reassess the other measures of impairment; and (3) if fixed airway obstruction does not appear to be the explanation, consider a step up in therapy, especially if the patient has a history of frequent moderate or severe exacerbations.

♦ If the history of exacerbations suggests poorer control than does the assessment of impairment, (1) reassess impairment; (2) review control of factors capable of making asthma worse (e.g., lack of adherence, adverse environmental exposure, or comorbidities); (3) review the written action plan, and be sure it includes oral prednisone for patients who have histories of severe exacerbations; and (4) consider a step up in therapy, especially if the patient has reduced FEV_1.

♦ For troublesome or debilitating side effects, explore a change in therapy. In addition, confirm maximal efforts to control factors capable of making asthma worse (See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma.").

♦ After treatment is adjusted, reevaluate in 2–6 weeks, depending on the level of control.

— If the patient's asthma is well controlled, see the following section on "Maintaining Control of Asthma."

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 3-month intervals 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 patient's written asthma action plan, the medications, and the patient's self-management behaviors (e.g., inhaler and peak flow monitoring techniques, actions to control factors that aggravate their asthma) (See "Component 2: Education for a Partnership in Asthma Care," figures 3–11 and 3–15.).

The Expert Panel recommends that, once asthma is well controlled and the control is achieved and maintained for at least 3 months, a reduction in pharmacologic therapy—a step down—can be considered. This will be helpful to identify the minimum therapy for maintaining good control of asthma (Evidence D). Reduction in therapy should be gradual and closely monitored, because asthma 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. 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 that is required to maintain control (Hawkins et al. 2003; Lemanske et al. 2001). Patients may relapse when the ICS is completely discontinued (Lemanske et al. 2001; Waalkens et al. 1993).

The Expert Panel recommends that, if asthma control is not achieved and maintained at any step of care (See figure 4–7.), several actions may be considered:

■ **Patient adherence and technique in using medications correctly should be assessed (Evidence B).** See "Component 2: Education for a Partnership in Asthma Care" for discussion on assessing adherence. Key questions to consider asking patients include:

   — Which medicines are you currently taking? How often?
   — Please show me how you take the medicine.
   — How many times a week do you miss taking the medication?
   — What problems have you had taking the medicine (cost, time, lack of perceived need)?
   — What concerns do you have about your asthma medicines?

■ **A temporary increase in anti-inflammatory therapy may be indicated to reestablish asthma control (Evidence D).** A deterioration of asthma may be characterized by gradual reduction in PEF (approximately 20 percent), by failure of SABA bronchodilators to produce a sustained response, by a reduced tolerance to activities or exercise, and by the development of increasing symptoms or nocturnal awakenings from asthma. To regain control of asthma, a short course of oral prednisone (See figure 4–8a.) is often effective. If asthma symptoms do not recur and pulmonary functions remain normal, no additional therapy is necessary. However, if the prednisone burst does not control symptoms, is effective only for a short period of time (e.g., less than 1–2 weeks), or is repeated frequently, the patient should be managed according to the next higher step of care.

■ **Other factors that diminish control may have to be identified and addressed (Evidence C).** These factors include the presence of a coexisting condition (e.g., rhinitis/sinusitis, gastroesophageal reflux, obesity), a new or increased exposure to allergens or irritants, patient or family barriers to adequate self-management behaviors, or psychosocial problems. In some cases, alternative diagnoses, such as VCD, should be considered.

■ **A step up to the next higher step of care may be necessary (Evidence A).**

■ **Consultation with an asthma specialist may be indicated (See "Component 1: Measures of Asthma Assessment and Monitoring.") (Evidence D). The Expert Panel recommends referral to an asthma specialist for consultation or comanagement if: there are difficulties achieving or maintaining control of asthma; immunotherapy or omalizumab is being considered; the patient requires step 4 care or higher; or the patient has had an exacerbation requiring a hospitalization.** (See "Component 1: Measures of Asthma Assessment and Monitoring."). Referral may be *considered* if a patient requires step 3 care (Evidence D).

Treatment: Pharmacologic Steps

The Expert Panel recommends that specific therapy should be tailored to the needs and circumstances of individual patients. Pharmacologic therapy must be accompanied at every step by patient education and measures to control those environmental factors or comorbid conditions that can make asthma worse (EPR―2 1997). See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma" which includes discussion of the role of allergen immunotherapy, and "Component 2: Education for a Partnership in Asthma Care." Figure 4–5 presents treatment options for the stepwise approach for managing asthma youths ≥12 years of age and adults. The recommendations for steps of pharmacologic therapy are intended to be general guidelines for assisting, not replacing, clinical decisionmaking. The recommendations are not intended to be prescriptions for individual treatment.

INTERMITTENT ASTHMA

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 (EPR―2 1997).** If effective in relieving infrequent symptoms and normalizing pulmonary function, intermittent use of SABA can continue on an as-needed basis. If significant symptoms recur or SABA is required for quick-relief treatment more than 2 days a week (with the exception of using SABA for exacerbations caused by viral infections and for EIB), the patient should be treated for persistent asthma (See below.).

■ **Patients who have intermittent asthma and experience EIB benefit from taking SABA, cromolyn, or nedocromil shortly before exercise (EPR―2 1997) (See in "Exercise-Induced Bronchospasm" in "Managing Special Situations in Asthma.").** Cromolyn or nedocromil may be beneficial if taken before unavoidable exposure to an aeroallergen known to exacerbate the patient's asthma (Cockcroft and Murdock 1987).

■ **The following actions for managing exacerbations due to viral respiratory infections are recommended (EPR―2 1997).** 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 must be repeated more frequently than every 6 weeks, a step up in long-term care is recommended. If the viral respiratory infection provokes a moderate-to-severe exacerbation, a short course of systemic corticosteroids should be considered. For those patients who have a history of severe exacerbations with viral

respiratory infections, systemic corticosteroids should be considered at the first sign of the infection.

■ **A detailed written asthma action plan is recommended for those patients who have intermittent asthma and particularly those who have 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 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 and PEF measurements), as well as specific recommendations for using SABA, early administering a course 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 or whether a stepup in long-term therapy is warranted.

PERSISTENT ASTHMA

The Expert Panel recommends the following therapy for persistent asthma:

■ **Daily long-term control medication is recommended for patients who have persistent asthma. The long-term control medication should be one with anti-inflammatory effects. Of the available medications, ICSs are the most effective single agents (Evidence A)** (see component 4—Medications).

■ **Quick-relief medication must be available to all patients who have persistent asthma. 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."). Increasing use of SABA or use more than 2 days a week for symptom control (not for preventing EIB) indicates the need to step up therapy.

■ **Consider treating patients who may have seasonal asthma (asthma symptoms only in relation to certain seasonal molds or pollens with few symptoms the rest of the year) as having persistent asthma during the season and as having intermittent asthma the rest of the year. Confirm characteristics of intermittent asthma out of season (Evidence D).** Some patients experience asthma symptoms only in relationship to certain pollens and molds. Asthma exacerbations in children are common in the fall and seem to correlate with increased exposure to viral respiratory infections in the school environment (Hammerman et al. 2002; Johnston et al. 2005).

■ **Consider treating patients who had two or more exacerbations requiring oral 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, Long-Term Control Medication

■　**Preferred treatment for step 2 care is daily ICS at a low dose (Evidence A).**

■　**Alternative, but not preferred, treatments include (listed alphabetically) cromolyn, LTRA, nedocromil (Evidence A), and sustained release theophylline (Evidence B). There is insufficient evidence to recommend LABA in combination with ICS for step 2 therapy.**

—　Cromolyn and nedocromil have some, but limited, effectiveness and a strong safety profile.

—　LTRAs (montelukast and zafirlukast) provide long-term control, prevent symptoms, and are alternative, but not preferred, therapies for patients who have mild persistent asthma, because studies comparing overall efficacy of ICS and LTRA favor ICS on most asthma outcome measures (Evidence A). (See section 3, "Component 4: Medications.") Zileuton, a leukotriene inhibitor, is not recommended in step 2 care, because no studies of zileuton specifically in patients who have mild persistent asthma have been reported, and zileuton requires liver function test monitoring (Evidence D).

—　Sustained-release theophylline is an alternative, but not preferred, long-term control medication. It is not preferred because the modest clinical effectiveness (theophylline is primarily a bronchodilator and its anti-inflammatory activity demonstrated thus far is modest) must be balanced against concerns about potential toxicity (See "Component 4: Medications."). Theophylline remains a therapeutic option for certain patients due to expense or need for tablet-form medication. Sustained-release theophylline is given to achieve a serum concentration of between 5 and 15 mcg/mL. Periodic theophylline monitoring is necessary to maintain a therapeutic—but not toxic—level.

—　Insufficient evidence is available to recommend LABA in combination with ICS in step 2 care (O'Byrne et al. 2001). In steroid naïve patients who have mild persistent asthma, the initiation of an ICS in combination with a LABA does not significantly reduce the rate of exacerbations or the use of SABA for quick relief over that achieved with ICS alone, although the combination therapy can improve lung function and symptom days compared to ICS alone (Ni et al. 2005). Thus, there is insufficient efficacy evidence to recommend this combination therapy in step 2 care. In addition, the possibility of rare but potentially life-threatening outcomes with LABAs (See "Component 4: Medications.") supports this recommendation.

—　A recent study has suggested that some patients who have mild persistent asthma may be successfully managed with intermittent use of low-dose ICS, because study participants taking daily budesonide, daily zafirlukast, or intermittent treatment with ICS and SABA (according to a symptom-based action plan) had similar improvement in morning PEF and a similarly low number of exacerbations (Boushey et al. 2005). However, other outcomes in this study were significantly better in patients taking regular versus intermittent ICS therapy (symptom-free days, prebronchodilator FEV_1, airway hyperresponsiveness, and inflammatory markers). Currently, data are insufficient to recommend intermittent use of ICS for most patients who have mild persistent asthma, although it may be considered as a step-down therapy strategy for patients who are well controlled on step 2 therapy. Further studies are needed to evaluate the use of intermittent therapy with either ICSs or leukotriene modifiers.

Step 3 Care, Long-Term Control Medications

■   **Consultation with an asthma specialist may be considered because the therapeutic options at this juncture pose a number of challenging risk/benefit considerations (Evidence D). Before increasing therapy, however, the clinician should review the patient's inhaler technique and adherence to therapy (Evidence B), as well as determine whether environmental factors, particularly allergens (Evidence A), or comorbid conditions are contributing to the patient's worsening asthma (Evidence C).**

■   **Preferred step 3 care options: Two equally acceptable options are available, given the consideration of both benefits and risks for each.**

— **Add a LABA to a low dose of ICS (Evidence A).** Studies on LABAs as adjunctive therapy have revealed both benefit and some risk. See "Component 4: Medications," section on "Safety of Long-Acting Beta$_2$-Agonists," for a complete discussion. In summary:

♦   Studies demonstrate the addition of a LABA (salmeterol or formoterol) to medications for patients whose asthma is not well controlled on a low to medium dose of ICSs improves lung function, decreases symptoms, and reduces exacerbations and use of quick-relief medication in most patients who have asthma (Bateman et al. 2004; EPR—2 1997; Greenstone et al. 2005; Masoli et al. 2005). See also Evidence Table 11: Inhaled Corticosteroids—Combination Therapy.

♦   A large clinical trial comparing daily treatment with salmeterol or placebo added to usual asthma therapy (Nelson et al. 2006) demonstrated an increased risk of asthma-related deaths in patients treated with salmeterol (13 deaths out of 13,176 patients treated for 28 weeks with salmeterol versus 3 deaths out of 13,179 patients treated with placebo). In addition, an increased number of severe asthma exacerbations were noted in the pivotal trials submitted to the FDA for formoterol approval, particularly in the higher dose formoterol arms of the trials (Mann et al. 2003). Thus the FDA determined that a Black Box warning was warranted on all preparations containing a LABA.

♦   The Expert Panel recommends that the established, beneficial effects of LABAs for the great majority of patients who have asthma not sufficiently controlled with ICS therapy alone be weighed carefully against the increased risk for potentially deleterious, although uncommon, side effects associated with the daily use of LABAs.

♦   Therefore, the Expert Panel has modified its previous recommendation (EPR—Update 2002) and has now concluded that, for patients who have asthma not sufficiently controlled with a low-dose ICS alone, the step-up option to increase the ICS dose should be given equal weight to that of the addition of a LABA to ICS.

OR

— **Continue the ICS as monotherapy by increasing the dose to the medium-dose range (Evidence A).** Studies of adults in whom the dose of ICS was at least doubled demonstrate some improvements in lung function and other outcomes in those patients who have asthma not completely controlled on a low-to-medium dose of ICS, although

these results are generally less effective than adding a LABA (Ind et al. 2003). In the GOAL study of 3,421 patients who had uncontrolled asthma, a substantial proportion of the patients who received a dose escalation of ICS achieved well-controlled (59 percent) or totally controlled (28 percent) asthma (Bateman et al. 2004). Furthermore, a study of 2,670 patients showed similar rates of exacerbations and nighttime awakenings among the daily medium-dose ICS and daily combination low-dose (ICS/formoterol) study treatment groups (O'Byrne et al. 2005). Both studies confirm the benefits of increasing the dose of ICS (see below for further discussion on weighing the benefits and risks of different step 3 care options).

Based on review of the evidence and in consideration of the potential benefits for improvements in the asthma control domains of impairment and risk, as well as consideration of the potential for adverse effects that exist for each therapeutic option, the Expert Panel recommends that either increasing the dose of the ICS to medium dose or adding LABA to low-dose ICS is an equally acceptable step-up option for patients whose asthma is not adequately controlled on a low dose of ICS.

Overall, the results of the Expert Panel's review of the evidence indicate that the choice one makes at this juncture of stepping up therapy should be based on which therapeutic outcome should be the focus for each individual patient: that is, the desired degree of asthma control in the domains of either *impairment* or *risk,* or both, weighed against the relative risks of side effects for the therapeutic options.

■   For the impairment domain, adding LABA, rather than increasing the dose of ICS, more consistently results in improvements in the impairment domain (EPR—Update 2002).

■   If the risk domain is of particular concern, then a balance of potential risks needs to be considered (See also "Component 4: Medications.").

   —   Adding LABA to low-dose ICS reduces the frequency of exacerbations to a greater extent than doubling the dose of ICS (Masoli et al. 2005), but adding LABA has the potential risk of rare life-threatening or fatal exacerbations.

   —   Increasing the dose of ICS can significantly reduce the risk of exacerbations, but this benefit may require up to a fourfold increase in the ICS dose (Pauwels et al. 1997). This may increase the potential risk of systemic effects, although within the medium-dose range the risk is small.

■   **Alternative, but not preferred, step 3 therapy is to add (listed alphabetically) an LTRA (Evidence A), theophylline (Evidence B), or zileuton (Evidence D) to low-dose ICS.**

   Considerations favoring one of these alternative combinations would be the patient's lack of response to or intolerance of the side effects of the LABA if that option was tried; marked preference for oral therapy; previous demonstration of superior responsiveness to the alternative class of drug; and/or financial considerations (theophylline is the least expensive).

   The addition of either LTRA, theophylline, or zileuton has produced modest improvement in lung function and some other outcomes in patients who have asthma that is not completely controlled by an ICS. The addition of theophylline, however, has not been shown to be more effective than doubling the dose of the ICS (Evans et al. 1997; Ukena et al. 1997).

LTRAs have produced improvements in lung function and in some but not all measures of asthma control in both adults (Laviolette et al. 1999) and children (Simons et al. 2001) whose asthma is not well controlled by ICSs. When the addition of the LTRA to an ICS has been compared with doubling the dose of the ICS, similar results were observed for a number of outcome measures (Price et al. 2003). Direct comparisons of the addition of an LTRA or a LABA to therapy for patients whose asthma is not well controlled by ICS show significantly greater improvement in lung function and other measures of asthma control for patients receiving the LABA and ICS combination (Ram et al. 2005). Because efficacy data are limited for zileuton as add-on therapy (Dahlen et al. 1998; Lazarus et al. 1998), and zileuton requires monitoring of liver function tests, the Expert Panel considers zileuton a less desirable alternative than LTRA or theophylline for step 3 add-on therapy.

- **If an alternative, but not preferred, treatment is initially administered and does not lead to improvement in asthma control, discontinue it and use a preferred step 3 option before stepping up to step 4 (Evidence D).**

Step 4 Care, Long-Term Control Medications

- **The preferred option is to increase the dose of ICS to the medium-dose range AND add a LABA (Evidence B).** This step is recommended for patients who have asthma not controlled by step 3 therapy. This approach is also recommended for those patients who experience recurring severe exacerbations requiring oral prednisone, ED visits, or hospitalizations. In a 1-year trial of combination therapy, the addition of a LABA to either low-dose or high-dose ICS significantly reduced both mild and severe exacerbation (Pauwels et al. 1997). In addition, fewer exacerbations occurred in the group receiving high-dose ICS compared with the group receiving the lower dose, although statistical analysis was not done. See also the discussion on LABA and combination therapy in "Component 4: Medications."

- **Alternative, but not preferred, step 4 therapy includes medium-dose ICS AND either LTRA or theophylline (Evidence B), or zileuton (Evidence D).**

- If the add-on therapy initially administered does not lead to improvement in asthma control, discontinue it and consider a trial of a different add-on therapy before stepping up (Evidence D).

Step 5 Care, Long-Term Control Medications

- **High-dose ICS and LABA is the preferred treatment (Evidence B).**

- **Omalizumab may be considered at this step for patients who have sensitivity to relevant perennial allergens (e.g., dust mites, cockroach, cat, or dog) (Evidence B) (Bousquet et al. 2004; Humbert et al. 2005).**

- **Clinicians who administer omalizumab are advised to be prepared and equipped for the identification and treatment of anaphylaxis that may occur, to observe patients for an appropriate period of time following each omalizumab injection (the optimal length of the observation is not established), and to educate patients about the risks of anaphylaxis and how to recognize and treat it if it occurs (e.g., using prescription auto injectors for emergency self-treatment, and seeking immediate medical care) (FDA 2007).**

■ **Consultation with an asthma specialist is recommended for patients who require this step of therapy (Evidence D).**

Step 6 Care, Long-Term Control Medications

■ **Add oral corticosteroids to step 5 therapy. Patients who are not controlled on step 5 therapy may require regular oral corticosteroids to achieve well-controlled asthma (EPR—2 1997).**

— Two studies have examined the benefit of LTRA as adjunctive therapy in patients who have asthma that is not controlled by ICS and LABA. One 2-week study found no benefit for the addition of an LTRA to high-dose ICS and, for most patients in the study, another medication (either theophylline, a LABA, oral corticosteroid, or a combination) (Robinson et al. 2001). Nathan et al. (2005) reported that adding montelukast for patients who had mild or moderate persistent asthma treated with combined fluticasone (100 mcg)–salmeterol did not improve asthma outcome compared to adding placebo. Studies are not available of other long-term control medications added to the combination of medium- to high-dose ICS and LABA in severe persistent asthma. These data are not definitive; therefore, due to the side effects associated with chronic oral corticosteroid therapy, before maintenance prednisone therapy is initiated, the following may be considered: a 2-week course of oral corticosteroids to confirm reversibility; or a combination of high-dose ICS + LABA + trial of either LTRA, low-dose theophylline, or zileuton (Evidence D).

— For patients who require long-term systemic corticosteroids:

♦ Use the lowest possible dose (single dose daily or on alternate days).

♦ Monitor patients closely for corticosteroid adverse side effects (See "Component 4: Medications.").

♦ When well-controlled asthma is achieved, make persistent attempts to reduce systemic corticosteroids. High-dose ICS therapy is preferable to oral systemic corticosteroids because ICSs have fewer systemic effects.

♦ Consultation with an asthma specialist is recommended.

SPECIAL ISSUES FOR ADOLESCENTS

The Expert Panel recommends that the pharmacologic management of asthma in school-age children and adolescents follows the same basic principles as those for adults, but the special circumstances of school and social development require special consideration (EPR—2 1997).

Assessment Issues

The Expert Panel recommends that pulmonary function testing should be performed by using comparison data from an appropriate reference population (ATS 1995; EPR—2 1997). Adolescents generally compare better to childhood norms than to adult predicted norms. Testing in a laboratory or clinic that specializes in children can result in higher pulmonary function values and more consistent data. Technicians who conduct pulmonary function testing

for children should have special training in achieving the best possible effort from young patients.

Treatment Issues

The Expert Panel recommends that adolescents (and younger children as appropriate) be directly involved in developing their written asthma action plans (See "Component 2: Education for a Partnership in Asthma Care."). Adolescents may experience more difficulties than younger children in adhering to a medication 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 on their emerging independence and adulthood. In teaching adolescents the same asthma self-management techniques expected of adults, the clinician should address adolescent developmental issues, such as building a positive self-image and confidence, increasing personal responsibility, and gaining problem-solving skills. To accomplish this approach, it is often helpful to see the adolescent initially without parents present and to involve the adolescent directly in setting goals for therapy, developing an appropriate asthma action plan, and reviewing the effectiveness of the 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 adolescent's efforts.

School Issues

The Expert Panel recommends that the clinician prepare a written asthma action plan for the student's school. Either encourage the youth or the parents to take a copy of the plan to the youth'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: 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. For a sample plan, See figure 3–16a, b.

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, youths 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 student 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. It may be helpful for some children to have a compressor-driven nebulizer available at the school.

Sports Issues

The Expert Panel recommends that clinicians encourage full participation in physical activities; physical activity at play or in organized sports is an essential part of a child's

life (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 "Exercise-Induced Bronchospasm."). Activity should be limited or curtailed only as a last resort.

SPECIAL ISSUES FOR OLDER ADULTS

Assessment Issues

The Expert Panel recommends that the extent of reversible airflow obstruction be determined because of the high prevalence of other obstructive lung disease (e.g., chronic bronchitis, emphysema) among the elderly (EPR—2 1997). Careful evaluation is required, because the precise cause of severe airflow obstruction can be difficult to identify in older patients who have asthma. A 2- to 3-week trial of therapy with systemic corticosteroids can help detect the presence of significant reversibility of the airway disease. Long-term control asthma medication can then be offered.
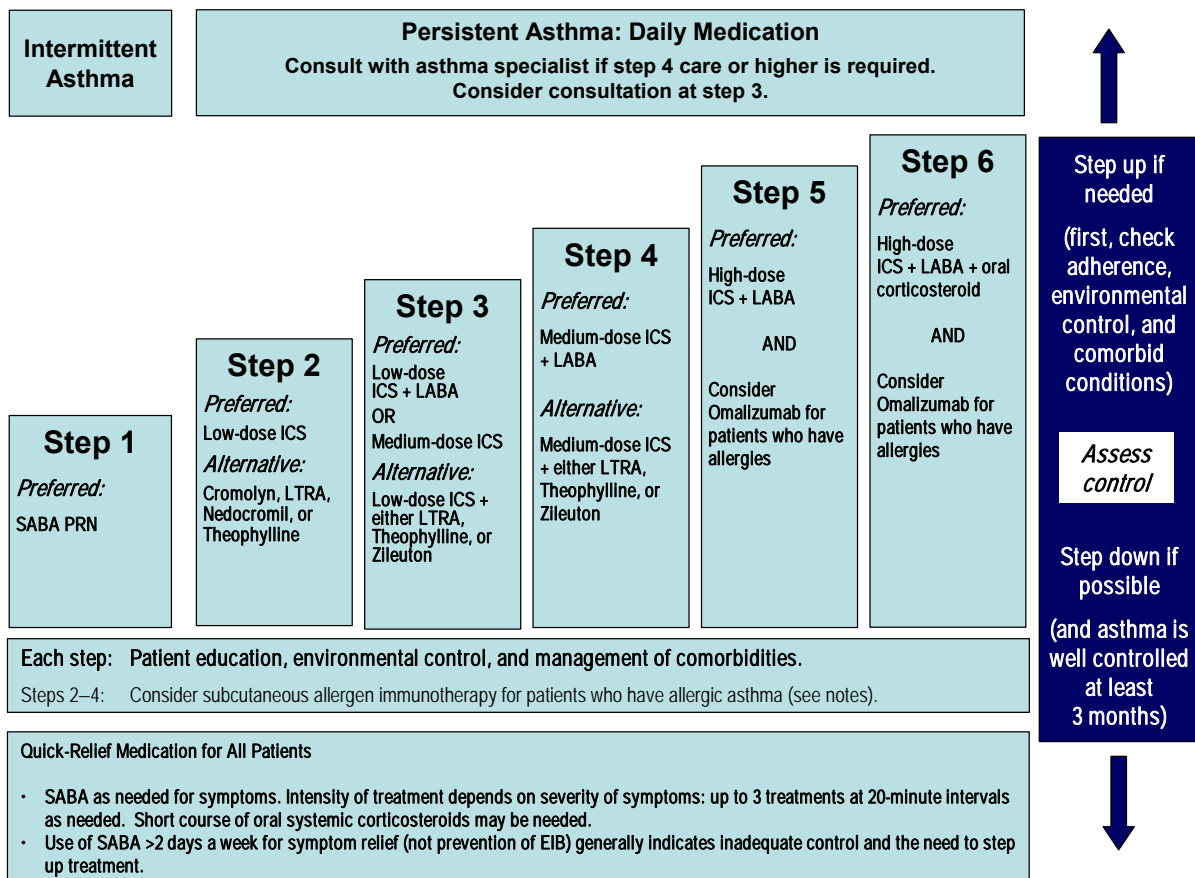
Treatment Issues

The Expert Panel recommends that adjustments in therapy may be necessary because asthma medications may have increased adverse effects in the elderly patient (EPR—2 1997).

■ Airway response to *bronchodilators* may change with age, although this is not clearly established. Older patients, especially those with preexisting ischemic heart disease, may also be more sensitive to beta$_2$-agonist side effects, including tremor and tachycardia. Concomitant use of an anticholinergic and a SABA may be beneficial to the older patient (Barros and Rees 1990; Gross et al. 1989; Ullah et al. 1981).

■ *Theophylline* clearance is reduced in elderly patients (Nielsen-Kudsk et al. 1988), causing increased blood levels of theophylline. In addition, age is an independent risk factor for developing life-threatening events from iatrogenic chronic theophylline overdose (patients 75 years of age or older have a 16-fold greater risk of death from theophylline overdose than do 25-year-old patients) (Shannon and Lovejoy 1990). The potential for drug interaction—especially with antibiotics and H$_2$-histamine antagonists such as cimetidine—is greater because of the increased use of medications in this age group. Theophylline and epinephrine may exacerbate underlying heart conditions.

■ *Systemic corticosteroids* can provoke confusion, agitation, and changes in glucose metabolism.

■ *Inhaled corticosteroid.* **Consider concurrent treatments with calcium supplements and vitamin D, and bone-sparing medications (e.g., bisphosphonates) in patients who have risk factors for osteoporosis or low bone mineral density (Evidence D).** ICS use may be associated with a dose-dependent reduction in bone mineral content, although low or medium doses appear to have no major adverse effect. Elderly patients may be more at risk due to preexisting osteoporosis, changes in estrogen levels that affect calcium utilization, and a sedentary lifestyle. The risk of not adequately controlling asthma may limit unnecessarily the patient's mobility and activities (See "Component 4: Medications."). An

approach for identifying patients at risk for accelerated bone loss from high-dose ICS therapy is to conduct bone densitometry when treatment begins and again 6 months later (NHLBI 1996), although the benefits of this approach have not yet been evaluated in clinical trials.

The Expert Panel recommends that medications taken for other diseases and conditions be adjusted as necessary, because some medications may exacerbate asthma (EPR—2 1997). Nonsteroidal anti-inflammatory agents for treating arthritis, beta-blockers for treating hypertension (particularly nonselective beta-blockers), or beta-blockers found in some eye drops used to treat glaucoma may exacerbate asthma. See "Component 4: Medications" for more details on drugs that can complicate asthma management.

The Expert Panel recommends that review of the patient's technique in using medications and devices is essential (Evidence B). Observation of technique for use of inhaler devices, peak flow meters, and spirometry is especially important in the elderly because physical (e.g., arthritis, visual) and cognitive impairments (recognized or unrecognized) can make acquisition and retention of proper technique difficult (Allen et al. 2003; Barr et al. 2002; Pezzoli et al. 2003; Wolfenden et al. 2002).

FIGURE 4–5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Intermittent Asthma	Persistent Asthma: Daily Medication
	Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

Step 6
Preferred:
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 5
Preferred:
High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 4
Preferred:
Medium-dose ICS + LABA
Alternative:
Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 3
Preferred:
Low-dose ICS + LABA
OR
Medium-dose ICS
Alternative:
Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 2
Preferred:
Low-dose ICS
Alternative:
Cromolyn, LTRA, Nedocromil, or Theophylline

Step 1
Preferred:
SABA PRN

Step up if needed
(first, check adherence, environmental control, and comorbid conditions)

Assess control

Step down if possible
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.

Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
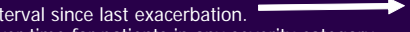
— Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting 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.

■ Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.

■ In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.

■ Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR—2 1997) and Evidence B for omalizumab.

■ 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 or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 4–6. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

— **Assessing severity and initiating treatment for patients who are not currently taking long-term control medications**

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV$_1$/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	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, and not more than 1x on any day	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 normal	• FEV$_1$ >80% predicted • FEV$_1$/FVC normal	• FEV$_1$ >60% but <80% predicted • FEV$_1$/FVC reduced 5%	• FEV$_1$ <60% predicted • FEV$_1$/FVC reduced >5%
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 Treatment (See figure 4–5 for treatment steps.)		Step 1	Step 2	Step 3	Step 4 or 5
				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: FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

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 assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of 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 4–7. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control		Classification of Asthma Control (≥12 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/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
	FEV$_1$ or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	0 ≤0.75* ≥20	1–2 ≥1.5 16–19	3–4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	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 4–5 for treatment steps)		• Maintain current step. • Regular followups every 1–6 months to maintain control. • Consider step down if well controlled for at least 3 months.	• Step up 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.

■
— *ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.
— Key: EIB, exercise-induced bronchospasm; ICU, intensive care unit

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 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 not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

■ Validated Questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain)

    ATAQ = Asthma Therapy Assessment Questionnaire© (See sample in "Component 1: Measures of Asthma Assessment and Monitoring.")
    ACQ = Asthma Control Questionnaire© (user package may be obtained at www.qoltech.co.uk or juniper@qoltech.co.uk)
    ACT = Asthma Control Test™ (See sample in "Component 1: Measures of Asthma Assessment and Monitoring.")
    Minimal Important Difference: 1.0 for the ATAQ; 0.5 for the ACQ; not determined for the ACT.

■ Before step up in therapy:
— Review adherence to medication, inhaler technique, environmental control, and comorbid conditions.
— If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step.

FIGURE 4–8a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS

Medication	Dosage Form	Adult Dose	Comments
Inhaled Corticosteroids (ICS) *(See figure 4–8b, "Estimated Comparative Daily Dosages for Inhaled Corticosteroids.")*			
Systemic Corticosteroids			*(Applies to all three corticosteroids)*
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	7.5–60 mg daily in a single dose in a.m. or qod as needed for control	■ 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.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	Short-course "burst": to achieve control, 40–60 mg per day as single or 2 divided doses for 3–10 days	
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc		■ There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.
Inhaled Long-Acting Beta$_2$-Agonists (LABA)			■ **Should not be used for symptom relief or exacerbations. Use with ICS.**
Salmeterol	DPI 50 mcg/ blister	1 blister q 12 hours	■ Decreased duration of protection against EIB may occur with regular use.
Formoterol	DPI 12 mcg/ single-use capsule	1 capsule q 12 hours	■ 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 Aerolizor™ inhaler and should not be taken orally.
Combined Medication			
Fluticasone/Salmeterol	DPI 100 mcg/50 mcg, 250 mcg/50 mcg, or 500 mcg/50 mcg HFA 45 mcg/21 mcg 115 mcg/21 mcg 230 mcg/21 mcg	1 inhalation bid; dose depends on severity of asthma	■ 100/50 DPI or 45/21 HFA for patient not controlled on low- to medium-dose ICS 250/50 DPI or 115/21 HFA for patients not controlled on medium- to high-dose ICS
Budesonide/ Formoterol	HFA MDI 80 mcg/4.5 mcg 160mcg/4.5 mcg	2 inhalations bid; dose depends on severity of asthma	■ 80/4.5 for patients who have asthma not controlled on low- to medium-dose ICS ■ 160/4.5 for patients who have asthma not controlled on medium- to high-dose ICS

■

FIGURE 4–8a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS (CONTINUED)

Medication	Dosage Form	Adult Dose	Comments
Cromolyn and Nedocromil			
Cromolyn	MDI 0.8 mg/puff	2 puffs qid	■ 4–6 week trial may be needed to determine maximum benefit.
	Nebulizer 20 mg/ampule	1 ampule qid	■ Dose by MDI may be inadequate to affect hyperresponsiveness.
Nedocromil	MDI 1.75 mg/puff	2 puffs qid	■ One dose before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective for EIB as SABA. ■ Once control is achieved, the frequency of dosing may be reduced.
Leukotriene Modifiers			
Leukotriene Receptor Antagonists			
Montelukast	4 mg or 5 mg chewable tablet 10 mg tablet	10 mg qhs	■ Montelukast exhibits a flat dose-response curve. Doses >10 mg will not produce a greater response in adults.
Zafirlukast	10 or 20 mg tablet	40 mg daily (20 mg tablet bid)	■ 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.
5-Lipoxygenase Inhibitor			
Zileuton	600 mg tablet	2,400 mg daily (give tablets qid)	■ For zileuton, monitor hepatic enzymes (ALT).
Methylxanthines			
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/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 important. ■ See next page for factors that can affect theophylline levels.
Immunomodulators			
Omalizumab	Subcutaneous injection, 150 mg/1.2 mL following reconstitution with 1.4 mL sterile water for injection	150–375 mg SC q 2–4 weeks, depending on body weight and pretreatment serum IgE level	■ Do not administer more than 150 mg per injection site. ■ Monitor for anaphylaxis for 2 hours following at least the first 3 injections.

Key: DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; IgE, immunoglobulin E; MDI, metered-dose inhaler; SABA, short-acting beta$_2$-agonist

FIGURE 4–8a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS (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 4–8b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS

Drug	Low Daily Dose Adult	Medium Daily Dose Adult	High Daily Dose Adult
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	>240–480 mcg	>480 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	180–600 mcg	>600–1,200 mcg	>1,200 mcg
Flunisolide 250 mcg/puff	500–1,000 mcg	>1,000–2,000 mcg	>2,000 mcg
Flunisolide HFA 80 mcg/puff	320 mcg	>320–640 mcg	>640 mcg
Fluticasone **HFA/MDI:** 44, 110, or 220 mcg/puff	88–264 mcg	>264–440 mcg	>440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100–300 mcg	>300–500 mcg	>500 mcg
Mometasone DPI 200 mcg/inhalation	200 mcg	400 mcg	>400 mcg
Triamcinolone acetonide 75 mcg/puff	300–750 mcg	>750–1,500 mcg	>1,500 mcg

Key: DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler

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.

■ MDI dosages are expressed as the actuator dose (the amount of the drug leaving the actuator and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, not all of which is available to the patient), which is used in many European countries and in some scientific literature. DPI doses are expressed as the amount of drug in the inhaler following activation.

■ 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- and 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 one-half the microgram dose of budesonide DPI to achieve comparable efficacy (Adams et al. 2005; Barnes et al. 1998; Nielsen and Dahl 2000).

FIGURE 4–8b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS (CONTINUED)

— The dose for beclomethasone in HFA inhaler should be approximately one-half the dose for beclomethasone in 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 mometasone DPI is based on product information and current literature (Bousquet et al. 2000; Fardon et al. 2004; Kemp et al. 2000; O'Connor et al. 2001). Mometasone is approved for once daily administration. Mometasone furoate by dry powder achieved effects similar to twice the dose of budesonide by dry powder (Bousquet et al. 2000) and comparable to a slightly higher dose of fluticasone propionate by dry powder (O'Connor et al. 2001).

— 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).

■ **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.

Adapted with permission from Barnes 1995.

— 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.

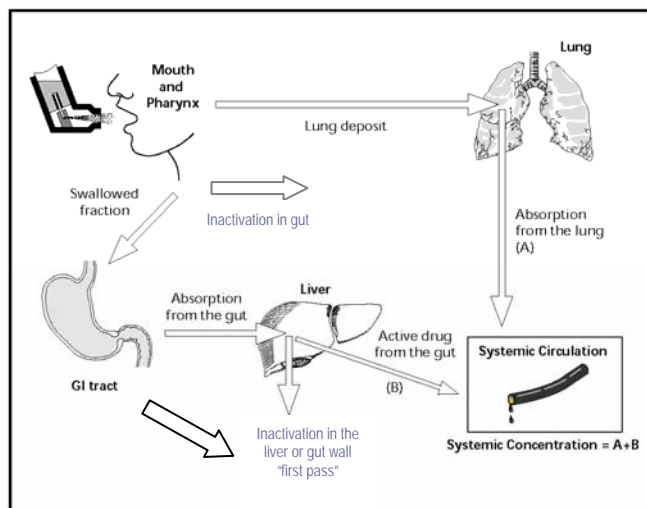— Oral bioavailability of the swallowed portion of the dose received:

♦ Approximately 50–80 percent of the dose from the MDI without a spacer/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 ICSs 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 4–8c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS

Medication	Dosage Form	Adult Dose	Comments
Inhaled Short-Acting Beta₂-Agonists (SABA)			
	MDI		*Applies to all four SABAs*
Albuterol CFC	90 mcg/puff, 200 puffs/canister	■ 2 puffs 5 minutes before exercise	■ An increasing use or lack of expected effect indicates diminished control of asthma.
Albuterol HFA	90 mcg/puff, 200 puffs/canister	■ 2 puffs every 4–6 hours as needed	■ Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need to step up therapy.
Pirbuterol CFC	200 mcg/puff, 400 puffs/canister		■ Differences in potency exist, but all products are essentially comparable on a per puff basis.
Levalbuterol HFA	45 mcg/puff, 200 puffs/canister		■ May double usual dose for mild exacerbations.
			■ Should prime the inhaler by releasing 4 actuations prior to use.
			■ Periodically clean HFA activator, as drug may block/plug orifice.
			■ 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%)	1.25–5 mg in 3 cc of saline q 4–8 hours as needed	■ May mix with budesonide inhalant suspension, cromolyn or ipratropium nebulizer solutions. 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	0.63 mg–1.25 mg q 8 hours as needed	■ Compatible with budesonide inhalant suspension. The product is a sterile-filled, preservative-free, unit dose vial.

■

FIGURE 4–8c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS (CONTINUED)

Medication	Dosage Form	Adult Dose	Comments
Anticholinergics			
	MDI		
Ipratropium HFA	17 mcg/puff, 200 puffs/canister	2–3 puffs q 6 hours	■ Evidence is lacking for anticholinergics producing added benefit to beta$_2$-agonists in long-term control asthma therapy.
	Nebulizer solution		
	0.25 mg/mL (0.025%)	0.25 mg q 6 hours	
	MDI		
Ipratropium with albuterol	18 mcg/puff of ipratropium bromide and 90 mcg/puff of albuterol	2–3 puffs q 6 hours	
	200 puffs/canister		
	Nebulizer solution		
	0.5 mg/3 mL ipratropium bromide and 2.5 mg/3 mL albuterol	3 mL q 4–6 hours	■ Contains EDTA to prevent discoloration of the solution. This additive does not induce bronchospasm.
Systemic Corticosteroids			***Applies to the first three corticosteroids***
Methylprednisolone	2, 4, 6, 8, 16, 32 mg tablets	■ Short course "burst": 40–60 mg/day as single or 2 divided doses for 3–10 days	■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc		■ The burst should be continued until symptoms resolve and the PEF is at least 80 percent of personal best. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
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	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; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow

■

References

Aburuz S, McElnay J, Gamble J, Millership J, Heaney L. Relationship between lung function and asthma symptoms in patients with difficult to control asthma. *J Asthma* 2005;42(10):859–64.

Adams N, Bestall J, Jones P. Inhaled beclomethasone at different doses for long-term asthma. *Cochrane Database Syst Rev* 2001;(1):CD002879.

Adams N, Bestall JM, Lasserson TJ, Jones PW. Inhaled fluticasone versus inhaled beclomethasone or inhaled budesonide for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;(2):CD002310.

Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000;55(7):566–73.

Affrime MB, Cuss F, Padhi D, Wirth M, Pai S, Clement RP, Lim J, Kantesaria B, Alton K, Cayen MN. Bioavailability and metabolism of mometasone furoate following administration by metered-dose and dry-powder inhalers in healthy human volunteers. *J Clin Pharmacol* 2000;40(11):1227–36.

Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. *Age Ageing* 2003;32(3):299–302.

American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152(3):1107–36.

Barnes NC, Hallett C, Harris TA. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;92(1):95–104.

Barr RG, Somers SC, Speizer FE, Camargo CA Jr; National Asthma Education and Prevention Program (NAEPP). Patient factors and medication guideline adherence among older women with asthma. *Arch Intern Med* 2002;162(15):1761–8.

Barros MJ, Rees PJ. Bronchodilator responses to salbutamol followed by ipratropium bromide in partially reversible airflow obstruction. *Respir Med* 1990;84(5):371–5.

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004;170(8):836–44.

Boulet LP, Cartier A, Ernst P, Larivee P, Laviolette M. Safety and efficacy of HFA-134a beclomethasone dipropionate extra-fine aerosol over six months. *Can Respir J* 2004;11(2):123–30.

Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Chinchilli VM, Craig TJ, DiMango EA, Deykin A, et al.; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352(15):1519–28.

Bousquet J, D'Urzo A, Hebert J, Barraza CH, Boulet LP, Suarez-Chacon R, Harnest U, Lundback B, Martinez Morales G, Nieminen MM, et al. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler. *Eur Respir J* 2000;16(5):808–16.

Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004;125(4):1378–86.

Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, Donnell D, Hannon S, Colice GL. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104(6):1215–22.

Chaplin MD, Rooks W, Swenson EW, Cooper WC, Nerenberg C, Chu NI. Flunisolide metabolism and dynamics of a metabolite. *Clin Pharmacol Ther* 1980;27(3):402–13.

Check WA, Kaliner MA. Pharmacology and pharmacokinetics of topical corticosteroid derivatives used for asthma therapy. *Am Rev Respir Dis* 1990;141(2 Pt 2):S44–51.

Clissold SP, Heel RC. Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs* 1984;28(6):485–518.

Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J Allergy Clin Immunol* 1987;79(5):734–40.

Corren J, Nelson H, Greos LS, Bensch G, Goldstein M, Wu J, Wang S, Newman K. Effective control of asthma with hydrofluoroalkane flunisolide delivered as an extrafine aerosol in asthma patients. *Ann Allergy Asthma Immunol* 2001;87(5):405–11.

Cowie RL, Underwood MF, Revitt SG, Field SK. Predicting emergency department utilization in adults with asthma: a cohort study. *J Asthma* 2001;38(2):179–184.

Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, Mastalerz L, Pinis G, Swanson LJ, Boodhoo TI, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1187–94.

Davies B. A comparison of beclomethasone dipropionate and budesonide in the treatment of asthma. *Br J Clin Pract* 1993;47(2):87–93.

Eisner MD, Katz PP, Yelin EH, Shiboski SC, Blanc PD. Risk factors for hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity. *Respir Res* 2001;2(1):53–60. Epub December 2000.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

EPR—Update 2002. Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics 2002 (EPR—Update 2002). NIH Publication No. 02-5074. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf.

Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997;337(20):1412–8.

Fardon TC, Lee DK, Haggart K, McFarlane LC, Lipworth BJ. Adrenal suppression with dry powder formulations of fluticasone propionate and mometasone furoate. *Am J Respir Crit Care Med* 2004;170(9):960–6. Epub June 2004.

Food and Drug Administration (FDA). 2007. FDA alert: Omalizumab (marketed as Xolair) information 2/2007. Available at: http://www.fda.gov/cder/drug/infopage/omalizumab/default.htm.

Fuhlbrigge AL, Adams RJ, Guilbert TW, Grant E, Lozano P, Janson SL, Martinez F, Weiss KB, Weiss ST. The burden of asthma in the United States: level and distribution are dependent on interpretation of the National Asthma Education and Prevention Program guidelines. *Am J Respir Crit Care Med* 2002;166(8):1044–9.

Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, Weiss ST. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107(1):61–7.

Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics* 2006;118(2):e347–55. Epub July 2006.

Gillman SA, Anolik R, Schenkel E, Newman K. One-year trial on safety and normal linear growth with flunisolide HFA in children with asthma. *Clin Pediatr (Phila)* 2002;41(5):333–40.

Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360(9347):1715–21.

Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, Ducharme FM. Combination of inhaled long-acting beta$_2$-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database Syst Rev* 2005;(4):CD005533.

Gross G, Thompson PJ, Chervinsky P, Vanden Burgt J. Hydrofluoroalkane-134a beclomethasone dipropionate, 400 microg, is as effective as chlorofluorocarbon beclomethasone dipropionate, 800 microg, for the treatment of moderate asthma. *Chest* 1999;115(2):343–51.

Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. *Am Rev Respir Dis* 1989;139(5):1188–91.

Hammerman SI, Becker JM, Rogers J, Quedenfeld TC, D'Alonzo GE Jr. Asthma screening of high school athletes: identifying the undiagnosed and poorly controlled. *Ann Allergy Asthma Immunol* 2002;88(4):380–4.

Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990;84(Suppl A):25–9.

Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003;326(7399):1115.

Heald D, Argenti D, Jensen B, Vaccaro S. The disposition of ^{14}C triamcinolone acetonide administrated as single oral dose of 100 microCi (800 mcg) to healthy volunteers. Presented at Asthma Theory to Treatment; 1995 July 15–17, Chicago, IL (data on file Rhône-Poulenc Rorer).

Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, Beeh KM, Ramos S, Canonica GW, Hedgecock S, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60(3):309–16.

Ind PW, Dal Negro R, Colman NC, Fletcher CP, Browning D, James MH. Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. *Respir Med* 2003;97(5):555–62.

Johnson SR, Marion AA, Vrchoticky T, Emmanuel PJ, Lujan-Zilbermann J. Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr* 2006;148(3):386–8.

Johnston NW, Johnston SL, Duncan JM, Greene JM, Kebadze T, Keith PK, Roy M, Waserman S, Sears MR. The September epidemic of asthma exacerbations in children: a search for etiology. *J Allergy Clin Immunol* 2005;115(1):132–8.

Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14(1):32–38.

Juniper EF, O'Byrne PM, Roberts JN. Measuring asthma control in group studies: do we need airway calibre and rescue beta$_2$-agonist use? *Respir Med* 2001;95(5):319–23.

Kelly HW. Comparison of inhaled corticosteroids. *Ann Pharmacother* 1998;32(2):220–32.

Kemp JP, Berkowitz RB, Miller SD, Murray JJ, Nolop K, Harrison JE. Mometasone furoate administered once daily is as effective as twice-daily administration for treatment of mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2000;106(3):485–92.

Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, Fuhlbrigge AL. A single measure of FEV$_1$ is associated with risk of asthma attacks in long-term follow-up. *Chest* 2004;126(6):1875–82.

Lasserson TJ, Cates CJ, Jones AB, Steele EH, White J. Fluticasone versus HFA-beclomethasone dipropionate for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;(4):CD005309. Update in *Cochrane Database Syst Rev* 2006;(2):CD005309.

Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, Zhang J, Reiss TF. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med* 1999;160(6):1862–8.

Lazarus SC, Lee T, Kemp JP, Wenzel S, Dube LM, Ochs RF, Carpentier PJ, Lancaster JF. Safety and clinical efficacy of zileuton in patients with chronic asthma. *Am J Manag Care* 1998;4(6):841–8.

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

Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, Drazen JM, Chinchilli VM, Craig T, Fish JE, et al.; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA* 2001;285(20):2594–603.

Lieu TA, Quesenberry CP, Sorel ME, Mendoza GR, Leong AB. Computer-based models to identify high-risk children with asthma. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1173–80.

Lipworth BJ. New perspectives on inhaled drug delivery and systemic bioactivity. *Thorax* 1995;50(2):105–10.

Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003;124(1):70–4.

Martin LE, Tanner RJ, Clark TJ, Cochrane GM. Absorption and metabolism of orally administered beclomethsone dipropionate. *Clin Pharmacol Ther* 1974;15(3):267–75.

Martin RJ, Szefler SJ, Chinchilli VM, Kraft M, Dolovich M, Boushey HA, Cherniack RM, Craig TJ, Drazen JM, Fagan JK, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. *Am J Respir Crit Care Med* 2002;165(10):1377–83.

Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005;60(9):730–4.

Mollmann H, Rohdewald P, Schmidt EW, Salomon V, Derendorf H. Pharmacokinetics of triamcinolone acetonide and its phosphate ester. *Eur J Clin Pharmacol* 1985;29(1):85–9.

Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM; NHBLI Asthma Clinical Research Network. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med* 2001;163(4):924–9.

Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113(1):59–65.

Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E, Dorinsky PM, Nelson HS. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest* 2005;128(4):1910–20.

National Heart, Lung, and Blood Institute (NHLBI). *NAEPP Working Group Report*: *Considerations for Diagnosing and Managing Asthma in the Elderly* (NHLBI 1996). NIH Publication No. 96-3662. U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute, 1996.

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129(1):15–26. Erratum in: *Chest* 2006;129(5):1393.

Ni CM, Greenstone IR, Ducharme FM. Addition of inhaled long-acting beta$_2$-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults. *Cochrane Database Syst Rev* 2005;(2):CD005307.

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

Nielsen-Kudsk JE, Mellemkjaer S, Siggaard C, Nielsen CB. Effects of pinacidil on guinea-pig airway smooth muscle contracted by asthma mediators. *Eur J Pharmacol* 1988;157(2−3):221–6.

O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164(8 Pt 1):1392–7.

O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekstrom T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171(2):129–36. Epub October 2004.

O'Connor B, Bonnaud G, Haahtela T, Luna JM, Querfurt H, Wegener T, Lutsky BN. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. *Ann Allergy Asthma Immunol* 2001;86(4):397–404.

Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337(20):1405–11. Erratum in: *N Engl J Med* 1998;338(2):139.

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

Pedersen S, Warner J, Wahn U, Staab D, Le Bourgeois M, Essen-Zandvliet E, Arora S, Szefler SJ; Pediatric Study Group. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: an open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics* 2002;109(6):e92.

Pezzoli L, Giardini G, Consonni S, Dallera I, Bilotta C, Ferrario G, Cristina SM, Annoni G, Vergani C. Quality of spirometric performance in older people. *Age Ageing* 2003;32(1):43–6.

Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, Konstantopoulos S, Rojas R, van Noord JA, Pons M, et al.; Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) International Study Group. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58(3):211–6.

Ram FS, Cates CJ, Ducharme FM. Long-acting beta$_2$-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev* 2005;(1):CD003137.

Richards J, Hirst P, Pitcairn G, Mahashabde S, Abramowitz W, Nolting A, Newman SP. Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants. *J Aerosol Med* 2001;14(2):197–208.

Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet* 2001;357(9273):2007–11.

Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab* 2005;90(7):4394–8. Epub March 2005.

Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB, Leong A, Johnson MS, Mendoza G, Cook EF. Relationship of validated psychometric tools to subsequent medical utilization for asthma. *J Allergy Clin Immunol* 2005;115(3):564–570.

Schatz M, Nakahiro R, Jones CH, Roth RM, Joshua A, Petitti D. Asthma population management: development and validation of a practical 3-level risk stratification scheme. *Am J Manag Care* 2004;10(1):25–32.

Schatz M, Zeiger RS, Vollmer WM, Mosen D, Cook EF. Determinants of future long-term asthma control. *J Allergy Clin Immunol* 2006;118(5):1048–53. Epub October 2006.

Shannon M, Lovejoy FH Jr. The influence of age vs peak serum concentration on life-threatening events after chronic theophylline intoxication. *Arch Intern Med* 1990;150(10):2045–8.

Shingo S, Zhang J, Reiss TF. Correlation of airway obstruction and patient-reported endpoints in clinical studies. *Eur Respir J* 2001;17(2):220–4.

Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, Laessig W, Schuster A, Perez-Frias J, Sekerel BE, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001;138(5):694–8.

Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352(21):2163–73. Epub May 2005.

Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1043–51.

Stahl E. Correlation between objective measures of airway calibre and clinical symptoms in asthma: a systematic review of clinical studies. *Respir Med* 2000;94(8):735–41.

Strunk RC, Mrazek DA, Fuhrmann GS, LaBrecque JF. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. *JAMA* 1985;254(9):1193–8.

Szefler SJ. Glucocorticoid therapy for asthma: clinical pharmacology. *J Allergy Clin Immunol* 1991;88(2):147–65.

Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, Craig TJ, Dolovich M, Drazen JM, Fagan JK, et al.; Asthma Clinical Research Network of the National Heart Lung, and Blood Institute. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109(3):410–8.

Thompson PJ, Davies RJ, Young WF, Grossman AB, Donnell D. Safety of hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol. *Respir Med* 1998;92 Suppl A:33–9.

Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, Leichtl S, Rathgeb F, Keller A, Steinijans VW. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. *Eur Respir J* 1997;10(12):2754–60.

Ullah MI, Newman GB, Saunders KB. Influence of age on response to ipratropium and salbutamol in asthma. *Thorax* 1981;36(7):523–9.

Vollmer WM, Markson LE, O'Connor E, Sanocki LL, Fitterman L, Berger M, Buist AS. Association of asthma control with health care utilization and quality of life. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1647–52.

Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, Gerritsen J, Duiverman EJ, Knol K, Kerrebijn KF. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. The Dutch CNSLD Study Group. *Am Rev Respir Dis* 1993;148(5):1252–7.

Wolfenden LL, Diette GB, Skinner EA, Steinwachs DM, Wu AW. Gaps in asthma care of the oldest adults. *J Am Geriatr Soc* 2002;50(5):877–83.

Wurthwein G, Rohdewald P. Activation of beclomethasone dipropionate by hydrolysis to beclomethasone-17-monopropionate. *Biopharm Drug Dispos* 1990;11(5):381–94.

Yurk RA, Diette GB, Skinner EA, Dominici F, Clark RD, Steinwachs DM, Wu AW. Predicting patient-reported asthma outcomes for adults in managed care. *Am J Manag Care* 2004;10(5):321–8.