

LITERATURE REVIEW

Links between allergic rhinitis and asthma

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ABSTRACT

Rhinitis and asthma are very common pathologies that sometimes appear concurrently. The international consensus called Allergic Rhinitis and Its Impact on Asthma (ARIA) highlights the idea that both upper and lower airways can be considered a unique entity influenced by a common inflammatory process, which may be amplified by related mechanisms. The increased prevalence of these diseases is associated with high morbidity and health costs. Asthma is usually found in the context of systemic allergic disease associated with numerous comorbidities. Rhinitis is considered a risk factor for asthma, 17 to 38% of patients with allergic rhinitis having asthma. Up to 80% of all asthmatic patients have allergic rhinitis. Asthma and allergic rhinitis have similar epidemiology, inflammation, common triggers, pathophysiological links and treatment outcomes. The ARIA guidelines and the IPCRG guidelines recommend a combined strategy for treating the upper and lower airways. Treating rhinitis can improve outcomes for asthma and vice versa.

KEYWORDS: asthma, allergic rhinitis, physiopathology, corticosteroids, antihistamines

INTRODUCTION

Rhinitis and asthma are very common pathologies that sometimes appear concurrently. The increased prevalence of these diseases is associated with high morbidity and health costs. In 2001, the Allergic Rhinitis and Its Impact on Asthma (ARIA) Workshop Group published an international statement in which the authors reviewed asthma classification (mild/moderate-severe and intermittent/persistent), epidemiology, pathophysiological mechanisms, rhinitis correlation, diagnosis and evidence-based treatment. In the 2010 Revision, ARIA presented new clinical practice guidelines for the management of allergic rhinitis (AR) and asthma comorbidities based on the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system¹.

Asthma is usually found in the context of systemic allergic disease associated with numerous comorbidities. Upper airway comorbidities of asthma include AR, sinusitis and otitis media with effusion, with consequent sleep and behavioral disorders. Treating the inflammation is the key of relieving symptoms and diminishing consequences and comorbidities in patients with asthma. In addition to the economic burden of asthma, which is

considerable, there are physical, emotional and social effects, leading to reduced quality of life (QoL) of patients and their families². Asthma incidence is high in allergic and non-allergic rhinitis.

Allergic rhinitis is defined as a symptomatic problem of the nose that appears after allergen exposure, with an IgE-mediated inflammation. Allergic rhinitis is a global health problem, which occurs in 10 to 50% of the population, with an increasing prevalence. This pathology is associated with effects on quality of life, with significant influence on sleep, cognitive and psychomotor function, participation in social activities and learning impairment in children. Allergic rhinitis has tended to be seen as an annoying nuisance rather than a serious disease. Available treatments can improve outcomes in rhinitis as well as associated allergic diseases such as asthma. Despite all this, allergic rhinitis still remains underdiagnosed and undertreated. Most importantly, rhinitis is almost always found in asthma and it is a risk factor for this chronic disease. Lienneberg et al. presented in their study performed on 734 subjects (tested on two occasions eight years apart) that all patients with allergic rhinitis from pollen, mite or animals had allergic asthma to the same allergen³.

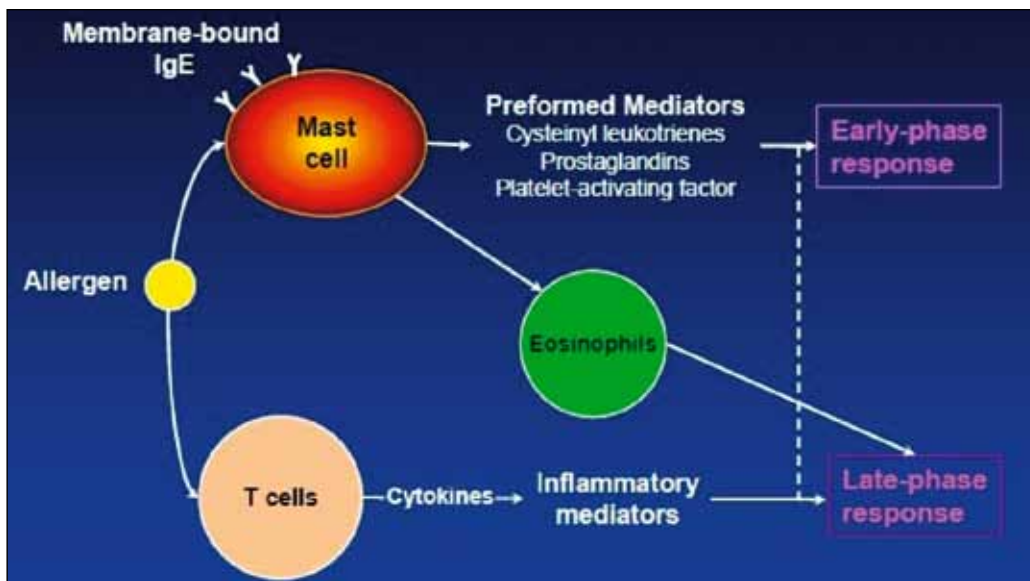


Figure 1 Inflammatory cells in allergic rhinitis and asthma (adapted from Casale T.B. et al., Clin Rev Allergy Immunol 2001 and Kay A.B., N Engl J Med 2001)^{24,25}

The international consensus called Allergic Rhinitis and Its Impact on Asthma (ARIA) highlights the idea that both upper and lower airways can be considered a unique entity, influenced by a common inflammatory process, which may be amplified by related mechanisms. The relation between allergic rhinitis and asthma is evident^{3,4}. Almost 30% of patients with allergic rhinitis have lung symptoms and manifestations of asthma, and more than 70% of asthma patients have nasal symptoms⁵. Rhinitis often precedes the onset of asthma^{5,6} and patients with allergic rhinitis have a high risk of developing asthma⁷. According to some studies, 25 to 43% of the patients diagnosed with rhinitis develop asthma within 10 years⁸. Allergic rhinitis is common in patients with asthma, increasing the risk of asthma symptoms exacerbation⁹⁻¹¹.

An adequate control of allergic rhinitis manifestations could diminish treatment and diagnosis costs. Health service use and costs for asthma were bigger for patients with both asthma and allergic rhinitis. Impairment of quality of life is observed in adults and in children with asthma and patients with AR and asthma.

ASTHMA AND RHINITIS

Asthma and allergic rhinitis have similar epidemiology, inflammation, common triggers, pathophysiological links and treatment outcomes. Most patients with asthma also have rhinitis¹², the rhinitis onset often being earlier. Rhinitis seems to be an inflammation marker and the severity of rhinitis is associated with the severity of asthma¹³. Asthma control^{14,15} is worse in patients with clinically and paraclinically diagnosed aller-

gic rhinitis. In adults with recent symptoms, rhinitis may be the first sign of occupational asthma.

As some studies show, children with asthma are more likely to present to hospital if they also have rhinitis¹⁶. That suggests that the presence of rhinitis can predict exacerbations in asthmatic children.

Allergic rhinitis and asthma have common triggers: outdoor allergens (pollens, molds, indoor allergens, house-dust mites, animal dander, insects, nonsteroidal antiinflammatory drugs, etc.).

Similar epidemiology

About 300 million people are affected worldwide. Asthma prevalence increases as communities adopt western lifestyles and become urbanised. Most patients with asthma (60 to 80%) have rhinitis¹⁷, with rhinitis often preceding the development of asthma.

Up to 80% of all asthmatic patients have allergic rhinitis¹⁷.

Allergic rhinitis is one of the most common chronic diseases in the world, affecting 10 to 50% of the population and its prevalence is increasing, especially in children. Although it is not usually a severe disease, rhinitis alters social life and affects school performance and work productivity¹⁸.

A long-term (23 years) follow-up study performed by Settipane RJ on 738 students with allergic rhinitis showed that the subjects were 3 times more likely to develop asthma than individuals without allergic rhinitis⁶.

Rhinitis and asthma are very common pathologies that appear concomitantly. In an analysis of medical resource used during asthma attacks in asthmatic patients with and without concomitant allergic rhinitis over 52 weeks, Bousquet showed that patients with AR and

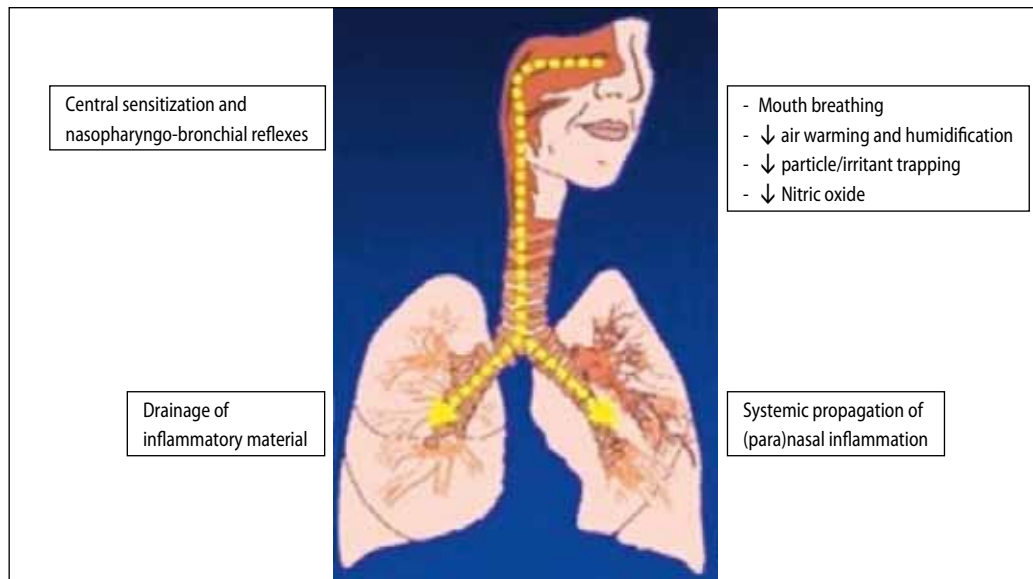


Figure 2 Allergic rhinitis and asthma pathophysiology (adapted from Togias A. JACI 2003²⁶)

asthma had an increased risk of ER visits¹⁹. Risk of hospitalization was higher in patients with AR and asthma.

Allergic rhinitis is more frequent in patients with asthma, more than 75% of the patients with allergic asthma and in more than 80% of those with nonallergic asthma^{13,20,21}. Asthma prevalence in patients with rhinitis varies from 15 to 40%.

There is a correlation between asthma and severity. The age of atopy manifestations beginning²² may be a predictor factor for asthma (onset of atopy at an early age) or allergic rhinitis (onset during adult life) development. When rhinitis begins in the 1st year of life, the development of asthma can be twice as high as when it starts after the 1st year²³.

Common inflammatory processes

Regarding the inflammatory processes of the respiratory mucosa, proinflammatory mediators and cells are the same in allergic rhinitis and asthma (Figure 1). Common inflammatory processes include common inflammatory cells and common inflammatory mediators. Pulmonary inflammation appears after nasal exposure to allergens; nasal inflammation occurs after bronchial stimulations; probably, systemic dissemination of inflammation response is the common mechanism that correlates asthma and allergic rhinitis.

There is a strong association between perennial rhinitis and asthma in nonatopic subjects with normal IgE levels; that sustains the hypothesis that rhinitis is an independent risk factor for asthma. In asthmatic patients, nasal inflammation is found, despite the presence of allergic rhinitis in atopic people²⁴.

Pathophysiological links

Pathophysiology is common in allergic rhinitis and

asthma (Figure 2). The nose is an organ with several functions, but the single most important one is probably conditioning inspired air. Impairment of this function is related to the presence or severity of asthma.

Effects of Poorly Conditioned Air

Breathing poorly conditioned air has effects on the lower airway, which have been described in experiments of exercise-induced bronchial provocation. Strohl et al²⁷ assessed the changes in airway resistance after breathing first cold dry air and then warm humid air through the mouth. They noticed that airway resistance increased 84% with exercise, while breathing cold dry air; it was unchanged with exercise while breathing warm humid air. People who practice winter sports tend to develop asthma. Repeated and prolonged exposure of airways to poorly conditioned air may determine functional and inflammatory disorders.

Similarities and Differences between Nasal and Bronchial Inflammation

In subjects with allergic rhinitis or asthma, the inflammatory infiltrate is the same, with the same mediators, Th2 lymphocyte, cytokines and adhesion molecules²⁷. The degree of inflammation may differ. Patients with moderate to severe asthma have an eosinophilic infiltration that is more important in the bronchi than in the nose; patients with mild asthma have a similar degree of inflammation in both localizations²⁸. Nasal eosinophils are present in asthmatic patients with or without nasal symptoms. Patients diagnosed with asthma have a thicker basement membrane, light muscle hypertrophy and more important epithelial desquamation; the nasal epithelium is less damaged in patients having only rhinitis²⁹.

Table 1
Treatment ARIA 2012 guidelines in allergic rhinitis and asthma

Asthma landscape	Allergic rhinitis landscape
• Fast relief: SABA	• Fast relief: anti-histamines
• Sustained relief: LABA	• Sustained & most effective relief –new antihistamines
• Antiinflammatory: ICS	• Antiinflammatory - intranasal corticosteroids
• Unmet medical need - Many patients - poor or uncontrolled asthma	• Unmet medical need - 20% severe chronic upper airway disease - 75% of patients on unproven combination therapy
Treatment - to simplify asthma management	More effective therapies urgently needed

SABA: short-acting beta-agonist; LABA: long-acting beta-agonist; ARIA guide 2012

Nasal Inflammation and Bronchial Response

The relation between rhinitis and the presence of inflammation and functional disorders in the lower airway have been investigated in multiple studies. Pulmonary hyperreactivity and changes in lung function appear in patients with allergenic rhinitis after nasal provocation with allergen³⁰⁻³².

Bronchial Inflammation and Nasal Response

Nasal and pulmonary symptoms appear after bronchial provocation with allergens in nonasthmatic patients allergic to pollen; an increased eosinophilia, eosinophilic and basophilic infiltration of the nasal and bronchial mucosae were also observed after the provocation test^{33,34}.

Interrelationship mechanisms

Different mechanisms have been proposed in order to explain the relation between nose and lungs in allergic respiratory disease:

- *Nasobronchial reflex.* Increased bronchial resistance is observed after nasal provocation with silica crystals aerosol.
- *Drainage of inflammatory mediators.* Aspiration of mediators from secretions arrive to the lower airway in inspired air, especially at night, determining a deterioration in lung function, increased bronchial hyperreactivity and symptoms on waking.
- *Systemic dissemination of mediators.* Eosinophils in nasal and bronchial mucosa increase 24 hours after allergen provocation; adhesion molecules were more expressed in both mucosae.

TREATMENT

Around 250.000 people die prematurely all around the world each year as a result of asthma^{18,35-37}. With the right treatment, most people with asthma can have

their disease controlled. The Global Initiatives for Asthma (GINA) guidelines identify eight goals for the long-term management of asthma: no (or minimum) daytime symptoms, no limiting activity, no night-time symptoms, no (or minimum) rescue medication, normal pulmonary function, no exacerbation (minimum represents less than two times per week)³⁸.

Many patients still have poorly controlled or uncontrolled asthma, although guidelines have proposed different therapeutic methods. Allergic rhinitis is an important risk factor for uncontrolled asthma and it increases the risk of asthma attacks about 3 fold, the risk of ER visits in patients with asthma about 2 fold, and with 50% the risk of severe exacerbation with hospitalization for asthma¹⁹.

According to ARIA 2012 guideline, treatment methods in allergic rhinitis and asthma are presented in Table 1.

The ARIA guidelines and the IPCRG guidelines recommend a combined strategy for treating the upper and lower airways. Treating rhinitis can improve outcomes for asthma and vice versa^{39,40}.

A retrospective cohort study of costs over a period of up to one year incurred by patients 12 to 60 years of age, with both allergic rhinitis and asthma, showed 61 % fewer hospitalizations in patients treated for AR⁴¹.

There are studies that suggest that antihistamines¹⁶, immunotherapy and leukotriene receptor antagonists⁴² improve both asthma and rhinitis symptoms in some patients. Some data suggest that nasal steroids alone may improve asthmatic manifestations in patients with allergic rhinitis⁴³. If asthma and rhinitis are both adequately controlled^{15,44}, use of healthcare resources is lower. Uncontrolled asthma determines high health care resource utilization, hospitalizations medication costs and low quality of life¹⁵.

Effect of Nasal Corticosteroids on Asthma

Topical nasal corticosteroids effects on bronchial inflammation and lung function was studied; it has been reported that correct treatment of rhinitis with intranasal steroids decreases the frequency of visits to the hospital for

asthma exacerbations^{41,45,46}. Pinto et al⁴⁷ showed that intranasal administration of budesonide to asthmatic patients associated a decrease in conditioning of inspired air. Intranasal steroids are the treatment of choice for persistent moderate to severe allergic rhinitis and may also improve nonallergic rhinitis. Nasal steroids reduced asthma symptoms in patients with seasonal AR and seasonal asthma^{48,49}.

When there is coexisting asthma, intranasal steroid use is associated with fewer emergency presentations for asthma⁴⁹. Intranasal steroids administration should begin before referring patients with nasal obstruction to an allergist or ear, nose and throat surgeon. Intranasal steroids appear safe for long term use, although it is prudent to use the lowest dose to control symptoms^{40,50}.

Effect of Antihistamines on Asthma

Antihistamines improved asthma symptoms in patients with seasonal AR and asthma. Antihistamines are one of the main therapeutic methods for allergic rhinitis treatment. Some of them have antiinflammatory effects, providing additional benefit, especially to ameliorate nasal obstruction. Loratadine and cetirizine may improve asthma symptoms in patients with allergic rhinitis, at different levels⁵¹⁻⁵³. Continuous treatment with cetirizine reduces the frequency and severity of bronchial symptoms⁵². Desloratadine and montelukast were equally effective in reducing asthma symptoms and use of bronchodilators in patients with seasonal allergic rhinitis and asthma⁵⁴. It has also been reported that the use of combined treatment (antihistamines and an antileukotriene) in patients with asthma and rhinitis seems to be more effective than the use of a single agent on its own.

Immunotherapeutic Effect on the Development of Asthma

Immunotherapy seems to be effective in the management of allergic rhinitis and allergic asthma^{55,56}. This therapy should be administered in optimal doses, by subcutaneous or sublingual administration. Allergic sensitization is the one that should determine the decision to administrate immunotherapy. The immunological effect of this therapy functions by restoring the normal equilibrium between Th1 and Th2 lymphocytes.

CONCLUSIONS

Allergic rhinitis diagnosis also needs patient's evaluation for asthma. Asthma diagnosis also needs patient's evaluation for rhinitis. ARIA and GINA recommend a combined strategy for the management of coexisting allergic rhinitis and asthma. The interrelationship of asthma and rhinitis highlights the need for an integrated management of the allergic respiratory disease.

An appropriate therapeutic strategy should combine safe and effective management of the upper and lower airways. Asthma and rhinitis are highly prevalent dis-

eases that are often present side by side. Allergic rhinitis is a major risk factor for the development of asthma. Other conditions of the paranasal sinuses, such as polyposis and sinusitis, are also often associated with asthma, and also influence the severity of asthma.

Several studies have shown clinical improvement and decreased bronchial inflammation after treatment of rhinitis with corticosteroids, antileukotrienes and antihistamines. Immunotherapy seems to alter the natural course of allergic respiratory disease and prevent the appearance of asthma in subjects with rhinitis. These findings reinforce the epidemiological and pathophysiological data on the interrelationship of asthma and rhinitis and serve to highlight the need for an integrated management of the allergic respiratory disease.

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