Asthma pharmacotherapy – the goal is optimised control

Asthma is one of the commonest chronic diseases in the world, with an estimated 300 million asthmatics worldwide.[1] In 2004 South Africa was estimated to have a prevalence of clinical asthma of 8.2%, and although ranked 25th in the world in terms of prevalence, South Africa was ranked 5th for asthma case fatality rates, with an estimated case fatality rate of 18.5 per 100 000.[1] It is also of concern that there is a rising prevalence in asthma symptoms in South Africa.[2]

The goal of chronic asthma management is good and sustained control of symptoms, so that the patient is symptom free, able to maintain normal activity levels (including exercise), with minimal adverse effects from medication.[3] A key component of effective asthma treatment is optimising pharmacotherapy.

Based on our current understanding of their mechanism of action, asthma drugs are classified and used as **controllers** and **relievers.**

Controller medications

Controllers are medications taken daily on a long-term basis.[4] There are 2 groups of controllers: those with anti-inflammatory action and those with a sustained bronchodilator action (Table I). These drugs are the cornerstone of effective asthma control.

Asthma is an episodic narrowing of the bronchi thought to be caused by an underlying chronic inflammatory disorder, and anti-inflammatory treatment is therefore recommended for all patients with chronic persistent asthma.

Inhaled corticosteroids

Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medication for the control of persistent asthma. They reduce asthma symptoms, improve quality of life, improve lung function, decrease airway hyper-responsiveness, control airway inflammation, reduce frequency and severity of exacerbations and reduce asthma mortality.[4] However, they do not cure asthma, and when discontinued, deterioration of control follows.[4] A major advantage of inhaled corticosteroids is that the drug is targeted directly to the site of inflammation in the lungs. This substantially diminishes the number and severity of side-effects without sacrificing treatment effectiveness. A small fraction of any inhaled drug can reach the systemic circulation by direct absorption from the airways or by absorption from the gastrointestinal tract when swallowed, but current evidence suggests that in adults, systemic effects of inhaled corticosteroids do not occur at doses of 400 µg or less budesonide or equivalent daily.[4] Inhaled glucocorticosteroids may cause oropharyngeal candidiasis and hoarseness, particularly at higher doses. The incidence of these local adverse effects can be reduced substantially by rinsing the mouth and throat with water after each dose and by the use of spacer devices attached to the dispenser, to improve drug delivery to the site of action and decrease drug deposition in the oral cavity. Inhaled corticosteroids differ in clinical potency (Table II). The equivalent of 200 - 500 µg/day of beclomethasone diproprionate (BDP) would be regarded as a low dose, and the equivalent of 1 000 µg or more of BDP a high dose.[3] High-dose inhaled corticosteroids give a relatively flat dose response curve, with little increase in clinical efficacy and an increased risk of systemic side-effects, such as easy bruising, adrenal suppression, osteoporosis, cataracts and glaucoma.

Table I. Classification of drugs used in the maintenance treatment of asthma[3]

CONTROLLERS

Anti-inflammatory action	**Sustained bronchodilator action but weak or unproven anti-inflammatory effect**
Inhaled corticosteroids • Beclomethasone • Budesonide • Ciclesonide • Fluticasone	Long-acting β_2-agonists • Salmeterol • Formoterol
Leukotriene receptor antagonists • Montelukast • Zafirlukast	Sustained-release theophylline preparations
Oral corticosteroids • Prednisone • Prednisolone • Methylprednisone • Methylprednisolone	

RELIEVERS

For quick relief of symptoms and use in acute attacks as when required (PRN) dosage only

Short-acting β_2-agonists
- Salbutamol
- Fenoterol
- Terbutaline

Anticholinergics
- Ipratropium bromide

Table II. Equivalent doses of inhaled glucocorticosteroids[3]

Drug	**Equivalent metered dose in asthma**
Beclomethasone	200 - 250 µg
Budesonide	200 µg
Ciclesonide	80 µg
Fluticasone	100 µg

Long-acting β_2-agonists

Two long-acting inhaled β_2-agonists (LABAs) are available in South Africa: salmeterol, and formoterol. They have a similar duration of bronchodilation but formoterol has a more rapid onset of action, and can be used to relieve symptoms in acute exacerbations in addition to its role in symptom prevention. LABAs have no anti-inflammatory effect. They should never be used as monotherapy in asthma as this has been shown to increase mortality.[5] Their role is as add-on therapy to inhaled corticosteroids. When inhaled glucocorticosteroids alone fail to achieve control of asthma, a LABA should be added as a first step, before increasing the dose of inhaled corticosteroids. Inhalation corticosteroids and LABAs are available in fixed-combination inhalers that deliver both glucocorticosteroids and long-acting inhaled β_2-agonists simultaneously (budesonide plus formoterol or fluticasone plus salmeterol). These formulations may be more convenient for patients and may thus improve adherence.[3] Long-acting inhaled β_2-agonists may be used to prevent exercise-induced bronchospasm and are useful for control of nocturnal symptoms. LABAs may cause tremor and palpitations. The regular use of β_2-agonists in both short- and long-acting forms may lead to decreased sensitivity to β_2-agonists, with reduced clinical response.[4]

Leukotriene receptor antagonists

Leukotriene receptor antagonists block the bronchoconstrictor and pro-inflammatory activity of cysteinyl leukotrienes (metabolites of arachodonic acid produced by mast cells, basophils and eosinophils) within the asthmatic airway.[6] They have a bronchodilator effect, reduce symptoms, improve lung function and reduce airway inflammation and asthma exacerbations. When used as monotherapy, they are not as effective as low-dose inhaled corticosteroids and they should therefore not be used as a substitute for glucocorticosteroids.[4] Leukotriene receptor antagonists added to inhaled corticosteroids are less effective than LABAs added to inhaled corticosteroids in the treatment of asthma.[7] They may be useful as add-on therapy in patients with moderate to severe asthma, who are already taking inhaled corticosteroids and a LABA but remain symptomatic, in patients who do not tolerate LABA side-effects, or to allow for a reduction in the dose of inhaled corticosteroid. Not all patients respond to leukotriene receptor antagonists, and they should be withdrawn if there is no improvement in symptoms after a 4-week trial of therapy.[3] Leukotriene receptor antagonists are well tolerated with few side-effects.[4]

Sustained-release theophyllines

Theophylline is a bronchodilator with very modest anti-inflammatory properties. It should not be prescribed without inhaled corticosteroids. As add-on therapy, theophylline is less effective than LABAs.[4] Theophylline has a high potential for side-effects and drug interactions due to its narrow therapeutic range. Adverse effects include gastrointestinal symptoms, cardiac arrhythmias and seizures. There is no role for oral short-acting theophyllines in chronic asthma.[3]

Oral corticosteroids

Oral glucocorticosteroids such as prednisone may be considered in patients with severe and poorly controlled asthma, but their use in chronic asthma management is limited by the risk of significant adverse effects. Patients who require long-term systemic glucocorticosteroids should receive preventive treatment for osteoporosis. Strategies include avoidance of smoking, regular exercise, calcium supplements and, in postmenopausal women, bisphosphonates or hormone replacement therapy.

Table III. Levels of asthma control[8]

Characteristic	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	≤ 2/week	> 2/week	3 or more features of partly controlled asthma in any week
Limitations of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for reliever/ rescue treatment	≤ 2/week	> 2/week	
Lung function (PEF/ FEV_1)	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	1 or more/year*	1 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.

Adapted from the *South African Medicines Formulary*, reproduced with permission.

Reliever medications

Relievers (Table III) quickly reverse bronchoconstriction and relieve symptoms. They are not an alternative to controller drugs. If relievers are needed more than twice a week this is an indication that control is suboptimal and that controller medication needs to be increased or improved.[3]

Short-acting β_2-agonists

Short-acting β_2-agonists are the drugs of choice for relief of bronchospasm during acute exacerbations. With optimal maintenance therapy they should only rarely be needed. Increased use is an indication of deterioration of asthma control. Patients should be instructed to seek medical attention if use of short-acting β_2-agonists increases. If response to β_2-agonist treatment during an exacerbation is not rapid and sustained, short-term treatment of the exacerbation with oral glucocorticosteroids may be needed.[4] Oral β_2-agonists should not be prescribed, as onset of action is slower than inhaled therapy and incidence of systemic side-effects such as tremor, tachycardia and headache is significantly higher.

Anticholinergics

Inhaled ipratroprium bromide is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists.[3,4] It may useful as an alternative bronchodilator for patients, particularly the elderly, who cannot tolerate the β_2-agonist side-effects. Inhalation of ipratroprium bromide can cause a dryness of the mouth and a bitter taste.

Selecting chronic maintenance therapy

South African treatment guidelines outline 6 therapeutic steps (Fig. 1). It is preferable to use a step-down approach, i.e. start at a higher category and decrease later once control has been achieved.

Step 1: All patients should be prescribed an inhaled short-acting β_2-agonist 200 µg as needed for use as symptom relief for acute asthma symptoms. If the β_2-agonist is required more than twice per week, go to step 2.

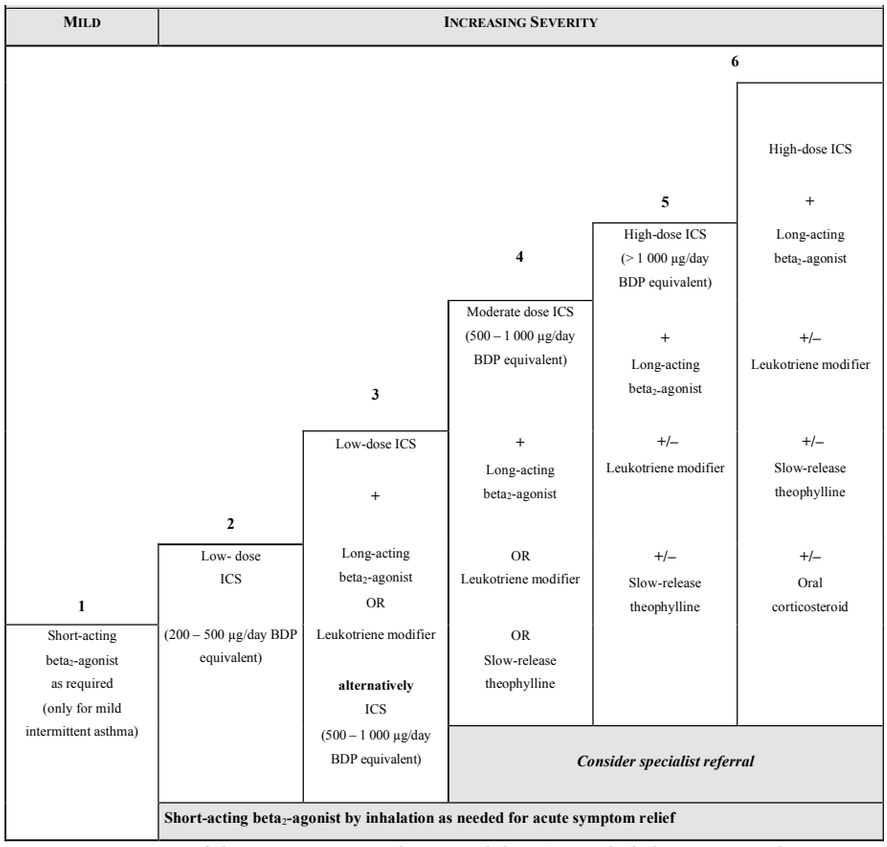

Fig. 1. Management of chronic persistent asthma in adults. ICS = inhaled corticosteroid; BDP = beclomethasone dipropionate. Reproduced with permission from the South African Medicines Formulary.[8]

Step 2: Regular twice-daily low-dose inhaled corticosteroids (200 - 500 µg/day beclomethasone or equivalent) should be added to the short-acting β_2-agonist. If still uncontrolled, go to step 3.

Step 3: There are three options in addition to an inhaled short-acting β_2-agonist:

- Add a long-acting β_2-agonist. This is the preferred option, unless the patient does not respond to a LABA, *or*
- An alternative is to double the dose of inhaled corticosteroids to moderate-dose (500 - 1 000 µg/day beclomethasone or equivalent), *or*
- Add a leukotriene receptor antagonist to the low-dose inhalation glucocorticosteroids.

If still uncontrolled, go to step 4. At this point, generalists should consider specialist referral.

Step 4: Add a moderate-dose inhaled corticosteroid (500 - 1 000 µg/day beclomethasone or equivalent) to the short-acting β_2-agonist *plus* an additional agent such as a long-acting β_2-agonist, a leukotriene receptor antagonist or a sustained-release theophylline. If still uncontrolled, go to step 5.

Step 5: Add a high-dose inhaled corticosteroid (>1 000 µg/day beclomethasone or equivalent) to the short-acting β_2-agonist *plus* more than one additional agent such as a long-acting β_2-agonist, a leukotriene receptor antagonist or sustained-release theophylline.

Step 6: Oral glucocorticosteroids in the lowest effective dose can be added.

If the patient is poorly controlled the following should be considered and excluded or addressed:[3]

- poor adherence
- concomitant medications that may aggravate asthma such as aspirin, non-steroidal anti-inflammatory drugs and β-blockers
- other medical conditions such as heart failure which may mimic bronchospasm clinically
- poor metered-dose inhaler technique: this may be addressed by use of a spacer device, or by use of an alternative formulation (dry powder inhaler or autohaler)
- patient confusion about when to use controller and reliever drugs
- exposure to trigger factors at home and work
- presence of gastro-oesophageal acid reflux disease
- inadequately treated rhinitis and/or sinusitis.

Asthma is common in South Africa, and case fatality rates are alarmingly high. This suggests that many patients receive suboptimal therapy and are poorly controlled, despite the availability of a range of drugs, formulations and delivery mechanisms, as well as local, evidence-based, treatment guidelines. The appropriate use of controller medications, particularly inhaled corticosteroids and LABAs, is critical in optimising symptom control.

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