Prophylactic treatment of asthma

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Abstract

Objective: to review basic concepts, inhalation therapy, classification of asthma and peculiarities of asthma in developing countries.

Sources: direct search in the Medline, HighWire and MD Consult databases.

Summary of the findings: inhaled corticosteroids are the drugs of choice for the treatment of asthma. Alternatively, other drugs, such as long-acting beta-agonists and antileukotrienes could be considered.

Conclusions: at an individual level, asthma treatment presents a satisfactory outcome. However, the great challenge for public health professionals and authorities is to provide treatment for asthmatic patients from low-income families living in developing countries.


Introduction

Asthma is characterized by a variable obstruction of air flow and bronchial hyperreactivity or hyperresponsiveness. Its main characteristic is the inflammation of the bronchial mucosa. In children, the disease is triggered off by multiple allergenic or nonallergenic stimuli, and consists of coughing, wheezing, tachypnea and dyspnea. The symptoms are intermittent or persistent; when persistent, prophylaxis is required.

The treatment involves well-defined, perhaps even ambitious objectives, which can be summarized as “normal life, with normal pulmonary function”. Its aim is to minimize as much as possible the frequency of exacerbations, the symptoms in the intercritical period, the use of relief bronchodilators, and to allow children to lead a normal social, sports and school life. The pulmonary function should be normalized, as well as the circadian variation of the peak expiratory flow. For this purpose, it is crucial to control the inflammatory phenomena and, consequently, bronchial hyperresponsiveness, thus reducing the severity of the disease. The recommendations of prophylactic anti-inflammatory drugs are quite comprehensive; therefore, the importance of the environmental context in the pathophysiology of the disease requires that the drug therapy be complemented by objective and rational environmental hygiene measures. Asthma in infancy will not be discussed in the present article due to its distinct characteristics, which involve diagnostic, therapeutic and prognostic peculiarities.
The strategy for the management and prevention of asthma, proposed by the National Institutes of Health/National Heart, Lung, and Blood Institute (NHLBI), revised in 2002, contemplates basic concepts and objectives to be attained by the prophylactic treatment of asthma, which will be succinctly revised in the following paragraphs.

**Basic concepts**

1. **Asthma in adults and children has the same physiopathological mechanisms**; however, due to the growth process in children, the consequences of the disease and the adverse effects of the treatment are different from those observed in adults.

2. **Most antiasthma drugs, such as corticosteroids, β2-agonists and theophylline, are more quickly metabolized by children than by adults. The younger the child, the higher the metabolization.**

3. **Inhaled corticosteroids are currently the most efficient drugs for the control of asthma, and are recommended for persistent asthma, regardless of the severity of the disease.**

4. **Long-term treatment with inhaled corticosteroids significantly reduces the frequency and severity of exacerbations.**

5. **Studies involving over 3,500 children treated throughout 13 years have not shown persistent adverse effects of inhaled corticosteroids on growth.**

6. **Once the control of asthma is obtained and maintained for at least three months, the maintenance treatment should be gradually reduced, being minimally kept for the control of symptoms.**

7. **Fast-acting β2-agonists are the most efficient agents used to relieve the symptoms of asthma, and are only recommended for the treatment of acute symptoms in children. The regular use of these drugs might be inefficient and harmful.**

**Objectives of the treatment**

The major objectives of the treatment are: relief or reduction of symptoms; maximization of pulmonary function; prevention of exacerbations and maintenance with minimum efficient prophylactic dose in order to mitigate the adverse effects of the treatment. Both the family and the patient should get enough information for support and better treatment compliance. The treatment should be planned bearing the following factors in mind: severity of asthma, benefits, risks and availability of each treatment, cultural preferences and the characteristics of the health system. The final selection of a therapeutic scheme should combine the clinician’s experience with family preferences and scientific evidence that is clinically relevant to the child.1

The prophylactic treatment should be assessed and monitored by clinical parameters, such as intensity of symptoms (night and day), ability to perform daily activities and need for relief drugs (short-acting β2-agonists). Whenever possible, the pulmonary function, with peak expiratory flow (PEF), forced expiratory volume in one second (FEV1) and variation of PEF, should be used. The potential adverse effects of the treatment should be properly verified.

The selection of the pharmacological treatment is based on the severity of the disease. Since asthma is a dynamic and chronic condition, treatment options should include interpersonal variations and the variability of the disease over time. A key aspect of any treatment is the monitoring of treatment effects (verification of pulmonary function and symptoms) and its adaptability to the variability of the disease.

**Assessment of the severity of the disease**

This assessment should precede any therapeutic decision and should be regularly checked on every consultation. Restricting the score to the frequency of asthma attacks will cause the severity of the disease to be underestimated. Therefore, the clinical classifications currently in use underscore the importance of symptomatology observed between exacerbations, intensity of exercise-induced bronchospasms, weekly use of beta-agonist bronchodilators, the follow-up of peak expiratory flow, and the occasional presence of obstructive ventilatory disease, detected by spirometry, which is performed during the follow-up at the outpatient clinic.

As shown in Table 1, the classification of asthma severity should be carried out by the assessment of symptoms, medical history, current treatment, clinical examination and, if possible, pulmonary function. Based on these alterations, the National Heart, Lung, and Blood Institute (NHBLI), conjointly with the World Health Organization, elaborated the document entitled Global Initiative for Asthma (GINA),1 which presents a classification with crescent levels of severity (1 to 4), applicable to several stages of treatment.

Nowadays, the distinction between severity and control of asthma is advocated. The information shown in Table 1 usually applies to new patients, before implementation of the treatment. For patients being followed up, the assessment of severity should be reflected on the therapeutic scheme, especially regarding the doses of inhaled corticoids. Thus, children who need doses of 400-500 μg/day of beclomethasone, but who are asymptomatic, have moderate asthma and, if they are symptomatic, they will be classified as having severe asthma.
Treatment

Environmental control

This type of control is essential to the treatment since it contributes towards minimizing inflammatory phenomena by reducing the exposure to allergens. Allergenic factors have a key role in the maintenance of bronchial inflammatory phenomena. The reduction of allergen load, especially of mites, helps to reduce the intensity of symptoms and bronchial hyperresponsiveness, and is based on the decrease of relative humidity (through aeration and sunlight incidence) on the one hand, and on the use of mattress and pillow covers, removal of carpets or alike, and removal of curtains or dust-gathering objects, on the other hand. Ideally, bedclothes should be washed in hot water (55 oC). The use of humidifiers is not recommended. The threshold for sensitization to mites is 2 µg/gram of household dust, and the risk for an asthma attack is 10 µg/gram of household dust.2,3 Environmental control also includes keeping pets away, controlling the population and movement of cockroaches, controlling mold growth, and controlling exposure to passive smoking.

Medications: major characteristics and routes of administration

The medications for control of asthma include controller or prophylactic drugs and the symptomatic or relief drugs. Prophylactic drugs are those administered daily in the long run with the aim of attaining and maintaining the control of the disease. Symptomatic drugs act quickly, with the aim of alleviating bronchoconstriction during exacerbations.

Route of administration

Prophylactic drugs may be inhaled or orally given. The advantage of inhaled drugs is that they can be offered in efficient concentrations, thus minimizing or avoiding systemic side effects. There are several inhaled drugs, namely dose-metered aerosols, spacers or inhalation chambers, with face mask, dry powder inhalers (single or multiple doses) and solution or suspension for nebulization. The selection of an inhaler should take into account the aspects regarding the efficiency of drug release, cost-effectiveness, safety and convenience, that is, adaptation of the child to the technical abilities required for application.1 Before the age of six, dose-metered aerosols coupled to spacers are the method of choice; after the age of six, dry powder inhalers are more appropriate, since dose-metered aerosols are only correctly used at the age of 10-12. The technical quality of inhalation should be verified on every consultation.

Recent meta-analyses, given the use of short-acting β2-agonists and corticosteroids by different inhalation devices, show that pressurized aerosols are equivalent to the other devices, with better cost-effectiveness. In infants and older children, information on pulmonary deposition of a certain drug is still scarce and for this reason, the selection of a device for the maintenance treatment should be related to the class of the drug. Due to potential side effects, the device for inhaled glycoproteicoids should be carefully chosen in order to guarantee optimal therapeutic effect, with minimal undesirable effects. In addition, the differences as to the first-pass metabolism of various inhaled glycoproteicoids should also influence the selection of the inhaler.2

Table 1 - Classification of asthma severity

<table>
<thead>
<tr>
<th></th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td>less than once a week</td>
<td>more than once a week and less than once a day</td>
<td>daily</td>
<td>daily</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>short and mild</td>
<td>can affect activity and sleep</td>
<td>can affect activity and sleep</td>
<td>frequent</td>
</tr>
<tr>
<td><strong>Night symptoms</strong></td>
<td>less than twice a month</td>
<td>more than twice a month</td>
<td>more than once a week</td>
<td>frequent</td>
</tr>
<tr>
<td><strong>FEV1 or EFP</strong></td>
<td>≥ 80%</td>
<td>≥ 80%</td>
<td>60-80%</td>
<td>&lt; 60%</td>
</tr>
<tr>
<td><strong>Variability of EFP</strong></td>
<td>&lt; 20%</td>
<td>20 – 30%</td>
<td>&gt; 30%</td>
<td>&gt; 30%</td>
</tr>
</tbody>
</table>

* FEV1: forced expiratory volume in the first second; EFP: expiratory flow peak
As far as comfort is concerned, the inhalation device should be portable, with no need for electric power, and should be easily operated, requiring minimal maintenance. Ease of operation is especially important in the treatment of infants and preschool children, who receive attention from different people in different periods of the day. The necessity of cooperation and coordination for the use of the device should be minimal. Passive cooperation, as accepted use of a face mask, may be expected from most preschool children and even from infants. Active cooperation, such as specific inhalation maneuvers and subsequent activation of the inhaler should be only expected from school-age children and adolescents. In case of infants and preschool children, a pressurized aerosol, with spacer and face mask, should be used (Table 2). With improved inhalation through the spacer, usually attained at the age of 4-6, the child should be encouraged to use the mouth piece instead of the face mask. At the age of six, a dry powder inhaler is the device of choice. By assessing the clinical efficiency of salbutamol in asthmatic children, we observed that Nebuchamber™ (stainless steel), Aerochamber™ (plastic) and Volumatic™ (plastic) were equally efficient. Nebulizers are not appropriate for maintenance treatment due to their cost, lack of comfort (they are large and heavy), longer inhalation time and longer monitoring of the procedure, aside from maintenance costs.

### Table 2 - Inhalation devices recommended for each age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>Device of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 years</td>
<td>pressurized inhaler with spacer and face mask</td>
</tr>
<tr>
<td>4-6</td>
<td>pressurized inhaler with spacer and mouth piece</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>powder inhaler, or pressurized inhaler with spacer</td>
</tr>
</tbody>
</table>

**Prophylactic drugs**

In general, childhood asthma is inadequately diagnosed and treated. Even with drugs that allow patients to lead a nearly normal life, the prevalence of asthma has been constantly on the rise, and so has the number of cases treated at emergency rooms and the number of hospital admissions due to acute asthma. The reasons for this paradoxism, especially in developing countries, stem from the lack of access to anti-inflammatory drugs. In order for the treatment with inhaled drugs to have the desired cost-effectiveness and the topic efficiency/systemic effect ratio, these drugs should be properly administered. Replacing a certain inhaled corticoid with another one with enhanced anti-inflammatory power will not have a positive effect if the technique remains inappropriate.

The drugs used for asthma control include inhaled glycosocorticoids, leukotriene modifiers, chromones (sodium cromoglycate and nedocromil sodium), methylxanthines and long-acting B₂-agonists (inhaled and oral). At present, inhaled glycosocorticoids are considered to be the most effective. The lack of scientific evidence about the efficiency of ketotifen on children does not justify its use.

### Inhaled glucocorticoids (IGC)

These drugs are highly efficient in controlling asthma and for that reason they are recommended for the treatment of persistent asthma at any stage of severity. Dose-response studies show a significant and quick clinical improvement of symptoms and pulmonary function with low doses of inhaled glucocorticoid (for example, 100 g of budesonide/day). However, the dose necessary to produce the maximum clinical effect depends on several factors, such as released dose, length of use, severity of asthma, drug/inhaler combination used, patient age, and length of asthma when the treatment was implemented. All of these factors reinforce the importance of personalized dosage. Most patients with persistent, mild or moderate asthma will have adequate control with 400 g or less of beclomethasone, or with an equivalent dose of another inhaled corticoid. It is important to emphasize that by treating the same patient with intranasal and inhaled corticoid simultaneously, pediatricians should bear in mind the potential risk of the cumulative effect of the drug.

A meta-analysis carried out by Calpin et al., including 24 randomized, placebo-controlled and double blind studies, revealed that inhaled corticosteroid therapy improves the clinical score by 50%, reducing the use of B₂-agonists to 37% and the use of systemic corticoids to 68%, in addition to increasing the peak expiratory flow to 38 l/minute. The control of symptoms during the intercritical period has a clear influence on the quality of life. Although inhaled glycosocorticoids reduce the number of exacerbations in school-age and preschool children, they are not equally efficient in some infants. Whether the reasons for this low efficiency in infants are due to little treatment adherence, low release of the medication, insufficient dose or distinct pathophysiological aspects of asthma in this age group are not clearly established.

The dose-response curve for inhaled fluticasone in moderate and severe asthma in adolescents and adults has a plateau at 100-200µg/day and reaches a peak around 500 µg/day. Efficiency is not increased above this dosage. The authors of this study argue that the association of a long-acting B₂-agonist with an inhaled corticosteroid may be more efficient than the increase in the dose of the corticosteroid above this dosage threshold.
Side effects

Among all anti-inflammatory drugs that are available for the treatment of asthma, greater attention should be given to inhaled corticosteroids, so as to assess the relationship between efficiency and safety. The presence of growth suppression is still a controversial point, since both uncontrolled asthma and the use of inhaled corticosteroids may affect growth. Skoner, in a recent review article, has assessed the relationship between efficiency and safety associated with inhaled corticosteroids. Children with mild asthma may be more susceptible to side effects, such as delayed growth, due to the more peripheral spectrum of the drug which consequently leads to higher pulmonary absorption; the same may happen to moderate and severe asthmatics, with the improvement of the pulmonary function. Another meta-analysis, which analyzed the relationship between inhaled corticosteroids and linear growth, recommends carefully monitoring stature and emphasizes the need to use the minimum effective dose with the aim of mitigating the effects on linear growth. Allen, in an extensive and well-founded review on the effect of inhaled corticosteroids on the growth of preschool children at the prepubertal stage, concluded that low doses of IGC do not cause systemic adverse effects. When used continually at high doses for longer periods, the differences as to the characteristics of the drugs, especially the efficiency of inactivation of the swallowed drug, may negatively affect the therapeutic success of the drug. Practically speaking, the history of therapeutic use for longer periods should be valued. The single administration of IGC has not been associated with any undesirable effect on the final height to be reached in adulthood, given the single use of IGC at recommended doses and the noncombined use with nasal corticosteroids. The risk for adverse effects may be minimized by the use of the minimum effective dose and by the reduced systemic availability, with the use of adequate inhalation devices and techniques, in cases in which high doses are required, by the selection of the most appropriate IGC for that condition.

Longitudinal and cross-sectional studies have not shown undesirable effects on bone mineralization. On the other hand, the local secondary effects, such as sensation of thirst (22%), dysphonia (11%), and oral candidiasis (11%) should not be overlooked; the latter two may be remarkably reduced with mouth-washing and/or toothbrushing after inhalation. The risk of cataract is an exception. Finally, it is important to underscore that the indication of inhaled corticosteroids in children causes an undeniable fear in parents and pediatricians and is equivocally related to the deleterious effects of systemic corticosteroids, such as osteoporosis, elevated risk of fractures, osteonecrosis, significant growth delay, arterial hypertension, diabetes and atrophy of the skin and muscles. Nevertheless, in aerosol form, even if swallowed or absorbed by the lungs, corticoids undergo a quick and significant catabolism in the liver, which contributes towards the production of poorly active (or totally inactive) metabolites. The increment of their anti-inflammatory activity and their affinity with the receptors restrict the potential secondary effects, especially of latest generation drugs.

The fact that the anti-inflammatory action of these drugs may modify the natural history of asthma, improves its prognosis in the long term or prevents bronchial remodeling still needs to be shown in the literature. On the other hand, there seems to be some doubt over the fact that their use determines the improvement of pulmonary function.

Long-acting Beta β2-agonists

These drugs have shown a real progress in the treatment of asthma, and consist of two available types of molecules: salmeterol and fenoterol. The latter has a peak action that is similar to that of salbutamol. These drugs are characterized by the induction of bronchodilation for 12 hours and by the control of night symptoms. They are especially recommended as additional treatment, combined with inhaled corticosteroids, but not as their substitute, or then as prophylaxis for exercise-induced asthma.

Long-term studies of salmeterol in children presented contradictory results. Children aged 4-11, with moderate persistent asthma, who received salmeterol (50 µg bid), showed higher FEV1 values than those who received placebo. The necessity for relief β2-agonist was significantly reduced in the group that received salmeterol. Similarily, Russel et al. have shown that children who stayed symptomatic with the use of 400 µg of inhaled corticoid had a significant clinical improvement after the introduction of salmeterol. On the other hand, a one-year-long study comparing the use of salmeterol and placebo, in children aged 6-14 years, showed negative results in terms of bronchial hyperresponsiveness and improvement of pulmonary function. Verbene et al. assessed children aged between six and 16 years, with mild to moderate asthma, who received salmeterol (50 µg bid) for 12 months, and did not find any improvement of FEV1 or in bronchial hyperresponsiveness, causing worsening of bronchial provocation parameters (PC20 decreased 0.73%). These paradoxical results seem to be associated with methodological differences, especially regarding the severity levels of asthma of the patients involved.

Despite the confirmed efficiency of salmeterol and formoterol in studies involving adults, as complementary therapy to inhaled corticosteroids, the questions about the development of tolerance and control of inflammation may negatively influence the selection of these drugs for the pediatric population. Albeit empirically, in patients for which clinical control is inadequate despite high doses of inhaled corticoids (doses equal to or greater than 750 µg of beclomethasone, or equivalent drug), a therapeutic test with salmeterol or formoterol, before opting for higher doses of corticoids, with the aim of avoiding secondary effects, should be attempted.
Leukotriene modifiers

In a study assessing the efficiency of montelukast, as monotherapy in children aged between two and five years, with persistent asthma (beta-agonist was necessary six days a week), with a daily dose of 4mg, in a 12-week study, the authors concluded that montelukast significantly reduced the daily score of asthma symptoms, the necessity for beta-agonists, the number of days with symptoms and the necessity for relief corticosteroids. In another group of children with persistent asthma, montelukast was well tolerated, reduced the symptoms of asthma and the use of beta-agonists and increased the number of asymptomatic days. Studies carried out with children showed clinical improvement, reduction of exacerbations, as well as an increase, although subtle, in FEV1. According to Warner, the available scientific evidence suggests that antileukotrienes may be used as additional therapy to inhaled corticosteroids, with the aim of reducing their doses, as well as the use of beta-agonists. According to the same author, recent studies suggest that these agents may be used as first-line therapy in children with mild asthma. In spite of these favorable studies, the position of the NHLBI stated in the GINA document is that further investigation on the effects of antileukotrienes on inflammation and control of the disease, long-term safety, and the effects on the progression of the disease is still necessary. Until these studies are available, the use of antileukotrienes for the treatment of asthma should be limited. A recent meta-analysis, involving 13 selected studies (of which only one was carried out with children), concluded that the combination of antileukotrienes with inhaled corticosteroids may slightly improve asthma control, if compared to the single use of inhaled corticosteroids; this, however, should not be recommended as an alternative to the increase of corticosteroid doses.

Chromones

For a long time, first-line maintenance treatment consisted of chromones. Currently, the role of sodium cromoglycate and nedocromil sodium in the prophylactic treatment of asthma, based upon studies available so far, is limited, especially among preschool children. Leflein has studied 287 children aged between two and six years, comparing cromoglycate with nebulized budesonide. The latter is considered more efficient since it reduced exacerbations and the administration of associated medications. This study reinforces the role of anti-inflammatory therapy with corticosteroid as first-line maintenance treatment of persistent asthma in preschool children. Although cromoglycate has proved to be safe for the prophylactic treatment of children with mild to moderate persistent asthma, its efficiency (which is similar to that of the placebo) and the necessity of 3-4 daily doses contributed towards its reduced use. The safety of nedocromil sodium is similar to that of cromoglycate, although it has an unpleasant taste. Just like cromoglycate, its effect on pulmonary function is arguable, suggesting that other anti-inflammatory drugs are preferable for the treatment of mild to moderate asthma.

A recent review, involving 24 studies of cromoglycate in children and adolescents younger than 18 years, considers the therapeutic rates inadequate and shows there is insufficient evidence that cromoglycate is beneficial in the maintenance treatment of asthmatic children.

Methylxanthines

Theophylline has had proven efficiency for several decades, but its safety, necessity for serum monitoring and dose adjustment give it a secondary role in treatment schemes. The role of theophylline in the long-term treatment of asthmatic children is limited.

Rational sequential approach

An appropriate approach to the treatment of asthma recommends that the number, dose and occasionally the frequency of medications be increased according to the severity of the disease. The ultimate objective is to achieve the treatment goals with the minimum of medication. When making a treatment plan, the necessity for a more aggressive treatment at the beginning should be assessed - which may include an initial course of oral glycoocorticoid to obtain the maximum control of asthma as soon as possible - and then reduction in medication. Another alternative is to begin the treatment with a dose that is adequate for the severity of the disease and then increase it gradually, if necessary. Once the adequate asthma control is maintained for about three months, a reduction in the dose of the drug or drugs in use may be carefully planned. This reduction is necessary in order to identify the minimal scheme for maintaining asthma control.

Table 3 shows the stages of therapeutic approach used to attain and maintain the control of asthma in children, according to the NHLBI, which considers the use of complementary drug for patients whose asthma is not controlled with the standard dose of IGC, instead of medium and high doses of IGC. The use of long-acting beta-agonists, theophylline, or antileukotrienes are regarded as alternatives. The preference for the former ones is unemphatically recommended.

The British consensus, published in 1997, proposes a simplified treatment scheme. This consensus considers inhaled corticosteroids as the main drug, and long-acting beta-agonists as complementary drugs. The difficulty in using slow-releasing theophylline (necessity for monitoring serum levels), inefficiency of chromones, and the scarce number of randomized controlled studies with antileukotrienes involving children justify the adoption of this treatment (Table 4).
The change from one stage to another should be made when the control is not achieved or is lost during treatment, and when one is certain that the medication is being given correctly. The frequency of symptoms (more than three times a week), such as cough, wheeze and dyspnea and the frequent use of short-acting β2-agonists, may indicate inadequate asthma control. The presence of night or morning symptoms is a useful sign. Measurements of expiratory peak flow and its variability help with the initial assessment of the severity and with the monitoring of the disease, pointing out changes in severity and providing data for reduction of treatment.

**Reduction of prophylactic medication**

Asthma is a dynamic disorder, with spontaneous or treatment-induced variations. Once the control of the disease is attained and maintained for at least three months, a gradual reduction of maintenance therapy should be attempted, with the aim of determining the dose or the minimal number of medications to maintain the control. In patients submitted to combined therapy, the reduction should be implemented by interrupting the additional therapy, which should be followed by the reduction of the inhaled glucocorticoid dose by 25% every 2-3 months. Patients should be checked at least every two months during the reduction phase.

**Other treatment options**

**Immunotherapy**

The specific desensitization treatment reduces the symptoms and the necessity for drug therapy, but does not have a consistent effect on pulmonary function. The effects

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### Table 3 - Asthma treatment

<table>
<thead>
<tr>
<th>Severity level</th>
<th>Daily control medication</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>No necessary</td>
<td></td>
</tr>
<tr>
<td>Intermittent asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>Inhaled glucocorticoid (100 - 400 µg of beclometasone or similar medication)</td>
<td>Slow-release theophylline, or Chromone, or Leukotriene modifiers</td>
</tr>
<tr>
<td>Mild persistent asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
<td>Inhaled glucocorticoid (400 - 800 µg of beclometasone or similar medication)</td>
<td>Inhaled glucocorticoid (&lt; 800 µg of beclometasone or similar medication) associated with: – Slow-release theophylline or – Long-acting β2-agonist or Inhaled glucocorticoid (&gt; 800 µg of beclometasone or similar medication) associated with: – Leukotriene modifier</td>
</tr>
<tr>
<td>Moderate persistent asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td>Inhaled glucocorticoid (&lt; 800 µg of beclometasone or similar medication) associated with one or more of the following medications, if necessary: – Slow-release theophylline, or – Long-acting β2-agonist – Leukotriene modifier – Oral glucocorticoid</td>
<td></td>
</tr>
<tr>
<td>Severe persistent asthma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All levels: short acting β2-agonist must be added to the daily prophylaxis regimen, whenever necessary, to relieve the symptoms, but it should not be administered more than 3 to 4 times a day.

All levels: once the control of asthma is attained and maintained for at least 3 months, a gradual reduction of the therapy should be performed in order to identify the minimal dose of medication to maintain control.
Table 4 - Simplified treatment plan according to the British consensus

<table>
<thead>
<tr>
<th>Severity level</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>Intermittent asthma</td>
</tr>
<tr>
<td>Short-acting $\beta_2$-agonist</td>
<td>Short-acting $\beta_2$-agonist to relieve occasional symptoms</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>Mild persistent asthma</td>
</tr>
<tr>
<td>Low dosage of inhaled corticosteroid:</td>
<td>200-400 $\mu$g of beclometasone or budesonide</td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
<td>Moderate persistent asthma</td>
</tr>
<tr>
<td>High dosage of inhaled corticosteroid:</td>
<td>400-800 $\mu$g of beclometasone or budesonide or low dosage of inhaled corticosteroid associated with long-acting $\beta_2$-agonist</td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td>Severe persistent asthma</td>
</tr>
<tr>
<td>High dosage of inhaled corticosteroid:</td>
<td>400-800 $\mu$g of beclometasone or budesonide associated with long-acting $\beta_2$-agonist</td>
</tr>
</tbody>
</table>

are more evident in patients with mild to moderate asthma and in those cases with bronchial hyperresponsiveness associated with a specific allergen. It is essential that the participation of a given allergen be shown at anamnesis by skin tests and, if necessary, by specific bronchial provocation tests.

Treatment of asthma in developing countries

The importance of the environment and of socioeconomic factors in the severity of asthma is widely acknowledged. The prevalence rate is higher and asthma is more severe in individuals or populations under precarious living conditions. Given the magnitude of the resources to be mobilized, either those associated with health education or those associated with the cost of maintenance treatment, we should question the viability of application of national and international consensuses under these circumstances. A survey carried out in 24 countries in Africa and in Asia revealed that most patients were not properly treated due to the unavailability and high cost of beta-agonists and inhaled corticoids, whose retail price reached 20% of an average monthly wage. This scenario more or less shows what occurs in Brazil, where the sale price of each flask of any of the commercial products, containing 200 doses of beclomethasone of 250 $\mu$g, may account for as much as 20% of the current minimum wage (about US$ 60,00) of an end consumer. If the diagnostic and therapeutic aspects of asthma are considered to be satisfactorily balanced in the available consensuses, the greatest challenge posed to developing countries lies in the wide availability of relief and controller medications for the economically underprivileged population. Cabral et al. have shown that the implementation of an educational program for asthma aimed at children from low-income families living in the city of São Paulo significantly reduced morbidity and social cost, but the purchase of inhaled corticoids caused an additional and hardly affordable expense for families in the long term.

An analysis of the Brazilian reality reveals that, in fact, material, financial and human resources have to be urgently redirected. There are significant expenses with inefficient medications, as is the case of aminophylline, and relatively high expenses with hospital admissions due to acute asthma (a single hospital admission costs about US$ 90,00 for the Unified Health System) when compared to the annual cost of inhaled corticoid therapy (about US$ 45,00/year, by the retail price).

On the other hand, successful experiments have been put into practice in some Brazilian cities. This is the case of Belo Horizonte, Betim, Brasília, Campo Grande, Caxias do Sul, Fortaleza, Porto Alegre, Rio de Janeiro, São José dos Campos and Vespasiano, among others, whose municipal governments have decided to implement programs for medical and pharmaceutical care to asthmatic patients, especially to those living on a low income. For instance, in Belo Horizonte, where the program has already benefited 13,000 children and adolescents, hospital admissions and admissions to emergency services decreased by 75%, comparatively to six to 12 before and after implementation of the program.
Final considerations

Before treating childhood asthma, the treatment of asthmatic children should receive special attention. This approach allows emphasizing the role of the patient in the success of the treatment to be prescribed and the expectation of a favorable therapeutic response and, therefore, of a quite satisfactory or perhaps normal quality of life. The success of treatment depends on an effective partnership between the health team or professional and the patient and his/her family, based on dialogue and health education. This dialogue should be especially established with the child, so that he/she can understand the impact caused by the disease, according to his/her own views and expectations. An example of this is the prescription of an inhalation device that does not correspond to the expectations of the patient, whose attitude may influence treatment adherence.36 In addition, the educational approach should be continued, considering internalized beliefs and concepts, different classes of medications, treatment schemes and, especially, the different inhalation devices that are currently available. The inadequate use of these systems and devices undoubtedly results in an apparent therapeutic failure. It is crucial to explain to the child and his/her family that severe persistent asthma is a chronic and threatening disease and that its deleterious effects outnumber the inconveniences of inhaled corticoid therapy.

References


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