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GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

UPDATED 2004

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be avoided by sensitive patients. Proof for the involvement of other dietary substances, including the yellow dye tartrazine, benzoate, and monosodium glutamate, is difficult to ascertain, and their role in exacerbating asthma is probably minimal. Confirmation of their relevance requires double-blind challenge before making specific dietary restrictions.

Avoidance of Certain Drugs

Some medications can exacerbate asthma. Aspirin and other nonsteroidal anti-inflammatory agents can cause severe exacerbations and should be avoided in patients with a history of reacting to these agents. Beta-blocker drugs administered orally or by eye drops may exacerbate bronchospasm and in general, should not be used by patients with asthma. If they are used, close medical supervision is essential. Avoidance of these drugs prevents exacerbations in susceptible patients.

Vaccination

Patients with moderate to severe asthma might be advised to receive an influenza vaccination every year[87,88]. The purification of the vaccine preparations has made adverse reactions to the vaccine less frequent. Inactivated influenza vaccine is safe to administer to adults and children with asthma, including those with severe asthma[622].

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PART 4A. ESTABLISH MEDICATION PLANS FOR LONG-TERM ASTHMA MANAGEMENT IN ADULTS

KEY POINTS:

- Preferred treatment recommendations in this report are based on efficacy and safety outcomes in populations. The response of individual patients may, of course, differ significantly from the mean response of the population. Decisions about treatment are often a compromise between what the physician recommends and what the patient is prepared to take.
- Medications for asthma can be administered in different ways, including inhaled, oral (ingested), and parenteral (subcutaneous, intramuscular, or intravenous). The major advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively to the airways, and systemic side effects are avoided or minimized.
- Although no cure for asthma has yet been found, it is reasonable to expect that in most patients with asthma, control of the disease can and should be achieved and maintained.
- Control of asthma can be achieved in many patients and can be defined as:
  - Minimal (ideally no) chronic symptoms, including nocturnal symptoms
  - Minimal (infrequent) exacerbations
  - No emergency visits
  - Minimal (ideally no) need for p.r.n. (as-needed) ß$_2$-agonist
  - No limitations on activities, including exercise
  - PEF circadian variation of less than 20 percent
  - (Near) normal PEF
  - Minimal (or no) adverse effects from medicine.
- Therapy should be selected on the basis of the severity of a patient's asthma, availability of anti-asthma medications, conditions of the health care system, and individual patient circumstances.
- For **intermittent asthma**, no daily medication is recommended for the vast majority of patients. Treatment of exacerbations should depend on the severity of the exacerbation. A rapid-acting inhaled β_2-agonist may be taken as needed to relieve asthma symptoms. The occasional patient with intermittent asthma, but severe exacerbations, should be treated as having moderate persistent asthma.
- Patients with **mild persistent asthma** require controller medication every day to achieve and maintain control of their asthma. Treatment with an inhaled glucocorticosteroid is preferred. Sustained-release theophylline, cromones, or a leukotriene modifier are other options.
- The preferred therapy for **moderate persistent asthma** is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting inhaled β_2-agonist twice daily. Sustained-release theophylline or a leukotriene modifier are alternatives to the β_2-agonist in this combination therapy. An alternative to combination therapy is a higher dose of inhaled glucocorticosteroid.

- The primary therapy for **severe persistent asthma** includes inhaled glucocorticosteroid at higher doses plus a long-acting inhaled β_2-agonist twice daily. Alternatives to the long-acting inhaled β_2-agonist for add-on treatment are an oral sustained-release theophylline, leukotriene modifier, or oral β_2-agonist. These drugs may also be added to the combination of high-dose inhaled glucocorticosteroid and long-acting inhaled β_2-agonist if necessary.
- Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

This section focuses on general aspects of the pharmacological treatment of asthma and on the long-term management of asthma in adults. A separate section discusses the management of asthma in children.

THE MEDICATIONS

Medications for asthma are used to reverse and prevent symptoms and airflow limitation and include controllers and relievers.

Controllers are medications taken daily on a long-term basis that are useful in getting and keeping persistent asthma under control. Controllers have been variably labeled as prophylactic, preventive, or maintenance medications and include anti-inflammatory agents and long-acting bronchodilators. Of all single medications, inhaled glucocorticosteroids are at present the most effective controllers. The so-called "antiallergic" agents may also be controllers, although there are insufficient data about their efficacy in the long-term management of asthma. It must be stressed that few clinical studies have addressed the question of how effective any of the anti-asthma medications are in getting asthma under complete control and in preventing symptoms and exacerbations.

Most studies have examined the effect of medications on one or more of the parameters of asthma control, for example, on reduction in the frequency of exacerbations, reduction in chronic symptoms, improvement in lung function, decreases in airway hyperresponsiveness, and improvement in the patient's quality of life[623]. Inhaled glucocorticosteroids suppress airway inflammation, reduce airway hyperresponsiveness, and control and prevent asthma symptoms[1,89-91]. Bronchodilators act principally to dilate the airways by relaxing airway smooth muscle. They reverse and/or inhibit bronchoconstriction and related symptoms of acute asthma, but do not reverse airway inflammation or reduce airway hyperresponsiveness[92,93]. Several long-term clinical studies have shown that treatment with anti-inflammatory agents is more effective than treatment with bronchodilators for long-term control of symptoms, improvement of lung function, and decrease of airway responsiveness[1,2,93-97].

Relievers include rapid-acting bronchodilators that act to relieve bronchoconstriction and its accompanying acute symptoms such as wheezing, chest tightness, and cough. Relievers have been variably labeled as quick-relief medicine or rescue medicine.

This section presents an overview of the characteristics of different controller and reliever medications. Some clinical studies have shown a substantial heterogeneity in individual patient responses to antiasthma medications[98]. However, the concepts of "responder" and "non-responder" developed in these studies are very often based on a single outcome measure such as morning PEF or FEV_1. Future developments in pharmacogenomics may result in asthma therapy that is more tailored to each patient's response to specific medications[99]. Further studies are needed before the current, empirical approach can be replaced by treatment selected on the basis of specific genotypes. Thus, the preferred treatment recommendations in this section are based on efficacy and safety outcomes in populations. The response of an individual patient to a given treatment may, of course, differ significantly from the population mean. Decisions about treatment are often a compromise between what the physician recommends and what the patient is prepared to take.

Route of Administration

Medications for asthma can be administered via different ways, including inhaled, oral (ingested), and parenteral (subcutaneous, intramuscular, or intravenous). The major advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively to the airways, and systemic side effects are avoided or minimized. Some of the drugs that are effective in asthma can only be used via inhalation because they are not absorbed when given orally (e.g., anticholinergics and cromones). The onset of action of bronchodilators is substantially quicker when they are given via inhalation than when these drugs are administered orally[100,101].

Aerosolized medications that are used to treat asthma are available as pressurized metered-dose inhalers (MDIs), breath-actuated MDIs, dry powder inhalers (DPIs), and

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nebulized or "wet" aerosols. Patients should be instructed in the use of the inhaler device, and their technique should be checked regularly. Inhaled asthma medications can be given either singly or in combination inhalers, the latter of which most often contain a glucocorticosteroid and a bronchodilator.

The disadvantage of pressurized MDI therapy is that training and skill are required to coordinate activation of the inhaler and the inhalation. The use of a spacer (holding chamber) improves drug delivery from an MDI (**Evidence A**)[102]. The spacer device allows discharge of the drug into a chamber where particles of medications are held in suspension for 10 to 30 seconds[103]. During this time, the patient can inhale the drug. Spacers also reduce deposition in the mouth and oropharynx, decreasing cough as well as the possibility of oral candidiasis when used to deliver glucocorticosteroids (**Evidence A**). Further, the use of spacers for the delivery of inhaled glucocorticosteroids decreases their systemic bioavailability and the risk of systemic side effects[104] (**Evidence B**). Some studies suggest that high doses of rapid-acting inhaled β_2-agonists administered from MDIs using spacer devices achieve bronchodilatation equivalent to that effected by nebulization in treating severe exacerbations[105,106]. A systematic review comparing MDI-plus-spacer versus wet-nebulizer delivery of high-dose rapid-acting inhaled β_2-agonists in patients with severe acute exacerbations of asthma showed these two delivery systems lead to equivalent clinical outcomes in adults but the MDI-plus-spacer system yields better clinical outcomes in children[102] (**Evidence B**). Breath-actuated aerosols may be helpful for patients who have difficulty using the pressurized MDI[107].

DPIs do not utilize freon propellants. They require an inhalation technique that is different from the MDI technique, and are generally easier to use. A minimal inspiratory flow rate is necessary to inhale from a DPI, and thus the DPI may be difficult for some patients to use during an exacerbation. The dosage should be adjusted to ensure adequate drug delivery at the inspiratory flow rate that patients can achieve. Some DPIs deliver pure drug, while others deliver the drug mixed with a filler (such as lactose), and thus the dosage should also take into account the fact that different DPIs yield different drug delivery to the lung. The dose of therapy may need to be adjusted when switching from an MDI to a DPI[108]. DPIs are more ecological than MDIs because they do not utilize chlorofluorocarbons (CFCs), but storage of some dry powder formulations may be more difficult in humid climates.

The CFCs in MDIs are now being replaced by hydrofluoroalkanes (HFAs)and the medication insert for dosage of the HFA preparations should be carefully reviewed by the clinician[109]. For bronchodilators the doses from CFC and HFA inhalers appear to be equivalent[109]. However, for some glucocorticosteroids the HFA formulations, which deliver a greater fraction of smaller particles to the lung, may result in both greater efficacy and greater systemic effects[110,111,624,666].

The therapeutic ratio is the relationship between the clinical and systemic effects of a given drug. This ratio is the only meaningful parameter to use for comparisons of different drugs or inhalers; for example increased lung deposition of an inhaled drug is normally associated with an increase in clinical effect until a plateau of the dose-response curve is reached so an inhaler that delivers 50% of the delivered dose to the intrapulmonary airways will normally have a greater clinical effect than an inhaler that delivers 10% to the lungs. On the other hand the drug has to be absorbed from the airway lumen to produce a clinical effect and all drug that is absorbed from the airway lumen subsequently goes into the systemic circulation. Therefore, a higher lung deposition of drug is often also associated with greater systemic effects, which often parallel the increase in clinical effect. So, a higher lung deposition normally allows the use of lower doses, but often does not change the relationship between clinical and systemic effects (the therapeutic ratio) for a given drug. The same considerations are normally true for increases in drug potency and receptor affinity.

- *Improved therapeutic ratio*: Increase in clinical effect is greater than the increase in systemic effects.
- *Reduced therapeutic ratio*: Increase in systemic effects is greater than the increase in clinical effects
- *Unchanged therapeutic ratio*: Increase in clinical effect is paralleled by an increase in systemic effects.

Controller Medications

Controller medications–medications used daily on a long-term basis to achieve and maintain control of persistent asthma–include inhaled glucocorticosteroids, systemic glucocorticosteroids, sodium cromoglycate (cromolyn sodium), nedocromil sodium, sustained-release theophylline, long-acting inhaled β_2-agonists, long-acting oral β_2-agonists, leukotriene modifiers, and systemic steroid-sparing therapies. Inhaled glucocorticosteroids are at present the most effective controller medications.

Inhaled glucocorticosteroids.

- *Mode of administration*–Inhaled.

- *Mechanisms of action*–Several studies have demonstrated that treatment with inhaled glucocorticosteroids for 1 month or more significantly reduces the pathological signs of airway inflammation in

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Figure 7-3. Estimated Comparative Daily Dosage for Inhaled Glucocorticosteroids

Drug	Low Daily Dose (μg)		Medium Daily Dose (μg)		High Daily Dose (μg)	
	Adult	Child	Adult	Child	Adult	Child
Beclomethasone-CFC	200-500	100-250	500-1000	250-500	>1000	>500
Beclomethasone-HFA	100-250	50-200	250-500	200-400	>500	>400
Budesonide-DPI	200-600	100-200	600-1000	200-600	>1000	>600
Budesonide-Neb Inhalation suspension	200-500	100-250	250-500	250-500		>1000
Flunisolde	500-1000	500-750	1000-2000	750-1250	>2000	>1250
Fluticasone	100-250	100-200	250-500	200-400	>500	>400
Mometasone furoate	200-400		400-800		>800	
Triamcinolone acetonide	400-1000	400-800	1000-2000	800-1200	>2000	>1200

Notes:
- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response in terms of several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effects.
- As CFC preparations are taken from the market, medication inserts for HFA preparations should be carefully reviewed by the clinician for the correct dosage level.

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asthma[90-93,112]. Airway hyperresponsiveness continues to improve with prolonged treatment[2].

- *Role in therapy*–Glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of asthma. Studies have demonstrated their efficacy in improving lung function, decreasing airway hyperresponsiveness[113], reducing symptoms, reducing frequency and severity of exacerbations, and improving quality of life[1,89-91,114] (**Evidence A**). Inhaled glucocorticosteroids are the preferred treatment for patients with persistent asthma at all levels of severity[667].

  Glucocorticosteroids differ in potency and bioavailability after inhalation, but relatively few studies have examined these differences. Dose comparison of glucocorticosteroids is difficult due to their long time course of action and the relative flatness of their dose-response curves. **Figure 7-3** lists approximately equipotent doses of different inhaled glucocorticosteroids administered via different inhalation devices[20]. A dose of 500 μg beclomethasone dipropionate (BDP) or equivalent daily controls asthma in the majority of patients. Because the dose-response curve of inhaled glucocorticosteroids is relatively flat for a number of outcome measures in asthma (e.g., symptoms, lung function measurements, airway responsiveness), going to a high dose of inhaled glucocorticosteroid provides little further benefit in terms of asthma control but increases the risk of side effects[115,625,668]. Add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids (**Evidence A**). There is, however, a clear relationship between the dose of inhaled glucocorticosteroids and the prevention of severe acute exacerbations of asthma[116]. Therefore, some patients with severe asthma may benefit from long-term treatment with higher doses of inhaled glucocorticosteroids, which allow the decrease or withdrawal of oral glucocorticosteroids in these patients. The safety profile of higher doses of inhaled glucocorticosteroids is clearly better than that of oral glucocorticosteroids[117,118].

- *Side effects*–Local adverse effects from inhaled glucocorticosteroids include oropharyngeal candidiasis, dysphonia, and occasional coughing from upper airway irritation. These effects may be prevented by use of spacer devices[119], gargling (and spitting out) with water, or gargling with a 1:50 dilution of amphotericin B[669].

  All inhaled glucocorticosteroids currently available are absorbed from the lung, so there is inevitably some systemic absorption. The risk of systemic adverse effects from inhaled glucocorticosteroids depends on the dose and the potency of the glucocorticosteroid as well as its bioavailability, absorption in the gut, first-pass metabolism in the liver, and the half-life of its systemically absorbed (from lung and possibly gut) fraction[120]. The systemic effects will therefore differ among the various in-

haled glucocorticosteroids. Several comparative studies have demonstrated that budesonide and fluticasone propionate (FP) have less systemic effect than BDP and triamcinolone[89,120,121]. The risk of systemic effects also depends on the delivery system; use of spacers decreases the systemic bioavailability and the risk of systemic side effects for most glucocorticosteroids[122].

Controlled clinical trials have demonstrated that long-term treatment with high doses of inhaled glucocorticosteroids may be associated with systemic effects, including skin thinning and easy bruising[123,124], adrenal suppression[104,120], and decreased bone mineral density[125,126,626,627]. Inhaled glucocorticosteroids have also been associated with cataracts and glaucoma in cross-sectional studies[127,128], but there is no evidence of post-capsular cataracts in prospective studies[129-131]. The clinical significance of the adrenal suppression or the decrease in osteoblast activity during treatment with high doses of inhaled glucocorticosteroids is not yet known. One difficulty in establishing this clinical significance lies in dissociating the effect of high-dose inhaled glucocorticosteroids from the effect of courses of oral glucocorticosteroids taken by patients with severe asthma. There is no evidence that supports the use of prophylactic treatment for osteoporosis in patients on inhaled glucocortiocosteroids. There are no data in malnourished populations on the possible effects of inhaled glucocorticosteroids on pulmonary tuberculosis or on calcium metabolism and bone density. The influence of inhaled glucocorticosteroids on growth is discussed in Chapter 7.4B, Establish Medication Plans for Long-Term Asthma Management in Infants and Children.

Current evidence suggests that in adults systemic effects of inhaled glucocorticosteroids are not a problem at doses of 500 μg or less BDP or equivalent daily, but some patients may be susceptible to systemic effects at lower doses. Inhaled glucocorticosteroids are effective controllers, and their use in the treatment of persistent asthma should be balanced against the possible risk of systemic effects. The risks of uncontrolled asthma should be weighed against the (probably limited) risk of this form of treatment.

Systemic glucocorticosteroids.

- *Mode of administration*–Oral (ingested) or parenteral.

- *Mechanisms of action*–The proposed mechanisms of action are the same as for inhaled glucocorticosteroids. However, systemic glucocorticosteroids may reach different target cells than inhaled glucocorticosteroids.

- *Role in therapy*–Long-term oral glucocorticosteroid therapy (daily or alternate-day) may be required to control severe persistent asthma, but its use is limited by the risk of significant adverse effects. Note that the therapeutic index (effect/side effect) of long-term inhaled glucocorticosteroids is always better than any form of long-term oral or parenteral glucocorticosteroid therapy in asthma[117,118]. Inhaled glucocorticosteroids are more effective than alternate-day oral glucocorticosteroids[117].

  If oral glucocorticosteroids have to be administered on a long-term basis, then attention should be paid to measures that minimize the systemic side effects. Oral preparations are preferred over parenteral for long-term therapy. Oral glucocorticosteroids such as prednisone, prednisolone, or methylprednisolone are preferred because of their minimal mineralocorticoid effect, their relatively short half-life, and their limited effects on striated muscle. The short half-life allows their use on an alternate-day schedule. Whenever possible, long-term therapy with oral glucocorticosteroids should be given once in the morning every day or every other day[117,132]. This generally allows sufficient control of the asthma and minimizes the systemic side effects. Some patients with very severe asthma may need daily and even twice-daily therapy with oral glucocorticosteroids.

- *Side effects*–The systemic side effects of long-term oral or parenteral glucocorticosteroid treatment include osteoporosis, arterial hypertension, diabetes, hypothalamic-pituitary-adrenal axis suppression, cataracts, glaucoma, obesity, skin thinning leading to cutaneous striae and easy bruising, and muscle weakness. Patients with asthma who are on long-term systemic glucocorticosteroids in any form should receive preventive treatment for osteoporosis[133,134].

  Although it is rare, adrenal failure may occur when a patient is withdrawn from long-term suppressive doses of oral glucocorticosteroids. Any such withdrawal should thus be observed for clinical and laboratory evidence of adrenal insufficiency. Withdrawal of oral glucocorticosteroids can also unmask underlying disease, such as Churg-Strauss Syndrome[135].

  Caution and close medical supervision are recommended when considering the use of systemic glucocorticosteroids in patients with asthma who also have tuberculosis, parasitic infections, osteoporosis, glaucoma, diabetes, severe depression, or peptic ulcers. If radiological signs of healed pulmonary tuberculosis are present in a patient who is taking long-term oral glucocorticosteroid therapy for asthma, and the patient has never been treated with

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effective antituberculosis drugs, then the patient should also be given chemoprophylaxis with isoniazid.

Fatal herpes virus infections have been reported among patients who are exposed to these viruses while taking systemic glucocorticosteroids, even short bursts. If a patient is exposed to varicella, the following actions should be considered: discontinue the systemic glucocorticosteroids, give the patient anti-zoster immunoglobulin, and consider acyclovir therapy if the patient develops progressive varicella[136,137]. Oral glucocorticosteroids also make patients more susceptible to herpes zoster infections, and the same steps should be taken as for the generalized varicella if the patient develops the infection.

Cromones: sodium cromoglycate and nedocromil sodium.

- Mode of administration–*Inhaled.*

- *Mechanisms of action*–The exact mechanisms of action of sodium cromoglycate and the related cromone nedocromil sodium are not fully understood, although these nonsteroidal anti-inflammatory medications partly inhibit the IgE-mediated mediator release from human mast cells in a dose-dependent way, and they have a cell-selective and mediator-selective suppressive effect on other inflammatory cells (macrophages, eosinophils, monocytes). There is some evidence that these medications inhibit a chloride channel on target cells[138]. The long-term effects of sodium cromoglycate on the chronic inflammatory changes in patients with asthma have not been directly demonstrated, except for one study in which prolonged treatment with sodium cromoglycate was associated with a significant decrease in the percentage of bronchial lavage eosinophils[139]. No long-term effect of nedocromil sodium on the chronic inflammatory changes in asthma has yet been demonstrated[140].

- *Role in therapy*–Sodium cromoglycate or nedocromil sodium may be used as controller therapy in mild persistent asthma. Administered prophylactically, these medications inhibit early- and late-phase allergen-induced airflow limitation and acute airflow limitation after exposure to exercise, cold dry air, and sulfur dioxide. Sodium cromoglycate reduces symptoms and the frequency of exacerbations[141], but studies have only inconsistently shown a benefit on nonspecific airway hyperresponsiveness. In adult patients with asthma, clinical trials show that nedocromil sodium improves symptoms and lung function, and reduces nonspecific airway responsiveness[142], although it is less effective than inhaled glucocorticosteroids[143] (**Evidence B**).

There is insufficient knowledge about the mechanisms of action to predict which patients will benefit from cromones; a 4- to 6-week therapeutic trial may be required to determine efficacy in individual patients.

- *Side effects*–Sodium cromoglycate and nedocromil sodium produce only minimal side effects, such as occasional coughing upon inhalation of the powder formulation. Some patients find the taste of nedocromil sodium unpleasant.

Methylxanthines.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–Theophylline is a bronchodilator that may have extrapulmonary effects, including anti-inflammatory effects[144]. The bronchodilator effect of theophylline may be related to phosphodiesterase inhibition and is seen at high concentrations (>10 mg/l), whereas the anti-inflammatory effect is due to an unknown mechanism and may occur at lower concentrations (5-10 mg/l). At low doses theophylline has some minor influence on chronic airway inflammation in asthma[145,146]. Most studies show little or no effect on airway hyperresponsiveness.

- *Role in therapy*–Sustained-release theophylline and aminophylline can be used as controller medications in asthma. Many clinical studies have shown that long-term treatment with sustained-release theophylline is effective in controlling asthma symptoms and improving lung function. When given as a sustained-release preparation, it has a long duration of action and is thus useful in the control of nocturnal symptoms that persist despite the regular treatment with anti-inflammatory therapy[147]. Theophylline is also useful as an additional bronchodilator in patients with severe asthma[148]. Now that theophylline at low doses has been shown to be effective in asthma control in both adults and children, it may be used in patients with milder disease and as an add-on therapy to low or high doses of inhaled glucocorticosteroids when further asthma control is needed[149-153] (**Evidence B**). As add-on therapy, theophylline is less effective than long-acting inhaled β_2-agonists[154,155] (**Evidence A**). It is, however, a less expensive option.

  Due to the risk of adverse effects, and the difficulty of monitoring therapy (see discussion of side effects below), theophylline is regarded in some countries as a therapy that should be reserved for use after inhaled glucocorticosteroids and inhaled β_2-agonists fail to

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Figure 7-4. Onset and Duration of Action of Inhaled β_2-Agonists

Onset of Action	Duration of Action	
	Short	Long
Rapid	Fenoterol Pirbuterol Procaterol Salbutamol (Albuterol) Terbutaline	Formoterol
Slow		Salmeterol

achieve therapeutic goals. In other countries, theophylline is recommended earlier in the course of daily long-term therapy because it is a bronchodilator useful for the control of asthma, especially of nocturnal asthma symptoms, and it is inexpensive.

- *Side effects*–At higher doses (10 mg/kg body weight/day or more), theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. The signs and symptoms of theophylline intoxication involve many different organ systems. Gastrointestinal symptoms, nausea, and vomiting are the most common early events. However, theophylline intoxication in children and adults can result in seizures and even death, and these events may not be preceded by evidence of central nervous system stimulation. Cardiopulmonary effects include tachycardia, arrhythmias, and, occasionally, stimulation of the respiratory center.

  Generally, serious toxic effects do not occur at serum concentrations below 15 µg per ml. Individual patient needs will vary, but a general approach to dosing and monitoring is to aim for a steady-state serum concentration for theophylline of between 5 and 15 µg per ml (28 to 85 µM) during long-term theophylline treatment. Monitoring of serum concentrations is advised when high-dose theophylline therapy (10 mg/kg body weight/day or more) is started and at occasional intervals thereafter. Monitoring is also advised when a patient develops an adverse effect on the usual dose, when expected therapeutic aims are not achieved, and when conditions or concomitant medications known to alter theophylline metabolism exist. For example, febrile illness, pregnancy, and anti-tuberculosis medications[670] reduce blood levels while liver disease, congestive heart failure and use of certain drugs including cimetidine, certain quinolones and certain macrolides increase the risk of toxicity. Lower doses of theophylline are associated with less frequent side effects, and there is less need for measurement of plasma levels in patients on low-dose therapy (unless there are problems of side effects or lack of therapeutic effect).

Long-acting inhaled β_2-agonists.

Long-acting inhaled β_2-agonists, including formoterol and salmeterol, have a duration of action lasting more than 12 hours. (Most rapid-acting inhaled β_2-agonists have a 4- to 6-hour duration of action). **Figure 7-4** compares the onset and duration of action of various inhaled β_2-agonists.

- *Mode of administration*–Inhaled.

- *Mechanisms of action*–Long-acting inhaled β_2-agonists are bronchodilator medications with activity that persists for at least 12 hours. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils[156,157]. Biopsy studies show that the chronic airway inflammation in asthma is not increased by treatment with long-acting inhaled β_2-agonists[92,158]; in fact, a small anti-inflammatory effect has been reported with long-term use[159,160]. Therapy with long-acting inhaled β_2-agonists produces bronchodilation comparable to, or better than, oral therapy. Long-acting inhaled β_2-agonists also provide long-term (>12 hours) protection against bronchoconstrictor stimuli[161]. Clinical pharmacology studies have shown that the duration of the bronchoprotective effect provided by long-acting inhaled β_2-agonists decreases when these medications are used on a regular basis[162,163]. The clinical significance of these findings is still unclear however, as long-term clinical studies do not indicate any decrease in efficacy over time[182]. Formoterol is a full agonist at the β_2-receptor, while salmeterol is a partial agonist[164], but the clinical significance of this difference is unclear[628].

- *Role in therapy*–Long-acting inhaled β_2-agonists should be considered when standard introductory doses of inhaled glucocorticosteroids fail to achieve control of asthma before raising the dose of inhaled glucocorticosteroids (**Evidence A**). Because long-term treatment with long-acting inhaled β_2-agonists does not appear to influence the persistent inflammatory changes in asthma, this therapy should *always* be combined with inhaled glucocorticosteroids[96,97] (**Evidence A**). Addition of long-acting inhaled β_2-agonists to a daily regimen of inhaled glucocorticosteroids improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of rapid-acting inhaled β_2-agonists[165-167], and reduces the number of exacerbations[165-167,116,168] (**Evidence A**).

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Several studies have now shown that adding a long-acting inhaled β_2-agonist (salmeterol or formoterol) in patients whose asthma is not controlled on either low or high doses of inhaled glucocorticosteroids results in better control of asthma (in terms of lung function and symptoms) than increasing the dose of inhaled glucocorticosteroids 2-fold or more[116,169,170,629] (**Evidence A**).

The greater efficacy of adding an inhaled long-acting β_2-agonist to an inhaled glucocorticosteroid than increasing the dose of inhaled glucocorticosteroids has led to the development of fixed combination inhalers (fluticasone propionate plus salmeterol, budesonide plus formoterol). Controlled studies have shown that delivering glucocorticosteroids and long-acting β_2-agonists together in a combination inhaler is as effective as giving each drug separately[182-184,671] (**Evidence B**). Use of this combination does not appear to be associated with masking or exacerbating airway inflammation[672] (**Evidence B**). Fixed combination inhalers are more convenient for patients, may increase compliance, ensure that the long-acting β_2-agonist is always accompanied by a glucocorticosteroid, and are usually less expensive than giving the two drugs separately.

Long-acting inhaled β_2-agonists may also be used to prevent exercise-induced bronchospasm and may provide longer protection than rapid-acting inhaled β_2-agonists[162]. Salmeterol and formoterol provide a similar duration of bronchodilation and protection against bronchoconstrictors, but there are pharmacological differences between them. Formoterol has a more rapid onset of action than salmeterol[171,172], which may make formoterol suitable for symptom relief as well as symptom prevention, although its effectiveness and safety as rescue medication needs further study.

- *Side effects*–Therapy with long-acting inhaled β_2-agonists causes fewer systemic adverse effects–such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia–than oral therapy. There is no evidence that long-acting inhaled β_2-agonists worsen exacerbations of asthma or the chronic airway inflammation in asthma[116,173,174].

Long-acting oral β_2-agonists.

Long acting oral β_2-agonists include slow-release formulations of salbutamol or terbutaline and bambuterol, a prodrug that is converted to terbutaline in the body.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–Long-acting oral β_2-agonists (sympathomimetics) are bronchodilators. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils.

- *Role in therapy*–Long-acting oral β_2-agonists may be helpful in controlling nocturnal symptoms of asthma. They may be used as an addition to inhaled glucocorticosteroids when standard doses do not sufficiently control nocturnal symptoms. Bambuterol appears to be as effective as salmeterol in controlling asthma in patients not controlled on low doses of inhaled glucocorticosteroids alone, although it may be associated with more frequent side effects[175,176].

- *Side effects*–Possible side effects include cardiovascular stimulation, anxiety, and skeletal muscle tremor. Adverse cardiovascular reactions may also occur with the combination of oral β_2-agonists and theophylline.

Leukotriene modifiers.

Leukotriene modifiers are a new class of antiasthma drugs that include cysteinyl leukotriene 1 (CysLT1) receptor antagonists (montelukast, pranlukast, zafirlukast) and a 5-lipoxygenase inhibitor (zileuton).

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–5-lipoxygenase inhibitors block the synthesis of all leukotrienes. Leukotriene receptor antagonists block the CysLT1 receptors on airway smooth muscle and other cells and thus inhibit the effects of cysteinyl leukotrienes that are released from mast cells and eosinophils. These mechanisms result in a small bronchodilator effect and reductions in allergen-, exercise-, and sulfur-dioxide-induced bronchoconstriction[177,178]. There is also evidence for some anti-inflammatory effects[179,180,630].

- *Role in therapy*–The role of leukotriene modifiers in asthma management remains under investigation. Clinical studies have demonstrated that leukotriene modifiers have a small and variable bronchodilator effect, reduce symptoms including cough[631], improve lung function, and reduce asthma exacerbations[177,178,181]. The effect of leukotriene modifiers is less than that of low doses of inhaled glucocorticosteroids[673], and, in patients already on inhaled glucocorticosteroids, leukotriene modifiers cannot substitute for this treatment without risking the loss of asthma control[182,183]. There is evidence that leukotriene modifiers used as add-on therapy reduce the dose of inhaled

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glucocorticosteroids required by patients with moderate to severe asthma[184], and may improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids[183,185,674,675] (**Evidence A**). Several short-term studies have demonstrated that leukotriene modifiers are less effective than long-acting inhaled B2-agonists as add on therapy[196,632,633,676] (**Evidence A**). However, a single one year study demonstrated equivalent effects of long-acting inhaled B2-agonists and leukotriene modifiers as add-on therapy on asthma exacerbations[677]. An advantage of leukotriene modifiers is their administration as a tablet. Some patients with aspirin-sensitive asthma may respond well to leukotriene modifiers[187].

- *Side effects*–Leukotriene modifiers are well tolerated, and few if any class-related effects have so far been recognized. Zileuton has been associated with liver toxicity, and monitoring of liver tests is recommended during treatment with this medication. There are several reports of Churg-Strauss syndrome in association with leukotriene modifier therapy[135]. In most but not all of these cases, the appearance of the Churg-Strauss syndrome was associated with a reduction in the dose of systemic glucocorticosteroids[188,189]. The causal relationship between leukotriene modifier therapy and Churg-Strauss syndrome is still unclear.

Anti-IgE

- *Mode of administration*–subcutaneous

- *Mechanism of action*–Antigen-specific IgE binds to high-affinity receptors on mast cells and basophils. Interaction with specific allergens cross-link cell-bond IgE to signal these cells to release preformed mediators (histamine) and initiate synthesis of other potential proinflammatory molecules (leukotrienes, cytokines, and chemokines)[634]. Thus, an antibody directed against IgE was considered a reasonable therapeutic target for allergic diseases, including asthma.

- *Role in therapy*–Anti-IgE allows for the reduction of glucocorticosteroids, and improves asthma control as indicated by fewer exacerbations, symptoms, and need for rescue medications[635,636]. A principal indication for anti-IgE, at present, is patients with severe, allergic asthma[637,678,679]. (**Evidence B**). Further investigation will help to provide additional clarification of the role of Anti-IgE therapy for asthma, although use of this treatment might be limited by the cost.

- *Side effects*–Based on several studies in asthma patients age 11-50 years, already receiving treatment with inhaled and/or oral glucocorticosteroids, anti-IgE appears safe[634-637].

Second generation antihistamines (H_1-antiantagonists)

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–The mechanism of action of anti-allergic H_1-antagonists (acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, loratidine, mizolastine, and terfenadine) in asthma has not been clearly established, but they are recognized to have some inhibitory effects on the allergic response.

- *Role in therapy*–Current evidence does not suggest a primary role for these agents in the treatment of asthma. They may have a small beneficial effect on asthma in subjects with concurrent rhinitis[190-192] (**Evidence B**).

- *Side effects*–The most frequent side effect of some second-generation antihistamines is still sedation, especially in the initial treatment period. Astemizole and terfenadine have been associated with severe cardiac side effects (torsade de point) and are therefore best avoided. Ketotifen may also cause weight gain.

Other oral antiallergic compounds.

Among oral antiallergic compounds introduced in some countries for the treatment of mild to moderate allergic asthma are tranilast, repirinast, tazanolast, pemirolast, ozagrel, celatrodast, amlexanox, and ibudilast.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–These compounds inhibit mast cell activation, interfere with the synthesis of allergic inflammatory mediators, or act as mediator antagonists.

- *Role in therapy*–Further studies on the relative efficacy of these compounds are needed before recommendations can be made about the inclusion of these oral anti-allergic compounds in the long-term treatment of asthma. Their antiasthma effect appears to be limited[193].

- *Side effects*–Sedation is potentially a side effect; other serious side effects have not yet been reported for this very heterogeneous class of drugs.

Systemic steroid-sparing therapies.

Several types of treatment have been tested to reduce the requirement for oral glucocorticosteroids in patients with severe asthma who experience significant side effects from glucocorticosteroids[194]. These steroid-sparing therapies include immunomodulators and some macrolides.

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- *Mode of administration*–Oral (ingested).

- *Role in therapy*–Therapeutic regimens to reduce the dose of oral glucocorticosteroids required by patients with severe asthma may include such medications as troleandromycin, methotrexate[195-197], cyclosporin[198], and gold[199,200]. These medications should be used only in selected patients under the supervision of an asthma specialist, as their potential steroid-sparing effect may not outweigh the risk of serious side effects. Two meta-analyses that considered the steroid-sparing effect of low-dose methotrexate showed a small overall benefit, but a relatively high frequency of adverse effects[201,202] (**Evidence B**). Intravenous immunoglobulin has been shown to have some steroid-sparing effect in some controlled trials, but has been found ineffective in others[203-205]. This treatment is also very expensive and has a high frequency of adverse effects, so it cannot be recommended. Some macrolides have a small steroid-sparing effect when used with methylprednisolone, decreasing metabolism of the glucocorticosteroid[206,207].

- *Side effects*–Side effects vary with the medication but commonly include nausea, vomiting, and abdominal pain. Less frequent but potentially severe adverse effects include hepatitis and hematological, teratogenic, and pulmonary effects.

Allergen-specific immunotherapy.

Specific immunotherapy (SIT) using allergen extracts has been administered in many countries for the treatment of allergic diseases, including asthma. The greatest benefit from this therapy has been obtained in the treatment of allergic rhinitis.

- *Mode of administration*–Subcutaneous injection. Sublingual administration currently under assessment.

- *Mechanisms of action*–Although the mechanisms of action of SIT have not been fully defined, some studies suggest that SIT may shift the immune system's balance from Th2 to Th1 cells, with increased production of interleukin (IL)-12 and interferon-γ[208,209]. SIT also increases the anti-inflammatory cytokine IL-10[210]. Precisely how and under what circumstances these changes affect immune regulation of allergic inflammation is not fully ascertained.

- *Role in therapy*–The greatest benefit of SIT has occurred when administered to patients with allergic rhinitis that has been unresponsive to conventional pharmacotherapy or specific environmental control or in circumstances in which patients do not wish to use medications for prolonged periods of time. Several studies have demonstrated that SIT using extracts of common aeroallergens may have some benefit in patients with allergic asthma[211,212], but several large, well-conducted studies have not demonstrated such a benefit[142,213]. A Cochrane review[214] that examined 54 randomized controlled trials of SIT in asthma confirmed the efficacy of this therapy in asthma (**Evidence A**). In particular, it emphasized the clinically useful outcomes of decreased symptom scores and medication requirements, as well as improved allergen-specific and nonspecific airway hyperresponsiveness. Importantly, the results of the Cochrane review were consistent and the number of patients studied was greater than 1,000, making interpretation of the meta-analysis valid. Despite this evidence, a number of questions remain to be addressed regarding the role of SIT in asthma therapy. First, which individuals are most likely to benefit? Second, is SIT directed at some aeroallergens more likely to be effective than that directed at other aeroallergens? Third, what is the long-term effectiveness of SIT compared to other forms of anti-inflammatory therapy? Finally, which clinical outcomes are most likely to be affected by SIT?

  Because of these questions, and the relatively modest effect of SIT in asthma especially compared to inhaled glucocorticosteroids, the possible benefits of this therapy must be measured in relation to the risk of adverse (occasionally fatal) effects and the inconvenience of the prolonged course of injection therapy, including a half-hour wait after each injection. Given the current state of information, SIT should be considered only after strict environmental avoidance and pharmacologic intervention, including inhaled glucocorticosteroids, have failed to control a patient's asthma[215]. There are no studies that compare SIT with pharmacologic therapy for asthma.

- *Side effects*–Local and systemic side effects may occur in conjunction with SIT administration. Reactions localized to the injection site may range from a minimal immediate wheal and flare to a large, painful, delayed allergic response. Systemic effects may include anaphylactic reactions, which may be life threatening, as well as severe exacerbations of asthma. These systemic reactions are best treated with subcutaneously administered epinephrine and other pharmacologic therapies[214]. Deaths from SIT have occurred in patients with severe asthma. Therefore, every patient with severe persistent asthma receiving SIT should undergo pulmonary function assessment prior to each SIT administration.

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Reliever Medications

Reliever medications–medications that act quickly to relieve bronchoconstriction and its accompanying acute symptoms–include rapid-acting inhaled β_2-agonists, systemic glucocorticosteroids, inhaled anticholinergics, short-acting theophylline, and short-acting oral β_2-agonists.

Rapid-acting inhaled β_2-agonists.

Rapid-acting inhaled β_2-agonists provide rapid relief of symptoms and include salbutamol (albuterol), terbutaline, fenoterol, reproterol, and pirbuterol. Formoterol has both a rapid onset and a long duration of action.

- *Mode of administration*–Inhaled.

- *Mechanisms of action*–Rapid-acting inhaled β_2-agonists (sympathomimetics) are bronchodilators. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells[156]. Therapy with rapid-acting inhaled β_2-agonists is comparable to or better than oral therapy in producing bronchodilatation and avoiding side effects. The clinical significance of β_2-receptor polymorphisms requires further examination[216]. There is no evidence of a difference in therapeutic ratio between R-albuterol compared to the normally used racemic (RS)-albuterol in terms of bronchodilator response or side effects[638].

- *Role in therapy*–Rapid-acting inhaled β_2-agonists are the medication of choice for treatment of acute exacerbations of asthma and are useful for the pretreatment of exercise-induced asthma[217] (**Evidence A**). Rapid-acting inhaled β_2-agonists are used to control episodic bronchoconstriction. Use of rapid-acting inhaled β_2-agonists as required for symptom control is recommended and provides a good indication of the need for further therapy. However, frequent or regularly scheduled use of rapid-acting inhaled β_2-agonists for long-term management of asthma does not adequately control asthma symptoms, peak flow variability, or airway hyperresponsiveness. In one study, regularly scheduled (as opposed to as-needed) therapy with the β_2-agonist fenoterol was associated with diminished control of asthma[218], but subsequent studies have shown no adverse effect of regular compared to as needed treatment with salbutamol in patients with mild to severe asthma[109-111]. In any case, regular treatment with rapid-acting inhaled β_2-agonists four times daily has largely been superseded by the use of long-acting inhaled β_2-agonists.

  Increased use–or even daily use–of rapid-acting inhaled β_2-agonists is a warning of deterioration of asthma and indicates the need to institute or to intensify the regular anti-inflammatory therapy. Similarly, failure to achieve a quick and sustained response to β_2-agonist treatment during an exacerbation mandates medical attention, and may indicate the need for short-term treatment with oral glucocorticosteroids.
  As-needed use of formoterol, a β_2-agonist with both a rapid onset and a long duration of effect, improves asthma control compared to as-needed use of the rapid- and short-acting β_2-agonist terbutaline in patients with moderate asthma who are taking inhaled glucocortocosteroids[219]. Formoterol has a well-documented role as controller therapy in asthma, and further studies are needed to identify its role as a reliever therapy.

- *Side effects*–Therapy with rapid-acting inhaled β_2-agonists causes fewer adverse systemic effects–such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia–than oral therapy.

Systemic glucocorticosteroids.

- *Mode of administration*–Oral (ingested) or parenteral.

- *Mechanisms of action*–See the section on systemic glucocorticosteroids in "Controller Medications" above.

- *Role in therapy*–Although onset of action of these medications is 4 to 6 hours, they are important in the treatment of severe acute exacerbations because they prevent progression of the asthma exacerbation, decrease the need for emergency department visits or hospitalizations, prevent early relapse after emergency treatment, and reduce the morbidity of the illness. Oral therapy is preferred and is as effective as intravenous hydro-cortisone[220,221] (**Evidence B**). Prednisone, prednisolone, and methylprednisolone are generally continued for 3 to 10 days following initial treatment of the exacerbation. A typical short course of oral glucocorticosteroids for an exacerbation is 30 mg prednisolone given daily for 5 to 10 days depending on the severity of the exacerbation. When the symptoms have subsided and the lung function has approached the personal best value, the oral glucocorticosteroids can be stopped or tapered, provided that treatment with inhaled glucocorticosteroids continues.

- *Side effects*–Potential adverse effects of high-dose short-term systemic therapy include reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, rounding of the face, mood alteration, hypertension, peptic ulcer, and aseptic necrosis

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of the femur. These side effects are generally not observed during a short course of oral or parenteral therapy.

Anticholinergics.

- *Mode of administration*–Inhaled.

- *Mechanisms of action*–Inhaled anticholinergic agents (ipratropium bromide, oxitropium bromide) are bronchodilators that block the effect of acetylcholine released from cholinergic nerves in the airways. When inhaled, these agents produce bronchodilation by reducing intrinsic vagal cholinergic tone to the airways. They also block reflex bronchoconstriction caused by inhaled irritants. They do not diminish the early and late allergic reactions and have no effect on airway inflammation. In asthma, inhaled anticholinergics are less potent bronchodilators than inhaled β_2-agonists, and in general, they have a slower onset of action (30 to 60 minutes to maximum effect).

- *Role in therapy*–Some reports show that ipratropium bromide has an additive effect when nebulized together with a rapid-acting β_2-agonist for exacerbations of asthma[222,223]. A meta-analysis of trials in which nebulized ipratropium bromide was added to a nebulized β_2-agonist showed the anticholinergic produced a statistically significant, albeit modest, improvement in pulmonary function, and significantly reduced the risk of hospital admission[224] (**Evidence B**). The benefits of ipratropium bromide in the long-term management of asthma have not been established, although it is recognized as an alternative bronchodilator for patients who experience such adverse effects as tachycardia, arrhythmia, and tremor from rapid-acting β_2-agonists.

- *Side effects*–Inhalation of ipratropium or oxitropium can cause a dryness of the mouth and a bitter taste. There is no evidence for any adverse effects on mucus secretion[225].

Methylxanthines.

- *Mode of administration*–Oral (ingested) or parenteral.

- *Mechanisms of action*–Theophylline is a bronchodilator that is, in general, less effective than an inhaled β_2-agonist.

- *Role in therapy*–Short-acting theophylline may be considered for relief of symptoms (although its onset of action is considerably longer than that of a rapid-acting β_2-agonist)[147] (**Evidence A**). The role of theophylline/aminophylline in treating exacerbations remains controversial. Short-acting theophylline may provide no additive bronchodilator effect over adequate doses of rapid-acting β_2-agonists, but it may benefit respiratory drive or respiratory muscle function and prolong or sustain the response to rapid-acting β_2-agonist between doses.

- *Side effects*–As already noted, theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. Short-acting theophylline should not be administered to patients already on long-term treatment with sustained-release theophylline unless the serum concentration of theophylline is known.

Short-acting oral β_2-agonists.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–Short-acting oral β_2-agonists are bronchodilators that relax airway smooth muscle.
- *Role in therapy*–Short-acting oral β_2-agonists are appropriate for use in the few patients who are unable to use inhaled medication.

- *Side effects*–The potential for adverse side effects such as cardiovascular stimulation, skeletal muscle tremor, hypokalemia, and irritability is more significant with oral therapy.

Alternative and Complementary Methods of Healing

Although alternative and complementary medicines may be popular with some patients, they have as yet been insufficiently researched, and their effectiveness is largely unproven. However, their use merits consideration[226,227]. The use of unconventional therapy is widespread, and it is associated with considerable individual health care expenditure[228]. In some countries traditional methods of healing are a primary way of treatment; in many countries, there has been a move toward using various traditional methods of healing. The scientific basis of these modes of therapy needs to be studied in detail, especially for countries in which these forms of therapy are frequently used. These traditional therapies are not validated by conventional standards, and it is difficult to evaluate traditional healing methods in randomized controlled trials. Furthermore, the psychotherapeutic benefit of a holistic approach, a characteristic of many traditional and alternative systems of medicine, cannot be excluded.

Although alternative and complementary healing methods cannot be recommended for asthma therapy until they have been studied more rigorously, the most widely known methods are described here.

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Acupuncture. The use of acupuncture originated over 2,000 years ago, and the technique was written up in detail soon thereafter. Traditional Chinese medicine is essentially holistic: The upset balance in disease is seen to be restored by diet, lifestyle, acupuncture, and herbs. Acupuncture is rarely used in this holistic way for the treatment of asthma in the West and in urban parts of China, where it is used as a complementary medicine. This holistic approach is very complex for investigation, and the available evidence points out that acupuncture *per se* is not indicated for the management of asthma[229]. In a review of 13 trials on the efficacy of acupuncture in the treatment of patients with asthma, a score was established based on 18 predefined methodological criteria. The results showed that the quality of even the eight better studies was mediocre, and the authors concluded that claims that acupuncture is effective in the treatment of asthma are not based on the results of well-performed clinical trials[230]. Another systematic review found only seven acceptable trials, and even in these the placebo was often inappropriate. In the acceptable trials, acupuncture did not produce a significant improvement in asthma[229]. Acupuncture is not entirely innocuous– acupuncture-associated hepatitis B, bilateral pneumothorax, and burns have all been described.

Homeopathy. There is no evidence that homeopathy is effective in asthma. A systematic review, which found only three relevant trials of homeopathy in asthma, did not reach any conclusions about efficacy and homoeopathic immunotherapy has been shown to be ineffective in the treatment of patients with asthma[231,639]. Nevertheless, homeopathy is widely used, and in some countries is the only alternative medicine accepted as part of government care. More rigorous trials are necessary to assess the efficacy of homeopathy.

Herbal medicine. Several modern treatments have their origins in the folk medicine tradition, including β_2-agonists, anticholinergics, methylxanthines, and sodium cromoglycate, the last of which was developed from analogs of the naturally occurring cromone khellin found in the West Asian plant *Amni visnaga*.

In different countries, several herbs are used in the treatment of asthma, and herbal remedies are quite popular for asthma and many other conditions. Since the beginning of time, humans have been using plants for healing. However, up to now, no controlled clinical trials of herbal folk remedies have been reported.

A public perception seems to be that because herbal remedies are "natural" they are safe. There are, however, no requirements on efficacy and safety for herbal treatments. Some of these popular remedies could be potentially dangerous, as exemplified by the occurrence of hepatic veno-occlusive disease associated with the consumption of the commercially available herb comfrey. Comfrey products are sold as herbal teas and herbal root powders, and their toxicity is due to the presence of pyrrolizidine alkaloids.

Dietary supplements. Although vitamin supplements are commonly taken by patients with asthma, regular dietary supplementation with vitamin C or magnesium adds no clinical benefit to current standard asthma therapy[680].

Ayurvedic medicine. "Ayurveda" is a Sanskrit word meaning knowledge of life. Ayurvedic medicine is a complex system of health care that has been practiced on the Indian subcontinent for thousands of years[232]. It consists of 20 separate components that include transcendental meditation, rasayanas (herbal preparations), pulse diagnosis, and yoga. The evidence that transcendental meditation may help in asthma is as yet poor and uncontrolled. The effect of one aspect of yoga breathing exercises, called pranayama, was well studied in a double-blind controlled trial that used a training and a placebo device. After two weeks there was no difference between the two groups regarding lung function, symptom score, and inhaler use[233]. However, there was a small but significant reduction in histamine reactivity in the group treated with pranayama breathing. The reason for this improvement is not clear. Ayurvedic medicine deserves attention in well-conducted clinical trials.

Ionizers. Ionizers impart a negative charge to particles dispersed in room air, which are attracted to walls and floors that carry a positive charge. Controlled trials failed to show a significant benefit in patients with asthma from the use of ionizers[234,681]. The negative ion generator in a room has several disadvantages, including production of ozone (a respiratory irritant). This therapy is not recommended for asthma.

Osteopathy and chiropractic manipulation. A controlled trial of chiropractic spinal manipulation showed no significant benefit of this therapy in asthma[235]. Other manual therapies, including osteopathy and physiotherapy, have so far not been shown to be helpful in asthma management[236]. The Alexander technique, consisting of a series of postural exercises, has been claimed to be beneficial in asthma management, but controlled trials have not been conducted[237].

Speleotherapy. Treatment of asthma with periods in underground environments, including salt mines, has been popular in some regions, such as Eastern Europe. However, there are few controlled studies of this therapy, and no conclusions can be made about its benefits until adequate controlled trials are conducted[238].

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Buteyko. Buteyko, a breathing technique consisting of a series of exercises in which subjects reduce the depth and the frequency of respiration, does not modify asthma, but may improve symptoms in some people, although the mechanism for this is not known[682]. A randomized controlled trial[239] concluded that patients with asthma who practiced the Buteyko breathing technique reduced their alveolar ventilation (this finding was especially prominent in patients who tended to hyperventilate) and their use of β_2-agonists. No objective change in measures of airway calibre or end-tidal $PaCO_2$ values were found. The results suggest that benefits, if any, may be in patients who tend to hyperventilate and use excessive amounts of β_2-agonist.

Other methods. Reports of the effects of hypnosis and suggestion, naturopathy, behavioral therapy, and biofeedback on asthma are either scarce or contradictory. Clearly, more rigorous studies are warranted. It is strongly recommended that conventional treatment be continued if these treatments –or other traditional healing methods–are tried.

A STEPWISE APPROACH TO PHARMACOLOGIC THERAPY

Although no cure for asthma has yet been found, it is reasonable to expect that in most patients with asthma control of the disease can and should be achieved and maintained. Control of asthma is defined as:

- Minimal (ideally no) chronic symptoms, including nocturnal symptoms
- Minimal (infrequent) exacerbations
- No emergency visits
- Minimal (ideally no) use of p.r.n. (as-needed) β_2-agonist
- No limitations on activities, including exercise
- PEF circadian variation of less than 20 percent
- (Near) normal PEF
- Minimal (or no) adverse effects from medicine.

Choice of Therapy

The selection of pharmacologic treatment options is made on the basis of asthma severity, the patient's current treatment, the pharmacological properties and availability of antiasthma treatment, and economic considerations. Because asthma is a dynamic as well as chronic condition, medication plans need to accommodate variability among patients as well as within individual patients over time. An essential aspect of any treatment plan is the need for monitoring the effect of the treatment (including use of measurements of lung function and symptoms) and adapting the treatment to the variability of the asthma. An approach to pharmacologic therapy that correlates with asthma severity permits this flexibility. As discussed previously, the classification of asthma severity should include symptom and medical history evaluation, current treatment, clinical examination, and measurements of lung function where possible.

An appropriate approach to therapy recommends that the number (type), dose, and eventually the frequency of medications are increased with increasing asthma severity. The aim is to accomplish the goals of therapy with the least possible medication. Thus in developing an asthma management plan, the health care professional must judge whether to give maximum treatment at the onset, which may include a burst or cycle of oral glucocorticosteroids and/or full doses of inhaled glucocorticosteroids plus long-acting β_2-agonists (**Evidence D**) in order to achieve control of the patient's asthma as quickly as possible, and then decrease the medication, or to start with treatment judged appropriate for the severity of the patient's asthma and increase treatment gradually if necessary. Once control is sustained for about 3 months, a reduction in therapy to a lower step can be carefully considered. This reduction in therapy is needed to identify the minimum therapy required to maintain control.

Few studies have as yet investigated the efficacy of various comprehensive therapeutic programs in accomplishing a broad set of therapeutic goals for controlling asthma. The recommendations that follow are thus based on an understanding of the pathology of asthma and an extrapolation from controlled clinical therapeutic trials that have evaluated the effects of particular antiasthma therapies on separate outcomes such as asthma symptoms, lung function, and the use of bronchodilators on an as-needed basis to relieve symptoms.

Figure 7-5 presents the stepwise approach to therapy to achieve and maintain control of asthma. The step system for classifying asthma severity takes into account the treatment that the patient is currently receiving (**Figure 5-7**). **Figure 7-5** presents all therapies that can be recommended for treating each step of asthma severity. Guidance for selecting among these available modalities is provided in the text. The cost of the medication is an obvious factor in determining the choice of treatment. Cost of treatment varies from country to country and is only one of the factors that contribute to the total cost of a disorder such as asthma.

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Figure 7-5. Recommended Medications by Level of Severity: Adults and Children Older Than 5 Years of Age

All Levels: In addition to regular daily controller therapy, rapid-acting inhaled β_2-agonist* should be taken as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Patient education is essential at every level.

Level of Severity**	Daily Controller Medications	Other Treatment Options***
Step 1 Intermittent Asthma****	• None necessary	
Step 2 Mild Persistent Asthma	• Low-dose inhaled glucocorticosteroid	• Sustained-release theophylline, *or* • Cromone, *or* • Leukotriene modifier
Step 3 Moderate Persistent Asthma	• Low-to-medium inhaled glucocorticosteroid *plus* long-acting inhaled β_2-agonist	• Medium-dose Inhaled glucocorticosteroid *plus* sustained-release theophylline, *or* • Medium-dose Inhaled glucocorticosteroid *plus* long-acting oral β_2-agonist, *or* • High-dose inhaled glucocorticosteroid *or* • Medium-dose Inhaled glucocorticosteroid *plus* leukotriene modifier
Step 4 Severe Persistent Asthma	• High-dose Inhaled glucocorticosteroid *plus* long-acting inhaled β_2-agonist, *plus* one or more of the following, if needed: • Sustained-release theophylline • Leukotriene modifier • Long-acting oral β_2-agonist • Oral glucocorticosteroid	

All Levels: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

* *Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral β_2-agonist, and short-acting theophylline.*
** *See **Figure 5-6** and **Figure 5-7** for classification of severity.*
*** *Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.*
**** *Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (**Evidence D**).*

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How To Achieve and Maintain Control of Asthma

This section describes the therapy appropriate for different steps of asthma severity. The presence of one or more features of clinical severity places a patient at the respective step (**Figure 5-6**). The current treatment should be included in the assessment of severity (**Figure 5-7**).

In the stepwise approach to therapy, progression to the next step is indicated when control is not achieved or is lost with the current treatment, and there is assurance the patient is using medication correctly. The frequent (e.g., more than 3 times a week) presence of such symptoms as cough, wheezing, and dyspnea, and the increased use of rapid-acting bronchodilators may indicate inadequate control of asthma. The presence of symptoms at night or early in the morning is an especially useful indicator. Measurement of PEF and its variability is helpful in the initial assessment of asthma severity and in monitoring the initial treatment, assessing changes in severity, and preparing for a reduction in therapy.

The treatments suggested for each step below are guidelines only; evidence levels assigned are based on references provided in the previous text. Specific medication plans should be tailored by the health care

professional depending on the availability of antiasthma medication, the conditions of the health care system, and individual patient circumstances. Repeated use of reliever medication more than 4 times a day indicates that the patient's asthma is not well controlled, and the intensity of treatment should be increased.

Step 1–Intermittent Asthma. A patient has intermittent asthma if the patient experiences symptoms (episodes of cough, wheezing, or dyspnea) less than once a week over a period of at least 3 months, and the episodes are brief, generally lasting only a few hours to a few days. Nocturnal asthma symptoms do not occur more than 2 times a month. In between exacerbations, the patient is asymptomatic and has completely normal lung function, i.e., a pretreatment baseline FEV_1 greater than 80 percent of predicted or PEF greater than 80 percent of personal best, and PEF variability of less than 20 percent.

Intermittent asthma includes the patient with allergy who is occasionally exposed to the allergen (e.g., cat or dog) that is responsible for causing his or her asthma symptoms, but who is completely symptom-free and has normal lung function when not exposed to the allergen. Intermittent asthma also includes the patient who has occasional exercise-induced asthma (e.g., under bad weather circumstances).

Intermittent asthma is not trivial. The severity of the asthma exacerbation may vary from patient to patient and from time to time. Severe exacerbations are rare in patients with intermittent asthma but can occur.

The low frequency of the symptomatic episodes and the fact that in between exacerbations the patient has completely normal lung function support the recommendations that no long-term treatment with a controller medication should be started. Further, patient compliance with long-term therapy could be low when the patient only experiences occasional symptoms. Rather, the exacerbations should be treated as such, depending on their severity.

Rapid-acting inhaled β_2-agonist as needed is recommended for the majority of patients with mild intermittent asthma (Evidence A). People with intermittent asthma with severe exacerbations should be treated as having moderate persistent asthma (Evidence D).

Treatment includes medication prior to exercise as needed (rapid-acting inhaled β_2-agonist is the preferred treatment; a cromone or a leukotriene modifier are alternative choices) (**Evidence B**) or upon allergen exposure (a cromone is the preferred treatment) (**Evidence B**). A rapid-acting inhaled β_2-agonist may be taken as needed to relieve asthma symptoms (**Evidence A**). An inhaled anticholinergic, short-acting oral β_2-agonist, or short-acting theophylline may be considered as alternatives to rapid-acting inhaled β_2-agonists, although these alternatives have a slower onset of action and/or a higher risk for side effects (**Evidence A**). Occasionally, more severe or prolonged exacerbations may require a short course of oral glucocorticosteroids.

If medication is required more than once a week over a 3-month period, the patient should be considered to have mild persistent asthma. The same applies if the lung function between exacerbations becomes abnormal.

Step 2–Mild Persistent Asthma. A patient has mild persistent asthma if he or she experiences symptoms and/or declines in lung function with sufficient frequency to warrant daily long-term therapy with controller medication. Mild persistent asthma is present if the patient experiences symptoms at least once a week but less than once a day over a 3-month period and some of the symptomatic episodes affect sleep and activity levels; and/or if the patient has chronic symptoms that require symptomatic treatment almost daily and experiences nocturnal asthma symptoms more than twice a month. The patient with mild persistent asthma has a pretreatment baseline PEF of more than 80 percent of predicted or personal best and PEF variability of 20 to 30 percent. Furthermore, cough variant asthma should be treated as mild persistent asthma.

Patients with mild persistent asthma require controller medication every day to achieve and maintain control of their asthma. The primary therapy for mild persistent asthma is regular use of anti-inflammatory medication taken on a daily basis. Treatment with an inhaled glucocorticosteroid is preferred (Evidence A). The suggested introductory dose of inhaled glucocorticosteroids is 200 to 500 μg per day of BDP or budesonide, 100 to 250 μg per day of fluticasone propionate (FP), or equivalent (Figure 7-3), divided over 1 or 2 dosings (Evidence B). Alternative controller medications (listed in order of increasing cost) are sustained-release theophylline, cromones, and leukotriene modifiers, but these are less effective than inhaled glucocorticosteroids or are effective in only a portion of patients, who cannot be identified without a treatment trial (**Evidence A**). Long-term treatment with sustained-release theophylline may be considered, but the need for monitoring of serum theophylline levels may make this treatment less feasible. Long-term trials that compare the effectiveness of these alternative controller medications in patients with mild persistent asthma are needed.

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In addition to regular controller therapy, a rapid-acting inhaled β_2-agonist should be available to take as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Other bronchodilator choices include an inhaled anticholinergic, short-acting oral β_2-agonist, or sustained-release theophylline, although these have a slower onset of action and/or a greater risk of side effects. Because of the risk of serious side effects, short-acting theophylline should not be used as a reliever medication if the patient is already on long-term controller therapy with sustained-release theophylline. Use of reliever medication more than 4 times a day indicates that the patient's asthma is not well controlled at the current treatment level, and the patient should be considered to have a higher step of asthma severity.

If the patient's long-term therapy was initiated with sustained-release theophylline, a cromone, or a leukotriene modifier, and symptoms persist after 4 weeks of this initial treatment, then inhaled glucocorticosteroids should be introduced. The inhaled glucocorticosteroids may be initiated instead of the other medication, or together with it to allow an overlap period.

Step 3–Moderate Persistent Asthma. Moderate persistent asthma is characterized by daily symptoms over a prolonged time or nocturnal asthma more than once a week. A patient with a pretreatment baseline PEF of more than 60 percent but less than 80 percent of predicted or personal best and PEF variability of 20 to 30 percent has moderate persistent asthma. If the patient's asthma is not controlled on a low dose of inhaled glucocorticosteroids (Step 2), then the asthma should also be considered moderate persistent.

Patients with moderate persistent asthma require controller medication every day to achieve and maintain control of their asthma. The preferred controller treatment for moderate persistent asthma is a combination of an inhaled glucocorticosteroid (200 to 1000 µg of BDP, 400 to 1000 µg of budesonide, 250 to 500 µg of fluticasone, or equivalent, divided over 2 dosings per day), and a long-acting inhaled β_2-agonist twice daily (Evidence A). If a patient's asthma is not controlled on a low dose of inhaled glucocorticosteroid (up to 500 µg of beclomethasone or equivalent), then regular treatment with a long-acting inhaled β_2-agonist should be added. If this is still not sufficient then the dose of inhaled glucocorticosteroid should be increased. A fixed combination inhaler containing a glucocorticosteroid and a long-acting β_2-agonist is a convenient way to deliver this medication. Use of a spacer device to deliver the inhaled glucocorticosteroid is recommended to reduce oropharyngeal side effects and systemic absorption.

Although combination therapy of glucocorticosteroid and a long-acting inhaled β_2-agonist is most effective and is the preferred option (**Evidence A**), alternative add-on therapies include the following (in increasing order of cost):

- Sustained-release theophylline. This is a less expensive option, but is also less effective than a long-acting inhaled β_2-agonist. Serum theophylline concentrations should be monitored, with a general therapeutic range of 5 to 15 µg per ml.

- Long-acting oral β_2-agonist. This option may be as effective as a long-acting inhaled β_2-agonist, although the risk of side effects is greater.

- Leukotriene modifier. This option is less effective than a long-acting inhaled β_2-agonist.

An alternative to this combination therapy is a higher dose of inhaled glucocorticosteroid, but adding another class of controller drug is preferable to increasing the inhaled glucocorticosteroid dose.

In addition to regular controller therapy, rapid-acting inhaled β_2-agonists should be available to take as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. An inhaled anticholinergic, short-acting oral β_2-agonist, or short-acting theophylline may be considered instead of the rapid-acting inhaled β_2-agonist, although these alternatives have a slower onset of action and/or a greater risk of side effects. Because of the risk of serious side effects, short-acting theophylline should not be used as a reliever medication if the patient is already on long-term controller therapy with sustained-release theophylline.

Step 4–Severe Persistent Asthma. Patients who have severe persistent asthma experience highly variable, continuous symptoms, and frequent nocturnal symptoms; have limited activities; and experience severe exacerbations in spite of medication. A patient with a pretreatment baseline PEF of less than 60 percent of predicted or personal best and PEF variability greater than 30 percent has severe persistent asthma. Control of asthma as defined earlier may not be possible.

In severe persistent asthma, the goal of therapy is to achieve the best possible results - the least symptoms, the least need for rapid-acting inhaled β_2-agonist, the best PEF, the least circadian (night to day) variation, and the least side effects from medication. Therapy usually requires multiple daily controller medications. Primary therapy includes inhaled glucocorticosteroids at higher doses (> 1000 µg per

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day of BDP or equivalent) plus a long-acting inhaled β_2-agonist twice daily (Evidence A). Better control may sometimes be achieved with 4-times-daily rather than twice-daily inhaled glucocorticosteroids[240,241] (**Evidence A**).

A long-acting inhaled β_2-agonist is preferred as add-on treatment, but alternatives are sustained-release theophylline, leukotriene modifier, or long-acting oral β_2-agonist (**Evidence B**). These medications may also be added to the combination therapy (high-dose inhaled glucocorticosteroid plus long-acting inhaled β_2-agonist). A rapid-acting inhaled β_2-agonist should also be available for use as needed. If needed, long-term oral glucocorticosteroids should be used in the lowest possible dose, and are best given as a single morning dose in order to minimize systemic side effects. When patients are switched from oral glucocorticosteroids to high-dose inhaled glucocorticosteroids, they should be monitored closely for evidence of adrenal insufficiency.

A nebulizer can deliver a higher dose of inhaled glucocorticosteroid (budesonide or FP), but there is little evidence that this results in fewer systemic effects than an equivalent dose of oral glucocorticosteroid[242,243]. In addition, this treatment is relatively expensive and may produce local side effects, such as soreness of the mouth. There is no evidence yet from controlled trials to recommend the use of nebulized glucocorticosteroids in stable asthma in adults.

Steroid-sparing therapies may be considered in patients with severe persistent asthma who have asthma that is controlled with oral glucocorticosteroids but who experience systemic side effects from this treatment (**Evidence B**). Such steroid-sparing therapies include methotrexate, cyclosporin A, and oral gold. These treatments are poorly effective and have side effects that are often more troublesome than those of steroids. They should therefore only be used if there is clear evidence of benefit, and patients on these therapies must be monitored carefully. All patients who require such therapy should be under the care of a specialist. Note that difficult-to-manage asthma may herald a life-threatening underlying disorder such as Churg-Strauss syndrome or other forms of systemic vasculitis[181].

The complexity of a multiple daily medication regimen is often a factor in patient nonadherence, and this in turn complicates control of asthma. Patients with severe persistent asthma may require particularly intensive patient education and referral to appropriate sources of support.

Reduction of Maintenance (Controller) Therapy

Asthma is a variable disorder, and spontaneous and therapy-induced variations in severity occur. Inhaled glucocorticosteroids reduce asthma severity over the long term. Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control. This will help reduce the risk of side effects and enhance patient adherence to the treatment plan. The therapy reduction should be done by gradually reducing the dose of inhaled glucocorticosteroids by approximately 25 percent every 3 months or withdrawing the bronchodilator in subjects on low doses of inhaled glucocorticosteroids. That is, reduction of therapy should follow the reverse order of what has just been described, with close monitoring of symptoms, clinical signs, and, as much as possible, lung function. Reduction of therapy in patients on combination therapy should begin with a reduction in the dose of inhaled glucocortiocosteroid. Once the dose of the glucocortiocosteroid is at 500 μg BDP or equivalent, then withdrawal of the add-on therapy may be considered (**Evidence D**). It is recommended that patients be reviewed at least every 3 months during the reduction phase.

Seasonal Asthma

A patient has seasonal asthma when he or she has asthma symptoms due to seasonal exposure to allergen. This may be intermittent in patients who are otherwise entirely asymptomatic with normal PEF values between seasons, or it may occur as a seasonal worsening of persistent asthma. The severity varies from patient to patient and from season to season. Treatment will vary accordingly but should follow the recommendations for the treatment of persistent asthma. Ideally, treatment should start just before the expected season or upon the first symptoms, and can be stopped at the end of the season when symptoms or lung function abnormalities are no longer present (**Evidence D**).

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PART 4B: ESTABLISH MEDICATION PLANS FOR LONG-TERM ASTHMA MANAGEMENT IN INFANTS AND CHILDREN

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KEY POINTS:

- Childhood and adult asthma share the same underlying pathophysiological mechanisms. However, because of the processes of physical and cognitive growth and development, the effects, and adverse effects, of asthma and asthma treatments in children differ from those in adults.
- Many asthma medications (e.g., glucocorticosteroids, β_2-agonists, theophylline) are metabolized faster in children than in adults, and young children tend to metabolize drugs faster than older children.
- Therapy should be selected on the basis of the severity of asthma in the individual patient, the availability of antiasthma medications, the characteristics of the health care system, and the individual patient's social, family, and economic circumstances.
- Inhaled glucocorticosteroids are at present the most effective controller medications and are therefore recommended for persistent asthma at any step of severity. Long-term treatment with inhaled glucocorticosteroids markedly reduces the frequency and severity of exacerbations.
- Long-term treatment with inhaled glucocorticosteroids has not been shown to be associated with any increase in osteoporosis or bone fracture. Studies including a total of over 3,500 children treated for mean periods of 1 to 13 years have found no sustained adverse effect of inhaled glucocorticosteroids on growth.
- Rapid-acting inhaled β_2-agonists are the most effective reliever therapy in asthma, and this class of drugs has been the mainstay of asthma treatment in children for many years. These drugs are the most effective bronchodilators available and are therefore the treatment of choice for acute asthma symptoms.
- Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

Childhood and adult asthma share the same underlying pathophysiological mechanisms. However, because of the processes of physical and cognitive growth and development, the effects, and adverse effects, of asthma and asthma treatments in children differ from those in adults. There are important age-related differences in anatomy, physiology, pathology, and drug metabolism, as well as effects from the unique social, emotional, and developmental characteristics of childhood. Therefore, the diagnosis and management of asthma in children must be considered in its own right, and not merely extrapolated from experience with adults. Because growth and development is a dynamic process, adverse effects may not become evident immediately, but only at a later stage of maturation. Thus, long-term outcome studies are particularly important to determine the possible effects of asthma and its treatments during childhood on skeletal, behavioral, cognitive, sexual, and immune growth, development, and maturation.

Children with asthma normally continue to grow until the age of 18. Within this childhood population it is convenient to make a distinction between *adolescents (puberty-18 years), school children (6 years-puberty), preschool children (1-6 years), and infants (< 1 year)*, as there are clinically important differences between these age groups in patterns of asthma symptoms, medication effects and side effects, and behavioral, cognitive, and social development. However, it may sometimes be more appropriate to collect data over broad age ranges and examine the effect of age as a covariant. In this section, the role in therapy of various drugs is discussed separately for each age group where such information is available. In developing a treatment plan, factors such as the severity of the individual patient's asthma, the benefits, risks, and availability of each treatment, cultural preferences, and the characteristics of the health care system need to be considered. The final choice of treatment should integrate the individual clinician's expertise with the patient's preferences and the best available evidence from systematic, clinically relevant research in children.

THE MEDICATIONS

Medications for the management of pediatric asthma include both controllers and relievers. Controllers are medications taken daily on a long-term basis to achieve and maintain control of asthma. Relievers act quickly to relieve bronchoconstriction and its accompanying acute symptoms such as wheezing, chest tightness, and cough.

Figure 7-6. Choice of Inhaler Device for Children*		
Age Group	**Preferred Device**	**Alternate Device**
Younger than 4 years	Pressurized metered-dose inhaler plus dedicated spacer with face mask	Nebulizer with face mask
4-6 years	Pressurized metered-dose inhaler plus dedicated spacer with mouthpiece	Nebulizer with face mask
Older than 6 years	Dry powder inhaler, or Breath-actuated pressurized metered-dose inhaler, or pressurized metered-dose inhaler with spacer	Nebulizer with mouthpiece

**Based on efficacy of drug delivery, cost effectiveness, safety, and convenience. Additional information about available inhaler devices can be found on www.ginasthma.org.*

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Many asthma medications (e.g., glucocorticosteroids, β_2-agonists, theophylline) are metabolized faster in children than in adults, and young children tend to metabolize drugs faster than older children. Although this rapid metabolism to inactive drug is advantageous from a safety perspective, it also means that when medication is administered orally, higher doses should be given to young children than to adults or older children. In this section, a summary of pharmacokinetic information is provided where such information is available.

Route of Administration

Medications for asthma can be administered via different ways, including inhaled, oral (ingested), and parenteral (subcutaneous, intramuscular, or intravenous). The major advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively to the airways, and systemic side effects are avoided or minimized. Some of the drugs that are effective in asthma can only be used via inhalation because they are not absorbed when given orally (e.g., anticholinergics and cromones). The onset of action of bronchodilators is substantially quicker when they are given via inhalation than when these drugs are administered orally[100,101]. The choice of inhaler device should emphasize the efficacy of drug delivery, cost effectiveness, safety, and convenience[244].

Information about lung dose for a particular drug formulation is seldom available for children. Differences between devices do not alter the potential maximum effect of a given drug, but they do result in different potencies for the same nominal dose of the drug given by different inhalers. If these differences are disregarded, clinically important over- or undertreatment may be seen. Dose recommendations need to be evaluated depending on the device to be used.

The choice of device for maintenance treatment should be related to the class of drug. The actual dose of β_2-agonist administered by inhaler is often greater than necessary, but the potential side effects are minimal. Due to the greater potential for side effects, however, inhaled glucocorticosteroids merit a more careful choice of device to ensure an optimal therapeutic effect with minimal side effects. The differences in first-pass metabolism of different inhaled glucocorticosteroids should also influence the choice of device. A spacer is advised when administering beclomethasone, flunisolide, triamcinolone, or budesonide by pressurized metered-dose inhaler (MDI). A spacer is not required for budesonide delivered from a turbohaler.

For maximum convenience, an inhaler device should be freely portable with no power requirement, and technically simple to operate with minimal maintenance requirements. Simplicity of operation is especially important in the treatment of infants and preschool children, who are often cared for by different people at different times of day (and night). Cooperation and coordination required to use a device should be minimal. Passive cooperation, such as the acceptance of a face mask, can be expected from most preschool children and even infants. Active cooperation, such as performing specific inhalation maneuvers and priming or activating a device, can only be expected in older children.

**"In this chapter recommendations for doses of inhaled glucocorticosteroids are given as "μg/day budesonide or equivalent," because a majority of the scientific literature on the use of these medications in children uses this comparison.*

For infants and preschool children, in whom active cooperation cannot be expected, a pressurized MDI used with a spacer and face mask is the device of choice for maintenance treatment. As cooperation improves, often around the age of 4 to 6 years, the child should be encouraged to use a mouthpiece rather than a face mask to inhale from the spacer. From the age of 6, a dry powder inhaler (DPI) or breath-activated MDI is the device of choice (**Figure 7-6**)[244,245].

Nebulizers are not preferred for maintenance treatment. Current nebulizers are expensive, bulky, time-consuming to use and care for, and require maintenance. Furthermore, a nebulizer provides imprecise drug delivery unless equipped with a dosimeter. In infants and young children when even passive cooperation cannot be achieved, the loose face mask of a jet nebulizer is often more acceptable than the close-fitting face mask of a spacer. However, parents should be advised of the advantages of the MDI with spacer and encouraged to persevere with attempts at its use.

During severe acute asthma, nebulizer treatment is preferred for all infants and most children. Often the child may have a fever, or may be physically exhausted by respiratory distress. This is not the ideal time to expect compliance with treatment requiring active cooperation, nor to promote the advantages of a closely fitted face mask with spacer. For these children, high doses of drugs are used, and the imprecise drug delivery from a nebulizer is of little concern in the short-term.

Controller Medications

Controller medications include inhaled glucocorticosteroids, systemic glucocorticosteroids, leukotriene modifiers, sodium cromoglycate (cromolyn sodium), nedocromil sodium, methylxanthines, long-acting inhaled β_2-agonists, and long-acting oral β_2-agonists. Inhaled glucocorticosteroids are at present the most effective controller medications. The evidence on the effects of ketotifen in children is insufficient to warrant its use.

Inhaled glucocorticosteroids.*

- *Mode of administration*–Inhaled.

- *Pharmacokinetics*–Most of the inhaled glucocorticosteroid deposited in the intrapulmonary airways is absorbed systemically; that deposited in the oropharynx is swallowed and absorbed from the gastrointestinal tract. A much higher proportion of the inhaled dose is deposited in the oropharynx, and a lower proportion in the intrapulmonary airways, in children compared to adults[246]. Children metabolize budesonide about 40 percent faster than adults[247,248]. The pharmacokinetics of other inhaled glucocorticosteroids have not been studied in children.

- *Role in therapy*–Inhaled glucocorticosteroids are the most effective controller therapy, and are therefore recommended treatment for persistent asthma at any step of severity (**Evidence A**). Dose-response studies and dose titration studies in children[249-252] demonstrate marked and rapid clinical improvements in symptoms and lung function at low doses of inhaled glucocorticosteroids (e.g., 100 μg budesonide daily)[250,253,254].

  However, the dose of inhaled glucocorticosteroid required to produce the maximum clinical effect depends on several factors: the outcome measure studied, the duration of administration of the inhaled glucocorticosteroid, the severity of the individual patient's asthma, the drug/inhaler combination used, the age of the patient, and the duration of asthma when treatment is initiated. For example, in patients with mild disease, low doses of inhaled glucocorticosteroids offer full protection against exercise-induced asthma[251], but children with more severe asthma may require four weeks' treatment with 400 μg/day budesonide to achieve a maximum protection against exercise-induced asthma. As a consequence of all these factors, each patient may have her/his own individual dose-response curve. This emphasizes the importance of regular, individual tailoring of the dose. If this is done, the majority of patients with mild to moderate asthma will be optimally controlled on 400 μg or less of budesonide or equivalent daily. As CFCs in MDIs are being replaced by hydrofluoroalkanes (HFAs), the medication insert for dosage of the HFA preparations should be carefully reviewed by the clinician[640].

  School children. Maintenance treatment with inhaled glucocorticosteroids controls asthma symptoms, reduces the frequency of acute exacerbations and the number of hospital admissions, improves quality of life, lung function, and bronchial hyperresponsiveness, and reduces exercise-induced bronchoconstriction in school-age children[2,113,149,255,256] (**Evidence A**).

  Symptom control and improvements in peak expiratory flow rate occur rapidly (after 1 to 2 weeks) at low doses (e.g., 100 μg/day), even in children with moderate to severe asthma[249-251,257], although longer treatment (1 to 3 months) with somewhat higher doses (e.g., 400 μg/day) is required to achieve maximum improvement in airway hyperresponsiveness as assessed by an exercise challenge test[258-260]. When inhaled glucocorticosteroid treatment is discontinued, there is usually a deterioration

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of asthma control and airway hyperresponsiveness to pretreatment levels within weeks to months, though in some patients the effect of the glucocorticosteroid is maintained for much longer[261].

When a child has already developed an exacerbation, a 4-fold increase in the daily dose of inhaled glucocorticosteroid or the introduction of oral glucocorticosteroid treatment have both been found to reduce the severity and duration of the exacerbation[262]. However, in one study a doubling of the inhaled glucocorticosteroid dose did not significantly modify exacerbations that had already developed[263].

Infants and preschool children. Randomized double-blind controlled trials of inhaled glucocorticosteroids in preschool children with asthma have generally shown significant and clinically relevant improvements in health outcomes, including day- and nighttime symptom scores for cough, wheeze, and dyspnea, physical activity, use of rescue treatment, and use of health care resources[264-269] (**Evidence A**). Lung function and airway hyperresponsiveness in wheezy children are also improved[270].

Although inhaled glucocorticosteroids typically reduce the number of asthma exacerbations in infants and preschool children[266,268], they may not completely control the disease in some children. Whether this is due to insufficient patient adherence, poor delivery of medication, insufficient dose of glucocorticosteroid, pharmacogenetic heterogeneity, or a distinct pathology in childhood asthma or in subgroups of wheezy young children needs to be studied.

The clinical benefits of systemic or inhaled glucocorticosteroids for viral-induced wheeze remain controversial. Some randomized double-blind controlled trials found no short- or long-term clinical benefits from the administration of systemic[271-274] or inhaled[275-279] glucocortiosteroids during the acute phase of viral-induced wheeze in previously healthy infants, though some short-term improvements have been reported in other studies[280,281]. A Cochrane review concluded that episodic high-dose inhaled glucocorticosteroids provide a partially effective strategy for the treatment of mild episodic viral-induced wheeze in children, but there is no current evidence to support maintenance low-dose inhaled glucocorticosteroids for the prevention and management of mild viral-induced wheeze[282].

- *Side effects*–The vast majority of studies evaluating the risk of systemic effects of inhaled glucocorticosteroids have been undertaken in children older than 5. Clinically relevant adverse effects should be studied in controlled, long-term clinical trials, using clinically relevant doses in groups of patients with a disease severity and age similar to the groups in which the drugs would normally be prescribed.

Figure 7-7. Summary: Growth and Asthma

- No controlled studies have reported any statistically or clinically significant adverse effect on growth of 100 to 200 μg per day of inhaled glucocorticosteroid[342,343].
- Growth retardation may be seen with all inhaled glucocorticosteroids when a sufficiently high dose is administered without any dose adjustment for disease severity[113,331].
- Growth retardation in both short- and medium-term studies is dose dependent[337].
- Important differences seem to exist between the growth-retarding effects of various inhaled glucocorticosteroids and inhalers[334-337].
- Different age groups seem to differ in susceptibility to the growth-retarding effects of inhaled glucocorticosteroids; children aged 4 to 10 are more susceptible than adolescents[308,338].
- Children with asthma treated with inhaled glucocorticosteroids have consistently been found to attain normal final adult height[308-310].
- Uncontrolled or severe asthma itself seems to adversely affect growth and final adult height[308,310,315,356].
- Glucocorticosteroid-induced changes in growth rate during the first year of treatment appear to be temporary and do not predict adult height[95,113,308].

Bones. The only potential clinically relevant adverse effects of inhaled glucocorticosteroids on bones are osteoporosis and fracture. Biochemical markers of bone metabolism (bone formation and degradation) and bone mineral density are the most commonly used surrogate markers for osteoporosis and risk of fracture in clinical trials. There have been no reports or studies showing an increased incidence of fractures in children treated with inhaled glucocorticosteroids. Several cross-sectional and longitudinal studies including a total of more than 700 patients found no adverse effects of long-term inhaled glucocorticosteroid treatment (mean daily dose about 450 μg) on bone mineral density[113,283-290] (**Evidence A**). Several short-term studies involving patients with mild asthma have reported that daily glucocorticosteroid doses of 400 μg or less have no effect on bone metabolism, but high doses (800 μg daily) lead to a reduction in both bone formation and degradation[283,291-295] (**Evidence A**).

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In adults the skeletal mass is decreasing over time, while in children it is increasing, with peak bone mass and density reached in early adulthood. Thus, maximal peak bone mass or density is probably the most clinically relevant outcome measure for assessing the influence of glucocorticosteroids on bones in children. Several confounding factors must be considered when the effects of glucocorticosteroids on bone metabolism in children are assessed. In children, the rate of bone modeling or turnover is much higher than in adults. Some chronic diseases have been reported to be associated with reduced peak bone mass in children[283]. Delayed puberty is also associated with a significantly lower peak bone mass/density[296,297], and delayed puberty is seen in many children with asthma and atopy, regardless of treatment. Other factors such as nutrition (including calcium intake), heredity (both parents), poor asthma control, and level of physical activity appear to have profound effects on peak bone mass formation[298-306]. Finally, children show a remarkable ability to repair glucocorticosteroid-induced bone loss. In one study, children under 3 years old with synacten-induced compression fractures of the spine had normal spinal x rays 5 to 10 years later[307]. Such repair is not seen in adults.

Growth. Important findings of studies on inhaled glucocorticosteroids and growth are summarized in **Figure 7-7**. Children with asthma treated with inhaled glucocorticosteroids have consistently been found to attain normal final adult height[308-310]. Studies including a total of more than 3,500 children treated for mean periods of 1 to 13 years found no sustained adverse effect of inhaled glucocorticosteroid treatment on growth[149,308,311-332]. A meta-analysis of 21 studies including a total of 810 patients compared attained height with expected height of children with asthma treated with inhaled or oral glucocorticosteroids[333]. Children treated with inhaled glucocorticosteroids attained normal height, while a significant–though weak–retardation of growth was found in children receiving oral glucocorticosteroids. Furthermore, there was no statistical retardation evidence that inhaled glucocorticosteroid therapy was associated with growth retardation, even at high doses or with long-term therapy.

However, inhaled glucocorticosteroid therapy can affect the growth rate of children with asthma, producing a retardation of growth when high doses are administered[113,331]. This growth retardation occurs with all inhaled glucocorticosteroids, although important differences seem to exist between the growth-retarding effects of various inhaled glucocorticosteroids and inhaler devices[334-337]. Children's susceptibility to the growth-retarding effects of inhaled glucocorticosteroids also depends on their age; children 4 to 10 years old are more susceptible than adolescents[308,338]. In addition, several studies have suggested that the systemic bioavailability and systemic effects of an inhaled drug are more pronounced in patients with mild asthma than in patients with more severe disease[339-341], probably due to differences in deposition pattern caused by a smaller airway diameter in more severe disease. This means that a given dose of inhaled glucocorticosteroid may be more likely to adversely affect the growth of a child with mild asthma than that of a child with more severe disease.

Growth retardation in both short- and medium-term studies of inhaled glucocorticosteroid treatment is dose dependent[337]. No controlled studies have reported any statistically or clinically significant adverse effect on growth of inhaled glucocorticosteroid doses of 100 to 200 μg per day[342,343]. In addition, glucocorticosteroid-induced changes in growth rate during the first year of treatment appear to be temporary and do not predict adult height[95,113,308].

Knemometry, a method that captures short-term changes in linear growth of the lower leg, may be a valuable adjunct or alternative to traditional growth studies because it facilitates controlled designs. Importantly, knemometry is not a measure of statural growth, but it is a very sensitive marker of systemic glucocorticosteroid activity. Thus far, all placebo-controlled, double-blind knemometry studies assessing the effects of inhaled glucocorticosteroids on lower leg growth have been undertaken in children with mild asthma who have not required continuous treatment[344-349]. These studies show that, in both school children and preschool children, the effect of inhaled glucocorticosteroids on lower leg growth rate is dose dependent. Low doses of inhaled glucocorticosteroid (200 μg per day or less) are not associated with any detectable effects. As in statural growth studies, growth inhibition dose-response curves in knemometry studies seem to differ between the various inhaled glucocorticosteroids.

When assessing the effects of inhaled glucocorticosteroids on growth in children with asthma, it is important to account for potential confounding factors. For example, many children with asthma experience a reduction in growth rate, most often toward the end of the first decade of life[313,314,350-355]. This reduced growth rate continues into the mid-teens and is associated with a delay in the onset of puberty. The pre-pubertal deceleration of growth rate resembles growth retardation. However, the delay in pubertal growth is also associated with a delay in skeletal maturation so that the child's bone age corresponds to his or her height. Ultimately, adult height is not decreased, although it is reached at a later than normal

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age[313,314,350-355]. Studies also suggest that poorly controlled asthma may itself adversely affect growth[308,312,315]. In one study, a daily inhaled glucocorticosteroid dose of 400 μg produced growth impairment, but this effect was smaller than the effect of low socioeconomic status on growth of children with severe asthma[356].

Although the influence of inhaled glucocorticosteroids on the growth of children with asthma has been studied extensively in school children, more research is necessary. Many studies conducted to date have had design flaws, and several have been retrospective or uncontrolled. Others have been conducted under conditions that are very different from the day-to-day treatment situation. Moreover, few data are available on the effect of inhaled glucocorticosteroid treatment on growth in infants and young children. These groups' rapid growth rates and somewhat different metabolism distinguish them from older children and may make these younger children more vulnerable to the adverse effects of drugs and/or disease. Therefore, the findings on the safety of inhaled glucocorticosteroids in school children or adults cannot be uncritically extrapolated to infants and preschool children. Studies should be undertaken to specifically address the effect of inhaled glucocorticosteroids on the rapid growth rates during the first 2 to 3 years of life, which is mainly influenced by factors similar to those controlling fetal growth, as well as growth from age 3 onward, which is mainly controlled by the endocrine system, particularly growth hormone[357].

Hypothalamic-pituitary-adrenal (HPA) axis. Adrenal suppression is the most extensively studied systemic effect of inhaled glucocorticosteroids, and its occurrence and magnitude have been examined in detail. Though differences exist between the various inhaled glucocorticosteroids and inhaler devices, treatment with inhaled glucocorticosteroid doses less than 400 μg daily is normally not associated with any significant suppression of the HPA axis in children[113,358,359]. At higher doses, small changes in HPA-axis function can be detected with sensitive methods. The clinical relevance of these findings needs further study.

Lung development. The observation that systemic glucocorticosteroids given during the first 2 weeks after birth (but not after this time) adversely affect alveolar development in rats[360] has raised fears that inhaled glucocorticosteroids may impair normal alveolar development. However, there are no human data on this subject. Thus, in situations where inhaled glucocorticosteroids have a definite positive clinical effect, concerns about their possible adverse effects on lung growth should not be a reason to withhold this treatment[361]. More studies of inhaled glucocorticosteroids and lung development are needed in infants.

Cataracts. Studies evaluating the risk of posterior subcapsular cataracts in more than 800 children receiving long-term (1 to 15 years) treatment with inhaled glucocorticosteroids have found that this treatment is not associated with an increased occurrence of cataract development[113,129,131,362].

Central nervous system effects. Published evidence of effects of inhaled glucocorticosteroids on the central nervous system is limited to isolated case reports in a total of 9 patients (3 adults and 6 children)[363-366] who exhibited hyperactive behavior, aggressiveness, insomnia, uninhibited behavior, and impaired concentration with this treatment. All patients returned to normal after the inhaled glucocorticosteroid was discontinued.

Oral candidiasis. Clinical thrush is seldom a problem in children treated with inhaled or systemic glucocorticosteroids. The occurrence of this side effect seems to be related to concomitant use of antibiotics, dose, dose frequency, and inhaler device. Spacers seem to reduce the incidence of oral candidiasis[367-370]. Mouth rinsing has not been reported to be beneficial. In any case, oral candidiasis is easily treated and rarely necessitates withdrawal of inhaled glucocorticosteroid treatment.

Dental side effects. There is no evidence that inhaled glucocorticosteroid treatment is associated with increased incidence of caries. However, an increased level of dental erosion has been reported in children with asthma[371-373]. This may be associated with a reduction in oral pH, which is mainly seen after inhalation of β_2-agonists[374].

Bruising and hoarseness. Although bruising and hoarseness have been reported to occur at increased frequency in adults treated with high doses of inhaled glucocorticosteroids, few studies have assessed the occurrence of these side effects in children. One study found that 178 children treated with inhaled budesonide at an average daily dose of about 500 μg for 3 to 6 years did not have an increased occurrence of bruising, tendency to bruise, hoarseness, or other noticeable voice change[129]. Hoarseness is reversible after withdrawal of inhaled glucocorticosteroid treatment, but unlike thrush it tends to recur when the treatment is reintroduced. Spacers do not appear to protect against dysphonia.

Other local side effects. There is no evidence of an increased incidence of lower respiratory tract infections, including tuberculosis, with chronic use of inhaled

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glucocorticosteroids. Although local skin changes around the mouth may occur in children treated with nebulized glucocorticosteroids inhaled through a face mask, there is no evidence that a similar process occurs in the airways when glucocorticosteroids are inhaled.

Systemic glucocorticosteroids.

- *Mode of administration*–Oral (ingested) or parenteral.

- *Role in therapy*–The use of oral glucocorticosteroids in the treatment of children with asthma is limited to acute exacerbations, whether viral-induced[280,375] or otherwise[376,377]. However, some studies have been unable to detect any effect of systemic glucocorticosteroids on exacerbations of asthma in children[378,379]. There is no evidence that systemic glucocorticosteroids cause reactivation of tuberculosis in children who have a strongly positive tuberculin reaction[380].

Leukotriene modifiers.

Leukotriene modifiers are a new class of anti-asthma drugs that include, for the treatment of asthma in children, the cysteinyl leukotriene 1 (CysLT1) receptor antagonists montelukast, pranlukast, and zafirlukast. The 5-lipoxygenase inhibitor zileuton has been approved in some countries for use in adults, but is not available for children.

- *Mode of administration*–Oral.

- *Role in therapy*–Leukotriene receptor antagonists may be used as add-on treatment for moderate persistent and severe persistent asthma in children whose asthma is insufficiently controlled by a low dose of inhaled glucocorticosteroids. Leukotriene receptor antagonists have not been studied as monotherapy in children with mild persistent asthma so there are no data to support their use. However, moderate improvements in lung function (in children 6 and older) and in asthma control (in children 2 and older) have been demonstrated with leukotriene receptor antagonist monotherapy in patients with severe disease[381-383] and in patients with moderate disease [384] (**Evidence B**). By extrapolation, this class of drug may be an alternative for monotherapy in some patients with mild persistent disease (**Evidence D**).

  Because the clinical effect of leukotriene modifiers begins a few hours to days after they are first administered, they are considered controller, not reliever, medications. Dose recommendations for children are based on pharmacokinetic studies; the optimal dosing is therefore uncertain.

Montelukast, approved for the treatment of asthma in children 2 years and older in some countries, is administered once daily[385]. The dosage (5 mg) yields a pharmacokinetic profile (single-dose area under the plasma concentration-time curve) in children comparable to that achieved with the 10-mg tablet in adults[386]. There is no difference in bioavailability in children compared to adults, and food does not appear to have a clinically important influence on the bioavailability of this medication.

Zafirlukast, approved for treatment of asthma in children 7 years and older in some countries, is administered twice daily. One study supports the use of a 10-mg BID (twice-daily) dose for long-term treatment of mild to moderate asthma in children[381]. The bioavailability of zafirlukast is reduced by up to 40 percent when the drug is taken with food. Zafirlukast is metabolized by the liver, and therapeutic concentrations of the drug inhibit the hepatic cytochrome P450. This effect creates a risk of drug interactions. Transient elevations of liver enzymes have also been reported[387,388].

Pranlukast is approved for treatment in children 2 years or older in some countries.

School children. Zafirlukast appears to be modestly effective in improving lung function and asthma control in children 12 years and older with moderate to severe asthma[389-391](**Evidence A**). Studies so far have failed to find a plateau of effects at the highest dose used, which suggests that higher doses may be more effective, although such doses are prohibited by the risk of side effects. In double-blind randomized controlled trials of children aged 6 to 14 with asthma[381,392], treatment with zafirlukast reduced nocturnal awakenings and provided 20 to 30 percent protection against exercise-induced bronchoconstriction 4 hours after the medication was taken.

Montelukast was compared to placebo in 336 children aged 6 to 14 with moderate to severe asthma[383]. Approximately one-third of the children in both groups received maintenance therapy with a constant dose of inhaled glucocorticosteroids during the study. The primary outcome measure, FEV_1, increased significantly, and the daily use of inhaled β_2-agonists decreased significantly, in the children who took montelukast compared to those who received the placebo. Montelukast appears to provide less protection against exercise-induced asthma than 400 μg budesonide per day[393].

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Preschool children. Montelukast, compared to placebo, provides significant therapeutic benefit, i.e. improvement in asthma signs and symptoms, for children, ages 2-5, with asthma[641] (**Evidence B**).

Cromones: sodium cromoglycate and nedocromil sodium.

- *Mode of administration*–Inhaled.

- *Role in therapy*–The role of sodium cromoglycate or nedocromil sodium in the long-term treatment of pediatric asthma is limited, particularly in preschool children. A clinical trial in children indicated that nedocromil sodium was associated with less prednisone use and fewer urgent care visits, but by all other measures was no different from placebo[113].

  School children. Sodium cromoglycate is less effective than inhaled glucocorticosteroids[255,285,395-400] with respect to symptoms, lung function, exercise-induced asthma, and airway hyperresponsiveness. Although some early placebo-controlled clinical trials found that sodium cromoglycate reduced symptoms, improved lung function, and decreased the need for rescue bronchodilators[401-403], a meta-analysis of 22 controlled clinical trials concluded that long-term treatment with sodium cromoglycate is not significantly better than placebo for management of asthma in children[404] (**Evidence A**).

  A Cochrane review concluded that nedocromil sodium used before exercise appears to reduce the severity and duration of exercise-induced bronchoconstriction[405]. A long-term placebo-controlled trial found a significant, albeit marginal, effect of nedocromil sodium (8 mg per day) on exacerbations, but all other outcome parameters were unaffected[113].

  Preschool children and infants. The clinical documentation on the use of sodium cromoglycate in preschool children is sparse, and there are no reports on infants. The available randomized double-blind controlled trials have yielded conflicting results. Several studies have been unable to demonstrate any effect of 20 mg nebulized sodium cromoglycate given 3 to 4 times daily on health outcomes[406-408] or lung function[409], while other studies have indicated that sodium cromoglycate has a significant effect[410-412]–of the same magnitude as theophylline[413,414]–on these parameters.

- *Side effects*–Cough, throat irritation, and bronchoconstriction are problems that occur in a small proportion of patients treated with sodium cromoglycate, and the hypotonicity of the nebulized solution may cause bronchoconstriction[415]. A bad taste, headache, and nausea are the most common side effects of nedocromil[350].

Methylxanthines.

The role of theophylline in the long-term treatment of children with asthma is limited, but the low cost of this treatment may justify more frequent use in some countries.

- *Mode of administration*–Oral.

- *Pharmacokinetics*–Because children metabolize theophylline very rapidly, frequent dosing (4 to 6 times a day) is required when plain tablets are used for long-term treatment. Therefore, sustained-release products are preferable for maintenance therapy, and they enable twice-daily dosing in most children.

  It is important to note that concomitant intake of food may change the absorption characteristics of many sustained-release theophylline products in an unpredictable way. Reduced absorption, dose dumping, and marked variations in absorption profiles may be seen[416], complicating the task of ensuring safe, effective treatment. Because the effect of concomitant food intake is quite unpredictable, only sustained-release products that have been shown to be well absorbed in combination with food should be used for maintenance treatment. In this respect, it is important to evaluate both mean and individual absorption profiles; the variation in absorption with food seems to be more pronounced in children than in adults[416]. Sustained-release theophylline products with reliable absorption profiles and complete bioavailability with food have been developed[417].

  Dose-response studies with theophylline in a limited number of children with asthma have mainly assessed bronchodilation[418,419] and protection against exercise-induced asthma[420,421]. Dose recommendations have been based on lean body weight and aim at plasma theophylline levels between 55 and 110 μmol/l, which may be required to achieve maximum bronchodilatory effect in children with acute wheeze. However, there is still considerable difference in opinion regarding the optimum plasma levels that should be obtained. Studies in adults and some studies in children suggest that lower levels may be sufficient to achieve a measurable effect on other outcomes in day-to-day management. For example, theophylline's anti-inflammatory effects may be seen at about one-half of the plasma levels required for maximum bronchodilatory effect[20]. Therefore, it seems rational to individualize the dose on the basis of the clinical effect rather than aiming at specific plasma levels, which are more useful in preventing intoxication. At

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present, good studies of therapy with low-dose theophylline in children are lacking.

Within each age group in children, interindividual variations in theophylline half-life may be up to 10-fold. Other drugs may affect theophylline metabolism, such as β_2-agonists (which increase clearance so that higher doses are required), as may viral infections (which reduce clearance). Therefore, the theophylline dose must always be individualized, and if high doses are used plasma theophylline levels must be measured two hours before administration of the next dose. When dose adjustments are made on the basis of serum theophylline concentrations, theophylline often shows dose-dependent kinetics so that, on average, the percent change in serum concentration is about 50 percent greater than the percent change in dose[422].

- *Role in therapy*–Sustained-release theophylline may be used as an alternative to inhaled glucocorticosteroids for maintenance therapy in mild persistent asthma and as add-on therapy with a low dose of inhaled glucocorticosteroids.

School children. Theophylline is significantly more effective than placebo at controlling symptoms and improving lung function, even at doses below the normally recommended therapeutic range[423-425] (**Evidence A**). Furthermore, a single dose of 15 mg/kg of sustained-release theophylline taken before bedtime is effective at preventing nocturnal asthma symptoms[425]. Long-term maintenance treatment offers a marginal protective effect against exercise-induced asthma[420,426]. Theophylline and oral β_2-agonists seem to have an additive effect on control of asthma[427,428], although it remains unclear whether the combination has any clear clinical advantage compared to either drug used alone.

Preschool children. There are indications that theophylline treatment has some beneficial clinical effects, such as bronchodilation, in this age group[429,430] (**Evidence C**). However, further double-blind studies are needed to assess the optimal dose and preference of theophylline relative to other treatments in young children.

Infants. The effect of long-term theophylline treatment has not been assessed in double-blind controlled studies in infants with wheeze.

- *Side effects*–Theophylline has a narrow therapeutic window and potentially lethal side effects when overdosed[431-433]. The most common side effects are anorexia, nausea, vomiting, and headache[431,432,434]. Mild central nervous stimulation, palpitations, tachycardia, arrhythmias, abdominal pain, diarrhea, and, rarely, gastric bleeding may also occur. When maintenance therapy with theophylline is begun, the initial dosage should be low because side effects seem to occur much more frequently if the initial dose is high. Some patients do not tolerate theophylline, regardless of what precautions are taken.

Theophylline has been reported to induce changes in mood and personality and to impair school performance in children[435,436], although these findings were not reproduced in another study[437].

Long-acting inhaled β_2-agonists.

- *Mode of administration*–Inhaled.

- *Role in therapy*–In children with asthma long-acting inhaled β_2-agonists are primarily used as add-on therapy in combination with inhaled glucocorticosteroids, either as maintenance treatment or as single-dose therapy before vigorous exercise. Inhaled formoterol has a rapid onset of action (3 minutes) and a maximum effect at 30 to 60 minutes after inhalation, much like the short-acting β_2-agonist salbutamol[438,439]. Inhaled salmeterol has a relatively slow onset of action, with a significant effect reported 10 to 20 minutes after inhalation of a single 50-μg dose[440], and an effect comparable to that of salbutamol after 30 minutes[441]. Because of its slow onset of action, salmeterol should not be used to treat acute asthma symptoms, including exercise-induced bronchoconstriction, or to treat patients with rapidly deteriorating asthma. Patients who take salmeterol should also have a short-acting β_2-agonist available at all times for the treatment of breakthrough symptoms.

Although long-acting inhaled β_2-agonists may be useful in some children with asthma, in contrast to the situation with adults there is insufficient documentation of the effectiveness of these drugs to support a general recommendation for their use in children. Randomized double-blind controlled trials of long-acting inhaled β_2-agonists as add-on treatment in children with poorly controlled asthma have so far yielded conflicting results[442-444]. Most of these trials have shown a statistically significant, albeit small, improvement in lung function[642], but for other outcomes, such as symptoms and exacerbations, the effect of these drugs is marginal and less than that seen in adults.

The recommended dose of formoterol for children (older than 6 years) is 4.5 μg twice daily, although individual patient responses to the medication can vary considerably and some patients may benefit from doses above the

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usual recommended level. The recommended dose of salmeterol for children (older than 4 years) is 50 μg twice daily. Some children achieve full bronchoprotection for more than 12 hours after a single dose of inhaled salmeterol or formoterol, although a considerable heterogeneity in the duration and magnitude of the response may be seen in different individuals[445].

- *Side effects*–Long-acting inhaled β_2-agonists are well tolerated in children, even after long-term use, with a side-effect profile comparable to that of short-acting β_2-agonists.

Long-acting oral β_2-agonists.

Long acting oral β_2-agonists include slow-release formulations of salbutamol or terbutaline and bambuterol, a prodrug that is converted to terbutaline in the body.

- *Mode of administration*–Oral (ingested).

- *Mechanisms of action*–Long-acting oral β_2-agonists (sympathomimetics) are bronchodilators. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils.

- *Role in therapy*–Long-acting oral β_2-agonists may be helpful in controlling nocturnal symptoms of asthma. They may be used as an addition to inhaled glucocorticosteroids when standard doses do not sufficiently control nocturnal symptoms[446,447].

- *Side effects*–Possible side effects include cardiovascular stimulation, anxiety, and skeletal muscle tremor. Adverse cardiovascular reactions may also occur with the combination of oral β_2-agonists and theophylline.

Reliever Medications

β_2-agonists.

Rapid-acting inhaled β_2-agonists have been the mainstay of asthma treatment in children for many years. These drugs are by far the most effective bronchodilators available and therefore the preferred treatment for acute asthma (**Evidence A**).

- *Mode of administration*–Inhaled, oral, and intravenous.

- *Role in therapy*–Rapid-acting β_2-agonists should preferably be given by inhalation since this allows bronchodilation to be achieved more rapidly, at a lower dose, and with fewer side effects than occurs with either oral or intravenous administration[447,448]. Furthermore, inhalation offers significant protection against exercise-induced asthma[449], which is not seen after systemic administration[450]. Generally quite low doses (25 percent of the normal dose in the inhaler) produce marked bronchodilation, while higher doses are required to protect effectively against various challenges[258].

Short-acting oral β_2-agonists have low systemic absorption and a high first-pass metabolism in the wall of the gastrointestinal tract and in the liver. Thus, the systemic bioavailability of these drugs after oral dosing is only about 10 to 15 percent when plain tablets are used. This figure is around 30 percent lower after administration of a slow-release product. Therefore, somewhat higher doses should be used when β_2-agonist therapy is changed from plain to slow-release tablets. Concomitant intake of food further reduces gastrointestinal bioavailability by about one-third[451]. Clearance of β_2-agonists is higher in children than in adults[452,453].

There is a significant correlation between plasma drug levels and bronchodilatory effect after systemic administration of β_2-agonists in children, although considerable inter-individual variations in this relationship exist[454,455]. Therefore, effective therapy cannot be assured by standardized dosing. Rather, dosing should be individualized, with monitoring of the therapeutic response and the occurrence of side effects to determine the proper dose[450]. A rational approach is to start oral treatment at around 0.15 mg/kg/day and then gradually increase the dose until sufficient clinical effect or systemic side effects are seen. Oral doses of about 0.5 mg/kg/day are often required to produce optimal clinical effects[450,455].

School children. Rapid-acting inhaled β_2-agonists have repeatedly proven superior to other drugs in the treatment of acute episodes of wheeze[456,457] (**Evidence A**). Furthermore, premedication with a single dose of these drugs effectively inhibits exercise-induced asthma[449,458]. The normal duration of bronchodilation produced by a single dose of rapid-acting inhaled β_2-agonist in children is 1 to 5 hours[459], although the duration of action of these drugs depends upon the outcome measure assessed. For example, the duration of protection against exercise-induced asthma is markedly shorter than the duration of bronchodilation[4,9].

Maintenance treatment with a short-acting oral β_2-agonist does not protect effectively against exercise-induced asthma[450], though it improves symptoms and peak expiratory flow rates and protects against nocturnal

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asthma, particularly when a slow-release product is used[427,450]. A combination of theophylline and short-acting oral β_2-agonist has been found to be more effective than either drug used alone[427], though it is not known whether the combination is preferable to single-drug therapy when the single drug is used in optimal doses.

Preschool children and infants. Bronchodilation[460-470] and bronchoprotection[471,472] with rapid-acting inhaled β_2-agonists have been demonstrated by objective measurements in preschool children. In infants, early studies failed to find any bronchodilator response to nebulized short-acting β_2-agonist[376,473-475], which led to the belief that short-acting β_2-agonists are ineffective in this age group. In these early studies a fall in transcutaneous oxygen was interpreted as a lack of bronchodilator response[476], although alternative explanations for this effect have since been presented, including acidity of the nebulizer solution[477] and ventilation-perfusion mismatch. Other studies have reported an increase in transcutaneous oxygen[478]. Moreover, more recent double-blind placebo-controlled studies have demonstrated significant bronchodilation[460-465], protection against bronchoconstrictor agents[471,472], and clinical improvement in infants treated with rapid-acting inhaled β_2-agonist either alone or in combination with glucocorticosteroids[280]. The reason for these inconsistent results is not clear, although the various studies have differed with respect to dose, inhaler device (spacer, nebulizer), baseline lung function, duration of symptoms, and method of lung function measurement, and the inconsistencies are only seen in bronchodilator effects. All studies find that short-acting β_2-agonists provide significant protection against bronchoconstriction induced by various challenges. Thus, it seems that infants have functional beta-adrenergic receptors from birth, and that stimulation of these receptors can produce the same effects as in older children.

- *Side effects*–As in adults, skeletal muscle tremor, headache, palpitations, and some agitation are the most common complaints in children when high doses of β_2-agonists are used. After systemic administration of these drugs, these complaints seem to occur when the top of the bronchodilatory dose-response curve is reached[454]. Side effects seem to disappear with continued use of the medication[479,480].

Anticholinergic agents.

- *Mode of administration*–Inhaled.

- *Pharmacokinetics*–Virtually all pharmacokinetic data in children concern ipratropium bromide delivered with a nebulizer, although it would be expected that the optimal dose from an MDI would be lower[481]. Various studies have found that increasing the dose above 250 μg provides no extra bronchodilation[482] or protection against exercise-induced asthma[483] or cold air hyperventilation. No formal dose-response studies have been performed in infants, but a dose of 25 μg/kg has produced beneficial effects in one study[461]. The optimal frequency of dosing remains unknown.

- *Role in therapy*–Anticholinergics have a limited role in the management of asthma in children.

  School children. The bronchodilator response to ipratropium bromide seems to be quite variable in school children, but is always less than the response to an inhaled β_2-agonist[484]. Furthermore, there is no benefit from adding the drug to regular β_2-agonist treatment for maintenance therapy[485,486].

  Preschool children. As in school children, bronchodilation is seen in preschool children after inhalation of a single dose of ipratropium bromide[487,488]. However, in one study regular treatment with ipratropium bromide (250 μg 3 times a day) was no better than placebo in the control of asthma in preschool children, and a recent meta-analysis concluded that the effect in children was marginal[488].

  Infants. A Cochrane review concluded that there is not enough evidence to support the uncritical use of anti-cholinergic agents for treatment of wheezing in infants, although patients using it at home were able to identify some benefits[489].

- *Side effects*–Paradoxical bronchoconstriction after inhalation and dryness of the mouth may be a problem in some patients[490,491]. Some of these problems reported in the past seemed to be due to benzalkonium chloride, which has now been removed from the nebulizer solution. No other important side effects are associated with anticholinergic treatment.

Alternative and Complementary Methods of Healing

See the section on management of asthma in adults.

A STEPWISE APPROACH TO PHARMACOLOGIC THERAPY

The stepwise treatment paradigm emphasizes that asthma at any age, even from early childhood, is a disease in which chronic airway inflammation underlies recurrent symptoms. Evidence suggests that any asthma more severe than intermittent is more effectively controlled by interventions

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that suppress and reverse this inflammation than by those that only treat the episodic bronchoconstriction and related symptoms.

The selection of pharmacologic treatment options is made on the basis of an individual patient's asthma severity, the patient's current treatment, the pharmacological properties and availability of various antiasthma treatments, and economic considerations. Because asthma is a dynamic as well as a chronic condition, medication plans must accommodate variability among patients as well as the variability of an individual patient's disease over time. An essential aspect of any treatment plan is monitoring of the effect of the treatment (including measurements of lung function and symptoms) and adaptation of the treatment to the variability of the asthma.

An approach to pharmacologic therapy in which treatment is correlated with asthma severity permits this flexibility. The classification of asthma severity should be made by means of evaluating the patient's symptoms, medical history, and current treatment, a clinical examination, and measurements of lung function where possible (**Figure 5-6** and **Figure 5-7**).

An appropriate approach to asthma therapy recommends that the number (type), dose, and eventually frequency of medications be increased with increasing asthma severity. The aim is to accomplish the goals of therapy with the least possible medication. In developing an asthma management plan, the health care professional must judge whether to give maximum treatment initially–which may involve a burst or cycle of oral glucocorticosteroids in order to achieve control of the patient's asthma as quickly as possible–and then decrease the medication, or to start with treatment judged appropriate for the severity of the patient's asthma and increase the treatment gradually if necessary. Once control of asthma is sustained for 3 months, a reduction in therapy can be carefully considered. This reduction in therapy is needed to identify the minimum therapy required to maintain control.

Figure 7-8 presents the stepwise approach to therapy to achieve and maintain control of asthma in children. The step system for classifying asthma severity takes into account the treatment that the patient is currently receiving (**Figure 5-7**). **Figure 7-8** presents all therapies that can be recommended for treating each step of asthma severity. Guidance for selecting among these available modalities is provided in the text. The cost of the medication is an obvious factor in determining the choice of treatment. Cost of treatment varies from country to country and is only one of the factors that contribute to the total cost of a disorder such as asthma.

How To Achieve and Maintain Control of Asthma

This section describes the therapy appropriate for different steps of asthma severity. The presence of one or more features of clinical severity places a patient at the respective step (**Figure 5-6**). The current treatment should be included in the assessment of severity (**Figure 5-7**).

In the stepwise approach to therapy, progression to the next step is indicated when control is not achieved or is lost with the current treatment, and there is assurance the patient is using medication correctly. The frequent (e.g., more than 3 times a week) presence of such symptoms as cough, wheezing, and dyspnea, and the increased use of rapid-acting bronchodilators, may indicate inadequate control of asthma. The presence of symptoms at night or early in the morning is an especially useful indicator. Measurement of PEF and its variability is helpful in the initial assessment of asthma severity and in monitoring the initial treatment, assessing changes in severity, and preparing for a reduction in therapy.

The treatments suggested for each step below are guidelines only; evidence levels assigned are based on references provided in the previous text. Specific medication plans should be tailored by the health care professional depending on the availability of antiasthma medication, the conditions of the health care system, and individual patient circumstances. Repeated use of reliever medication more than 4 times a day indicates that the patient's asthma is not well controlled, and the intensity of treatment should be increased.

School children

Step 1–Intermittent Asthma. **Rapid-acting inhaled β_2-agonists may be used as reliever medications (Evidence A).** However, in some cases "as-needed" treatment may be insufficient, such as in physically active children who do not normally exercise on a planned schedule. Regular controller treatment (particularly inhaled glucocorticosteroids) may be considered in such children (**Evidence D**).

Step 2–Mild Persistent Asthma. **Inhaled glucocorticosteroids (< 100-400 μg budesonide or equivalent per day) are recommended for maintenance treatment (Evidence A).** Alternative controller medications (listed according to increasing cost of the medication) are sustained-release theophylline (**Evidence C**) and cromones (**Evidence C**). Monotherapy with drugs other than glucocorticosteroids leaves the underlying inflammatory process in asthma less controlled. Studies of monotherapy

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Figure 7-8. Recommended Medications by Level of Severity for Children Younger Than 5 Years of Age

All Levels: In addition to regular daily controller therapy, rapid-acting inhaled β_2-agonist* should be taken as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Patient education is essential at every level.

Level of Severity**	Daily Controller Medications	Other Treatment Options***
Step 1 Intermittent Asthma****	• None necessary	
Step 2 Mild Persistent Asthma	• Low-dose inhaled glucocorticosteroid	• Sustained-release theophylline, *or* • Cromone, *or* • Leukotriene modifier
Step 3 Moderate Persistent Asthma	• Medium-dose inhaled glucocorticosteroid	• Medium-dose Inhaled glucocorticosteroid *plus* sustained-release theophylline, *or* • Medium-dose Inhaled glucocorticosteroid *plus* long-acting oral β_2-agonist, *or* • High-dose inhaled glucocorticosteroid *or* • Medium-dose Inhaled glucocorticosteroid *plus* leukotriene modifier
Step 4 Severe Persistent Asthma	• High-dose inhaled glucocorticosteroid *plus* long-acting inhaled β_2-agonist, *plus* one or more of the following, if needed: • Sustained-release theophylline • Leukotriene modifier • Long-acting oral β_2-agonist • Oral glucocorticosteroid	

All Levels: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

* *Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral β_2-agonist, and short-acting theophylline.*
** *See **Figure 5-6** and **Figure 5-7** for classification of severity.*
*** *Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.*
**** *Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (**Evidence D**).*

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with long-acting β_2-agonists in children show some benefit but the results are inconsistent. Leukotriene modifiers have not been studied in children with mild persistent asthma; thus, there are no data to support their use. However, moderate effects have been demonstrated with leukotriene modifiers in patients with more severe disease, and by extrapolation this class of drug may also be considered an alternative controller therapy in some patients (**Evidence D**). Long-term trials that compare the effectiveness of the various alternative controller medications in children with mild persistent asthma are needed.

Step 3–Moderate Persistent Asthma. **A higher dose (400-800 μg budesonide or equivalent per day) of inhaled glucocorticosteroid should be used as controller medication (Evidence A)**. For children who have frequent asthma symptoms despite regular treatment with less than 800 μg inhaled glucocorticosteroid daily, a higher dose of inhaled glucocorticosteroid should be considered (**Evidence D**), but adding another class of controller drug is preferable to increasing the inhaled glucocorticosteroid dose. Long-acting inhaled β_2-agonists are the most studied add-on medications (**Evidence B**). Alternative add-on therapies include sustained-release theophylline (**Evidence B**) and leukotriene modifiers (**Evidence B**). The response to these various medications differs from patient to patient, and the choice of add-on therapy should be individually tailored. Long-term trials that compare the effectiveness of the various alternative add-on therapies in children with moderate persistent asthma are needed.

Step 4–Severe Persistent Asthma. **A higher dose (> 800 μg budesonide or equivalent per day) of inhaled glucocorticosteroid should be used as controller treatment (Evidence B).** If the patient's asthma remains uncontrolled, adding another class of controller drug should be considered. Although a long-acting inhaled β_2-agonist is the best-studied and preferred option for add-on therapy (**Evidence B**), alternatives include sustained-release theophylline (**Evidence C**) and leukotriene modifiers (**Evidence B**). If long-term therapy with oral glucocorticosteroids is needed, these drugs should be used in the lowest possible dose (**Evidence C**), and are best given as a single morning dose in order to minimize systemic side effects. When patients are transferred from oral glucocorticosteroids to high-dose inhaled glucocorticosteroids, they should be monitored for evidence of adrenal insufficiency. Again, the patient's response to the various treatment options should be observed, and the choice of treatment should be individually tailored.

Preschool children and infants. Although there are no well-conducted clinical trials to provide scientific evidence for the proper treatment of asthma at each step of severity in these age groups, a treatment algorithm similar to that used in school children is recommended for preschool children and infants. Some adjustments must be made to account for the fact that in these younger children it is difficult to predict the need for reliever medications. At this age, children rarely communicate a need for reliever treatment, and caregivers are often unaware of the signals to observe and are unfamiliar with the drug treatment. These considerations argue for early introduction of controller treatment rather than reliance on "as-needed" rescue treatment. Preschool children and infants with wheeze represent a more heterogeneous group than school children. Thus, the specificity of the asthma diagnosis in children under 3 is poor, and aerosol treatment may present an obstacle to regular treatment.

Young children with asthma may be hospitalized with severe symptoms related to an upper airway infection. Courses of inhaled or oral glucocorticosteroids during such infections may reduce duration and severity of exacerbations, but there is no current evidence to support low-dose maintenance therapy with inhaled glucocorticosteroids in children younger than 3.

Reduction of Maintenance (Controller) Therapy

Asthma is a variable disorder, and spontaneous and therapy-induced variations in its severity occur. Inhaled glucocorticosteroids reduce asthma severity over the long term. **Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.** This will help reduce the risk of side effects and enhance patient adherence to the treatment plan. Reduction of therapy should include close monitoring of symptoms, clinical signs, and, as much as possible, lung function, and should follow the reverse order of what has just been described. In patients on combination therapy the reduction in therapy should begin with a reduction in the dose of inhaled glucocorticosteroid by 25 percent every 3 months. Once the dose of the glucocorticosteroid is at less than 800 μg budesonide per day or equivalent, then the add-on therapy should be stopped (**Evidence D**). It is recommended that patients be reviewed at least every 3 months during the reduction phase.

PART 5: ESTABLISH PLANS FOR MANAGING EXACERBATIONS

KEY POINTS:

- Treatment of exacerbations depends on the patient, experience of the health care professional, therapies that are most effective for the particular patient, availability of medications, and emergency facilities.
- Primary therapies for exacerbations are the repetitive administration of rapid-acting inhaled β_2-agonist, the early introduction of systemic glucocorticosteroids, and oxygen supplementation.
- Crucial to successful treatment of exacerbations is close monitoring of the patient's condition and response to treatment with serial measurements of lung function.
- Severe exacerbations of asthma are life-threatening medical emergencies. Care must be expeditious, and treatment is often most safely undertaken in a hospital or a hospital-based emergency department.

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