DR RICARDO JOSE SARANZ (Orcid ID : 0000-0002-9716-1825)

Article type : Unsolicited Review

Subclinical lower airways correlates of chronic allergic and non-allergic rhinitis

Short title: *Subclinical lung impact of rhinitis*

Authors:

Ricardo J. Saranz *, Alejandro Lozano *, Natalia A. Lozano *, Marina F. Ponzio **, Álvaro A. Cruz ***

* Allergy and Immunology Division, Clínica Universitaria Reina Fabiola, Facultad de Medicina Universidad Católica de Córdoba; Córdoba, Argentina.

** INICSA-CONICET, Cátedra de Fisiología Humana, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Córdoba, Argentina.

***ProAR-Nucleo de Excelência em Asma da Universidade Federal da Bahia, and CNPq, Salvador, Brazil.

Correspondence: Ricardo J. Saranz MD. Allergy and Immunology Division- Clínica Universitaria Reina Fabiola, Facultad de Medicina, Universidad Católica de Córdoba. Oncativo 1248 -X5004FHP- Córdoba, Argentina. Tel/Fax: 54-351-4142121; e-mail: rsaranz@arnet.com.ar

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.12938

Authors' contributions

Ricardo J. Saranz ; e-mail: rsaranz@arnet.com.ar

Conception and design of the idea, search, analysis and interpretation of the literature. Article writing and critical review and approval of the final version.

Alejandro Lozano; e-mail: aloza@uccor.edu.ar

Conception and design of the idea, search, analysis and interpretation of the literature. Article writing and critical review and approval of the final version.

Natalia A. Lozano; e-mail: nati_lozano@hotmail.com

Search, analysis and interpretation of the literature. Article writing and critical review and approval of the final version.

Marina F. Ponzio; e-mail: mponzio@mater.fcm.unc.edu.ar

Search, analysis and interpretation of the literature. Article writing and critical review and approval of the final version.

Alvaro A. Cruz; e-mail: cruz.proar@gmail.com

Search, analysis and interpretation of the literature. Article writing and critical review and approval of the final version.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

The present study was performed using funds from the Secretaría de Investigación y Vinculación Tecnológica of the Universidad Católica de Córdoba.

Summary

The upper and lower airways behave as a physiological and pathophysiological unit. Subclinical lower airways abnormalities have been described in patients with rhinitis without asthma. These are expressed as bronchial hyperreactivity, abnormalities in lung function and bronchial inflammation, likely as a result of the same phenomenon with systemic inflammatory impact that reaches both the nose and the lungs, which for unknown reasons does not always have a full clinical expression.

Patients with rhinitis are at increased risk of developing asthma; therefore most authors suggest a careful clinical evaluation and monitoring of these patients, especially if symptoms related to inflammation in the lower airways are observed.

Although current treatments, such as H1-antihistamines, intranasal steroids and allergen immunotherapy are quite effective for the management of rhinitis, it is difficult to prove their capacity to prevent asthma among subjects with rhinitis. Evidence showing that the treatment of rhinitis has a favorable impact on indicators of bronchial hyperreactivity and inflammation among subjects that have no symptoms of asthma, is more frequently described.

In this review we address the frequency and characteristics of lower airway abnormalities in subjects with rhinitis, both in pediatric and adult populations, their likely predictive value for the development of asthma and the possibilities for therapeutic intervention that could modify the risk of subjects with rhinitis towards presenting asthma.

Key words

Allergic rhinitis, non-allergic rhinitis, bronchial hyperreactivity, spirometry, fraction of exhaled nitric oxide.

Introduction: The "one airway, one disease" holistic model

Rhinitis is one of the commonest chronic inflammatory disease of human pathology, which becomes relevant for its negative impact in the quality of life of children and adults suffering from the condition, and the high healthcare costs (1).

The "one airway, one disease" paradigm has been extensively investigated by several authors and disseminated over the past two decades through a series of ARIA (*Allergic Rhinitis and Its Impact on Asthma*) publications (1-3).

The nose, middle ear, paranasal sinuses, larynx and trachea are all related by contiguity with bronchi and respiratory bronchioles acting as an anatomical and functional unit, whose connection and inter-relation is supported not only by anatomical and physiological evidence but also by epidemiological, genetic, clinical and therapeutic (4).

This model has been extensively investigated concerning the relationship between rhinitis and asthma (4-9). Patients with rhinosinusitis are more likely to develop asthma, and rhinitis is almost ubiquitous in patients with asthma. Between 80% and 90% of patients with asthma present symptoms of rhinitis (10) and 10-40% of those consulting for rhinitis simultaneously have asthma (1,5). Furthermore, and regardless of the etiology, rhinitis is a risk factor for the development of asthma (11-13). The severity of rhinitis and its treatment may influence asthma control (14,15).

The links between rhinitis and asthma are probably multifaceted. Numerous local pathophysiological mechanisms, common to allergic rhinitis (AR) and non-allergic (NAR), have been proposed as possible explanations to the intimate connections between the nasal and bronchial dysfunction, such as the forced mouth breathing secondary to nasal obstruction, the decreased bronchial beta adrenergic response, the stimulation of a sinonasal-bronchial reflex, the altered breathing pattern and the propagation of the inflammatory secretions from the nose through aspiration of nasal secretions (postnasal drip) and mediators of inflammation to the bronchi (4,5,9,16). However, those

studies have not been able to fully clarify as how these mechanisms, by themselves, can explain the nose-lung inter-relationship in health and disease (4,9).

The local inflammatory process mediated by immunoglobulin E (IgE) and common to nose and bronchi, may also have a relevant pathogenic role. Inflammation associated to allergen exposure and accentuated by bacterial superantigens with local IgE production in the mucosa, without demonstrable “in vivo” skin tests or "in vitro" IgE, is gaining increasing physiopathogenic relevance (17).

A common eosinophilic inflammatory mechanism is currently the most accepted. The systemic model of allergic disease has established the pathogenic concept of bloodstream dissemination of a systemic inflammatory phenomenon with varying clinical manifestations according to the target affected organ (18). This mechanism indicates that the "target" site of the allergic reaction is the entire airway, from the nose to the bronchioles and alveoli, and not only in the area where the reaction is triggered (19). However, this description does not explain the interaction between NAR and asthma. NAR corresponds to distinct phenotypes with unclear pathogenesis.

Many patients with rhinitis of any type, with no asthma, present subclinical (asymptomatic) dysfunction of their lower airways such as bronchial hyperreactivity (BHR), inflammation and impairment of lung function, which could be associated with an increased risk for the development of clinical asthma (7,9,20).The objectives of this review are to describe the subclinical lower airway abnormalities in patients with rhinitis but without asthma, its probable progression and the possible effects of therapeutic intervention on its natural evolution.

Bronchial hyperreactivity in allergic and non-allergic rhinitis without asthma

BHR is a characteristic but not exclusive phenomenon of asthma, because it can be manifested in other respiratory and non-respiratory diseases, although its definitive clinical implications are still unknown (21).

Different studies have demonstrated that between 13 and 57% of adults and children with chronic rhinitis, showing no clinical evidences of asthma, present non-specific BHR to methacholine, cold air, histamine, adenosine 5'-monophosphate (AMP) or exercise (22-32) (Table 1).

The observed occurrence of BHR depends on the bronchial challenge method used, it is in the range of mild bronchial hyperreactivity, that is quantitatively higher to that of normal individuals and lower than in the population of patients with asthma (21,27).

Most subjects with allergic rhinitis demonstrate a dose-response curve in the range of BHR to the methacholine bronchial provocation test, showing also a "plateau" effect; this means that when exposed to the cholinergic agent, a significant number of patients with rhinitis without asthma show a limited bronchoconstrictory response, different to that observed in patients with asthma (33). Those that exhibit a maximum bronchoconstrictory response without "plateau" effect, also show a variability of the peak flow similar to asthma; therefore in these patients we could predict a probable greater future risk of developing the disease (33).

In individuals with seasonal rhinitis, the natural exposure to pollen produces an increase in bronchial reactivity, with subsequent decrease out the season, a phenomenon existing also in patients with asthma. Madonini et al. (25), in patients with hay fever before and during the season, observed that the incidence of BHR increased from 11% to 48% during the pollen season. In addition, patients with rhinitis caused by perennial allergens, express a greater degree of bronchial reactivity than those with seasonal nasal allergies (13).

Airway hyperresponsiveness was also demonstrated upon bronchial challenge with methacholine in a 28.1% of 342 adult patients with persistent moderate-severe allergic rhinitis without asthma (30). The severity of BHR was associated with sensitization to trees and mites, with rhinitis for over 5 years and with Forced Expiratory Volume in the first second of the Forced Vital Capacity (FEV1) <86% of the predicted value. The same authors, recently demonstrated in a study of 4781 patients between 17 and 56 years old, showing allergic rhinitis without asthma, that BHR to methacholine was expressed by 39.3% of the subjects and that Forced Expiratory Flow between 25 and 75% of Vital Capacity (FEF25-75%) values lower than a 65% are predictive of severe BHR (OR = 12.9) (34).

The occurrence of BHR to methacholine seems to be more frequent in the allergic rhinitis phenotype. A study in children with rhinitis without asthma, using the methacholine bronchoprovocation test, demonstrated a two-fold higher BHR prevalence in AR compared to NAR (55.7% vs 25.5% respectively) (31). The event was more frequent in persistent than in intermittent rhinitis (62.8% vs 47.6%), but was not associated with the symptoms severity. Recently, Chawes et al. (35) reported an increased cold air bronchial reactivity in children with allergic rhinitis without asthma that was not reproduced in NAR.

In young adults, BHR to methacholine was more frequent in patients with AR than in those with NAR (12.2% vs 6.1%, p = 0.01) (32). On the other hand, these findings could not be reproduced in the challenge with exercise: children with NAR had a higher prevalence of exercise-induced bronchoconstriction than those with the allergic phenotype (36).

Lozano et al. (37) describe the effects of exercise upon nasal and lung function in children with allergic rhinitis without asthma. They conclude that the prevalence of exercise-induced asthma was 29% and that lung function is affected earlier (from 5 minutes) than nasal function, showing a resistance increase and a decrease of nasal airflow measured by rhinomanometry, from 20 minutes post-effort. It is speculated that this difference in the time response is related to anatomical and physiological features of the nasal passages than for the pathogenesis of the process.

Subclinical impairment of lung function

Many studies have demonstrated spirometric abnormalities in patients with rhinitis without clinical expression of asthma, with variations in its frequency according to the threshold of abnormality considered for spirometric parameters (38-44) (Table 2).

Ciprandi et al. (38) in a study of 392 adults with persistent and moderate-severe AR without bronchial symptoms, detected spirometric abnormalities in 87% of the patients, considering as a criterion of abnormality a value of FEF25-75% below than 80% of predicted. The same authors, in a latter study (42) found that the prevalence of this abnormality decreased to 17.8% by defining the FEF25-75% threshold of abnormality to less than 65% of the predicted value.

In children and adolescents with allergic rhinitis the prevalence of lung function impairment estimated is between 25% and 42% (39,43,44) (Table 2). A study performed by our group (43), showed that asymptomatic spirometric abnormalities were observed in 25% of children between 6 and 18 years old with allergic rhinitis and no asthma. On the contrary of other authors observations, who observed a greater impairment of the FEF25-75% value (39,44), we demonstrated that the most frequently affected parameter was the ratio between Forced Expiratory Volume in the first second of the Forced Vital Capacity and the Forced Vital Capacity (FEV1/FVC), either alone or in combination with other spirometric parameters.

The spirometric abnormalities are directly proportional to the clinical severity of rhinitis (41,45), implaying that patients with persistent, moderate-severe rhinitis have the lower pulmonary function measurements as compared to those with intermittent and mild rhinitis. This observation has been described both in allergic and non-allergic rhinitis and therefore is likely to be inherent to the rhinitis condition and unrelated to the etiology (45).

The reduction in FEF25-75% and FEV1 has been associated with a longer duration of rhinitis, nasal eosinophilia and nasal airflow reduction in both, seasonal and perennial rhinitis (20). Ianiero et al. (43) demonstrated that a high body mass index and blood eosinophilia were also risk factors for the impairment in lung function found by spirometry. The final connotations of these findings are not clear, but it reinforce the hypothesis that systemic eosinophilic inflammation may affect the nose and the bronchi and contribute to the lung function reduction described in AR (18,19).

The obstructive ventilatory defect of patients with rhinitis is potentially reversible with a bronchodilator. Ciprandi et al. (42) observed a positive bronchodilator response in approximately 2/3 of young adults with allergic rhinitis. An impairment of FEF25-75% associated with a longer duration of rhinitis was predictive of the reversibility to the bronchodilator test. (OR = 11.3; p <0.001).

Capasso et al. (46), showed an improvement in FEV1 > 12% in 21.5% of children with AR. Reversibility was associated with lower basal FEV1 levels, longer duration of rhinitis and perennial symptoms of rhinitis. This seems to express an early impairment of the intrathoracic airway function in patients with nasal symptoms only. Expert reseachers suggest that this could have not only diagnostic but also prognostic and therapeutic implications. These findings support the recommendation for performing spirometry in patients with persistent, moderate to severe rhinitis, but not unnecessarily for the routine workup of patients with rhinitis classified as mild and intermittent (1-3).

To the best of our knowledge, there have been only a few studies evaluating BHR and bronchodilator response in AR using impulse oscillometry; this methodology has emerged as a powerful tool for evaluating pulmonary function in children who have failed to perform a forced expiration test or have small changes in pulmonary function.

Kim et al (47) observed that the bronchodilator response in reactance at 5 Hz (Δ X5) and the reactance area (Δ AX) increased more in the asthma and AR groups than in the controls. Subjects with rhinitis also presented more airway inflammation as indicated by a higher FeNO. These impulse oscilometry parameters are more sensitive in detecting changes in pulmonary function than spirometry.

Lower airway inflammatory involvement in rhinitis

Inflammatory signs in the lower airway were demonstrated in patients with AR without concurrent asthma symptoms (48-53).

The existence of inflammatory cells, mainly eosinophils, was initially observed both in subjects with asthma or hay fever (without asthma), even outside the season, and associated to BHR (48).

In patients with allergic rhinitis to grass pollen, after a nasal provocation outside the pollen season, an increase in the number of eosinophils, the concentration of eosinophilic cationic protein (ECP) in induced sputum and an increased bronchial reactivity to methacholine was observed, compared to patients challenged with dilluent (49). After natural exposure to the pollen season in adult patients with seasonal allergic rhinitis without asthma, Panzner et al. (49) were able to reproduce the increase in eosinophils and ECP in induced sputum.

In patients with allergic rhinitis induced by mites, but without asthma, nasal provocation with the allergen produced a significant increase in blood, nasal secretions and induced sputum eosinophils, with a simultaneous worsening of the BHR to methacholine and pulmonary function (53). This fact adds further evidence for the existence of a pathophysiological connection between BHR and inflammation in rhinitis.

The measurement of exhaled nitric oxide (FeNO), endogenously produced in the airway cells by nitric oxide synthase and under the influence of Th2, IL-4 and IL-13 cytokines, is considered as an indirect method to assess bronchial inflammation mediated by eosinophils (54). Most evidence suggest that patients with AR present higher levels of exhaled nitric oxide than those with NAR (13,32,52,55-60) (Table 3, Figure 1).

In a study that included children with AR, NAR and healthy controls (13), it was found that the former ones had higher levels of FeNO than NAR patients (15.9 vs. 6.6 ppb). Another study also showed a significant increase in FeNO values in patients with AR during the pollen season, compared to healthy controls and asymptomatic atopic individuals (55). This indicates the existence of inflammation in the lower airway, a phenomenon enhanced with seasonal pollen exposure in patients with allergic rhinitis without asthma.

Increased FeNO was observed in AR with and without BHR (47, 58). Children with AR and BHR had slightly higher FeNO values than patients without BHR. In adults with allergic rhinitis the coexistence of high levels of FeNO with HRB to methacholine was demonstrated (58), reinforcing the association between BHR and eosinophilic inflammation found in a previous study (48). The FeNO threshold associated with the presence of BHR in patients with persistent allergic rhinitis was established at 27 ppb. This shows a direct relationship between inflammation and BHR in allergic rhinitis and possibly, the co-existence of both phenomena may be biomarkers of the future development of asthma.

The characteristics of bronchial inflammation in NAR are less well known. Wang et al. (32) observed that patients with NAR manifest dysfunction of the small airway, eosinophilia in sputum and elevated FeNO, although of a lower magnitude than in AR (Figure 1).

Studies about remodeling of the lower airway in rhinitis are scarce and related to indirect indicators of this this process. Patients with seasonal rhinitis and BHR to methacholine, expressed in induced sputum a significant increase of the vascular endothelial growth factor-A (VEGF-A) and endostatin,

components associated with angiogenesis of the bronchial remodeling (61). Adults with moderate-severe persistent allergic rhinitis with eosinophilia in sputum, had an increased expression of mRNA for matrix metalloproteinase-9 (MMP-9) and of the rate MMP-9 / TIMP-1 (tissue inhibitor of metalloproteinases-1), both mediators related to a pattern of airway fibrosis (62). These findings may be relevant to the lung function abnormalities found in AR but requires confirmation and better understanding in future studies.

Nasal nitric oxide (nNO) measurement is an area of ongoing research interest for the evaluation of nasal inflammation, with the advantage of being a noninvasive and quick method. However, because of its dual origins, paranasal sinuses and nasal mucosa, the clinical usefulness of nNO is controversial.

Gupta et al. (59) observed that AR and asthma‑AR groups had higher nNO levels compared to the control group and asthma group. In patients with asthma, nNO was positively correlated with FeNO, blood eosinophil count, bronchial responsiveness and poor asthma control (63). This study suggests a clinical utility of nNO in subjects with asthma, but there are no studies which define a prognostic value of nNO for the evolution of rhinitis towards asthma.

Emerging role of other biomarkers

Biological markers are measurable indicators used to examine any aspects of health or disease. Any type of analyses can be considered a biomarker when it provides information about the pathophysiology of an underlying disease, the course and severity of an illness, and/or the response to treatment (64). Biomarkers obtained mainly from minimally invasive sampling such as exhaled breath condensate (EBC), nasal epithelial cells and secretions and peripheral blood measurements, are used to predict or to monitor treatment response and very few used to estimate the disease risk and anticipate disease progression (65).

Periostin, for example, is a well-investigated, systemic biomarker of type 2 inflammation (66) in asthmatic patients that is superior to blood eosinophil counts; on the other hand, osteopontin levels in sputum showed a highly significant correlation with neutrophilic asthma phenotype associated with smoking and indicates disease severity (65). It should be highlited that most biomarkers are currently suited only for research settings and still need to be validated and qualified for predicting the risk of progression from rhinitis to asthma.

Prognostic value of subclinical pulmonary abnormalities

The prognosis of pulmonary disorders without clinical expression in children and adults with rhinitis are not clear. Two studies (22,26), claim that the presence of bronchial hyperresponsiveness in the asthmatic range helps to identify patients with rhinitis at risk for developing asthma, giving to this finding a clear prognostic value. This, however, is not universally accepted; Prieto et al. (67) in a follow-up of adults for 5.8 years and Añibarro et al. (68) in children controlled for over 4 years, did not obtained the same results. Prospective studies for longer periods of these patients with bronchial hyperreactivity may bring light to this controversy.

The FeNO increase in children with allergic rhinitis may be a potential predictive biomarker of asthma development as well. Recently, Di Cara et al. (60) showed that 21 of 109 children with AR developed asthma after 5 years of follow-up. All of them exhibited at the study entry a FeNO > 35 ppb. The risk was proportional to the initial value of FeNO: every 10 ppb above the limit of 35 ppb, corresponded with more than twice the risk of developing asthma. This study is the first evidence of the utility of FeNO determinations to provide information of the subclinical bronchial compromise as a predictor of asthma in children with AR.

An association between FeNO > 34 ppb and a positive response to bronchodilator, compatible with subclinical asthma has been reported (69). Probably, the initial eosinophilic inflammation found is a risk factor for a subsequent clinical expression of asthma in children with rhinitis, independently of the initial baseline lung function.

Although FEF25-75% has been proposed as early marker of bronchial impairment (38-40), the prognostic value of existing subclinical spirometric abnormalities in patients with rhinitis has been only evaluated in a recent study that found that children with rhinitis, allergen sensitization and abnormal lung function, experienced a higher risk of developing BHR and asthma (70). The bronchial obstruction and bronchodilator reversibility that many of these patients exhibit represent a functional "asthmatic" behavior and require careful clinical follow-up, but additional prospective studies are needed for more precise estimates of the future risk of developing asthma in these patients.

Effect of therapeutic interventions

The hypothesis that rhinitis is a risk factor for the development of asthma may have therapeutic implications, reason why we might speculate that rhinitis treatment in early stages of life can reduce the march towards asthma (71).

While different therapeutic strategies with intranasal steroids, antihistamines and allergen immunotherapy were proved to be effective in the rhinitis management, and also some studies have demonstrated a beneficial effect on subclinical lung abnormalities of patients with rhinitis, their role to avoid progression to asthma is not well established (1-3, 71).

Pharmacotherapy

Of the existing pharmacological options of treatments for rhinitis, nasal steroids are the most effective and demonstrate favorable effects on lung function and BHR. Intranasal corticosteroids have a beneficial impact on lung function in children with rhinitis and without asthma. A case-control

study in children with allergic severe-moderate persistent rhinitis to mites, assessed the impairment of pulmonary function and its improvement after the treatment with antihistamines for 10 days and intranasal budesonide for 3 months (72). The nasal steroid significantly improved FEV1, FEV1/FVC ratio and FEF25-75% in these patients. The same author (44), examined the response to intranasal budesonide and triamcinolone in children with AR without asthma with impaired lung function; after 12 months of treatment, 2/3 patients had a significant increase in FEF 25-75% and FEV1 although they did not reach the levels of children with AR and normal lung function.

The nasal administration of a topical glucocorticosteroid may help improve asthma symptoms, lung function and nonspecific bronchial hyperresponsiveness to methacholine and exercise (73). Beclomethasone administered topically in the nose was compared to placebo in adult patients with seasonal rhinitis by *Ambrosia sp*. The steroid was effective to improve rhinitis symptoms and to prevent the seasonal increase in bronchial reactivity to methacholine (74). The nasal application of the same steroid for six weeks in children and adolescents with perennial allergic rhinitis reduced BHR to methacholine compared with a placebo group, simultaneously with a symptomatic relief of rhinitis (75).

The use of fluticasone nasal spray in adult patients with seasonal rhinitis was found to improve the nasal symptoms and to reduce the number of eosinophils in blood and bronchoalveolar lavage (76). The endonasal application of triamcinolone acetonide for four weeks in adults with AR produced a significant reduction of FeNO and levels of condensed hydrogen peroxide in breathing, obtaining an antiinflammatory effect beyond the steroid site of application (77). Although there is speculation of a "systemic" effect of topical steroids, responsible for the "remote" anti-inflammatory effect, their final action mechanism is not yet definitively clarified.

Although it has been shown that intranasal corticosteroids may improve, at least partially, asymptomatic pulmonary abnormalities, it is not clear if they can prevent the progression to asthma in patients with rhinitis; therefore, they are not currently recommended in the clinical guidelines for this purpose (78).

Oral H1-antihistamines have an established role in the treatment of rhinitis, but are far less effective for bronchial hyperresponsiveness and asthma. The administration of cetirizine in young adults with allergic rhinitis, had a protective effect on BHR measured 6 hours after a nasal allergen challenge (79), however. The systemic action of these agents would be responsible for the improvement of the nasal symptoms and the concurrent lower airway functional impairment. An anti-inflammatory action of cetirizine that produces a slight decrease in eosinophils recruitment has been reported (79).

The use of montelukast have a modest effect on rhinitis symptoms (80), and the impact on lower airway dysfunction and the development of asthma of such patients has not been evaluated.

Allergen specific immunotherapy (SIT)

Subcutaneous or sublingual SIT, improves rhinitis and is the only treatment found to alter the natural history of the atopic march from rhinitis to asthma so far. The beneficial effect of allergen immunotherapy on bronchial hyperresponsiveness in patients with rhinitis has been evaluated in recent studies (81-83).

Grembiale et al. (81), in a randomized, double-blind, placebo-controlled study, that included patients with rhinitis monosensitized to *Dermatophagoides pteronyssinus*, evaluated the effect of SIT on methacholine threshold concentration causing a 20% fall of FEV1 (PC20 FEV1) and the development of asthma. After two years, patients treated with SIT showed a significant improvement of four times the methacholine PC20 FEV1 compared to placebo treated patients. Of these, 9% developed asthma

against none in the group treated with SIT. The study showed that this treatment in monosensitized subjects reduces BHR in patients with rhinitis and can potentially become an appropriate strategy to prevent the progression of non-specific bronchial reactivity and the development of asthma.

The preventive effect of allergen SIT on asthma development and the improvement of non-specific bronchial hyperreactivity in patients with AR has been recently confirmed in the PAT (Preventive Allergy Treatment) study (82). In children with seasonal allergic rhino-conjunctivitis, the use of SIT reduced the development of asthma and BHR to methacholine at the end of 3 years of treatment. With sublingual immunotherapy (SLIT), Marogna et al. (83) reproduced similar results: the number of children with bronchial hyperreactivity to methacholine decreased significantly after three years of SLIT to mites and pollens as compared to the control group (OR, 0.24; 95% CI, 0.12- 0.47).

Currently, clinical guidelines agree that the specific allergen immunotherapy is the only treatment with the potential ability to modify the natural history of an allergic respiratory disease, although also warn about the need for further randomized long-term studies for a final suggestion as a strategy for primary prevention of asthma in subjects with allergic rhinitis (2,3,78,84,85).

Biological agents

Novel biologics agents have been studied in the treatment of AR, nasal polyps and allergic asthma, especially for the management of severe uncontrolled phenotypes (86). Among these, omalizumab, a humanized monoclonal anti-IgE antibody, is broadly available today (86, 87). Omalizumab controls both upper and lower airway diseases, reducing nasal and asthma symptoms, decreasing exacerbations, and improving quality of life in patients aged 6 years and older. Mepolizumab, a monoclonal antibody that blocks the binding of IL-5 to eosinophils, has also shown a beneficial effect on severe eosinophilic asthma and chronic rhinosinusitis with eosinophilic nasal polyposis in adults (86, 87). Because these treatments have systemic effects, it is difficult to design a study to assess how much the improvement in asthma is associated with rhinitis improvement. The effect of these

biological agents in preventing the progression of rhinitis to asthma and their impact on lung abnormalities in patients with rhinitis without asthma, are still unknown.

Other therapeutic approaches

Vitamin D: Adequate intake of vitamin D3 promotes lung development, antimicrobial mechanisms and reduces the profile of proinflammatory cytokines, which may contribute to a decrease in the risk of asthma (88). However, a causal association between vitamin 3 insuficiency or deficiency and asthma is not yet demonstrated and overall, the results are conflicting: none of the trials using vitamin D (before and after birth) reduced total IgE levels or allergen sensitization and only a marginal effect was demonstrated in the incidence of rhinitis symptoms at school age (89). Therefore, based on the available evidence, the use of vitamin D supplementation is not recomended for the primary prevention of allergic respiratory diseases.

The microbiota and use of probiotics: The composition of the airway microbiota reflects the characteristics of the airway environment, with differences between those observed in health and disease. In chronic rhinosinusitis patients, *Staphylococcus aureus* and anaerobes among others, which have been detected by DNA sequencing, may be considered to change the sinus mucosa immune function. The airway microbiome could be a useful marker of disease progression and predictor of treatment efficacy (90).

Modifying the microbiota is believed to modulate the host global immune response, which reduces sensitization and allergic inflammation. This has led to the hypothesis that pre- and probiotics, administered pre- and postnatally, might be protective for allergies by modification of the intestinal microbiota which modulates the immune response, probably by enhancing the T helper 1 profile activity (91).

Data deriving from studies in which the preventive effect of probiotics on asthma, wheezing and rhinoconjunctivitis was evaluated, showed only limited or non-significant benefits. Therefore the benefits of probiotic supplementation for AR and their potential to prevent asthma develoment are still unclear (91).

Conclusions and unmeet needs

The "one airway, one disease" concept arises from an existent anatomical, physiological and pathological links between the upper and lower airways, in a single interrelation model of identity. This suggests a common chronic allergic inflammatory process of the respiratory system that can explain the subclinical bronchial abnormalities in patients with AR; however the model cannot be applied with the same rigor in the non-allergic rhinitis phenotype. Therefore, it is necessary to study the potential existence of inflammatory disorders without clinical expression and their characteristics in individuals with non-allergic rhinitis without asthma, and also establish, with a higher degree of precision, the prognosis and natural evolution of patients with rhinitis that show BHR, impairment in lung function and evidence of subclinical endobronchial inflammation. A proposed evolutionary model can be observed in Figure 2.

Finally, further studies are needed to clarify the predictive value of novel biomarkers to detect early lower airway compromise in patients with rhinitis, the role of intranasal corticosteroids and novel biological agents as a strategy to prevent the development of asthma, the impact of current treatment options on lower airway functional abnormalities in non-allergic rhinitis patients and to assess the sustained effects of allergen immunotherapy after discontinuation.

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N, et. al. Allergic Rhinitis and its Impact on Asthma. ARIA workshop report. *J Allergy Clin Immunol* 2001; 108(5): S147-S334.

2. Cruz AA, Popov T, Pawankar R Annesi-Maesano I, Fokkens W, Kemp J, el al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA2LEN. *Allergy* 2007: 62 (Suppl. 84): 1–41.

3. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy* 2008; 63: S8-S160.

4. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003: 58: 691–706.

5. Fasano MB. Combined airways: impact of upper airway on lower airway. *Curr Opin Otolaryngol & Head and Neck Surg* 2010, 18:15–20.

6. Cruz A. The "united airways" require an holistic approach to management. *Allergy* 2005; 60: 871-874.

7. Serrano C, Valero A, Picado C. Rinitis y asma: una vía respiratoria, una enfermedad. *Arch Bronconeumol* 2005; 41(10): 569-78.

8. Antonicelli L, Braschi MC, Bresciani M, et al. The complex link between severity of asthma and rhinitis in mite allergic patients. *Respir Med* 2013; 107: 23-29.

9. Agresta MF, Saranz RJ, Lozano A, Lozano NA. The relationship between rhinitis and asthma: is that all?. *Rev Fac Cien Med Univ Nac Córdoba* 2014; 71(2):111-121.

10. Kapsali T, Horowitz E, Diemer F, Togias A. Rhinitis is ubiquitous in allergic asthmatics. *J Allergy Clin Immunol* 1997; 99: S138.

11. Leynaert B, Neukirch C, Kony S, et. al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004; 113: 86-93.

12. Eriksson J, Bjerg A, Lötvall J, et. al. Rhinitis phenotypes correlate with different symptom presentation and risk factor patterns of asthma. *Respir Med* 2011:105; 1611-1621.

13. Chawes BL, Bønnelykke K, Kreiner-Møller E, et. al. Children with allergic and nonallergic rhinitis have a similar risk of asthma. *J Allergy Clin Immunol* 2010; 126: 567-73.

14. Ponte EV, Franco R, Nascimento HF, Souza-Machado A, Cunha S, Barreto ML, Naspitz C, Cruz A. Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. *Allergy* 2008: 63: 564–569

15. Camargos P, Ibiapina C, Lasmar L, Cruz AA. Obtaining concomitant control of allergic rhinitis and asthma with a nasally inhaled corticosteroid. *Allergy* 2007,62:310-6.

16. Togias A. Mechanisms of nose-lung interaction. *Allergy* 1999; 54 (Suppl 57):94-105.

17. Kariyawasam HH, Rotiroti G. Allergic rhinitis, chronic rhinosinusitis and asthma: unravelling a complex relationship. *Curr Opin Otolaryngol Head Neck Surg* 2013, 21:79–86.

18. Denburg J. The nose, the lung and the bone marrow in allergic inflammation. *Allergy* 1999; 54:73-80.

19. Braunstahl GJ, Overbeek SE, Fokkens WJ, Kleinjan A, McEuen et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med* 2001; 164: 858-865.

20. Ciprandi G, Cirillo I. The lower airway pathology of rhinitis. *J Allergy Clin Immunol* 2006; 118: 1105-1109.

21. Saranz RJ. Hiperreactividad bronquial en rinitis alérgica. *Alergia (SAIC)* 1996; XIII (3-4): 74-78.

22. Townley RG, Ryo UY, Kolotkin BM, Kang B. Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. *J Allergy Clin Immunol* 1975; 56: 429–42.
23. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; 7: 235-243.
24. Ramsdale HE, Morris MM, Roberts RS, Hargreave FE. Asymptomatic bronchial hyper-responsiveness in rhinitis. *J Allergy Clin Immunol* 1985; 75:573-577.
25. Madonini E, Briatico-Vangosa G, Pappacoda A, Maccagni A et al. Seasonal increase of bronchial reactivity in allergic rhinitis. *J Allergy Clin Immunol* 1987; 79:358-363.
26. Braman SS, Barrows AA, DeCotiis BA, Settipane GA, Corrao WM. Airway hyperresponsiveness in allergic rhinitis. A risk factor for asthma. *Chest* 1987; 91: 671-674.
27. Saranz RJ, Lozano A, Alvarez JS, Croce VH. Factors associated to bronchial hyperresponsiveness in children and adolescents with allergic rhinitis. *J Allergy Clin Immunol* 1997; 99 (1): S 418.
28. Prieto L, Gutiérrez V, Liñana J, Marín J. Bronchoconstriction induced by inhaled adenosine 5´-monophosphate in subjects with allergic rhinitis. *Eur Respir J* 2001; 17: 64-70.
29. Choi SH, Yoo Y, Yu J, et al. Bronchial hyperresponsiveness in young children with allergic rhinitis and its risk factors. *Allergy* 2007; 62:1051-1056.
30. Cirillo I, Pistorio A, Tosca M, et. al. Impact of allergic rhinitis on asthma: effects on bronchial hyperreactivity. *Allergy* 2009; 64: 439–444.
31. Kim SW, Han DH, Lee SJ, et. al. Bronchial hyperresponsiveness in pediatric rhinitis patients: The difference between allergic and non-allergic rhinitis. *Am J Rhinol Allergy* 2013; 27: 63-68.
32. Wang Q, Ji J, Xie Y, Guan W, Zhan Y, Wang Z, Wu K, Zhong N. Lower airway inflammation and hyperresponsiveness in nonasthmatic patients with non-allergic rhinitis. *J Thorac Dis* 2015; 7:1756-1764.

33. Prieto L, Gutiérrez V, Morales C, Perpiñan J, Inchaurraga I. Variability of peak flow rate in allergic rhinitis and mild asthma: relationship to maximal airway narrowing. *Ann Allergy Asthma Immunol* 1998; 80: 151-158.

34. Ciprandi G, Tosca MA, Signori A, et. al. Bronchial hyperreactivity in patients with allergic rhinitis: Forced expiratory flow between 25 and 75% of vital capacity might be a predictive factor. *Allergy Asthma Proc* 2011; 32: 4-8.

35. Chawes BLK. Upper and lower airway pathology in young children with allergic and non-allergic rhinitis. *Dan Med Bull* 2011; 58(5): 1-23.

36. Rakkhong K, Kamchaisatian W, Vilaiyu S, Sasisakulporn C et al. Exercise-induced bronchoconstriction in rhinitis children without asthma. *Asian Pac J Allergy Immunol* 2011; 29: 278-83.

37. Lozano A, Alvarez JS, Grenat AR, Saranz RJ, Croce JS, Sasia L, Croce VH. Respuesta nasal y bronquial al ejercicio: similitudes y diferencias. *Alerg Inmunol Clin* 2002;19 (1-2): 22-26.

38. Ciprandi G, Cirillo I, Pistorio A. Impact of allergic rhinitis on asthma: effects on spirometric parameters. *Allergy* 2008; 63: 255-260.

39. Ciprandi G, Capasso M. Association of childhood perennial allergic rhinitis with subclinical airflow limitation. *Clin Exp Allergy* 2010; 40: 398-402.

40. Ciprandi G, Cirillo I, Klersy C. Lower airways are affected also in asymptomatic patients with recent onset of allergic rhinitis*. Laryngoscope* 2010; 120: 1288-1291.

41. Mohammad Y, Shaaban R, Ibrahim M, Ismail M. Lung function changes in non-asthmatic allergic rhinitis patients: a case series. *Prim Care Respir* J 2011; 20(4): 454-456.

42. Ciprandi G, Signori A, Tosca MA, Cirillo I. Bronchodilation test in patients with allergic rhinitis. *Allergy* 2011; 66: 694–698.

43. Ianiero L, Saranz RJ, Lozano NA, Lozano A, Sasia LV, Ramírez M, Cuestas E. Analysis of the flow-volume curve in children and adolescents with allergic rhinitis without asthma. *Arch Argent Pediatr* 2013; 111(4): 322-327.

44. Kessel A. The impact of intranasal corticosteroids on lung function in children with allergic rhinitis. *Pediatr Pulmonol* 2014; 49:932–937.

45. Saranz RJ, Lozano A, Valero A, Lozano NA, Bovina Martijena MP, Agresta F, Ianiero L, Ponzio MF. Impact of rhinitis on lung function in children and adolescents without asthma. *Allergol Immunopathol (Madr)* 2016. http://dx.doi.org/10.1016/j.aller.2016.04.006

46. Capasso M, Varricchio A, Ciprandi G. Impact of allergic rhinitis on asthma in children: effects on bronchodilation test. *Allergy* 2010; 65:264-268.

47. Kim YH, Park HB, Kim MJ, et. al. Fractional exhaled nitric oxide and impulse oscillometry in children with allergic rhinitis. *Allergy Asthma Immunol Res* 2014; 6 (1): 27-32.

48. Foresi A, Leone C, Pelucchi A, Mastropasqua B, Chetta A, D'Ippolito R, Marazzini L et al. Eosinophils, mast cells and basophils in induced sputum from patients with seasonal allergic rhinitis and perennial asthma: Relationship to methacoline responsiveness. *J Allergy Clin Immunol* 1997;100:58-64.

49. Bonay M, Neukirch C, Grandsaigne M, et al. Changes in airway inflammation following nasal allergic challenge in patients with seasonal rhinitis. *Allergy* 2006; 61:111-118.

50. Panzner P, Malkusová I, Vachová M, Liska M, et al. Bronchial inflammation in seasonal allergic rhinitis with or without asthma in relation to natural exposure to pollen allergen. *Allergol Immunopathol (Madr)* 2015; 43(1): 3-9.

51. Inal A, Kendirli SG, Yilmaz M, et. al. Indices of lower airway inflammation in children monosensitized to house dust mite after nasal allergen challenge. *Allergy* 2008; 63:1345-1351.

52. Rolla G, Guida G, Heffler E, Badiu I, Bommarito L, De Stefani A et al. Diagnostic classification of persistent rhinitis and its relationship to exhaled nitric oxide and asthma. A clinical study of a consecutive series of patients. *Chest* 2007; 131:1345–1352.

53. Wang W, Xian M, Xie Y, Zheng J, Li J. Aggravation of airway inflammation and hyper-responsiveness following nasal challenge with *Dermatophagoides pteronyssinus* in perennial allergic rhinitis without symptoms of asthma. *Allergy* 2016; 71: 378–386.

54. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Resp Crit Care Med* 2011; 184(5): 602-15.

55. Makris MP, Gratziou C, Aggelides XS, et. al. Exhaled nitric oxide, bronchial hyperresponsiveness and spirometric parameters in patients with allergic rhinitis during pollen season. *Iran J Allergy Asthma Immunol* 2011; 10(4): 251-260.

56. Lee KJ, Cho SH, Lee SH, Tae K et al. Nasal and exhaled nitric oxide in allergic rhinitis. *Clin Exp Otorhinol* 2012; 5: 228-233.

57. Kalpaklioglu AF, Kalkan IK. Comparison of orally exhaled nitric oxide in allergic versus non-allergic rhinitis. *Am J Rhinol Allergy* 2012; 26(2): e50-4.

58. Ciprandi G, Ricciardolo FLM, Schiavetti I, Cirillo I. Allergic rhinitis phenotypes based on bronchial hyperreactivity to methacholine. *Am J Rhinol Allergy* 2014; 18: e214-218.

59. Gupta N, Goel N, Kumar R. Correlation of exhaled nitric oxide, nasal nitric oxide and atopic status: A cross‐sectional study in bronchial asthma and allergic rhinitis. *Lung India* 2014; 31: 342-347.

60. Di Cara G, Marcucci F, Palomba A; Milioni M; Pecoraro L; Ciprandi G et al. Exhaled nitric oxide in children with allergic rhinitis: A potential biomarker of asthma development. *Ped Allergy Immunol* 2014; 26: 85-87.

61. Yılmaz I, Bayraktar N, Ceyhan K, Seçil D, Yüksel S, Mısırlıgil Z, Bavbek S. Evaluation of vascular endothelial growth factor A and endostatin levels in induced sputum and relationship to bronchial hyperreactivity in patients with seasonal allergic rhinitis. *Am J Rhinol Allergy* 2013; 27:181-6.

62. Yang MS, Lee HA, Kim MH, Song WJ,Kim TW,Kwon JW,Kim SH, et al. Rhinitis patients with sputum eosinophilia show decreased lung function in the absence of airway hyperresponsiveness. *Allergy Asthma Immunol Res* 2013; 5:232-238.

63. Krantz C, Janson C, Borres MP, Nordvall L, Alving K, Malinovschi A. Nasal nitric oxide is associated with exhaled NO, bronchial responsiveness and poor asthma control. *J Breath Res* 2014; 8(2): 026002. doi: 10.1088/1752-7155/8/2/026002.

64. Skevaki C, Van den Berg J, Jo Skevaki C, Van den Berg J, Jones N, Garssen J, Vuillermin P, LevinM et al. Immune biomarkers in the spectrum of childhood noncommunicable diseases, *J Allergy Clin Immunol* 2016; 137:1302-16.

65. Zissler UM, Esser-von Bieren J, Jakwerth CA, Chaker AM, Schmidt-Weber CB1. Current and future biomarkers in allergic asthma. *Allergy* 2016; 71:475-494.

66. Robinson D, Humbert M, Buhl R, Cruz AC, Inoue H, Korom S, Hanania NA, Nair P. Revisiting Type 2-high and Type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy* 2017; 47:161-175.

67. Prieto L, Bertó JM, Gutierrez V. Airway responsiveness to methacholine and risk of asthma in patients with allergic rhinitis. *Ann Allergy* 1994; 72: 534-539.

68. Añibarro B, García-Ara MC, Díaz MF, Boyano T, Ojeda JA. Nonspecific bronchial hyperresponsiveness and development of asthma in children with hay fever. *Pediatr Allergy Immunol* 1995; 6: 200-203.

69. Ciprandi G, Tosca MA, Capasso M. High exhaled nitric oxide levels may predict bronchial reversibility in allergic children with asthma or rhinitis*. J Asthma* 2013; 50:33-38.

70. Lee E, Lee SH, Kwon JW, Kim Y, Cho HJ, Yang SI, et al. A rhinitis phenotype associated with increased development of bronchial hyperresponsiveness and asthma in children. *Ann Allergy Asthma Immunol* 2016; 117: 21-28.

71. Morjaria JB, Caruso M, Rosalia E, et. al. Preventing progression of allergic rhinitis to asthma. *Curr Allergy Asthma Rep* 2014; 14: 412.

72. Kessel A, Halloun H, Bamberger E, Kugelman A, et al. Abnormal spirometry in children with persistent allergic rhinitis due to mite sensitization: The benefit of nasal corticosteroids. *Pediatr Allergy Immunol* 2008:19: 61–66.

73. Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. *Allergy* 2013; 68: 569–579.

74. Corren J, Adinoff A, Buchmeier A, Irvin C. Nasal beclometasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992; 90: 250-256.

75. Watson W, Becker A, Simons FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993; 91: 97-101.

76. Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone priopionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996; 98: 274-282.

77. Sandrini A, Ferreira IM, Jardim JR, Zamel N, Chapman KR. Effect of nasal triamcinolone acetonide on lower airway inflammatory markers in patients with allergic rhinitis. *J Allergy Clin Immunol* 2003; 111:313-320.

78. Brozek JL,Bousquet J, Baena-Cagnani CE, Bonini S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; 126: 466-76.

79. Aubier M, Neukirch C, Piffer C, Melac M. Effect of cetirizine on bronchial hyperresponsiveness in patients with seasonal allergic rhinitis and asthma. *Allergy* 2001; 56: 35-42.

80. Cingi C, Muluk NB, Ipci K, Şahin E. Antileukotrienes in upper airway inflammatory diseases. *Curr Allergy Asthma Rep* 2015; 15: 64. DOI 10.1007/s11882-015-0564-7

81. Grembiale RD, Camporora Naty S, Tranfa CME, Djukanovic R, Mársico SA. Effect of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2000; 162: 2048-2052.

82. Jacobsen L, Niggemann B, Dreborg S, et. al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62: 943–948.

83. Marogna M, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco AD, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008; 101: 206–11.

84. Fiocchi A, Fox AT. Preventing progression of allergic rhinitis: the role of specific immunotherapy. *Arch Dis Child Educ Pract Ed* 2011; 96: 91-100.

85. Tsilochristou OA1, Douladiris N, Makris M, Papadopoulos NG. Pediatric allergic rhinitis and asthma: can the march be halted?. *Paediatr Drugs* 2013; 15:431-40.

86. Boyman O, Kaegi C, Akdis M, Bavbek S, Bossios A, Chatzipetrou A et al. EAACI IG biologicals task force paper on the use of biologic agents in allergic disorders. *Allergy* 2015; 70:727–754.

87. Draikiwicz S, Oppenheimer J. What is the current role of biologics in the management of patients with severe refractory asthma?. *Ann Allergy Asthma Immunol* 2016; 116:383-387.

88. Mirzakhani H, Al-Garawi A, Weiss ST, Litonjua AA. Vitamin D and its role in allergic disease. *Clin Exp Allergy* 2015; 45:114–125.

89. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo Jr CA et al. Prenatal, perinatal, and childhood vitamin D exposure and their association with childhood allergic rhinitis and allergic sensitization. *J Allergy Clin Immunol* 2016; 137:1063-1070.

90. Keshavarzian A, Tobin MC, Landay A.Schleimer RP. A comprehensive review of the nasal microbiome in chronic rhinosinusitis (CRS). *Clin Exp Allergy* 2016; 46:21–41.

91. Zuccotti G, Meneghin F, Aceti A, Barone G, Callegari ML, Di Mauro A et al. Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. *Allergy* 2015; 70:1356–1371.

Legends

Table 1: Prevalence of bronchial hyperresponsiveness among patiens with chronic rhinitis.

Table 2: Frequency of spirometric abnormalities among patients with allergic rhinitis.

Table 3: Studies of analysis of the fraction of exhaled nitric oxide (FeNO) in patients with rhinitis.

Figure 1: Diagram representative of the approximate distribution of the fraction of exhaled nitric oxide values in healthy individuals, atopic patients and patients with rhinitis and asthma.

Figure 2: Proposed evolutionary model from rhinitis to asthma.

(Modified from Agresta et al. *Rev Fac Cien Med Univ Nac Córdoba* 2014; 71: 111-121).

Table 1:

Reference		N	Rhinitis phenotype	Age	BPT	Prevalence
Townley RG et al. *1975* [22]	*JACI*	27	PAR-SAR	23,6 *	Methacholine	55,0%
Cockcroft DW et al. *Allergy 1977* [23]	*Clin*	23	PAR-SAR	20 – 62**	Histamine	22,0%
Ramsdale EH et al. *1985* [24]	*JACI*	25	PAR-SAR	33*	Methacholine Cold air	40,0%
Madonini E et al. *1987* [25]	*JACI*	27	SAR	20,3*	Carbachol	48,1%
Braman S et al. *Chest 1987* [26]		40	SAR	27.4*	Methacholine	40,0%
Saranz RJ et al. *1997* [27]	*JACI*	42 23	PAR-SAR PAR-SAR	14.1* 14.3*	Methacholine Exercise	57.0% 13.0%
Prieto L et al. *Respir J 2001* [28]	*Eur*	28 28	PAR-SAR PAR-SAR	30,9* 30,9*	Methacholine AMP	39,0% 36,0%
Choi SH et al. *2007* [29]	*Allergy*	83	PAR-SAR	4 – 6**	Methacholine	32,5%
Cirillo I et al *2009* [30]	*Allergy*	342	PAR-SAR	23,6*	Methacholine	28,1%
Kim SW et al *Am J Rhinol Allergy 2013* [31]		176 51	PAR-SAR NAR	6-15** 6-15**	Methacholine	55,7% 25,5%

Wang Q et al	377	PAR-SAR	28.0*		12,2 %
J Thorac Dis 2015 [32]	262	NAR	29.8*	Methacholine	6,1%

N: number; BPT: Bronchial provocation test; PAR: Perennial allergic rhinitis; SAR: Seasonal allergic rhinitis; NAR: Non-allergic rhinitis; * Years (mean) ** Years (range); AMP: Adenosine 5´ monophosphate.

Table 2:

Reference	N	Rhinitis phenotype	Age	Lung function abnormality prevalence	More affected spirometric parameter
Ciprandi G et al. *Allergy 2008* [38]	392	P – S	20-49*	87%	FEF25-75% (<80%)
Ciprandi G el al. *Clin Exp Allergy 2010* [39]	200	P – S	8-16*	42%	FEF25-75% (<80%)
Ciprandi G et al. *Laryngoscope 2010* [40]	1539	P – S	17-56*	23%	FEF25-75% (<75%)
Mohammad Y et al. *Prim Care Respir J 2011* [41]	60	P – S	28± 9**	16,2%	FEF25-75% (<65%)
Ciprandi G et al. *Allergy 2011* [42]	1469	P – S	18-48*	17,8%	FEF25-75% (<65%)
Ianiero L et al. *Arch Argent Ped 2013* [43]	84	P – S	6-18*	25%	FEV1/FVC (<80%)
Kessel A *Pediatr Pulmonol 2014* [44]	202	P – S	11.6±3,4**	26,3%	FEF25-75% (<80%)

N: Number; P: Perennial; E: Seasonal;* Years (range); **Years (mean ± DS); FEF25-75%: Forced expiratory flow between 25 and 75% of vital capacity; FEV1/FVC: ratio between forced expiratory volume in the first second of the forced vital capacity and the forced vital capacity.

Table 3:

Reference	N	Rhinitis phenotype	Age	Results
Rolla G et al. Chest 2007 [52]	108	AR vs NAR vs CRS	11-75*	Higher FeNO in AR vs NAR (p:0.002) Higher FeNO in CRS vs NAR (p < 0.001)
Chawes BL K at al. *JACI 2010* [13]	290	AR vs NAR vs control group	7	Higher FeNO in AR vs NAR and control group (p<0.001)
Makris MP et al. *Iran J Allergy Asthma Immunol 2011* [55]	26	SAR	16-47*	Higher FeNO in AR with BHR to methacholine during the pollen season
Lee KJ et al. *Clin Exp Otorhinol 2012* [56]	35 34	PAR vs control group	22.7±8.7** 26.9±11.0**	Higher FeNO in AR vs control group (p=0.003)
Kalpaklioglu AF et al. *Am J Rhinol Allergy 2012* [57]	171	AR vs NAR	32.6 ± 3.2**	Higher FeNO in AR vs. NAR
Ciprandi G et al. *Am J Rhinol Allergy 2014* [58]	298	PAR y SAR	28.9 ± 6.0**	BHR to methacholine associated to FeNO > 25ppb
Gupta N et al. *Lung India* 2014 [59]	90	AR vs NAR vs asthma vs control group	6-38*	Higher FeNO in AR vs. NAR but less than allergic and non- allergic asthma
Kim YH et al. *Allergy Asthma Immunol Res. 2014* [47]	196	PAR and SAR vs asthma vs control group	7.9-11.1*	Higher FeNO en AR group vs. control group (P=0,005) but less than asthma group (P < 0.0001)

Di Cara G et al. *Pediatr Allergy Immunol 2014* [60]	109	PAR – SAR	7-13*	All children with AR that developed asthma after 5 years shown a basal FeNO >35 ppb.

N: number; AR: allergic rhinitis; NAR: Non-allergic rhinitis; CRS: Chronic rhinosinusitis; PAR: Perennial allergic rhinitis; SAR: Seasonal allergic rhinitis; BRH: Bronchial hyperreactivity. * Years (range); **Years (mean ± DS)

FIGURE CAPTIONS:

Figure 1: Diagram representative of the approximate distribution of the fraction of exhaled nitric oxide values in healthy individuals, atopic patients and patients with rhinitis and asthma.

NAR: Non-allergic rhinitis

Figure 2: Proposed evolutionary model from rhinitis to asthma. (Modified from Agresta et al., Rev. Fac. Cs. Med. Univ. Nac. Córdoba 2014; 71: 111-121).

BHR: Bronchial hyperreactivity; LF: Lung function