# CHAPTER

# 3

# *ASTHMA*

# *TREATMENTS*

**KEY POINTS:**

- Medications to treat asthma can be classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms.
- Asthma treatment can be administered in different ways—inhaled, orally, or by injection. The major advantage of inhaled therapy is that drugs are delivered directly into the airways, producing higher local concentrations with significantly less risk of systemic side effects.
- Inhaled glucocorticosteroids are the most effective controller medications currently available.
- Rapid-acting inhaled $\beta_2$-agonists are the medications of choice for relief of bronchoconstriction and for the pretreatment of exercise-induced bronchoconstriction, in both adults and children of all ages.
- Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.

## INTRODUCTION

The goal of asthma treatment is to achieve and maintain clinical control. Medications to treat asthma can be classified as controllers or relievers. **Controllers** are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. They include inhaled and systemic glucocorticosteroids, leukotriene modifiers, long-acting inhaled $\beta_2$-agonists in combination with inhaled glucocorticosteroids, sustained-release theophylline, cromones, anti-IgE, and other systemic steroid-sparing therapies. Inhaled glucocorticosteroids are the most effective controller medications currently available. **Relievers** are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms. They include rapid-acting inhaled $\beta_2$-agonists, inhaled anticholinergics, short-acting theophylline, and short-acting oral $\beta_2$-agonists.

## ASTHMA MEDICATIONS: ADULTS

**Route of Administration**

Asthma treatment for adults can be administered in different ways—inhaled, orally or parenterally (by subcutaneous, intramuscular, or intravenous injection). The major advantage of inhaled therapy is that drugs are delivered directly into the airways, producing higher local concentrations with significantly less risk of systemic side effects.

Inhaled medications for asthma are available as pressurized metered-dose inhalers (MDIs), breath-actuated MDIs, dry powder inhalers (DPIs), soft mist inhalers, and nebulized or "wet" aerosols* . Inhaler devices differ in their efficiency of drug delivery to the lower respiratory tract, depending on the form of the device, formulation of medication, particle size, velocity of the aerosol cloud or plume (where applicable), and ease with which the device can be used by the majority of patients. Individual patient preference, convenience, and ease of use may influence not only the efficiency of drug delivery but also patient adherence to treatment and long-term control.

Pressurized MDIs (pMDIs) require training and skill to coordinate activation of the inhaler and inhalation. Medications in these devices can be dispensed as a suspension in chlorofluorocarbons (CFCs) or as a solution in hydrofluoroalkanes (HFAs). For a pMDI containing CFCs, the use of a spacer (holding chamber) improves drug delivery, increases lung deposition, and may reduce local and systemic side effects[1]. However, CFC inhaler devices are being phased out due to the impact of CFCs upon the atmospheric ozone layer, and are being replaced by HFA devices. For pMDIs containing bronchodilators, the switch from CFC to HFA inhalers does not result in a change in efficacy at the same nominal dose[2]. However, for some glucocorticosteroids, the HFA formulations provide an aerosol of smaller particle size that results in less oral deposition (with associated reduction in oral side effects), and correspondingly greater lung deposition. This may result in greater systemic efficacy at equivalent ex-actuator doses, but also greater systemic exposure and risk of side effects[3-5]. Clinicians are advised to consult the package inserts of each product to confirm the recommended dose equivalent to currently used drugs. Some of these comparisons are provided in **Figure 3-1**.

*Information on various inhaler devices available can be found on the GINA Website (http://www.ginasthma.org).*

Pressurized MDIs may be used by patients with asthma of any severity, including during exacerbations. Breath-actuated aerosols may be helpful for patients who have difficulty using the "press and breathe" pressurized MDI[6]. Soft mist inhalers appear to require less coordination. Dry powder inhalers are generally easier to use, but they require a minimal inspiratory flow rate and may prove difficult for some patients. DPIs differ with respect to the fraction of ex-actuator dose delivered to the lung. For some drugs, the dose may need to be adjusted when switching from an MDI to a DPI[7]. Nebulized aerosols are rarely indicated for the treatment of chronic asthma in adults[8].

## CONTROLLER MEDICATIONS

### *Inhaled glucocorticosteroids**

*Role in therapy* - Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. Studies have demonstrated their efficacy in reducing asthma symptoms[9], improving quality of life[9], improving lung function[9], decreasing airway hyperresponsiveness[10], controlling airway inflammation[11], reducing frequency and severity of exacerbations[12], and reducing asthma mortality[13]. However, they do not cure asthma, and when they are discontinued deterioration of clinical control follows within weeks to months in a proportion of patients[14,15].

Inhaled glucocorticosteroids differ in potency and bioavailability, but because of relatively flat dose-response relationships in asthma relatively few studies have been able to confirm the clinical relevance of these differences[191]. **Figure 3-1** lists approximately equipotent doses of different inhaled glucocorticosteroids based upon the available efficacy literature, but the categorization into dosage categories does not imply that clear dose-response relationships have been demonstrated for each drug.

The efficacy of some products varies when administered via different inhaler devices[16]. Most of the benefit from inhaled glucocorticosteroids is achieved in adults at relatively low doses, equivalent to 400 ug of budesonide per day[17]. Increasing to higher doses provides little further benefit in terms of asthma control but increases the risk of side effects[17,18]. However, there is marked individual variability of responsiveness to inhaled glucocorticosteroids and because of this and the recognized poor adherence to treatment with inhaled glucocorticosteroids, many patients will require higher doses to achieve full therapeutic benefit. As tobacco smoking reduces the responsiveness to inhaled glucocorticosteroids, higher doses may be required in patients who smoke.

**Figure 3-1. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids for Adults †**

| Drug | Low Daily Dose (μg) | Medium Daily Dose (μg) | High Daily Dose (μg)‡ |
|---|---|---|---|
| Beclomethasone dipropionate | 200 - 500 | >500 - 1000 | >1000 - 2000 |
| Budesonide* | 200 - 400 | >400 - 800 | >800 - 1600 |
| Ciclesonide* | 80 - 160 | >160 - 320 | >320 - 1280 |
| Flunisolide | 500 - 1000 | >1000 - 2000 | >2000 |
| Fluticasone | 100 - 250 | >250 - 500 | >500 - 1000 |
| Mometasone furoate* | 200 - 400 | >400 - 800 | >800 - 1200 |
| Triamcinolone acetonide | 400 - 1000 | >1000 - 2000 | >2000 |

† Comparisons based upon efficacy data.

‡ Patients considered for high daily doses except for short periods should be referred to a specialist for assessment to consider alternative combinations of controllers. Maximum recommended doses are arbitrary but with prolonged use are associated with increased risk of systemic side effects.

* Approved for once-daily dosing in mild patients.

**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 clinical control and adjust the dose accordingly. 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.
- Designation of low, medium, and high doses is provided from manufacturers' recommendations where possible. Clear demonstration of dose-response relationships is seldom provided or available. The principle is therefore to establish the minimum effective controlling dose in each patient, as higher doses may not be more effective and are likely to be associated with greater 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 equivalent correct dosage.

**In this section recommendations for doses of inhaled glucocorticosteroids are given as "μ/day budesonide or equivalent," because a majority of the clinical literature on these medications uses this standard.*

To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids. There is, however, a clear relationship between the dose of inhaled glucocorticosteroids and the prevention of severe acute exacerbations of asthma[12]. Therefore, some patients with severe asthma may benefit from long-term treatment with higher doses of inhaled glucocorticosteroids.

*Side effects:* Local adverse effects from inhaled glucocorticosteroids include oropharyngeal candidiasis, dysphonia, and occasionally coughing from upper airway irritation. For pressurized MDIs the prevalence of these effects may be reduced by using certain spacer devices[1]. Mouth washing (rinsing with water, gargling, and spitting out) after inhalation may reduce oral candidiasis. The use of prodrugs that are activated in the lungs but not in the pharynx (e.g., ciclesonide)[19], and new formulations and devices that reduce oropharyngeal deposition, may minimize such effects without the need for a spacer or mouth washing.

Inhaled glucocorticosteroids are absorbed from the lung, accounting for some degree of systemic bioavailability. The risk of systemic adverse effects from an inhaled glucocorticosteroid depends upon its dose and potency, the delivery system, systemic bioavailability, first-pass metabolism (conversion to inactive metabolites) in the liver, and half-life of the fraction of systemically absorbed drug (from the lung and possibly gut)[20]. Therefore, the systemic effects differ among the various inhaled glucocorticosteroids. Several comparative studies have demonstrated that ciclesonide, budesonide, and fluticasone propionate at equipotent doses have less systemic effect[20-23]. Current evidence suggests that in adults, systemic effects of inhaled glucocorticosteroids are not a problem at doses of 400 μg or less budesonide or equivalent daily.

The systemic side effects of long-term treatment with high doses of inhaled glucocorticosteroids include easy bruising[24], adrenal suppression[1,20], and decreased bone mineral density[25,26]. Inhaled glucocorticosteroids have also been associated with cataracts[27] and glaucoma in cross-sectional studies[28,29], but there is no evidence of posterior-subcapsular cataracts in prospective studies[30-32]. One difficulty in establishing the clinical significance of such adverse effects 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 use of inhaled glucocorticosteroids increases the risk of pulmonary infections, including tuberculosis, and inhaled glucocorticosteroids are not contraindicated in patients with active tuberculosis[33].

***Leukotriene modifiers.***

*Role in therapy* - Leukotriene modifiers include cysteinyl-leukotriene 1 (CysLT1) receptor antagonists (montelukast, pranlukast, and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton). Clinical studies have demonstrated that leukotriene modifiers have a small and variable bronchodilator effect, reduce symptoms including cough[34], improve lung function, and reduce airway inflammation and asthma exacerbations[35-37]. They may be used as an alternative treatment for adult patients with mild persistent asthma[38-40], and some patients with aspirin-sensitive asthma respond well to leukotriene modifiers[41]. However, when used alone as controller, the effect of leukotriene modifiers are generally less than that of low doses of inhaled glucocorticosteroids, and, in patients already on inhaled glucocorticosteroids, leukotriene modifiers cannot substitute for this treatment without risking the loss of asthma control[42,43]. Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe asthma[44], and may improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids[43,45-47]. With the exception of one study that demonstrated equivalence in preventing exacerbations[48], several studies have demonstrated that leukotriene modifiers are less effective than long-acting inhaled $\beta_2$-agonists as add-on therapy[49-51,192]. A controlled release formulation of zileuton allows this medication to be used on a twice daily basis with effects equivalent to that of standard zileuton used four times a day[203].

*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[204], and monitoring of liver tests is recommended during treatment with this medication. The apparent association of leukotriene modifiers with Churg-Strauss syndrome is probably largely the result of reductions in the doses of systemic and/or inhaled glucocorticosteroids unmasking the underlying disease, but a causal association in some patients cannot be entirely excluded[52-54].

***Long-acting inhaled $\beta_2$-agonists.***

*Role in therapy* - Long-acting inhaled $\beta_2$-agonists, including formoterol and salmeterol, should not be used as monotherapy in asthma as these medications do not appear to influence the airway inflammation in asthma. They are most effective when combined with inhaled glucocorticosteroids[55,56,193], and this combination therapy is the preferred treatment when a medium dose of inhaled glucocorticosteroid alone fails to achieve control of

asthma. Addition of long-acting inhaled $\beta_2$-agonists to a daily regimen of inhaled glucocorticosteroids improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of rapid-acting inhaled $\beta_2$-agonists[57-59], reduces the number of exacerbations[12,57-62], and achieves clinical control of asthma in more patients, more rapidly, and at a lower dose of inhaled glucocorticosteroids than inhaled glucocorticosteroids given alone[63].

This greater efficacy of combination treatment has led to the development of fixed combination inhalers that deliver both glucocorticosteroid and long-acting $\beta_2$-agonist simultaneously (fluticasone propionate plus salmeterol, budesonide plus formoterol). Controlled studies have shown that delivering this therapy in a combination inhaler is as effective as giving each drug separately[64, 65]. Fixed combination inhalers are more convenient for patients, may increase compliance[66], and ensure that the long-acting $\beta_2$-agonist is always accompanied by a glucocorticosteroid. In addition, combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance. Both components of budesonide-formoterol given as needed contribute to enhanced protection from severe exacerbations in patients receiving combination therapy for maintenance[67,194] and provide improvements in asthma control at relatively low doses of treatment[67-70].

Long-acting $\beta_2$-agonists may also be used to prevent exercise-induced bronchospasm, and for this purpose may provide longer protection than rapid-acting inhaled $\beta_2$-agonists[71]. 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[72, 73], which may make formoterol suitable for symptom relief as well as symptom prevention[68].

*Side effects* - Therapy with long-acting inhaled $\beta_2$-agonists causes fewer systemic adverse effects—such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia—than oral therapy. The regular use of rapid-acting $\beta_2$-agonists in both short and long acting forms may lead to relative refractoriness to $\beta_2$-agonists[74]. Data indicating a possible increased risk of asthma-related death associated with the use of salmeterol in a small group of individuals[75] led to advisories from the US Food and Drug Administration (FDA)‡ and Health Canada§ that long-acting $\beta_2$-agonists are not a substitute for inhaled or oral glucocorticosteroids, and should only be used in combination with an appropriate dose of inhaled glucocorticosteroid as determined by a physician. A meta-analysis of all studies of salmeterol added to inhaled glucocorticosteroids has concluded that this combination does not increase the risk for asthma-related deaths or intubations when compared to inhaled glucocorticosteroids alone[205]. No influence of $\beta_2$-adrenergic receptor phenotypes upon the efficacy or safety of long-acting $\beta_2$-agonist therapy has been observed when administered in combination with inhaled glucocorticosteroids whether by the single inhaler for maintenance and relief method or at a regular fixed dose in adults[206].

***Theophylline.***

*Role in therapy* - Theophylline is a bronchodilator and, when given in a lower dose, has modest anti-inflammatory properties[77-79]. It is available in sustained-release formulations that are suitable for once- or twice-daily dosing. Data on the relative efficacy of theophylline as a long-term controller is lacking. However, available evidence suggests that sustained-release theophylline has little effect as a first-line controller[80]. It may provide benefit as add-on therapy in patients who do not achieve control on inhaled glucocorticosteroids alone[81-83]. Additionally in such patients the withdrawal of sustained-release theophylline has been associated with deterioration of control[84]. As add-on therapy, theophylline is less effective than long-acting inhaled $\beta_2$-agonists[85,86].

*Side effects* - Side effects of theophylline, particularly at higher doses (10 mg/kg body weight/day or more), are significant and reduce their usefulness. Side effects can be reduced by careful dose selection and monitoring, and generally decrease or disappear with continued use. Adverse effects include gastrointestinal symptoms, loose stools, cardiac arrhythmias, seizures, and even death. Nausea and vomiting are the most common early events. Monitoring is advised when a high dose is started, if the patient develops an adverse effect on the usual dose, when expected therapeutic aims are not achieved, and when conditions known to alter theophylline metabolism exist. For example, febrile illness, pregnancy, and anti-tuberculosis medications[87] reduce blood levels of theophylline, while liver disease, congestive heart failure, and certain drugs including cimetidine, some quinolones, and some macrolides increase the risk of toxicity. Lower doses of theophylline, which have been demonstrated to provide the full anti-inflammatory benefit of this drug[82], are associated with less frequent side effects, and plasma theophylline levels in patients on low-dose therapy need not be measured unless overdose is suspected.

‡ http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2003/serevent_hpc-cps_e.html
§ www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2003/serevent_hpc-cps_e.html

***Cromones: sodium cromoglycate and nedocromil sodium.***

*Role in therapy* – The role of sodium cromoglycate and nedocromil sodium in long-term treatment of asthma in adults is limited. Efficacy has been reported in patients with mild persistent asthma and exercise-induced bronchospasm. Their anti-inflammatory effect is weak and they are less effective than a low dose of inhaled glucocorticosteroid[88].

*Side effects* - Side effects are uncommon and include coughing upon inhalation and sore throat. Some patients find the taste of nedocromil sodium unpleasant.

***Long-acting oral $\beta_2$-agonists.***

*Role in therapy* - Long acting oral $\beta_2$-agonists include slow release formulations of salbutamol, terbutaline, and bambuterol, a prodrug that is converted to terbutaline in the body. They are used only on rare occasions when additional bronchodilation is needed.

*Side effects* - The side effect profile of long acting oral $\beta_2$-agonists is higher than that of inhaled $\beta_2$-agonists, and includes cardiovascular stimulation (tachycardia), anxiety, and skeletal muscle tremor. Adverse cardiovascular reactions may also occur with the combination of oral $\beta_2$-agonists and theophylline. Regular use of long-acting oral $\beta_2$-agonists as monotherapy is likely to be harmful and these medications must always be given in combination with inhaled glucocorticosteroids.

***Anti-IgE.***

*Role in therapy* - Anti-IgE (omalizumab) is a treatment option limited to patients with elevated serum levels of IgE. Its current indication is for patients with severe allergic asthma[89] who are uncontrolled on inhaled glucocorticosteroids, although the dose of concurrent treatment has varied in different studies. Improved asthma control is reflected by fewer symptoms, less need for reliever medications, and fewer exacerbations[90,91]. Further investigations will likely provide additional clarification of the role of anti-IgE in other clinical settings.

*Side effects:* As indicated by several studies involving asthma patients ages 12 years and older[207], who were already receiving treatment with glucocorticosteroids (inhaled and/or oral) and long-acting $\beta_2$-agonists[89], anti-IgE appears to be safe as add-on therapy[92-94].

***Systemic glucocorticosteroids.***

*Role in therapy* - Long-term oral glucocorticosteroid therapy (that is, for periods longer than two weeks as a glucocorticosteroid "burst") may be required for severely uncontrolled asthma, but its use is limited by the risk of significant adverse effects. The therapeutic index (effect/side effect) of long-term inhaled glucocorticosteroids is always more favorable than long-term systemic glucocorticosteroids in asthma[95,96]. If oral glucocorticosteroids have to be administered on a long-term basis, attention must be paid to measures that minimize the systemic side effects. Oral preparations are preferred over parenteral (intramuscular or intravenous) for long-term therapy because of their lower mineralocorticoid effect, relatively short half-life, and lesser effects on striated muscle, as well as the greater flexibility of dosing that permits titration to the lowest acceptable dose that maintains control.

*Side effects* - The systemic side effects of long-term oral or parenteral glucocorticosteroid treatment include osteoporosis, arterial hypertension, diabetes, hypothalamic-pituitary-adrenal axis suppression, obesity, cataracts, glaucoma, 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 (**Figure 3-2**)[97-99]. Although it is rare, withdrawal of oral glucocorticosteroids can elicit adrenal failure or unmask underlying disease, such as Churg-Strauss Syndrome[54,100]. 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. Fatal herpes virus infections have been reported among patients who are exposed to these viruses while taking systemic glucocorticosteroids, even short bursts.

***Oral anti-allergic compounds.***

*Role in therapy* - Several oral anti-allergic compounds have been introduced in some countries for the treatment of mild to moderate allergic asthma. These include tranilast, repirinast, tazanolast, pemirolast, ozagrel, celatrodast, amlexanox, and ibudilast. In general, their anti-asthma effect appears to be limited[101], but studies on the relative efficacy of these compounds are needed before recommendations can be made about their role in the long-term treatment of asthma.

*Side effects* - Sedation is a potential side effect of some of these medications.

**Figure 3-2. Glucocorticosteroids and Osteoporosis**

Asthma patients on high-dose inhaled glucocorticosteroids or oral glucocorticosteroids at any dose are considered at risk of developing osteoporosis and fractures, but it is not certain whether this risk exists for patients on lower doses of inhaled glucocorticosteroids[1]. Physicians should consider monitoring patients who are at risk. The following summarizes monitoring and management but more detailed guidelines for the management of steroid-induced osteoporosis are available[2,3].

***Screening*** - Chest X-rays should be reviewed for the presence of vertebral fractures. Wedging, compressions, and cod-fishing of vertebral bodies are synonymous with fractures, and indicate those who are at the highest risk for future fractures. In men, this may be a better predictor of fracture risk than bone mineral density (BMD). BMD measurements by dual energy X-ray absorptiomety (DXA scan) should be undertaken in:

- Any patient with asthma who has been taking oral glucocorticosteroids for over 6 months duration at a mean daily dose of 7.5 mg prednisone/prednisolone or above.
- Post-menopausal women taking over 5 mg prednisone/prednisolone daily for more than 3 months.
- Any patient with asthma and a history of vertebral or other fractures that may be related to osteoporosis.

Bone density measurements should also be offered to:

- Post-menopausal women taking > 2 mg inhaled BDP or equivalent daily
- Any patient who is receiving frequent short courses of high-dose oral glucocorticosteroids

Osteoporosis is present if the bone density in lumbar spine or femoral neck shows :

- T-score below -2.5 (2.5 standard deviations below the mean value of young normal subjects of the same sex in patients 19-69 years).
- Z-score below -1 (1 standard deviation below the predicted value for age and sex).

***Follow-up scanning*** - Repeat scanning should be done:

- In 2 years in those whose initial scan was not osteoporotic but in whom treatment (as above) with oral glucocorticosteroids continues.
- In 1 year for those with osteoporosis on the first scan who are started on osteoporosis treatment.

***Management***

- General measures include avoidance of smoking, regular exercise, use of the lowest dose of oral glucocorticosteroid possible, and a good dietary intake of calcium.
- For women with osteoporosis up to 10 years post-menopausal offer bisphosphonates or hormone therapy[4,5,6] (**Evidence A**).
- For men, pre-menopausal women, and women more than 10 years since menopause consider treatment with a bisphosphonate[7] (**Evidence A**).

**References**


1. Goldstein MF, Fallon JJ, Jr., Harning R. Chronic glucocorticoid therapy-induced osteoporosis in patients with obstructive lung disease. *Chest* 1999; 116:1733-1749.
2. Eastell R, Reid DM, Compston J, Cooper C, Fogelman I, Francis RM et al. A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. *J Intern Med* 1998; 244:271-292.
3. Sambrook PN, Diamond T, Ferris L, Fiatarone-Singh M, Flicker L, MacLennan A et al. Corticosteroid induced osteoporosis. Guidelines for treatment. *Aust Fam Physician* 2001; 30:793-796.
4. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-33.
5. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, Pettinger M, Stefanick ML, Wactawski-Wende J, Watts NB. "Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density." *JAMA* 2003;290(13):1729-1738.
6. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ*. 2002;167:S1-34.
7. Homik J, Cranney A, Shea B, Tugwell P, Wells G, Adachi R et al. Bisphosphonates for steroid induced osteoporosis. *Cochrane Database Syst Rev* 2000;CD001347.


***Other controller therapies.***

*Role in therapy* - Various therapeutic regimens to reduce the dose of oral glucocorticosteroids required by patients with severe asthma have been proposed. These medications should be used only in selected patients under the supervision of an asthma specialist, as their potential steroid-sparing effects may not outweigh the risk of serious side effects. Two meta-analyses of the steroid-sparing effect of low-dose methotrexate showed a small overall benefit, but a relatively high frequency of adverse effects[102,103]. This small potential to reduce the impact of glucocorticosteroid side effects is probably insufficient to offset the adverse effects of methotrexate[104]. Cyclosporin[105] and gold[106,107] have also been shown to be effective in some patients. The macrolide, troleandromycin, has a small steroid-sparing effect when used with systemic methylprednisolone, but its effect may result from the macrolide decreasing metabolism of the glucocorticosteroid and therefore not improving safety. However, other effects of the long-term use of macrolides in asthma remain under study[108]. The use of intravenous immunoglobulin is not recommended[109-111].

*Side effects* - Macrolide use is frequently associated with nausea, vomiting, and abdominal pain and occasionally liver toxicity. Methotrexate also causes gastrointestinal symptoms, and on rare occasions hepatic and diffuse pulmonary parenchymal disease, and hematological and teratogenic effects.

***Allergen-specific immunotherapy.***

*Role in therapy* - The role of specific immunotherapy in adult asthma is limited. Appropriate immunotherapy requires the identification and use of a single well-defined clinically relevant allergen. The later is administered in progressively higher doses in order to induce tolerance. A Cochrane review[112] that examined 75 randomized controlled trials of specific immunotherapy compared to placebo confirmed the efficacy of this therapy in asthma in reducing symptom scores and medication requirements, and improving allergen-specific and non-specific airway hyperresponsiveness. Similar modest effects were identified in a systematic review of sublingual immunotherapy (SLIT)[196]. Specific immunotherapy has long-term clinical effects and the potential of preventing development of asthma in children with allergic rhino conjunctivitis up to 7 years after treatment termination[208].

However, in view of the relatively modest effect of allergen-specific immunotherapy compared to other treatment options, these benefits must be weighed against the risk of adverse effects and the inconvenience of the prolonged course of injection therapy, including the minimum half-hour wait required after each injection. Specific immunotherapy should be considered only after strict environmental avoidance and pharmacologic intervention, including inhaled glucocorticosteroids, have failed to control a patient's asthma[113]. There are no studies that compare specific immunotherapy with pharmacologic therapy for asthma. The value of immunotherapy using multiple allergens does not have support.

*Side effects* - Local and systemic side effects may occur in conjunction with specific immunotherapy 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. Deaths from specific immunotherapy have occurred in patients with severe asthma.

**Reliever Medications**

Reliever medications act quickly to relieve bronchoconstriction and its accompanying acute symptoms.

***Rapid-acting inhaled $\beta_2$-agonists.***

*Role in therapy* - Rapid-acting inhaled $\beta_2$-agonists are the medications of choice for relief of bronchospasm during acute exacerbations of asthma and for the pretreatment of exercise-induced bronchoconstriction. They include salbutamol, terbutaline, fenoterol, levalbuterol HFA[209], reproterol, and pirbuterol. Formoterol, a long-acting $\beta_2$-agonist, is approved for symptom relief because of its rapid onset of action, but it should only be used for this purpose in patients on regular controller therapy with inhaled glucocorticosteroids.

Rapid-acting inhaled $\beta_2$-agonists should be used only on an as-needed basis at the lowest dose and frequency required. Increased use, especially daily use, is a warning of deterioration of asthma control and indicates the need to reassess treatment. Similarly, failure to achieve a quick and sustained response to $\beta_2$-agonist treatment during an exacerbation mandates medical attention, and may indicate the need for short-term treatment with oral glucocorticosteroids.

*Side effects* - Use of oral $\beta_2$-agonists given in standard doses are associated with more adverse systemic effects such as tremor and tachycardia than occur with inhaled preparations.

***Systemic glucocorticosteroids.***

*Role in therapy* - Although systemic glucocorticosteroids are not usually thought of as reliever medications, they are important in the treatment of severe acute exacerbations because they prevent progression of the asthma exacerbation, reduce the need for referral to emergency departments and hospitalization, prevent early relapse after emergency treatment, and reduce the morbidity of the illness. The main effects of systemic glucocorticosteroids in acute asthma are only evident after 4 to 6 hours. Oral therapy is preferred and is as effective as intravenous hydrocortisone[114]. A typical short course of oral glucocorticosterods for an exacerbation is 40-50 mg[115] prednisolone given daily for 5 to 10 days depending on the severity of the exacerbation. When symptoms have subsided and lung function has approached the patient's personal best value, the oral glucocorticosteroids can be stopped or tapered, provided that treatment with inhaled glucocorticosteroids continues[116]. Intramuscular injection of glucocorticosteroids has no advantage over a short course of oral glucocorticosteroids in preventing relapse[114,116].

*Side effects* - Adverse effects of short-term high-dose systemic therapy are uncommon but include reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, rounding of the face, mood alteration, hypertension, peptic ulcer, and aseptic necrosis of the femur.

***Anticholinergics.***

*Role in therapy* - Anticholinergic bronchodilators used in asthma include ipratropium bromide and oxitropium bromide. Inhaled ipratropium bromide is a less effective reliever medication in asthma than rapid-acting inhaled $\beta_2$-agonists. A meta-analysis of trials of inhaled ipratropium bromide used in association with an inhaled $\beta_2$-agonist in acute asthma showed that the anticholinergic produces a statistically significant, albeit modest, improvement in pulmonary function, and significantly reduces the risk of hospital admission[117]. 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 $\beta_2$-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[118].

***Theophylline.***

*Role in therapy* - Short-acting theophylline may be considered for relief of asthma symptoms[119]. The role of theophylline in treating exacerbations remains controversial. Short-acting theophylline may provide no additive bronchodilator effect over adequate doses of rapid-acting $\beta_2$-agonists, but it may benefit respiratory drive.

*Side effects* - 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 to be low and/or can be monitored.

***Short-acting oral $\beta_2$-agonists.***

Short-acting oral $\beta_2$-agonists are appropriate for use in the few patients who are unable to use inhaled medication. However, their use is associated with a higher prevalence of adverse effects.

**Complementary And Alternative Medicine**

The roles of complementary and alternative medicine in adult asthma treatment are limited because these approaches have been insufficiently researched and their effectiveness is largely unproven. Generally, these therapies have not been validated by conventional standards. Although the psychotherapeutic role of the therapist forms part of the placebo effect of all treatments, this aspect is viewed as an integral part of the so-called holistic approach used by practitioners of complementary and alternative methods, and mitigates against performance of the large, multicenter, placebo-controlled randomized studies required to confirm efficacy. However, without these the relative efficacy of these alternative measures will remain unknown[120].

Complementary and alternative therapies include acupuncture, homeopathy, herbal medicine, Ayurvedic medicine, ionizers, osteopathy and chiropractic manipulation, and speleotherapy among others. Dietary supplements, including selenium therapy[197] are not of proven benefit. Apart from those mentioned below, there have been no satisfactory studies from which conclusions about their efficacy can be drawn.

A single controlled trial of chiropractic spinal manipulation failed to show benefit of this therapy in asthma[121], and a systematic review of homeopathy found only three relevant trials with inconclusive results. Although one study of the Butyeko breathing method suggested minor benefit, a later study of two physiologically-contrasting breathing techniques showed similar improvements in reliever and inhaled glucocorticosteroids use in both groups, suggesting that perceived improvement with these methods are the result of non-physiological factors[122]. A randomized controlled trial indicated that the practice of Sahaja yoga has limited beneficial effects on asthma for some objective and subjective measures, although there were no significant differences between the intervention and control groups at the 2 month follow up assessment[198]. An integrated breathing and relaxation technique (Papworth method) appears to ameliorate respiratory symptoms, dysfunctional breathing and adverse mood but there is no evidence of effect on objective measures of respiratory function[210].

*Side effects* - Acupuncture-associated hepatitis B, bilateral pneumothorax, and burns have been described. Side effects of other alternative and complementary medicines are largely unknown. However, some popular herbal medicines could potentially be 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.

**See also the "Asthma Medications: Adults" section at the beginning of this chapter for more information on the therapeutic role and side effects of various therapies. In this section, only information specific to children is provided.

## ASTHMA TREATMENT: CHILDREN**

### Route of Administration

Inhaled therapy is the cornerstone of asthma treatment for children of all ages. Almost all children can be taught to effectively use inhaled therapy. Different age groups require different inhalers for effective therapy, so the choice of inhaler must be individualized. Information about the lung dose for a particular drug formulation is seldom available for children, and marked differences exist between the various inhalers. This should be considered whenever one inhaler device is substituted with another. In addition, the choice of inhaler device should include consideration of the efficacy of drug delivery, cost, safety, ease of use, convenience, and documentation of its use in the patient's age group[123-125]. In general, a metered-dose inhaler (MDI) with spacer is preferable to nebulized therapy due to its greater convenience, more effective lung deposition, lower risk of side effects, and lower cost. Based on these considerations, a general strategy for choosing inhalers in children is given in **Figure 3-3**.

**Figure 3-3: Choosing an Inhaler Device for Children with Asthma***

| 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 mouthpiece |
| Older than 6 years | Dry powder inhaler, *or* breath-actuated pressurized metered-dose inhaler, *or* pressurized metered-dose inhaler with spacer and mouthpiece | Nebulizer with mouthpiece |

**Based on efficacy of drug delivery, cost effectiveness, safety, ease of use, and convenience.*

Spacers retain large drug particles that would normally be deposited in the oropharynx, reducing oral and gastrointestinal absorption and thus systemic availability of the inhaled drug. This is mainly important when inhaled glucocorticosteroids with first-pass metabolism (beclomethasone dipropionate, flunisolide, triamcinolone, and budesonide) are given via pressurized MDI. Use of a spacer also reduces oropharyngeal side effects. During acute asthma attacks, an MDI should always be used with a spacer, as in this situation a child may be unable to correctly coordinate inhalation with actuation of the MDI. Commercially produced spacers with well-characterized drug output characteristics are preferable. If these are not available or feasible, a homemade spacer (for example, one made from a 500 ml plastic cold drink bottle) may be used[126]. Nebulizers have rather imprecise dosing, are expensive, are time consuming to use and care for, and require maintenance. They are mainly reserved for children who cannot use other inhaler devices. In severe acute asthma exacerbations a nebulizer is often used, although an MDI with a spacer is equally effective[127].

### Controller Medications

Controller medications for children include inhaled and systemic glucocorticosteroids, leukotriene modifiers, long-acting inhaled $\beta_2$-agonists, theophylline, cromones, and long-acting oral $\beta_2$-agonists.

***Inhaled glucocorticosteroids.***

*Role in Therapy* - Inhaled glucocorticosteroids are the most effective controller therapy, and are therefore the recommended treatment for asthma for children of all ages. **Figure 3-4** lists approximately equipotent doses of different inhaled glucocorticosteroids administered via different inhalation devices.

Children older than 5 years. Dose-response studies and dose titration studies in children[128,129] demonstrate marked and rapid clinical improvements in symptoms and lung function at low doses of inhaled glucocorticosteroids (e.g., 100-200 μg budesonide daily)[130-134], and mild disease is well controlled by such doses in the majority of patients[132]. Early intervention with inhaled budesonide is associated with improved asthma control and less additional asthma medication use[211]. Some patients require higher doses (400 μg/day) to achieve optimal asthma control and effective protection against exercise-induced asthma. Only a minority of patients require treatment with high doses of inhaled glucocorticosteroids[133,134]. In children older than 5 years, 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[10]. Symptom control and improvements in lung function occur rapidly (after 1 to 2 weeks), although longer treatment (over the course of months) and sometimes higher doses may be required to achieve maximum improvements in airway hyper-responsiveness[10]. When glucocorticosteroid treatment is discontinued, asthma control deteriorates within weeks to months[10].

**Figure 3-4. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids for Children**

| Drug | Low Daily Dose (μg) | Medium Daily Dose (μg) | High Daily Dose (μg)‡ |
|---|---|---|---|
| Beclomethasone dipropionate | 100 - 200 | >200 - 400 | >400 |
| Budesonide* | 100 - 200 | >200 - 400 | >400 |
| Budesonide-Neb | 250 - 500 | >500 - 1000 | >1000 |
| Ciclesonide* | 80 - 160 | >160 - 320 | >320 |
| Flunisolide | 500 - 750 | >750 - 1250 | >1250 |
| Fluticasone | 100 - 200 | >200 - 500 | >500 |
| Mometasone furoate* | 100 - 200 | >200 - 400 | >400 |
| Triamcinolone acetonide | 400 - 800 | >800 - 1200 | >1200 |

† Comparisons based upon efficacy data.

‡ Patients considered for high daily doses except for short periods should be referred to a specialist for assessment to consider alternative combinations of controllers. Maximum recommended doses are arbitrary but with prolonged use are associated with increased risk of systemic side effects.

* Approved for once-daily dosing in mild patients.

**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 clinical control and adjust the dose accordingly. 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.
- Designation of low, medium, and high doses is provided from manufacturers≤recommendations where possible. Clear demonstration of dose-response relationships is seldom provided or available. The principle is therefore to establish the minimum effective controlling dose in each patient, as higher doses may not be more effective and are likely to be associated with greater 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 equivalent dosage.

Children 5 years and younger. Treatment with inhaled glucocorticosteroids in children 5 years and younger with asthma generally produces similar clinical effects as in older children, but dose-response relationships have been less well studied. The clinical response may differ depending on the inhaler and the child≤s ability to use the inhaler correctly. With use of a spacer device, daily doses ≤ 400 μg of budesonide or equivalent result in near-maximum benefits in the majority of patients[136,137]. Use of inhaled glucocorticosteroids does not induce remission of asthma and it returns when treatment is stopped[138].

The clinical benefits of intermittent systemic or inhaled glucocorticosteroids for children with intermittent, viral-induced wheeze remain controversial. While some studies in older children found small benefits, a study in young children found no effects on wheezing symptoms[139]. There is no evidence to support the use of maintenance low-dose inhaled glucocorticosteroids for preventing early transient wheezing[136,139,199].

*Side effects* - The majority of studies evaluating the systemic effects of inhaled glucocorticosteroids have been undertaken in children older than 5 years.

Growth. When assessing the effects of inhaled glucocorticosteroids on growth in children with asthma, it is important to consider potential confounding factors. For example, many children with asthma receiving inhaled glucocorticosteroids experience a reduction in growth rate toward the end of the first decade of life[140]. 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 velocity 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[140,141]. Ultimately, adult height is not decreased, although it is reached at a later than normal age. The use of 400 μg inhaled budesonide or equivalent per day to control asthma has less impact on growth than does low socioeconomic status[141]. A summary of the findings of studies on inhaled glucocorticosteroids and growth is provided in **Figure 3-5**.

Bones. The potential clinically relevant adverse effects of inhaled glucocorticosteroids on bones in children are osteoporosis and fracture. Several cross-sectional and longitudinal epidemiologic studies have assessed the effects of long-term inhaled glucocorticosteroid treatment on these outcomes[132,135,143-149]. The conclusions are summarized in **Figure 3-6**.

**Figure 3-5. Summary: Glucocorticosteroids and Growth in Children[140-142]**

- Uncontrolled or severe asthma adversely affects growth and final adult height.
- No long-term controlled studies have reported any statistically or clinically significant adverse effects on growth of 100 to 200 μg per day of inhaled glucocorticosteroids.
- Growth retardation may be seen with all inhaled glucocorticosteroids when a high dose is administered.
- Growth retardation in both short- and medium-term studies is dose dependent.
- Important differences seem to exist between the growth-retarding effects of various inhaled glucocorticosteroids and inhalers.
- Different age groups seem to differ in their susceptibility to the growth-retarding effects of inhaled glucocorticosteroids; children aged 4 to 10 are more susceptible than adolescents.
- Glucocorticosteroid-induced changes in growth rate during the first year of treatment appear to be temporary.
- Children with asthma treated with inhaled glucocorticosteroids attain normal adult height (predicted from family members) but at a later age.

**Figure 3-6. Summary: Bones and Glucocorticosteroids in Children[10,143,144]**

- No studies have reported any statistically significant increased of risk of fractures in children taking inhaled glucocorticosteroids.
- Oral or systemic glucocorticosteroid use increases the risk of fracture. The risk of fracture increases along with the number of treatments, with a 32% increase at four courses ever. Use of inhaled glucocorticosteroids reduces the need for systemic courses.
- Controlled longitudinal studies of 2 to 5 years≤duration and several cross-sectional studies found no adverse effects of inhaled glucocorticosteroid treatment on bone mineral density.
- No prospective studies have followed children on inhaled glucocorticosteroid treatment until peak bone mineral density has been reached.

Hypothalamic-pituitary-adrenal (HPA) axis. Though differences exist between the various inhaled glucocorticosteroids and inhaler devices, treatment with inhaled glucocorticosteroid doses of less than 200 μg budesonide or equivalent daily is normally not associated with any significant suppression of the HPA axis in children[135]. At higher doses, small changes in HPA axis function can be detected with sensitive methods[148]. The clinical relevance of these findings is not known, since there have not been reports of adrenal crisis in clinical trials of inhaled glucocorticosteroids in children. However, adrenal crisis has been reported in children treated with excessively high doses of inhaled glucocorticosteroids[150].

Cataracts. Inhaled glucocorticosteroids have not been associated with an increased occurrence of cataract development in children[30,135].

Central nervous system effects. Although isolated case reports have suggested that hyperactive behavior, aggressiveness, insomnia, uninhibited behavior, and impaired concentration may be seen with inhaled glucocorticosteroid treatment, no increase in such effects has been found in two long-term controlled trials of inhaled budesonide involving more than 10,000 treatment years[132,135].

Oral candidiasis, hoarseness, and bruising. Clinical thrush is seldom a problem in children treated with inhaled or systemic glucocorticosteroids. This side effect seems to be related to concomitant use of antibiotics, high daily doses, dose frequency, and inhaler device. Spacers reduce the incidence of oral candidiasis[151]. Mouth rinsing is beneficial[152]. The occurrence of hoarseness or other noticeable voice changes during budesonide treatment is similar to placebo[30]. Treatment with an average daily dose of 500 μg budesonide for 3 to 6 years is not associated with an increased tendency to bruise[30].

Dental side effects. Inhaled glucocorticosteroid treatment is not associated with increased incidence of caries. However, the increased level of dental erosion reported in children with asthma[153] may be due to a reduction in oral pH that may result from inhalation of $\beta_2$-agonists[154].

Other local side effects. The long-term use of inhaled glucocorticosteroids is not associated with an increased incidence of lower respiratory tract infections, including tuberculosis.

***Leukotriene modifiers.***

Children older than 5 years. Leukotriene modifiers provide clinical benefit in children older than 5 years at all levels of severity[155-159], but generally less than that of low-dose inhaled glucocorticosteroids[160]. Leukotriene modifiers provide partial protection against exercise-induced bronchoconstriction within hours after administration with no loss of bronchoprotective effect[200]. As add-on treatment in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers provide moderate clinical improvements, including a significant reduction in exacerbations[161,162]. Combination therapy is less effective in controlling asthma in children with moderate persistent asthma than increasing to moderate doses of inhaled glucocorticosteroids[201].

Children 5 years and younger. In addition to the efficacy as described above[163,164], leukotriene modifiers reduce viral-induced asthma exacerbations in children ages 2-5 with a history of intermittent asthma[164].

*Side effects* - No safety concerns have been demonstrated from the use of leukotriene modifiers in children.

***Long-acting inhaled $\beta_2$-agonists.***

*Role in therapy* - Long-acting inhaled $\beta_2$-agonists are primarily used as add-on therapy in children older than 5 years whose asthma is insufficiently controlled by medium doses of inhaled glucocorticosteroids or as single-dose therapy before vigorous exercise. Monotherapy with long-acting inhaled $\beta_2$-agonists should be avoided[75].

Children older than 5 years. Long-acting inhaled $\beta_2$-agonists have mainly been studied in children older than 5 years as add-on therapy for patients whose asthma is not controlled on low to high doses of inhaled glucocorticosteroids. Significant improvements in peak flow and other lung function measurements have been found in most studies[55,165-169]. However, their effects on other outcomes such as symptoms and need for reliever medication have been less consistent and have only been observed in about half of the trials conducted. Add-on treatment with long-acting inhaled $\beta_2$-agonists has not been shown to reduce the frequency of exacerbations[170]. Inhalation of a single dose of long-acting inhaled $\beta_2$-agonist effectively blocks exercise-induced bronchoconstriction for several hours[171]. With daily therapy the duration of the protection is somewhat reduced[171], but is still longer than that provided by short-acting $\beta_2$-agonists.

Combination products containing an inhaled glucocorticosteroid and a long-acting inhaled $\beta_2$-agonist are preferred to long-acting inhaled $\beta_2$-agonist and inhaled glucocorticosteroids administered by separate inhalers. Fixed combination inhalers ensure that the long-acting $\beta_2$-agonist is always accompanied by a glucocorticosteroid.

Children 5 years or younger. The effect of long-acting inhaled $\beta_2$-agonists has not yet been adequately studied. Combination therapy with budesonide and formoterol used both as maintenance and rescue has been shown to reduce asthma exacerbations in children ages 4 years and older with moderate to severe asthma[202].

*Side effects* - Although long-acting inhaled $\beta_2$-agonists are well-tolerated in children, even after long-term use, because of inconsistency of reports on their effects on exacerbations of asthma, they are not the recommended option when more than one controller is required[170]. If used, long-acting $\beta_2$-agonists should only be used in combination with an appropriate dose of inhaled glucocorticosteroid as determined by a physician, preferably in a fixed combination inhaler.

***Theophylline.***

*Role in therapy* - Theophylline has been shown to be effective as monotherapy and as add-on treatment to inhaled or oral glucocorticosteroids in children older than 5 years. It is significantly more effective than placebo at controlling day and night symptoms and improving lung function[172-174]. Maintenance treatment offers a marginal protective effect against exercise-induced bronchoconstriction[175]. Add-on treatment with theophylline has been found to improve asthma control and reduce the maintenance glucocorticosteroid dose necessary in children with severe asthma treated with inhaled or oral glucocorticosteroids[176,177]. A few studies in children 5 years and younger also suggest some clinical benefit. However, the efficacy of theophylline is less than that of low-dose inhaled glucocorticosteroids.

Most clinical evidence regarding the use of theophylline in children has been obtained from studies in which plasma theophylline levels were maintained within the therapeutic range of 55-110 µmol/L (5-10 µg/ml). Further studies suggest that its controller functions may occur at lower plasma levels (corresponding to doses of around 10 mg/kg/day). Sustained-release products are preferable for maintenance therapy, since they enable twice-daily dosing. Sustained-release products with reliable absorption profiles and complete bioavailability with and without concomitant food intake are preferred.

Theophylline elimination may vary up to tenfold between individuals. Measurement of plasma theophylline levels is not necessary in otherwise healthy children when doses less than 10 mg/kg/day are used. However, when higher doses are used or when drugs that may increase theophylline levels are also used chronically, plasma theophylline levels should be measured two hours before administration of the next dose once steady state has been reached (after 3 days).

*Side effects* - The most common side effects of theophylline are anorexia, nausea, vomiting, and headache[178]. Mild central nervous stimulation, palpitations, tachycardia, arrhythmias, abdominal pain, diarrhea, and, rarely, gastric bleeding may also occur. These side effects are mainly seen at doses higher than 10 mg/kg/day. The risk of adverse effects is reduced if treatment is initiated with daily doses around

5 mg/kg/day and then gradually increased to 10 mg/kg/day. Severe overdosing with theophylline can be fatal.

***Cromones: sodium cromoglycate and nedocromil sodium.***

*Role in therapy* - Sodium cromoglycate and nedocromil sodium have a limited role in the long-term treatment of asthma in children. One meta-analysis has concluded that long-term treatment with sodium cromoglycate is not significantly better than placebo for management of asthma in children[179]. Another has confirmed superiority of low dose inhaled glucocorticosteroids over sodium cromoglycate in persistent asthma, but as there were no placebo arms in these studies, the efficacy of sodium cromoglycate cannot be confirmed from the studies reviewed; no between treatment difference in safety was observed[180].

Nedocromil sodium has been shown to reduce exacerbations, but its effect on other asthma outcomes is not superior to placebo[135]. A single dose of sodium cromoglycate or nedocromil sodium attenuates bronchospasm induced by exercise or cold air[181]. Studies of the use of these medications in children 5 years and younger are sparse and results are conflicting.

*Side effects* - Cough, throat irritation, and bronchoconstriction occur in a small proportion of patients treated with sodium cromoglycate. A bad taste, headache, and nausea are the most common side effects of nedocromil[182].

***Long-acting oral $\beta_2$-agonists.***

Treatment with long-acting oral $\beta_2$-agonist such as slow release formulations of salbutamol, terbutaline, and bambuterol reduces nocturnal symptoms of asthma[183,184]. Due to their potential side effects of cardiovascular stimulation, anxiety, and skeletal muscle tremor, their use is not encouraged. If used, dosing should be individualized, and the therapeutic response monitored to limit side effects[185]. Long-acting oral B2-agonist therapy offers little or no protection against exercise-induced bronchoconstriction.

***Systemic glucocorticosteroids.***

Because of the side effects of prolonged use, oral glucocorticosteroids in children with asthma should be restricted to the treatment of acute severe exacerbations, whether viral-induced or otherwise.

**Reliever Medications**

***Rapid-acting inhaled ß2-agonists and short-acting oral $\beta_2$-agonists.***

*Role in therapy* - Rapid-acting inhaled $\beta_2$-agonists are the most effective bronchodilators available and therefore the preferred treatment for acute asthma in children of all ages. The inhaled route results in more rapid bronchodilation at a lower dose and with fewer side effects than oral or intravenous administration[186]. Furthermore, inhaled therapy offers significant protection against exercise-induced bronchoconstriction and other challenges for 0.5 to 2 hours (long acting $\beta_2$-agonists offer longer protection)[187]. This is not seen after systemic administration[188]. Oral therapy is rarely needed and reserved mainly for young children who cannot use inhaled therapy.

*Side effects* - Skeletal muscle tremor, headache, palpitations, and some agitation are the most common complaints associated with high doses of $\beta_2$-agonists in children. These complaints are more common after systemic administration and disappear with continued treatment[189].

***Anticholinergics.***

*Role in therapy* - Inhaled anticholinergics are not recommended for long-term management of asthma in children[190].

**REFERENCES**


1. Brown PH, Greening AP, Crompton GK. Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. *Thorax* 1993;48(3):233-8.
2. Dolovich M. New delivery systems and propellants. *Can Respir J* 1999;6(3):290-5.
3. Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered- dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12(6):1346-53.
4. Harrison LI, Soria I, Cline AC, Ekholm BP. Pharmacokinetic differences between chlorofluorocarbon and chlorofluorocarbon-free metered dose inhalers of beclomethasone dipropionate in adult asthmatics. *J Pharm Pharmacol* 1999;51(11):1235-40.
5. Juniper EF, Price DB, Stampone PA, Creemers JP, Mol SJ, Fireman P. Clinically important improvements in asthma-specific quality of life, but no difference in conventional clinical indexes in patients changed from conventional beclomethasone dipropionate to approximately half the dose of extrafine beclomethasone dipropionate. *Chest* 2002;121(6):1824-32.

6. Langley PC. The technology of metered-dose inhalers and treatment costs in asthma: a retrospective study of breath actuation versus traditional press-and- breathe inhalers. *Clin Ther* 1999;21(1):236-53.

7. Newman SP. A comparison of lung deposition patterns between different asthma inhalers. *J Aerosol Med* 1995;8 Suppl 3:21-6S.

8. Newman SP. Inhaler treatment options in COPD. *Eur Respir Rev* 2005;14(96):102-8.

9. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyper-responsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142(4):832-6.

10. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054-63.

11. Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson SA. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. A quantitative light and electron microscopic study. *Am Rev Respir Dis* 1992;145(4 Pt 1):890-9.

12. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337(20):1405-11.

13. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343(5):332-6.

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

15. Jayasiri B, Perera C. Successful withdrawal of inhaled corticosteroids in childhood asthma. *Respirology* 2005;10:385-8.

16. National Heart, Lung, and Blood Institute, Guidelines for Diagnosis and Management of Asthma. http://www.nhlbi.nih.gov/guidelines/asthma/ Date last updated: July 2007. Date last accessed, July 15, 2007.

17. Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. *Med J Aust* 2003;178(5):223-5.

18. Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, *et al.* Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109(3):410-8.

19. Lipworth BJ, Kaliner MA, LaForce CF, Baker JW, Kaiser HB, Amin D, *et al.* Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. *Ann Allergy Asthma Immunol* 2005;94(4):465-72.

20. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med* 1999;159(9):941-55.

21. Barnes PJ. Efficacy of inhaled corticosteroids in asthma. *J Allergy Clin Immunol* 1998;102(4 Pt 1):531-8.

22. Kamada AK, Szefler SJ, Martin RJ, Boushey HA, Chinchilli VM, Drazen JM, *et al.* Issues in the use of inhaled glucocorticoids. The Asthma Clinical Research Network. *Am J Respir Crit Care Med* 1996;153(6 Pt 1):1739-48.

23. Lee DK, Bates CE, Currie GP, Cowan LM, McFarlane LC, Lipworth BJ. Effects of high-dose inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal axis in asthmatic patients with severely impaired lung function. *Ann Allergy Asthma Immunol* 2004;93(3):253-8.

24. Mak VH, Melchor R, Spiro SG. Easy bruising as a side-effect of inhaled corticosteroids. *Eur Respir J* 1992;5(9):1068-74.

25. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;343(26):1902-9.

26. Pauwels RA, Yernault JC, Demedts MG, Geusens P. Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. Belgian Multicenter Study Group. *Am J Respir Crit Care Med* 1998;157(3 Pt 1):827-32.

27. Ernst P, Baltzan M, Deschenes J, Suissa S. Low-dose inhaled and nasal corticosteroid use and the risk of cataracts. *Eur Respir J* 2006;27(6):1168-74.

28. Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA* 1997;277(9):722-7.

29. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337(1):8-14.

30. Agertoft L, Larsen FE, Pedersen S. Posterior subcapsular cataracts, bruises and hoarseness in children with asthma receiving long-term treatment with inhaled budesonide. *Eur Respir J* 1998;12(1):130-5.

31. Toogood JH, Markov AE, Baskerville J, Dyson C. Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. *J Allergy Clin Immunol* 1993;91(2):571-9.

32. Simons FE, Persaud MP, Gillespie CA, Cheang M, Shuckett EP. Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoids. *Lancet* 1993;342(8874):776-8.

33. Bahceciler NN, Nuhoglu Y, Nursoy MA, Kodalli N, Barlan IB, Basaran MM. Inhaled corticosteroid therapy is safe in tuberculin-positive asthmatic children. *Pediatr Infect Dis J* 2000;19:215-8.

34. Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. *J Asthma* 2002;39(4):291-7.

35. Lipworth BJ. Leukotriene-receptor antagonists. *Lancet* 1999;353(9146):57-62.

36. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med* 1999;340(3):197-206.

37. Barnes NC, Miller CJ. Effect of leukotriene receptor antagonist therapy on the risk of asthma exacerbations in patients with mild to moderate asthma: an integrated analysis of zafirlukast trials. *Thorax* 2000;55(6):478-83.

38. Noonan MJ, Chervinsky P, Brandon M, Zhang J, Kundu S, McBurney J, *et al.* Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma. Montelukast Asthma Study Group. *Eur Respir J* 1998;11(6):1232-9.

39. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. *Arch Intern Med* 1998;158(11):1213-20.

40. Leff JA, Busse WW, Pearlman D, Bronsky EA, Kemp J, Hendeles L, *et al.* Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998;339(3):147-52.

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

42. Bleecker ER, Welch MJ, Weinstein SF, Kalberg C, Johnson M, Edwards L, *et al.* Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. *J Allergy Clin Immunol* 2000;105(6 Pt 1):1123-9.

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

44. Lofdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, *et al.* Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *BMJ* 1999;319(7202):87-90.

45. Virchow JC, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. *Am J Respir Crit Care Med* 2000;162(2 Pt 1):578-85.

46. Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, *et al.* Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58(3):211-6.

47. Vaquerizo MJ, Casan P, Castillo J, Perpina M, Sanchis J, Sobradillo V, *et al.* Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003;58(3):204-10.

48. Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening AP, Haahtela T, *et al.* Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. *BMJ* 2003;327(7420):891.

49. Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, *et al.* Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. J *Allergy Clin Immunol* 2000;106(6):1088-95.

50. Fish JE, Israel E, Murray JJ, Emmett A, Boone R, Yancey SW, *et al.* Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. *Chest* 2001;120(2):423-30.

51. Ringdal N, Eliraz A, Pruzinec R, Weber HH, Mulder PG, Akveld M, *et al.* The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. *Respir Med* 2003;97(3):234-41.

52. Wechsler ME, Finn D, Gunawardena D, Westlake R, Barker A, Haranath SP, *et al.* Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. *Chest* 2000;117(3):708-13.

53. Wechsler ME, Pauwels R, Drazen JM. Leukotriene modifiers and Churg-Strauss syndrome: adverse effect or response to corticosteroid withdrawal? *Drug Saf* 1999;21(4):241-51.

54. Harrold LR, Andrade SE, Go AS, Buist AS, Eisner M, Vollmer WM, *et al.* Incidence of Churg-Strauss syndrome in asthma drug users: a population-based perspective. *J Rheumatol* 2005;32(6):1076-80.

55. Lemanske RF, Jr., Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, *et al.* Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA* 2001;285(20):2594-603.

56. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF, Jr., Sorkness CA, *et al.* Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285(20):2583-93.

57. Pearlman DS, Chervinsky P, LaForce C, Seltzer JM, Southern DL, Kemp JP, *et al.* A comparison of salmeterol with albuterol in the treatment of mild-to- moderate asthma. *N Engl J Med* 1992;327(20):1420-5.

58. Kesten S, Chapman KR, Broder I, Cartier A, Hyland RH, Knight A, *et al.* A three-month comparison of twice daily inhaled formoterol versus four times daily inhaled albuterol in the management of stable asthma. *Am Rev Respir Dis* 1991;144 (3 Pt 1):622-5.

59. Wenzel SE, Lumry W, Manning M, Kalberg C, Cox F, Emmett A, *et al.* Efficacy, safety, and effects on quality of life of salmeterol versus albuterol in patients with mild to moderate persistent asthma. *Ann Allergy Asthma Immunol* 1998;80(6):463-70.

60. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000;320(7246):1368-73.

61. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153(5):1481-8.

62. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet* 1994;344(8917):219-24.

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

64. Lalloo UG, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, *et al.* Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. *Chest* 2003;123(5):1480-7.

65. Kips JC, O'Connor BJ, Inman MD, Svensson K, Pauwels RA, O'Byrne PM. A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. *Am J Respir Crit Care Med* 2000;161(3 Pt 1):996-1001.

66. Stoloff SW, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004;113(2):245-51.

67. Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T, *et al.* Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest* 2006;129(2):246-56.

68. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, *et al.* Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171(2):129-36.

69. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, *et al.* Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin* 2004;20(9):1403-18.

70. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, *et al.* Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J* 2005;26(5):819-28.

71. Nelson JA, Strauss L, Skowronski M, Ciufo R, Novak R, McFadden ER, Jr. Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998;339(3):141-6.

72. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lotvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *Eur Respir J* 1997;10(11):2484-9.

73. van Noord JA, Smeets JJ, Raaijmakers JA, Bommer AM, Maesen FP. Salmeterol versus formoterol in patients with moderately severe asthma: onset and duration of action. *Eur Respir J* 1996;9(8):1684-8.

74. Newnham DM, McDevitt DG, Lipworth BJ. Bronchodilator subsensitivity after chronic dosing with eformoterol in patients with asthma. *Am J Med* 1994;97(1):29-37.

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

76. Reference deleted.

77. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. *Lancet* 1994;343(8904):1006-8.

78. Kidney J, Dominguez M, Taylor PM, Rose M, Chung KF, Barnes PJ. Immunomodulation by theophylline in asthma. Demonstration by withdrawal of therapy. *Am J Respir Crit Care Med* 1995;151(6):1907-14.

79. Barnes PJ. Theophylline: new perspectives for an old drug. *Am J Respir Crit Care Med* 2003;167(6):813-8.

80. Dahl R, Larsen BB, Venge P. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. *Respir Med* 2002;96(6):432-8.

81. Rivington RN, Boulet LP, Cote J, Kreisman H, Small DI, Alexander M, et al. Efficacy of Uniphyl, salbutamol, and their combination in asthmatic patients on high-dose inhaled steroids. *Am J Respir Crit Care Med* 1995;151(2 Pt 1):325-32.

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

83. Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, *et al.* Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. *Eur Respir J* 1997;10(12):2754-60.

84. Baba K, Sakakibara A, Yagi T, Niwa S, Hattori T, Koishikawa I, *et al.* Effects of theophylline withdrawal in well-controlled asthmatics treated with inhaled corticosteroid. *J Asthma* 2001;38(8):615-24.

85. Davies B, Brooks G, Devoy M. The efficacy and safety of salmeterol compared to theophylline: meta- analysis of nine controlled studies. *Respir Med* 1998;92(2):256-63.

86. Wilson AJ, Gibson PG, Coughlan J. Long acting beta-agonists versus theophylline for maintenance treatment of asthma. *Cochrane Database Syst Rev* 2000;2.

87. Ahn HC, Lee YC. The clearance of theophylline is increased during the initial period of tuberculosis treatment. *Int J Tuberc Lung Dis* 2003;7(6):587-91.

88. Szefler SJ, Nelson HS. Alternative agents for anti-inflammatory treatment of asthma. *J Allergy Clin Immunol* 1998;102 (4 Pt 2):S23-35.

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

90. Milgrom H, Fick RB, Jr., Su JQ, Reimann JD, Bush RK, Watrous ML, *et al.* Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb- E25 Study Group. *N Engl J Med* 1999;341(26):1966-73.

91. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, *et al.* Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108(2):184-90.

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

93. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, *et al.* Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34(4):632-8.

94. Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, *et al.* Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004;170(6):583-93.

95. Mash B, Bheekie A, Jones PW. Inhaled vs oral steroids for adults with chronic asthma. *Cochrane Database Syst Rev* 2000;2.

96. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson SA. Bioequivalent doses of budesonide and prednisone in moderate and severe asthma. *J Allergy Clin Immunol* 1989;84(5 Pt 1):688-700.

97. Recommendations for the prevention and treatment of glucocorticoid- induced osteoporosis. American College of Rheumatology Task Force on Osteoporosis Guidelines. *Arthritis Rheum* 1996;39(11):1791-801.

98. Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. *Thorax* 2004;59(9):761-8.

99. Eastell R, Reid DM, Compston J, Cooper C, Fogelman I, Francis RM, *et al.* A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. *J Intern Med* 1998;244(4):271-92.

100. Guillevin L, Pagnoux C, Mouthon L. Churg-strauss syndrome. *Semin Respir Crit Care Med* 2004;25(5):535-45.

101. Kurosawa M. Anti-allergic drug use in Japan--the rationale and the clinical outcome. *Clin Exp Allergy* 1994;24(4):299-306.

102. Aaron SD, Dales RE, Pham B. Management of steroid-dependent asthma with methotrexate: a meta- analysis of randomized clinical trials. *Respir Med* 1998;92(8):1059-65.

103. Marin MG. Low-dose methotrexate spares steroid usage in steroid-dependent asthmatic patients: a meta-analysis. *Chest* 1997;112(1):29-33.

104. Davies H, Olson L, Gibson P. Methotrexate as a steroid sparing agent for asthma in adults. *Cochrane Database Syst Rev* 2000;2.

105. Lock SH, Kay AB, Barnes NC. Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. *Am J Respir Crit Care Med* 1996;153(2):509-14.

106. Bernstein IL, Bernstein DI, Dubb JW, Faiferman I, Wallin B. A placebo-controlled multicenter study of auranofin in the treatment of patients with corticosteroid-dependent asthma. Auranofin Multicenter Drug Trial. *J Allergy Clin Immunol* 1996;98(2):317-24.

107. Nierop G, Gijzel WP, Bel EH, Zwinderman AH, Dijkman JH. Auranofin in the treatment of steroid dependent asthma: a double blind study. *Thorax* 1992;47(5):349-54.

108. Richeldi L, Ferrara G, Fabbri L, Lasserson T, Gibson P. Macrolides for chronic asthma. *Cochrane Database Syst Rev* 2005(3):CD002997.

109. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. *Clin Immunol* 1999;91(2):126-33.

110. Salmun LM, Barlan I, Wolf HM, Eibl M, Twarog FJ, Geha RS, *et al.* Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomized trial. *J Allergy Clin Immunol* 1999;103(5 Pt 1):810-5.

111. Jakobsson T, Croner S, Kjellman NI, Pettersson A, Vassella C, Bjorksten B. Slight steroid-sparing effect of intravenous immunoglobulin in children and adolescents with moderately severe bronchial asthma. *Allergy* 1994;49(6):413-20.

112. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003(4):CD001186.

113. Bousquet J, Lockey R, Malling HJ, Alvarez-Cuesta E, Canonica GW, Chapman MD, *et al.* Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998;81(5 Pt 1):401-5.

114. Harrison BD, Stokes TC, Hart GJ, Vaughan DA, Ali NJ, Robinson AA. Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet* 1986;1(8474):181-4.

115. Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA, Jr. Corticosteroid therapy for acute asthma. *Respir Med* 2004;98(4):275-84.

116. O'Driscoll BR, Kalra S, Wilson M, Pickering CA, Carroll KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. *Lancet* 1993;341(8841):324-7.

117. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med* 1999;107(4):363-70.

118. Tamaoki J, Chiyotani A, Tagaya E, Sakai N, Konno K. Effect of long term treatment with oxitropium bromide on airway secretion in chronic bronchitis and diffuse panbronchiolitis. *Thorax* 1994;49(6):545-8.

119. Weinberger M, Hendeles L. Theophylline in asthma. *N Engl J Med* 1996;334(21):1380-8.

120. Hondras MA, Linde K, Jones AP. Manual therapy for asthma. *Cochrane Database Syst Rev* 2005(2):CD001002.

121. Balon JW, Mior SA. Chiropractic care in asthma and allergy. *Ann Allergy Asthma Immunol* 2004;93 (2 Suppl 1):S55-60.

122. Slader CA, Reddel HK, Spencer LM, Belousova EG, Armour CL, Bosnic-Anticevich SZ, Thien FC, Jenkins CR. Double blind randomised controlled trial of two different breathing techniques in the management of asthma. *Thorax* 2006 Aug;61(8):651-6.

123. Bisgaard H. Delivery of inhaled medication to children. *J Asthma* 1997;34(6):443-67.

124. Pedersen S. Inhalers and nebulizers: which to choose and why. *Respir Med* 1996;90(2):69-77.

125. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, *et al.* Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005;127(1):335-71.

126. Zar HJ, Weinberg EG, Binns HJ, Gallie F, Mann MD. Lung deposition of aerosol—a comparison of different spacers. *Arch Dis Child* 2000;82(6):495-8.

127. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2006(2):CD000052.

128. Shapiro G, Bronsky EA, LaForce CF, Mendelson L, Pearlman D, Schwartz RH, *et al.* Dose-related efficacy of budesonide administered via a dry powder inhaler in the treatment of children with moderate to severe persistent asthma. *J Pediatr* 1998;132(6):976-82.

129. Agertoft L, Pedersen S. A randomized, double-blind dose reduction study to compare the minimal effective dose of budesonide Turbuhaler and fluticasone propionate Diskhaler. *J Allergy Clin Immunol* 1997;99(6 Pt 1):773-80.

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

131. Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev* 2005(1):CD002738.

132. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, *et al.* Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361(9363):1071-6.

133. Adams NP, Bestall JC, Jones PW, Lasserson TJ, Griffiths B, Cates C. Inhaled fluticasone at different doses for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005(3):CD003534.

134. Powell H, Gibson PG. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. *Cochrane Database Syst Rev* 2004(2):CD004109.

135. Reference 135 deleted.

136. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1500-6.

137. Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol* 2001;108(4):540-6.

138. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354(19):1985-97.

139. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354(19):1998-2005.

140. Pedersen S. Do inhaled corticosteroids inhibit growth in children? *Am J Respir Crit Care Med* 2001;164(4):521-35.

141. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343(15):1064-9.

142. Sharek PJ, Bergman DA. Beclomethasone for asthma in children: effects on linear growth. *Cochrane Database Syst Rev* 2000;2.

143. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. *Am J Respir Crit Care Med* 1998;157(1):178-83.

144. Hopp RJ, Degan JA, Biven RE, Kinberg K, Gallagher GC. Longitudinal assessment of bone mineral density in children with chronic asthma. *Ann Allergy Asthma Immunol* 1995;75(2):143-8.

145. Schlienger RG, Jick SS, Meier CR. Inhaled corticosteroids and the risk of fractures in children and adolescents. *Pediatrics* 2004;114(2):469-73.

146. van Staa TP, Bishop N, Leufkens HG, Cooper C. Are inhaled corticosteroids associated with an increased risk of fracture in children? *Osteoporos Int* 2004;15(10):785-91.

147. van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;18(5):913-8.

148. Kemp JP, Osur S, Shrewsbury SB, Herje NE, Duke SP, Harding SM, *et al.* Potential effects of fluticasone propionate on bone mineral density in patients with asthma: a 2-year randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2004;79(4):458-66.

149. Roux C, Kolta S, Desfougeres JL, Minini P, Bidat E. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. *Pediatrics* 2003;111(6 Pt 1): e706-13.

150. Todd G, Dunlop K, McNaboe J, Ryan MF, Carson D, Shields MD. Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996;348(9019):27-9.

151. Selroos O, Backman R, Forsen KO, Lofroos AB, Niemisto M, Pietinalho A, *et al.* Local side-effects during 4-year treatment with inhaled corticosteroids- -a comparison between pressurized metered-dose inhalers and Turbuhaler. *Allergy* 1994;49(10):888-90.

152. Randell TL, Donaghue KC, Ambler GR, Cowell CT, Fitzgerald DA, van Asperen PP. Safety of the newer inhaled corticosteroids in childhood asthma. *Paediatr Drugs* 2003;5(7):481-504.

153. Shaw L, al-Dlaigan YH, Smith A. Childhood asthma and dental erosion. *ASDC J Dent Child* 2000;67(2):102-6, 82.

154. Kargul B, Tanboga I, Ergeneli S, Karakoc F, Dagli E. Inhaler medicament effects on saliva and plaque pH in asthmatic children. *J Clin Pediatr Dent* 1998;22(2):137-40.

155. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, *et al.* Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115(2):233-42.

156. Ostrom NK, Decotiis BA, Lincourt WR, Edwards LD, Hanson KM, Carranza Rosenzweig JR, *et al.* Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr* 2005;147(2):213-20.

157. Garcia Garcia ML, Wahn U, Gilles L, Swern A, Tozzi CA, Polos P. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics* 2005;116(2):360-9.

158. Ng D, Salvio F, Hicks G. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev* 2004(2):CD002314.

159. Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TF, Seidenberg BC, *et al.* Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998;133(3):424-8.

160. Vidal C, Fernandez-Ovide E, Pineiro J, Nunez R, Gonzalez-Quintela A. Comparison of montelukast versus budesonide in the treatment of exercise-induced bronchoconstriction. *Ann Allergy Asthma Immunol* 2001;86(6):655-8.

161. Phipatanakul W, Cronin B, Wood RA, Eggleston PA, Shih MC, Song L, *et al.* Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. *Ann Allergy Asthma Immunol* 2004;92(4):420-5.

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

163. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108(3):E48.

164. Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, *et al.* Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;171(4):315-22.

165. Russell G, Williams DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. *Ann Allergy Asthma Immunol* 1995;75(5):423-8.

166. Malone R, LaForce C, Nimmagadda S, Schoaf L, House K, Ellsworth A, *et al.* The safety of twice-daily treatment with fluticasone propionate and salmeterol in pediatric patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005;95(1):66-71.

167. Zimmerman B, D'Urzo A, Berube D. Efficacy and safety of formoterol Turbuhaler when added to inhaled corticosteroid treatment in children with asthma. *Pediatr Pulmonol* 2004;37(2):122-7.

168. Meijer GG, Postma DS, Mulder PG, van Aalderen WM. Long-term circadian effects of salmeterol in asthmatic children treated with inhaled corticosteroids. *Am J Respir Crit Care Med* 1995;152(6 Pt 1):1887-92.

169. Bisgaard H. Long-acting beta(2)-agonists in management of childhood asthma: A critical review of the literature. *Pediatr Pulmonol* 2000;29(3):221-34.

170. Bisgaard H. Effect of long-acting beta2 agonists on exacerbation rates of asthma in children. *Pediatr Pulmonol* 2003;36(5):391-8.

171. Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997;99(5):655-9.

172. Katz RM, Rachelefsky GS, Siegel S. The effectiveness of the short- and long-term use of crystallized theophylline in asthmatic children. *J Pediatr* 1978;92(4):663-7.

173. Bierman CW, Pierson WE, Shapiro GG, Furukawa CT. Is a uniform round-the-clock theophylline blood level necessary for optimal asthma therapy in the adolescent patient? *Am J Med* 1988;85(1B):17-20.

174. Pedersen S. Treatment of nocturnal asthma in children with a single dose of sustained-release theophylline taken after supper. *Clin Allergy* 1985;15(1):79-85.

175. Magnussen H, Reuss G, Jorres R. Methylxanthines inhibit exercise-induced bronchoconstriction at low serum theophylline concentration and in a dose-dependent fashion. *J Allergy Clin Immunol* 1988;81(3):531-7.

176. Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. *N Engl J Med* 1981;304(2):71-5.

177. Brenner M, Berkowitz R, Marshall N, Strunk RC. Need for theophylline in severe steroid-requiring asthmatics. *Clin Allergy* 1988;18(2):143-50.

178. Ellis EF. Theophylline toxicity. *J Allergy Clin Immunol* 1985;76 (2 Pt 2):297-301.

179. Tasche MJ, Uijen JH, Bernsen RM, de Jongste JC, van Der Wouden JC. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: a systematic review. *Thorax* 2000;55(11):913-20.

180. Guevara JP, Ducharme FM, Keren R, Nihtianova S, Zorc J. Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. *Cochrane Database Syst Rev* 2006(2):CD003558.

181. Spooner CH, Saunders LD, Rowe BH. Nedocromil sodium for preventing exercise-induced bronchoconstriction. *Cochrane Database Syst Rev* 2000;2.

182. Armenio L, Baldini G, Bardare M, Boner A, Burgio R, Cavagni G, *et al.* Double blind, placebo controlled study of nedocromil sodium in asthma. *Arch Dis Child* 1993;68(2):193-7.

183. Kuusela AL, Marenk M, Sandahl G, Sanderud J, Nikolajev K, Persson B. Comparative study using oral solutions of bambuterol once daily or terbutaline three times daily in 2-5-year-old children with asthma. Bambuterol Multicentre Study Group. *Pediatr Pulmonol* 2000;29(3):194-201.

184. Zarkovic JP, Marenk M, Valovirta E, Kuusela AL, Sandahl G, Persson B, *et al.* One-year safety study with bambuterol once daily and terbutaline three times daily in 2-12-year-old children with asthma. The Bambuterol Multicentre Study Group. *Pediatr Pulmonol* 2000;29(6):424-9.

185. Lonnerholm G, Foucard T, Lindstrom B. Oral terbutaline in chronic childhood asthma; effects related to plasma concentrations. *Eur J Respir Dis* 1984;134 Suppl:205-10S.

186. Williams SJ, Winner SJ, Clark TJ. Comparison of inhaled and intravenous terbutaline in acute severe asthma. *Thorax* 1981;36(8):629-32.

187. Dinh Xuan AT, Lebeau C, Roche R, Ferriere A, Chaussain M. Inhaled terbutaline administered via a spacer fully prevents exercise- induced asthma in young asthmatic subjects: a double-blind, randomized, placebo-controlled study. *J Int Med Res* 1989;17(6):506-13.

188. Fuglsang G, Hertz B, Holm EB. No protection by oral terbutaline against exercise-induced asthma in children: a dose-response study. *Eur Respir J* 1993;6(4):527-30.

189. Bengtsson B, Fagerstrom PO. Extrapulmonary effects of terbutaline during prolonged administration. *Clin Pharmacol Ther* 1982;31(6):726-32.

190. McDonald NJ, Bara AI. Anticholinergic therapy for chronic asthma in children over two years of age. *Cochrane Database Syst Rev* 2003(3):CD003535.

191. Adams NP, Jones PW. The dose-response characteristics of inhaled corticosteroids when used to treat asthma: an overview of Cochrane systematic reviews. *Respir Med* 2006 Aug;100(8):1297-306.

192. Deykin A, Wechsler ME, Boushey HA, Chinchilli VM, Kunselman SJ, Craig TJ, DiMango E, Fahy JV, Kraft M, Leone F, Lazarus SC, Lemanske RF Jr, Martin RJ, Pesola GR, Peters SP, Sorkness CA, Szefler SJ, Israel E; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Combination therapy with a long-acting beta-agonist and a leukotriene antagonist in moderate asthma. *Am J Respir Crit Care Med* 2007 Feb 1;175(3):228-34.

193. Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance long-acting beta-agonist and inhaled corticosteroid on asthma control and asthma exacerbations. *J Allergy Clin Immunol* 2007 Feb;119(2):344-50.

194. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006 Aug 26;368(9537):744-53.

195. Bleecker ER, Yancey SW, Baitinger LA, Edwards LD, Klotsman M, Anderson WH, Dorinsky PM. Salmeterol response is not affected by beta2-adrenergic receptor genotype in subjects with persistent asthma. *J Allergy Clin Immunol* 2006 Oct;118(4):809-16.

196. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006 Oct;61(10):1162-72.

197. Shaheen SO, Newson RB, Rayman MP, Wong AP, Tumilty MK, Phillips JM, Potts JF, Kelly FJ, White PT, Burney PG. Randomised, double blind, placebo-controlled trial of selenium supplementation in adult asthma. *Thorax* 2007 Jun;62(6):483-90.

198. Manocha R, Marks GB, Kenchington P, Peters D, Salome CM. Sahaja yoga in the management of moderate to severe asthma: a randomised controlled trial. *Thorax* 2002;57:110-5.

199. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A; IFWIN study team. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy INfants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006 Aug 26;368(9537):754-62.

200. de Benedictis FM, del Giudice MM, Forenza N, Decimo F, de Benedictis D, Capristo A. Lack of tolerance to the protective effect of montelukast in exercise-induced bronchoconstriction in children. *Eur Respir J* 2006 Aug;28(2):291-5.

201. Jat GC, Mathew JL, Singh M. Treatment with 400 microg of inhaled budesonide vs 200 microg of inhaled budesonide and oral montelukast in children with moderate persistent asthma: randomized controlled trial. *Ann Allergy Asthma Immunol* 2006 Sep;97(3):397-401.

202. Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006 Dec;130(6):1733-43.

203. Nelson H, Kemp J, Berger W, Corren J, Casale T, Dube L, Walton-Bowen K, LaVallee N, Stepanians M. Efficacy of zileuton controlled-release tablets administered twice daily in the treatment of moderate persistent asthma: a 3-month randomized controlled study. *Ann Allergy Asthma Immuno* 2007 Aug;99(2):178-84.

204. Watkins PB, Dube LM, Walton-Bowen K, Cameron CM, Kasten LE. Clinical pattern of zileuton-associated liver injury: results of a 12-month study in patients with chronic asthma. *Drug Saf* 2007;30(9):805-15.

205. Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, Yancey S. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. *Ann Intern Med* 2008 Jul 1;149(1):33-42. Epub 2008 Jun 3.

206. Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to long-acting beta2-agonist therapy: a pharmacogenetic analysis of two randomised studies. *Lancet* 2007 Dec 22;370(9605):2118-25.

207. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005;60(3):302-8.

208. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al; (The PAT investigator group). Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007 Aug;62(8):943-8.

209. Pearlman DS, Rees W, Schaefer K, Huang H, Andrews WT. An evaluation of levalbuterol HFA in the prevention of exercise-induced bronchospasm. *J Asthma* 2007 Nov;44(9):729-33.

210. Holloway EA, West RJ. Integrated breathing and relaxation training (the Papworth method) for adults with asthma in primary care: a randomised controlled trial. *Thorax* 2007 Dec;62(12):1039-42. Epub 2007 Jun 15.

211. Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen YZ, Lamm CJ, O'Byrne PM; START Investigators Group. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol* 2008 May;121(5):1167-74. Epub 2008 Apr 11.

# CHAPTER

# 4

# *ASTHMA MANAGEMENT AND PREVENTION*

## INTRODUCTION

Asthma has a significant impact on individuals, their families, and society. Although there is no cure for asthma, appropriate management that includes a partnership between the physician and the patient/family most often results in the achievement of control.

The goals for successful management of asthma are to:

- Achieve and maintain control of symptoms
- Maintain normal activity levels, including exercise
- Maintain pulmonary function as close to normal as possible
- Prevent asthma exacerbations
- Avoid adverse effects from asthma medications
- Prevent asthma mortality.

These goals for therapy reflect an understanding of asthma as a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Clinical studies have shown that asthma can be effectively controlled by intervening to suppress and reverse the inflammation as well as treating the bronchoconstriction and related symptoms. Furthermore, early intervention to stop exposure to the risk factors that sensitized the airway may help improve the control of asthma and reduce medication needs. Experience in occupational asthma indicates that long-standing exposure to sensitizing agents may lead to irreversible airflow limitation.

The management of asthma can be approached in different ways, depending on the availability of the various forms of asthma treatment and taking into account cultural preferences and differing health care systems. The recommendations in this chapter reflect the current scientific understanding of asthma. They are based as far as possible on controlled clinical studies, and the text references many of these studies. For those aspects of the clinical management of asthma that have not been the subject of specific clinical studies, recommendations are based on literature review, clinical experience, and expert opinion of project members.

The recommendations for asthma management are laid out in five interrelated components of therapy:

1. Develop Patient/Doctor Partnership
2. Identify and Reduce Exposure to Risk Factors
3. Assess, Treat, and Monitor Asthma
4. Manage Asthma Exacerbations
5. Special Considerations.

## COMPONENT 1: DEVELOP PATIENT/DOCTOR PARTNERSHIP

**KEY POINTS:**

- The effective management of asthma requires the development of a partnership between the person with asthma and his or her health care professional(s) (and parents/caregivers, in the case of children with asthma).
- The aim of this partnership is guided self-management—that is, to give people with asthma the ability to control their own condition with guidance from health care professionals.
- The partnership is formed and strengthened as patients and their health care professionals discuss and agree on the goals of treatment, develop a personalized, written self-management plan including self-monitoring, and periodically review the patient≤s treatment and level of asthma control.
- Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.
- Personal asthma action plans help individuals with asthma make changes to their treatment in response to changes in their level of asthma control, as indicated by symptoms and/or peak expiratory flow, in accordance with written predetermined guidelines.

## INTRODUCTION

The effective management of asthma requires the development of a partnership between the person with asthma and his or her health care professional(s) (and parents/caregivers in the case of children with asthma). The aim of this partnership is to enable patients with asthma to gain the knowledge, confidence, and skills to assume a major role in the management of their asthma. The partnership is formed and strengthened as patients and their health care professionals discuss and agree on the goals of treatment, develop a personalized, written self-management action plan including self-monitoring, and periodically review the patient≤s treatment and level of asthma control (**Figure 4.1-1**).

This approach is called guided self-management and has been shown to reduce asthma morbidity in both adults (**Evidence A**) and children (**Evidence A**). A number of specific systems of guided self-management have been

developed[1-10] for use in a wide range of settings, including primary care[1,4,6], hospitals[2,3,7,10], emergency departments[8], and internet-based home monitoring[340], and among such diverse groups as pregnant women with asthma[11], children and adolescents[12,13], and in multi-racial populations[14]. Guided self-management may involve varying degrees of independence, ranging broadly from patient-directed self-management in which patients make changes without reference to their caregiver, but in accordance with a prior written action plan, to doctor-directed self-management in which patients rely follow a written action plan, but refer most major treatment changes to their physician at the time of planned or unplanned consultations. Cochrane systematic reviews[13,15-18] have examined the role of education and self-management strategies in the care of asthma patients.

**Figure 4.1-1. Essential Features of the Doctor-Patient Partnership to Achieve Guided Self-Management in Asthma**

- Education
- Joint setting of goals
- Self-monitoring. The person with asthma is taught to combine assessment of asthma control with educated interpretation of key symptoms
- Regular review of asthma control, treatment, and skills by a health care professional
- Written action plan. The person with asthma is taught which medications to use regularly and which to use as needed, and how to adjust treatment in response to worsening asthma control
- Self-monitoring is integrated with written guidelines for both the long-term treatment of asthma and the treatment of asthma exacerbations.

## ASTHMA EDUCATION

Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. Although the focus of education for small children will be on the parents and caregivers, children as young as 3 years of age can be taught simple asthma management skills. Adolescents may have some unique difficulties regarding adherence that may be helped through peer support group education in addition to education provided by the health care professional[12].

**Figure 4.1-2** outlines the key features and components of an asthma education program. The information and skills training required by each person may vary, and their ability or willingness to take responsibility similarly differs. Thus all individuals require certain core information and skills, but most education must be personalized and given to the person in a number of steps. Social and psychological support may also be required to maintain positive behavioral change.

**Figure 4.1-2. Education and the Patient/Doctor Partnership**

**Goal:** To provide the person with asthma, their family, and other caregivers with suitable information and training so that they can keep well and adjust treatment according to a medication plan developed with the health care professional.

**Key components:**

- ❑ Focus on the development of the partnership
- ❑ Acceptance that this is a continuing process
- ❑ A sharing of information
- ❑ Full discussion of expectations
- ❑ Expression of fears and concerns

**Provide specific information, training, and advice about:**

- ❑ Diagnosis
- ❑ Difference between “relievers” and “controllers”
- ❑ Potential side effects of medications
- ❑ Use of inhaler devices
- ❑ Prevention of symptoms and attacks
- ❑ Signs that suggest asthma is worsening and actions to take
- ❑ Monitoring control of asthma
- ❑ How and when to seek medical attention

**The person then requires:**

- ❑ A guided self-management plan
- ❑ Regular supervision, revision, reward, and reinforcement

*Good communication* is essential as the basis for subsequent good compliance/adherence[19-22] (**Evidence B**). Key factors that facilitate good communication are[23]:

- A congenial demeanor (friendliness, humor, and attentiveness)
- Engaging in interactive dialogue
- Giving encouragement and praise
- Empathy, reassurance, and prompt handling of any concerns
- Giving of appropriate (personalized) information
- Eliciting shared goals
- Feedback and review

*Teaching health care professionals to improve their communication skills* can result in measurably better outcomes–including increased patient satisfaction, better health, and reduced use of health care–and these benefits may be achieved without any increase in consultation times[24]. Studies have also shown that *patients can be trained to benefit more from consultations*. Patients taught how to give information to doctors in a clearer manner, information-seeking techniques, and methods of checking their understanding of what the doctor had told them gained significant improvements in compliance and overall health[25].

**At the Initial Consultation**

Early in the consultation the person with asthma needs information about the diagnosis and simple information about the types of treatment available, the rationale for the specific therapeutic interventions being recommended, and strategies for avoiding factors that cause asthma symptoms. Different inhaler devices can be demonstrated, and the person with asthma encouraged to participate in the decision as to which is most suitable for them. Some of these devices and techniques for their use are illustrated on the GINA Website (http://www.ginasthma.org). Criteria for initial selection of inhaler device include device availability and cost, patient skills, and preferences of the health professional and patient[26-28]. Patients should be given adequate opportunity to express their expectations of both their asthma and its treatment. A frank appraisal should be made of how far their expectations may or may not be met, and agreement should be made about specific goals for therapy.

At the initial consultation, verbal information should be supplemented by the provision of written or pictorial[29, 30] information about asthma and its treatment. The GINA Website (http://www.ginasthma.org) contains patient educational materials, as well as links to several asthma websites. The patient and his or her family should be encouraged to make a note of any questions that arise from reading this information or as a result of the consultation, and should be given time to address these during the next consultation.

**Personal Asthma Action Plans**

Personal asthma action plans help individuals with asthma make changes to their treatment in response to changes in their level of asthma control, as indicated by symptoms and/or peak expiratory flow, in accordance with written predetermined guidelines[23,31,32].

The effects were greatest where the intervention involved each of the following elements: education, self-monitoring, regular review, and patient-directed self-management using a written self-management action plan (**Evidence A**). Patients experience a one-third to two-thirds reduction in hospitalizations, emergency room visits, unscheduled visits to the doctor for asthma, missed days of work, and nocturnal wakening. It has been estimated that the implementation of a self-management program in 20 patients prevents one hospitalization, and successful completion of such a program by eight patients prevents one emergency department visit[16-18,23]. Less intensive interventions that involve self-management education but not a written plan are less effective[15]. The efficacy is similar regardless of whether patients self-adjust their medications according to an individual written plan or adjustments of medication are made by a doctor[15] (**Evidence B**). Thus, patients who are unable to undertake guided self-management can still achieve benefit from a structured program of regular medical review. Although interactive computerized asthma education programs may improve patient asthma knowledge and symptoms, their effect on objective clinical outcomes is less consistent[353].

Examples of self-management plans that have been recommended can be found on several Websites (UK National Asthma Campaign Plan, http://www.asthma.org.uk; International Asthma Management Plan “Zone System,” http://www.nhlbisupport.com/asthma/index.html; New Zealand “Credit Card” System, http://www.asthmanz.co.nz.

An example of the contents for an asthma plan for patients to maintain control of asthma is shown in **Figure 4.1-3**.

**Follow-Up and Review**

Follow-up consultations should take place at regular intervals. At these visits, the patient≤s questions are discussed, and any problems with asthma and its initial treatment are reviewed. Inhaler device technique should be assessed regularly, and corrected if inadequate[33]. Follow-up consultations should also include checking the person≤s adherence/compliance to the medication plan and recommendations for reducing exposure to risk factors. Symptoms (and where appropriate, home peak flow recordings) noted in the diary are also reviewed regularly. After a period of initial training, the frequency of home peak flow and symptom monitoring depends in part on the level of control of the person≤s asthma. Routine follow-up visits may be an effective time to review the written self-managment plan and its understanding[354]. Educational messages should be reviewed and repeated or added to if necessary. A single page prompt to clinicians has been shown to improve the provision of preventive care to children with asthma during office visits[341].

**Improving Adherence**

Studies of adults and children[34] have shown that around 50% of those on long-term therapy fail to take medications as directed at least part of the time. Patient concern about side-effects of inhaled glucocorticosteroids whether real or perceived may influence adherence[342]. *Non-adherence may be defined* in a nonjudgmental way as the failure of treatment to be taken as agreed upon by the patient and the health care professional. *Non-adherence may be identified* by prescription monitoring, pill counting, or drug assay, but at a clinical level it is best detected by asking about therapy in a way that acknowledges the likelihood of

incomplete adherence (e.g., “So that we may plan therapy, do you mind telling me how often you actually take the medicine?”). Specific drug and non-drug factors involved in non-adherence are listed in **Figure 4.1-4**.

**Fig 4.1-3 Example Of Contents Of An Action Plan To Maintain Asthma Control**

**Your Regular Treatment:**
1. **Each day take _____**
2. **Before exercise, take _____**

**WHEN TO INCREASE TREATMENT**
**Assess your level of Asthma Control**
**In the past week have you had:**

| | | |
|---|---|---|
| **Daytime asthma symptoms more than 2 times ?** | **No** | **Yes** |
| **Activity or exercise limited by asthma?** | **No** | **Yes** |
| **Waking at night because of asthma?** | **No** | **Yes** |
| **The need to use your [rescue medication] more than 2 times?** | **No** | **Yes** |
| **If you are monitoring peak flow, peak flow less than_____?** | **No** | **Yes** |

***If you answered YES to three or more of these questions, your asthma is uncontrolled and you may need to step up your treatment.***

**HOW TO INCREASE TREATMENT**
**STEP-UP your treatment as follows and assess improvement every day:**
**_____ [Write in next treatment step here]**
**Maintain this treatment for _____ days [specify number]**

**WHEN TO CALL THE DOCTOR/CLINIC.**
**Call your doctor/clinic: _____ [provide phone numbers]**
**If you don t respond in _____ days [specify number]**
**_____ [optional lines for additional instruction]**

**EMERGENCY/SEVERE LOSS OF CONTROL**
- ✓**If you have severe shortness of breath, and can only speak in short sentences,**
- ✓**If you are having a severe attack of asthma and are frightened,**
- ✓**If you need your reliever medication more than every 4 hours and are not improving.**

1. **Take 2 to 4 puffs _____ [reliever medication]**
2. **Take ____mg of _____ [oral glucocorticosteroid]**
3. **Seek medical help: Go to _____; Address_____ Phone: _____**
4. **Continue to use your _____[reliever medication] until you are able to get medical help.**

**Figure 4.1-4. Factors Involved in Non-Adherence**

| Drug factors | Non-drug factors |
|---|---|
| Difficulties with inhaler devices | Misunderstanding or lack of instruction |
| Awkward regimes (e.g., four times daily or multiple drugs) | Fears about side effects |
| Side effects | Dissatisfaction with health care professionals |
| Cost of medication | Unexpressed/undiscussed fears or concerns |
| Dislike of medication | Inappropriate expectations |
| Distant pharmacies | Poor supervision, training, or follow-up |
| | Anger about condition or its treatment |
| | Underestimation of severity |
| | Cultural issues |
| | Stigmatization |
| | Forgetfulness or complacency |
| | Attitudes toward ill health |
| | Religious issues |

**Self-Management in Children**

Children with asthma (with the help of their parents/ caregivers) also need to know how to manage their own condition. Simple educational interventions (designed to teach self-management skills) among children admitted to the hospital with asthma have been shown to significantly reduce the readmission rate and reduce morbidity[13]. A systematic review found that educational programs for the self-management of asthma in children and adolescents led to improvements in lung function and feelings of self-control, and reduced absences from school, the number of days with restricted activity, and the number of emergency department visits[13,343]. For children, symptom-based action plans are more effective than those based on peak flows[355].

## THE EDUCATION OF OTHERS

The education of the general public about asthma is helpful in that it enables members of the public to recognize asthma symptoms and their consequences and encourages those with asthma to seek medical attention and follow their asthma management program. Greater awareness of asthma is also likely to help dispel misconceptions that may exist about the condition and reduce feelings of stigmatization on the part of patients.

Specific advice about asthma and its management should be offered to school teachers and physical education instructors, and several organizations produce materials for this purpose. Schools may need advice on improving the environment and air quality for children with asthma[35]. It is also helpful for employers to have access to clear advice about asthma. Most occupations are as suitable for those with asthma as for those without, but there may be some circumstances where caution is needed.

## COMPONENT 2: IDENTIFY AND REDUCE EXPOSURE TO RISK FACTORS

**KEY POINTS:**

- Pharmacologic intervention to treat established asthma is highly effective in controlling symptoms and improving quality of life. However, measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented wherever possible.
- At this time, few measures can be recommended for prevention of asthma because the development of the disease is complex and incompletely understood.
- Asthma exacerbations may be caused by a variety of risk factors, sometimes referred to as "triggers," including allergens, viral infections, pollutants, and drugs.
- Reducing a patient≤s exposure to some categories of risk factors improves the control of asthma and reduces medication needs.
- The early identification of occupational sensitizers and the removal of sensitized patients from any further exposure are important aspects of the management of occupational asthma.

## INTRODUCTION

Although pharmacologic intervention to treat established asthma is highly effective in controlling symptoms and improving quality of life, measures to prevent the development of asthma, asthma symptoms, and asthma by avoiding or reducing exposure to risk factors should be implemented wherever possible[36]. At this time, few measures can be recommended for prevention of asthma because the development of the disease is complex and incompletely understood. This area is a focus of intensive research, but until such measures are developed prevention efforts must primarily focus on prevention of asthma symptoms and attacks.

## ASTHMA PREVENTION

Measures to prevent asthma may be aimed at the prevention of allergic sensitization (i.e., the development of atopy, likely to be most relevant prenatally and perinatally), or the prevention of asthma development in sensitized people.

Other than preventing tobacco exposure both *in utero* and after birth, there are no proven and widely accepted interventions that can prevent the development of asthma.

Allergic sensitization can occur prenatally[37,38]. There is currently insufficient information on the critical doses and timing of allergen exposure to permit intervention in this process, and no strategies can be recommended to prevent allergic sensitization prenatally. Prescription of an antigen-avoidance diet to a high-risk woman during pregnancy is unlikely to reduce substantially her risk of giving birth to an atopic child[39]. Moreover, such a diet may have an adverse effect on maternal and/or fetal nutrition.

The role of diet, particularly breast-feeding, in relation to the development of asthma has been extensively studied and, in general, infants fed formulas of intact cow≤s milk or soy protein compared with breast milk have a higher incidence of wheezing illnesses in early childhood[40]. Exclusive breast-feeding during the first months after birth is associated with lower asthma rates during childhood[41].

The “hygiene hypothesis” of asthma, though controversial, has led to the suggestion that strategies to prevent allergic sensitization should focus on redirecting the immune response of infants toward a Th1, nonallergic response or on modulating T regulator cells[42], but such strategies currently remain in the realm of hypothesis and require further investigation. The role of probiotics in the prevention of allergy and asthma is also unclear[43]. Exposure to cats has been shown to reduce risk of atopy in some studies[44].

Exposure to tobacco smoke both prenatally and postnatally is associated with measurable harmful effects, including effects on lung development[45] and a greater risk of developing wheezing illnesses in childhood[46]. Although there is little evidence that maternal smoking during pregnancy has an effect on allergic sensitization[47], passive smoking increases the risk of allergic sensitization in children[47,48]. Both prenatal and postnatal maternal smoking is problematic[49]. Pregnant women and parents of young children should be advised not to smoke (**Evidence B**).

Once allergic sensitization has occurred, there are theoretically still opportunities to prevent the actual development of asthma. Whether $H_1$-antagonists (antihistamines)[50,51] or allergen-specific immunotherapy[52,53] can prevent the development of asthma in children who have other atopic diseases remains an area of investigation, and these interventions cannot be recommended for wide adoption in clinical practice at this time.

## PREVENTION OF ASTHMA SYMPTOMS AND EXACERBATIONS

Asthma exacerbations may be caused by a variety of factors, sometimes referred to as "triggers," including allergens, viral infections, pollutants, and drugs. Reducing a patient≤s exposure to some of these categories of risk factors (e.g., smoking cessation, reducing exposure to secondhand smoke, reducing or eliminating exposure to occupational agents known to cause symptoms, and avoiding foods/additives/drugs known to cause symptoms) improves the control of asthma and reduces medication needs. In the case of other factors (e.g., allergens, viral infections and pollutants), measures where possible should be taken to avoid these. Because many asthma patients react to multiple factors that are ubiquitous in the environment, avoiding these factors completely is usually impractical and very limiting to the patient. Thus, medications to maintain asthma control have an important role because patients are often less sensitive to these risk factors when their asthma is under good control.

### Indoor Allergens

Among the wide variety of allergen sources in human dwellings are domestic mites, furred animals, cockroaches, and fungi. However, there is conflicting evidence about whether measures to create a low-allergen environment in patients≤homes and reduce exposure to indoor allergens are effective at reducing asthma symptoms[54,55]. The majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to clinical improvement[55-57]. It is likely that no single intervention will achieve sufficient benefits to be cost effective. However, among inner-city children with atopic asthma, an individualized, home-based, comprehensive environmental intervention decreased exposure to indoor allergens and resulted in reduced asthma-associated morbidity[58]. More properly powered and well-designed studies of combined allergen-reduction strategies in large groups of patients are needed.

***Domestic mites.*** Domestic mite allergy is a universal health problem[59]. Since mites live and thrive in many sites throughout the house, they are difficult to reduce and impossible to eradicate (**Figure 4.2-1**). No single measure is likely to reduce exposure to mite allergens, and single chemical and physical methods aimed at reducing mite allergens are not effective in reducing asthma symptoms in adults[55,60-62] (**Evidence A**). One study showed some efficacy of mattress encasing at reducing airway hyperresponsiveness in children[63] (**Evidence B**). An integrated approach including barrier methods, dust removal, and reduction of microhabitats favorable to mites has been suggested, although its efficacy at reducing symptoms has only been confirmed in deprived populations with a specific environmental exposure[58] (**Evidence B**) and a recommendation for its widespread use cannot be made.

***Furred animals.*** Complete avoidance of pet allergens is impossible, as the allergens are ubiquitous and can be found in many environments outside the home[64], including schools[65], public transportation, and cat-free buildings[66]. Although removal of such animals from the home is encouraged, even after permanent removal of the animal it can be many months before allergen levels decrease[67] and the clinical effectiveness of this and other interventions remains unproven (**Figure 4.2-1**).

***Cockroaches***. Avoidance measures for cockroaches include eliminating suitable environments (restricting havens by caulking and sealing cracks in the plasterwork and flooring, controlling dampness, and reducing the availability of food), restricting access (sealing entry sources such as around paperwork and doors), chemical control, and traps. However, these measures are only partially effective in removing residual allergens[68] (**Evidence C**).

**Figure 4.2-1: Effectiveness of Avoidance Measures for Some Indoor Allergens***

| Measure | Evidence of effect on allergen levels | Evidence of clinical benefit |
|---|---|---|
| **House dust mites** | | |
| Encase bedding in impermeable covers | **Some** | **None (adults) Some (children)** |
| Wash bedding in the hot cycle (55-60°C) | **Some** | **None** |
| Replace carpets with hard flooring | **Some** | **None** |
| Acaricides and/or tannic acid | **Weak** | **None** |
| Minimize objects that accumulate dust | **None** | **None** |
| Vacuum cleaners with integral HEPA filter and double-thickness bags | **Weak** | **None** |
| Remove, hot wash, or freeze soft toys | **None** | **None** |
| | | |
| **Pets** | | |
| Remove cat/dog from the home | **Weak** | **None** |
| Keep pet from main living areas/bedrooms | **Weak** | **None** |
| HEPA-filter air cleaners | **Some** | **None** |
| Wash pet | **Weak** | **None** |
| Replace carpets with hard flooring | **None** | **None** |
| Vacuum cleaners with integral HEPA filter and double-thickness bags | **None** | **None** |

**Adapted from* Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2)LEN). *Allergy* 2005;60(9):1112-1115.

***Fungi.*** Fungal exposure has been associated with exacerbations from asthma and the number of fungal spores can best be reduced by removing or cleaning mold-laden objects[69]. In tropical and subtropical climates, fungi may grow on the walls of the house due to water seepage and humidity. To avoid this, the walls could be tiled or cleaned as necessary. Air conditioners and dehumidifiers may be used to reduce humidity to levels less than 50% and to filter large fungal spores. However, air conditioning and sealing of windows have also been associated with increases in fungal and house dust mite allergens[70].

**Outdoor Allergens**

Outdoor allergens such as pollens and molds are impossible to avoid completely. Exposure may be reduced by closing windows and doors, remaining indoors when pollen and mold counts are highest, and using air conditioning if possible. Some countries use radio, television, and the Internet to provide information on outdoor allergen levels. The impact of these measures is difficult to assess.

**Indoor Air Pollutants**

The most important measure in controlling indoor air pollutants is to avoid passive and active smoking. Secondhand smoke increases the frequency and severity of symptoms in children with asthma. Parents/caregivers of children with asthma should be advised not to smoke and not to allow smoking in rooms their children use. In addition to increasing asthma symptoms and causing long-term impairments in lung function, active cigarette smoking reduces the efficacy of inhaled and systemic glucocorticosteroids[71,72] (**Evidence B**), and smoking cessation needs to be vigorously encouraged for all patients with asthma who smoke. Other major indoor air pollutants include nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, sulfur dioxide, formaldehyde, and biologicals (endotoxin)[73]. However, methods to control or prevent exposure to these pollutants, such as venting all furnaces to the outdoors, and maintaining heating systems adequately, have not been adequately evaluated and can be expensive (**Evidence D**).

**Outdoor Air Pollutants**

Several studies have suggested that outdoor pollutants aggravate asthma symptoms[74, 356], possibly having an additive effect with allergen exposure[75]. Outbreaks of asthma exacerbations have been shown to occur in relationship to increased levels of air pollution, and this may be related to a general increase in pollutant levels or to an increase in specific allergens to which individuals are sensitized[76-78]. Most epidemiological studies show a significant association between air pollutants–such as ozone, nitrogen oxides, acidic aerosols, and particulate matter–and symptoms or exacerbations of asthma. On occasion, certain weather and atmospheric conditions, e.g., thunderstorms[79] favor the development of asthma exacerbations by a variety of mechanisms, including dust and pollution, increases in respirable allergens, and changes in temperature/humidity.

Avoidance of unfavorable environmental conditions is usually unnecessary for patients whose asthma is controlled. For patients with asthma that is difficult to control, practical steps to take during unfavorable environmental conditions include avoiding strenuous physical activity in cold weather, low humidity, or high air pollution; avoiding smoking and smoke-filled rooms; and staying indoors in a climate-controlled environment.

**Occupational Exposures**

Occupational exposures account for a substantial proportion of adult asthma incidence[357]. The early identification of occupational sensitizers and the removal of sensitized patients from any further exposure are important aspects of the management of occupational asthma (**Evidence B**). Once a patient has become sensitized to an occupational allergen, the level of exposure necessary to induce symptoms may be extremely low, and resulting exacerbations become increasingly severe. Attempts to reduce occupational exposure have been successful especially in industrial settings, and some potent sensitizers, such as soy castor bean, have been replaced by less allergenic substances[80] (**Evidence B**). Prevention of latex sensitization has been made possible by the production of hypoallergenic gloves, which are powder free and have a lower allergen content[81,82] (**Evidence C**). Although more expensive than untreated gloves, they are cost effective.

**Food and Food Additives**

Food allergy as an exacerbating factor for asthma is uncommon and occurs primarily in young children. Food avoidance should not be recommended until an allergy has been clearly demonstrated (usually by oral challenges)[83]. When food allergy is demonstrated, food allergen avoidance can reduce asthma exacerbations[84] (**Evidence D**).

Sulfites (common food and drug preservatives found in such foods as processed potatoes, shrimp, dried fruits, beer, and wine) have often been implicated in causing severe asthma exacerbations but the likelihood of a reaction is dependent on the nature of the food, the level of residual sulfite, the sensitivity of the patient, the form of residual sulfite and the mechanism of the sulfite-induced reaction[85]. The role of other dietary substances—including the yellow dye tartrazine, benzoate, and monosodium glutamate—in exacerbating asthma is probably minimal; confirmation of their relevance requires double-blind challenge before making specific dietary restrictions.

### Drugs

Some medications can exacerbate asthma. Aspirin and other nonsteroidal anti-inflammatory drugs can cause severe exacerbations and should be avoided in patients with a history of reacting to these agents[86]. Beta-blocker drugs administered orally or intraocularly may exacerbate bronchospasm (**Evidence A**) and close medical supervision is essential when these are used by patients with asthma[87].

### Influenza Vaccination

Patients with moderate to severe asthma should be advised to receive an influenza vaccination every year[88] or at least when vaccination of the general population is advised. However, routine influenza vaccination of children[89] and adults[90] with asthma does not appear to protect them from asthma exacerbations or improve asthma control. Inactivated influenza vaccines are associated with few side effects and are safe to administer to asthmatic adults and children over the age of 3 years, including those with difficult-to-treat asthma[91]. There are data to suggest that intranasal vaccination in children under age 3 may be associated with an increased incidence of asthma exacerbations[92].

### Obesity

Increases in body mass index (BMI) have been associated with increased prevalence of asthma, although the mechanisms behind this association are unclear[93]. Weight reduction in obese patients with asthma has been demonstrated to improve lung function, symptoms, morbidity, and health status[94] (**Evidence B**).

### Emotional Stress

Emotional stress may lead to asthma exacerbations, primarily because extreme emotional expressions (laughing, crying, anger, or fear) can lead to hyperventilation and hypocapnia, which can cause airway narrowing[95,96]. Panic attacks, which are rare but not exceptional in some patients with asthma, have a similar effect[97,98]. However, it is important to note that asthma is not primarily a psychosomatic disorder.

### Other Factors That May Exacerbate Asthma

Rhinitis, sinusitis, and polyposis are frequently associated with asthma and need to be treated. In children, antibiotic treatment of bacterial sinusitis has been shown to reduce the severity of asthma[99]. However, sinusitis and asthma may simply coexist. Apart from sinusitis, there is little evidence that bacterial infections exacerbate asthma. Gastroesophageal reflux can exacerbate asthma, especially in children, and asthma sometimes improves when the reflux is corrected[100,101]. Many women complain that their asthma is worse at the time of menstruation, and premenstrual exacerbations have been documented[102]. Similarly, asthma may improve, worsen, or remain unchanged during pregnancy[103].

A randomized clinical trial of a self-regulation, telephone counseling intervention emphasizing sex and gender role factors in the management of asthma indicated that a program with a focus on asthma management problems particular to women can significantly assist female asthma patients[358].

## COMPONENT 3: ASSESS, TREAT, AND MONITOR ASTHMA

**KEY POINTS:**

- The goal of asthma treatment, to achieve and maintain clinical control, can be reached in a majority of patients with a pharmacologic intervention strategy developed in partnership between the patient/family and the doctor.
- Treatment should be adjusted in a continuous cycle driven by the patients≤asthma control status. If asthma is not controlled on the current treatment regimen, treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
- In treatment-naïve patients with persistent asthma, treatment should be started at *Step 2*, or, if very symptomatic (uncontrolled), at *Step 3*. For *Steps 2* through *5*, a variety of controller medications are available.
- At each treatment step, reliever medication should be provided for quick relief of symptoms as needed.
- Ongoing monitoring is essential to maintain control and to establish the lowest step and dose of treatment to minimize cost and maximize safety.

## INTRODUCTION

The goal of asthma treatment, to achieve and maintain clinical control, can be reached in a majority of patients[104,344] with a pharmacologic intervention strategy developed in partnership between the patient/family and the doctor. Each patient is assigned to one of five “treatment steps” depending on their current level of control and treatment is adjusted in a continuous cycle driven by changes in their asthma control status. This cycle involves:

- Assessing Asthma Control
- Treating to Achieve Control
- Monitoring to Maintain Control

In this Component, this cycle is described for long-term treatment of asthma. Treatment for exacerbations is detailed in Component 4.

## ASSESSING ASTHMA CONTROL

Each patient should be assessed to establish his or her current treatment regimen, adherence to the current regimen, and level of asthma control. A simplified scheme for recognizing controlled, partly controlled, and uncontrolled asthma in a given week is provided in **Figure 4.3-1**. This is a working scheme based on current opinion and has not been validated. Several composite control measures (e.g., Asthma Control Test[105], Asthma Control Questionnaire[106-108], Asthma Therapy Assessment Questionnaire[109], Asthma Control Scoring System[110]) have been developed and are being validated for various applications, including use by health care providers to assess the state of control of their patients≤asthma and by patients for self-assessments as part of a written personal asthma action plan. Uncontrolled asthma may progress to the point of an exacerbation, and immediate steps, described in Component 4, should be taken to regain control.

## TREATING TO ACHIEVE CONTROL

The patient≤s current level of asthma control and current treatment determine the selection of pharmacologic treatment. For example, if asthma is not controlled on the current treatment regimen, treatment should be stepped up until control is achieved. If control has been maintained for at least three months, treatment can be stepped down with the aim of establishing the lowest step and dose of treatment that maintains control (see *Monitoring to Maintain Control* below). If asthma is partly controlled, an increase in treatment should be considered, subject to whether more effective options are available (e.g., increased dose or an additional treatment), safety and cost of possible treatment options, and the patient≤s satisfaction with the level of control achieved. The scheme presented in **Figure 4.3-2** is based upon these principles, but the range and sequence of medications used in each clinical setting will vary depending on local availability (for cost or other reasons), acceptability, and preference.

**Treatment Steps for Achieving Control**

Most of the medications available for asthma patients, when compared with medications used for other chronic diseases, have extremely favorable therapeutic ratios. Each step represents treatment options that, although not of identical efficacy, are alternatives for controlling asthma. *Steps 1* to *5* provide options of increasing efficacy, except for *Step 5* where issues of availability and safety influence the selection of treatment. *Step 2* is the initial treatment for most treatment-naïve patients with persistent asthma symptoms. If symptoms at the initial consultation suggest that asthma is severely uncontrolled (**Figure 4.3-1**), treatment should be commenced at *Step 3*.

At each treatment step, a reliever medication (**rapid-onset bronchodilator**, either short-acting or long-acting) should be provided for quick relief of symptoms. However, regular use of reliever medication is one of the elements defining uncontrolled asthma, and indicates that controller treatment should be increased. Thus, reducing or eliminating the need for reliever treatment is both an important goal and measure of success of treatment. For *Steps 2* through *5*, a variety of controller medications are available.

***Step 1: As-needed reliever medication.*** *Step 1* treatment with an as-needed reliever medication is reserved for untreated patients with occasional daytime symptoms (cough, wheeze, dyspnea occurring twice or less per week, or less frequently if nocturnal) of short duration (lasting only a few hours) comparable with

**Figure 4.3-1. Levels of Asthma Control**

| Characteristic | Controlled (All of the following) | Partly Controlled (Any measure present in any week) | Uncontrolled |
|---|---|---|---|
| **Daytime symptoms** | None (twice or less/week) | More than twice/week | **Three or more features of partly controlled asthma present in any week** |
| **Limitations of activities** | None | Any | |
| **Nocturnal symptoms/awakening** | None | Any | |
| **Need for reliever/ rescue treatment** | None (twice or less/week) | More than twice/week | |
| **Lung function (PEF or $FEV_1$)‡** | Normal | < 80% predicted or personal best (if known) | |
| **Exacerbations** | None | One or more/year* | One in any week† |

** Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.*

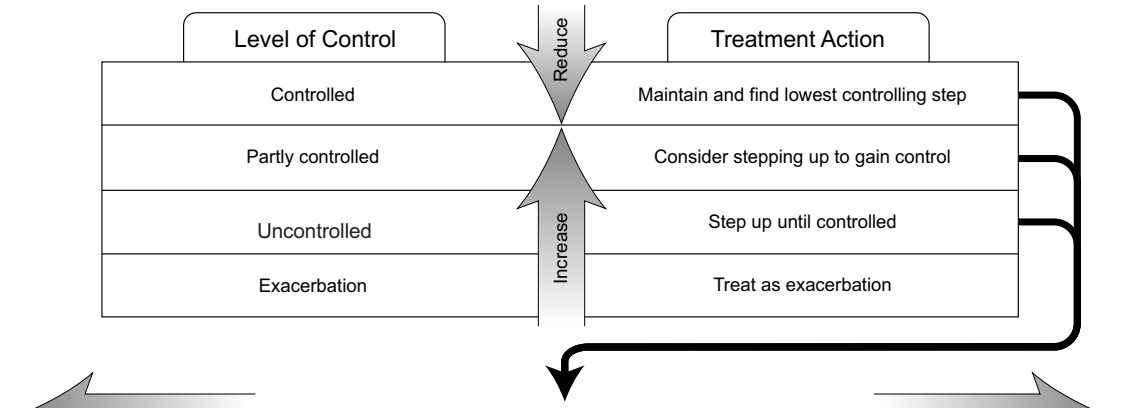
*† By definition, an exacerbation in any week makes that an uncontrolled asthma week.*

*‡ Lung function is not a reliable test for children 5 years and younger.*

**Figure 4.3-2.**

## Management Approach Based On Control

**For Children Older Than 5 Years, Adolescents and Adults**




| Step 1 | Step 2 | Step 3 | Step 4 | Step 5 |
|---|---|---|---|---|
| Asthma education<br>Environmental control | | | | |
| As needed rapid-acting $\beta_2$-agonist | As needed rapid-acting $\beta_2$-agonist | | | |
| Controller options *** | Select one | Select one | Add one or more | Add one or both |
| | Low-dose inhaled ICS* | Low-dose ICS plus long-acting $\beta_2$-agonist | Medium-or high-dose ICS plus long-acting $\beta_2$-agonist | Oral glucocorticosteroid (lowest dose) |
| | Leukotriene modifier ** | Medium-or high-dose ICS | Leukotriene modifier | Anti-IgE treatment |
| | | Low-dose ICS plus leukotriene modifier | Sustained release theophylline | |
| | | Low-dose ICS plus sustained release theophylline | | |

* ICS=inhaled glucocorticosteroids
** =Receptor antagonist or synthesis inhibitors
***Preferred controller options are shown in shaded boxes

*Alternative reliever treatments include inhaled anticholinergics, short-acting oral* $\beta_2$-agonists*, some long-acting* $\beta_2$-agonists*, and short-acting theophylline. Regular dosing with short and long-acting* $\beta_2$-agonist *is not advised unless accompanied by regular use of an inhaled glucocorticosteroid.*

**Figure 4.3-2: Management Approach Based on Control For Children 5 Years and Younger**

The available literature on treatment of asthma in children 5 years and younger precludes detailed treatment recommendations. The best documented treatment to control asthma in these age groups is inhaled glucocorticosteroids and at Step 2, a low-dose inhaled glucocorticosteroid is recommended as the initial controller treatment. Equivalent doses of inhaled glucocorticosteroids, some of which may be given as a single daily dose, are provided in **Chapter 3** (**Figure 3-4**).

controlled asthma (**Figure 4.3-1**). Between episodes, the patient is asymptomatic with normal lung function and there is no nocturnal awakening. When symptoms are more frequent, and/or worsen periodically, patients require regular controller treatment (see *Steps 2* or higher) in addition to as-needed reliever medication[111-113] (**Evidence B**).

For the majority of patients in *Step 1*, a **rapid-acting inhaled $\beta_2$-agonist** is the recommended reliever treatment[114] (**Evidence A**). An inhaled anticholinergic, short-acting oral $\beta_2$-agonist, or short-acting theophylline may be considered as alternatives, although they have a slower onset of action and higher risk of side effects (**Evidence A**).

*Exercise-induced bronchoconstriction*. Physical activity is an important cause of asthma symptoms for most asthma patients, and for some it is the only cause. However, exercise-induced bronchoconstriction often indicates that the patient's asthma is not well controlled, and stepping up controller therapy generally results in the reduction of exercise-related symptoms. For those patients who still experience exercise-induced bronchoconstriction despite otherwise well-controlled asthma, and for those in whom exercise-induced bronchoconstriction is the only manifestation of asthma, a rapid-acting inhaled $\beta_2$-agonist (short- or long-acting), taken prior to exercise or to relieve symptoms that develop after exercise, is recommended[115]. A leukotriene modifier[116,345] or cromone[117] are alternatives (**Evidence A**). Training and sufficient warm-up also reduce the incidence and severity of exercise-induced bronchoconstriction[118,119] (**Evidence B**). Information on treatment of exercise-induced asthma in athletes can be found in a Joint Task Force Report prepared by the European Respiratory Society, the European Academy of Allergy and Clinical Immunology, and GA(2)LEN[359] and the World Anti-Doping Agency website (http://www.wada-ama.org).

***Step 2: Reliever medication plus a single controller.*** Treatment *Steps 2* through *5*, combine an as-needed reliever treatment with regular controller treatment. At *Step 2*, a **low-dose inhaled glucocorticosteroid** is recommended as the initial controller treatment for asthma patients of all ages[111,120] (**Evidence A**). Equivalent doses of inhaled glucocorticosteroids, some of which may be given as a single daily dose, are provided in **Figure 3-1** for adults and in **Figure 3-4** for children 5 years and younger.

Alternative controller medications include **leukotriene modifiers**[121-123] (**Evidence A**), appropriate particularly for patients who are unable or unwilling to use inhaled glucocorticosteroids, or who experience intolerable side effects such as persistent hoarseness from inhaled glucocorticosteroid treatment and those with concomitant allergic rhinitis[124,125] (**Evidence C**).

Other options are available but not recommended for routine use as initial or first-line controllers in *Step 2*. **Sustained-release theophylline** has only weak anti-inflammatory and controller efficacy[126-130] (**Evidence B**) and is commonly associated with side effects that range from trivial to intolerable[131,132]. **Cromones (nedocromil sodium and sodium cromoglycate)** have comparatively low efficacy, though a favorable safety profile[133-136] (**Evidence A**).

***Step 3: Reliever medication plus one or two controllers.*** At *Step 3*, the recommended option for adolescents and adults is to combine a **low-dose of inhaled glucocorticosteroid with an inhaled long-acting $\beta_2$-agonist,** either in a combination inhaler device or as separate components[137-144] (**Evidence A**). Because of the additive effect of this combination, the low-dose of glucocorticosteroid is usually sufficient, and need only be increased if control is not achieved within 3 or 4 months with this regimen (**Evidence A**). The long-acting $\beta_2$-agonist formoterol, which has a rapid onset of action whether given alone[145-148] or in combination inhaler with budesonide[149,150], has been shown to be as effective as short-acting $\beta_2$-agonist in acute asthma exacerbation. However its use as monotherapy as a reliever medication is strongly discouraged since it must always be used in association with an inhaled glucocorticosteroid.

For all children but particularly those 5 years and younger, combination therapy has been less well studied and the addition of a long-acting $\beta_2$-agonist may not be as effective as increasing the dose of inhaled glucocorticosteroids in reducing exacerbations[151-153]. However, the interpretation of some studies is problematic as not all children received concurrent inhaled glucocorticosteroids[152,153].

If a combination inhaler containing formoterol and budesonide is selected, it may be used for both rescue and maintenance. This approach has been shown to result in reductions in exacerbations and improvements in asthma control in adults and adolescents at relatively low doses of treatment[154-157] (**Evidence A**). Whether this approach can be employed with other combinations of controller and reliever requires further study.

Another option for both adults and children, but the one recommended for children[158], is to increase to a **medium-dose of inhaled glucocorticosteroids**[104,159-161] (**Evidence A**). For patients of all ages on medium- or high-dose of inhaled glucocorticosteroid delivered by a pressurized metered-dose inhaler, use of a spacer device is recommended to improve delivery to the airways, reduce oropharyngeal side effects, and reduce systemic absorption[162-164] (**Evidence A**).

Another option at *Step 3* is to combine a low-dose inhaled glucocorticosteroid with leukotriene modifiers[165-173] (**Evidence A**). Alternatively, the use of sustained-release theophylline given at low-dose may be considered[129] (**Evidence B**). These options have not been fully studied in children 5 years and younger.

***Step 4: Reliever medication plus two or more controllers.*** The selection of treatment at *Step 4* depends on prior selections at *Steps 2* and *3*. However, the order in which additional medications should be added is based, as far as possible, upon evidence of their relative efficacy in clinical trials. Where possible, patients who are not controlled on *Step 3* treatments should be r**eferred to a health professional with expertise in the management of asthma** for investigation of alternative diagnoses and/or causes of difficult-to-treat asthma.

The preferred treatment at *Step 4* is to combine a **medium- or high-dose of inhaled glucocorticosteroid with a long-acting inhaled $\beta_2$-agonist.** However, in most patients, the increase from a medium- to a high-dose of inhaled glucocorticosteroid provides relatively little additional benefit[104,159-161,174] (**Evidence A**), and the high-dose is recommended only on a trial basis for 3 to 6 months when control cannot be achieved with medium-dose inhaled glucocorticosteroid combined with a long-acting $\beta_2$-agonist and/or a third controller (e.g. leukotriene modifiers or sustained-release theophylline )[130,175,346] (**Evidence B**). Prolonged use of high-dose inhaled glucocorticosteroids is also associated with increased potential for adverse effects. At medium- and high-doses, twice-daily dosing is necessary for most but not all inhaled glucocorticosteroids[176] (**Evidence A**). With budesonide, efficacy may be improved with more frequent dosing (four times daily)[177] (**Evidence B**). (Refer to **Figure 3-1** for adults and **Figure 3-4** for children 5 years and younger for recommendations on dosing and frequency for different inhaled glucocorticosteroids.)

**Leukotriene modifiers** as add-on treatment to medium-to high-dose inhaled glucocorticosteroids have been shown to provide benefit (**Evidence A**), but usually less than that achieved with the addition of a long-acting $\beta_2$-agonist[165-168,175,178] (**Evidence A**). The addition of a low-dose of **sustained-release theophylline**[130] to medium- or high-dose inhaled glucocorticosteroid and long-acting $\beta_2$-agonist may also provide benefit (**Evidence B**)[129].

***Step 5: Reliever medication plus additional controller options.*** Addition of **oral glucocorticosteroids** to other controller medications may be effective[179] (**Evidence D**) but is associated with severe side effects[180] (**Evidence A**) and should only be considered if the patient≤s asthma remains severely uncontrolled on *Step 4* medications with daily limitation of activities and frequent exacerbations. Patients should be counseled about potential side effects and all other alternative treatments must be considered.

Addition of **anti-IgE treatment** to other controller medications has been shown to improve control of allergic asthma when control has not been achieved on combinations of other controllers including high-doses of inhaled or oral glucocorticosteroids[181-186] (**Evidence A**).

## MONITORING TO MAINTAIN CONTROL

When asthma control has been achieved, ongoing monitoring is essential to maintain control and to establish the lowest step and dose of treatment necessary, which minimizes the cost and maximizes the safety of treatment. On the other hand, asthma is a variable disease, and treatment has to be adjusted periodically in response to loss of control as indicated by worsening symptoms or the development of an exacerbation.

Asthma control should be monitored by the health care professional and preferably also by the patient at regular intervals, using either a simplified scheme as presented in **Figure 4.3-1** or a validated composite measure of control. The frequency of health care visits and assessments depends upon the patient≤s initial clinical severity, and the patient≤s training and confidence in playing a role in the ongoing control of his or her asthma. Typically, patients are seen one to three months after the initial visit, and every three months thereafter. After an exacerbation, follow-up should be offered within two weeks to one month (**Evidence D**).

**Duration and Adjustments to Treatment**

For most classes of controller medications, improvement begins within days of initiating treatment, but the full benefit may only be evident after 3 or 4 months[187, 360]. In severe and chronically undertreated disease, this can take even longer[188].

The reduced need for medication once control is achieved is not fully understood, but may reflect the reversal of some of the consequences of long-term inflammation of the airways. Higher doses of anti-inflammatory medication may be required to achieve this benefit than to maintain it. Alternatively, the reduced need for medication might simply represent spontaneous improvement as part of the cyclical natural history of asthma. Rarely, asthma may go into remission particularly in children aged 5 years and younger and during puberty. Whatever the explanation, in all patients the minimum controlling dose of treatment must be sought through a process of regular follow-up and staged dose reductions.

At other times treatment may need to be increased either in response to loss of control or threat of loss of control (return of symptoms) or an acute exacerbation, which is defined as a more acute and severe loss of control that requires urgent treatment. (An approach to exacerbations is provided in Component 4.4.)

**Stepping Down Treatment When Asthma Is Controlled**

There is little experimental data on the optimal timing, sequence, and magnitude of treatment reductions in asthma, and the approach will differ from patient to patient depending on the combination of medications and the doses that were needed to achieve control. These changes should ideally be made by agreement between patient and health care professional, with full discussion of potential consequences including reappearance of symptoms and increased risk of exacerbations.

Although further research on stepping down asthma treatment is needed, some recommendations can be made based on the current evidence:

- When **inhaled glucocorticosteroids alone** in medium- to high-doses are being used, a 50% reduction in dose should be attempted at 3 month intervals[189-191] (**Evidence B**).

- Where control is achieved at a low-dose of inhaled glucocorticosteroids alone, in most patients treatment may be switched to once-daily dosing[192,193] (**Evidence A**).

- When asthma is controlled with a **combination of inhaled glucocorticosteroid and long-acting $\beta_2$-agonist**, the preferred approach to is to begin by reducing the dose of inhaled glucocorticosteroid by approximately 50% while continuing the long-acting $\beta_2$-agonist[150] (**Evidence B**). If control is maintained, further reductions in the glucocorticosteroid should be attempted until a low-dose is reached, when the long-acting $\beta_2$-agonist may be stopped (**Evidence D**). An alternative is to switch the combination treatment to once-daily dosing[194]. A second alternative is to discontinue the long-acting $\beta_2$-agonist at an earlier stage and substitute the combination treatment with inhaled glucocorticosteroid monotherapy at the same dose contained in the combination inhaler. However, for some patients these alternative approaches lead to loss of asthma control[137,150] (**Evidence B**).

- When asthma is controlled with **inhaled glucocorticosteroids in combination with controllers other than long-acting $\beta_2$-agonists**, the dose of inhaled glucocorticosteroid should be reduced by 50% until a low-dose of inhaled glucocorticosteroid is reached, then the combination treatment stopped as described above (**Evidence D**).

- **Controller treatment may be stopped** if the patient's asthma remains controlled on the lowest dose of controller and no recurrence of symptoms occurs for one year (**Evidence D**).

**Stepping Up Treatment In Response To Loss Of Control**

Treatment has to be adjusted periodically in response to worsening control, which may be recognized by the minor recurrence or worsening of symptoms[195]. Treatment options are as follows:

- **Rapid-onset, short-acting or long-acting $\beta_2$-agonist bronchodilators.** Repeated dosing with bronchodilators in this class provides temporary relief until the cause of the worsening symptoms passes. The need for repeated doses over more than one or two days signals the need for review and possible increase of controller therapy.

- **Inhaled glucocorticosteroids.** Temporarily doubling the dose of inhaled glucocorticosteroids has not been demonstrated to be effective, and is no longer recommended[194,196] (**Evidence A**). A four-fold or greater increase has been demonstrated to be equivalent to a short course of oral glucocorticosteroids in adult patients with an acute deterioration[195] (**Evidence A**). The higher dose should be maintained for seven to fourteen days but more research is needed in both adults and children to standardize the approach.

- **Combination of inhaled glucocorticosteroids and rapid and long-acting $\beta_2$-agonist bronchodilator (e.g. formoterol) for combined relief and control.** The use of the combination of a rapid and long-acting $\beta_2$-agonist (formoterol) and an inhaled glucocorticosteroid (budesonide) in a single inhaler both as a controller and reliever is effective in maintaining a high level of asthma control and reduces exacerbations requiring systemic glucocorticosteroids and hospitalization[111,156,157,197] (**Evidence A**). The benefit in preventing exacerbations appears to be the consequence of early intervention at a very early stage of a threatened exacerbation since studies involving doubling or quadrupling doses of combination treatment once deterioration is established (for 2 or more days) show some benefit but results are inconsistent[195]. Because there are no studies using this approach with other combinations of controller and relievers, other than budesonide/formoterol, the alternative approaches described in this section should be used for patients on other controller therapies. Combination therapy with budesonide and formoterol used both as maintenance and rescue has been shown to reduce asthma exacerbations in children ages 4 years and older with moderate to severe asthma[347].