Abstract

Asthma is an inflammatory disease of the airways, particularly sensitive to specific and nonspecific stimuli leading to an intense and quick response of all of bronchiolar system. The airways become inflamed, producing thick mucus and rapid narrowing of the airways. These changes lead to the patient to cough, wheezing, chest pain and dyspnea. Asthma is a global health problem and its prevalence is increasing both children and adults. The World Health Organization estimates that at least 155 million in the world are asthmatics. Asthma represents 0.4% of all deaths in hospitalized patients, which is a very high as there are effective treatments for your control. The authors present a review of the treatment and management of asthma. The aim of this study is to update and rationalize the use of medications in asthma from the analysis of the control of the disease.

Keywords: Asthma; Drug utilization; Adrenal-cortex hormones; Therapeutics; Review.

Introduction

Asthma is a complex disease and includes different phenotypes associated with different responses to treatment.1 An individualized management strategy evaluated at each visit with regard to the level of disease control being achieved with the medication being used is currently the most effective asthma treatment method.2 To achieve asthma control, drugs can be used for rapid relief and on-going prevention.3 However, rather than relying solely on medications, it is also important to avoid exposure to the factors that exacerbate asthma when possible, and to explain to the patient what asthma is and the importance of controlling it. Moreover, when prescribing inhaled medication, it is important to explain to the patients the proper method of using the device.2
Initiating asthma management – controlling exposure to causative factors and changing lifestyle

To improve asthma control and reduce the need for medication, patients should take decisive behavioral measures, which include avoiding the risk factors that cause their symptoms. These measures may also include improving fitness and lung function via increased exercise, although in some individuals this is not practical as it can trigger bronchoconstriction (table 1).

Learning to use medications and inhalers

The majority of drugs used for the treatment of asthma in adults are administered via inhalation. The main advantage of inhaled therapy is that the drugs are released directly into the lungs, resulting in high localized concentrations with less risk of adverse effects. Lung deposition depends on the type of inhaler device used. Most patients can efficiently use the vast majority of devices that are available to administer various formulations. The proper method for preparation of the device and inhalation of the medication should be thoroughly explained to patients. For example, it should be ensured that the patient knows to breathe in through the inhaler with the mouth closed around it, and that they then hold their breath for 10 s. Where applicable, the patient should then verify that the powder has been completely inhaled. Moreover, it is important to instruct patients to rinse their mouths after inhalation of the medication, and gargle, to avoid the onset of oral candidiasis and dysphonia.7

A brief review of the medications used to treat asthma

A) Maintenance drugs

Glucocorticoids are the most effective inhaled anti-inflammatory medications for the treatment of persistent asthma, and in many patients, asthma can be satisfactorily controlled using monotherapy with such drugs.8 In some patients, however, this form of monotherapy is insufficient, and increasing the doses inhaled provides little benefit and increases the risk of adverse effects. To achieve clinical control in these patients, it is preferable to add a long-acting inhaled β-2 agonist to the treatment plan, which increases the effect of inhaled glucocorticoid.9 Table 2 shows a comparison of doses of different types of inhaled corticosteroids, and table 3 provides some important details on this class of drugs.

The administration of long-acting inhaled β-2 agonists (LABA) as monotherapy should be avoided. They do not act on airway inflammation in asthma, and recent work has shown

Table 1: Non-pharmacological management of asthma.

- Avoid smoking and passive smoking
- Maintain ideal weight
- Avoid exposure to allergens
- Encourage breastfeeding in infancy – this has a protective effect against asthma
- Avoid environmental pollution
- Avoid dust in the home
- Avoid animals in the home
- Engage in physical activity, provided this does not trigger symptoms
that this class of medication, when used as a monotherapy in asthma, may lead to increased exacerbations and deaths.5,10,11 The major long-acting inhaled β-2 agonists are formoterol and salmeterol. Formoterol is effective in both the short and the long term, unlike salmeterol, which has long-term effects only. These drugs can be used in combination with inhaled glucocorticoids in patients aged over 4 years, when glucocorticoids alone are not effective in controlling asthma. The effectiveness of this combination treatment has led to the development of fixed-combination drug inhalers12,13 (table 4). The addition of a LABA to an inhaled corticosteroid results in a greater anti-inflammatory effect as compared to inhaled corticosteroids in high doses. LABAs facilitate translocation of the glucocorticoid-receptor protein complex to the cell nucleus.14,15 The long-acting β-2 agonists can also be taken orally. Terbutaline and balbuterol are used only on rare occasions in combination with other bronchodilators. Table 5 provides important details about this class of drugs.

Other important drugs in the control of asthma are leukotriene inhibitors, oral steroids, xanthines, and anti IgE antibody (omalizumab).3,16-19 Details of these drugs are provided in table 6. Other less frequently used asthma therapies, or those that are still under study, are summarized in table 7.3,20-24

### Table 2: Equivalent doses of daily glucocorticosteroids for adults.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low daily dose (μg)</th>
<th>Medium daily dose (μg)</th>
<th>High daily dose (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>200 – 500</td>
<td>&gt; 500 – 1000</td>
<td>&gt; 1000 – 2000</td>
</tr>
<tr>
<td>Budesonide</td>
<td>200 – 400</td>
<td>&gt; 400 – 800</td>
<td>&gt; 800 – 1600</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>80 – 160</td>
<td>&gt; 160 – 320</td>
<td>&gt; 320 – 1280</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500 – 1000</td>
<td>&gt; 1000 – 2000</td>
<td>&gt; 2000</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>100 – 250</td>
<td>&gt; 250 – 500</td>
<td>&gt; 500 – 1000</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>200</td>
<td>≥ 400</td>
<td>≥ 800</td>
</tr>
<tr>
<td>Triancinolone</td>
<td>400 – 1000</td>
<td>&gt; 1000 – 2000</td>
<td>&gt; 2000</td>
</tr>
</tbody>
</table>


### Table 3: Inhaled glucocorticoids and asthma.

- Medication is very important in asthma control
- Reduces symptoms, improves quality of life, and improves spirometric parameters
- Reduces frequency and severity of exacerbations
- Reduces asthma-related hospitalization and mortality
- Smoking reduces the response to glucocorticoids in asthmatics
- Local side effects: oropharyngeal candidiasis, dysphonia and cough – owing to these symptoms, orientation in oral hygiene is essential
- Systemic side effects: bruising, inhibition of the hypothalamic-pituitary - adrenal axis and decreased bone mineral density.
B) Rescue medications

The main rescue medications and their characteristics are summarized in table 8.3

C) Specific immunotherapy with allergen

Allergic asthmatics that are controlled with anti-inflammatory medication, and have stable lung function (FEV1% predicted > 70%), but experience on-going exacerbations triggered by contact with environmental allergens to which they are sensitized, can benefit from allergen-specific immunotherapy. A reduction in the incidence and severity of symptoms can be achieved, thus reducing the number of visits to the emergency room and the use of relief medication. Patients who have associated allergic rhinitis gain additional benefit by way of a reduction in allergic responses of the entire airway (upper and lower).25

Understanding the dynamics of asthma control

The old asthma classification system, which classifies the patient’s asthma as either intermittent or persistent, is useful in that it defines the pattern of the patient's asthma. However, over the years this classification system proved inadequate for guiding the formulation of an effective treatment plan.26 Various new classification systems have been proposed to aid in the management of asthma. The most widely accepted system by GINA is summarized below,27 in tables 9 and 10. This classification system describes 5 stages of control. At each stage, appropriate treatment options are recommended. Patients classified as having mild to moderate persistent asthma according to the old classification system should initiate their treatment in accordance with the recommendations provided at stage 2.

### Table 4: Principal combinations of inhaled LABA and glucocorticoid.

<table>
<thead>
<tr>
<th>Combinations</th>
<th>Presentations</th>
<th>Mode of inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol + budesonide</td>
<td>6/200 µg and 12/400 µg</td>
<td>Aerolizer®</td>
</tr>
<tr>
<td>Formoterol + budesonide</td>
<td>6/100 µg, 6/200 µg and 6/400 µg</td>
<td>Turbohaler®</td>
</tr>
<tr>
<td>Formoterol + budesonide</td>
<td>6/100 µg</td>
<td>Spray MDO</td>
</tr>
<tr>
<td>Salmeterol + fluticasone</td>
<td>50/100 µg, 50/250 µg and 50/500 µg</td>
<td>Diskus®</td>
</tr>
<tr>
<td>Salmeterol + fluticasone</td>
<td>25/125 µg and 25/50 µg</td>
<td>Spray MDI</td>
</tr>
<tr>
<td>Formoterol + beclometasone</td>
<td>6/100 µg</td>
<td>Spray, pressurized</td>
</tr>
</tbody>
</table>


### Table 5: Aspects of LABA treatment in asthma.

- Potent and prolonged bronchodilator and protective action;
- Contraindicated in asthma as a monotherapy; should always be used in conjunction with an anti-inflammatory drug;
- Formoterol has rapid onset of action and also has long-term benefits. Salmeterol provides only long-term benefits;
- Side effects: when inhaled, adverse effects are uncommon and restricted to cardiovascular stimulation, tremble, and transient hypokalemia.
Table 6: Comments on some important asthma control drugs.

| **Anti-leukotrienes** | • Low and variable bronchodilator effect  
| | • Reduces cough, improves lung function, reduces inflammation of the airways and reduces asthma exacerbations  
| | • When used as monotherapy are less effective than inhaled corticosteroids in low doses  
| | • Can be used as a means of steroid-sparing  
| | • Main side effects are abdominal pain, rash, headache, arthralgia and angioedema  
| | • The only drug of this class available in Brazil is montelukast. Dose: 10 mg once a day  

| **Xanthines** | • Little anti-inflammatory activity when used as monotherapy  
| | • Can be added to patients inadequately controlled with inhaled corticosteroids and LABA  
| | • Available in Brazil; bamifylline and theophylline  
| | • Several side effects described; mainly gastrointestinal and neurological symptoms, and cardiac arrhythmias  

| **Oral corticosteroids** | • Has strong anti-inflammatory potency; however, its extended use is limited owing to side effects  
| | • Used to control severe asthma - the lowest possible dose should be used, and it should be introduced when the patient is already using inhaled corticosteroid + LABA at higher doses  
| | • Should be used for 7–10 days at the maximum dose of 40–60 mg after treatment of acute asthma. If used only on some days, there is no need for titration.  
| | • Side effects: hyperglycemia, fluid retention, osteoporosis, weight gain, hypertension, etc.  

| **Anti-IgE** | • Recombinant humanized monoclonal IgE-specific antibody  
| | • Rationale for use: IgE plays a central role in the pathophysiology of asthma  
| | • Inhibits the binding of IgE to its high affinity receptor  
| | • Inhibits bronchoconstriction induced by allergens in early and late phases of inflammation  
| | • Reduces the number of exacerbations and use of steroid  
| | • Administered subcutaneously every 2–4 weeks  
| | • Dose is based on patient’s weight and IgE level  
| | • Contraindicated in patients weighing ≤150 kg with an IgE level <30 or >700 UI/L  
| | • Major side effects are nausea, diarrhea, rash, bruising, and local reactions at the application site.  

Table 7: Asthma therapeutics that are used less frequently or remain under study.

| **Chromones** | • Principal representative of this group is cromolyn sodium  
| | • Short anti-inflammatory effect and less effective than low-doses of inhaled corticosteroids  
| | • Alternative drugs for exercise-induced bronchospasm  
| | • Side effects: cough and throat irritation  

| **Methotrexate** | • Two meta-analyses with low-dose methotrexate showed a small benefit in patients with severe steroid-dependent; however, some side effects were associated with methotrexate use  

| **Ciclosporine** | • Effective in some patients without a precise indication in asthma  

| **Etanercept** | • A recent study showed no benefit in patients with severe asthma compared to the benefit of this drug in patients with other chronic inflammatory diseases. Further asthma studies are required  

| **Lebrikizumab** | • Monoclonal interleukin-13-specific antibody  
| | • Administered subcutaneously  
| | • Interleukin-13 plays an important role in the pathophysiology of asthma and may contribute to reduced efficacy of treatment with corticosteroids in some asthma patients  
| | • Interleukin-13 induces the secretion of peristin, which is a protein of the cellular matrix produced by epithelial airway cells. Peristin may contribute to the process of bronchial remodeling.  
| | • A recent study showed improved pulmonary function, primarily in patients presenting with high pre-treatment peristin levels  

| **Mepolizumab** | • Monoclonal interleukin-5-specific antibody  
| | • Administered intravenously  
| | • Interleukin-5 is a potent eosinophilic interleukin  
| | • Three clinical studies have not demonstrated efficacy in patients with asthma; however, a recent study showed a reduction in the dose of corticosteroid in asthma patients who showed persistence of eosinophils in sputum despite the use of inhaled and oral corticosteroids  

| **Tiotropium** | • Inhaled drug approved for use in COPD patients; however, it is not yet approved for asthma  
| | • Long-acting anticholinergic, administered once a day  
| | • A recent study demonstrated improvement in symptoms and lung function in patients inadequately controlled with inhaled corticosteroids  
| | • Future studies still needed  

| **Thermoplasty** | • Bronchoscopy procedure involving radiofrequency ablation, which reverses the narrowing of airways; it is aimed at improving symptoms and reducing exacerbations  

The dynamics of the treatment and control of asthma
of this new system. Individuals with more severe asthma should start their treatment according to the recommendations at stage 3.28

When the patient returns for a follow-up visit, they are re-evaluated and classified as having controlled, partly controlled, or uncontrolled asthma.28 If their asthma is classified as being under control, the medication is maintained. Moreover, if their asthma remains controlled for at least 3 months, the treatment can be moved a “step down.” Reducing the medication by one step may entail reducing the dose of inhaled corticosteroids, or removing the beta-2 agonist, among other measures.28 If the asthma is classified as partially controlled, the treatment must be increased one step, and the patient should be subsequently reevaluated to verify that control has been achieved.28 The dynamics surrounding the classification of the level of control are shown in table 9, and the recommended courses of treatment for each stage are shown in table 10.

Two important procedures should be followed:

1) For all treatment steps, relief medications should be added as necessary. However, regular use of rescue medications is one of the defining elements of uncontrolled asthma, and indicates that the addition of other medications is required; the patient should be moved up to the next step of control.28

2) Every patient classified as uncontrolled should be advised about the correct use of the inhalation device. It is important to

Table 8: Drugs for immediate relief of asthma symptoms.

<table>
<thead>
<tr>
<th>Short-acting β-2 agonists</th>
<th>• Medication of choice for immediate relief of bronchoconstriction</th>
<th>• Salbutamol and fenoterol are the main representatives. Formoterol also has long-term action</th>
<th>• The need for multiple administrations throughout the day indicates deterioration of asthma control</th>
<th>• Side effects: tremble, cardiac arrhythmias, and hypokalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting anticholinergics</td>
<td>• Main representative of this group of drugs is ipratropium bromide</td>
<td>• Less effective than beta agonists for immediate relief</td>
<td>• Drug alternative for patients with tremble and cardiac arrhythmias</td>
<td>• Side effects: dry mouth, urinary retention, and glaucoma</td>
</tr>
</tbody>
</table>

Table 9: Control levels of patients with asthma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controlled (every item)</th>
<th>Partially controlled (some present)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None to minimal (2 or fewer per week)</td>
<td>More than 2 per week</td>
<td></td>
</tr>
<tr>
<td>Limitation of activities</td>
<td>None</td>
<td>At least 1</td>
<td>3 or more characteristics of asthma partially controlled * †</td>
</tr>
<tr>
<td>Awakenings</td>
<td>None</td>
<td>At least 1</td>
<td></td>
</tr>
<tr>
<td>Need for relief/rescue drugs</td>
<td>None to minimal (2 or fewer per week)</td>
<td>More than 2 per week</td>
<td></td>
</tr>
<tr>
<td>Pulmonary function or FEV₁ ‡</td>
<td>Normal</td>
<td>&lt;80% predicted or personal best value, if known</td>
<td></td>
</tr>
</tbody>
</table>

B. Assessment of future risk (risk of exacerbations, instability, rapid decline in lung function, side effects)

Characteristics associated with an increased risk of side effects:
Unsatisfactory clinical control, frequent exacerbations in the previous year, having been admitted to ICU for asthma, low FEV₁, smoking, need for high doses of medication.

Source: 2008 revision of GINA.
request that the patient demonstrates how they are using the inhaler device, to ensure that the failure of control is not simply due to incorrect use of the inhaler device.7

Difficult to control asthma

Although most patients may achieve overall control of their asthma, some patients do not achieve stability via standard therapies. Asthma is defined as difficult to control when the patient experiences on-going symptoms despite the instigation of step 4 of treatment. These patients may have a poor response to inhaled glucocorticoids, and require high doses. Where a diagnosis of difficult to control asthma is suspected, the following should be undertaken:

a) Confirmation of the diagnosis of asthma.

b) Investigations to and verify adherence to treatment.

c) Past and/or present smoking statuses should be considered, and where applicable, the patient should be encouraged to cease smoking.4

d) The presence of comorbidities that may aggravate asthma, such as chronic rhino-sinusitis, gastroesophageal reflux, and obesity/obstructive sleep apnea should be investigated.

e) The use of medications such as aspirin and β-blockers should be investigated.28

Exercise induced asthma

Bronchoconstriction induced by exercise is experienced by patients with asthma triggered by physical activity. Bronchoconstriction induced by exercise often indicates that the disease is not well controlled, requiring an increase in the measures taken to control it; moving the patient up one step with regard to control therapy. For those of whom exercise-induced bronchocons-

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education on Asthma</td>
<td>Control of the environment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting β-2 agonists</td>
<td>Short-acting β-2 agonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Select one</td>
<td>Select one</td>
<td>Select one or more from step 3</td>
<td>Add one or more from step 4</td>
<td></td>
</tr>
<tr>
<td>Low-dose of ICS*</td>
<td>Low-dose of ICS plus long-acting β-2 agonist</td>
<td>Medium or high dose of ICS plus long-acting β2-agonist</td>
<td>Oral glucocorticosteroid (low dose)</td>
<td></td>
</tr>
<tr>
<td>Options for control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>Medium or high dose of ICS</td>
<td>Leukotriene modifiers</td>
<td>Treatment with Anti-IgE</td>
<td></td>
</tr>
<tr>
<td>Low-dose of ICS plus long-acting theophylline</td>
<td>Low-dose of ICS plus long-acting theophylline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ICS = inhaled glucocorticosteroid

The dynamics of the treatment and control of asthma

Table 10: Treatment based on management control (for children over 5 years, adolescents, and adults)
Restriction is the only manifestation of asthma, the use of a short action inhaled β-2 agonist is recommended, 15 to 30 min before physical activity. Anti-leukotrienes or chromones are alternative treatments.28

### Conclusion

Asthma is a prevalent inflammatory disease and must be treated appropriately. Knowledge of the main treatment options and how to manage patients with asthma at each visit is essential in order to achieve the goal of keeping the disease under control.

### References

Table 11: Data on clinical history and physical examination indicative of severity in acute asthma.

- History of previous exacerbations requiring hospitalization in ICU
- Difficult to control asthma
- Presence of comorbidities
- Tachypnea with severe dyspnea
- Tachycardia
- Speak with short sentences
- Cyanosis of extremities
- Sweating
- Signs of exhaustion
- Absence of breath sounds or greatly reduced
- Retraction of intercostal muscles
- Agitation, confusion, and sleepiness
- FEV₁ < 30%; SaO₂ < 90%; PaO₂ < 60 mmHg


11. Nelson HS, Weiss ST, Bleecker ER. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129:15-26


25. Abamson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. Cochrane Database


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