South African Family Practice 2015; 57(4):31-36

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

REVIEW

Approach to asthma in adults

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Abstract

Asthma is a chronic inflammatory disease that causes hyper-responsiveness of the bronchial tree, with reversible airflow obstruction. The condition places a significant burden on our healthcare system. Chronic asthma can cause remodelling of the airway. Patients suffering from asthma should be aware of its signs and symptoms, as well as factors that can precipitate an asthmatic attack. Asthma is mostly classified as either acute or chronic. The diagnosis of asthma is based on identification of both a characteristic pattern of respiratory symptoms and variable expiratory airflow limitation. Treatment is based on how the patient presents, and includes bronchodilators, inhaled corticosteroids and mast cell stabilisers. This article provides an overview of the diagnosis, characterisation and treatment of asthma.

Keywords: asthma, bronchodilator, inhaled corticosteroid, β_2 agonist, peak expiratory flow, spirometry, SABA, LABA

Introduction

Asthma is a chronic inflammatory disease of the airways, associated with bronchial hyper-responsiveness and reversible airflow obstruction. It is one of the most common chronic diseases in the world. It is estimated that approximately 300 million people worldwide suffer from asthma. Estimates of the prevalence of asthma range from 7% in France and Germany, to 11% in the USA, and 15-18% in the UK. Approximately 20% of patients suffer from severe asthma, of which 20% is inadequately controlled.[1] Furthermore, asthma is reportedly increasing worldwide, as communities in the developing world adopt Western lifestyles and become urbanised. The World Health Organization recognised asthma as being of major public health importance in 2013.[2]

The magnitude of the burden of asthma may be underappreciated. This is partly owing to health systems, such as primary healthcare services that are overwhelmed by communicable respiratory diseases, such as pneumonia or tuberculosis.[3] The burden of asthma is underappreciated in countries like South Africa, where the burden of respiratory diseases such as pneumonia, tuberculosis and human immunodeficiency virus (HIV)-associated lung disease is well known.[3] Asthma is the eighth leading contributor to the burden of disease in South Africa, and is the second most important chronic disease after HIV/acquired immune deficiency syndrome.[3,4] Despite the availability of medication, asthma remains poorly controlled in many patients.[3,5]

The emphasis in asthma treatment is on achieving effective control. The Global Initiative for Asthma's goals are to achieve and maintain control of the symptoms, maintain pulmonary function as close to normal as possible, and to prevent exacerbations and mortality.[6]

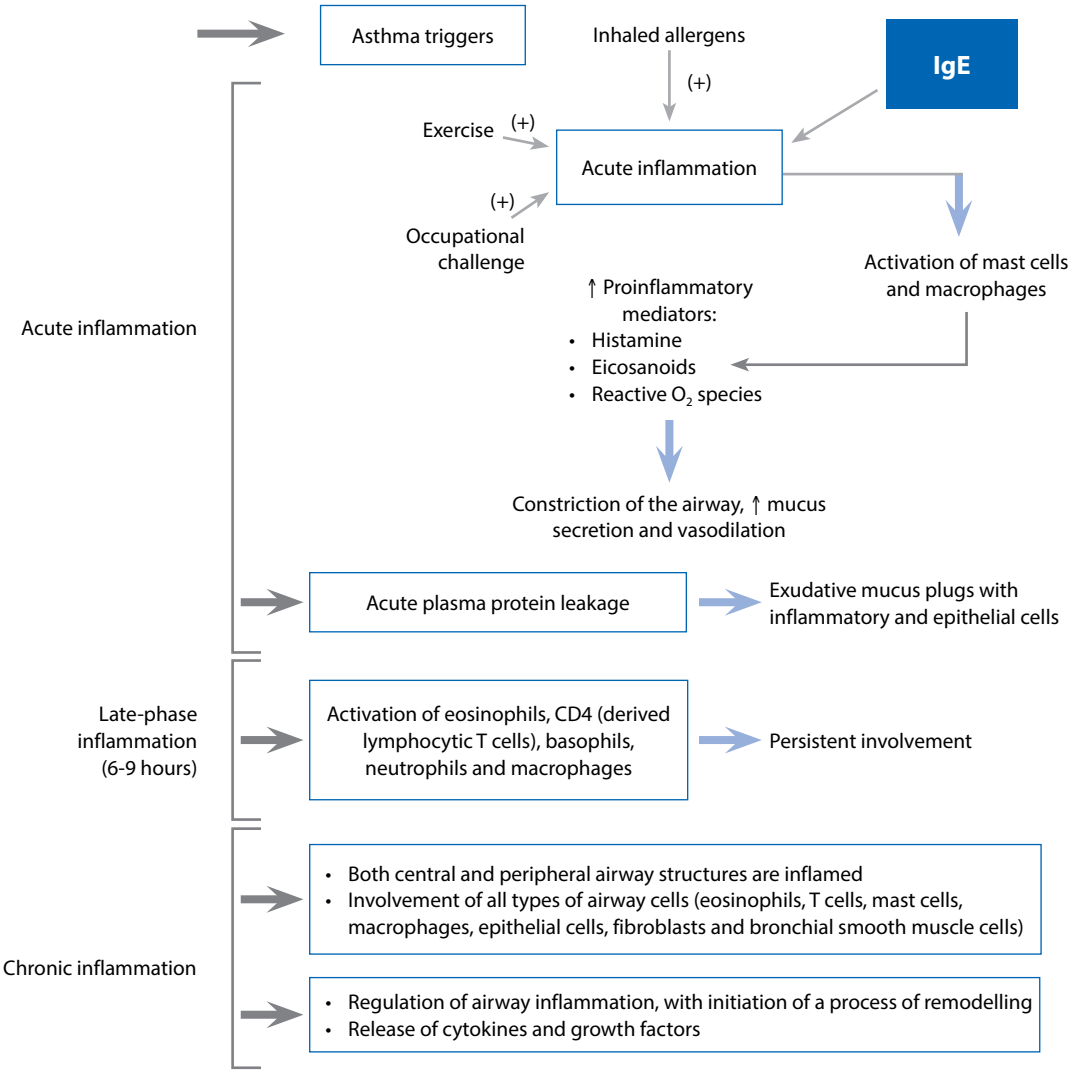
Improper or inadequate implementation of the guidelines is a major reason for poor asthma management in South Africa.[3] Challenges to successful implementation include factors within the healthcare system and the individual behaviour of healthcare providers, as well as that of patients or caregivers. Moreover, socio-economic and structural barriers that impair access to healthcare services remain important obstacles.[3]

A large number of patients have not yet benefited from advances in asthma treatment, and are still insufficiently controlled, placing severe limits on daily life, and placing them at risk of asthma-related morbidity and mortality.[7] Asthma is the most common chronic inflammatory disease, with resistance in the intrapulmonary airways due to abnormalities of airway function.[8]

Pathological components of asthma can be described as cellular inflammation, including bronchitis, and the remodelling of the structural elements of the airway wall.[9] This includes inflammation of the airway, constriction of the airway via smooth muscle contraction, the hypersecretion of mucus, bronchial hyper-responsiveness, and additional narrowing of the airway due to mucosal oedema and sloughing of the epithelial cells.[10] Figure 1 provides a diagrammatic overview of the pathophysiology of asthma.[8]

Precipitating factors

Several trigger factors can contribute to an asthma attack. Avoiding these factors can help to reduce asthma exacerbations and asthma severity.[11] Table I presents the precipitating factors of asthma, with examples of asthma triggers.[12]



CD4: cluster of differentiation 4, IgE: immunoglobulin E

Figure 1: Diagrammatic representation of the pathophysiology of asthma[8]

Table I: Precipitating asthma factors[12]

Viral respiratory infections
- Rhinovirus (most common)
- *Other:* Respiratory syncytial virus, parainfluenza virus, coronavirus and influenza viruses

Environmental factors
- *Air pollution:* Ozone, sulphur dioxide and tobacco smoke
- *Allergens:* Airborne pollen, furry animals, fungal spores, house dust mites and cockroaches

Occupational factors
- *Industrial inhalants and irritants:* Hay, mould, Arabic gum, spices, flour dust and chemicals, i.e. azo dyes, polyvinyl chloride, formaldehyde, ethylenediamine and anhydrides

Food additives
- *Preservatives:* Sulphites and benzalkonium chloride
- *Metabisulphites:* In wine, beer and dried fruit

Medication
- *Cyclo-oxygenase inhibitors:* Aspirin and nonsteroidal-anti-inflammatory drugs
- Non-selective β blockers

Nutritional and exercise-related factors
- Obesity
- Vitamin D insufficiency in children
- Exercise in a cold, dry climate

Psychological factors
- Stress, anxiety and depression

Gastroenterology factors
- Gastro-oesophageal reflux disease

Signs and symptoms

Acute asthma

Acute asthma, also referred to as asthma exacerbations, is an episodic asthma attack that progresses rapidly. Therefore, early recognition and rescue medication is of high importance.[13] The signs of an acute asthma attack include an increased heart rate, tachypnoea, cyanotic or pale skin, expiratory and inspiratory wheezing, a hyperinflated chest and a dry hacking cough. During an acute asthma attack, patients can experience anxiety, severe dyspnoea, tightness of the chest, or a burning sensation and shortness of breath. Also, they may be unable to speak a full sentence and can be in acute distress.[12]

Chronic asthma

Chronic asthma is a lifelong condition that varies in nature from daily to intermittent symptoms, and patients need to be permanently managed and treated. Signs and symptoms may persist during exercise, or when exposed to an allergen. The signs of chronic asthma include a dry hacking cough, expiratory wheezing or signs of allergic rhinitis and/or eczema. Episodes of dyspnoea, coughing at night, tightness of the chest, wheezing or stridor are the symptoms of chronic asthma.[12]

Table II: Classification of asthma severity[11]

Intermittent		**Chronic persistent**	
Mild **I**	**Mild** **II**	**Moderate** **III**	**Severe** **IV**
Daytime symptoms ≤ 2 per week	Daytime symptoms 3-4 per week	Daytime symptoms ≥ 4 per week	Daytime symptoms are continuous
Night-time symptoms ≤ 1 per month	Night-time symptoms 2-4 per month	Night-time symptoms ≥ 4 per month	Night-time symptoms are frequent
PEF ≥ 80%	PEF ≥ 80%	PEF 60-80%	PEF ≤ 60%

PEF: peak expiratory flow

Classification

It is important to classify the severity of a patient's asthma before implementing the initial treatment. This will assist in reviewing management of the condition once periodic assessment for asthma control has been established. Making the diagnosis of asthma is based on the identification of both a characteristic pattern of respiratory symptoms and variable expiratory airflow limitation.[6]

The following needs to be considered:

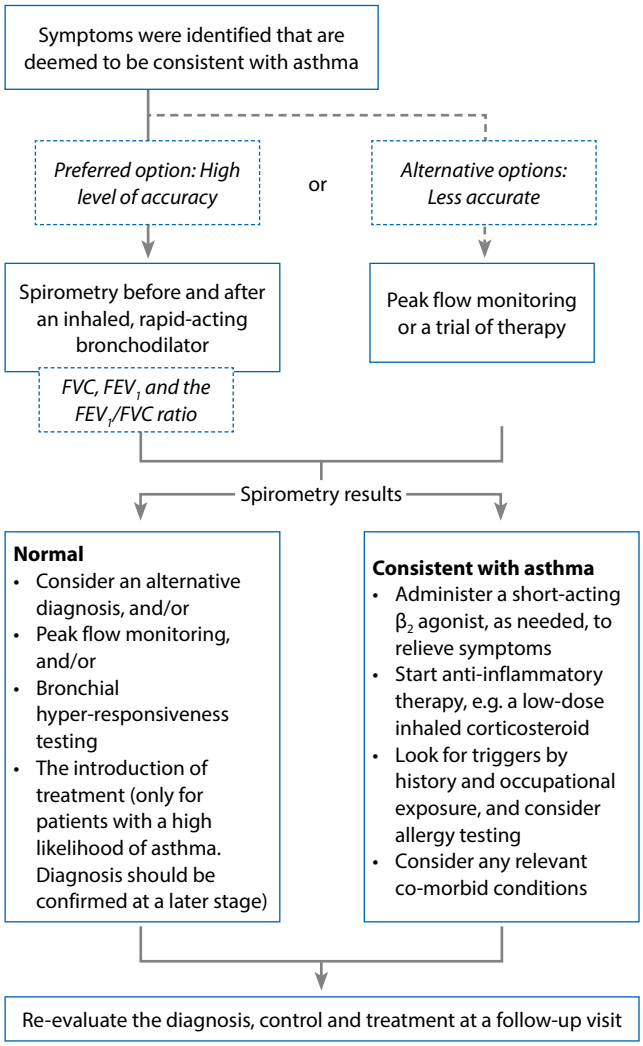
- *Whether or not the symptoms of recurrent airway obstruction are present, based on a history and the examination:* This refers to a history of coughing, recurrent wheezing, recurrent difficulty in breathing, recurrent chest tightness, symptoms occurring or worsening at night or with exercise, a viral infection, exposure to allergens and irritants, changes in the weather, hard laughing or crying, stress or other factors.
- The use of spirometry in all patients > 5 years of age, to determine whether or not the airway obstruction is at least partially reversible.
- Other causes of obstruction.

Table II shows the four categories of severity of asthma, which may be classified into one of two groups, namely mild intermittent or chronic persistent asthma. Daytime symptoms include coughing, wheezing and a tight chest, and night-time symptoms include coughing, wheezing, a tight chest and nocturnal wakening.[11]

Diagnosis

An objective measurement of airflow is required to clinically diagnose asthma. Bronchodilator responsiveness, increased day-to-day or periodic variability, or bronchial challenge testing for bronchial hyper-responsiveness are components that need to be demonstrated in order to make a diagnosis of asthma. The identification and assessment of these components is of great value in improving the understanding and management of asthma.[9]

The approach to diagnosing asthma should start with a patient with recurrent respiratory symptoms prompted by sporadic symptoms of wheezing, coughing, breathlessness, sputum or tightness of the chest. Any alternative diagnosis should be excluded.[8] The diagnostic algorithm for asthma is shown in Figure 2, in which step-by-step procedures can be followed to diagnose and then treat asthma.[12]



FEV_1: forced expiratory volume 1, FVC: forced vital capacity

Figure 2: A diagnostic algorithm for asthma[12]

The spirometer is used for an objective lung function test called spirometry, and can be used to confirm airway obstruction. By adding a bronchodilator, i.e. a short-acting β2 agonist, reversibility of obstruction can be demonstrated, if present.[8]

The spirometry test measures the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC), i.e. the maximum volume of air that can be exhaled. The ratio of FEV_1/FVC can then be calculated. The patient should be told to take in the largest breath possible, and to seal his or her lips around the mouthpiece of the spirometer. He or she then has to blow the air out as fully and as rapidly as possible. The FEV_1/FVC ratio in a normal adult population is usually greater than 0.80. Airflow

obstruction is diagnosed in values of less than 0.80. Following the administration of a bronchodilator, an FEV_1/FVC ratio of less than 0.70 identifies airway obstruction associated with chronic obstructive pulmonary disease (COPD).[8]

If the spirometry results are nondiagnostic for a patient who has a normal FEV_1/FVC ratio, but asthma is still suspected, further objective tests are available to confirm the presence of this condition. The next step is to promote peak flow monitoring, using a measuring device called a peak flow meter (Figure 2). The fastest rate of expired flow is measured in this test. The patient should be advised to take the deepest breath possible, and then to blow it out as fast and hard as possible into the peak flow meter.[8]

The normal values of peak expiratory flow (PEF) for men aged 15-85 years with a height measurement between 160 cm and 190 cm is 420-670 ml/minute, and for women aged 15-85 years with a height measurement between 152 cm and 183 cm, 310-470 ml/minute.[13]

The two parameters supporting the diagnosis and confirmation of asthma using the peak flow meter are:

- A periodic variation in PEF of more than 20%, or with twice daily readings of more than 10% at each reading.
- An improvement of at least 60 ml/minute or at least 20% after inhalation of a rapid-acting bronchodilator.[8]

Management approach

The effective management of asthma involves the ability to step up the treatment when asthma control is not achieved, or to step it down once good asthma control has been established. Therefore, patients should be reviewed frequently until the desired level of control is achieved.[11,14] Table III provides parameters that may be used to define good asthma control.[14]

Table III: Parameters that define effective asthma control[14]

Asthma control	Check (✓)
No daytime symptoms	
No night-time awakening due to asthma	
No need for rescue medication (acute attacks)	
No exacerbations	
No limitations on activities, including exercise	
Normal lung function	
No side-effects	

This can be further classified (Table IV) as controlled, partly controlled or uncontrolled asthma, for a given week. The patient must be assessed for adherence and the level of his or her asthma control. Complete control of asthma is possible, and should be achieved with minimal side-effects.[11]

A patient with poor asthma control presents with the following factors, and should be assessed for a re-evaluation of the asthma treatment:[14]

- The use of β2 agonists three or more times a week.
- Sporadic symptoms three or more times a week.
- Nocturnal awakening one night per week due to symptoms.

The following should be carried out with the patient in order to achieve asthma control:[11]

- Determine the reasons for poor adherence.
- Clarify misunderstandings in terms of differences between relievers and controllers.
- Check the inhaler technique.
- Identify exposure to trigger factors at home or work.
- Check for the presence of gastro-oesophageal (acid) reflux disease.
- Assess for rhinitis and sinusitis.
- Identify other medication that may aggravate asthma, such as aspirin, non-steroidal anti-inflammatory drugs and β blockers.
- Identify other medical conditions, such as COPD, that may be aggravating the asthma.

Stepwise approach

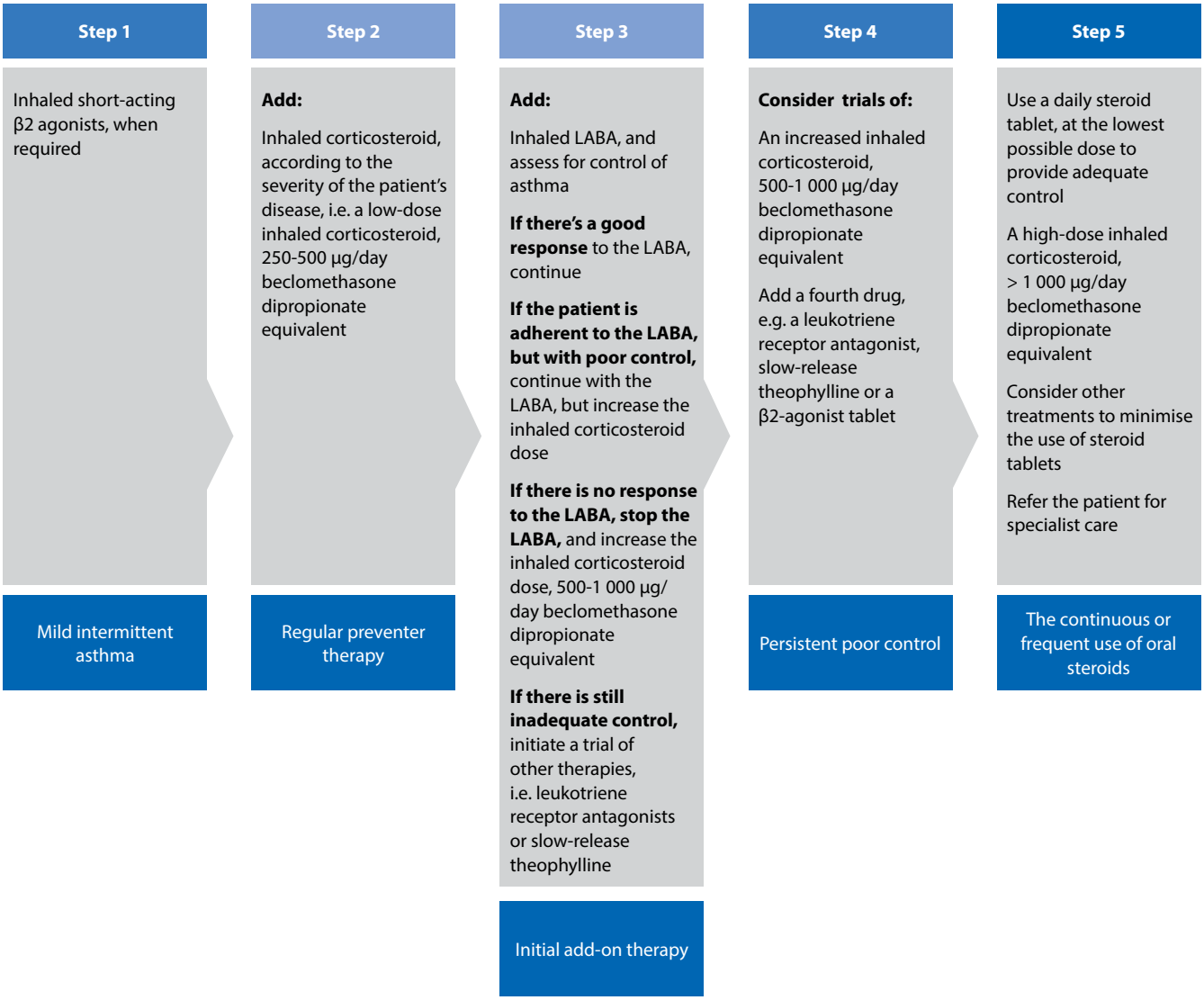
The patient should be initiated on the step that is most appropriate to his or her level of disease. Figure 3 provides an overview of the stepwise approach that should be followed in the management of asthma in adults.[4,15]

The pharmacotherapeutic approach to the treatment of bronchial asthma may also be applied to other airway conditions that are associated with bronchoconstriction or bronchospasm, and a resultant decrease in pulmonary or respiratory function. Drug treatment should be aimed at relieving the major symptom, i.e. dyspnoea due to bronchoconstriction or bronchospasm, or to modify ("control") the disease process through anti-inflammatory and anti-allergic action. Therefore, these therapeutic approaches should also be applied to the management of COPD, and the latter also applies to the treatment of allergic rhinitis.[4,16]

Table IV: Levels of asthma control[11]

Characteristics	Controlled (all of the following)	Partly controlled (any measurement present in any week)	Uncontrolled
Daytime symptoms	≤ 2 per week	> 2 per week	Three or more features of partially controlled asthma in any week
Activities limited	None	Any	
Nocturnal symptoms and night awakenings	None	Any	
Need for reliever or rescue treatment	≤ 2 per week	> 2 per week	
Lung function (PEF)	Normal	< 80% predicted or personal best	
Exacerbations	None	≥ 1 per year	One in any week

PEF: peak expiratory flow



LABA: long-acting β_2 agonist

Figure 3: Management of asthma in adults[4,15]

The bronchodilators

These drugs cause relaxation of the bronchial smooth muscle, and therefore facilitate bronchodilatation. The bronchial smooth muscle contains both muscarinic and β_2-adrenergic receptors. This provides for two possible mechanisms of drug action, i.e. active bronchodilatation and passive bronchodilatation.[15-17]

The selective β_2-receptor agonists

These drugs are selective agonists at the β2-adrenergic receptors (also referred to as the β_2 adrenoceptors) of the bronchial smooth muscle when they are inhaled directly into their biophase, i.e. when a localised effect is achieved on the smooth muscle of the lower respiratory tract. When administered intravenously, or even by mouth, they lose their selectivity and produce cardiac (β_1 receptor) and other systemic effects as well. Salbutamol (also known as albuterol), fenoterol, hexoprenaline and terbutaline are examples of short-acting β_2 agonists (SABAs). These drugs act as active bronchodilators by increasing the concentration of cyclic adenosine 3′, 5′-monophosphate (cAMP). Therefore, it can be said that they act as physiological antagonists of the spasmogens causing the bronchoconstriction. Patients should be monitored for tachycardia, palpitations, skeletal muscle tremors and an increase in arterial blood pressure. In contrast to the SABAs, which have an average onset of action of approximately half an hour or less, and a duration of action in the range of 4-6 hours, the long-acting β_2 agonists (LABAs) have a slower onset and a more sustained duration of action, lasting up to 12 hours. Salmeterol and formoterol, as well as the newer arformoterol and indacterol, are examples of LABAs.[15-17]

Theophylline, a methylxanthine, is a systemic bronchodilator with a narrow therapeutic index. Therefore, therapeutic drug monitoring is required. It differs from the previously mentioned drugs in that it inhibits the enzyme, phosphodiesterase. This produces nonselective β-receptor effects through an increase in the cAMP concentration. It is a second-line drug. Caffeine is a methylxanthine as well, and may be used as an alternative to aminophylline to prevent apnoea of prematurity. Aminophylline is theophylline ethylenediamine, which is more water soluble and may be administered intravenously. In addition to their systemic β-adrenergic effects, the methylxanthines also have a stimulatory effect on the central nervous system, resulting in increased levels of alertness, and can cause gastric irritation.[15-17]

The antimuscarinic drugs

Ipratropium bromide is the short-acting drug of choice, since it does not cause thickening of the bronchial secretions. Blocking the muscarinic receptors inhibits acetylcholine-induced bronchoconstriction, and implies that the adrenergic stimulation of β_2 adrenoceptors in the bronchial smooth muscle will not be opposed by parasympathetic outflow from the vagus nerves. This results in bronchodilatation. Therefore, ipratropium bromide is a passive bronchodilator. Tiotropium bromide is a long-acting muscarinic antagonist. Both drugs are of particular importance in the management of COPD, and they cause very few systemic side-effects because they are poorly absorbed following inhalation. Enhanced bronchodilatation may be achieved when combining ipratropium bromide with a short-acting, selective β_2 agonist, such as salbutamol or fenoterol, owing to the synergism between their mechanisms of action.[15-17]

The disease modifiers

The inhaled glucocorticosteroids

The inhaled glucocorticosteroids, such as budesonide, beclomethasone, ciclesonide and fluticasone, are considerably safer for long-term use than the systemic corticosteroids. They alter the course of the disease process and are life saving in the long run. However, they do not manage acute bronchospasm, but decrease bronchial hyper-reactivity and the risk of a relapse. Nasal sprays are also available for the management of allergic rhinitis. In addition to budesonide, beclomethasone and fluticasone, mometasone and triamcinolone are available for the latter indication. Inhaled glucocorticosteroids may give rise to oral thrush, i.e. oral candidiasis. Therefore, patients are encouraged to rinse their mouths with clean water following the use of steroid inhalers. These drugs are the main anti-inflammatory agents used in the management of asthma.[15-17]

The leukotriene receptor antagonists

The leukotriene receptor antagonists are effective in controlling exercise- and aspirin-induced asthma, and may also be used in the chronic treatment of asthma. Zafirlukast and montelukast are examples. They are competitive antagonists of the cysteinyl leukotriene receptor 1. They have the advantage of oral administration, and montelukast is even available as sprinkles and in a chewable tablet form for paediatric use.[15-17]

Zileuton is a 5-lipoxygenase inhibitor, and therefore acts as a leukotriene synthesis inhibitor. Zileuton has the added advantage of also inhibiting the formation of leukotriene B4. The so-called mast cell stabilisers, such as sodium cromoglycate (also known as cromolyn sodium) and ketotifen, may be used in (allergic) asthma prophylaxis, as well as for the prevention and treatment of allergic rhinitis. These drugs act by stabilising the plasma membranes of the mast cells. This prevents these cells from degranulating and releasing histamine and other spasmogens. The term "mast cell stabiliser" is actually somewhat limiting because sodium cromoglycate, and the closely related nedocromil sodium, have effects on a number of other cells that form part of the inflammatory response as well, while ketotifen also acts as an antagonist at the H_1 receptors.[15-17]

The novel monoclonal antibody, omalizumab, is an immunoglobulin E (IgE) antagonist that is administered subcutaneously once or twice a month. However, it may elicit allergic reactions, or even anaphylaxis itself, as it is a protein-therapeutic agent.[17]

Conclusion

Asthma may be described as a condition of reversible airflow obstruction, and can be effectively managed with the right treatment. Patients should be diagnosed timeously and treated aggressively, with appropriate monitoring. Dosages of inhaled corticosteroids can be increased, depending on the patient's response to treatment. Patients who are resistant to treatment should be referred to a respiratory specialist. Monoclonal antibodies might assist in reducing the IgE-mediated immune response elicited during an asthmatic attack.

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