SECTION 3, COMPONENT 4: MEDICATIONS

KEY POINTS: MEDICATIONS

Medications for asthma are categorized into two general classes: long-term control medications used to achieve and maintain control of persistent asthma and quick-relief medications used to treat acute symptoms and exacerbations.

Long-term control medications (listed in alphabetical order)

- **Corticosteroids:** Block late-phase reaction to allergen, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation. They are the most potent and effective anti-inflammatory medication currently available (Evidence A). ICSs are used in the long-term control of asthma. Short courses of oral systemic corticosteroids are often used to gain prompt control of the disease when initiating long-term therapy; long-term oral systemic corticosteroid is used for severe persistent asthma.

- **Cromolyn sodium and nedocromil:** Stabilize mast cells and interfere with chloride channel function. They are used as alternative, but not preferred, medication for the treatment of mild persistent asthma (Evidence A). They can also be used as preventive treatment prior to exercise or unavoidable exposure to known allergens.

- **Immunomodulators:** Omalizumab (anti-IgE) is a monoclonal antibody that prevents binding of IgE to the high-affinity receptors on basophils and mast cells. Omalizumab is used as adjunctive therapy for patients ≥12 years of age who have allergies and severe persistent asthma (Evidence B). Clinicians who administer omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur (see discussion in text).

- **Leukotriene modifiers:** Include LTRAs and a 5-lipoxygenase inhibitor. Two LTRAs are available—montelukast (for patients >1 year of age) and zafirlukast (for patients ≥7 years of age). The 5-lipoxygenase pathway inhibitor zileuton is available for patients ≥12 years of age; liver function monitoring is essential. LTRAs are alternative, but not preferred, therapy for the treatment of mild persistent asthma (Step 2 care) (Evidence A). LTRAs can also be used as adjunctive therapy with ICSs, but for youths ≥12 years of age and adults they are not the preferred adjunctive therapy compared to the addition of LABAs (Evidence A). Zileuton can be used as alternative but not preferred adjunctive therapy in adults (Evidence D).

- **LABAs:** Salmeterol and formoterol are bronchodilators that have a duration of bronchodilation of at least 12 hours after a single dose.

  — LABAs are not to be used as monotherapy for long-term control of asthma (Evidence A).

  — LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma (step 3 care or higher in children ≥5 years of age and adults) (Evidence A for ≥12 years of age, Evidence B for 5–11 years of age).

- — Of the adjunctive therapies available, LABA is the preferred therapy to combine with ICS in youths ≥12 years of age and adults (Evidence A).
- — In the opinion of the Expert Panel, the beneficial effects of LABA in combination therapy for the great majority of patients who require more therapy than low-dose ICS alone to control asthma (i.e., require step 3 care or higher) should be weighed against the increased risk of severe exacerbations, although uncommon, associated with the daily use of LABAs (see discussion in text).
  - ♦ For patients ≥5 years of age who have moderate persistent asthma or asthma inadequately controlled on low-dose ICS, the option to increase the ICS dose should be given equal weight to the option of adding LABA.
  - ♦ For patients ≥5 years of age who have severe persistent asthma or asthma inadequately controlled on step 3 care, the combination of LABA and ICS is the preferred therapy.
- — LABA may be used before exercise to prevent EIB (Evidence A), but duration of action does not exceed 5 hours with chronic regular use. Frequent and chronic use of LABA for EIB is discouraged, because this use may disguise poorly controlled persistent asthma (Evidence D).
- — In the opinion of the Expert Panel, the use of LABA for the treatment of acute symptoms or exacerbations is not currently recommended (Evidence D).

■ **Methylxanthines:** Sustained-release theophylline is a mild to moderate bronchodilator used as alternative, not preferred, adjunctive therapy with ICS (Evidence A). Theophylline may have mild anti-inflammatory effects. Monitoring of serum theophylline concentration is essential.

Quick-relief medications (listed in alphabetical order)

■ **Anticholinergics:** Inhibit muscarinic cholinergic receptors and reduce intrinsic vagal tone of the airway. Ipratropium bromide provides additive benefit to SABA in moderate-to-severe asthma exacerbations. May be used as an alternative bronchodilator for patients who do not tolerate SABA (Evidence D).

■ **SABAs:** Albuterol, levalbuterol, and pirbuterol are bronchodilators that relax smooth muscle. Therapy of choice for relief of acute symptoms and prevention of EIB (Evidence A).

■ **Systemic corticosteroids:** Although not short acting, oral systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations (Evidence A).

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- Information about asthma medications has been updated based on review of evidence published since 1997. *This updated report* (EPR—3: Full Report 2007) *continues to emphasize that the most effective medications for long-term therapy are those shown to have anti-inflammatory effects.*
- New medications—immunomodulators—are available for long-term control of asthma.
- New data on the safety of LABAs are discussed, and the position of LABA in therapy has been revised (see text). The most significant difference is that for youths ≥12 years of age and adults who have moderate persistent asthma or asthma inadequately controlled on low-dose ICS, the option of increasing the dose of medium-dose ICS should be given equal weight to the option of adding LABA to low-dose ICS.
- The estimated clinical comparability of different ICS preparations has been updated. (See Section 4, "Managing Asthma Long-Term," figures 4–4b and 4–8b.) The significant role of ICSs in asthma therapy continues to be supported.

Introduction

See Section 1, "Overall Methods Used To Develop This Report," for the literature search strategies and tallies of results used to update each class of medication discussed in this section. Evidence Tables were prepared for: 11, Inhaled Corticosteroids: Combination Therapy; 12, Inhaled Corticosteroids: Dosing Strategies; 13, Immunomodulators: Anti-IgE; 14, Leukotriene Receptor Antagonists: Monotherapy/Effectiveness Studies; 15, Bronchodilators: Safety of Long-Acting Beta$_2$-Agonists; 16, Bronchodilators: Levalbuterol.

Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. Recommendations in this "Component 4: Medications," reflect the scientific concepts that asthma is a chronic disorder with recurrent episodes of airflow limitation, mucus production, and cough and that the severity of the underlying asthma may vary over time. Asthma medications are categorized into two general classes: long-term control medications taken daily on a long-term basis to achieve and maintain control of persistent asthma (these medications are also known as long-term preventive, controller, or maintenance medications) and quick-relief medications taken to provide prompt reversal of acute airflow obstruction and relief of accompanying bronchoconstriction (these medications are also known as reliever or rescue medications). Patients who have persistent asthma require both classes of medication. Figures 3–22 and 3–23 present summaries of the indications, mechanisms, potential adverse effects, and therapeutic issues for currently available long-term control and quick-relief medications. The discussion in this component includes the following: an overview of asthma medications—both long-term control and quick-relief—and an overview of complementary alternative medicine strategies.

Overview of the Medications

LONG-TERM CONTROL MEDICATIONS

The Expert Panel recommends that long-term control medications be taken daily on a long-term basis to achieve and maintain control of persistent asthma. The most effective long-term-control medications are those that attenuate the underlying inflammation characteristic of asthma (Evidence A).

Long-term control medications include ICSs, inhaled long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators. Because eosinophilic and lymphocytic inflammation is a constant feature of the mucosa of the airways in asthma, the most effective long-term control medications are those that attenuate inflammation (Haahtela et al. 1991; Kerrebijn et al. 1987; Van Essen-Zandvliet et al. 1992). The Expert Panel defines anti-inflammatory medications as those that cause a reduction in the markers of airway inflammation in airway tissue or airway secretions (e.g., eosinophils, mast cells, activated lymphocytes, macrophages, and cytokines; or ECP and tryptase; or extravascular leakage of albumin, fibrinogen, or other vascular protein) and thus decrease the intensity of airway hyperresponsiveness. Because many factors contribute to the inflammatory response in asthma, many drugs may be considered anti-inflammatory. It is not yet established, however, which anti-inflammatory actions are responsible for therapeutic effects, such as reduction in symptoms, improvement in expiratory flow, reduction in airway hyperresponsiveness, prevention of exacerbations, or prevention of airway wall remodeling.

Inhaled Corticosteroids

Mechanism

The Expert Panel concludes that ICSs are the most potent and consistently effective long-term control medication for asthma (Evidence A). The broad action of ICSs on the inflammatory process may account for their efficacy as preventive therapy. Their clinical effects include reduction in severity of symptoms; improvement in asthma control and quality of life; improvement in PEF and spirometry; diminished airway hyperresponsiveness; prevention of exacerbations; reduction in systemic corticosteroid courses, ED care, hospitalizations, and deaths due to asthma; and possibly the attenuation of loss of lung function in adults (Barnes et al. 1993; Barnes and Pedersen 1993; Dahl et al. 1993; Fabbri et al. 1993; Gustafsson et al. 1993; Haahtela et al. 1991; Jeffery et al. 1992; Kamada et al. 1996; Pauwels et al. 2003; Rafferty et al. 1985; Suissa et al. 2000; Van Essen-Zandvliet et al. 1992).

Which of these clinical effects depend on specific anti-inflammatory actions of corticosteroids is not yet clear. Corticosteroids suppress the generation of cytokines, recruitment of airway eosinophils, and release of inflammatory mediators. These anti-inflammatory actions of corticosteroids have been noted in clinical trials and analyses of airway histology (Booth et al. 1995; Busse 1993; Djukanovic et al. 1992; Duddridge et al. 1993; Laitinen et al. 1991, 1992; Levy et al. 1995; McGill et al. 1995). The anti-inflammatory effects of corticosteroids are mediated through receptors that modulate inflammatory gene expression.

ICSs do not have the same bioavailability as oral systemic corticosteroids; hence, the risk of potential side effects is substantially reduced with ICSs.

Inhaled Corticosteroid Insensitivity

The Expert Panel concludes that sensitivity and consequently clinical response to ICS can vary among patients (Evidence B).

Variation in sensitivity to ICS therapy may be related to high levels of inflammation, corticosteroid-insensitive pathways, or structural changes refractory to corticosteroid therapy (Leung and Bloom 2003). Corticosteroid responsiveness is decreased in smokers (Chalmers et al. 2002; Chaudhuri et al. 2003) and persons who have asthma with predominantly neutrophilic inflammation (Gauvreau et al. 2002; Green et al. 2002). Also, African American children who have poor control of their asthma appear to have an increased risk for corticosteroid insensitivity; this could be related to diminished glucocorticoid responsiveness at the cellular level, specifically T lymphocytes (Chan et al. 1998; Federico et al. 2005).

Efficacy of Inhaled Corticosteroids as Compared to Other Long-Term Control Medications as Monotherapy

The Expert Panel concludes that studies demonstrate that ICSs improve asthma control more effectively in both children and adults than LTRAs or any other single long-term control medication (Evidence A).

For the EPR—3: Full Report 2007, the evidence of the efficacy of ICS therapy compared to other single daily long-term control medications in patients ≥5 years of age was obtained from nine randomized trials, most of which compared ICS to LTRA; five of these trials had placebo control groups (Garcia-Garcia et al. 2005; Ostrom et al. 2005; Szefler et al. 2002, 2005; Zeiger et al. 2006). These studies confirm findings discussed in EPR—Update 2002. Patients who have mild or moderate persistent asthma and are treated with ICS, compared to other single long-term control medications, demonstrate greater improvements in prebronchodilator FEV_1; reduced airway hyperresponsiveness, symptom scores, exacerbation rates, and symptom frequency; as well as less use of supplemental SABA, fewer courses of oral systemic corticosteroids, and less use of hospitalization. The evidence does not suggest, however, that ICS use is associated with improved long-term postbronchodilator FEV_1 (CAMP 2000).

Studies comparing ICS to cromolyn or theophylline are limited, but available evidence shows that neither of these long-term control medications appears to be as effective as ICS in improving asthma outcomes.

Efficacy of Inhaled Corticosteroid and Adjunctive Therapy (Combination Therapy)

The Expert Panel recommends that when patients ≥12 years of age require more than low-dose ICS alone to control asthma (i.e., step 3 care or higher), a therapeutic option is to add LABA to ICS (Evidence A). Alternative, but not preferred adjunctive therapies include LTRA (Evidence B), theophylline (Evidence B), or, in adults, zileuton (Evidence D). (See Evidence Table 11, Inhaled Corticosteroids: Combination Therapy.) For children 0–11 years of age, LABA, LTRA, and, in children 5–11 years of age, theophylline may be considered as adjunctive therapies in combination with ICS (Evidence B, based on extrapolation from studies in older children and adults; see also section 4, "Managing Asthma Long Term" for recommendations on adjunctive therapies at different steps of care for different age groups in children).

Although numerous studies have examined adjunctive therapy in adults, adjunctive therapy has not been studied adequately in children 5–11 years of age, and it has not been evaluated at all in children less than 4 years of age. An extensive review of the literature on this topic, conducted for the EPR—Update 2002, concluded that strong evidence in adults and older children indicates that the combination of ICS and LABA leads to improvements in lung function and symptoms and reduced need for quick-relief SABA. Adding an LTRA or theophylline to ICS or doubling the dose of ICS also was shown to improve outcomes, but the evidence was not as substantial as with the addition of LABA (EPR—Update 2002).

The current review of the evidence supports this conclusion. The 2006 evidence review included studies comparing the combination of ICS and LABA to either baseline dose of ICS (two articles) or increasing doses of ICS (eight articles); comparing the combination of ICS and LTRA to baseline doses of ICS (three articles) or increasing doses of ICS (one article); comparing the combination of ICS and LABA to ICS and LTRA (seven articles); and comparing the combination of ICS and one LABA to another LABA (two articles), as well as three Cochrane Review meta-analyses (See Evidence Table 11, Inhaled Corticosteroids: Combination Therapy for complete citations.). The weight of the evidence reviewed continues to demonstrate that the addition of LABA to ICS leads to greater improvement in lung function, symptoms, and less use of SABA than increasing the dose of ICS or using LTRA as adjunctive therapy. Studies on the addition of LTRA to ICS have limitations that preclude conclusions, although the studies reveal a trend showing that LTRA improved lung function and some but not all trials report improvements in some measures of asthma control (See also the section below on "Leukotriene Modifiers."). Recent data indicate potential risks that need to be considered for uncommon but life-threatening exacerbations associated with the daily use of LABAs (See the section below on "Safety of Inhaled Long-Acting $Beta_2$-Agonists."). See also section 4 on "Managing Asthma Long Term" for a discussion of issues to consider regarding combination therapy compared to increasing the dose of ICS.

Dose-Response and Delivery Device

The Expert Panel concludes that dosages for ICSs vary, depending upon the specific product and delivery devices. (See figure 3–24 for issues on delivery devices; see figures 4–4b, and 4–8b in section 4, "Managing Asthma Long Term," for comparative ICS dosages.) For all ICS preparations, the dose-response relationship appears to flatten in patients who have mild or moderate asthma for most clinical parameters and lung function in the low- to medium-dose range (Evidence C).

Although most of the benefits of treatment are achieved with a low dose, the dose-response to ICS may vary, based on the response measured (e.g., improvement in lung function, prevention of exacerbations, or improvement in bronchial hyperresponsiveness, individual variability in response to ICS, and disease severity). Several studies show that for patients who have mild or moderate persistent asthma, use of higher doses improves asthma control modestly if at all (Bousquet et al. 2002; Holt et al. 2001; Kemp et al. 2000; Masoli et al. 2004a; Nayak et al. 2000; Powell and Gibson 2003; Szefler and Eigen 2002). However, the dose-response continued to improve at a higher dose for patients who have severe asthma (Masoli et al. 2004b). This efficacy of low-dose ICS therapy may account for the success of once-per-day treatment of patients who have mild or moderate persistent asthma, using several ICS preparations—both ICS alone (Casale et al. 2003; Jonasson et al. 2000; Jones et al. 1994; Noonan et al. 2001; Pincus et al. 1995) and in combination with LABA (Buhl et al. 2003). This efficacy may also account for the finding that mild and moderate asthma are as well controlled by starting treatment with a low, standard dose of an ICS as by starting with a high dose (Chanez et al.

2001; Reddel et al. 2000). These generalizations may not apply to patients who have more severe, uncontrolled asthma or to patients who have frequent, severe exacerbations. In these patients, twice-daily therapy with a higher dose may be necessary (Noonan et al. 1995; Pauwels et al. 1997), although control is achieved in a higher proportion of patients, and at a lower ICS dose, when it is given in combination with a LABA (Bateman et al. 2003, 2004).

Variability in Response and Adjustable Dose Therapy

The Expert Panel recommends that, given the variations over time in the severity of the pathophysiologic processes underlying asthma, it may be useful to adjust anti-inflammatory therapy accordingly (Evidence B). (See Evidence Table 12, Inhaled Corticosteroids: Dosing Strategies.)

Several studies have shown that, for most patients whose asthma has been well controlled for at least 2 months by a high dose of an ICS alone, a 50 percent reduction in dose does not lead to loss of control (Aalbers et al. 2004; Hawkins et al. 2003; Leuppi et al. 2003; Thoonen et al. 2003). This finding does not mean, however, that treatment with an ICS can be stopped altogether, for studies show that asthma control in most patients can worsen within a few weeks when treatment is discontinued (CAMP 2000; Dahl et al. 2002). Trials are now focusing on clinical features or "biomarkers" to distinguish between those patients who need continued treatment and those in whom it can be reduced or discontinued (Deykin et al. 2005; Leuppi et al. 2003).

Whether ICS treatment should be increased temporarily in response to some index of worsening asthma is also being examined. The effectiveness of this adjustable dose approach may be a function of timing or of dose. When asthma symptoms have worsened to the point of qualifying as an asthma exacerbation (See section 5 on "Managing Exacerbations of Asthma" for definition.), simply doubling the regular maintenance dose of ICS treatment does not appear to be effective (FitzGerald et al. 2004; Harrison et al. 2004). Studies that have shown benefit to patients from treatment with an adjustable dose regimen have employed greater increase in the dose of ICS (e.g., fourfold) and/or have made this adjustment earlier, at the first appearance of worsening symptoms (Aalbers et al. 2004; Boushey et al. 2005; Foresi et al. 2000; Harrison et al. 2004; Ind et al. 2004; Leuppi et al. 2003; Reddel and Barnes 2006; Thoonen et al. 2003). An interesting application of this approach was made possible by the development of an inhaler containing both budesonide (an ICS) and formoterol (a LABA with a rapid onset of action). Although this product does not have approved labeling for use as an acute quick-relief medication, one study has shown that use of a low dose of budesonide from this combination inhaler twice daily (maintenance therapy) plus additional use for relief of symptoms (adjustable therapy) was associated with a lower rate of asthma exacerbations and a lower cumulative dose of budesonide than was twice daily treatment with a fourfold greater dose of budesonide alone (Bisgaard et al. 2006; O'Byrne et al. 2005; Rabe et al. 2006).

Another approach to adjustable therapy with an ICS is to link the dose adjustments to measurement of a biomarker of airway inflammation. Three biomarkers have been examined: bronchial reactivity to methacholine (Sont et al. 1999), sputum eosinophils (Green et al. 2002), and the concentration of nitric oxide in exhaled air (FeNO) (Smith et al. 2005). In these studies, biomarker-adjusted therapy reduced the rate of asthma exacerbations. In two of the studies (Green et al. 2002; Smith et al. 2005), the cumulative dose of ICS was reduced as well as in comparison to standard maintenance therapy alone.

Safety of Inhaled Corticosteroids

KEY POINTS: SAFETY OF INHALED CORTICOSTEROIDS

- ICSs are the most effective long-term therapy available for mild, moderate, or severe persistent asthma; in general, ICSs are well tolerated and safe at the recommended dosages (Evidence A).
- The potential but small risk of adverse events from the use of ICS treatment is well balanced by their efficacy (Evidence A).
- The dose-response curve for ICS treatment begins to flatten for many measures of efficacy at low to medium doses, although some data suggest that higher doses may reduce the risk of exacerbations. Most benefit is achieved with relatively low doses, whereas the risk of adverse effects increases with dose (Evidence B).
- To reduce the potential for adverse effects, the following measures are recommended:
  - Spacers or valved holding chambers (VHCs) used with non-breath-activated MDIs reduce local side effects (Evidence A), but there are no data on use of spacers with ultra fine particle hydrofluoroalkane (HFA) MDIs.
  - Advise patients to rinse their mouths (rinse and spit) after inhalation (Evidence B).
  - Use the lowest dose of ICS that maintains asthma control. Evaluate patient adherence and inhaler technique as well as environmental factors that may contribute to asthma severity before increasing the dose of ICS (Evidence B).
  - To achieve or maintain control of asthma, consider adding a LABA to a low or medium dose of ICS rather than using a higher dose of ICS (Evidence A).
  - For children, monitor growth (Evidence A). See "Key Points: Inhaled Corticosteroids and Linear Growth in Children."
  - In adult patients, consider supplements of calcium (1,000–1,500 mg per day) and vitamin D (400–800 units a day), particularly in perimenopausal women (Evidence D). Bone-sparing therapy (e.g., bisphosphonate), where appropriate, may be considered for patients on medium or high doses of ICS, particularly for those who are at risk of osteoporosis or who have low bone mineral density (BMD) scores by dual energy x ray absorptiometry (or DEXA) scan (Evidence C). In children, age-appropriate dietary intake of calcium and exercise should be reviewed with the child's caregivers (Evidence D).

The Expert Panel concludes that ICSs are the most effective long-term therapy available for patients who have persistent asthma and, in general, ICSs are well tolerated and safe at the recommended dosages (Evidence A). Systemic activity has been identified, particularly at high doses (See figures 4–4b and 4–8b.), for a definition of high-, medium-, and low-dose ICSs), but their clinical significance remains unclear (Leone et al. 2003). Furthermore, there may be interindividual variations in dose-response effects; thus, some patients may

experience effects at lower doses. See Key Points, above, for a summary of recommendations to minimize the potential for adverse effects. In general, the potential for adverse effects must be weighed against the risk of uncontrolled asthma; to date, evidence supports the use of ICS, especially at low and medium doses (Barnes et al. 1993; CAMP 2000; EPR—Update 2002; Leone et al. 2003; Tinkelman et al. 1993; Van Essen-Zandvliet et al. 1992).

The Expert Panel recommends the following actions to minimize potential adverse effects of ICS. Specific recommendations and evidence rank are presented under "Prevention and Treatment."

Local Adverse Effects

Oral candidiasis (thrush) is one of the most common adverse effects of ICSs. Positive throat cultures of *Candida* can be identified in about 45–58 percent of patients, whereas clinical thrush is diagnosed in only 0–34 percent of patients (Rinehart et al. 1975; Shaw and Edmunds 1986; Toogood et al. 1980). With lower dosages of ICS, candidiasis is uncommon (5 percent) (Rinehart et al. 1975), although it is more frequent in adults than in children. **Prevention and Treatment:** Use a spacer or VHC with a non-breath-activated MDI to reduce the incidence of colonization and clinical thrush; rinse mouth with water after inhalation (Selroos and Halme 1991). No data are available on the use of spacers or VHCs with ultrafine-particle-generated HFA MDIs. Administer ICS less frequently (bid versus qid). Topical or oral antifungal agents should be used to treat active infections (EPR—2 1997).

Dysphonia is reported in 5–50 percent of patients who use an ICS and is associated with vocal stress and increasing dosages of ICS (Toogood et al. 1980). **Prevention and Treatment:** Use a spacer or VHC with a non-breath-activated MDI, temporarily reduce dosage, or rest for vocal stress (EPR—2 1997).

Reflex cough and bronchospasm. **Prevention and Treatment:** These effects can be reduced by slower rates of inspiration and/or use of a spacer or valved holding chamber or by pretreatment with SABA. There is no convincing evidence that the routine use of a SABA before each dose of ICS increases intrapulmonary delivery of the ICS or reduces dosage requirement (EPR—2 1997).

Systemic Adverse Effects

Linear growth. A reduction in growth velocity may occur in children or adolescents as a result of inadequate control of chronic diseases such as asthma or from the use of corticosteroids for treatment. Overall, however, the available cumulative data about children suggest that, although low or medium doses of ICS may have the potential of decreasing growth velocity, the effects are small, nonprogressive, and may be reversible (CAMP 2000; Guilbert et al. 2006; Leone et al. 2003). Furthermore, studies of early intervention with low- or medium-dose ICS showed significantly improved asthma outcomes, despite a small reduction in growth velocity (Guilbert et al. 2006; Pauwels et al. 2003).

The long-term prospective studies on growth involved budesonide, the retrospective analyses included studies on beclomethasone, and several shorter term studies have been performed on a variety of moieties, but the results have been generalized to include all ICS preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of ICS on growth is a drug-class effect. When high doses of ICS are necessary to achieve satisfactory asthma

control, the use of adjunctive long-term control therapy should be initiated to reduce the dose of ICS and thus minimize possible dose-related long-term effects on growth. **Prevention and Treatment:** Physicians should monitor the growth of children and adolescents who are taking corticosteroids by any route and should weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression or delay if a child's or an adolescent's growth appears slowed (Evidence D).

KEY POINTS: INHALED CORTICOSTEROIDS AND LINEAR GROWTH IN CHILDREN

In the opinion of the Expert Panel:

- The potential risks of ICSs are well balanced by their benefits.
- Growth rates are highly variable in children. Short-term evaluations may not be predictive of final adult height attained.
- Poorly controlled asthma may delay growth in children.
- In general, children who have asthma tend to have longer periods of reduced growth rates before puberty (males more than females).
- The potential for adverse effects on linear growth from ICS appears to be dose dependent. In treatment of children who have *mild or moderate persistent asthma*, low- to medium-dose ICS therapy may be associated with a possible, but not predictable, adverse effect on linear growth. The clinical significance of this potential systemic effect has yet to be determined. High doses of ICS have greater potential for growth suppression.
- Use of high doses of ICS by children who have *severe persistent asthma* has significantly less potential than use of oral systemic corticosteroids for having an adverse effect on linear growth.
- Studies in which growth has been carefully monitored suggest the growth-velocity effect of ICS occurs in the first several months of treatment and is generally small and nonprogressive.
- In general, the efficacy of ICSs is sufficient to outweigh any concerns about growth or other systemic effects. However, ICSs, as with any medications, should be titrated to as low a dose as needed to maintain good control of the child's asthma.

Bone mineral density. Low and medium doses of ICS appear to have no serious adverse effects on BMD in children (CAMP 2000; Roux et al. 2003). A small, dose-dependent reduction in BMD may be associated with ICS use in patients older than 18 years of age (Ip et al. 1994; Israel et al. 2001), but the clinical significance of these findings is not clear. A large observational study of older patients (>65 years of age) with prolonged use of ICS showed that, at <2,000 mcg/day of beclomethasone or equivalent, there was no increase in the risk of fractures (Suissa et al. 2004). Data in adults suggest a cumulative dose relationship to the

effects of ICS on BMD (Wong et al. 2000). **Prevention and Treatment:** In patients who have risk factors for osteoporosis or low BMD scores, consideration can be given to bone-protecting therapies (e.g., bisphosphonates), although data are mixed in supporting the use of these therapies specifically in asthma patients who are taking ICS (Campbell et al. 2004; Kasayama et al. 2005) (Evidence C). Measuring BMD may be considered every 1–2 years, depending on duration and dose of ICS and oral corticosteroid treatment as well as previous BMD scores (Evidence D).

Disseminated varicella. Although high doses of ICS theoretically present risks similar to those of systemic corticosteroid treatment, the reports of disseminated varicella in patients receiving only ICS are rare, causality is *not* clear, and there is no evidence that recommended doses of the ICSs are immunosuppressive. Cases have been reported of children who have severe persistent asthma, and are taking immunosuppressive doses of systemic corticosteroids, developing fatal disseminated disease from varicella infection (Kasper and Howe 1990; Silk et al. 1988). Other case reports indicate complications for patients who have *Strongyloides* or tuberculosis and who take high doses of systemic corticosteroids. **Prevention and Treatment of Varicella:** Children who require episodic therapy with systemic corticosteroids and who have not had clinical varicella should receive the varicella vaccine (EPR—2 1997). The vaccine should not be administered to patients who are receiving immunosuppressive doses of systemic corticosteroids (2 mg/kg or more of prednisone equivalent or 20 mg/day of prednisone for more than 1 month), unless this dosage is discontinued for at least 1 month. Children who have completed a short prednisone course may receive varicella vaccine without delay (American Academy of Pediatrics 1995; CDC 1994). Children and adults on treatment with immunosuppressive doses of corticosteroids who have not been immunized against varicella and are exposed to varicella infection are candidates for oral antiviral therapy (e.g., valacyclovir). If they develop clinical varicella, intravenous antiviral therapy should be given (EPR—2 1997).

Dermal thinning and increased ease of skin bruising. These effects have been observed in patients treated with ICS. The effect is dose dependent, but the threshold dose is variable (Capewell et al. 1990).

Ocular effects. In children, low- and medium-dose ICS therapy appears to have no significant effects on the incidence of subcapsular cataracts or glaucoma (CAMP 2000). In adults, high cumulative lifetime exposure (greater than 2,000 mg of beclomethasone dipropionate or equivalent) to ICS may increase the prevalence of cataracts, as suggested in three retrospective studies of adult and elderly patients (Evidence C) (Cumming et al. 1997; Garbe et al. 1998; Jick et al. 2001). A retrospective, case-control study showed an association between long-term ICS use and the development of glaucoma (Garbe et al. 1997). A subsequent cross-sectional, retrospective study in adults reported an association between elevated intraocular pressure and glaucoma in patients who had a family history of glaucoma and used ICS, particularly at higher doses (defined in this study as more than 4 puffs per day). There was no increase in risk in ICS users who did not have a family history of glaucoma (Mitchell et al. 1999). **Prevention and Treatment:** These data suggest the advisability of periodic assessments and treatments, if indicated, for increased intraocular pressures in asthma patients who use ICS, particularly at higher doses, and have a family history of glaucoma (Evidence C).

Hypothalamic-pituitary-adrenal axis function. The available evidence indicates that, on average, children may experience only clinically insignificant, if any, effects of low- or medium-dose ICS on the hypothalamic-pituitary-adrenal (HPA) axis (Leone et al. 2003). Rarely, however, some individuals may be more susceptible to the effects of ICS even at conventional doses.

Glucose metabolism. In a study of children, ICS at dosages from 400 to 1,000 mcg/day (budesonide) did not affect fasting glucose or glycosolated hemoglobin. At 1,000 mcg/day, a significantly greater rise in fasting serum insulin levels and glucose during a glucose tolerance test was noted, but results remained within normal limits (Turpeinen et al. 1991).

Oral Systemic Corticosteroids

The Expert Panel recommends that chronic administration of oral systemic corticosteroids as a long-term-control medication be used only for the most severe, difficult-to-control asthma because of well-documented risk for side effects (EPR—2 1997).

The Expert Panel recommends that, because the magnitude of adverse effects is often related to the dose, frequency of administration, and the duration of corticosteroid use (Evidence A), every consideration should be given to minimize systemic corticosteroid doses and maximize other modes of therapy (Evidence D). It is necessary, therefore, to monitor for the development and progression of adverse effects and to take appropriate steps to minimize the risk and impact of adverse corticosteroid effects (Evidence D).

Oral systemic corticosteroids suppress, control, and reverse airway inflammation. However, side effects with chronic administration include adrenal suppression, growth suppression, dermal thinning, hypertension, Cushing's syndrome, cataracts, and muscle weakness. Chronic corticosteroid use can also result in immunologic attenuation with loss of delayed-type hypersensitivity, diminished immunoglobulin G (IgG) levels without change in functional antibody response, potential for reactivation of latent tuberculosis infection, and possible increased risk for infection, especially the development of severe varicella (Spahn et al. 2003).

Cromolyn Sodium and Nedocromil

Cromolyn and nedocromil are alternative, not preferred, medications for the treatment of mild persistent asthma (Evidence A). They can also be used as preventive treatment before exercise or unavoidable exposure to known allergens (EPR—2 1997)**.** Although cromolyn and nedocromil have distinct properties (Clark 1993), they have similar anti-inflammatory actions. The mechanism of cromolyn and nedocromil appears to involve the blockade of chloride channels (Alton and Norris 1996) and modulate mast cell mediator release and eosinophil recruitment (Eady 1986). The two compounds are equally effective against allergen challenge (Gonzalez and Brogden 1987), although nedocromil appears to be more potent than cromolyn in inhibiting bronchospasm provoked by exercise (de Benedictis et al. 1995; Novembre et al. 1994), by cold dry air (Juniper et al. 1987), and by bradykinin aerosol (Dixon and Barnes 1989).

Dosing recommendations for both nedocromil and cromolyn are for administration four times a day, although nedocromil has been shown to be clinically effective with twice-daily dosing (Creticos et al. 1995; EPR—2 1997).

Cromolyn sodium and nedocromil have been shown to provide symptom control greater than placebo in some but not all clinical trials (Konig 1997; Petty et al. 1989; Tasche et al. 2000) and to confer protection against exacerbations of asthma leading to hospitalization, particularly in children (Donahue et al. 1997), and ED visits (Adams et al. 2001). These results, along with the excellent safety profile, justify consideration of cromolyn and nedocromil as treatment options. However, a systematic review (van der Wouden et al. 2003) concluded that insufficient evidence existed to conclude that cromolyn had a beneficial effect on maintenance treatment of childhood

asthma. Compared to placebo, nedocromil reduces both urgent care visits as well as the need for prednisone, which are meaningful clinical outcomes. However, nedocromil is no different than placebo on all other outcome measures (CAMP 2000). Overall, nedocromil is significantly less effective than ICS in improving outcomes measures (CAMP 2000). Nedocromil has not been studied adequately in children younger than 5 years of age. As a result of these disparate findings (i.e., some, but limited, effectiveness and strong safety profile), the Expert Panel's opinion is that cromolyn for children of all ages and nedocromil for children ≥5 years of age could be considered in the treatment of persistent asthma for children of all ages, but they are not preferred therapies. The Expert Panel's review of the literature in 2006 found that no new studies have been published that would change these conclusions.

Immunomodulators

Many different pharmaceutical agents have been tested for their ability to provide long-term control and/or steroid-sparing effects. These agents are loosely defined as immunomodulators. New information is available and discussed here on methotrexate, soluble interleukin-4 (IL-4) receptor, anti-IL-5, recombinant IL-12, cyclosporin A, intravenous immunoglobulin (IVIG), clarithromycin, omalizumab (anti-IgE), and others. For discussion of immunotherapy as an asthma management strategy, see "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma."

Omalizumab

The Expert Panel recommends that omalizumab may be considered as adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA (Evidence B). (See Evidence Table 13, Immunomodulators: Anti-IgE.)

Omalizumab, a recombinant DNA-derived humanized monoclonal antibody to the Fc portion of the IgE antibody, binds to that portion preventing the binding of IgE to its high-affinity receptor (FcεRI) on mast cells and basophils. The decreased binding of IgE on the surface of mast cells leads to a decrease in the release of mediators in response to allergen exposure. Omalizumab also decreases FcεRI expression on basophils and airway submucosal cells (Djukanovic et al. 2004; Lin et al. 2004). That study also showed significant decreases in sputum and bronchial eosinophils as well as in CD3+, CD4+, and CD8+ T cells in bronchial biopsy (Djukanovic et al. 2004). The vast majority of patients in clinical trials of omalizumab had moderate or severe persistent asthma incompletely controlled with ICS (Walker et al. 2004); all had atopy and IgE ≥30 IU/mL. Adding omalizumab to ICS therapy generally produced a significant reduction in asthma exacerbations (Busse et al. 2001a; Soler et al. 2001; Vignola et al. 2004) but not always (Holgate et al. 2004; Milgrom et al. 2001). (See Evidence Table 13, Immunomodulators: Anti-IgE.) Omalizumab, added to ICS, was associated with a small but significant improvement in lung function (Busse et al. 2001a; Soler et al. 2001). In two trials, one open-label, in patients who had severe persistent asthma inadequately controlled on ICS plus LABAs, omalizumab reduced asthma exacerbations and ED visits (Ayres et al. 2004; Humbert et al. 2005). Omalizumab appears to have a modest steroid-sparing effect, allowing a median reduction of 25 percent over that of placebo in the trials (Busse et al. 2001a; Holgate et al. 2004; Milgrom et al. 2001; Soler et al. 2001). Omalizumab has not been compared in clinical trials to the other adjunctive therapies for moderate persistent asthma (LABAs, leukotriene modifiers, and theophylline), all of which improve outcomes and allow reduction of ICS dose. Omalizumab is the only adjunctive therapy, however, to demonstrate added efficacy to high-dose ICS plus LABA in patients who have severe persistent allergic asthma (Humbert et al. 2005). In studies

of patients who have severe persistent asthma, omalizumab resulted in clinically relevant improvements in quality-of-life scores in significantly more patients (approximately 60 percent) than did placebo (approximately 43 percent) (Holgate et al. 2004; Humbert et al. 2005).

Omalizumab is approved for patients 12 years and older who have proven sensitivity to aeroallergens: studies have been done in patients who have sensitivity to dust mite, cockroach, cat, or dog. One study of omalizumab in children 6–12 years of age demonstrated nonsignificant reductions in exacerbations and no improvement in lung function but did show small but significant reduction in ICS dose compared to placebo (Milgrom et al. 2001).

Urticaria and anaphylactic reactions have been reported in 0.1 percent of cases (Berger et al. 2003; FDA 2003; Holgate et al. 2004; Lanier et al. 2003). Postmarketing surveys have identified anaphylaxis in an estimated 0.2 percent of treated patients, which resulted in an FDA alert (FDA 2007). Most of these reactions occurred within 2 hours of the omalizumab injection, and after the first, second, or third injections. However, reactions have occurred after many injections and after many hours. Therefore, 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 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).

Adverse effects reported from omalizumab in the trials have also included injection-site pain and bruising in up to 20 percent of patients (Holgate et al. 2004). In the trials reported to the FDA, twice as many patients receiving omalizumab had malignancies (20 of 48,127, or 0.5 percent) as did those receiving placebo (5 of 2,236, or 0.2 percent), but there were no trends for a specific tumor type.

Antibiotics

In the opinion of the Expert Panel, the data at present are insufficient to support a recommendation about the use of macrolide in chronic asthma.

Some, but not all, data—including a recent controlled trial—have shown an effect of the macrolide antibiotic, clarithromycin, in the treatment of asthma (Kostadima et al. 2004; Kraft et al. 2002). Although it has been shown that clarithromycin can interfere with the clearance of methylprednisolone (Fost et al. 1999), this did not appear to be the mode of action. Preliminary data suggest that clarithromycin may enhance glucocorticoid effect on lymphocyte activation (Spahn et al. 2001).

Recent evidence suggesting that telithromycin may provide benefit in recovery from acute exacerbations has not linked the benefit with antibiotic activity of the drug (Johnston et al. 2006). Macrolide antibiotics, however, have potential risk for liver toxicity.

Others

The Expert Panel concludes that current evidence does not support the use of methotrexate, soluble IL-4 receptor, humanized monoclonal antibody against IL-5 or IL-12, cyclosporin A, IVIG, gold, troleandomycin (TAO), or colchicine for asthma treatment (Evidence B).

For methotrexate, the evidence from a new meta-analysis does not support use of the treatment, given the side effects of the drug (Aaron et al. 1998; Davies et al. 2000).

Use of soluble IL-4 receptor gave promising initial results on moderate to severe asthma (Borish et al. 1999), but subsequent trials were less successful, and it is unlikely to be marketed (Borish et al. 2001).

A humanized monoclonal antibody directed against IL-5 depleted eosinophils from blood and induced sputum but had no effect on airway hyperresponsiveness, on the late asthmatic reaction to inhaled allergen, or in patients who have severe persistent asthma (Flood-Page et al. 2003; Kips et al. 2003; Leckie et al. 2000). Recombinant IL-12 also reduced blood and sputum eosinophils, but it had no significant effects on airway hyperresponsiveness or the late asthmatic reaction to allergen (Bryan et al. 2000). These findings suggest that neither biological will be useful in clinical asthma.

Despite further interesting studies on the mechanism of action of cyclosporin A (Khan et al. 2000), data from controlled trials are not convincing (Evans et al. 2001); given the toxicity of the drug, the data make it difficult to recommend.

Data from open-label trials of IVIG have shown clinical and biomarker benefit in steroid-dependent asthma (Landwehr et al. 1998; Mazer and Gelfand 1991; Spahn et al. 1999). Two controlled trials, however, have failed to establish a clinical benefit of IVIG in such patients (Kishiyama et al. 1999; Niggemann et al. 1998) and showed significant adverse effects. The Expert Panel concludes, from available data, that the use of IVIG in asthma is not recommended.

Trials have suggested limited or no usefulness for oral gold (Bernstein et al. 1996), TAO (Nelson et al. 1993), and colchicine (Fish et al. 1997; Newman et al. 1997).

Leukotriene Modifiers

The Expert Panel recommends that LTRAs are an alternative, not preferred, treatment option for mild persistent asthma (Step 2 care) (Evidence A). LTRAs can also be used as adjunct therapy with ICS, but for youths ≥12 years of age and adults they are not the preferred, adjunct therapy compared to the addition of LABAs (Evidence A). A 5-lipoxygenase inhibitor (zileuton) is an alternative treatment option that is less desirable than LTRAs due to more limited efficacy data and the need for liver function monitoring (Evidence D). (See Evidence Table 14, Leukotriene Receptor Antagonists: Monotherapy/Effectiveness Studies.)

Leukotrienes are potent biochemical mediators—released from mast cells, eosinophils, and basophils—that contract airway smooth muscle, increase vascular permeability, increase mucus secretions, and attract and activate inflammatory cells in the airways of patients who have asthma (Henderson 1994).

Three leukotriene modifiers—montelukast, zafirlukast, and zileuton—are available as oral tablets for the treatment of asthma. Leukotriene modifiers comprise two pharmacologic classes of compounds: 5-lipoxygenase pathway inhibitors (e.g., zileuton), and LTRAs (e.g., montelukast and zafirlukast, which block the effects of the CysLT1 receptor). Only montelukast (for children as young as 1 year of age) and zafirlukast (for children as young as 7 years of age) are approved for use in children.

Leukotriene receptor antagonists. The LTRAs have been demonstrated to provide statistically significant but modest improvement in lung function when used as monotherapy in both adults and children as young as 5 years of age as well as in asthma control outcomes other than lung function in patients as young as 2 years of age (Bisgaard et al. 2005; Bleecker et al. 2000; Busse et al. 2001b,c; Garcia-Garcia et al. 2005; Jenkins et al. 2005; Ostrom et al. 2005; Pearlman et al. 2000; Szefler et al. 2005; Zeiger et al. 2005, 2006) (see Evidence Table 14). In general, these studies included patients who had either mild or moderate persistent asthma, although the classification of severity was not always clear in the studies, nor was it consistently applied. When comparing overall efficacy of LTRA to ICS in both children and adult patients who have persistent asthma, most outcome measures (e.g., reduction in exacerbations, improvements in symptom-free days and FEV_1) significantly and clearly favored ICS (Busse et al. 2001b,c; Ducharme et al. 2003; Garcia-Garcia et al. 2005; Jenkins et al. 2005; Ostrom et al. 2005; Sorkness et al. 2007; Zeiger et al. 2006). See Evidence Table 14: Leukotriene Receptor Antagonists: Monotherapy/Effectiveness Studies.

Three randomized, controlled, double-blind studies in children 5–15 years of age demonstrated the greater effectiveness of ICS (fluticasone) compared to montelukast (Garcia-Garcia et al. 2005; Ostrom et al. 2005; Sorkness et al. 2007). All three reported significantly greater improvements in lung function and total symptom scores as well as reduction in exacerbations; one demonstrated that montelukast was not inferior to fluticasone in rescue-free days (defined in the study as any day without asthma rescue medication and with no asthma-related resource use) (Garcia-Garcia et al. 2005), but the other two showed superiority of fluticasone compared to montelukast for percentage of rescue-free days.

A randomized, cross-over, double-blind study of 140 children 6–17 years of age, in which children received either ICS or LTRA (montelukast) for 8 weeks followed by 8 weeks of the other medication, examined what factors might predict individual variation in response to different medications. The study suggests that children who have higher levels of eosinophilic/allergic airway inflammation (nitric oxide, IgE levels, total eosinophil levels) or low pulmonary function (measured by FEV_1/FVC or FEV_1) are more likely to respond favorably to ICS than to LTRA. Children who do not have these markers appeared to respond equally to treatment with ICS or LTRA (Szefler et al. 2005; Zeiger et al. 2006).

LTRAs have been demonstrated to attenuate EIB (Mastalerz et al. 2002; Moraes and Selvadurai 2004).

LTRAs may be considered as an alternative treatment option for patients whose response to ICSs may be compromised. For example, a controlled trial noted that active cigarette smoking impairs the efficacy of short-term ICS treatment in adults who had mild asthma (Chalmers et al. 2002). However, patients who smoke should be advised to quit smoking. See “Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma” and “Component 2: Education for a Partnership in Care.”

Zafirlukast, an LTRA, has been demonstrated to attenuate the late response to inhaled allergen and post-allergen-induced bronchial responsiveness (Dahlen et al. 1994; Taylor et al. 1991). A study comparing zafirlukast to placebo in patients who have mild or moderate asthma demonstrated that patients treated with zafirlukast experienced modest improvement in FEV_1 (mean improvement of 11 percent above placebo), had improved symptom scores, and reduced albuterol use (average decline of 1 puff/day) (Spector et al. 1994). Zafirlukast can cause a significant increase in the half-life of warfarin. Consequently, for those individuals receiving zafirlukast and warfarin, it will be necessary to closely monitor prothrombin times and adjust

doses of warfarin accordingly. Cases of hepatic dysfunction have occurred with zafirlukast. Although most patients improved with discontinuation of zafirlukast, some have gone on to fulminate hepatic failure resulting in receiving a transplant or in death. Patients should be advised to be alert for signs and symptoms of hepatitis (anorexia, abdominal pain, nausea, jaundice, and pruritis); if these occur, they should discontinue zafirlukast and have liver enzymes (ALT) monitored.

The use of LTRA as adjunctive therapy in moderate or severe asthma has not been studied adequately in children 5–11 years of age and has not been studied at all in children less than 4 years of age. Limitations in the studies comparing addition of LTRA to a fixed dose of ICS (i.e., adding LTRA when patients are not adequately controlled with ICS alone) preclude definitive conclusions, although they reveal a trend showing that LTRA improved lung function and some but not all measures of asthma control (Laviolette et al. 1999; Robinson et al. 2001; Simons et al. 2001; Vaquerizo et al. 2003). One study in adults compared the combination of LTRA and ICS to increasing the dose of ICS and reported similar outcomes for the two approaches (Price et al. 2003). In a 24-week trial in patients who had poorly controlled asthma, the addition of theophylline or montelukast led to small improvement in lung function but did not improve episodes of poor asthma control, symptoms, or quality of life (American Lung Association Asthma Clinical Research Centers 2007). Studies comparing LTRA to LABA as adjunctive therapy in adults show significantly greater improvement in lung function and other asthma control measures with the LABA adjunctive therapy (EPR—Update 2002; Ram et al. 2005).

5-lipoxygenase inhibitor. Zileuton has not been studied in patients less than 12 years of age. It has been demonstrated to provide immediate and sustained improvements in FEV_1 (mean increase of 15 percent above placebo) in placebo-controlled trials in patients who have mild or moderate asthma (Israel et al. 1993, 1996). Compared to placebo, the patients who had moderate asthma treated with zileuton experienced significantly fewer exacerbations requiring oral systemic corticosteroids (Israel et al. 1996), thus suggesting anti-inflammatory action. Zileuton is capable of attenuating bronchoconstriction from exercise (Meltzer et al. 1996) and from aspirin in aspirin-sensitive individuals (Israel et al. 1993). One large, randomized, open label, study in adults who had asthma (Lazarus et al. 1998) and one small cross-over study in aspirin-sensitive adults who had asthma (Dahlen et al. 1998) demonstrated clinical benefits to adding zileuton to existing therapy; the large trial also reported elevated liver enzymes. Because liver toxicity has been found in some subjects receiving zileuton, it is recommended that hepatic enzymes (ALT) be monitored in patients who take this medication. Furthermore, zileuton is a microsomal cytochrome P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline; doses of these drugs should be monitored accordingly. Due to the limited efficacy data and the need for liver function monitoring, zileuton is a less desirable alternative than LTRAs.

Inhaled Long-Acting Beta$_2$-Agonists

The principal action of beta$_2$-agonists is to relax airway smooth muscle by stimulating beta$_2$-receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. Due to their increased lipophilicity prolonging retention in lung tissue, the LABAs have a duration of bronchodilation of at least 12 hours after a single dose (Kips and Pauwels 2001). The LABAs effectively block EIB for 12 hours after a single dose; however, with chronic regular administration, this effect does not exceed 5 hours (Ramage et al. 1994; Simons et al. 1997).

The Expert Panel concludes the following regarding the use of LABAs:

- **LABAs are used as an adjunct to ICS therapy for providing long-term control of symptoms (Evidence A). Of the adjunctive therapies available, LABA is the preferred treatment to combine with ICS in youths ≥12 years of age and adults (Evidence A).**

- **LABAs are not recommended for use as monotherapy for long-term control of persistent asthma (Evidence A).**

- **Use of LABA is not currently recommended to treat acute symptoms or exacerbations of asthma (Evidence D).** Studies are underway examining the potential use of formoterol in acute exacerbations and in adjustable-dose therapy in combination with ICS; see the discussion below in the section on "Quick-Relief Medications" and on "Inhaled Short-Acting $Beta_2$-Agonists."

- **LABA may be used before exercise to prevent EIB (Evidence B), but frequent and chronic use of LABA for EIB may indicate poorly controlled asthma which should be managed with daily anti-inflammatory therapy.**

- **Safety issues have been raised regarding LABAs. The Expert Panel reviewed the safety data provided to the FDA Pulmonary and Allergy Drugs Advisory Committee as well as the extensive accumulation of clinical trials and meta-analyses on the use of LABA, both as monotherapy and in conjunction with ICS. The Expert Panel concluded that LABAs should not be used as monotherapy as long-term control medication in persistent asthma but that LABAs should continue to be considered for adjunctive therapy in patients ≥5 years of age who have asthma that requires more than low-dose ICS. For patients inadequately controlled on low-dose ICS, the option to increase the ICS dose should be given equal weight to the addition of a LABA. For patients who have more severe persistent asthma (i.e., those who require step 4 care or higher), the Expert Panel continues to endorse the use of a combination of LABA and ICS as the most effective therapy. The basis of this opinion is discussed below.** (See Evidence Table 15, Bronchodilators: Safety of Long-Acting $Beta_2$-Agonists.)

Safety of Long-Acting Beta$_2$-Agonists

KEY POINTS: SAFETY OF INHALED LONG-ACTING BETA$_2$-AGONISTS

- The addition of LABA (salmeterol or formoterol) to the treatment of patients whose asthma is not well controlled on low- or medium-dose ICS improves lung function, decreases symptoms, and reduces exacerbations and use of SABA for quick relief in most patients (EPR—Update 2002; Greenstone et al. 2005; Masoli et al. 2005).
- A large clinical trial comparing daily treatment with salmeterol or placebo added to usual asthma therapy (Nelson et al. 2006) resulted in 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 with placebo). In addition, increased numbers 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 LABA for the great majority of patients whose asthma is not well controlled with ICS alone should be weighed against the increased risk for severe exacerbations, although uncommon, 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 ICS alone, the option to increase the ICS dose should be given equal weight to the option of the addition of a LABA to ICS.
- Daily use of LABA generally should not exceed 100 mcg salmeterol or 24 mcg formoterol.
- It is not currently recommended that LABA be used for treatment of acute symptoms or exacerbations.
- LABAs are not to be used as monotherapy for long-term control. Patients should be instructed not to stop ICS therapy while taking salmeterol or formoterol even though their symptoms may significantly improve.

General Safety. LABAs induce sustained relaxation of airway smooth muscle that allows twice-daily administration. The two LABAs currently available for the treatment of asthma are salmeterol and formoterol. They have slightly different properties in that salmeterol is a partial agonist and formoterol is a full agonist, but the only clinically relevant difference is that formoterol has a more rapid onset of bronchodilation (similar to albuterol) (Kips and Pauwels 2001). Both are highly selective beta$_2$-adrenergic receptor agonists that produce clinically relevant cardiovascular effects (tachycardia, QTc interval prolongation, and hypokalemia) at doses approximately 4–5 times those recommended (Guhan et al. 2000; Ostrom 2003;

Palmqvist et al. 1999). Other dose-dependent sympathomimetic effects include tremor and hyperglycemia. Because the LABAs are devoid of any clinically apparent anti-inflammatory activity (Currie et al. 2003; Lazarus et al. 2001), they should not be used as monotherapy for long-term control of persistent asthma. Discontinuation of ICS therapy following initiation of LABA results in an increase in asthma exacerbations (Lemanske et al. 2001). Of greatest concern have been the reports of an increased risk of severe asthma exacerbations, both life-threatening and fatal, associated with regular LABA use (Mann et al. 2003; Nelson et al. 2006) that has resulted in a Black Box Warning label for products in the United States containing either salmeterol or formoterol.

Early recognition of the potential dangers of LABAs followed a large, randomized, prospective postmarketing study in approximately 25,000 patients in the United Kingdom. The study reported an increased (although not statistically significant) number of deaths in patients treated with salmeterol (42 mcg/day) versus albuterol (180 mcg four times/day) added to usual asthma therapy (12 of 16,787 patients taking salmeterol versus 2 of 8,393 patients on albuterol) (Castle et al. 1993). However, an observational, prescription-event monitoring program in the United Kingdom evaluating 15,407 patients taking salmeterol found no evidence that salmeterol contributed to the death of any of the patients (Mann et al. 1996). Similarly, a retrospective review of a large, health insurance claims database in the United States, comparing a cohort of 2,708 patients receiving salmeterol to 3,825 recipients of sustained release theophylline, found no increase in ED visits, hospitalizations, or ICU admissions among those receiving salmeterol during the year following initiation of therapy (Lanes et al. 1998).

Due to the concerns generated by the initial United Kingdom study, a large, randomized, placebo-controlled, 28-week trial of salmeterol versus placebo added to usual care in adults who had asthma was performed to assess the safety of salmeterol (Nelson et al. 2006). The goal was to enroll approximately 60,000 patients, and the primary outcome variable was combined respiratory-related deaths or respiratory-related, life-threatening experiences; secondary end points included all-cause deaths, asthma-related deaths, and combined asthma-related deaths or life-threatening experiences. A planned interim analysis of more than 26,000 patients found no increase in the primary outcome but did find an increased risk of asthma-related deaths and combined asthma-related death or life-threatening experiences in the total population. Although the study was not designed to assess subgroups, a subgroup analysis reported that African Americans, who were 18 percent of the total population, experienced a significant increased risk for the primary end point as well as combined asthma-related death or life-threatening experiences. In addition, an analysis of serious asthma exacerbations in the pivotal trials submitted to the FDA for marketing approval of formoterol revealed an increased number of these events in patients receiving formoterol, particularly at the higher dose of 48 mcg daily that exceeds current labeling (Chowdhury 2005; Mann et al. 2003). A followup analysis of the same data reiterated the potential risks (Salpeter et al. 2006). The data from the Salmeterol Multicenter Asthma Research Trial (SMART), Chowdhury, and Mann and colleagues prompted the FDA to convene a meeting of the Pulmonary and Allergy Drugs Advisory Committee (www.fda.gov/cder/drug/advisory/LABA.htm) (FDA 2005). This group, in conjunction with the FDA, determined that these data represented a serious safety concern for the use of LABAs but that the significant benefit provided by these agents to a large number of patients, particularly in conjunction with ICS therapy, warranted continued use of LABA as adjunctive therapy for patients who have asthma that is not well controlled with ICS alone.

A meta-analysis of trials, performed for the EPR—Update 2002, reported greater benefit in measures of asthma control with the addition of a LABA compared to doubling the dose of ICS

(EPR—Update 2002). A Cochrane Library systematic review of 85 RCTs (60 studies with salmeterol and 25 studies with formoterol) comparing LABA with a placebo in chronic asthma (Walters et al. 2003) reported a decrease in severe asthma exacerbations (defined as requiring intervention other than as-needed SABA) associated with LABA use. Additional meta-analyses showed that the addition of LABA compared to increasing the ICS dose improved lung function and symptom control (Ni et al. 2005), reduced exacerbations (Masoli et al. 2005), and did not increase serious asthma exacerbations or participant withdrawals due to worsening asthma. A recent case-control study of 532 asthma patients who died from asthma did not find a positive association between LABA use and death (Anderson et al. 2005). A more recent large, postmarketing study (2,085 patients) of adding formoterol, either 24 mcg or 12 mcg twice daily, to usual care (65 percent receiving concomitant anti-inflammatory therapy) failed to detect an increase risk of serious asthma exacerbations (Wolfe et al. 2006).

A mechanism for a direct effect of LABAs in producing exacerbations has not been established. The primary hypotheses for LABAs' increasing the risk of severe, life-threatening asthma exacerbations include: (1) a direct adverse effect of LABA on bronchial smooth muscle, resulting in more severe obstruction following any bronchoconstrictive stimulus, or (2) maintenance of lung function in the face of worsening underlying inflammation, leading either to a catastrophic increase in obstruction or to patients' delaying seeking appropriate medical attention for a severe exacerbation. Clinical trials clearly demonstrate that, in patients who have persistent asthma, discontinuation of ICS after starting LABA results in increased markers of inflammation and increased risk of exacerbations (Lazarus et al. 2001; Lemanske et al. 2001; Mcivor et al. 1998). In patients who have mild asthma, the increase in exacerbations occurs despite benefits in measures of daily asthma control such as symptoms, as-needed use of SABA, and PEFs (Lazarus et al. 2001). Unlike regular use of SABA, the regular daily administration of LABA has not produced an increase in bronchial hyperresponsiveness (Cheung et al. 1992; Lazarus et al. 2001; Simons 1997; Van Schayck et al. 2002; Walters et al. 2003).

Genetic studies assessing the role of the polymorphism at codon 16 of the $beta_2$-adrenergic receptor gene have produced inconclusive results. A cross-over study by Taylor and coworkers (2000) reported that, during 24 weeks of treatment with placebo, albuterol, and salmeterol, the number of major exacerbations was significantly increased for homozygous Arg-16 subjects (only 17 subjects) during albuterol treatment compared with placebo but not during salmeterol treatment. In addition, researchers found no adverse effect of salmeterol on morning peak flow in the homozygote Arg-16 subjects compared with placebo or compared to homozygous Gly-16 subjects. More recently, Wechsler and colleagues (2006) reported that homozygote Arg-16 subjects (n = 8) who were taking salmeterol and an ICS had lower FEV_1, increased symptom scores, and increased use of SABA compared with Gly/Gly subjects (*n* = 22) taking the same combination therapy. On the other hand, Bleecker (2006) reported that, in a study of patients receiving LABA and ICS (N = 183), there were no differences in clinical response between Arg/Arg or Gly/Gly genotypes.

Studies assessing the qualitative nature of exacerbations have shown no difference in the rapidity of onset or severity of obstruction, reporting of symptoms, or use of SABA whether patients who had asthma were receiving LABA or not (Matz et al. 2001; Tattersfield et al. 1999). However, the patients in these studies were all receiving ICS as well as LABA. No studies have specifically addressed whether patients who take LABA delay seeking medical attention for deterioration of asthma, but this effect would be difficult to assess.

What ameliorative role, if any, the concomitant administration of ICS has on the potential for severe asthma exacerbations associated with LABA use has not been studied adequately. In a meta-analysis, the addition of LABA to ICS produced a significant reduction in severe exacerbations, but only a borderline significant decrease occurred in studies of patients who were not receiving ICS (Walters et al. 2003). In large clinical trials of at least 1 year duration, with severe exacerbations as a primary end point, LABA added to low- to medium-dose ICS significantly reduced the number of severe exacerbations in patients who had moderate asthma (O'Byrne et al. 2001; Pauwels et al. 1997) and reduced the number of patients who withdrew from the study because of an excessive number of exacerbations (Tattersfield et al. 1999). These results have been confirmed in a recent meta-analysis (Masoli et al. 2005). Although the study was not designed to assess subgroups or to assess concomitant medication use during the trial, no increase in the primary outcome of asthma deaths or life-threatening experiences was seen in association with salmeterol in the 12,265 patients who self-reported taking ICS at baseline in the SMART trial; however, this finding should not be considered conclusive (Nelson et al. 2006).

On the other hand, there did not appear to be a protective effect of ICS in the number of serious exacerbations reported in the formoterol pivotal trials. Although not statistically significant, an increased number of exacerbations were observed in the formoterol group (Chowdhury 2005). Thus, while the data do not necessarily support an increased risk of severe or serious exacerbations in patients who are taking LABA and are receiving concomitant ICS, data are also insufficient to establish definitively that ICS therapy completely obviates the risk. Further research is urgently needed to clarify this issue.

Methylxanthines

The Expert Panel recommends that sustained-release theophylline is an alternative but not preferred treatment for mild persistent asthma (Step 2 care) (Evidence A); it may also be used as alternative but not preferred adjunctive therapy with ICS (Evidence B). Theophylline, the principally used methylxanthine, provides mild or moderate bronchodilation in persons who have asthma. Theophylline is a nonselective phosphodiesterase inhibitor; as such, it has exhibited mild anti-inflammatory activity according to some but not all studies (Jaffar et al. 1996; Kidney et al. 1995; Page et al. 1998).

Theophylline produces minimal to no effect on airway reactivity and significantly less control of asthma than low-dose ICS does (Dahl et al. 2002; Reed et al. 1998). The addition of theophylline to ICS produces a small improvement in lung function similar to doubling the dose of ICS (Evans et al. 1997; Lim et al. 2000; Suessmuth et al. 2003). In a 24-week randomized, placebo-controlled trial in patients who had poorly controlled asthma, the addition of theophylline or montelukast led to small improvement in lung function but did not improve episodes of poor asthma control, symptoms, or quality of life (American Lung Association Asthma Clinical Research Centers 2007). Thus, the main use of theophylline is as adjunctive therapy to ICS. Sustained-release theophylline may be considered as a nonpreferred alternative long-term preventive therapy when issues arise concerning cost or a patient's aversion to inhaled medication. Monitoring serum concentrations of theophylline is essential to ensure that toxic concentrations are avoided. For sustained-release theophyllines, the serum concentration is obtained in the middle of the dosing interval, at least 3–5 days after initiation of theophylline and then at least 2 days after initiation of any factor known to affect theophylline clearance significantly. If patients experience signs and symptoms of toxicity (e.g., severe headache, tachycardia, nausea and vomiting), theophylline should be discontinued and a serum concentration obtained.

Tiotropium Bromide

Tiotropium bromide is a new, long-acting inhaled anticholinergic indicated once daily for COPD; this drug has not been studied in the long-term management of asthma (Gross 2004), and it has not received FDA-approved labeling for use in treating asthma. Ipratropium bromide, a short-acting anticholinergic, also has not demonstrated effectiveness in long-term management of asthma (Kerstjens et al. 1992).

QUICK-RELIEF MEDICATIONS

Quick-relief medications are used to provide prompt relief of bronchoconstriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing. These medications include SABAs and anticholinergics (ipratropium bromide). Although the onset of action is slow (>4 hours), systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses.

Anticholinergics

The Expert Panel concludes that ipratropium bromide, administered in multiple doses along with SABA in moderate or severe asthma exacerbations in the ED, provides additive benefit (Evidence B). Patients who have more severe obstruction of airways appear to benefit the most (Rodrigo and Castro-Rodriguez 2005). Ipratropium bromide has been used, with some success, as a quick-relief medication to avoid use of as-needed albuterol in clinical research trials in patients who have mild asthma (Israel et al. 2004). It has not been compared adequately to SABAs, however, nor does it have FDA-approved labeling for use in treatment of asthma.

Inhaled Short-Acting Beta$_2$-Agonists

The Expert Panel recommends that SABAs are the drug of choice for treating acute asthma symptoms and exacerbations and for preventing EIB (Evidence A). The SABAs (albuterol, levalbuterol, pirbuterol, etc.) relax airway smooth muscle and cause a prompt (within 3–5 minutes) increase in airflow. All synthetic beta$_2$-agonists exist chemically as racemic mixtures; however, the therapeutic activity primarily resides in the (R)-enantiomers and not the (S)-enantiomers. Due to the stereoselectivity of biological systems, the (R)-enantiomers are more active than the (S)-enantiomers. In vitro studies have suggested a possible deleterious effect of the (S)-enantiomer of albuterol on airway smooth muscle responsiveness and other airway cells (Berger 2003; Waldeck 1999). Therefore, a product containing only the active enantiomer of albuterol (levalbuterol) was developed and approved for clinical use. Some clinical studies suggested an improved efficacy of levalbuterol over racemic albuterol (Carl et al. 2003; Nelson et al. 1998) when administered in equal (R)-albuterol doses; however, other trials have failed to detect any advantage of levalbuterol over racemic albuterol (Cockcroft and Swystun 1997; Lotvall et al. 2001; Qureshi et al. 2005). (See also Evidence Table 16, Bronchodilators: Levalbuterol.) Concerns about the safety of SABAs are discussed below.

Formoterol, a LABA, has an onset of action similar to the SABAs (within 5 minutes) due to its lower lipophilicity than salmeterol (onset at 15 minutes) (Grembiale et al. 2002; Kips and Pauwels 2001). In acute bronchospasm induced by methacholine or exercise, formoterol improves FEV_1 as rapidly as inhaled albuterol or terbutaline (Hermansen et al. 2006; Politiek et al. 1999). In a large, 12-week comparison trial in patients receiving ICS therapy, formoterol was

as effective as terbutaline when used by outpatients as a quick-relief medication; fewer patients in the group that used formoterol experienced severe asthma exacerbations (Tattersfield et al. 2001). Initial studies of formoterol delivered by DPI showed rapid improvement in lung function in patients who presented in the ED with acute exacerbation (Bateman et al. 2006; Boonsawat et al. 2003). The onset of action and efficacy is comparable when formoterol is administered with budesonide in combination inhalers (Balanag et al. 2006; Bateman et al. 2006). This result has led numerous investigators to assess the efficacy of the combination inhaler for adjustable therapy in conjunction with standard administration (see discussion in the section above on "Inhaled Corticosteroids, Variability in Response and Adjustable Dose Therapy.") Although the Expert Panel is not currently recommending the use of formoterol as therapy for acute exacerbations, nor is formoterol approved for this indication, this area of research clearly warrants further investigation.

Safety of Inhaled Short-Acting Beta$_2$-Agonists

KEY POINTS: SAFETY OF INHALED SHORT-ACTING BETA$_2$-AGONISTS

- SABAs are the most effective medication for relieving acute bronchospasm (Evidence A).
- Increasing use of SABA treatment or using SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control of asthma and the need for initiating or intensifying anti-inflammatory therapy (Evidence C).
- Regularly scheduled, daily, chronic use of SABA is not recommended (Evidence A).

The Expert Panel recommends the use of SABA as the most effective medication for relieving acute bronchoconstriction; SABAs have few negative cardiovascular effects (Evidence A).

The Expert Panel does not recommend regularly scheduled, daily, long-term use of SABA (Evidence A).

SABAs are the mainstay of treatment for acute symptoms of bronchospasm. This is true both in routine outpatient management of persons who have asthma and for their treatment in the clinic or ED. The main SABAs in use today (i.e., albuterol, levalbuterol, and pirbuterol) are effective agonists and have few negative cardiovascular effects. In contrast, in the past, two SABAs (isoprenaline and fenoterol) which were less selective or used at higher doses have been associated with severe and fatal attacks of asthma. In addition, regular use of fenoterol produced a significant diminution in control of asthma and in objective measurements of pulmonary function (Sears et al. 1990). Regularly scheduled use of albuterol in patients who have mild or moderate asthma, compared to use of albuterol on an as-needed basis, resulted in no significant differences between groups in levels of asthma control. The regularly scheduled use of albuterol produced neither demonstrable benefits nor harmful effects (Dennis et al. 2000; Drazen et al. 1996). On the basis of these and other studies (Cockcroft et al. 1993; Ernst et al. 1993; Mullen et al. 1993; O'Connor et al. 1992; Suissa et al. 1994; Van Schayck et al. 1991), the regularly scheduled daily use of SABA is not recommended.

The frequency of SABA use can be clinically useful as a barometer of disease activity, because increasing use of SABA has been associated with increased risk for death or near death in patients who have asthma (Spitzer et al. 1992). Use of more than one SABA canister every 1–2 months is also associated with an increased risk of an acute exacerbation that requires an ED visit or hospitalization (Crystal-Peters et al. 2002; Lieu et al. 1998; Schatz et al. 2005). Thus, the use of more than one SABA canister (e.g., albuterol, 200 puffs per canister), predominantly for quick-relief treatment during a 1-month period, most likely indicates overreliance on this drug and suggests inadequate control of asthma (Spitzer et al. 1992).

Over the last few years, further studies have identified problems with chronic use of albuterol, especially when used without ICS (Eisner et al. 2001; Lemaitre et al. 2002). The possibility that regular albuterol use may be deleterious in some patients who have asthma was supported by studies that showed an increased risk of exacerbations in subjects who had elevated markers of inflammation as well as in those not taking ICS (Wraight et al. 2003, 2004).

Several different mechanisms have been proposed for the adverse effects of regular use of SABA. Evidence has been reported for increased expression of CxCL8 (Gordon et al. 2003) and increased response to allergen challenge (Swystun et al. 2000) and exercise (Hancox et al. 2002). In addition, decreases in lung function after stopping chronic use have been reported with regular use of SABAs (Hancox et al. 2000; Israel et al. 2000; Van Schayck et al. 2002). It is not possible to state with confidence which of these mechanisms is responsible for the increased exacerbation rate seen in large-scale observational studies.

Sequencing of the $beta_2$-agonist receptor gene has made it possible to identify polymorphisms, some of which may be relevant to the function of the receptor. Two studies have shown that subjects who are homozygous for arginine at position 16 (Arg/Arg 16) are more likely than patients who are homozygous for glycine (Gly/Gly 16) to experience decline in lung function when taking regularly scheduled daily albuterol treatment (Israel et al. 2000, 2004), although, as noted in "Component 1: Measures of Asthma Assessment and Monitoring," the clinical significance of the difference in lung function has not been established. In addition, a retrospective genetic analysis reported that patients who have Arg/Arg 16 and regularly received albuterol experienced increased exacerbations compared to patients who had Arg/Gly and Gly/Gly (Taylor et al. 2000). Due to the complex genetic nature of the $beta_2$-agonist receptor and its response, the current findings are not definitive in identifying the functional variant responsible for this adverse effect or the number of individuals in whom this effect may occur. The current data leave little doubt, however, that regularly scheduled administration of SABA can result in deleterious effects on lung function and asthma control in a subset of patients who have asthma. Although the mechanism of this effect is not clear, its association with polymorphisms of the $beta_2$-receptor is becoming more clear.

Systemic Corticosteroids

The Expert Panel recommends the use of oral systemic corticosteroids in moderate or severe exacerbations (Evidence A).

The Expert Panel recommends that multiple courses of oral systemic corticosteroids, especially more than three courses per year, should prompt a reevaluation of the asthma management plan for a patient (Evidence C). The risk of adverse effects from systemic corticosteroids depends on dose and duration. Systemic corticosteroids can speed resolution of airflow obstruction and reduce the rate of relapse (Rowe et al. 2001a, b; Rowe et al. 2004; Scarfone et al. 1993; Smith et al. 2003). Common adverse effects of systemic corticosteroids

include the potential for growth suppression, osteoporosis, cataracts, myopathy, adrenal suppression, increased appetite with weight gain, and development of cushingoid habitus consisting of moon facies, buffalo hump, central obesity with wasting of extremities, atrophy of the skin with the development of striae, and hirsutism. Psychologic disturbances—from increased emotional lability to frank psychosis—can occur, as well as hypertension, peptic ulcer disease, atherosclerosis, aseptic necrosis of bone, and diabetes mellitus. High-dose systemic corticosteroids can be immunosuppressive; if such treatment is used, appropriate steps should be taken to monitor and prevent infection (Spahn et al. 2003).

In regard to risk of adverse effects related to short courses of systemic corticosteroids, little information is available, and available studies used different products at varying doses. One epidemiologic study suggests that children, 4–17 years of age, who require more than four courses of oral corticosteroids (average duration 6.4 days) as treatment for underlying disease have an increased risk of fracture (van Staa et al. 2003). Another study concluded that multiple short courses of oral corticosteroids (median four courses in the preceding year) in the treatment of asthma in children 2–17 years of age were not associated with any lasting effect on bone metabolism, bone mineralization, or adrenal function (Ducharme et al. 2003). In another study, children who received four or more bursts of oral corticosteroids for acute asthma exacerbations in the previous year demonstrated a subnormal response of the HPA axis to hypoglycemic stress or ACTH (Dolan et al. 1987).

ROUTE OF ADMINISTRATION

Medications for asthma can be administered by either inhaled or systemic routes. Systemic routes are oral (ingested) or parenteral (subcutaneous, intramuscular, or intravenous). The major advantages of delivering drugs directly into the lungs via inhalation are that higher concentrations can be delivered more effectively to the airways and that systemic side effects are lessened (Newhouse and Dolovich 1986). Some drugs are therapeutically active in asthma only when inhaled (e.g., most ICS preparations, cromolyn, salmeterol).

Inhaled medications, or aerosols, are available in a variety of devices that differ in technique required and quantity of drug delivered to the lung. See figure 3–24 for a summary of issues to consider for different devices including inhalers, spacers, and nebulizers. Whatever device is selected, patients should be instructed in its use, and their technique should be checked regularly.

Alternatives to CFC-Propelled MDIs

Many inhaled medications currently used for asthma are available in MDIs. Historically, MDI technology has utilized chlorofluorocarbons (CFCs) as propellants. CFCs usually constitute 95 percent or more of the formulation emitted from an MDI. CFCs are metabolically stable, and even the portion of an actuation that is systemically absorbed is quickly excreted unchanged via exhalation. CFCs have been found to deplete stratospheric ozone, however, and have been banned internationally. Although a temporary medical exemption has been granted, it is expected that MDIs with CFC propellant will be phased out completely. For example, albuterol CFC will be phased out by the end of 2008. Alternatives include MDIs with other propellants (nonchlorinated propellants such as HFA 134a do not have ozone-depleting properties); multidose, breath-activated DPIs; and other handheld devices with convenience and delivery characteristics similar to current MDIs. MDIs with HFA 134a have been approved for use with albuterol, levalbuterol, beclomethasone dipropionate, and fluticasone propionate. Additional non-CFC products and delivery systems are expected in the future. Albuterol MDIs with HFA

propellant deliver comparable doses to the lung and produce comparable efficacy and safety as albuterol CFC-MDIs (Lumry et al. 2001; Ramsdell et al. 1999; Shapiro et al. 2000a,b). Beclomethasone dipropionate with HFA propellant delivers a significantly greater dose to the lungs than its respective CFC-MDIs, however, resulting in lower recommended doses (figures 4–4a, b, c; 4–8a, b, c) (Busse et al. 1999; Leach et al. 1998; Richards et al. 2001), whereas fluticasone propionate with HFA propellant delivers slightly less drug to the lungs than the CFC-MDI but dosage recommendations are unchanged. During the phaseout of CFC products, clinicians will need to be informed of the alternatives and assist their patients in the transition to non-CFC products.

Spacers and Valved Holding Chambers

"Spacer" is a generic term that refers to simple open tubes that are placed on the mouthpiece of an MDI to extend it away from the mouth of the patient. Spacers have consisted of manufactured and homemade devices such as plastic bottles, corrugated ventilation tubing, toilet tissue cores, etc. Spacers have also been integrated with the MDI (triamcinolone acetonide, flunisolide HFA).

VHCs are manufactured devices (Aerochamber, Optichamber, Prochamber, Vortex) that have one-way valves that do not allow the patient to exhale into the device. Thus, patients—either very young children or infants or those who for some other reason are unable to cooperate—can breathe normally and have someone else actuate the device without loss of the actuated dose and obviating the need for coordinating actuation and inhalation.

Both spacers and VHCs are intended to retain large particles emitted from the MDI so they do not deposit in the oropharynx and thereby lead to a higher proportion of small, respirable particles being inhaled. They perform this function to various degrees, however, depending upon their size and shape as well as the formulation of the MDI (drug, propellant, and/or excipients). Thus, a spacer or VHC can increase lung delivery of a drug from one MDI and decrease lung delivery from another (Ahrens et al. 1995; Dolovich 2000). In addition, in vitro and in vivo studies comparing various spacers and VHCs with the same MDI have demonstrated a two- to six-fold variation in the respirable dose emitted from the devices and two- to five-fold difference in systemic availability of the drug (Asmus et al. 2004; Liang et al. 2002).

VHCs are preferred over spacers because the vast majority of controlled clinical trials demonstrating safety and efficacy of drugs administered by MDIs that do not have integrated spacers and use an add-on device have been performed with VHCs (Dolovich et al. 2005). However, due to the significant variation found between the performance of specific VHCs and MDIs, it may be preferable to use the same combination of MDI and VHC reported in the individual drug study to achieve comparable results. No specific combination of MDI and VHC currently has been specifically approved by the FDA for use together.

Complementary and Alternative Medicine

KEY POINTS: COMPLEMENTARY AND ALTERNATIVE MEDICINE

- It is recommended that the clinician ask patients about all medications and treatments they are using for asthma and advise the patients that complementary and alternative medicines and treatments are not a substitute for the clinician's recommendations for asthma treatment (Evidence D).
- Evidence is insufficient to recommend or not recommend most complementary and alternative medicines or treatments.
- Acupuncture is not recommended for the treatment of asthma (Evidence B).
- Patients who use herbal treatments for asthma should be cautioned that there is the potential for harmful ingredients in herbal treatments and for interactions with recommended asthma medications (Evidence D).

Alternative healing methods are not substitutes for recommended asthma management strategies (i.e., pharmacologic therapy, environmental control measures, or patient education). Although alternative healing methods may be popular, clinical trials that adequately address safety and efficacy are limited, and their scientific basis has not been established.

The most widely known complementary and alternative medicine methods are acupuncture, homeopathy, herbal medicine, and Ayurvedic medicine (which includes transcendental meditation, herbs, and yoga).

Because complementary and alternative medicine is reported to be used by as much as one-third of the U.S. population (Eisenberg et al. 1993), it is important to inquire about all the medications and interventions a patient uses and advise the patient accordingly (See "Component 2: Education for a Partnership in Asthma Care.").

ACUPUNCTURE

The Expert Panel does not recommend the use of acupuncture for the treatment of asthma (Evidence B). Acupuncture involves the superficial insertion of thin needles along acupuncture points or acupoints on the body. (Acupressure is an alternative method of stimulating the same acupoints.) Two Cochrane database systematic reviews (Linde et al. 2000; McCarney et al. 2004) of 7 and 11 randomized trials (with 174 and 324 participants, respectively) using real acupuncture and sham acupuncture to treat asthma or asthma-like symptoms found no statistically significant or clinically relevant effects for acupuncture compared to sham acupuncture. Both reviews concluded that adequate evidence to make recommendations about the value of acupuncture in asthma treatment is lacking. A meta-analysis of 11 RCTs published in the period 1970–2000, comparing real acupuncture with placebo acupuncture, found no evidence of an effect of acupuncture in reducing asthma symptoms (Martin et al. 2002).

CHIROPRACTIC THERAPY

The Expert Panel concludes that there is insufficient evidence to recommend the use of chiropractic or related techniques in the treatment of asthma.

Chiropractic therapy and other forms of spinal or bodily manipulation or massage have been reported anecdotally to benefit patients who have asthma. Systematic reviews of chiropractic techniques in asthma (Balon and Mior 2004) and related therapies, such as the Alexander technique (Dennis 2000), found few randomized, controlled studies. Those studies, where available, showed mixed results, with perhaps some benefit in symptoms or health-related quality-of-life measures but no definitive improvement on more objective measures of asthma outcomes.

HOMEOPATHY AND HERBAL MEDICINE

The Expert Panel concludes that there is insufficient evidence to support effectiveness of homeopathy and that more clinical trial and observational data are necessary.

The Expert Panel concludes that there is insufficient evidence to recommend herbal products for treating asthma. Furthermore, because herbal products are not standardized, one must be aware that some may have harmful ingredients and that some may interact with other pharmaceutical products that the patient may be taking (Evidence D).

Homeopathy deals with the use of diluted substances which cause symptoms in the undiluted form. A systematic review of homeopathy for asthma included six RCTs. The trials were of variable quality and used different homeopathic treatments, which limit the ability to reliably assess the possible role of homeopathy in asthma (McCarney et al. 2004).

A variety of herbal products have been used alone and as adjunctive therapy for asthma with positive results in small trials that have not been duplicated (Gupta et al. 1998; Khayyal et al. 2003; Lee et al. 2004; Urata et al. 2002). The National Center for Complementary and Alternative Medicine of the National Institutes of Health encourages the development of well-designed clinical trials to assess with clarity the role of herbal products.

BREATHING TECHNIQUES

The Expert Panel concludes there is insufficient evidence to suggest that breathing techniques provide clinical benefit to patients who have asthma. Controlled studies have been conducted with breathing exercises (Holloway and Ram 2004), inspiratory muscle training (Ram et al. 2003; Weiner et al. 2002), and Buteyko breathing (Cooper et al. 2003) (raising blood PCO_2 through hypoventilation). A systematic review of breathing exercises identified seven studies meeting inclusion criteria (Holloway and Ram 2004). Treatment interventions and outcome measurements varied greatly in these studies. Thus, although there was a suggestion of improvement in such outcomes as SABA use, quality of life, and exacerbations in persons who have asthma, no reliable conclusions could be drawn regarding the use of breathing exercises for treatment of asthma in clinical practice (Holloway and Ram 2004). Inspiratory muscle training has also been examined in a systematic review (Ram et al. 2003). In three studies in which the maximum inspiratory pressure (PI_{max}) was reported, it was significantly improved compared to controls. In one study, increased PI_{max} in women was accompanied by decreased perception of dyspnea and decreased SABA use (Weiner et al. 2002). A recent

randomized, double-blind, controlled study of 57 patients assessed the impact of two different breathing techniques on the use of SABA, controlling for the advice given to patients regarding the use of either breathing technique before using SABA. A marked reduction in SABA use was observed with both breathing techniques, but no significant changes occurred in the quality of life or in any physiological markers. This study suggests that, in mild persistent asthma, using breathing techniques before using SABA might curb overuse of SABA, and that the process of practicing breathing techniques may be more important than the type of breathing technique used (Slader et al. 2006). Larger studies are needed to confirm study findings.

RELAXATION TECHNIQUES

The Expert Panel concludes that, despite some encouraging data from small studies, further positive data from randomized, controlled studies will be necessary before relaxation techniques can be recommended in the treatment of asthma. Recent controlled studies have been conducted to investigate whether relaxation techniques, including biofeedback and hypotherapy, may be beneficial in asthma. Preliminary data suggest that relaxation techniques may help improve not only symptoms (which in studies appeared to improve nonspecifically) but also lung function (Lehrer et al. 2004; Loew et al. 2001). Due to limitations of size and clearly prespecified hypotheses, these studies would need further confirmation. A systematic review of RCTs of relaxation techniques (Huntley et al. 2002) concluded that there was a lack of data from well-conducted studies of relaxation therapies to recommend them in the treatment of asthma. This review did find some evidence, however, that muscle relaxation techniques in particular may lead to improvements in lung function.

YOGA

There is a paucity of well-controlled studies on the effects of yoga on asthma outcomes. A recent, well-controlled pilot study of one type of yoga (Iyengar) showed no significant effects on physiologic or health-related quality-of-life measures (Sabina et al. 2005).

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Corticosteroids (Glucocorticoids) ***Inhaled (ICS):*** Beclomethasone dipropionate Budesonide Flunisolide Fluticasone propionate Mometasone furoate Triamcinolone acetonide	*Indications* ■ Long-term prevention of symptoms; suppression, control, and reversal of inflammation. ■ Reduce need for oral corticosteroid. *Mechanisms* ■ **Anti-inflammatory.** Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. ■ Reverse beta$_2$-receptor downregulation. Inhibit microvascular leakage.	■ Cough, dysphonia, oral thrush (candidiasis). ■ In high doses (see figures 4-4b and 4–8b), systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising) (Barnes and Pedersen 1993; Kamada et al. 1996). In low-to-medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established (CAMP 2000; Guilbert et al. 2006).	■ Spacer/holding chamber devices with nonbreath-activated MDIs and mouth washing after inhalation decrease local side effects. ■ Preparations are not absolutely interchangeable on a mcg or per puff basis (see figures 4–4b and 4–8b for estimated clinical comparability). New delivery devices may provide greater delivery to airways; this change may affect dose. ■ The risks of uncontrolled asthma should be weighed against the limited risks of ICS therapy. The potential but small risk of adverse events is well balanced by their efficacy. (See text.) ■ "Adjustable dose" approach to treatment may enable reduction in cumulative dose of ICS treatment over time without sacrificing maintenance of asthma control. ■ Dexamethasone is not included as an ICS for long-term control because it is highly absorbed and has long-term suppressive side effects.
Systemic: Methylprednisolone Prednisolone Prednisone	*Indications* ■ For short-term (3–10 days) "burst": to gain prompt control of inadequately controlled persistent asthma. ■ For long-term prevention of symptoms in severe persistent asthma: suppression, control, and reversal of inflammation. *Mechanisms* ■ Same as inhaled.	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. ■ Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances—impaired immune function. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and *Strongyloides.*	■ Use at lowest effective dose. For long-term use, alternate-day a.m. dosing produces the least toxicity. If daily doses are required, one study shows improved efficacy with no increase in adrenal suppression when administered at 3 p.m. rather than in the morning (Beam et al. 1992).

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Cromolyn Sodium and Nedocromil	*Indications* ■ Long-term prevention of symptoms in mild persistent asthma; may modify inflammation. ■ Preventive treatment prior to exposure to exercise or known allergen. *Mechanisms* ■ **Anti-inflammatory.** Blocks *early* and late reaction to allergen. Interferes with chloride channel function. Stabilizes mast cell membranes and inhibits activation and release of mediators from eosinophils and epithelial cells. ■ Inhibits acute response to exercise, cold dry air, and SO_2.	■ Cough and irritation. ■ 15–20 percent of patients complain of an unpleasant taste from nedocromil.	■ Therapeutic response to cromolyn and nedocromil often occurs within 2 weeks, but a 4- to 6-week trial may be needed to determine maximum benefit. ■ Dose of cromolyn by MDI (1 mg/puff) may be inadequate to affect airway hyperresponsiveness. Nebulizer delivery (20 mg/ampule) may be preferred for some patients. ■ Safety is the primary advantage of these agents.
Immunomodulators			
Omalizumab (Anti-IgE) For subcutaneous use	*Indications* ■ Long-term control and prevention of symptoms in adults (≥12 years old) who have moderate or severe persistent allergic asthma inadequately controlled with ICS. *Mechanisms* ■ Binds to circulating IgE, preventing it from binding to the high-affinity (FcεRI) receptors on basophils and mast cells. ■ Decreases mast cell mediator release from allergen exposure. ■ Decreases the number of FcεRIs in basophils and submucosal cells.	■ Pain and bruising of injection sites has been reported in 5–20 percent of patients. ■ Anaphylaxis has been reported in 0.2 percent of treated patients. ■ Malignant neoplasms were reported in 0.5 percent of patients compared to 0.2 percent receiving placebo; relationship to drug is unclear.	■ Monitor patients following injection. Be prepared and equipped to identify and treat anaphylaxis that may occur. ■ The dose is administered either every 2 or 4 weeks and is dependent on the patient's body weight and IgE level before therapy. ■ A maximum of 150 mg can be administered in one injection. ■ Needs to be stored under refrigeration at 2–8 °C. ■ Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Leukotriene Receptor Antagonists (LTRAs)	*Mechanisms* ■ **Leukotriene receptor antagonist;** selective competitive inhibitor of $CysLT_1$ receptor.		■ May attenuate EIB in some patients, but less effective than ICS therapy (Vidal et al. 2001). ■ Do not use LTRA + LABA as a substitute for ICS + LABA.
Montelukast tablets and granules	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥1 year of age. May also be used with ICS as combination therapy in moderate persistent asthma.	■ No specific adverse effects have been identified. ■ Rare cases of Churg-Strauss have occurred, but the association is unclear.	■ A flat dose-response curve, without further benefit, if dose is increased above those recommended.
Zafirlukast tablets	■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥7 years of age. May also be used with ICS as combination therapy in moderate persistent asthma.	■ Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.	■ Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. INRs should be monitored during coadministration. ■ Patients should be warned to discontinue use if they experience signs and symptoms of liver dysfunction (right upper quadrant pain, pruritis, lethargy, jaundice, nausea), and patients' ALTs should be monitored.
5-Lipoxygenase Inhibitor	*Mechanisms* ■ Inhibits the production of leukotrienes from arachidonic acid, both LTB_4 and the cysteinyl leukotrienes.		
Zileuton tablets	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. ■ May be used with ICS as combination therapy in moderate persistent asthma in patients ≥12 years of age.	■ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.	■ Zileuton is microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly. ■ Monitor hepatic enzymes (ALT).

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Long-Acting Beta$_2$-Agonists (LABA) *Inhaled LABA:* Formoterol Salmeterol	*Indications* ■ Long-term prevention of symptoms, added to ICS ■ Prevention of EIB. ■ *Not to be used to treat acute symptoms or exacerbations.* *Mechanisms* ■ **Bronchodilation.** Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP, producing functional antagonism of bronchoconstriction. ■ Compared to SABA, salmeterol (but not formoterol) has slower onset of action (15–30 minutes). Both salmeterol and formoterol have longer duration (>12 hours) compared to SABA.	■ Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose. ■ A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established. ■ Potential risk of uncommon, severe, life-threatening or fatal exacerbation; see text for additional discussion regarding safety of LABAs.	■ Not to be used to treat acute symptoms or exacerbations. ■ Should not be used as monotherapy for long-term control of asthma or as anti-inflammatory therapy. ■ May provide more effective symptom control when added to standard doses of ICS compared to increasing the ICS dosage. ■ Clinical significance of potentially developing tolerance is uncertain, because studies show symptom control and bronchodilation are maintained. ■ Decreased duration of protection against EIB may occur with regular use.
Oral: Albuterol, sustained-release			■ Inhaled route is preferred because LABAs are longer acting and have fewer side effects than oral sustained-release agents. Oral agents have not been adequately studied as adjunctive therapy with ICS.
Methylxanthines Theophylline, sustained-release tablets and capsules	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma or as adjunctive with ICS, in moderate or persistent asthma. *Mechanisms* ■ **Bronchodilation.** Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism. ■ May affect eosinophilic infiltration into bronchial mucosa as well as decreases T-lymphocyte numbers in epithelium. ■ Increases diaphragm contractility and mucociliary clearance.	■ Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia. ■ Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism.	■ Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors which can produce significant changes in steady-state serum theophylline concentrations. ■ Patients should be told to discontinue if they experience toxicity. ■ Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of SABA. Serum concentration monitoring is mandatory.

Key: anti-IgE, anti-immunoglobulin E, EIB, exercise-induced bronchospasm; INR, International Normalized Ratio; LABA, long-acting beta$_2$-agonist; MDI, metered-dose inhaler; SABA, inhaled short-acting beta$_2$-agonist

FIGURE 3–23. QUICK-RELIEF MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Short-Acting Beta$_2$-Agonists (SABA) *Inhaled SABA:* Albuterol Levalbuterol Pirbuterol	*Indications* ■ Relief of acute symptoms; quick-relief medication. ■ Preventive treatment for EIB prior to exercise. *Mechanisms* ■ **Bronchodilation.** Binds to the beta$_2$-adrenergic receptor, producing smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction.	■ Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.	■ Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. The less beta$_2$-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses. Oral systemic beta$_2$-agonists are not recommended. ■ For patients who have intermittent asthma, regularly scheduled daily use neither harms nor benefits asthma control (Drazen et al. 1996). Regularly scheduled daily use is not recommended. ■ Regular use >2 days/week for symptom control (not prevention of EIB), increasing use, or lack of expected effect indicates inadequate asthma control. ■ For patients frequently using SABA, anti-inflammatory medication should be initiated or intensified. ■ Levalbuterol at one-half the mcg dose produces clinically comparable bronchodilation and systemic side effects as racemic albuterol.

FIGURE 3–23. QUICK-RELIEF MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Anticholinergics Ipratropium bromide	*Indications* ■ Relief of acute bronchospasm (See Therapeutic Issues column.). *Mechanisms* ■ **Bronchodilation.** Competitive inhibition of muscarinic cholinergic receptors. ■ Reduces intrinsic vagal tone of the airways. May block reflex bronchoconstriction secondary to irritants or to reflux esophagitis. ■ May decrease mucous gland secretion.	■ Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes. If used in the ED, produces less cardiac stimulation than SABAs.	■ Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. Does not block EIB. ■ Multiple doses of ipratropium in the ED provide additive effects to SABA. ■ May be alternative for patients who do not tolerate SABA. ■ Treatment of choice for bronchospasm due to beta-blocker medication. ■ Has not proven to be efficacious as long-term control therapy for asthma.
Corticosteroids *Systemic:* Methylprednisolone Prednisolone Prednisone	*Indications* ■ For moderate or severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce rate of relapse. *Mechanisms* ■ **Anti-inflammatory.** See figure 3–22.	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, facial flushing, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and *Strongyloides.*	■ Short-term therapy should continue until patient's symptoms resolve. This usually requires 3–10 days but may require longer. — Action may begin within an hour. ■ There is no evidence that tapering the dose following improvement is useful in preventing a relapse in asthma exacerbations. ■ Other systemic corticosteroids such as hydrocortisone and dexamethasone given in equipotent daily doses are likely to be as effective as prednisolone.

Key: ED, emergency department; EIB, exercise-induced bronchospasm

FIGURE 3–24. AEROSOL DELIVERY DEVICES

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Metered-dose inhaler (MDI) Beta$_2$-agonists Corticosteroids Cromolyn sodium Anticholinergics	≥5 years old (<5 with spacer or valved holding chamber (VHC) mask)	Actuation during a slow (30 L/min or 3–5 seconds) deep inhalation, followed by 10-second breathhold. Under laboratory conditions, open-mouth technique (holding MDI 2 inches away from open mouth) enhances delivery to the lung. This technique, however, has not been shown to enhance clinical benefit consistently compared to closed-mouth technique (inserting MDI mouthpiece between lips and teeth).	Slow inhalation and coordination of actuation during inhalation may be difficult, particularly in young children and elderly. Patients may incorrectly stop inhalation at actuation. Deposition of 50–80 percent of actuated dose in oropharynx. Mouth washing and spitting is effective in reducing the amount of drug swallowed and absorbed systemically (Selroos and Halme 1991). Lung delivery under ideal conditions varies significantly between MDIs due to differences in formulation (suspension versus solution), propellant (chlorofluorocarbon (CFC) versus hydrofluoralkane (HFA)), and valve design (Dolovich 2000). For example, inhaled corticosteroid (ICS) delivery varies from 5–50 percent (Kelly 2003).
Breath-actuated MDI Beta$_2$-agonist	≥5 years old	Tight seal around mouthpiece and slightly more rapid inhalation than standard MDI (see above) followed by 10-second breathhold.	May be particularly useful for patients unable to coordinate inhalation and actuation. May also be useful for elderly patients (Newman et al. 1991). Patients may incorrectly stop inhalation at actuation. Cannot be used with currently available spacer/valved-holding chamber (VHC) devices.
Dry powder inhaler (DPI) Beta$_2$-agonists Corticosteroids Anticholinergics	≥4 years old	Rapid (60 L/min or 1–2 seconds), deep inhalation. Minimally effective inspiratory flow is device dependent. Most children <4 years of age may not generate sufficient inspiratory flow to activate the inhaler.	Dose is lost if patient exhales through device after actuating. Delivery may be greater or lesser than MDI, depending on device and technique. Delivery is more flow dependent in devices with highest internal resistance. Rapid inhalation promotes greater deposition in larger central airways (Dolovich 2000). Mouth washing and spitting is effective in reducing amount of drug swallowed and absorbed (Selroos and Halme 1991).

FIGURE 3–24. AEROSOL DELIVERY DEVICES (CONTINUED)

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Spacer or valved holding chamber (VHC)	≥4 years old <4 years old VHC with face mask	Slow (30 L/min or 3–5 seconds) deep inhalation, followed by 10-second breathhold immediately following actuation. Actuate only once into spacer/VHC per inhalation (O'Callaghan et al. 1994). If face mask is used, it should have a tight fit and allow 3–5 inhalations per actuation (Amirav and Newhouse 2001; Everard et al. 1992). Rinse plastic VHCs once a month with low concentration of liquid household dishwashing detergent (1:5,000 or 1–2 drops per cup of water) and let drip dry (Pierart et al. 1999; Wildhaber et al. 2000).	Indicated for patients who have difficulty performing adequate MDI technique. May be bulky. Simple tubes do not obviate coordinating actuation and inhalation. The VHCs are preferred. Face mask allows MDIs to be used with small children. However, use of a face mask reduces delivery to lungs by 50 percent (Wildhaber et al. 1999). The VHC improves lung delivery and response in patients who have poor MDI technique. The effect of a spacer or VHC on output from an MDI depends on both the MDI and device type; thus data from one combination should not be extrapolated to all others (Ahrens et al. 1995; Dolovich 2000). Spacers and/or VHCs decrease oropharyngeal deposition and thus decrease risk of topical side effects (e.g., thrush) (Salzman and Pyszczynski 1988; Toogood et al. 1984). Spacers will also reduce the potential systemic availability of ICSs with higher oral absorption (Brown et al. 1990; Selroos and Halme 1991). However, spacer/VHCs may increase systemic availability of ICSs that are poorly absorbed orally by enhancing delivery to lungs (Dempsey et al. 1999; Kelly 2003). No clinical data are available on use of spacers or VHCs with ultrafine-particle-generated HFA MDIs. Use antistatic VHCs or rinse plastic nonantistatic VHCs with dilute household detergents to enhance delivery to lungs and efficacy (Lipworth et al. 2002; Pierart et al. 1999; Wildhaber et al. 2000). This effect is less pronounced for albuterol MDIs with HFA propellant than for albuterol MDIs with CFC propellant (Chuffart et al. 2001). As effective as nebulizer for delivering SABAs and anticholinergics in mild to moderate exacerbations; data in severe exacerbations are limited.

FIGURE 3–24. AEROSOL DELIVERY DEVICES (CONTINUED)

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Nebulizer Beta$_2$-agonists Corticosteroids Cromolyn sodium Anticholinergics	Patients of any age who cannot use MDI with VHC and face mask.	Slow tidal breathing with occasional deep breaths. Tightly fitting face mask for those unable to use mouthpiece. Using the "blow by" technique (i.e., holding the mask or open tube near the infant's nose and mouth) is not appropriate.	Less dependent on patient's coordination and cooperation. Delivery method of choice for cromolyn sodium in young children. May be expensive; time consuming; bulky; output is dependent on device and operating parameters (fill volume, driving gas flow); internebulizer and intranebulizer output variances are significant (Dolovich 2000). Use of a face mask reduces delivery to lungs by 50 percent (Wildhaber et al. 1999). Nebulizers are as effective as MDIs plus VHCs for delivering bronchodilators in the ED for mild to moderate exacerbations; data in severe exacerbations are limited. Choice of delivery system is dependent on resources, availability, and clinical judgment of the clinician caring for the patient (Cates et al. 2002; Dolovich et al. 2005). Potential for bacterial infections if not cleaned properly.

Key: ED, emergency department; SABAs, inhaled short-acting beta$_2$-agonists
*See figures in "Component 2: Education for a Partnership in Asthma Care" for description of MDI and DPI techniques.

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