Pulmonology in adolescence

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Abstract

Objective: to review concepts, long-term treatment schemes and peculiarities of the approach to adolescents with respiratory allergy, asthma and/or allergic rhinitis.

Methods: the data were obtained by systematic revision of studies published in the Bireme database between 1990 and 2001.

Results: most teenagers with asthma and/or rhinitis prefer to view their disease as episodic and do not accept the need for regular medication. These factors combined with the fear of being different from their peer group are responsible for poor treatment adherence.

Conclusions: it is extremely important that adolescent patients affected by asthma and/or allergic rhinitis be well-informed about their condition and receive proper medication; however, the following should also be considered: 1) open communication between the clinician and adolescent patients 2) inquiry into the fears and anxieties of the patient 3) shared responsibility for the treatment.


Introduction

Epidemiological studies on prevalence of allergic diseases, especially respiratory allergic ones, have documented the increase in these diseases worldwide. Acquisition of a unique, self-applicable and reproducible instrument has allowed for obtaining data that can be used in comparison of distinct populations and, to some extent, in helping to investigate different causes for the increase. In Brazil, epidemiological data on prevalence of allergic respiratory diseases are rare and recent.

Bronchial asthma

Asthma is a chronic disease of the airways characterized by 1) reversible airflow obstruction (partial in some patients) either spontaneously or with treatment; 2) inflammation, in which several cells play an important role, especially mast and eosinophil cells; 3) increase in airway responsiveness to a variety of stimuli (bronchial hyperresponsiveness); 4) recurring episodes of wheezing, dyspnea, chest tightness, and cough chiefly at night and in the morning, after waking up.¹

Recent advancements on the understanding of the pathophysiology of asthma, and on developing new pharmaceuticals have stimulated the establishing of national and international consensuses for management of asthma. These consensuses are aimed at establishing therapeutic strategies, especially for children and adults.²,³ In this sense, little attention has been given to adolescents.

This lack of attention may be a result of the following factors: 1) of the belief among physicians and pediatricians that asthma “disappears” with age, making parents and children perceive adolescence as “paradise on earth” or as a “happy ending for the long and hard journey of childhood” in relation to the disease; or 2) of the fact that adolescence

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is understood by some as “no man’s land” (pediatrician x physician).\textsuperscript{4}

**Epidemiology**

Despite advancements in the understanding of this disease and the availability of more specific treatment, the prevalence of asthma and its morbidity and mortality are increasing worldwide. This trend is especially prominent and worrisome in adolescents and young adults.\textsuperscript{5} Studies on asthma mortality, carried out in the city of São Paulo and in the state of Rio Grande do Sul, southeastern and southern Brazil, respectively, reported an increase in this mortality, especially with adolescence. Asthma is one of the most common chronic diseases in adolescence\textsuperscript{5} and the main cause of school absenteeism.\textsuperscript{8}

However, little is known about how asthma develops through childhood and adolescence. Despite the fact that epidemiological studies have indicated the possibility for remission or reduction of asthma symptoms between 10 and 20 years of age, the rates of recrudescence after asymptomatic intervals are reportedly high.\textsuperscript{9} Longitudinal studies have, thus, estimated that despite the possibility of asthma disappearing during puberty in 30 to 50\% of children, recrudescence is frequent, and persistent symptoms affect 30 to 80\% of adult patients.\textsuperscript{2}

In Brazil, recent data collected by the International Study of Asthma and Allergies in Childhood (ISAAC), which was carried out in different cities (Recife, Salvador, Itabira, Uberlândia, São Paulo, Curitiba, and Porto Alegre), indicated a variable cumulative prevalence of asthma diagnosis, ranging from 4.7 to 20.7\% for schoolchildren aged six to seven years, and from 4.8 to 21.9\% for students aged 13 to 14 years.\textsuperscript{1}

**Onset and exacerbation factors**

Asthma can be caused or exacerbated by multiple factors, depending on age groups. In infants and younger children (up to 3 years of age), upper airway infections (flu, cold, tonsillitis) are important onset factors for asthma.\textsuperscript{10} In adolescents, in turn, acute exacerbations can be caused or deteriorated, especially, by inhaled allergens (household mites: D. pteronyssinus, D. farinae, and Blomia tropicalis; fungi; dander, saliva, and urine of household pets: cats, dogs, and birds; remains of insects and cockroaches) and by sudden changes in temperature.\textsuperscript{1,10} Inhalation of nonspecific allergens such as strong odors, tobacco smoke, and so on can also cause onset of symptoms by nonimmune mechanisms; the same follows for exercises, inhalation of cold, dry air, and nonsteroidal antiinflammatory drugs.\textsuperscript{1}

**Treatment between attacks**

**Overall considerations**

The main objectives of asthma treatment between attacks are: controlling symptoms, preventing acute exacerbations, maintaining normal pulmonary function proof and practice of exercise, avoiding side-effects of the medication, preventing development of irreversible airway obstruction and asthma mortality.\textsuperscript{1,2} Asthma can be controlled in almost all patients, and the earlier the diagnosis and introduction of a management scheme, the better the outcome.

Adolescence is a transitional period between child and adulthood during which important psychological and physical changes take place. During this period in life, adolescents detach themselves from the family and try to engage in relationships with their peers; in this sense, acceptance becomes very important. The continuous need for approval makes adolescents try to fit in more and more with their peer groups.\textsuperscript{4}

The day-to-day settings in which adolescents participate are usually more hostile than those of younger children, and require the development of certain abilities to face them. For example, it is necessary that adolescents become more independent, or less dependent from their parents, and more intimate with their peers.\textsuperscript{4} The combination of a chronic disease, such as asthma, with the inherent problems of adolescence can provoke feelings of failure, hopelessness, anger, self-censorship, loss of self-esteem, and fear; all of which represent an additional burden on adolescents. Consequently, the firm objective of becoming independent from the family occurs together with loathing the possibility of being different from other adolescents.\textsuperscript{11}

Studies on self-image, self-esteem, and cognitive and emotional disorders have shown different results. On the one hand, preliminary studies did not show differences between asthmatics and healthy controls;\textsuperscript{12} on the other, later studies indicated higher scores for depression and low self-esteem in asthmatic subjects;\textsuperscript{11} and emotional (anxiety, depression, and hostility) as well as cognitive disorders were observed in severe asthmatic adolescents.\textsuperscript{13}

Considering that asthma is a chronic and inflammatory disease affecting the airways, some patients require continuous use of medication to control the inflammation. However, most adolescents perceive their disease as episodic\textsuperscript{4} and, thus, do not understand the need for regular use of medication and are reluctant to seek specialized medical care.\textsuperscript{14} Moreover, intelligence level, schooling, and ability to understand information on the nature of asthma present little correlation with adherence to treatment schemes. For example, it is known that even when information is provided in written and clear form, approximately 75\% of asthmatics do not make correct use of the prescribed medication. As a result, treatment approaches based merely on explaining and recommending treatment of the disease are doomed to failure.\textsuperscript{4,15}

Thus, adequate treatment of adolescents involves, first of all, trying to find out the anxieties and fears related to asthma and its treatment. On that account, asking questions such as “What do you worry about in relation to having asthma?” or, still, “What do you worry about in relation to regular use of medication?” can help to establish better
communication between the doctor and the adolescent, allowing for the establishment of a partnership between the two. This negotiation is important since it offers the adolescent a certain level of authority over the situation; in this sense, he or she can also feel more confident that asthma and its treatment will not hinder normal activities and progress in adult life.\textsuperscript{16}

Treatment plans should be simple and include essential elements such as: what measures to take in case asthma deteriorates; how to decrease medication dosage if asthma improves; how to treat acute attacks; and when to seek medical assistance.\textsuperscript{4}

**Classification of asthma according to severity**

Asthma can present different manifestations, varying from intense attacks that are easily recognized to mild symptoms that may not be perceived. Hence, to establish an adequate treatment plan, it is important to diagnose the severity of the disease based on presence of symptoms, limitation of physical activities, emergency healthcare assistance, and changes in pulmonary function proof (examined outside episodes of acute exacerbation). According to the II Brazilian Consensus on Management of Asthma, the disease is classified into Mild, Moderate, or Severe.\textsuperscript{1}

Mild asthma patients characteristically present symptoms (wheezing, chest tightness, breathlessness, and cough) a maximum of twice a week or only when exercising; these symptoms generally do not last long and can be relieved with bronchodilators. Mild asthma patients can perform normal activities and usually do not have to be absent from work or school for more than one day; asthma attacks do not last longer than one day per month, are easily controlled with bronchodilators, and do not require emergency healthcare services. In general, sleep is interrupted by acute exacerbations a maximum of twice a month. Bronchodilators are used for symptom relief once or twice a week (excepting occasional use of bronchodilators following exercise-induced bronchospasms). In mild asthma patients, peak expiratory flow rate (PEF) and forced expiratory volume in one second (FEV1) at medical appointments before use of bronchodilators are usually above 90\% of personal best value (PBV).

Moderate asthma patients, in turn, present symptoms more than twice a week, but symptoms are not persistent. Asthma attacks last longer than one day a month and do not require repeated administration of systemic corticosteroids for control of symptoms, or hospital admission. Nighttime symptoms are common in moderate asthma patients and sleep is interrupted by attacks more than twice a month, but not more than twice a week. Physical activity is affected and patients present absenteeism from work and school. Bronchodilators are used for symptom relief more than twice a week, but not daily, and less than twice a day. PEF and FEV1 at medical appointments are usually below 90\% of PBV or, in other words, below the lower estimated value. However, PEF and FEV1 parameters normalize after use of bronchodilators. In monitoring of PEF, minimum values are observed between 75 and 90\% of PBV.

Severe asthma patients manifest persistent symptoms, life-threatening attacks and require frequent use of systemic corticosteroids. Nighttime symptoms are frequent and sleep is interrupted by asthma once or twice a week. Severe asthma affects normal daily activities with patients being frequently absent from work or school. Use of bronchodilators for relief of symptoms is usually required more than twice daily, and oral or parenteral administration of corticosteroids is frequent. PEF and FEV1 are usually below 90\% of PBV or below the lower estimated value after administration of bronchodilators. Minimum PEF during three-week monitoring is below 75\% of PBV.

**Nonpharmacological treatment**

**Environment control**

Environment control measures in relation to airborne and nonspecific allergens should always be observed; avoiding or, at least, controlling exposure to these factors can reduce symptoms and allow for long-term decrease in airway inflammation. Adolescents spend a considerable amount of time in their bedrooms and it is in these settings that measures should be applied more intensively. Avoidance measures comprise\textsuperscript{1}:

a) Use mite-proof covers (mattress, pillow, and quilt); these covers are washable and can be made of polyurethane;

b) Avoid sweeping and dusting; perform weekly cleaning of all bedroom surfaces (including draperies; window paneling; and the topmost surfaces of furniture, such as closets) using a damp cloth;

c) Perform weekly, careful vacuum-cleaning of mattress, pillow, bedside area, and bedroom floor;

d) Use dehumidifiers to help control relative air humidity; however, these devices can make the environment excessively dry, causing attacks of allergic cough and thus exacerbating asthma attacks. Humidifiers are contraindicated in bedrooms of allergic patients since they facilitate proliferation of fungi;

e) Replace feather or floss pillows and covers, as well as wool covers, with synthetic pillows and covers. All bed linen should be washed in hot water (60 degrees C) weekly;

f) Avoid rugs, carpets, and curtains; give preference to washable flooring, to shutter-type blinds, and to material that can be cleaned with damp cloth;

g) Avoid objects that accumulate dust such as stuffed animals (soft toys), boxes, suitcases, cushion, and so on;
h) Avoid accumulation of mildew and humidity; solution of phenic acid at 3 to 5% can be applied to mildewy spots until final solution to humidity. However, phenic acid is volatile, has a strong odor, and can cause irritation of the airways; in this sense, the patient should not be the one to apply the solution and the house should be well-ventilated for six hours before residents can return.

i) Avoid having furry pets in the household; if not, pets should be bathed at least once a week and cannot, in any way, remain in the bedroom;

j) Avoid use of powder, perfumes, disinfectants, and cleaning products with strong odors. Heat-activated insecticides, though odorless, can irritate the respiratory mucosa;

k) Maintain the household environment insect-free (cockroaches) avoiding accumulation of dust, old paper, and food crumbs; it is recommended to use baits and or periodical extermination;

l) Prevent active and passive smoking inside the household.

Specific immunotherapy

Specific immunotherapy (SI) consists of manipulation of the immune system of patients with the objective of changing response to allergens (immunomodulation). As to what concerns allergic diseases, SI has been used as a therapeutic resource for control and reduction of symptoms for approximately 90 years. Despite the well-established use of SI in seasonal respiratory allergies (pollinosis) and in responses to Hymenoptera insects (bees, wasps, and ants), its application in asthma patients is still controversial. Thus mild or moderate IgE-mediated asthma patients and who have not benefited from rigorous environment control and pharmacological treatments are candidates to SI.

Pharmacological treatment

Pharmacological treatment of asthma is aimed at relieving bronchial obstruction and decreasing airway hyperresponsiveness. Based on the main mechanism of action, the drugs used can be divided into two groups: relief (short-acting beta-2-agonists; ipratropium bromide; methylxanthines; and systemic corticosteroids), which are administered for control of acute symptoms; and control (long-acting beta-2-agonists; chromones; inhaled corticosteroids; and antileukotrienes), which are administered for prolonged periods for inflammation control. Inhalation is the preferred form of administration in asthma since it allows for direct action of the medication on the affected organ. However, hand-mouth coordination is one of the obstacles for a more general use of inhalation. In this sense, when indicating use of metered-dose inhalers it is important to provide adequate orientation for patients, and to carry out examinations at every medical appointment.

Erroneous use of the medication has been an important factor in failure of asthma control. For patients who cannot use metered-dose inhalers, the use of spacers (valved, if possible) is recommended (750 ml). Dry powder inhalers are forced-inspiration activated, do not depend on inspiration being synchronized with inhaler activation, and thus are easier to use. Nebulized solutions can be delivered using a common compressor and with saline solution.

Medication

Short-acting beta-2-agonists (salbutamol, fenoterol, and terbutalin) are the drugs elected for cases of acute exacerbations and exercise-induced asthma. When inhaled (metered-dose inhalers, dry powder inhalers, or nebulized solutions) the agonists present rapid action within a maximum of 15 minutes. These medications relax airway smooth musculature, increase mucociliary transport, decrease vascular permeability, and can modulate release of mastocytes and basophils.

Earlier evidence indicated an association between regular use of short-acting, inhaled beta-2-agonists with poor asthma control and increase in mortality. However, recent studies do not confirm these observations. When continuous use of beta-2-agonists is necessary, they should be combined with antiinflammatory agents. Long-acting beta-2-agonists allow for potent and prolonged activation of beta-2-adrenoceptors in airway smooth muscle cells, endothelial cells, mast cells and epithelial cells; thus inducing reduced vascular permeability, inhibition of inflammatory mediators, stimulation of ciliary function and modulation of ion and water transport across the bronchial mucosa. The routine use of the medications allows for better control of asthma, of acute exacerbations, and for decrease in consumption of short-acting beta-2-agonists.

Theophylline is the main methylxanthine used in the treatment of asthma. Despite the fact that its mechanism of action is still not well-defined, theophylline acts as a bronchodilator depending on its serum level. When used in slow-release preparations, theophylline produces prolonged bronchodilation and is useful in the control of nocturnal asthma. Others have also reported mild antiinflammatory function and potential decrease in respiratory muscle fatigue. Theophylline can also cause important adverse effects and monitoring serum levels of this methylxanthine (ideal concentration of 5 to 15 µg/ml) has been reported necessary. Several authors reserve application of theophylline after failure of beta-2-agonists and of corticotherapy.
Inhaled anticholinergic agents, such as ipratropium bromide (IB) provoke bronchodilation by decreasing intrinsic vagal tonus of the airways and blocking reflex bronchoconstriction caused by inhaled allergens. When used in the recommended dosage and by inhalation, the mode of action of IB is restricted to the respiratory tree, especially the bronchial smooth muscle. It allows for competitive inhibition of acetylcholine at muscarinic receptors, induces bronchodilation less intense than that of beta-2-agonist agents, and decreases mucous gland secretion. A recent study indicated that combined beta-2-agonists and IB can be beneficial during acute asthma exacerbations in adolescents and adults.

The chromones (disodium chromoglycate and sodium nedocromil) are applied as control medication. Disodium chromoglycate, available for administration with metered-dose inhalers, dry powder inhalers, and nebulized solutions, inhibits immediate and late asthma response induced by allergens; it also inhibits exercise, cold-air, and sulfur dioxide induced bronchospasms. The mechanism of chromones is still not well-defined, but it is believed that it stabilizes the mast cell membrane by preventing the release of mediators. The onset of chromone action is variable and early therapy is recommended for four to six weeks with six-hour intervals for determining therapeutic effectiveness. Sodium nedocromil can inhibit release of mediators and decrease or modulate allergen-induced hyperresponsiveness, similarly to the disodium chromoglycate. This medication is available in the form of inhaled metered-dose inhalers and is administered twice daily.

The cysteinyl leukotriene receptor antagonists are increasingly being used in our setting. These antagonists operate with competitive antagonism to leukotrienes, which are important mediators in the physiopathology of asthma involved in attraction of neutrophils to the inflammation site (chemotactic activity); in airway smooth muscle contraction; in increase in vascular permeability; in promoting vasodilation; in mucus hypersecretion; in edema in the mucosa; and in decrease in mucociliary transport. Initial studies with adults indicated that these medications are capable of blocking exercise- and aspirin-induced asthma and, also, asthma induced by other nonsteroidal antiinflammatories; moreover, they act on bronchial inflammation, this was shown according to decrease in mediators and induced sputum eosinophils. Later studies corroborate part of these results in children. Accordingly, leukotriene receptor antagonists are considered alternative medications to low-dose, inhaled corticosteroids, and to chromoglycate and nedocromil acting, moreover, as "corticoid savers" in corticoid-dependent patients. In our setting, it is possible to find mantelukast (MK) and zafirlukast (ZK). In this sense, in patients aged more than 12 years, MK is administered in a single, daily dose at 10 mg, and ZK twice daily at 20 mg.

Corticosteroids (CS) are the most efficient antiinflammatory drugs for the treatment of airway inflammation. The mechanisms of primary action are interference in arachidonic acid metabolism and in leukotriene and prostaglandin synthesis thus directly preventing migration and activation of inflammatory cells, and increasing sensitivity and response of beta-receptors in bronchial smooth muscle. CS can be inhaled or systemic (oral or parenteral). Inhalation is the preferred mode of delivery of CS; moreover, inhaled CS combine high local antiinflammatory potency and lower incidence of side-effects.

In general, inhaled CS are well-tolerated and safe when used in the recommended dosages. However, recent studies have indicated growth retardation in children even with low-dose, transient CS administration. Corticosteroids control symptoms, decrease exacerbations and hospitalization, promote improvement of pulmonary function, and decrease bronchial hyperresponsiveness. Current clinical evidence indicate that early use of inhaled CS prevents irreversible structural alterations resulting from airway remodeling. In our setting, we have access to beclomethasone dipropionate, budesonide, triamcinolone acetate, flunisolide, and fluticasone propionate. The combination of intense, topical antiinflammatory action and absence of systemic action indicates ideal inhaled CS.

Systemic CS are mainly indicated for acute asthma exacerbations when the treatment applied is unsuccessful, or for patients with severe asthma and in treatment with inhaled CS. Early use of CS in severe asthma exacerbations can prevent progression of attacks, need for emergency care services, and for hospitalizations, hence decreasing disease morbidity. In addition, patients with severe asthma intractable with usual medication (including high-dose inhaled CS and long-acting beta-2-agonists) require regular and planned administration of oral CS.

Systemic CS are, preferably, administered short-term (seven to 10 days) followed by appropriate intervals without medication. In cases that require continuous, prolonged therapy it is always necessary to administer the lowest dose possible for control of symptoms with a single morning dose in alternate days. Preparations with intermediate half-life duration are recommended, such as prednisone, prednisolone, deflazacort, and methylprednisolone. Prednisone is the most widely used medication due to the shorter half-life and to causing less side-effects. The deflazacort has a milder effect on bone metabolism. It is always important to monitor patients in relation to side-effects of administration of CS.

Treatment scheme

The II Brazilian Consensus on Management of Asthma proposes that:

Treatment of mild asthma should be limited to episodes of acute exacerbations with administration of inhaled, short-acting beta-2-agonists. In case it is not possible administer inhaled medication, beta-2-agonists or theophylline can be
administered orally. In adolescents with exercise-induced asthma, it is possible to indicate previous use of chromoglycate or nedocromil.

The Consensus recommends administration of antiinflammatory agents for patients with moderate asthma. Positively, the CS are the main antiinflammatory agents and their action is rapid, conversely to the case of other pharmaceuticals. However, the possible side-effects following use of CS requires a more upclose and frequent follow-up of patients. For relief of symptoms, it is possible to administer, whenever necessary, inhaled short-acting beta-2-agonists (maximum of four times daily).

The treatment scheme for inhaled CS (metered-dose inhalers, dry powder inhalers) should be initiated with reevaluation of patients at every four to six weeks. If patient status is under control, the CS dose should be decreased gradually and, if possible, replaced with chromoglycate or nedocromil. If the patient status is not controlled, it is suggested that long-acting beta-2-agonists, or slow-release theophylline (8 to 9 mg/kg/day), be administered as an adjunct; patients should be submitted to reevaluation after three months. If improvement is observed, administration of theophylline and/or the beta-2-agonist should be interrupted, and of inhaled CS decreased. Next, the treatment should be replaced with chromoglycate or nedocromil. If patient status is not controlled, it is suggested that inhaled CS dosage be increased two-fold and maintained until the stabilization of patient clinical status. Upon reevaluation of patients, interrupting administration of pharmaceuticals should follow the opposite pattern of the scheme.

If the clinical status does not improve, patients should be reexamined as having severe asthma, in which case short-term administration of oral CS is recommended. In case long-term administration of CS is necessary, it is preferred to adopt alternate-day applications or to maintain the lowest dosage possible for control of clinical status. When clinical status is controlled, oral CS should be interrupted and suspension of other medication being administered should follow the same steps of moderate asthma treatment.

Initial dosage of inhaled CS varies from 500µg to 1,000µg of beclomethasone dipropionate (or equivalent medication) per day. The use of spacers is recommended, followed by oral hygiene for elimination of CS deposits in the oropharynx and thus decrease in CS dose intake.

Leukotriene antagonists have been indicated as alternative medication for severe asthmatic patients since they allow for decrease in need for CS and, especially, for low-dose inhaled CS.

Figure 1 shows the steps in pharmacological treatment of asthma according to the II Brazilian Consensus on Management of Asthma.\textsuperscript{1}

Special considerations regarding adolescence

Factors related to administration of the medication, including pathways, devices, and frequency, in addition to matters of side-effects, seem to present a decisive influence on the disposition of asthmatic adolescents to comply with the treatment.

As indicated above, inhaled administration of medication is, without question, advantageous considering that it allows for lower doses and, thus, for lower risk for side-effects. Use of valved spacers is also recommended since these devices, in addition to being efficient, are easy-to-use.\textsuperscript{1,2} But due to the large volume of these devices, adolescents usually do not comply with treatments that use them. Metered-dose inhalers and dry powder inhalers are easier to carry and tend to be more popular with adolescents. However, it is estimated that two-thirds of adults and half the children, even following proper instructions, do not use them adequately. Moreover, the greater the number of times the medication needs to be administered, the lower the compliance of patients with the treatment scheme.\textsuperscript{29}

These data corroborate the difficulty in maintaining disodium chromoglycate as an antiinflammatory, considering that it should be administered four times daily. On the other hand, inhaled CS are effective independently of severity of asthma and currently represent the most widely indicated treatment for moderate and severe asthma; inhaled CS, in this sense, should be administered twice daily.\textsuperscript{28} However, adherence to this treatment can be influenced by anxiety in relation to possible side-effects, especially in relation to growth.\textsuperscript{4} Usually, there is a physiological delay in puberty in asthmatic patients, independently of severity and of treatment established.\textsuperscript{30} In general, oral medication has good acceptance with adolescents.\textsuperscript{51}

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\caption{Stages of pharmacological treatment of asthma}
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Allergic rhinitis

Allergic rhinitis (AR) is defined as a syndrome clinically characterized by intense nasal itch, sneeze, nasal blockage, and coryza; such symptoms are a consequence of the intense inflammatory process affecting the nasal mucosa. In addition to these main symptoms, patients also complain of itchy eyes, ears, throat, palate; lacrimation; periorbital edema; photophobia; headache; sore throat; postnasal drip; feelings of heaviness in the head and plugged ear; loss of taste; hyposmia; fatigue; and weak concentration.32

Rhinitis can be perennial or seasonal. In perennial rhinitis, symptoms are manifest year-round. In turn, in seasonal rhinitis, symptoms are episodic and manifest during certain months of the year.33,36 The latter type of rhinitis is very rare in Brazil.33

Epidemiology

AR is currently one of the most common allergic diseases. Though its diagnosis is based on an array of symptoms of variable intensity, little is known about its epidemiology. AR has genetic characteristics with higher incidence on individuals whose parents are allergic, with no prevalence according to sex or race. AR can start manifesting itself at different ages and it is more frequent in older children and adolescents.33

ISAAC data collected in the city of São Paulo, Brazil, show a 34.7% prevalence of rhinitis for subjects aged six to seven years, and approximately 30% for those aged 13 to 14 years.34,35

Despite the fact that AR is understood as a highly prevalent disease, there are few studies reporting its effects on the quality of life of patients.33 It is known that AR patients, especially those with perennial AR, suffer from important restrictions to their daily activities - not only due to discomfort caused by nasal symptoms, but also due to that caused by related symptoms, such as headaches, overall feeling of discomfort, weak concentration, and sleeping disorders.32,33,36 In addition, among students and adolescents the limitation in social activities, often misinterpreted as apathy, distraction, and lack of interest, can cause negative effects on the emotional well-being of these patients.36

In adolescents with AR, the main reasons for low compliance with the treatment are inconvenience and embarrassment caused by use of nasal sprays. Thus, this group of patients requires special attention, and treatment approach should not be restricted to prescribing adequate medication. It is fundamental for teachers and peers of patients to become engaged in working towards a solution for the problem, considering that they exert an important influence on adolescents.36

Another important factor is that adolescents in general neither seek, nor make adequate use of, healthcare services; thus making it more difficult to provide the information and guidance necessary for control of the disease.36

Onset and deterioration factors

As in the case of asthma, the main onset and deterioration factors for AR attacks are allergens in ambient air (dust; mites; fungi; pet dander, urine, and saliva; cockroaches; and pollen). Strong odors and tobacco smoke are the main nonspecific allergens that cause onset of symptoms by nonimmune mechanisms.32

Treatment

Overall considerations

The main objective of AR treatment is to restore the nasal function while aiming at maintaining functional integrity of the whole airway system. Treatment should always be adapted to severity, frequency, and duration of symptoms and, also, to patient age, complications, and response to other previous treatments. In this sense, current AR treatment is based on two main principles: nonpharmacological treatment (ambient control measures and specific immunotherapy) and pharmacological treatment37 (Figure 2).

Nonpharmacological treatment

Ambient control

Ambient control measures for airborne allergens should always be applied, even if they are not fully effective, considering that these measures can improve patient clinical status and decrease need for pharmacological treatment. Accordingly, the measures are similar to those applied for asthma patients.1,37-39

Specific immunotherapy

Specific immunotherapy can be indicated in cases of perennial or seasonal AR in which the allergen causing the symptoms to appear is well-determined and rigorous ambient control and pharmacotherapy have not rendered satisfactory.37 Effectiveness of specific immunotherapy is checked against reduction in daily symptoms and in provoked nasal reactions with, for example, allergen extracts from grass pollen and mites (D. pteronyssinus). In turn, the use of nonspecific allergens such as fungal extracts present ambiguous effectiveness and should be restricted to controlled studies and research.37,39

Pharmacotherapy

Pharmacotherapy remains as one of the main allies in managing AR. It is used following failure to establish adequate ambient control or insufficiency of ambient control itself to reduce and control symptoms. Whenever possible, pharmacotherapy should be indicated prophylactically; in other words, administered before manifestation of symptoms.37-39
hematoencephalic barrier, thus not being able to sedate liposolubility and are rarely able to cross the more complex chemical structure. These agents present low among others.37-39
clemastin, dexchlorpheniramine, hydroxyzine, prometazine, and, thus, capable of crossing the hematoencephalic barrier, simple chemical structure. They are considerably liposoluble generation. The classical H1-antihistamines present a more classical, or first generation, and nonclassical, or second generation. The classical H1-antihistamines are particularly useful in the control of sneezing, nose itch and coryza; they have no effect on nasal blockage. The earlier the application of the medication, the more effective the action. Choice of H1-antihistamines should be individualized, based on the needs of each patient and on the experience of the attending physician.37-40

Continued use of H1-antihistamines can be followed by lack of beneficial effects. This phenomenon is called tolerance. The interruption of the treatment with H1-antihistamines and its replacement with other different agent can reestablish the H1-antihistaminic action.37,39

As to what concerns the activity of H1-antihistamines on the central nervous system, they are classified into classical, or first generation, and nonclassical, or second generation. The classical H1-antihistamines present a more simple chemical structure. They are considerably liposoluble and, thus, capable of crossing the hematoencephalic barrier, binding to H1 receptors in the CNS and sedating patients. Some of the classical H1-antihistamines available are clemastin, dextchlorpheniramine, hydroxyzine, prometazine, among others.37-39

In turn, the nonclassical H1-antihistamines present a more complex chemical structure. These agents present low liposolubility and are rarely able to cross the hematoencephalic barrier, thus not being able to sedate patients. In addition, these agents have a longer half-life that allows their administration in 12 or 24-hour intervals. Studies carried out with H1-antihistamines have shown, also, that prolonged use of these agents neither reduces effectiveness nor induces tolerance. The new generation of H1-antihistamines includes cetirizin, ebastine, epinastine, fexofenadine, loratadine, and mequitazine available for oral administration. For topical use, there are the azelastine, and levocabastine, all of which present important local action blocking itch, sneezing, and coryza but with little effect on nasal blockage.37-39

The astemizole and the terfenadine were taken out of the world market due to their cardiac side-effects (Torsades de Pointes, arrhythmia, and prolonged QTc interval) when administered in doses higher than recommended or when in combination with drugs that use the same hepatic metabolic pathways, such as the case of the azole antifungal agents (for example, fluconazole, itraconazole, and miconazole) and of some macrolides (for example, erythromycin and claritromycin).32,37

It is important to underscore that many H1-antihistamines are also capable of reducing, in vitro, the release of mediators of mast and basophil cells; moreover, some H1-antihistamines also present the capacity of reducing, in vitro, the capacity to decrease migration of eosinophils. This type of action of H1-antihistamines is not related to blocking of H1-receptors and is apparently the result of a direct effect of the concentration of the pharmaceutical. There is no evidence that these mechanisms are clinically relevant considering the dosage used for the treatment of rhinitis. Loratadine, cetirizine, azelastine, ketotifen, chlorpheniramine, diphenydramine, azatadine, and epinastine are some of the examples of H1-antihistamines that manifest this type of action.39,40

The nasal decongestants present agonist and beta-adrenergic properties and reduce nasal blockage; however, they have not effect on coryza, sneezing and nasal itch. The decongestants can be administered in drops or nasal spray (for example, naphazoline and oxymethazoline) or orally (for example, ephedrine and pseudoephedrine). Topical nasal decongestants should not be administered for over seven to 10 days, since there is the possibility for rebound congestion after prolonged use of the medication, which can be followed by rhinitis medicamentosa and atrophic rhinitis.37-39

Infants and small children can absorb the imidazolic derivatives causing depression of the CNS, coma, and hypothermia. In small children, these derivatives can be used to facilitate sleeping during rhinitis exacerbations and to allow for introduction of topical CS.32

Oral decongestants, in turn, even when used for prolonged periods of time, do not have a rebound effect.37,39 In our setting, oral decongestants are available only in combination with H1-antihistamines. Oral decongestants should be applied with caution to pediatric patients and parents should be oriented to decrease dosage or even

In addition to nasal hygiene with saline solution, the other elements in the arsenal for the treatment of AR are H1-antihistamines, decongestants, anticholinergics, chromones, and corticosteroids.32,37-39

H1-antihistamines (classical and nonclassical) compete with histamines for H1 receptors representing, thus, a fundamental therapeutic ally against AR symptoms. In practice, they can be used for both relief of acute, intermittent symptoms and in the prolonged treatment of perennial rhinitis. H1-antihistamines are particularly useful in the control of sneezing, nose itch and coryza; they have no effect on nasal blockage. The earlier the application of the medication, the more effective the action. Choice of H1-antihistamines should be individualized, based on the needs of each patient and on the experience of the attending physician.


Figure 2 - Treatment schemes for allergic rhinitis

<table>
<thead>
<tr>
<th>Mild Rhinitis</th>
<th>Moderate Rhinitis</th>
<th>Moderate Rhinitis + Conjunctivitis</th>
<th>Severe Rhinitis + Conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid allergens, if possible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral / intranasal H1 antihistaminic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids and/or Anti-H1 drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromoglycate or topical anti-H1 / Decongestants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>± Oral corticosteroid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific Immunotherapy should be considered</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
interrupt administration of the drug in the presence of undesirable side-effects, such as hypothermia, sedation, and sleepiness.\textsuperscript{32}

In general, these drugs should be used as an adjunct therapy for symptomatic treatment in patients with several blockage; however, the use of oral decongestants does not exclude the need for more specific treatments.\textsuperscript{37-39}

Anticholinergic agents are drugs capable of inhibiting muscarine receptors. These receptors are important for the production of nasal secretion but have little or no role in vascular control and do not act on nerve sensory terminals. In this sense, anticholinergic agents can be useful in the control of coryza, but do not act on nasal blockage, sneezing or nasal itch.\textsuperscript{37,39} In our setting, the anticholinergic agent available for topical nasal use is ipratropium bromide, which can be used after 12 years of age.

Similarly to the vasoconstrictors, the topical anticholinergic agents should be used as an additional symptomatic treatment in the more resistant cases.\textsuperscript{37,39}

The disodium chromoglycate and the sodium nedocromil are antiinflammatory drugs capable of stabilizing, in vitro, the mast cell membrane and thus inhibit the release of histamine by these cells. These drugs are also capable of inhibiting the chemotaxy of eosinophils and neutrophils on the inflammation site and thus reduce inflammation. Their effects are optimized when administered before the exposure to allergens.\textsuperscript{39}

In Brazil, only the disodium chromoglycate is available for topical nasal use; this medication presents a relative effectiveness in cases of mild to moderate AR severity, with relief of itch, coryza, and sneezing but with no important effect on nasal blockage.

Disodium chromoglycate is a very safe medication, with practically no side effects and that can thus be applied during infancy. One of its great disadvantages is that, in order to maintain the desired effect, it requires repeated application during the day; oftentimes, this disadvantage results in low compliance with the treatment. The use of the nasal solution of disodium chromoglycate is recommended at 2 or 4\textsuperscript{\%}.\textsuperscript{37-39}

The symptoms of AR are a result of accumulation and activation of inflammatory cells with release of chemical mediators, resulting in an inflammatory process. In this sense, considering that CS are potent antiinflammatory agents, they assume an important role in the treatment of rhinitis, showing effectiveness in reducing the infiltration of inflammatory cells, the number of mast and eosinophil cells (especially) in the nasal mucosa; hyperresponsiveness and vascular permeability; and release of mediators by mast cells. This medication can be applied with topical or systemic administration (oral or parenteral).\textsuperscript{37,39,40}

Modern nasal topical CS present characteristics of high therapeutic effectiveness, which allows for a greater local effect at the expense of minimal systemic effects. This type of medication can be applied for prolonged periods of time, conversely to topical decongestants.\textsuperscript{37,39} Moreover, these CS reduce intensity of all symptoms, including nasal blockage; their optimal therapeutic effect is observed after the second week of use. In patients with concurrent edema in the mucosa, the use of other pharmaceuticals as adjuncts should be considered, especially the combination H1-antihistamines and oral decongestants or, still, topical decongestants (for a maximum of 10 days).\textsuperscript{37-39} As a result of reducing nasal blockage, these combinations improve sleeping and decrease abandonment of treatment.

In Brazil, beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, and triamcinolone are available in freon-propelled aerosol or in atomizers with aqueous solutions.

Though topical CS can be effective and safe, prolonged use can allow for local side-effects (more frequent when used in the form of aerosol) including: irritation, bleeding, sneezing, dryness, burning, scaling, and, very rarely, soreness to perforation of the nasal septum. Systemic absorption of the drugs is minimal when administered in the recommended dosage; reports of inhibition of the hypothalamic-pituitary-adrenal axis are very rare.\textsuperscript{37,39}

Once symptoms are controlled in the patient, it is recommended to decrease topical CS dosage and resume administration of the initial stages of treatment.\textsuperscript{37-39}

Short cycles of oral CS can be used in severe and urgent cases or, still, in the presence of chronic sinusitis or intense rhinitis exacerbations. These drugs should always be administered with precaution and in case there are no absolute contraindications. Whenever possible, an additional medication should be used as an adjunct for control of symptoms, thus allowing for lower doses of steroids and maintenance of symptomatic control after the effects of the medication have ceased. Consequently, when use of CS is necessary, it is recommended to administer those with intermediate half-life duration, such as: prednisone, prednisolone, methylprednisolone, and deflazacort. Preference should always be given to treatment schemes with single morning doses for a maximum of seven to 10 days.\textsuperscript{37-39}

In general, the use of parenteral drugs that cause deposition is not recommended considering that, though effective, they can cause severe side-effects that are difficult to reverse; moreover, they inhibit the adrenal cortex function for long periods of time.\textsuperscript{37}

Final comments

The relationship between asthma and rhinitis can be verified in the facts that: a) millions of people suffering from both AR and asthma; b) AR with partial or complete obstruction of upper airways can contribute significantly to asthma; and c) proper management of AR helps to improve rhinitis and coexisting asthma. Sinusitis is commonly associated with rhinitis and asthma, and it is an important determinant factor for the severity of asthma; moreover, its treatment is related to the reduction of the severity of
asthma, especially in children. Patients with combined asthma and rhinitis should be submitted to treatment of both; to be sure, that is the only way to ensure better effectiveness and control, especially of asthma.

References

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