

Approach to asthma in adults

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Abstract

Asthma is a chronic inflammatory disease that causes hyperresponsiveness 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 a chronic inflammatory disease; 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.

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Introduction

Asthma is a chronic inflammatory disease of the airways associated with bronchial hyperresponsiveness and reversible airflow obstruction. It is one of the most common chronic diseases in the world. It is estimated that around 300 million people worldwide suffer from asthma. Estimates of the prevalence of asthma range from 7% in France and Germany to 11% in the United States (US) and 15–18% in the United Kingdom (UK). Approximately 20% of these patients suffer from severe asthma, of which 20% is inadequately controlled.¹ Furthermore, asthma is reportedly increasing worldwide as the communities in the developing world adopt Western lifestyles and become urbanised. In 2013 the World Health Organisation (WHO) recognised asthma as being of major public health importance.²

The magnitude of the burden of asthma may be underappreciated; this is partly due to health systems such as primary healthcare services that are overwhelmed by communicable respiratory diseases such as pneumonia or tuberculosis.³ In countries like South Africa (SA), where the burden of respiratory diseases such as pneumonia, tuberculosis and HIV-associated lung disease is well known, the burden of asthma is under-appreciated.³ Asthma is the eighth leading contributor to the burden of disease in SA and is the second most important chronic disease after HIV/AIDS.^{3,4} Despite the availability of medications, asthma remains poorly controlled in many patients.^{3,5}

The emphasis of asthma treatment is to achieve effective control. The Global Initiative for Asthma (GINA) 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

In SA, improper or inadequate implementation of guidelines is a major reason for poor asthma management.³ Challenges to successful implementation include factors within the healthcare system and individual behaviours of healthcare providers, as well as 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 the advances in asthma treatment and are still insufficiently controlled, placing severe limits on daily life and putting them at risk for 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 remodelling of the structural elements of the airway wall.⁹ This includes inflammation of the airway, constriction of the airway via smooth muscle contraction, hypersecretion of mucus, bronchial hyperresponsiveness, 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.

Precipitating factors

There are several trigger factors that can contribute to an asthma attack. Avoiding these factors can help to reduce

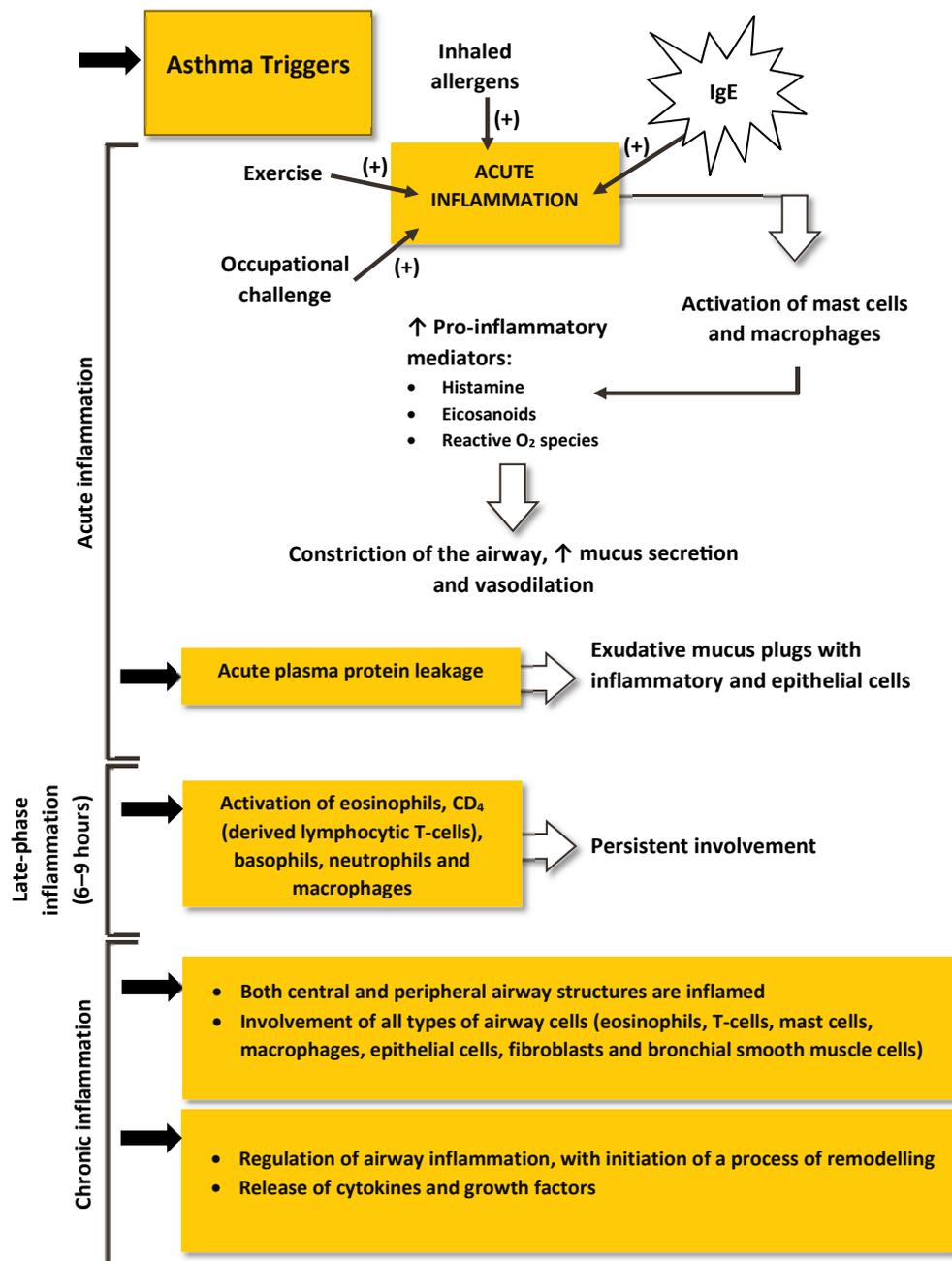


Figure 1. Diagrammatic representation of the pathophysiology of asthma

asthma exacerbations and asthma severity.¹¹ Table I presents the precipitating factors of asthma with examples of these asthma triggers.¹²

Signs and symptoms of 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: increased heart rate, tachypnoea, cyanotic or pale skin, expiratory and inspiratory wheezing, hyperinflated chest, and a dry hacking cough. The symptoms that a patient experiences during an acute asthma attack are: anxiety, severe dyspnoea, tightness of the chest, or a burning sensation, shortness of breath, unable to speak full sentences, and the patient will be in acute distress.¹²

Chronic asthma is a life-long 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. The symptoms of chronic asthma are: episodes of dyspnoea, coughing at night, tightness of the chest, wheezing or stridor.¹²

Classification of asthma

Before implementing the first treatment for asthma it is important to classify the severity of a patient's asthma. This will assist in reviewing the management of the condition when periodic assessment for asthma control is established. Making the diagnosis

Table I. Precipitating factors of asthma

| |
|---|
| Viral respiratory infections |
| <i>Rhinovirus (most common)</i> |
| <i>Other: respiratory syncytial virus (RSV), parainfluenza virus, coronavirus and influenza viruses</i> |
| Environmental factors |
| <i>Air pollution: ozone, sulphur dioxide and tobacco smoke</i> |
| <i>Allergens: airborne pollens, furry animals, fungal spores, house-dust mites and cockroaches</i> |
| Occupational factors |
| <i>Industrial inhalants and irritants: hay, mould, Arabic gum, spices, flour dust and chemicals (azo-dyes, polyvinyl chloride, formaldehyde, ethylenediamine, anhydrides, etc.)</i> |
| Food additives |
| <i>Preservatives: sulphites, benzalkonium chloride</i> |
| <i>Metabisulfites: in wine, beer and dried fruit</i> |
| Medication |
| <i>Cyclooxygenase (COX) inhibitors: aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs)</i> |
| <i>Nonselective β-blockers</i> |
| Nutritional factors |
| <i>Obesity</i> |
| <i>Vitamin D-insufficiency in children</i> |
| <i>Exercise in a cold, dry climate</i> |
| Psychological factors |
| <i>Stress, anxiety, depression</i> |
| Gastroenterology factors |
| <i>Gastro-oesophageal reflux disease (GORD)</i> |

of asthma is based on identifying both a characteristic pattern of respiratory symptoms and variable expiratory airflow limitation.⁶

The following need to be considered:

- Determine that symptoms of recurrent airway obstruction are present, based on history and 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 shows the **four categories of severity of asthma** that may be classified into one of two groups, namely mild intermittent or

chronic persistent asthma. Daytime symptoms include any cough, wheeze and tight chest, and night-time symptoms include any cough, wheeze, tight chest and nocturnal wakening.¹¹

Diagnosis of asthma

To clinically recognise asthma, objective measurement of airflow is required. Bronchodilator responsiveness, increased day-to-day or periodic variability, or bronchial challenge testing (for bronchial hyperresponsiveness) are components that need to be demonstrated to recognise asthma. To improve the understanding and management of asthma, identification and assessment of these components are of great value.⁹

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.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

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.⁸

The spirometry test measures the forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC, the maximum volume of air that can be exhaled), the ratio of FEV₁/FVC can then be calculated. The patient should be informed to take in the biggest breath possible and to seal his or her lips around the mouthpiece of the spirometer. The patient then has to blow the air out as fully and as rapidly as possible. The FEV₁/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 FEV₁/FVC ratio of less than 0.70, following the administration of a bronchodilator, identifies airway obstruction associated with chronic obstructive pulmonary disease (COPD).⁸

If the spirometry results are non-diagnostic for a patient that has a normal FEV₁/FVC ratio, but asthma is still suspected, further objective tests are available to confirm the presence of this condition. In Figure 2 the next step is to promote peak flow monitoring using a measuring device called a peak flow meter. The fastest rate of expired flow is measured in this test. The patient

Table II. Classification of asthma severity

| INTERMITTENT | CHRONIC PERSISTENT | | |
|--|--|--|-------------------------------------|
| Mild | Mild | Moderate | Severe |
| I | II | III | IV |
| Daytime symptoms ≤ 2 per week | Daytime symptoms 3–4 per week | Daytime symptoms ≥ 4 per week | Daytime symptoms continuous |
| Night-time symptoms ≤ 1 per month | Night-time symptoms 2–4 per month | Night-time symptoms ≥ 4 per month | Night-time symptoms frequent |
| PEF ≥ 80% | PEF ≥ 80% | PEF 60–80% | PEF ≤ 60% |

[PEF: peak expiratory flow]

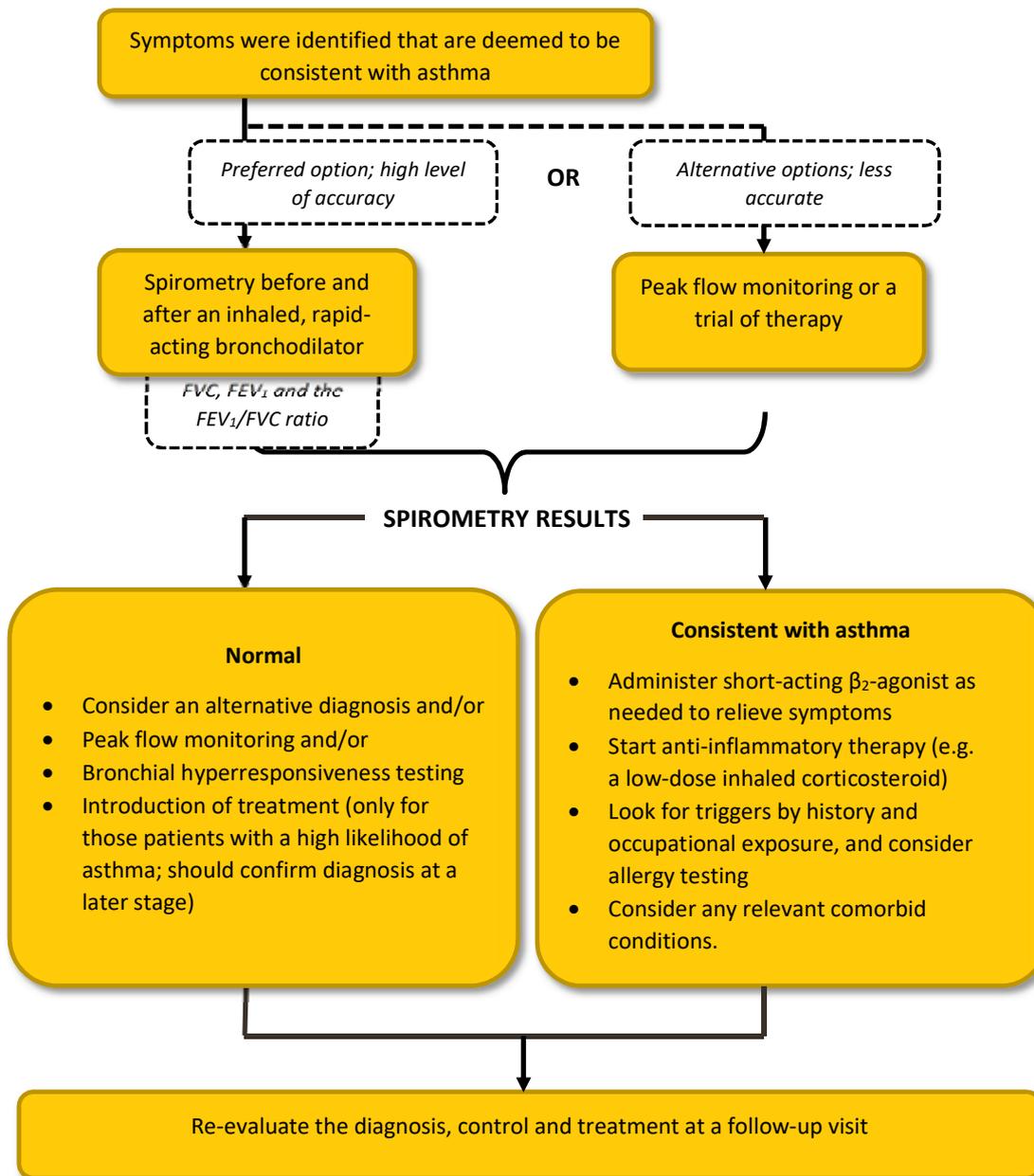


Figure 2. A diagnostic algorithm for asthma (adapted from⁸)

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 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, is 310–470 ml/min.¹³

The two parameters supporting the diagnosis and confirmation of asthma using the peak flow meter are as follows: periodic variation in PEF 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.⁸

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.^{11,14} Table III provides parameters that may be used to define good asthma control.¹⁴

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.¹¹

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 | |

Table IV. Levels of asthma control

| CHARACTERISTIC | 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/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 | One (1) in any week |
| Exacerbations | None | ≥ 1 per year | |

Poor asthma control presents with the following factors and should be assessed for re-evaluation of asthma treatment¹⁴:

- Use of β₂-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 are¹¹:

- 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 like COPD that may aggravate asthma

Stepwise approach

The patient should be initiated on the step that is most appropriate to their level of disease. Figure 3 provides an overview of the stepwise approach followed in the management of asthma in adults.

| | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 |
|--|--|--|--|--|---|
| Preferred disease control | | Low-dose ICS | Low-dose ICS [moderate-dose preferred in children 6–11 yrs.] OR LABA | Medium or high-dose ICS OR LABA | REFER for add-on treatment |
| Alternative options for disease control | Consider low-dose ICS | Leukotriene receptor-antagonist (LTRA) OR Low-dose theophylline* | Medium or high-dose ICS OR Low-dose ICS PLUS LTRA OR Low-dose ICS PLUS theophylline* | ADD tiotropium [in adults only] High-dose ICS PLUS LTRA OR High-dose ICS PLUS theophylline* | ADD tiotropium [in adults only] OR ADD low-dose OCS |
| Symptomatic relief | Short-acting β ₂ -agonist (SABA), as needed | | Short-acting β ₂ -agonist (SABA), as needed OR Low-dose ICS/formoterol | | |

*Theophylline is not recommended in children 6–11 yrs.

[ICS: inhaled corticosteroid; LABA: long-acting β₂-agonist; OCS: oral corticosteroid]

Figure 3. Suggested, step-wise approach to the management of asthma¹⁶

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 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-inflammatory and anti-allergic action. Therefore, these therapeutic approaches may also be applied to the management of chronic obstructive pulmonary disease (COPD), and the latter also applies to the treatment of allergic rhinitis.^{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, namely **active** bronchodilatation and **passive** bronchodilatation:^{15,16,17}

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 SA), as well as the newer arformoterol (not yet available in SA) and indacaterol (available in SA).^{15,16,17,18}

Fixed combination inhalers are 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.¹⁸

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.^{15,16,17}

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 bronchodilatation. 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 bronchodilatation 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.^{15,16,17}

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 hyperreactivity 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.^{15,16,17}

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 'cysteinyl'-LT (cysLT1)-receptor, they have the advantage of oral administration, and montelukast is even available as a sprinkle and in a chewable tablet form for paediatric use.^{15,16,17}

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 B₄ (LTB₄). 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 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, and ketotifen also acts as an antagonist at H₁-receptors.^{15,16,17}

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.¹⁷

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-mediated immune response elicited during an asthmatic attack.

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