



The Roadmap From Allergic Rhinitis to Asthma

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Abstract

Purpose of review Upper and lower airways display some common characteristic described as a holistic model. Because rhinitis may proceed asthma, it is imperative to understand the mechanisms and risk factors responsible for the progression from rhinitis to asthma. **Recent findings** Subclinical lower airway abnormalities have been observed in patients with rhinitis without asthma. Recent evidence indicates that these patients may have an increased risk of developing asthma. Environmental and genetic factors can contribute to enhance this possibility. The treatments of rhinitis have also been shown to be beneficial to the lower airway, and therefore potentially modify the natural evolution of the atopic march.

Summary Lower airway disease is a good predictor for the roadmap from rhinitis to asthma. The shared genetic link and environmental factors could be essential for this progression. Albeit treatment of rhinitis has a beneficial effect on lower airway defects, their role to prevent the progression to asthma remains yet to be confirmed.

Introduction

Rhinitis is one of the most frequent chronic diseases of human pathology, manifested in different phenotypes. However, doctors and patients often underestimate their impact on the quality of life and, in particular, school and work activities and their evolutionary possibilities [1].

Traditionally, rhinitis and asthma have been considered as dissociated diseases. Newer epidemiological evidences established a causal relationship considering rhinitis as a risk factor for asthma [2]. At present, the relationship is in a holistic phase of identity in which both pathologies are associated to a common inflammatory disorder of the entire respiratory tract, with clinical manifestations related to different organs [2, 3].

The link between the upper and lower airways has significant physiological, epidemiological, and clinical interest and has direct therapeutic implications, based on a holistic concept [4]. Although not in all patients, rhinitis coexist with asthma; the “identity” hypothesis has a pathophysiological basis, given that a large number of patients with rhinitis indeed have subclinical pulmonary abnormalities that potentially can have prognostic implications [5•].

The objectives of this review are to describe the epidemiological and pathophysiological links between the upper and lower airways, the subclinical pulmonary correlates in patients with rhinitis, their evolutionary implications, and the impact that a therapeutic intervention could have on their natural evolution.

Epidemiologic link

Although some weak evidences suggest that asthma may precede rhinitis, most of the studies in children and adults report that the onset of rhinitis precedes asthma development and that the incidence of asthma is higher in individuals with rhinitis.

Rhinitis is ubiquitous in patients with asthma [1]. This association seems to be independent of atopic sensitization, because occurs in more than 75% of the patients with allergic asthma and in more than 80% of those with non-allergic asthma. [1]. However, Togias et al. [6••] in a study of 619 urban children and adolescent with asthma described that rhinitis was present in a 93.5%, and, in relation of its phenotypes, perennial allergic rhinitis (AR) with seasonal exacerbations was most common (34.2%) and non-allergic rhinitis (NAR) was least common (11.3%).

An epidemiological study that included over 18,000 patients between 16 and 75 years old provides less convincing data: among those who had asthma diagnosis, a 63.9% was associated with AR, a 39.8% with chronic rhinitis, and 8.4% with chronic rhinosinusitis [7].

Rhinitis increases the possibility of suffering asthma. A multicenter and multinational study of over 10,000 adult patients from European Community Respiratory Health Survey (ECRHS) [8] showed that asthma prevalence was 6 times higher in individuals with rhinitis than in those without the disease (7, 6 to 22.6% vs. 1 to 6%). Furthermore, a study including over 139,000 school-age children demonstrated a higher incidence of asthma in children with rhinitis compared with children without rhinitis (20.8 vs. 7.7% in children 6–7 years; 13.5 vs. 4.0% at 13–14 years, and 12.4 vs. 3.8% in adolescents aged 16–17 years) [9].

Increased prevalence of asthma was present in children with both, allergic and non-allergic rhinitis. Chawes et al. [10] observed asthma with equal frequency in preschool children with AR and NAR. Although the coexistence of both diseases can vary according to the type and number of sensitizations [11], this co-morbid association can be expressed beyond allergy-driven mechanisms [10].

Several studies have shown that both the AR and NAR phenotypes contribute to an increased risk of development and persistence of asthma. Young adults with rhinitis have a three times higher risk of developing asthma compared to normal individuals. In a longitudinal study of approximately 1000 students, Settipane et al. [12] described that, 23 years after recruitment, the prevalence of asthma was 10.5%, in those patients that presented AR and was only a 3.6% among those who did not.

In another longitudinal study including 6461 young adults followed for a period of 8.8 years, compared with healthy subjects, patients with AR had a 3.65-fold relative risk of developing asthma, and in those patients with NAR, the risk was slightly lower (2.75-fold) [13]. Rhinitis is associated with an increased risk of asthma development also from childhood. Recently, a longitudinal study in children from the Tucson cohort diagnosed with rhinitis at age 6 years [14••] demonstrated that both allergic and non-allergic forms confer an increased risk of developing asthma in adulthood. Thus, rhinitis, regardless of its origin and age of onset, is indeed a risk factor for asthma development.

Pathophysiological mechanisms of nose-lung interaction

Numerous local mechanisms have been described to explain the nexus between nose and lungs, but many of them do not have enough scientific support to support the pathology within the “single airway” concept [3, 15, 16].

The proposed theories are the obligatory mouth breathing secondary to nasal obstruction, the neural modulation by a naso-bronchial reflex, and the aspiration of inflammatory content from the nose to the bronchial tract [16•]. The decrease of beta-adrenergic bronchial response and the production of nasal nitric oxide are less relevant [15].

Nasal blockage causes compensatory mouth breathing, losing the natural protective functions of the nose. However, nasal clipping in patients with AR did not produced an increase in the asthmatic response, nor was there a relationship between the nasal blockage degree (induced by nasal challenge with allergens) and the changes in bronchial reactivity, and therefore, the impact of mouth breathing on the lower airway is not relevant [17, 18].

Research about the nasal-sinus-pulmonary reflex was described as early as the beginning of the twentieth century. Studies that evaluated the effect application of allergens, histamine, and capsaicin in the nose of non-atopic and atopic individuals on lower airway resistance yielded contradictory results [19]. Therefore, more studies are required to confirm its physiopathogenic role [15].

The idea that proinflammatory products in nasosinusal secretions of patients with rhinosinusitis could be aspirated into the lower airways is one of the oldest hypotheses. However, studies with aspiration of nasal secretions or radiolabeled allergens failed to demonstrate their presence in the bronchial mucosa, and this is the reason why most authors consider that it is unlikely that this mechanism plays a critical role in the upper and lower airway interaction [15, 16, 20]. Although these local mechanisms may be common for AR and NAR, most of the studies are inconclusive to explain the nose-lungs connection.

More recent studies have shown a systemic inflammatory connection between nose and lungs through the blood circulation, applicable to the allergic respiratory disease phenotype [18]. Under the model of a relationship between AR and asthma, an inflammatory physiopathological nexus has been demonstrated in the extensive research of Braunstahl et al. [18, 21, 22]. The

challenge with allergens in the nose triggers a specific communication between the airway and the bone marrow, through signaling processes of hematopoietic cytokines, stimulating the production of progenitors of the eosinophilic-basophilic lineage in the bone marrow [21]. Migration of these cells into bronchial tract could explain the reason why many patients with AR present anatomopathological signs of inflammation and hyper-reactivity throughout the entire airway, yet only have clinical manifestations at the nasal level [3, 15, 18].

The evolution of this process can be reversed from the bronchi to the nose. Segmental bronchoprovocation with grass pollen in subjects with seasonal AR produces an increased nasal degranulation of mast cells and an increase in the basophils influx towards the nasal and bronchial mucosa, with simultaneous elevation of IL-5 and eotaxin serum levels, an effect not observed in healthy controls [22]. Therefore, the final target site of the allergic reaction is the entire airway and not only the portion where the reaction is naturally or exogenously triggered.

The description of this pathophysiological model does not explain the interaction between rhinitis and asthma not caused by allergens. Recent evidence highlights the Th1 lymphocyte role, associated with immunity against viruses and bacteria and Th17 related to neutrophilic inflammation [23]. An increase of Th17 lymphocytes in blood circulation and nasal and bronchial tissue that induce a predominantly neutrophilic infiltration has been reported in patients with rhinitis, chronic rhinosinusitis, and asthma [24]. It remains to be more broadly established the connecting mechanisms between the upper and lower airways for the non-allergic phenotypes in the context of the “united airway disease.”

The local inflammatory, allergen-immunoglobulin E (IgE) mediated phenomenon in the nose and bronchi, named “entropy,” may also have a pathogenic role [25]. Bacterial superantigens (i.e., from *Staphylococcus aureus*), likely play an emergent role as a potent airway inflammatory enhancement cofactor. This mechanism poses a medical challenge for the differential diagnosis against non-allergic phenotypes of rhinitis and asthma [26].

Subclinical lower airway correlates in chronic rhinitis

Bronchial hyper-reactivity (BHR) is an essential but not exclusive pathophysiological characteristic of asthma, which can be manifested in other respiratory diseases such as rhinitis [5•].

Studies in children and adults with AR without clinical expression of asthma have shown that between 12.2 and 55.7% of patients exhibit BHR to methacholine, cold air, histamine, adenosine 5'-monophosphate (AMP), and exercise [10, 27–37]. The observed differences may be related to sensitivity and specificity of the bronchial provocation methods used, as well as to dissimilar definitions of BHR.

Many patients with rhinitis exhibit not only observed airway hypersensitivity to inhaled pharmacologic stimuli such as methacholine or histamine, but also an excessive airway narrowing because an absent maximal response plateau, like as patients with asthma. [38, 39]. On the other hand, while only patients with allergic asthma display hyper-responsiveness on proximal central airway, patients with AR or asthma display a similar pattern of peripheral airway responsiveness that is different from that observed in non-atopic control [40••]. This “asthmatic behavior” of the small airway may predict the development of asthma in patients with AR.

BHR in patients with AR was associated with sensitization to trees pollens and mites, longer rhinitis duration, and forced expiratory volume in the first second (FEV1) $\leq$ 86% of the predictive value [33]. Forced expiratory flow between 25 and 75% of vital capacity (FEF 25–75%) values $\leq$ 65% constitutes a predictor of severe BHR (OR = 12.9) [41]. In addition, peripheral blood eosinophil percentage may be an alternative marker to predict BHR in AR patients [37].

BHR is more frequent in the AR phenotype; a study in children using methacholine challenge demonstrated a twice higher BHR prevalence in AR than in NAR (55.7 vs. 25.5% respectively) and was more frequent in persistent than intermittent rhinitis [35]. Patients with persistent AR and male gender were found to develop BHR earlier in the disease progression [37]. Chawes et al. [10] also reported an increase in bronchial responsiveness to cold dry air hyperventilation in children with AR without asthma, but not in those with NAR.

Numerous studies have shown lung function abnormalities, evaluated mainly using spirometry [42–47] and impulse oscillometry [48, 49] in patients with rhinitis without asthma symptoms. Between 17.8 and 87% of adult patients with AR present some degree of spirometric alteration [42, 45]. These variations are due to the abnormality threshold established for the chosen functional parameters. In all of them, the most affected spirometric variable was FEF25–75%.

In children and adolescents with rhinitis, the prevalence of lung function impairment is estimated to be

between 22.2 and 42% [43, 44, 46, 47]. In two studies, we demonstrated spirometric abnormalities in 25% and 22.2% of children and adolescents with rhinitis without asthma; the index between the forced expiratory volume in the first second of the forced vital capacity and the forced vital capacity (FEV1/FVC) were the most affected parameters, either alone or combined with other spirometric variables [46, 47].

The risk factors associated with the spirometric alterations were nasal and blood eosinophilia, high body mass index, reduction of nasal airflow, and a longer persistence of rhinitis [42, 44, 46]. In addition, the clinical grade of rhinitis can influence the magnitude of the functional defect: the persistent and moderate-severe forms exhibited a greater degree of pulmonary impairment [47].

The airflow obstruction in patients with rhinitis is potentially reversible with a bronchodilator. A positive bronchodilator response was found in 21.5% of children [50] and approximately 2/3 of young adults with AR [45]. A FEF25–75 cutoff value $\leq$ 71% may already discriminate patients with reversibility [45]. However, considering as a dissociated conditions, frequency, and severity of rhinitis, we could not reproduce similar findings because the reversibility obtained between groups was not significant [47].

Forced oscillations technique (FOT) is an emergent and more sensitive technique for detecting small changes in lung function than spirometry. Kim et al. [48] observed that the bronchodilator response in reactance at 5 Hz (D 95) and the reactance area (D AX) increased more in the asthma and AR groups than in controls simultaneously with higher FeNO. Skylogianni et al. [49••] have shown that, at AR exacerbation, children who developed asthma had significantly larger changes in FEV1, FEF25–75%, respiratory resistance (Rrs), and reactance (Xrs) after bronchodilator administration compared to controls.

A bidirectional inflammatory process may be the most important link between the upper and lower airways. Therefore, many patients with AR without asthma symptoms show inflammation in the lower airway as demonstrated by the induced sputum and exhaled nitric oxide (FeNO) [48, 51–56].

In patients with AR induced by pollen allergens, after nasal challenge outside the pollen season, an increase in the number of eosinophils and eosinophil cationic protein (ECP) in induced sputum and increased bronchial reactivity to methacholine was observed [52], a phenomenon that was able to reproduce with natural

Table 1. Summary of studies about the predictive value of lower airway abnormalities for asthma development in patients with chronic rhinitis

Reference	Patients with AR (n)	Age (years)	Method of study	Follow-up time (years)	Predictive value for asthma development
Townley RG et al. JACI 1975 [27]	27	11–47*	MTC challenge	1,5	BHR to MTC may be of value in predicting asthma in hay fever patients
Braman SS et al. Chest 1987 [30]	40	12–54*	MTC challenge	4–5,3	AR patients with BHR to MTC are at greater risk to develop asthma.
Prieto L et al. Ann Allergy 1994 [66]	66	16–51*	MTC challenge	5,8	A single determination MTC PC20 was not a reliable marker of development of asthma.
Añibarro B et al. Ped Allergy Immunol 1995 [67]	15	6–12*	MTC challenge	4	Neither the presence nor the degree of previous BHR was useful for predicting asthma development.
Koh YY et al. Clin Exp Allergy 2002 [39]	141	10–16*	MTC challenge	7	A increased maximal airway response to MTC was a good predictor for development of asthma in children with AR.
Ferdousi HA et al. Ped Allergy Immunol 2005 [68]	28	7–13*	MTC challenge and IHCA	2	Children with hay fever and BHR has high risk of developing asthma
Di Cara G et al. Ped Allergy Immunol 2014 [69]	109	7–13*	FeNO	5	FeNO > 35 ppb was predictive for asthma development
Ciprandi G et al. Int Arch Allergy Immunol 2017 [70•]	553	28.8	FeNO	2	Patients with AR and high FeNO levels (> 50 ppb) progressed to asthma
Lee E et al. Ann Allergy Asthma Immunol 2016 [71]	512	6–8*	Spirometry and MTC challenge	4	Children with AR and impaired lung function developed BHR and asthma
Skylogianni E et al. Allergol Immunopath 2018 [49••]	73	6	Spirometry/FOT	5	Children with SAD developed asthma

AR, Allergic rhinitis; MTC, methacholine; FOT, forced oscillations technique; BHR, bronchial hyper-reactivity; SAD, small airway dysfunction; IHCA, isocapnic hyperventilation of cold air; FeNO, exhaled nitric oxide; ppb, parts per billion; * age range

exposure during the pollen season [55]. A significant increase of eosinophils in blood, nasal secretion, and induced sputum and simultaneous BHR to methacholine and pulmonary function aggravation has been reported in patients with AR without asthma exposed to nasal provocation with mites [56]. This demonstrates a connection between these physiopathological events as a response to the allergic stimulus in rhinitis.

The measurement of FeNO, produced endogenously by nitric oxide synthetase in bronchial epithelial cells and some inflammatory cells, is considered as an indirect method to detect bronchial inflammation mediated by eosinophils [57]. The vast majority of the studies indicate that the increase in FeNO is almost exclusive of the allergic phenotype of rhinitis, with similar or lower values than those of allergic asthma [10, 36, 48, 53, 54, 58].

Haccuria et al. [40••] describes that FeNO levels were elevated to a similar extent in both asthma and AR and that large proportion of the increased NO production reported in AR patients appears to originate in lower peripheral airways like as asthmatic patients. This can be explained because both conditions share the same driven type 2 T-helper cell inflammatory process [59].

FeNO is intensified by exposure to seasonal pollen in patients with AR without asthma [53]. In adults with AR, the coexistence of elevated FeNO levels with methacholine BHR was demonstrated [58]. Possibly, the coexistence of both phenomena reinforces the risk for a progressive evolution to asthma.

On the other hand, FeNO levels were positively correlated with the percentage of eosinophils in sputum [60] and with peripheral blood eosinophil count and serum total ECP [61] in AR patients, demonstrating the similarity of these methods to detect subclinical bronchial inflammation in patients with rhinitis alone. FeNO may therefore be an ideal non-invasive and simple method for detecting lower airway involvement in AR.

Evidences about airway inflammation in NAR are scarce. Wang et al. [36] observed that patients with NAR exhibited small airway dysfunction and elevated FeNO and eosinophils in sputum although of lesser magnitude than AR. This findings suggests similar characteristics underlying the bronchial inflammation between both phenotypes; however, others anatomopathological features should be more extensively studied.

The bronchial remodeling reflects structural changes in the airway wall components and their organization secondary to injury after exposition to allergic and non-

allergic stimuli. This is a characteristic of the airway in asthmatic patients, but also in atopic patients without asthma and patients with AR [62]. Although scarce, there is some histopathological evidence of lung remodeling in animal model and patients with AR. In a guinea pig model with AR bronchial wall thickness, increased collagen deposition, epithelial layer thickness, and smooth muscle thickness in the airways were significantly increased [63].

Subjects with seasonal rhinitis and BHR expressed a significant increase in VEGF-A and endostatin, factors associated with angiogenesis of bronchial remodeling found in induced sputum [64]. Adults with persistent moderate-severe AR with eosinophilia in sputum showed a higher expression of mRNA for MMP-9 and in the MMP-9/TIMP-1 coefficient, both mediators related to airway fibrosis [65]. Bronchial remodeling can contribute to the progressive decline of lung function in asthma, but its definitive outcome in patients with rhinitis should be confirmed in future studies.

From rhinitis to asthma: what are the steps?

Subclinical lower airway abnormalities: are there any predictive biomarkers?

Since the 1970s, many studies have confirmed that the existence of pulmonary alterations without clinical expression in children and adults with rhinitis implies an increased risk of developing asthma, but the foundations of these claims were the result of some more recent and better designed longitudinal studies (Table 1).

Research about the asthma predictive value of BHR in patients with rhinitis yielded contradictory results. Ferdousi et al. [68] demonstrated that BHR to methacholine (PD20FEV1) and to cold air challenge are of value to reveal subclinical asthma in children with hay fever, but Koh et al. [39] demonstrated in adolescents with AR that an increased maximal airway response to methacholine was shown to be a better predictor for the future development of asthma, than a single determination of PC20 FEV1. However, two studies conducted in adults [66] and children [67] did not show the same results. To our knowledge, no studies have evaluated the predictive value of BHR in NAR. Probably, the predictive value of BHR in AR depends on its association with other subclinical pulmonary alterations and the challenge is the identification of modifiable factors related to its onset and progression.

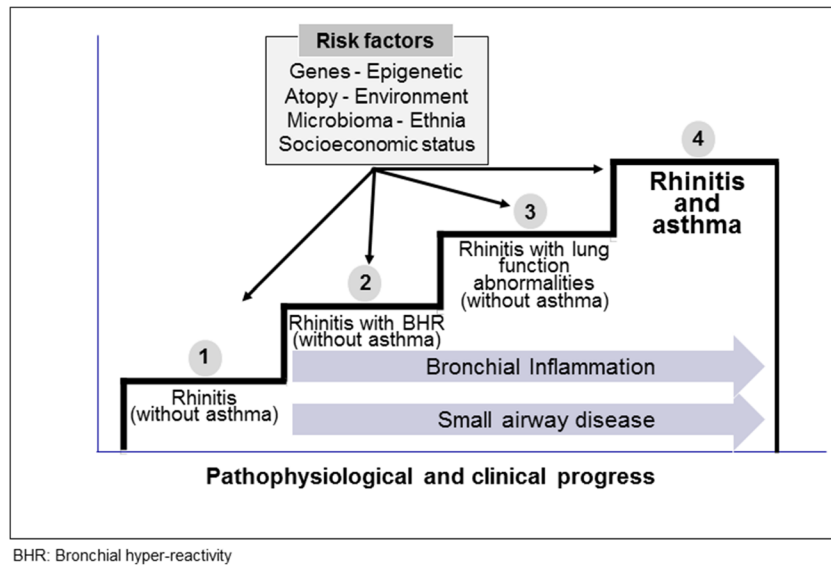


Fig. 1. A proposed model for the steps and risk factors from rhinitis to asthma development.

The increase in FeNO levels in children with AR can be a predictive biomarker of asthma development. An association between FeNO > 34 ppb with a positive response to bronchodilator was reported, compatible with subclinical asthma [72]. Di Cara et al. [69] demonstrated that 21 of 109 children with AR developed asthma after 5 years of follow-up. All of them exhibited at the beginning of the study a FeNO > 35 ppb. The risk was proportional to the initial value of FeNO: every 10 ppb above the limit of 35 ppb corresponded to more than twice the risk of developing asthma (OR, 2.4). Recently, one study in young adults with AR [70•] obtained similar results: increased FeNO levels were associated with impaired lung function and more frequent BHR; in a 2-year follow-up study, 22 out of 82 of those patients (26.8%) with high FeNO levels (> 50 ppb) developed asthma.

The lung function abnormalities in patients with rhinitis could imply an increased risk for asthma development. A recent study found that children with rhinitis, allergens sensitization, and abnormal lung function experienced a greater risk of developing BHR and asthma in a prospective 4-year follow-up study [71]. Skylogianni et al. [49••] performed the first longitudinal study in children with rhinitis and demonstrated, using FOT, that the dysfunction in the small airway has a predictive value for the development of asthma, independently of other conditions such as eczema, maternal asthma, and allergic sensitization.

Therefore, the existence of subclinical changes in lung function and its reversibility to bronchodilator that many of these patients show represents an “asthmatic” functional behavior and requires of a careful monitoring of the clinical evolution [73••].

Genetic link between rhinitis and asthma

Rhinitis usually precedes the development of asthma; however, this possibility does not include all of those individuals who suffer from rhinitis [13, 14].

Allergic diseases are complex and development involves both environmental and genetic factors and the latter play an important role with an estimated heritability of 70% to 90% [74, 75].

Asthma and rhinitis share a greater number of genes than those expected by chance and their associated proteins exhibit a high degree of functional interaction network [76, 77]. Approximately 15 pathways are involved in the multimorbidity of asthma, eczema, and rhinitis, including the IL4 signaling pathway related to GATA3 [77]. Using the Phenopedia tool of the HuGE Navigator software, 1113 genes have been reported for asthma and 199 genes for rhinitis, of which 23 are shared by both diseases [4]. Consequently, it is highly likely that those who express genes in a shared way simultaneously or progressively develop both diseases,

although epigenetic changes could contribute to the comorbidity between rhinitis and asthma [78].

Role of nasal microbiota and microbial exposure

The composition of the airway microbiota reflects the characteristics of the airway environment, with differences between those observed in health and disease [79]. Such exposure can have the ability to modify immune maturation in early life.

The microbiological composition of respiratory tract differs between patients with rhinitis alone, rhinitis, and wheezing and healthy people. Nasal microbiome could be involved in development of early-onset rhinitis and wheeze in infants [80•]. An increase of Oxalobacteraceae family (*Proteobacteria phylum*) and Aerococcaceae family (*Firmicutes phylum*) was associated with rhinitis and concomitant wheeze [80•]. Therefore, the airway microbiome could be a useful marker of disease progression and predictor of different possibilities of therapeutic intervention [81].

Factors such as environmental microbial diversity and endotoxin levels exposure associated to community lifestyle may have a critical role in early life for development of asthma [82]. This may impact on profiles of genes, cytokines, and immune cells in peripheral blood related to the response of immunity innate to bacterial lipopolysaccharides [83]. Therefore, the measurement of those innate immune changes could be a useful biomarker to define asthma risk.

Probably, the progress from rhinitis to asthma is gradual, with BHR and impaired lung function as a middle step, associated with a parallel increase in bronchial inflammation and the clinical expression of asthma as the final step. Moreover, the genetic determinants shared between asthma and AR and analysis of ethnic and environmental microbial exposure differences should aid in resolving the pathogenic molecular mechanisms of disease progression along the so-called atopic march (Fig. 1).

Treatment to prevent the development of asthma comorbidity

The demonstration that rhinitis is a risk factor for asthma development and the existence of subclinical pulmonary abnormalities allow us to speculate that the treatment of rhinitis using intranasal steroids, antihistamines, and immunotherapy with allergens (mainly in the early stages of life) can reduce the progression to asthma [84, 85].

Towards mechanisms that have not been definitively clarified, the use of intranasal corticosteroid (INCS) spray in patients with rhinitis and asthma may be useful to improve asthma symptoms, pulmonary function, and non-specific BHR [86], all effects also described in patients with rhinitis without asthma. In children with perennial AR, with impaired pulmonary function (but without underlying asthma), short-term use of nasal Budesonide along 3 months [43], and long-term use of intranasal Budesonide or Triamcinolone for 12 months [87] significantly reversed, although partially, the alteration in FEV1, FEV1/FVC index, and FEF 25–75%.

Fluticasone nasal spray, applied in adult patients with seasonal rhinitis, produced a significant symptomatic improvement and a simultaneous reduction in the number of blood in and bronchoalveolar lavage eosinophils [88]. The intranasal use of triamcinolone acetonide for 4 weeks in adults with AR reduced FeNO and H2O2 condensed in respiration [89]. Thus, steroids have an anti-inflammatory effect at a distance from the site of their application.

These findings do not provide support for a disease-modifying effect of inhaled corticosteroids after they are discontinued and therefore are not currently being suggested by the clinical guidelines for this objective [90].

Oral H1-antihistamines (cetirizine, fexofenadine) and montelukast have a modest anti-inflammatory effect, but they do not have any evidence of a preventive impact on asthma development [85••].

Immunotherapy with allergens (AIT) improves rhinitis symptoms and can potentially modify the natural evolution of the atopic march. Subcutaneous IT can have a beneficial effect on BHR in patients with AR without asthma. A 2-year treatment with subcutaneous IT with *Dermatophagoides pteronissinus* in adults with AR achieved a significant improvement on methacholine PC20 compared to those treated with placebo; however, the preventive effect on asthma development did not showed significant differences ($p = 0.49$) [91]. The Preventive Allergy Treatment study in children with seasonal AR, treatment with IT reduced the development of asthma and methacholine BHR after 3 years of treatment, effect sustained 7 years after its suspension [92].

Two randomized, open-controlled study in children with rhinoconjunctivitis with sublingual IT (SLIT) with pollen extract for 3 years would have the same preventive effect but they did not evaluated if this effect continues after the end of the treatment [93, 94]. The GRAZAX Asthma Prevention (GAP) Trial with SQ grass SLIT Tablet [95] establishes a preventive effect of asthma

at the end of trial but did not show an effect on the time to onset of asthma. A recent meta-analysis concluded a preventive effect to allergen IT at the short term for asthma prevention, and suggest that due to heterogeneity of published studies, the evidence on preventive, and long-term effects of AIT is suggestive but not definitive accepted [96••].

New biological monoclonal antibody (mAb) agents such as omalizumab (anti IgE mAb), mepolizumab

(anti IL-5 mAb), and dupilumab (anti-IL-4 receptor α mAb) have been effective in the treatment of refractory asthma, rhinitis, and nasal polyposis driven by type 2 immune mechanism [97, 98]. New drugs are in early-stage clinical trials and are promising [99•]; however, it cannot be determined, due to its systemic effect, whether the improvement in asthma is due to favorable effect on upper airway pathology.

Conclusions and future perspectives

The model “an airway, a disease” should be considered by all physicians who assist patients with rhinitis since a fragmented approach can have diagnostic, prognostic, and erroneous therapeutic connotations.

Existence of abnormalities in lower airway, mainly in patients with AR, is a potential biomarker of asthma development and the genetic link, microbiota composition, and environmental factors could help to understand the underlying disease mechanisms necessary for this progression. The phenotypic identification of rhinitis would help to recognize subgroups and biomarkers of high risk of asthma development that could potentially be treated to prevent progression to multimorbidity.

Current treatments of rhinitis, including AIT, have short-term effects on asthma evolution. Newer therapeutic approaches based on precision medicine are promising for preventive purpose but need to be evaluated in long-term studies.

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Compliance with Ethical Standards

Conflict of Interest

Ricardo Saranz declares that he has no conflict of interest. Alejandro Lozano declares that he has no conflict of interest. Natalia Lozano declares that she has no conflict of interest. Graciela Alegre declares that she has no conflict of interest. Marina Ponzio Biol declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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