Rhinitis, Sinusitis and Asthma: hard to dissociate?*

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ABSTRACT
The objective of this study was to review the literature and to discuss epidemiological and physiopathological aspects and therapeutical implications of an unified approach to allergic rhinosinusitis and asthma. The bibliographic survey was based on the information provided by the following databases: Medline, MD Consult, Highwire, Medscape, LILACS and through direct search over thirty years, using the terms allergic rhinitis and asthma. Fifty-five original articles were selected in the no systematically review addressing the issue of clinical association between allergic rhinosinusitis and asthma. It is noteworthy that in the late years, with the use of specific topical medications for the lower airways or else, to the upper airways, the therapeutical approach has been distinct. However, numerous epidemiological surveys, immunopathological and clinical studies demonstrate the inter-relationship between asthma and allergic rhinosinusitis, characterized by: i) allergic rhinitis is associated to asthma and constitute an independent risk factor for its occurrence; ii) the immunopathological characteristics of allergic rhinitis and asthma are similar; iii) allergic rhinitis and asthma are manifestations of a systemic disease; iv) control of rhinitis favors asthma control. taking into consideration the close inter-relationship between allergic rhinitis and asthma, the approach to diagnosis, treatment and prophylaxis of these illnesses should be integrated. Therapeutical options that allow for the simultaneous control of asthma and allergic rhinitis offer advantages related both to costs and tolerability.

Keywords: Asthma/epidemiology; Asthma/physiopathology; Asthma/drug therapy; Sinusitis/epidemiology; Sinusitis/drug therapy; Sinusitis/physiopathology; Rhinitis, allergic, perennial
INTRODUCTION

The clinical association between allergic rhinitis and asthma has been recognized for centuries. However, in recent years, the increased use of inhaled substances designed specifically to treat the upper or lower airways has resulted in distinct differences between the therapeutic approaches to treating the upper airways and those taken to treat the lower airways. The introduction of terms such as “allergic rhinobronchitis” and “united airways disease” into the literature might facilitate the assimilation of the concept of contiguous allergic inflammation of the airways or, at least, might serve to alert the professionals who exclusively treat the lower airways to the fact that it might be necessary to also treat the upper airways - and vice versa.(1)

With the increase in the number of epidemiological studies regarding the coexistence of allergic rhinitis and asthma, the importance of upper airway infections as an exacerbating factor for asthma has been widely discussed, as has the presence of rhinitis as a risk factor for sinusitis.(2)

Despite the differences in the geographic distribution and epidemiological associations among asthma, rhinitis, and sinusitis, the coexistence of asthma, rhinitis or sinusitis has been observed since the time of Galen.(3) This fact has been interpreted as indicating that these are two distinct diseases or that these two conditions are manifestations of the same disease which simultaneously attacks the upper and lower respiratory tracts, probably due to common risk factors and pathogeneses, which appears to be more evident.

Based on these findings, specialists from several countries, together with the World Health Organization, have prepared a document on allergic rhinosinusitis and its impact on asthma, entitled Allergic Rhinitis and Its Impact on Asthma. This document had the following objectives: to update knowledge regarding allergic rhinitis; to draw attention to the impact of allergic rhinitis on asthma; to provide evidence-based results regarding diagnostic methods and available treatments; to evaluate the magnitude of the problem in developing countries.(4-5)

Within this context, the objective of the present study was to review the epidemiological aspects, pathophysiological aspects and therapeutic implications related to this unified approach to allergic rhinosinusitis and asthma.

METHODS

A nonsystematic review of the literature over the past thirty years was carried out, based on the information available from various databases, including the following: Medline, MD Consult, Highwire, Medscape and Literatura Latinoamericana y del Caribe en Ciencias de la Salud (Latin American and Caribbean Health Sciences Literature). Direct searches were conducted using the terms ‘allergic rhinitis’ and ‘asthma’.

RESULTS AND DISCUSSION

Evidence of the associations among respiratory tract diseases has led to the united airways disease hypothesis.

Epidemiology

Numerous studies have documented the coexistence of allergic rhinitis and asthma.(1-5) It is estimated that 60% to 78% of asthma patients suffer from allergic rhinitis.(1-5) In addition, allergic rhinitis has been recognized as a risk factor for the development of asthma in approximately 20% to 38% of cases.(6) Based on recent results obtained through questionnaires applied to patients with asthma, these percentages are probably below the true frequency.

In a study involving 475 individuals with asthma (adolescents and adults), a high prevalence of allergic rhinitis was found, and, based on that, the authors suggested the denomination "united airways disease" to describe this syndrome.(7-8)

In a complementary fashion, the International Study on Asthma and Allergies in Childhood showed that, on a worldwide scale, the prevalence of symptoms associated with rhinosinusitis ranged from 0.8% to 14.9% among children from six to seven years of age, and from 1.4% to 39.7% among those from thirteen to fourteen years of age.(9) The same study revealed that the comorbidity between asthma and rhinitis can reach 80%.(9) The authors also stated that patients with asthma frequently present nasal symptoms that are more difficult to control than is the asthma itself.(9) There are difficulties involved in studying the inter-relationship between diseases of the upper respiratory tract and those of the lower respiratory tract, due to the limitations of basic laboratory resources for their diagnosis. However, epidemiological studies have
contributed to defining the relationships among sinusitis, rhinitis and asthma through identifying possible risk factors, describing the natural histories and determining the prognoses for these diseases.\(^{(3)}\)

Sinusitis is commonly associated with asthma, and evidence suggests a cause-and-effect relationship, rhinosinusitis being capable of triggering or exacerbating asthma. It has been shown that 30% to 70% of asthma patients have experienced at least one episode of sinusitis, whereas 34% of patients with sinusitis also have asthma.\(^{(3)}\)

However, the inter-relationship between these entities has yet to be defined, since there have been no appropriately controlled observational studies.\(^{(3)}\)

A multicenter study carried out in 31 countries in Europe, the USA and Oceania involved 90,478 adults between twenty and forty-four years of age, analyzing asthma and rhinosinusitis symptoms. Of those 90,478 subjects, 10,210 participated in a follow-up clinical study to identify individuals with asthma and rhinosinusitis. At the study endpoint, both the epidemiological survey and the clinical profiles demonstrated that rhinosinusitis is the leading isolated predictor of the development of asthma.\(^{(10-11)}\)

Using a prospective study design, another group of authors tested the hypothesis that rhinitis is a risk factor for asthma in adults. The study was conducted over a twenty-year period, monitoring 173 patients who stated that they did not have asthma prior to the study outset. Those who presented the disease after the age of twenty were compared with 2,177 controls. The results demonstrate that allergic rhinitis increased the risk of asthma in adults by four times.\(^{(12-13)}\)

**Pathogenesis of "allergic respiratory disease of the united airway"**

The relationship between the upper and lower airways has been described since the XIX century. In 1870, Kratchmer conducted an experimental study and observed that chemical irritation of the nasal mucosa resulted in bronchoconstriction in cats and rabbits.\(^{(14)}\)

In a study of the inflammatory mechanisms of the upper and lower airways, 8 patients with pollen-specific allergic rhinitis (but without asthma) were submitted to bronchial provocation tests, together with 8 healthy controls. The authors observed a decrease in the parameters of the pulmonary function tests and nasal function tests, as well as increased numbers of eosinophils in the nasal and bronchial mucosae after bronchial provocation in the rhinitis patients.\(^{(15)}\) They concluded that there was an inflammatory response throughout the respiratory tract in the patients with rhinitis, whereas no alterations were observed in the control group patients.\(^{(15)}\)

The same group of researchers also submitted a similar group of subjects (9 patients with allergic rhinitis but without asthma and 9 healthy controls) to nasal antigen provocation tests. They detected an increase in eosinophils and adhesion molecules in the nasal and bronchial mucosae of the patients with allergic rhinitis after the nasal antigen provocation. These findings reinforce the hypothesis that contact with an antigen via the upper respiratory tract results in inflammation of the entire airway.\(^{(16)}\)

In a study of 27 adult subjects: (9 presenting both diseases, 8 presenting asthma without rhinosinusitis and 10 healthy controls), the relationship between allergic rhinitis and asthma was also demonstrated through nasal and bronchial biopsies, as well as eosinophil counts. Eosinophil counts were the same in the patients with asthma only as in those presenting both diseases but were significantly lower in the control group patients. These results suggest that asthma and rhinitis are a single disease.\(^{(18)}\)

In another study, involving patients with severe asthma, tomography was used to show that the degree of chronic sinusitis is directly related to the degree of lower airway inflammation and to the severity of eosinophilia. These results suggest that asthma is a systemic disease and is not restricted to the respiratory tract.\(^{(19)}\)

Based on various studies, one author defined chronic allergic inflammatory airway disease as a disease presenting a broad spectrum of severity, capable of inducing asthma or rhinosinusitis. The milder cases would present rhinosinusitis alone, and the most severe cases would present rhinosinusitis.
accompanied by asthma.\(^{20}\) For anatomical reasons, the primary target of allergens and environmental chemical irritants is the upper respiratory tract. After impairment of the entire respiratory tract, rhinitis and asthma follow parallel courses. In order to test the hypothesis that asthma and rhinosinusitis are manifestations of a single disease, the researcher postulated that the following premises should be evaluated: allergic rhinitis coexists with allergic asthma; allergic rhinitis is a predisposing factor for asthma; patients with asthma and rhinitis present rhinitis that is more severe than that seen in patients who present rhinitis in isolation; and, finally, among the patients with asthma who present rhinitis, the asthma profile is more severe in those individuals with more accentuated rhinitis.\(^{21-22}\)

The role of the environment

In susceptible patients, exposure to allergens produces severe bronchoconstriction, which can be followed by a late asthma response a few hours after the contact, producing nonspecific hyperresponsiveness of the nasal and bronchial airways for some days or even weeks. Continuous exposure to small quantities of allergens present in house dust can produce a chronic inflammatory response, resulting in long-term bronchial hyperresponsiveness. The role of the allergens in house dust as triggering agents of asthma exacerbations is well-known, especially the Dermatophagoides pteronyssinus, the principal allergen in house dust. An eight-week randomized controlled study determined the beneficial effect that rigorous environmental control measures against house dust allergens have on airway hyperresponsiveness. These measures even included applying liquid nitrogen in the room of the patients. It is noteworthy that all of the patients studied had previously tested positive for allergy to D. pteronyssinus. The group that avoided contact with dust presented improvement in their symptoms score and a greater number of daily wheeze-free hours, as well as increases in peak expiratory flow and in dose level provoking a 20% drop in forced expiratory volume in one second (DL20). These results demonstrate that control measures to minimize contact with house dust, combined with an initial application of liquid nitrogen in the room of the patients, reduces airway hyperresponsiveness and facilitates disease control. Although the use of liquid nitrogen is impracticable outside of the research environment, the researchers pointed out that the use of chemical acaricides can be a practical solution for the control of domestic allergens in the future.\(^{2}\)

However, in a recent systematic review of the literature, it was concluded that the definition of adequate environmental control measures for asthma patients has yet to be investigated.\(^{24-25}\)

In the city of Camaragibe, Brazil, households in which children and adolescents with asthma lived were evaluated regarding environmental control. The guidelines were followed by 67% of the patients with asthma. However, there was no significant correlation between adequate environmental control and lower frequency of asthma attacks. One significant finding of this open study was the high level of compliance with the instructions. The authors interpreted this as evidence that there is no significant association between environmental control and lower frequency of asthma attacks.\(^{26}\)

Similarities and differences between nasal and bronchial mucosae in asthma and rhinitis

It is known that nasal and bronchial mucosae present morphological similarities and differences. In healthy individuals, the nasal and bronchial mucosae present similar structure, the former with a great supply of subepithelial capillaries, arterial systems and cavernous venous sinusoids, whereas smooth muscles is found from the trachea to the bronchioles.\(^{27}\)

Regarding embryology, the origin of the nose is ectodermic, whereas that of the bronchi is endodermic. Physiologically, the nasal and bronchial epithelial cells differ in terms of their cohesion. In inflammation of the airway mucosa, the inflammatory infiltrate seen in asthma is similar to, albeit of a different magnitude than, that seen in rhinitis: the nasal eosinophilic inflammation is universal in patients with asthma, independent of the clinical presentation, with or without nasal symptoms.\(^{24-27}\)

Airway remodeling

Remodeling means 'to model again' (in a form that differs from the original) but also has the meaning of 'to rebuild'. It can be observed in inflamed tissues in the nasal as well as the bronchial mucosae of patients with asthma and allergic rhinitis.\(^{27}\) It is considered an important factor in the pathogenesis of airflow obstruction and of bronchial hyperresponsiveness in patients with asthma.\(^{28-29}\) It is seen to a lesser extent in the noses of individuals with rhinitis than in the bronchi of those with asthma.

In 1992, it was suggested that bronchial
remodeling be recognized as an essential component of asthma. Bronchial remodeling is a complex process that involves factors of bronchial inflammation, resulting in structural alterations (thickening of the bronchial wall) or functional alterations (irreversible airflow obstruction). The principal components of asthma-related bronchial remodeling are as follows: alteration of the deposition/degradation of extracellular matrix components; neovascularization of the submucosa; hypertrophy and hyperplasia of the smooth muscle; hyperplasia of mucous glands; hyperplasia of goblet cells; and alterations of the bronchial epithelium.\(^{(30)}\)

It has been demonstrated that remodeling of the lower airways occurs in patients with rhinitis in isolation, as well as in patients with rhinitis and asthma. Further studies are necessary in order to characterize this process in the nasal mucosa.\(^{(31-32)}\)

**Immunopathology and the involvement of the bone marrow as an explanation for the single disease of the airways**

In asthma, the bronchial inflammation is measured principally by the T helper-2 lymphocyte (TH2) that secretes cytokines, involved in the allergic inflammation, in addition to B lymphocyte stimulators, which are responsible for the production of IgE and other antibodies. T helper-1 lymphocytes (TH1) predominantly produce interferon gamma and interleukin-2. TH1 cytokines and TH2 cells tend to be reciprocally regulatory. When this balance is upset it may explain the physiopathology of asthma. There is experimental evidence that when the TH2 lymphocytes are free from the restrictive influence of interferon gamma, they provoke inflammation of the airways.\(^{(33-34)}\) Recently, some authors researched the T-bet, a transcription factor that induces the differentiation of T helper cells in TH1, and is important for the production of interferon gamma. The T-bet was not found in interbronchial lymphocytes of patients with asthma. However, it was detected in the control patients.\(^{(14)}\) This finding suggests a modulating role of the interferon gamma in asthma, and is coherent with the hypothesis that an imbalance between TH1 and TH2 may contribute to the occurrence of asthma.\(^{(15)}\)

Through bronchial biopsies in 8 adult patients with seasonal rhinitis, one group of authors quantified the cytological values and the cytokines during and after the pollen season. Greater concentrations of interleukin-5, lymphocytes and eosinophils were identified in the bronchi of the patients with allergic rhinitis during the season associated with rhinitis. The authors even speculated that rhinitis can constitute a risk factor for the development of asthma in predisposed individuals.\(^{(36)}\)

Although there is epidemiological, neurophysiologic and clinical evidence about the relationship between allergic rhinitis and asthma, the mechanisms known today do not explain the cellular recruitment by the same pathway, both upper and lower respiratory tracts. A study highlights the role of the bone marrow in providing inflammatory cells for the upper and lower airways.\(^{(37)}\)

Various clinical studies in patients with allergic rhinitis, with or without asthma, atopic eczema or nasal polyps, have demonstrated a stimulation of basophils/eosinophil progenitors in the peripheral blood, with fluctuations related to the symptomatology, seasonal allergen exposure and extension of the atopy. There is evidence of the capacity of inflamed upper respiratory airways of patients with allergic rhinitis or nasal polyps of producing hematopoietic growth factors that guide the differentiation and maturation of basophils/eosinophils and of mastocytes progenitors. This means that the airway mucosa is able to promote the differentiation of progenitors of inflammatory cells found in the circulation.\(^{(37-38)}\)

In a study involving canine models, expression of myeloid progenitors was observed as a bone marrow response to bronchial provocation, which was accompanied by cell division, both in the blood as in the bronchoalveolar lavage fluid, suggesting a direct link between the lung and the bone marrow in the allergic inflammatory processes of the airways. This bone marrow response can be blocked by pretreatment with inhaled steroids and suggests that topical corticosteroids have a systemic effect on cell recruitment to the airways. These findings have been recently confirmed in humans. It was also reported that basophil/eosinophil progenitors present receptors for interleukin-5, a hematopoietic growth factor, which can be a marker of bone marrow progenitor production. In the near future, therapies specific to the bone marrow will be considered for the treatment of chronic inflammation, for patients with rhinitis as well as for those with asthma.\(^{(37-38)}\) The author of the canine model study stated that asthma and rhinitis are both parts of the same systemic process, in which the bone marrow contributes actively, interacting with
hematopoietic tissue signals, which maintain the chronic airway inflammation. Eosinophils and their progenitors can acquire a self-stimulating phenotype, producing their own growth factor and perpetuating the inflammatory process in asthma and rhinitis.\(^{37}\)

**Immunotherapy**

The treatment of allergic diseases is based on general principles of environmental control, drug therapy, immunotherapy and patient education. A recent study presented specific immunotherapy (SIT) and the monoclonal anti-IgE antibody as promising treatments for allergic rhinitis and asthma, with long-term benefits, if appropriate doses of standard allergens are administered. However, there are problems associated with SIT, in particular, there is a risk of anaphylactic reactions. In addition, the clinical effect may be incomplete in the first year of treatment, especially in polysensitized patients.\(^{38}\)

The monoclonal anti-IgE antibody induces the reduction of serum-free IgE levels in humans and reduces the symptoms mediated by this immunoglobulin, independent of the allergic specificity of the IgE involved. Anti-IgE has been shown to be efficacious in reducing the severity of the symptoms of seasonal allergic rhinitis and of asthma, provided that it is administered via subcutaneous injection, from every two hours to every four weeks.\(^{37}\) There are studies reporting that anti-IgE reductions the need to use antihistamines for rhinitis and inhaled corticosteroids for asthma. In a randomized double-blind study involving children and adolescents with seasonal allergic rhinitis, SIT used in conjunction with IgE was found to result in 48% fewer symptoms than did the use of SIT alone. The additive effect of immunotherapy combined with anti-IgE reflects the complementary manner in which these immunobiological products interact. Whereas SIT is an active immunizing agent, anti-IgE reduces the immune response by decreasing the serum levels of free IgE. The clinical response to SIT generally requires years to become fully effective. Initially, while the response is incomplete, anti-IgE could be used as an additive in the treatment of allergic diseases.\(^{39-40}\)

In a study comprising cases from six European pediatric hospitals, 205 children with seasonal rhinitis were analyzed, of which 97 received immunotherapy with pollen antigen for three years, and 108 were used as controls. At the end of the study, it was observed that the immunotherapy acted in the prevention of asthma symptoms and in the reduction of the symptoms of allergic rhinitis.\(^{41}\)

The aforementioned studies notwithstanding, it is important to stress that the current evidence suggests that inhaled, nasal corticosteroids should be used to manage asthma and allergic rhinitis, and that immunotherapy should be reserved for specific situations.

**Clinical and therapeutic implications**

Despite the evidence of the inter-relationship between asthma and allergic rhinitis, in current clinical practice, there is resistance to recognizing the association between allergic rhinosinusitis and asthma, as well as to acknowledging that the treatment of one induces the improvement of the other. These findings emphasize the importance of medical education in the assessment and concomitant treatment of both.\(^{42}\)

Allergic rhinitis is a disease that affects individuals in the productive period of their lives and can be prejudicial, since it results in absenteeism, at work or at school.\(^{43}\) It causes significant discomfort to the patient and requires active intervention.

Two observational studies recently demonstrated that the treatment of allergic rhinitis in patients with asthma and rhinitis reduces the number of emergency room visits, as well as the number of hospitalizations, due to asthma.\(^{44-45}\) In a three-year retrospective cohort study, 13,844 patients over five years of age were identified as having been diagnosed with asthma.\(^{44-45}\) The association between asthma and rhinitis was demonstrated through the use of intranasal corticosteroids or oral antihistamines. The rate at which patients sought emergency medical care was lower among the patients who were being treated for rhinitis.\(^{45}\) Another retrospective cohort study was conducted with the aim of determining the frequency of hospitalizations and emergency room visits among asthma patients with rhinitis. The authors observed 4944 rhinitis patients, from twelve to sixty years of age, treated with antihistamines and nasal corticosteroids. A higher incidence of asthma exacerbations was observed among the patients who were not being treated for rhinitis. This study, however, presents some limitations, as the authors themselves pointed out: the use of inconsistent diagnostic algorithms, which resulted in the inclusion of patients who had received diagnoses that were incorrect/unclear, as well as of those who were using oral corticosteroids for reasons other than asthma and
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Antagonists of inflammatory mediators, such as histamine, partially neutralize the allergen-induced airway obstruction. However, the limited protection provided by the antihistamines, in the prevention or relief of bronchoconstriction, inspired a search for other important mediators in the physiopathology of asthma. Some substances, such as thromboxane A2 or the platelet activating factor, have marked effects on the airways but seem to have no effect on allergen-induced alterations, since the antagonists of these substances produce little or no inhibition of the immediate and late phases of asthma. However, scientific evidence has indicated that leukotrienes are coadjuvants of histamine in the obstructive phenomenon of asthma, and that leukotriene antagonists act in the inhibition of the reaction in the immediate phase. However, in the late phase, the leukotriene antagonist effect varies.

Chronic sinusitis and asthma are entities in which there are these similar inflammatory reactions and that frequently coexist. In a classic study, 48 children who had presented cough and wheezing for a minimum period of three months, together with alterations suggestive of sinusitis in the X-ray of the facial sinuses, were treated (for sinusitis) with antibiotic therapy or, when called for, antibiotic therapy combined with surgery. After this phase, it was possible to suspend the topic steroid of all the patients and the bronchodilator of 38 children (79% of the total). The authors concluded that sinusitis can be an aggravating factor for bronchial hyperresponsiveness, and that the treatment of the sinusitis improves the asthma symptoms. In a study conducted in Brazil, 66 children were recruited in order to evaluate the clinical response and bronchial hyperresponsiveness to methacholine after the clinical treatment for sinusitis. Children with allergic rhinitis were compared with children with rhinitis and asthma, and with normal children, subdivided in groups with and without sinusitis. Sulfamethoxazole-trimethoprim, nasal saline solution, prednisone, antihistamine and nasal decongestant were all used in the treatment. The bronchoprovocation tests performed before and 30 days after the treatment demonstrated that improvements in pulmonary function occurred only in the patients with asthma and rhinitis treated for sinusitis. It was concluded that the opacity of one or both maxillary sinuses justifies the treatment of sinusitis, since there is improvement of the symptoms and relief of bronchial hyperresponsiveness. However, both were open, uncontrolled studies, and the patients used systemic corticosteroids. Therefore, the improvement presented may be a consequence of the systemic effect of this medication, which is more perceptible in patients who are more symptomatic.

| Chart 1 - Conduct in rhinosinusitis and asthma according to the paradigm established in chronic allergic respiratory disease |
|---------------------------------|---------------------------------|
| **Epidemiology** | **Old view (fragmented)** | **Current view (integrated)** |
| | Similar, strong association, possible cause-and-effect relationship | Similar, strong association found in allergic and nonallergic rhinitis, manifestations of the same disease |
| **Pathogenesis** | Frequent atopy in rhinitis and asthma, Eosinophils | Chronic inflammation, high IgE, activation of mastocytes in rhinosinusitis and in asthma, systemic Disease |
| **Diagnosis** | Emphasis on imaging examinations to investigate possible etiologic agents of rhinosinusitis, such as bacterial agents, which would make the asthma difficult to control | Investigation of rhinosinusitis symptoms in patients with asthma and of asthma symptoms in patients with rhinosinusitis. Understanding that rhinosinusitis is present in almost all asthma patients and that an accentuated thickening of the sinus mucosa can result from allergic inflammation |
| **Treatment** | Use of nasal and inhaled topical medications for the treatment of rhinosinusitis and of asthma, overuse of antibiotic therapy for the treatment of rhinosinusitis | The use of nasal and inhaled topic medication; search for a unified treatment: use of oral antihistamines, antileukotrienes, anti-IgE, immunotherapy, nasal inhalation of corticosteroids |
or in those who present bronchial hyperresponsiveness. The proper use of nasal corticosteroids relieves the seasonal symptoms of asthma, exertion-induced bronchoconstriction, and airway responsiveness, as well as improving peak expiratory flow, in patients with rhinitis and asthma. Oral antihistamines, with or without decongestants, can provide at least a transient improvement in pulmonary function.\(^{[50-51]}\)

In a randomized, double-blind study involving 21 patients between the ages of seven and seventeen, all with mild asthma and allergic rhinitis, intranasal beclomethasone was compared to a placebo in terms of their effects on bronchial responsiveness. The patients were treated with beclomethasone or intranasal placebo and were monitored by measuring their peak expiratory flow. The methacholine bronchoprovocation testing performed before the initiation of treatment and at the end of the treatment, demonstrated a lessening of the symptoms of asthma and allergic rhinitis, as well as reduced bronchial hyperresponsiveness. The authors concluded that a clear relationship exists between the upper and lower airways, although they admitted that the mechanism of interaction remains unknown.\(^{[10]}\)

In another study, 18 adult patients with a history of seasonal allergic rhinitis and asthma, together with bronchial hyperresponsiveness to methacholine, were treated, throughout the pollen season, with intranasal beclomethasone or with a placebo in order to evaluate the effect of the treatment on bronchial responsiveness and on the clinical parameters of asthma. The patients under active treatment presented less bronchial hyperresponsiveness at the end of the treatment than did those receiving the placebo. These results provide additional evidence that allergic rhinitis can provoke significant effects in the lower airways and should therefore be investigated and addressed in all patients with asthma.\(^{[52]}\)

In a randomized study conducted in Brazil, 78 children between five and seventeen years of age with allergic rhinitis and asthma were evaluated in terms of the efficacy of the use of 500 g of beclomethasone dipropionate, administered via a facial mask (with nasal inhalation). The control group received 200 g of beclomethasone dipropionate in intranasal aqueous solution and 500 g of beclomethasone dipropionate through a spacer connected to the mouth piece. Clinical score, peak inspiratory nasal flow, peak expiratory flow and forced expiratory volume in one second were used as parameters in the evaluation of the two treatment modalities. Since there were no significant differences between the groups, the authors suggested that this alternative form of treatment would be useful in patients presenting asthma-allergic rhinitis comorbidity, especially in developing countries.\(^{[53]}\)

It is thus necessary to treat both allergic rhinitis and asthma in order to control the symptoms and improve the quality of life of the patients. However, the Brazilian situation, as is the case in other developing countries, often makes it difficult to provide thorough and proper drug treatment of the airway disease, whether for the control of rhinitis or of asthma, underscoring the importance of prioritizing the treatment of inflammation of the lower airways.\(^{[53]}\)

Final comments

The idea that asthma and rhinitis are distinct entities has been gradually supplanted by the concept that they represent a continuum of inflammation, involving the respiratory tract as a whole, spanning time and space in the life of the patient. Epidemiologic studies and clinical trials have unequivocally demonstrated the relationship between asthma and allergic rhinosinusitis. Further studies are needed in order to clarify the mechanisms involved in the interaction between the upper and lower airways.

![Figure 1 - Three different phases in the evolution of the understanding of the inter-relationship between rhinitis and asthma](image-url)
Based on this paradigm - asthma and rhinitis as a single disease\textsuperscript{1-5,33-50} - the approaches to diagnosis, treatment and prophylaxis should be simultaneous and integrated. Therefore, we should highlight the importance of developing pharmacological agents or methods of administration of inhaled corticosteroids that are capable of treating upper and lower airway inflammation simultaneously, thereby potentially reducing costs and providing better quality of life for the patients.

REFERENCES

32. Braunstahl GJ, Fokkens WJ, Overbeek SE, KleinJan A, Hoogsteden HC, Prins JB. Mucosal and systemic


