

PHARMACOLOGICAL MANAGEMENT OF ASTHMA

Krishan Chugh, Mohit Kehar

Centre for Child Health, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi-110060, India

Abstract : A critical evidence based review of the present knowledge has resulted in development of consensus guidelines for management of Asthma by various institutions like GINA, BTS and IAP. These guidelines have now started focusing on 'control' of asthma. The 'grades' of asthma have been redefined in a simpler and more practical manner. Grade I is now named Intermittent Asthma thereby indicating that preventive therapy is not required in contrast to other three grades of asthma which have been called mild, moderate and severe persistent asthma, thereby implying that preventive pharmacological therapy is required for these grades. It is now recognized that increasing the dose of inhaled corticosteroids (ICS) to beyond 400-800 mcg per day budesonide (or its equivalent) does not give dose related additional benefit and safety issues become important at higher doses. Hence, add on therapy should be the next step. Studies on effect of ICS on growth indicate that moderate doses do not have any significant effect on final height of the child even after years of use. Similarly ICS do not result in higher incidence of bone fractures while more than four courses of oral steroids at any time do. Theophyllines are acknowledged to provide both reliever and preventer effect. However, the effects are modest and side effects of theophyllines are significantly higher. A strategy to use formoterol and budesonide combination inhaler for both reliever and preventive therapy has been found to be useful in some trials. Guidelines for stepping down therapy once control is achieved have been laid down recently. Overall, reducing the dose of ICS to low dose levels takes priority over withdrawing add on therapies.

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

An overall concept for asthma management is oriented around the focus on asthma control. Achieving and maintaining asthma control is emphasized as the goal of asthma treatment. Before the treatment starts the patient has to be assigned into one of the following categories depending on severity of symptoms:

Intermittent

- Symptoms less than once a week
- Brief exacerbations
- Nocturnal symptoms not more than twice a month
- FEV1 or PEF 80% predicted or more
- PEF or FEV1 variability <20%

Mild persistent

- Symptoms more than once a week but less than once a day
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than twice a month
- FEV1 or PEF ≥80% predicted
- PEF or FEV1 variability <20–30%

Moderate persistent

- Symptoms daily
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than once a week
- Daily use of inhaled short-acting β_2 -agonist
- FEV1 or PEF 60–80% predicted
- PEF or FEV1 variability >30%

Severe persistent

- Symptoms daily

- Frequent exacerbations
- Frequent nocturnal asthma symptoms
- Limitation of physical activities
- FEV1 or PEF 60% predicted
- PEF or FEV1 variability >30%

Asthma control - The patient's level of asthma control and current treatment determine the selection of pharmacologic treatment (Table 1). Like if asthma is not controlled in a patient on the current treatment regimen, which he is taking, then 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. 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. Medications to treat asthma can be classified as controllers or relievers.

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 FEV1) [‡]	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.

Controllers are medications taken daily on a long-term basis to keep asthma under clinical control, they act chiefly through their anti-inflammatory effects.

- Inhaled and systemic glucocorticosteroids, (Inhaled glucocorticosteroids are the most effective controller medications currently available)
- Leukotriene modifiers,
- Long-acting inhaled beta 2-agonists in combination with inhaled glucocorticosteroids,
- Sustained-release theophylline,
- Cromones,
- Anti-IgE, and
- Systemic steroid-sparing therapies.

Correspondence: Dr.Krishan Chugh, Director, Centre for Child Health, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi-110060, India

Relievers are medications used on as-needed basis that have quick onset of action and reverse bronchoconstriction and relieve its symptoms.

- Rapid-acting inhaled beta 2-agonists,
- Inhaled anticholinergics,
- Short-acting theophylline,
- Short-acting oral beta agonists.

Inhaled therapy is the *cornerstone of asthma treatment* for children of all ages. It's seen that 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 (Table 2). In general, a metered-dose inhaler (MDI) with spacer is preferable to nebulizer therapy due to its greater convenience, more effective lung deposition, lower risk of side effects, and lower cost of the therapy. Therapy with nebulizers has imprecise dosing, is expensive, and is 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

Table 2 : Choosing an inhaler device for children with asthma

Age Group	Preferred Device	Alternate Device
Younger than 4 years	Pressurized metered-dose inhaler <i>plus</i> dedicated spacer with face mask	Nebulizer with face mask
4 – 6 years	Pressurized metered-dose inhaler <i>plus</i> 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

STEP WISE MANAGEMENT OF ASTHMA

Step 1: Mild Intermittent Asthma- This requires short-term bronchodilator therapy Options are:

- Inhaled short-acting β_2 agonists
- Inhaled ipratropium bromide
- β_2 agonist tablets or syrup
- Theophyllines.

Short-acting inhaled β_2 agonists work more quickly and/or with fewer side effects than the alternatives and its seen that using short acting β_2 agonists on SOS basis is at least as good as regular (four times daily) administration Various studies have correlated the need for use of short acting β_2 agonist with asthma control. Good asthma control is associated with little or no need for short-acting β_2 agonist.

Using two or more canisters of β_2 agonists per month or >10-12 puffs per day is a marker of poorly controlled asthma that puts individuals at risk of fatal or near-fatal asthma²

Step 2: Introduction of Regular Preventer Therapy-Indications: Inhaled steroids should be considered for adults, children aged 5-12 years and children under the age of five with any of the following features²⁰:

- Using inhaled β_2 agonists three times a week or more
- Symptomatic three times a week or more
- Waking one night a week.

In addition, inhaled steroids should be considered in adults and children aged 5-12 who has had an exacerbation of asthma requiring

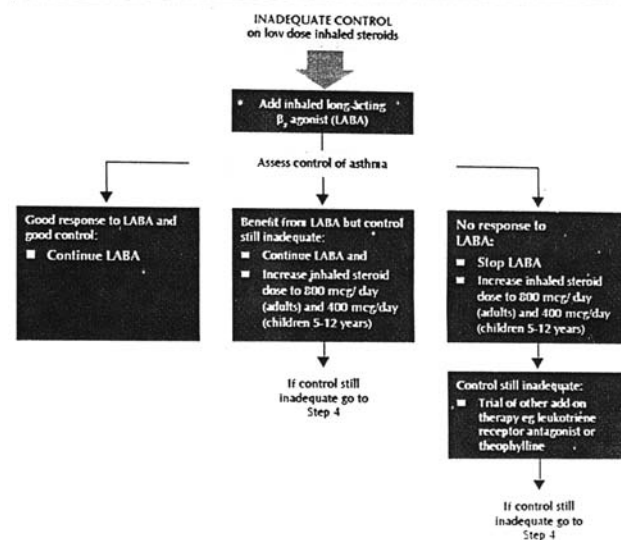
oral corticosteroids in the last two years. Inhaled steroids are the most effective preventer drugs for adults and older children for achieving good control on asthma and there is enough evidence demonstrating that, at recommended doses, they are also safe and effective in infants and younger children with asthma. About the starting dose there have been two schools of thought; one follows step up and other step down protocol. In mild to moderate asthma, starting at very high doses of inhaled steroids and stepping down confers no benefit⁵¹, so starting dose of inhaled steroids should be appropriate to the severity of disease and we should titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained. On frequency of administrations its been seen that most current inhaled steroids are slightly more effective when taken twice rather than once daily, but may be used once daily in some patients with milder disease.

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. (Table3) Fig.1.

Estimated equipotent daily doses of inhaled Glucocorticosteroids for children

Drug	Low Daily Dose (μ g)	Medium Daily Dose (μ g)	High Daily Dose (μ g) [†]
Beclomethasone dipropionate	100 - 200	>200 - 400	>400
Budesonide*	100 - 200	>200 - 400	>400
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.



Safety of Inhaled Steroids

A. Growth: Its one of the key questions asked by parents when the child is being started on steroids as controller medication. Few important aspects about growth and ICS are that⁵

- 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 100-200 μ g/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 4–10 yrs 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

B.) Bone: The 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 ^{6,7}. The summary of these studies are

- No studies have reported any statistically significant increased 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 after four courses
- Use of inhaled glucocorticosteroids reduces the need for systemic courses
- Controlled longitudinal studies of 2–5 yrs 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

C. Hypothalamic- pituitary-adrenal (HPA) axis abnormalities -It is seen that treatment with inhaled glucocorticosteroid doses of less than 200 ug budesonide or equivalent daily is normally not associated with any significant suppression of the HPA axis in children. At higher doses, small changes in HPA axis function can be detected with sensitive methods. However, in few studies adrenal crisis has been reported in children treated with excessively high doses of inhaled glucocorticosteroids.

D. Cataracts. Inhaled glucocorticosteroids have not been associated with an increased occurrence of cataract in children

E. Central nervous system effects. Few isolated case reports have shown that inhaled steroids are associated with CNS adverse effects however no increase in such effects has been found in two long-term controlled trials of inhaled budesonide involving more than 10,000 treatment years ^{8,9}

F. Oral candidiasis, hoarseness, and bruising. Clinical thrush is seldom a problem in children treated with inhaled or systemic glucocorticosteroids and this side effect may seem to be related to use of antibiotics, high daily doses, dose frequency and inhaler device. Giving the medication via spacers has been shown to reduce the incidence of oral candidiasis, and along with this mouth rinsing was found to be beneficial. In a study the occurrence of hoarseness or other noticeable voice changes during budesonide treatment is similar to placebo. Treatment with an average daily dose of 500-ug budesonide for 3 to 6 years is not associated with an increased tendency to bruise.

Other Prevent Therapies

A. LTRA : These Provide clinical benefit in children aged >5 yrs at all levels of severity but less than that of low-dose inhaled glucocorticosteroids. Leukotriene modifiers provide partial protection against exercise-induced bronchoconstriction within hours

B. LABA : Addition of long acting inhaled beta 2-agonists to a daily regimen of inhaled glucocorticosteroids (> 5 year of age)

- Improves symptom scores
- Decreases nocturnal asthma
- Improves lung function
- Decreases the use of rapid-acting inhaled β_2 - agonists
- Reduces the number of exacerbations and achieves clinical

control of asthma in more patients, more rapidly, and at a lower dose of inhaled glucocorticosteroids than inhaled glucocorticosteroids given alone

C. Theophyllines: Have been shown to be effective as monotherapy and as add-on treatment to inhaled or oral glucocorticosteroids in children aged >5 yrs, though adverse effects are common.

- It is significantly more effective than placebo at controlling day and night symptoms and improves lung function
- Marginal protective effect against exercise induced bronchoconstriction
- Reduces the maintenance glucocorticosteroid dose
- Efficacy of theophylline is less than that of low-dose inhaled glucocorticosteroids
- Sustained-release products are preferable for maintenance therapy, since they enable twice-daily dosing
- Plasma theophylline level is not necessary in otherwise healthy children when doses less than 10 mg/kg/day are used
- Adverse effects are reduced if treatment is initiated with daily doses ~ 5 mg/kg/day and then gradually increased to 10 mg/kg/day

D. Doxophyllin (7-(1,3-dioxalan-2-ylmethyl) theophylline): is a novel xanthine bronchodilator, which differs from theophylline in that it contains a dioxalane group in position 7. Similar to theophylline, its mechanism of action is related to the inhibition of phosphodiesterase activities, but in contrast it appears to have decreased affinities towards adenosine A1 and A2 receptors, which may account for its better safety profile- CNS side effects are claimed to be less.

E. Cromones: Sodium cromoglycate and nedocromil sodium- these products have a limited role in the long-term treatment of asthma in children. Nedocromil sodium has been shown to reduce exacerbations, but its effect on other asthma outcomes is not superior to placebo. There are some studies which suggest there use in exercise / cold induced asthma¹¹.

Step 3: Initial Add-On Therapy- Some Patients With Asthma May Not Be Adequately Controlled At Step 2.

But before we add a new therapy we should: (a) recheck compliance; (b) inhaler technique and (c) eliminate trigger factors

No exact dose of inhaled steroid can be specified at which to add another therapy But in general in adult patients taking inhaled steroids at doses of 200-800 mcg/day and in children taking inhaled steroids at a dose of 400 mcg/day add on therapy may be of value:

- (1.) Inhaled long-acting β_2 agonist (LABA), – It has been shown in studies that the first choice as add-on therapy to inhaled steroids in adults and children (5-12 years) is an inhaled long-acting β_2 agonist, which should be added before going above a dose of 400 mcg BDP or equivalent per day and certainly before going above 800 mcg BDP. If for instance it is found that asthma control remains suboptimal after the addition of an inhaled long-acting β_2 agonist then the dose of inhaled steroids should be increased to 800 mcg/day in adults or 400 mcg/day in children (5-12 years), if not already on these doses.
- (2.) Leukotriene receptor antagonists may provide improvement in lung function, a decrease in exacerbations, and an improvement in symptoms if added at this stage.
- (3.) Theophyllines may improve lung function and symptoms, but side effects are more
- (4.) Slow-release β_2 agonist tablets may also improve lung function and symptoms, but side effects are more. Addition of short-acting anticholinergics is of no value

COMBINATION INHALERS

No difference in efficacy was noticed whether ICS and LABA are

given in combination or via different inhalers. Main advantage is of guaranteeing that the long-acting β_2 agonist is not taken without inhaled steroid. Further using one inhaler instead of two separate ones is more convenient. A strategy to use formoterol and budesonide combination inhaler for both reliever and preventive therapy has been found to be useful in some trials¹².

Step 4: Poor Control On Moderate Dose Of Inhaled Steroid + Addon Therapy Addition of Fourth Drug -

Is indicated in a very small group of whose patients asthma is not adequately controlled on a combination of short acting β_2 agonist as required, inhaled steroid (800 mcg daily), and an additional drug, usually a long-acting β_2 agonist. There are very few trials available to guide therapy in this group. The available options are:

- Increasing inhaled steroids to 2000 mcg/day (adults) or 800 mcg/day (children 5-12 years)
- Leukotriene receptor antagonists
- Theophyllines
- Slow release β_2 agonist tablets, though caution needs to be used in patients already on long-acting β_2 agonists

Due to lack of controlled trials it is very difficult to tell which of these is best but side effects seems to be more with theophyllines and β_2 agonist tablets.

Step 5: Continuous or Frequent Use of Oral Steroids

For the very small number of patients not controlled at step 4, we can use daily steroid tablets in the lowest dose to provide control.

STEROID SPARING MEDICATION

The aim of treatment is to control the asthma using the lowest possible steroid dose or, if possible, to stop long term steroid tablets completely. There are following available medications:

- In adults, the recommended method of eliminating or reducing the dose of steroid tablets is inhaled steroids, at doses of up to 2,000 mcg/day, if required.
- In children aged 5-12 years consider very carefully before going above an inhaled steroid dose of 800 mcg/day.
- Some studies have shown a role for a trial of treatment with long-acting β_2 agonists, Leukotriene receptor antagonists, and theophyllines for about six weeks. They should be stopped if no improvement in steroid dose, symptoms or lung function is detected.
- Immunosuppressants (methotrexate, cyclosporin and oral gold) decrease long term steroid tablet requirements, but all have significant side effects.
- Continuous subcutaneous terbutaline infusion has been reported to be beneficial in severe asthma but efficacy and safety have not been assessed in RCTs.
- Anti-TNF alpha therapy has been investigated in severe asthma but these studies are too small and too short term to allow recommendation of anti-TNF therapy outside the context of a controlled clinical trial
- ANTI IgE - 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 who are uncontrolled on high doses of inhaled glucocorticosteroids (although the dose of concurrent treatment has varied in different studies). Cost is prohibitively high.
- IVIG -The use of intravenous Immunoglobulin is not recommended.

STEPPING DOWN THERAPY

- When inhaled glucocorticosteroids alone are being used in medium-to-high doses, a 50% reduction in dose should be attempted at 3-month intervals
- Where control is achieved at a low dose of inhaled glucocorticosteroids alone, in most patients treatment may be switched to once-daily dosing
- When asthma is controlled with a combination of inhaled glucocorticosteroid and long-acting β_2 -agonist: The preferred

approach is to begin by reducing the dose of inhaled glucocorticosteroid by ~50% while continuing the long-acting β_2 -agonist. If control is maintained, further reductions in the glucocorticosteroid dose should be attempted until a low dose is reached, when the long-acting β_2 -agonist may be stopped

- When asthma is controlled with inhaled glucocorticosteroids in combination with controllers other than long-acting β_2 - agonists, dose of inhaled glucocorticosteroids should be reduced by 50% until a low dose of inhaled glucocorticosteroids is reached, then the combination treatment stopped as described previously
- Controller treatment may be stopped if the patient's asthma remains controlled on the lowest dose of controller and no recurrence of symptoms occur for 1 yr

Oral Prednisolone for Pre-school children with Acute Viral induced wheezing

Attacks of wheezing induced by upper respiratory viral infections are common in preschool children between the ages of 10 months and 6 years. A short course of oral prednisolone is widely used to treat preschool children with wheezing who present to a hospital, but there is conflicting evidence^{13,14,15} regarding its efficacy in this age group. In a recent study it was concluded that in preschool children presenting to a hospital with mild-to-moderate wheezing associated with a viral infection, oral Prednisolone was not superior to placebo¹⁶⁻¹⁸.

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