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RESEARCH ARTICLE

PHARMACOLOGICAL CONTROL OF ASTHMA: AN UPDATE

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ABSTRACT

Worldwide bronchial asthma is one of the most common non communicable disease of rising prevalence. The main feature of bronchial asthma is bronchial eosinophilic inflammation induced bronchospasm in genetically predisposed known and unknown agents. The goal of pharmacological control includes, neutralize precipitating factors of bronchospasm and reduce inflammation. Though the modern step care management is not so difficult but the difficulty remains in adherence to the ideal treatment schedule for the patient and also for the physician. This issue is concerned about the up to date pharmacotherapy of bronchial asthma so that the physician can manage the patient effectively and efficiently. The ultimate aim of our paper is to help the asthma patient to maintain their daily activity with minimum or no symptoms in a safe and cost effective way.

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INTRODUCTION

The term Asthma is derived from Greek word meaning 'panting' in the time of Hippocrates (460-370 BC) (Bourke and Brewis, 1998). Asthma is a substantial health problem worldwide, with high and increasing prevalence rates in many countries (Burney *et al*., 1973-86), a substantial morbidity-reflected in hospital admission rate (Halton and Newacheck, 1986), use of medical services (Anderson, 1989). Asthma and drug use (Klaukka *et al*., 1991), and worrying trends in mortality rate in some countries (Sears *et al*., 1992). The global burden of asthma is 130 million, mortality is 60,000 deaths annually, many of which occur in young people and are potentially preventable (Sears *et al*., 1992). Modern pharmacological therapy of asthma dates from the turn of the century when adrenal extract was first used to treat asthma. Management of asthma has improved enormously over the past 20-30 years due to advances in both drug discovery and in the way that drugs and care are delivered (Sears *et al*., 1992; Michael *et al*., 1987).

Goal of Drugs Treatment

The aim of asthma therapy is to maintain control of asthma with the least amount of medication and hence minimal risk for adverse effects of drugs. Pharmacological control of asthma is defined as (a) preventing chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion). (b) Maintaining nearly normal pulmonary function. (c) Maintaining normal activity levels (including exercise and other physical activities), (d) preventing recurrent exacerbation of asthma and minimizing the reed for medical emergency department visits or hospitalization. (e) Providing optimal pharmacotherapy with minimal or no side effect and (f) meeting patients' and families' satisfaction with asthma care (John Morrison and Roslan Harun, 1995).

Classification of Asthma severity

Asthma management by drugs is given stepwise on the basis of severity of chronic asthma. Asthma severity is classified in to four steps/types for stepwise approach for the effective pharmacological control (Michael *et al*., 1087; John Morrison and Roslan Harun, 1995) are shown in the Table-1.

Step care therapy of Asthma

The step wise approach for managing asthma is described in International guidelines (British guidelines on asthma management, 1995). A simplified approach follows as shown in the Table-2.

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Table 1. Classification of severity of asthma

Step/Type	Symptoms*	Nighttime symptoms	Lung Function
Step 4 Severe Persistent	a) Continual symptoms b) Limited physical activity. c) Frequent exacerbations	Frequent	a) FEV_1 or PEF ≤ 60% predicted a) PEF variability >30%
Step 3 Mederate Persistent.	a) Daily symptoms *b)* Daily use of inhaled short acting β_2 *agonists* c) Exacerbations affect activity d) Exacerbations ≥ 2 times a week	>I time a week	a) FEV_1 or PEF>60%-<80% predicted b) PEF variability 20-30%
Step 2 Mild Persistent	a) Symptoms >2 times a week but < I time a day b) Exacerbations may affect activity	>2 times a month	a) FEV_1 *or PEF ≥ 80%* predicted b) PEF variability 20-30%
Step 1 Mild Intermittent	a) Symptoms < 2 times a week b) Asymptomatic and normal PEF between exacerbation c) Exacerbation brief; intensity may vary	≤2 times a month	a) FEV_1 or PEF ≥80% predicted b) PEF variability 20%

*The presence of one of the features of severity is sufficient to place a patient in that category.

Table 2. The step wise approach for managing asthma

Steps	Long-term control	Quick relief
Steps 4 Sever Persistent	Inhaled corticosteroid (high dose); Long acting inhaled (β_2 agonist/sustained release theophylline; and Oral corticosteroid daily	Inhaled short-acting β_2 agonist as needed for symptoms. Increasing use of short-acting β_2 agonist indicates the need for additional long-term control therapy
Steps 3 Moderate Persistent	Inhaled corticosteroid (high dose); or Inhaled corticosteroid (low dose) and long acting inhaled β_2 agonist/sustained release theophylline or if needed Inhaled corticosteroid (high dose) and long acting inhaled β_2 agonist/sustained release theophylline	Inhaled short-acting β_2 agonist as needed for symptoms Increasing use of short acting β_2 agonist indicates the need for additional long-term control therapy
Steps 2 Mild Persistent	Inhaled corticosteroid (low dose); or Cromolyn or nedocromil (usually children): Antileukohienes may be considered	Inhaled short-acting β_2 agonist as needed for symptoms. Increasing use of short-acting β_2 agonist indicates the need for additional long-term control therapy
Steps 1 Mild Intermittent	No daily medication needed	Inhaled short-acting β_2 agonist as needed for symptoms. Increasing use of short-acting β_2 agonist indicates the need for additional long-term control therapy

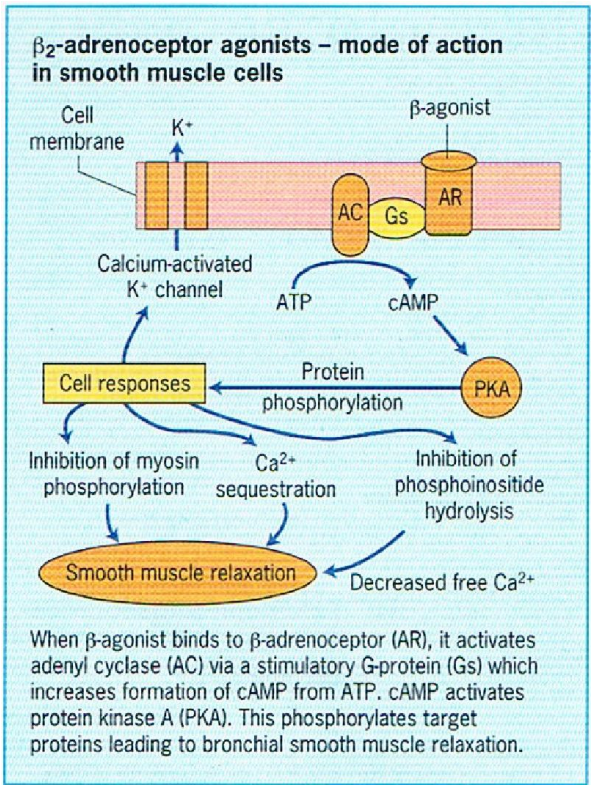

Fig. 1. The mode of action of β_2-adrenoceptor agonists on smooth muscle cells

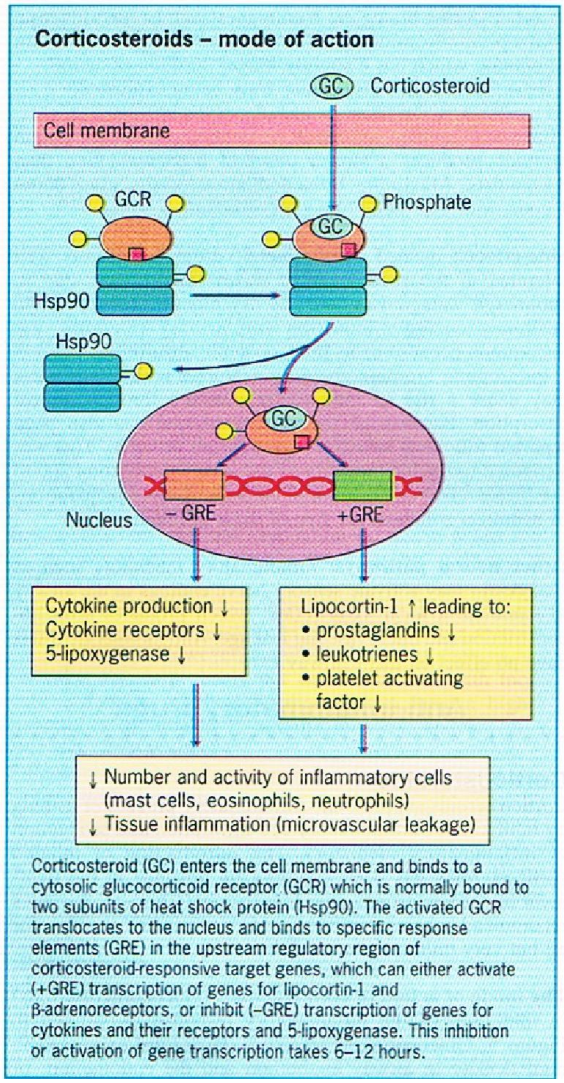

Fig. 2. The Flow chart shows the mode of action of corticosteroids

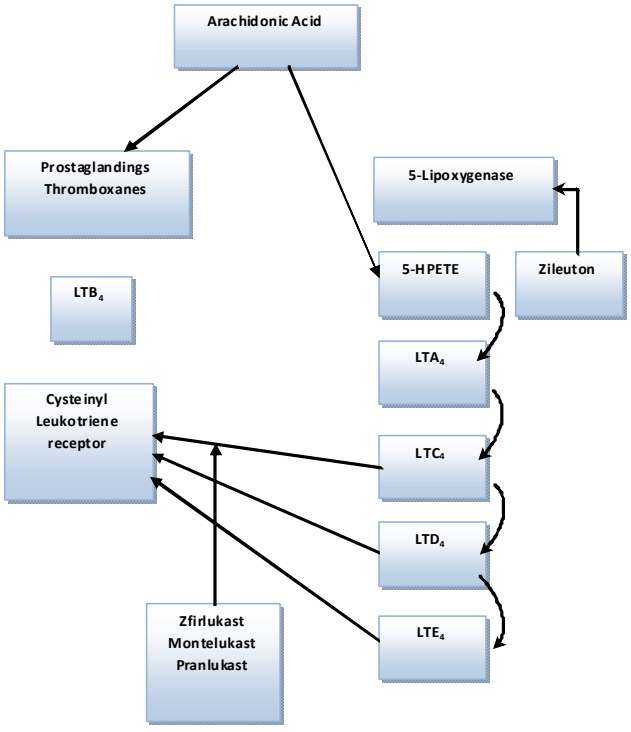

Fig. 3. Arachidonic acid metabolism Cysteinyl leukotrienes interact with a specific receptor which is blocked by antagonists. 5-lipoxygenase is blocked by zileution

The clinicians must judge patient's needs at what step to initiate therapy. The more aggressive approach of gaining prompt control with a higher level of therapy is preferred. Continual monitoring is essential to ensure that asthma control is achieved. Control is indicated by (a) minimal symptoms, (b) absence of night-time awakenings, (c) no activity limitations, (d) PEF values indicating less than 10%-20% variability and (e) PEFR consistently greater than 80% of the patients personal best. Once control is achieved and sustained for 3-6 months, a reduction in therapy, a step down, is appropriate and helpful to identify the minimum therapy for maintaining control. The does of inhaled corticosteroid may be reduced by about 25% every 2-3 months to the lowest does possible to maintain control. Patients may relapse if steroids are completely discontinued. If control is not maintained, consider step up. A rescue course of oral steroid may be needed at any step. Of course, patient medication technique, adherence and environmental control should be reviewed beforehand. However, the step care therapy at different steps of asthma severity are intended to be general guidelines, not prescriptions for individual treatment. Also, the heterogeneous nature of asthma dose not lend itself to rigid stepwise algorithmic approaches (Spear, 2000).

Asthma Medications

Asthma medications are categorized in to two classes; (a) long term control medications, also known as preventive, controller or maintenance medications and including corticosteroids, cromones, antileukotrienes and corticosteroids sparing therapies (methotrexate, gold, cyclosporin A). (b) Quick relief medications, also known as reliever which includes β_2 agonists, theophylline, anticholinergics (John Morrison and Roslan Harun, 1995; Barnes, 1999). Inhaled β_2 agonists are the most effective bronchodilators and have minimal side effects where used correctly (Barnes, 1999; Lipworth, 1999). They relaxes airway smooth muscles directly, but may cause bronchodilatation indirectly by inhibiting the release of mediators from inflammatory cells, or neurotransmitters from cholinergic nerves (John Morrison and Roslan Harun, 1995; Barnes, 1999). The mode of action of β_2-adrenoceptor agonists (Michael *et al*., 1987; John Morrison and Roslan Harun, 1995) are shown in the Fig 1. Short-acting inhaled β_2 agonists (e.g. salbutamol) are the medications of choice for exacerbations of asthma, prevention of EIB (exercise induced bronchospasm) and bronchoconstriction on exposure to cold air or allergens (John Morrison and Roslan Harun, 1995; Barnes, 1999; Lipworth, 1999). Also Nebulized β_2 agonists (e.g. salbutamol) are the medications of choice in acute severe asthma. Onset of action is within 5-10 minutes and it persists for 3-4 hours (less in severe asthma) (John Morrison and Roslan Harun, 1995; Lipworth, 1999). Daily does of inhaled salbutamol ranges from 100-200 µgms (1-2 puffs) up to 3-4 times. Daily use of short acting β_2 agonists is not recommended, used as only need basis (Cockeroft *et al*., 1993; O' Connor *et al*., 1992). Regular use of short acting β_2 agonists may worsen control of asthma (Sears *et al*., 1990). Inhaled long-acting β_2 agonists (e.g. salmeterol) have duration of action of about 12 hours after a single dose (D'Alonzo *et al*., 1994). They attenuate EIB for longer periods than do short acting β_2 agonists (Green and Price, 1992) and improve nocturnal symptom (Fltzpatrick *et al*., 1990). Daily dose of inhaled salmeterol is 50-100 µgms twice daily (British National Formulary, 2000). Adding a long acting β_2 agonists to a low dose inhaled corticosteroid produces comparable control to monotherapy with a higher dose of inhaled corticosteroid (Pauwels *et al*., 1997). Tolerance to the airway effects of β_2 agonists develops when these drugs are given regularly and that this is more pronounced for loss of Broncho protective activity than bronchodilator activity. Controlled release oral salbutamol may be used to treat nocturnal symptoms like inhaled long-acting β_2 agonists (Lipworth, 1999). Unwanted side effects resulting from stimulation of extra-pulmonary β_2 receptor including tremor, tachycardia, restlessness, hypoxemia and hypokalaemia are more common with oral and intravenous administration (Barnes, 1999).

Corticosteroids

Inhaled corticosteroids have revolutionized the treatment of asthma. The mechanism of action of corticosteroids in asthma is poorly understood: it is most likely related to their anti-inflammatory properties (Barnes, 1999). The Inhibit a variety of inflammatory cells, cytokine expression, and transcription factors which are involved in inflammatory process. The mode of action of corticosteroids (John Morrison and Roslan Harun, 1995) and are shown in the Fig 2. Modern asthma management guidelines emphasized early intervention with inhaled corticosteroids, which may prevent any long term decline in lung function resulting from bronchial fibrosis (British guidelines on asthma management, 1995). Daily dose of inhaled beclomethasone is 400-800 µgms daily (low dose) and 800-2000 µgms twice daily (high dose), for mild to moderate asthma, once daily regimen of up to 800 µgms of beclomethasone maintenance treatment may be adequate. Side effects of high dose inhaled corticosteroids include adrenal suppression, osteoporosis, growth suppression, skin bruising, cataracts, glaucoma, metabolic abnormalities and psychiatric disturbances (Barnes, 1999). Available data suggest that the beneficial effects of inhaled corticosteroids on disease control will outweigh any potential systemic bioactivity in terms of long term growth in asthmatic children. No effect of this drug on the final achieved about height has been shown (Allen *et al*., 1994; Silvestein *et al*., 1997). Evidence indicates, in post-menopausal women, bone density may be reduced by long term exposure to inhaled corticosteroids and is related to cumulative dose and duration of treatment (Toogood *et al*., 1995; Wisniewski *et al*., 1997), which may be reduce by oestrogen replacement therapy or biphosphonate drugs. Long term treatment with high dose of inhaled corticosteroids is associated with a increased risk of posterior sub capsular cataract and glaucoma (Cumming *et al*., 1997; Garbe *et al*., 1997). Skin bruising is more prevalent in elderly and is associated with adrenal suppression (Roy *et al*., 1996; Gupta *et al*., 2000). Local side effects are dysphonia, cough and oral candidasis. Once or twice daily dosing, regular mouth rinsing and use of large volume spacer reduce the occurrence of candidiasis. Stepwise approach for managing asthma may need a short rescue course of systemic corticosteroids: a) at any time and any step during a period of gradual deterioration, b) to establish control as quickly as possible when initiating therapy. The dose of Prednisolone is 40-60 mg, a single morning p.o. and has an similar effect of intravenous hydrocortisone

(Barnes, 1999). It should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days, may be longer. For long term control of asthma, oral corticosteroid may be given daily or on alternate days in moming single minimal dose (John Morrison and Roslan Harun, 1995; Barnes, 1999). Hypomalamo-pituitary-axis adrenal suppression occurs when a dose of Prednisolone of more than 7.5-10 mg daily is used (in step 4). Significant suppression usually does not occur after a short course. It is a problem after a several months or years (Barnes, 1999). Methotrexate, cyclosporine, gold, intravenous immunoglobulin and hydroxyachloroquine are used in selected asthma cases as corticosteroid sparing therapy. However, their use remains complicated because of highly variable effects, potential toxicity and limited clinical experiences (Jarjour *et al*., 1996).

Cromones

Cromones include sodium chromoglycate and the structurally related nidocromil sodium. Initial investigation suggested that chromoglycate acts as a mast cell stabilizer, but this effect is weak in human mast cells. Cromones inhibit bronchoconstriction induced by sulphur dioxide, metabisulphite and brakdykinin, which are believed to act through activation of sensory nerves in airways (Barnes, 1999). They also inhibit the early and late asthmatic response to allergen challenge and EIB (Alton and Norris, 1996). Recent evidence suggests that they may block a type of chloride channels that may be expressed in sensory nerves, mast cells and other inflammatory cells (Barnes, 1999). The two components are equally effective against allergen challenge, although nedocromil seems to be more potent in inhibiting EIB (De Benedictis *et al*., 1995). Cromones are given four times daily and may also be taken before exercise in children with EIB. They are not effective in all patients and predicting response is impossible (Barnes, 1999). Side effects are rare which includes throat irritation, coughing and wheeze with chromoglycate and sensation of flushing with nedocromil (Barnes, 1999).

Methylxanthines

They are theophylline and aminophylline. Aminophylline is a stable mixture of theophylline and ethylenediamine, which confers 20 times solubility in water (Barnes, 1999). The mode of action in asthma is yet to be established. Several mode of action have been proposed: (a) Inhibition of phosphodiesterases leading to increased intracellular CAMP, which is likely responsible for bronchodilatation. But the required dose is high, plasma concentration of theophylline becomes 10-20 mg/L. Actually, at this level side effects develops. (b) Adenosine receptor antagonism: adenosine is a bronchoconstrictor in asthmatics via activation of mast cells. Recent evidence suggests that low serum concentration of theophylline (5-10 mg/L) are mildly anti-inflammatory. This finding led to a reappraisal of theophylline's role as second line controller treatment in addition to inhaled corticosteroid (Evans *et al*., 1997). Sustained release theophylline's main role is controlling nocturnal symptoms. Intravenous aminophylline is used to manage severe exacerbation of asthma, if nebulized β_2 agonist fails. Side effects include nausea, vomiting, headache, cardiac arrhythmias and seizures (Barnes, 1999).

Anticholinergics

They are ipratropium bromide and oxytropium, specific antagonists of muscarinic receptors and inhibit cholinergic nerve induced bronchoconstriction. Anti-cholinergic drugs may have an additive effect with high dose inhaled corticosteroid in the management of chronic asthma and severe exacerbation, when there is inadequate control of asthma or side effects with theophylline and β_2 agonists (John Morrison and Roslan Harun, 1995; Barnes, 1999; British National Formulary, 2000). Inhaled ipratropium bromide is well tolerated. Nebulized ipratropium bromide may precipitate glaucoma in elderly patients as a result of a direct effect of the nebulized drug on the eye, this is avoided by use of a mouthpiece rather than a face mask (Barnes, 1999).

Anti-histamines

Anti-histamines usually have no helpful effect in controlling asthma, but may be used to treat associated allergic rhinitis, conjunctivitis and ureticaria. Cetirizine and loratidine are examples of potent, selective type-1 histamine receptor antagonist (Lipworth, 1999). Preliminary data suggest that antihistamines and leukotrienes antagonists may show additive effects on control in asthma and allergic rhinitis (Malmstrom *et al*., 1998).

Anti-leukotrienes

These are new class of anti-asthma agents recently introduced into clinical practice. They are of two categories on the basis of their site of action: (a) leukotriene receptor antagonists (LTRA) and include montelukast, zafirlukast and pranlukast; and (b) 5-lipoxygenase inhibitor, zileuton. The cysteinyl leukotrienes are metabolites of arachidonic acid comprising leukotrienes C_4, D_4, E_4. They are produced in excessive amount in asthmatics, interacting with at least one specific receptor in the lungs causing various effects: (a) bronchoconstriction (100-1000 times more potent than histamine). (b) bronchial smooth muscle hyper responsiveness. (c) inflammatory cell recruitment. (d) vascular permeability leading to tissue oedema and air flow obstruction and (e) mucus formation leading to further air flow obstruction (Dempsey, 2000) as shown in the Figure 3. Anti-leukotrienes exhibit both bronchodilator and anti-inflammatory activity. Long term administration reduces asthma symptoms and the need for rescue β_2 agonist and improves lung function (Gaddy *et al*., 1992). Anti-leukotrienes may be useful in patients whose asthma is not controlled on inhaled corticosteroids, and may be as effective as or more effective than doubling the dose of inhaled corticosteroids. Inhaled corticosteroids are not very effective in inhibiting the production of leukotrienes in asthma (Dempsey, 2000). Anti-leukotrienes reduce allergen induced, exercise induced and cold air induced asthma by about 50-70% and inhibit aspirin induced asthma completely. A recent study suggests anti-leukotrienes may be beneficial in premenstrual asthma. Anti-leukotrienes are effective in treating coexistent allergic rhinitis (Howarth, 2000) and other conditions like atropie dermatitis and eosinophilic gastroenteritis (Neustrom and Friesen, 1999). The response to anti-leukotrienes is difficult to predict, genetic polymorphisms of the enzymes controlling biosynthesis of

leukotrienes may be important predictor. A major advantage is that they are orally active, so long term compliance is good. Side effects are uncommon, may cause mild liver dysfunction. A few cases of Churg-Strauss syndrome have been observed; this may be because of unmasking of the underlying condition caused by tapering of oral corticosteroids. Both montelukast and zafirlukast are avoided in pregnancy, lactation and hepatic impairment (Summary of product characteristics. Singulair. Hertfordshire, UK: Merck Sharp & Dohme Ltd. January 1998; Summary of product characteristics. Accolate. Cheshire. UK: Zeneca Ltd., July 1998).

Omalizumab

It is the recombinant humanized monoclonal antibody against IgE used in the treatment of patient with allergic asthma, who are sensitive to external allergen and produce excessive IgE. An excess of IgE is the root cause of allergic asthma and omalizumab prevents IgE from binding to mast cell and eventually release of histamine and other mediators which causes bronchoconstriction. Omalizumab is administered by subcutaneous injection every 2 to 4 weeks.

Newer Modality of Asthma Therapy

There are the therapeutic procedure for the asthma patient and are in the very experimental stages. The basis of practice of this type of treatment focused on airway remodeling, which is thought to be the ultimate pathogesis of asthma. Two types of newer modality are in experimental stage

(a) Bronchoplasty : In this process stent is applied to dilate the constricted bronchi.
(b) Broncho thermoplasty : Here hyperplastic bronchial smooth musical is reduces by thermal coagulation.

Conclusion

Pharmacological control of asthma relies heavily on β_2 agonists and corticosteroids. Inhaled corticosteroids should be used as early as possible as first line anti-inflammatory therapy. Inspite of these drugs, many patients continue to have considerable morbidity. These patients require a new addition to treatment. In this respect the position of antileukotrienes in the treatment of asthma requires long term studies.

In Bangladesh, 90% asthmatics are away from modern treatment. There are many false beliefs about asthma and its management aspects particularly about use of inhalers, spacers, and alternate medicine. Asthma management will improve if physicians spend more time in patients education along with prescribing drugs.

Ethical Issues

The authors declare no competing financial interest.

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