

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
<p>Corticosteroids (Glucocorticoids)</p> <p>Inhaled (ICS): Beclomethasone dipropionate Budesonide Flunisolide Fluticasone propionate Mometasone furoate Triamcinolone acetonide</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term prevention of symptoms; suppression, control, and reversal of inflammation. ■ Reduce need for oral corticosteroid. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Anti-inflammatory. Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. ■ Reverse beta₂-receptor downregulation. Inhibit microvascular leakage. 	<ul style="list-style-type: none"> ■ 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). 	<ul style="list-style-type: none"> ■ 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.
<p>Systemic: Methylprednisolone Prednisolone Prednisone</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ 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. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Same as inhaled. 	<ul style="list-style-type: none"> ■ 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 <i>Strongyloides</i>. 	<ul style="list-style-type: none"> ■ 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	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term prevention of symptoms in mild persistent asthma; may modify inflammation. ■ Preventive treatment prior to exposure to exercise or known allergen. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Anti-inflammatory. Blocks <i>early</i> 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 SO₂. 	<ul style="list-style-type: none"> ■ Cough and irritation. ■ 15–20 percent of patients complain of an unpleasant taste from nedocromil. 	<ul style="list-style-type: none"> ■ 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.
<p>Immunomodulators</p> <p>Omalizumab (Anti-IgE)</p> <p>For subcutaneous use</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term control and prevention of symptoms in adults (≥12 years old) who have moderate or severe persistent allergic asthma inadequately controlled with ICS. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ 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)	<p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Leukotriene receptor antagonist; selective competitive inhibitor of CysLT₁ receptor. 		<ul style="list-style-type: none"> ■ 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	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ No specific adverse effects have been identified. ■ Rare cases of Churg-Strauss have occurred, but the association is unclear. 	<ul style="list-style-type: none"> ■ A flat dose-response curve, without further benefit, if dose is increased above those recommended.
Zafirlukast tablets	<ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation. 	<ul style="list-style-type: none"> ■ 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	<p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Inhibits the production of leukotrienes from arachidonic acid, both LTB₄ and the cysteinyl leukotrienes. 		
Zileuton tablets	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia. 	<ul style="list-style-type: none"> ■ 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)
<p>Long-Acting Beta₂-Agonists (LABA)</p> <p><i>Inhaled LABA:</i></p> <p>Formoterol Salmeterol</p> <p><i>Oral:</i> Albuterol, sustained-release</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term prevention of symptoms, added to ICS ■ Prevention of EIB. ■ <i>Not to be used to treat acute symptoms or exacerbations.</i> <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ 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. ■ 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.
<p>Methylxanthines</p> <p>Theophylline, sustained-release tablets and capsules</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term control and prevention of symptoms in mild persistent asthma or as adjunctive with ICS, in moderate or persistent asthma. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ 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 beta₂-agonist; MDI, metered-dose inhaler; SABA, inhaled short-acting beta₂-agonist

FIGURE 3–23. QUICK-RELIEF MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
<p>Short-Acting Beta₂-Agonists (SABA)</p> <p><i>Inhaled SABA:</i> Albuterol Levalbuterol Pirbuterol</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Relief of acute symptoms; quick-relief medication. ■ Preventive treatment for EIB prior to exercise. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Bronchodilation. Binds to the beta₂-adrenergic receptor, producing smooth muscle relaxation following adenylyate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction. 	<ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. The less beta₂-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses. Oral systemic beta₂-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	<i>Indications</i> <ul style="list-style-type: none"> ■ Relief of acute bronchospasm (See Therapeutic Issues column.). <i>Mechanisms</i> <ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ 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. 	<ul style="list-style-type: none"> ■ 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 <i>Systemic:</i> Methylprednisolone Prednisolone Prednisone	<i>Indications</i> <ul style="list-style-type: none"> ■ For moderate or severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce rate of relapse. <i>Mechanisms</i> <ul style="list-style-type: none"> ■ Anti-inflammatory. See figure 3–22. 	<ul style="list-style-type: none"> ■ 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 <i>Strongyloides</i>. 	<ul style="list-style-type: none"> ■ Short-term therapy should continue until patient's symptoms resolve. This usually requires 3–10 days but may require longer. <ul style="list-style-type: none"> — 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
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 beta₂-agonists

*See figures in “Component 2: Education for a Partnership in Asthma Care” for description of MDI and DPI techniques.