A 2019 update: approach to asthma management 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 the signs and symptoms thereof, as well as the factors that can precipitate an asthmatic attack. Asthma is mostly classified as either acute or chronic; the diagnosis of asthma is based on identifying 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 on the diagnosis, characterisation and treatment of asthma.

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

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Introduction

Asthma is a disease of the airways which has been recognised and recorded since the times of the ancient Greek physicians, Aretaeus and Hippocrates.[1,2,3] It is one of the most common chronic diseases in the world, characterised by bronchial hyper-responsiveness and reversible airflow limitation. Asthma can be phenotypically classified into allergic, non-allergic, paediatric, late-onset, obesity, occupational, severe asthma, as well as asthma with fixed airflow obstruction and asthma in the elderly.[4-7] According to The Global Asthma Report (2018), asthma is estimated to affect 339 million people worldwide.[8]

Schellack et al. (2015) highlights The Global Initiative for Asthma's (GINA) emphasis on goals to achieve and maintain control of the symptoms, maintain pulmonary function as close to normal as possible, and to prevent exacerbations and mortality in the effective management of asthma.[5] In The Global Asthma Report (2018) mention is made of the WHO-CHOICE method, which is aimed at evaluating the costs and outcomes of activities involved in asthma management.[8] This method assesses evidence of effectiveness and cost of intervention, medication, administration and training. Some other measures to improve delivery of asthma care outlined in this report include recommendations regarding inclusion of essential asthma medicines in national Essential Medicines Lists (EMLs) based on medicines that are available and affordable in each given country.

Despite a marked decline in asthma-related deaths between the periods 2001–2005 and 2011–2015, South Africa retains one of the highest death rates globally, estimated at 18.5 deaths per 100 000 asthma cases.[8] This is due to inadequate implementation of guidelines advising on asthma management.[5] Shortcomings may be attributed to challenges within the healthcare system, along with behaviours of healthcare providers, patients and/or caregivers. Additional factors precipitating the high asthma prevalence in South Africa (currently ranked 25th worldwide) include urbanisation, obesity, respiratory infections such as pneumonia and tuberculosis, and exposure to environmental pollutants. This may suggest a need to look into appropriate diagnosis, treatment and access to care.[9-12]

The pathology of asthma is made up of an interaction between airway inflammation (including bronchitis) and airway remodelling.[5,13] Features of airway remodelling include mucus hypersecretion, subepithelial fibrosis, smooth muscle hypertrophy and angiogenesis. These precipitate a degree of airway limitation/constriction, which leads to limited lung function and obstruction of airflow. A diagrammatical overview of the pathophysiology in Figure 1.

Precipitating factors

Continued exposure to triggers is a major factor compromising adequate control in asthma.[14] Education of patients on identifying and avoiding asthma-precipitating factors helps reduce exacerbations and improves control, taking into consideration the severity of one's condition.[5,6,10] Some precipitating factors are categorised in Table I.

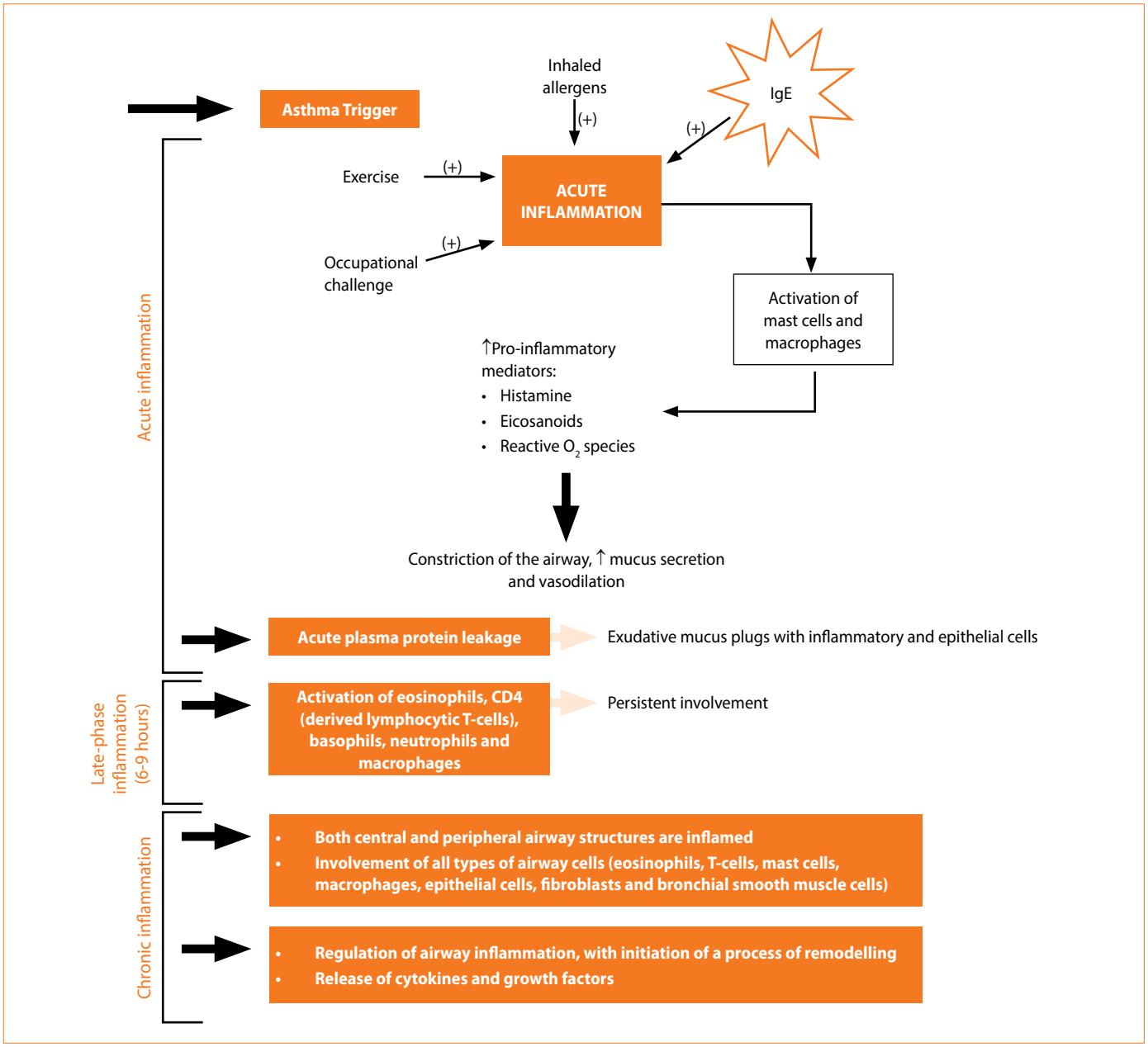


Figure 1. Diagrammatic representation of the pathophysiology of asthma

Signs and symptoms of asthma

Acute asthma, also referred to as asthma exacerbations, can be described as an episodic asthma attack that progresses rapidly; therefore, early recognition and administration of rescue medication is of utmost importance.[15] The symptoms that a patient experiences during an acute asthma attack include anxiety, severe dyspnoea, tightness or burning sensation in the chest, shortness of breath, inability to speak full sentences, and acute respiratory distress. On physical examination the patient may present with an increased heart rate, tachypnoea, cyanotic or pale skin, expiratory and inspiratory wheezing, hyper-inflated chest, and a dry hacking cough.[16]

Chronic asthma is a life-long condition that varies in nature from daily to intermittent symptoms. Persistent patient management and treatment is essential. Signs and symptoms may be triggered 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. The symptoms of chronic asthma are episodes of dyspnoea, nocturnal cough, chest tightness and wheezing or stridor.[16]

Classification of asthma

Classifying a patient's degree or severity of asthma, is compulsory before implementing the first treatment for asthma. This will assist in reviewing the management of the condition when periodic assessment for asthma control is established. Asthma diagnosis is based on identifying a characteristic pattern of respiratory symptoms and variable expiratory airflow obstruction.[17]

Table I. Precipitating factors of asthma

Viral respiratory infections
- Rhinovirus (particularly subtypes A and C)
- Respiratory syncytial virus (most frequent in infants and young children)
- Least frequent: parainfluenza virus, coronavirus, adenovirus and influenza viruses

Environmental factors
- Air pollution/irritants: ozone, sulphur dioxide, tobacco smoke (prenatal exposure also implicated), motor vehicle emissions, particulate matter, strong fumes (to include cosmetics/aerosol sprays)
- Allergens: airborne pollen, animal fur, fungal spores, house-dust mites and cockroaches, mould and damp
- Weather changes

Occupational factors
- Industrial inhalants and irritants: hay, mould, Arabic gum, spices, flour dust and chemicals (azo-dyes, polyvinyl chloride, formaldehyde, ethylenediamine, anhydrides, etc.)

Food additives
- Preservatives: sulphites, benzalkonium chloride
- Metabisulfites: in wine, beer and dried fruit

Medication
- Cyclooxygenase (COX) inhibitors: aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs)
- Paracetamol
- Non-selective β-blockers

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

Psychological factors
- Stress, anxiety, depression

Gastroenterology factors
- Gastro-oesophageal reflux disease (GORD)

The following need to be considered:

- Determine if symptoms of recurrent airway obstruction are present based on patient history and physical examination:
  - History of cough, recurrent wheezing, recurrent difficulty in breathing, recurrent chest tightness.
  - Symptoms occur or worsen at night or with exercise, viral infection, exposure to allergens and irritants, changes in weather, hard laughing or crying, stress or other factors.
- In all patients > 5 years of age, use spirometry to determine whether airway obstruction is at least partially reversible.
- Consider other causes of obstruction.

Table II illustrates four categories for determining the severity of asthma and may be classified into one of two groups, namely mild intermittent or chronic persistent asthma. Daytime symptoms refer to any cough, wheeze and chest tightness. Night-time symptoms include any cough, wheeze, tight chest and nocturnal wakening.[18]

Diagnosis of asthma

Objective airflow measurement is required to clinically identify 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 to recognise asthma. Identification and assessment of these components are of great value in comprehending asthma management.[19]

The approach to diagnosing asthma should start with a patient with recurrent respiratory symptoms that are prompted by sporadic symptoms of wheezing, coughing, breathlessness, sputum or tightness of the chest. Any alternative diagnosis should be excluded.[20] 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.[16]

The spirometer is used for an objective lung function test called spirometry and can be used to confirm airway obstruction. By adding a bronchodilator (short-acting β_2-agonist) reversibility of obstruction can be demonstrated, if present.[20]

The spirometry test measures the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC, the maximum volume of air that can be exhaled). The ratio of FEV_1/FVC can then be calculated. The patient is told to breathe in the largest breath possible and to seal the lips around the mouthpiece of the spirometer. The patient must then 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. An FEV_1/FVC ratio of less than 0.70, following the administration of a bronchodilator, indicates airway obstruction associated with chronic obstructive pulmonary disease (COPD).[20]

If the spirometry results are non-diagnostic for a patient that has a normal FEV_1/FVC ratio, but asthma is still suspected considering the patient's signs and symptoms, further objective tests are available to confirm the presence of this condition, for instance promoting peak flow monitoring by using a measuring device called a peak flow meter. Peak flow monitoring measures the fastest expired flow rate. The patient should be advised to take the deepest possible breath and then to blow it out as fast and hard as possible into the peak flow meter.[20]

Table II. Classification of asthma severity

	Category	Daytime symptoms	Night-time symptoms	PEF
MILD INTERMITTENT	I	≤ 2 per week	≤ 1 per month	≥ 80%
CHRONIC PERSISTENT	II (Mild)	3–4 per week	2–4 per month	≥ 80%
	III (Moderate)	≥ 4 per week	≥ 4 per month	60–80%
	IV (Severe)	Continuous	Frequent	≤ 60%

[**PEF:** peak expiratory flow]

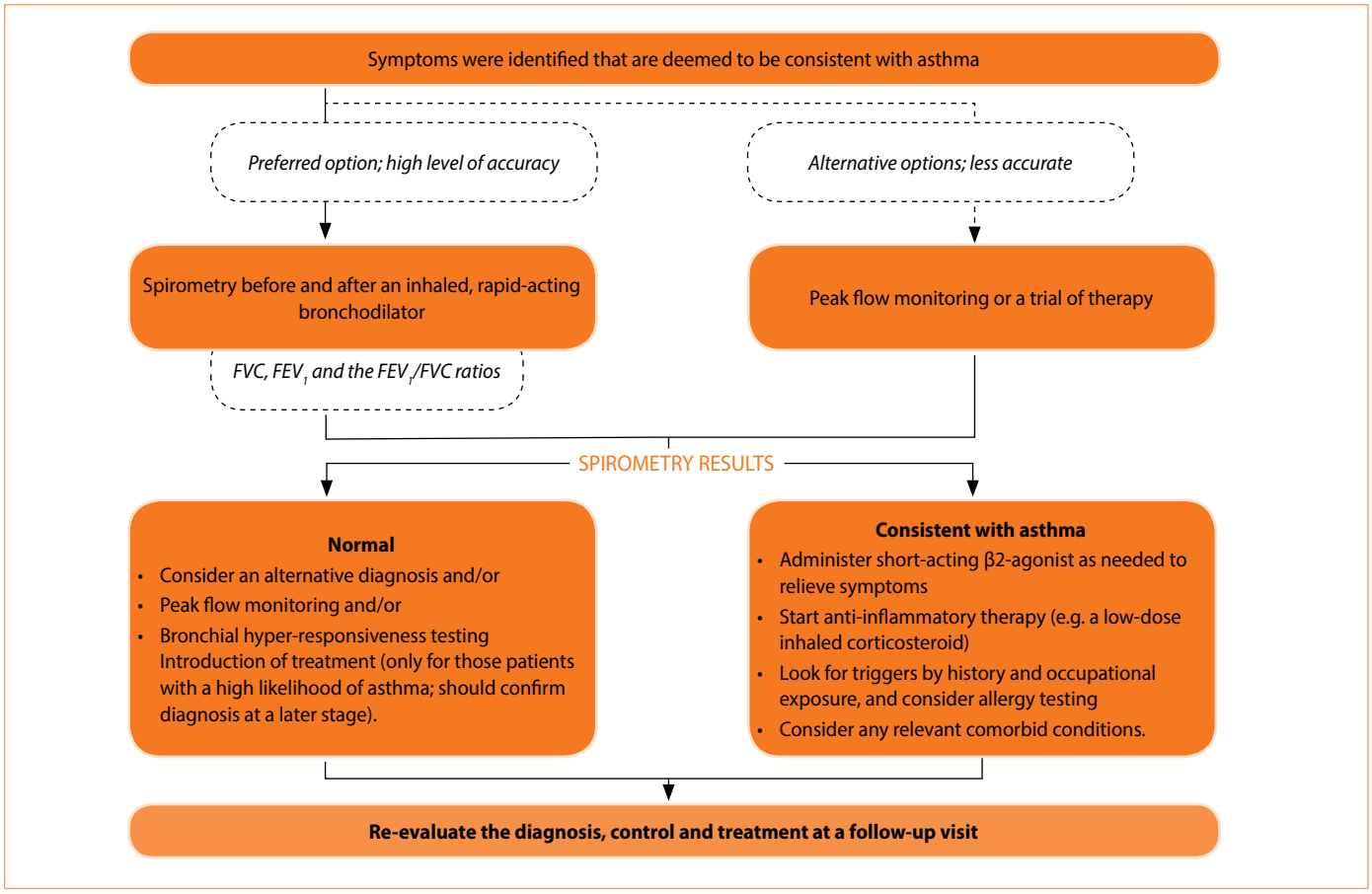


Figure 2: Diagnostic algorithm for asthma (adapted from reference[20])

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

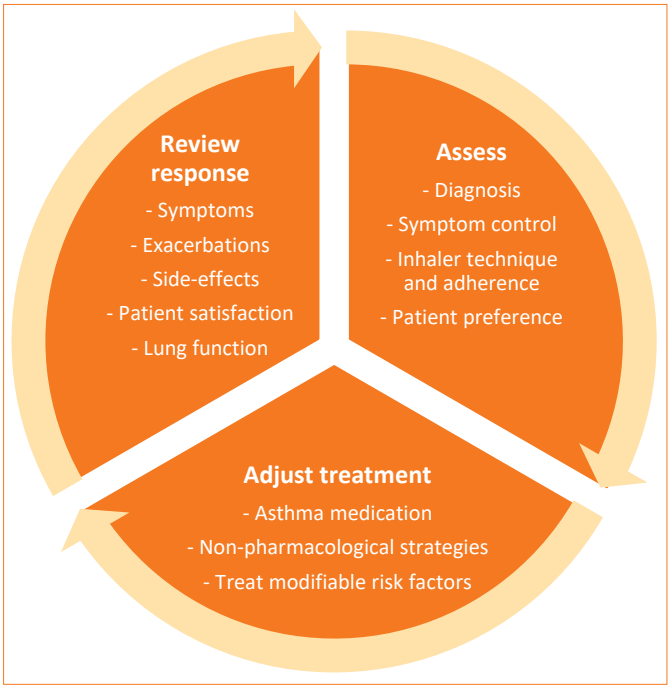
The two parameters supporting the diagnosis and confirmation of asthma using the peak flow meter are as follows: periodic variation in peak expiratory flow of more than 20% (or, with twice-daily readings of more than 10% at each reading), and an improvement of at least 60 ml/min or at least 20% after inhalation of a rapid-acting bronchodilator.[16]

The management approach to asthma

The effective management of asthma involves the ability to step up the treatment when asthma control is not achieved, or to step down once good asthma control is established. Therefore, patients should be reviewed frequently until the desired level of control is achieved.[18,21] Pharmacological and non-pharmacological treatment are adjusted in a continuous cycle that involves assessment, treatment and review.

Non-pharmacological interventions include[17]:

- Cessation of smoking
- Physical activity
- Avoidance of occupational exposures
- Avoidance of medications that make asthma worse (NSAIDs and aspirin)
- Healthy diet
- Avoidance of indoor allergens
- Weight reduction
- Dealing with emotional stress



Box-1: The control-based asthma management cycle

Table III provides parameters that may be used to define good asthma control.[21]

Table III. Parameters that define effective asthma control

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 further be classified (Table IV) as controlled, partly controlled or uncontrolled asthma, for a given week. The patient can be assessed for adherence and the level of his/her asthma control. Complete control of asthma is possible and should be achieved with minimal side-effects.[18]

Poor asthma control presents with the following factors and should be assessed for re-evaluation of asthma treatment[21]:

- Use of β_2-agonists three or more times a week
- Sporadic symptoms three or more times a week, or
- Nocturnal awakening one night per week due to symptoms.

Factors that can be re-assessed with the patient to achieve asthma control are[18]:

- Assess for reasons of poor adherence
- Clarify misunderstandings in terms of the difference 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, NSAIDs and beta-blockers
- Identify other medical conditions such as COPD that may aggravate asthma

Stepwise approach

The patient should be initiated on the step that is most appropriate to their level of disease. Table V provides an overview of the stepwise approach followed in the management of asthma in adults.[17]

The pharmacotherapeutical 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 may be aimed at relieving the major symptom (i.e. dyspnoea due to such bronchoconstriction or bronchospasm), or to modify (i.e. 'control') the disease process through anti-

Table IV. Levels of asthma control[22]

CHARACTERISTIC	CONTROLLED (All of the following)	PARTLY CONTROLLED (Any measurement present in any week)	UNCONTROLLED
Daytime symptoms	≤ 2 per week	> 2 per week	Three (3) or more features of partially controlled asthma in any week
Activities limited	None	Any	
Nocturnal symptoms/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 (1) in any week

Table V. Stepwise approach in the management of asthma in adults

	Step 1 (Mild intermittent asthma)	Step 2 (Regular preventer therapy)	Step 3 (Initial add-on therapy)	Step 4 (Persistent poor control)	Step 5 (The continuous or frequent use of oral steroids)
PREFERRED CONTROLLER CHOICE	Inhaled SABA, when needed	Low dose ICS (250–500 mcg/day beclometasone)	Low dose ICS (500–1000 mcg/day beclometasone) or LABA	Med/High ICS (500–1000 mcg/day beclometasone) /LABA	Refer for add on treatment e.g Ipratropium, anti-IgE, anti-IL5
OTHER CONTROLLER OPTIONS	Consider low-dose ICS	Leukotriene receptor antagonist (LRTA) Low-dose theophylline	Med/High-dose ICS Low-dose ICS + LRTA (or theophylline)	Add ipratropium Med/High-dose ICS + LRTA (or theophylline)	Add low-dose OCS
RELIEVER	As-needed SABA		As-needed SABA or low-dose ICS/ formoterol		

SABA: short-acting β_2 agonist; ICS: inhaled corticosteroids; LABA: long-acting β_2 agonist; OCS: oral corticosteroid; LRTA: leukotriene receptor antagonist

inflammatory and anti-allergic action. Therefore, these therapeutic approaches may also be applied to the management of COPD, and the latter also applies to the treatment of allergic rhinitis.[23]

The bronchodilators

These drugs cause relaxation of the bronchial smooth muscle, and therefore facilitate bronchodilation. The bronchial smooth muscle contains both muscarinic and β_2-adrenergic receptors. This provides for two possible mechanisms of drug action, namely active bronchodilation and passive bronchodilation[23-25]:

The selective β_2-receptor agonists: These drugs are selective agonists at the adrenergic β_2-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 will produce cardiac (β_1-receptor) and other systemic effects as well. Examples of short-acting agents (SABA) are salbutamol (also known as albuterol), fenoterol, hexoprenaline and terbutaline. By increasing the concentration of cAMP, these drugs act as active bronchodilators. 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 short-acting β_2-agonists, which have an average onset of action of approximately half an hour (or less), and a duration of action in the range of four to six hours, the long-acting β_2-agonists (LABA) will have a slower onset and more sustained duration of action, lasting up to 12 hours. Examples of the latter are salmeterol, formoterol and vilanterol (newly available in South Africa (SA)), as well as the newer arformoterol (not yet available in SA) and indacterol (available in SA).[23-26]

Fixed combination inhalers available in South Africa to ensure that a LABA is accompanied by an inhaled corticosteroid (ICS) due to decrease in asthma-related mortality in LABA monotherapy. Examples include fluticasone/salmeterol and budesonide/formoterol. Newer ICS/LABA combination inhalers include fluticasone furoate/vilanterol.[26]

Theophylline, a methylxanthine, is a systemic bronchodilator with a narrow therapeutic index. Therapeutic drug monitoring is therefore required. It differs from the above-mentioned drugs in that it inhibits the enzyme phosphodiesterase. This produces non-selective 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 in the prevention of apnoea of prematurity (AOP). Aminophylline is theophylline ethylene diamine, 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 (CNS), resulting in increased levels of alertness, and can cause gastric irritation.[23-25]

The anti-muscarinic drugs: The short-acting drug of choice is ipratropium bromide, since it does not cause thickening of the bronchial secretions. Blocking the muscarinic receptors will inhibit acetylcholine-induced bronchoconstriction, and implies that 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 bronchodilation. Therefore, ipratropium bromide is a passive bronchodilator. Tiotropium bromide is a long-acting muscarinic antagonist (LAMA). Both drugs are of particular importance in the management of COPD, and, because they are poorly absorbed following inhalation, they cause very few systemic side-effects. Enhanced bronchodilation may be achieved when combining ipratropium bromide with a short-acting, selective β_2-agonist, such as salbutamol or fenoterol, due to the synergism between their mechanisms of action.[23-25]

The disease modifiers

The inhaled glucocorticosteroids: such as budesonide, beclomethasone, ciclesonide and fluticasone, are much safer for long-term use than systemic corticosteroids. They will alter the course of the disease process and are life-saving in the long run. They will, however, not manage acute bronchospasm, but will 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 also available for the latter indication. Inhaled glucocorticosteroids may give rise to oral thrush (i.e. oral candidiasis) and patients are therefore encouraged to rinse their mouths with clean water following the use of their steroid inhalers. These drugs are the main anti-inflammatory agents used in the management of asthma.[23-25]

The leukotriene receptor-antagonists: effective in controlling exercise- and aspirin-induced asthma, and may also be used in the chronic treatment of asthma. Examples are zafirlukast and montelukast. They are competitive antagonists of the cysLT1-receptor and have the advantage of oral administration, and montelukast is even available as a sprinkle and in a chewable tablet form for paediatric use.[23-25]

Zileuton is a 5-lipoxygenase (5-LOX) inhibitor and therefore acts as a leukotriene synthesis inhibitor. Zileuton has the added advantage of also inhibiting the formation of leukotriene B_4 (LTB_4). 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 mast cells. This prevents these cells from degranulation and release of 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, and ketotifen also acts as an antagonist at H_1-receptors.[23-25]

The novel monoclonal antibody, omalizumab, is an immunoglobulin E (IgE)-antagonist that is administered subcutaneously once or twice per month. However, being a protein-therapeutic agent, may elicit allergic reactions (or even anaphylaxis) itself.[25]

Conclusion

Asthma may be described as a condition of reversible airflow obstruction, and with the right treatment it can be effectively managed. Patients should be diagnosed timeously and treated aggressively, with the inclusion of 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-medicated-immune response elicited during an asthmat attack.

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