

The link between allergic rhinitis and asthma: the united airways disease

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Rhinitis and asthma are often associated and the two disorders interact at various levels. Rhinitis typically precedes the development of asthma and can contribute to unsatisfactory asthma control. The presence and type of asthma is influenced by sensitization, and the duration and severity of allergic rhinitis. Nasal symptoms, airflow and markers of inflammation directly correlate with lower airway involvement. Local tissue factors, such as microbial stimuli and systemic inflammatory mechanisms, play a role in the clinical expression of the allergic airway syndrome. There is increasing evidence that suggests a major involvement of airway epithelial cells in the pathogenesis of both asthma and allergic rhinitis. Even in patients with rhinitis who do not have asthma, subclinical changes in the lower airways and inflammatory mediators can be detected. The pathogenic role of paranasal sinus infections in respiratory allergy has been better elucidated but there remains a need for further research. Treatment of established rhinitis may affect asthma control and could have some impact on airway obstruction, but a direct effect of rhinitis therapy on lower airway inflammation remains to be clearly established.

KEYWORDS: allergy • asthma • lower airways • rhinitis • sinusitis • united airways disease • upper airways

The link existing between the upper and lower airways has been observed repeatedly in the past, but the concept of united airways disease (UAD) is a matter of recent years [1]. Clinical, epidemiological, functional and immunological relationships between the two compartments have been confirmed at the experimental level and appear in the official documents of scientific and regulatory societies (FIGURE 1) [2]. This is the consequence of the increasingly detailed pathogenetic knowledge acquired over the last 15 years. An growing amount of evidence for the frequent coexistence of the two diseases is now available, and the role of upper airways infections in exacerbating asthma has also been confirmed [3]. Moreover, rhinitis has been identified as an independent risk factor for asthma development, and this has allowed us to identify possible strategies for rhinitic patients, with the aim of preventing asthma onset [4]. Other relevant information comes from the assessment of the relationships between paranasal sinus disease, infections and asthma [5], and the likelihood of occupational asthma development in subjects with occupational rhinitis [6]. The nose–bronchi functional links have been partially clarified by an understanding of the mechanisms sustaining

allergic inflammation, concluding that allergy is not a disease of a specific organ, but rather a disorder of the whole respiratory tract with a wide range of clinical manifestations [7]. Overall, these observations have contributed to the genesis of the term UAD [8].

Patients who have asthma and rhinitis tend to have more severe disease with higher treatment costs, thus the concept of ‘one airway disease’ had a noticeable impact on the management of these disorders, including their treatment and prophylaxis [9,10]. Since allergic rhinitis (AR) is frequently associated with or precedes asthma, the Allergic Rhinitis and Its Impact on Asthma (ARIA), endorsed by the WHO, clearly underlines the role of AR as a risk factor for asthma and suggests considering bronchial involvement in patients with AR [2].

Epidemiological data

The link between rhinitis and asthma has been the object of several epidemiological investigations, which consistently showed an important overlap of the two diseases [3]. Approximately 19–38% of patients with AR have concomitant asthma and 30–80% of asthmatics have AR, although these figures probably underestimate

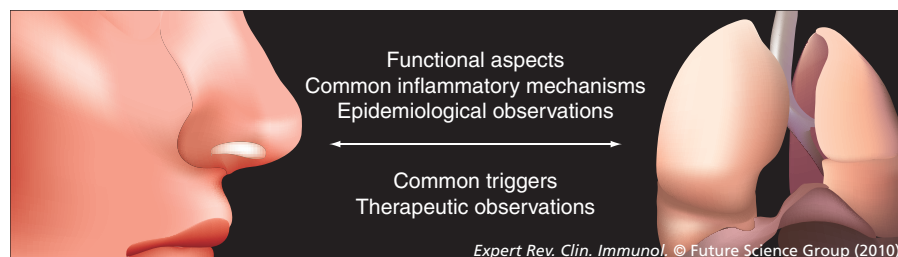


Figure 1. Summary of the features suggesting a bidirectional link between the upper and lower airways.

the phenomenon, as recent surveys found symptoms of rhinitis in 98.9% of allergic asthmatics and in 78.4% of nonallergic asthmatics [11]. The natural history of the disease is apparent from longitudinal studies. When patients are followed up for long periods, it can be observed that rhinitis usually precedes asthma. In a 23-year-long study, individuals with AR were found to be approximately three-times more likely to develop asthma than negative controls [12]; the odds ratio for rhinitis and asthma onset association after 7 years was 7.1 compared with 3.9 for controls [13,14]. The Tasmanian Asthma Study, which also investigated the temporal sequence of this association, confirmed that childhood AR increased the likelihood (two- to sevenfold increased risk) of new-onset asthma after childhood and the likelihood of having persisting asthma from childhood into middle age [15]. In a recent survey of 99 subjects followed for 10 years from the diagnosis of rhinitis, asthma or both, it was observed that 32% of rhinitis sufferers developed asthma and 50% of asthmatics developed rhinitis [16]. These results are reinforced by evidence provided by a study on conscripts to military service that showed that 70% of asthmatics were also affected by rhinitis [17].

Allergic rhinitis is considered a risk factor for developing asthma, but it is possible that this term is not totally correct in the sense that this condition may represent an early stage of UAD that can progress to full-blown asthma.

A large proportion of patients with AR alone have bronchial hyperreactivity (BHR) [18]. Additional data supporting this hypothesis come from a rigorous study by Kapsali *et al.*, in which rhinitis was documented in 90% of allergic asthmatics [19]. On the other hand, the analysis of the nonatopic population by the European Community Respiratory Health Survey (ECRHS) showed that perennial rhinitis is an independent risk factor for asthma, even in the absence of markers of atopy [20]. A similar interpretation came from the 8-year-follow up data from the same survey of 6461 participants, 20–44 years of age, without asthma at baseline [21]. This fact seems to be due to functional and neural mechanisms, however, the nature of this relationship remains unclear. Recently in a Spanish–Portuguese study, 49% of 3225 patients with AR and a mean age of 27 years, had concomitant asthma, the severity of which was associated with the duration and severity of AR. Patients with concomitant asthma had a significantly higher number of aeroallergen sensitizations than those without asthma. Rhinitis sufferers with perennial allergen sensitization are clearly at an increased risk for asthma [22].

In the Swiss Link Allergic Rhinitis in Asthma (LARA) survey, asthmatic patients with or without AR recruited by primary care physicians, pulmonologists and allergists from their daily practice were evaluated. Overall, 950 (76%) asthma patients had AR and 294 (24%) did not. Patients with AR were on average younger (42 ± 16 vs 50 ± 19 years) and fewer used inhaled corticosteroids (75 vs 88%). Asthma was uncontrolled in 53% of patients with AR

and in 57% without AR [23].

The coexistence of sinusitis and asthma, particularly in children, has been known for several years [24,25]; the involvement of paranasal sinuses is considered to be very important for the development of lower respiratory tract diseases [26]. Multiple studies have demonstrated that most patients with nonallergic asthma have chronic nasal symptoms as well as radiographic evidence of sinus mucosal disease [27]. Similarly, pre-existing symptoms of rhinitis place nonallergic patients at a higher risk for developing asthma [20].

Recent research into upper airway and sinus inflammation and remodeling may reveal new perspectives and lead to a classification of sinus disease that will facilitate appropriate clinical and epidemiological studies.

The bidirectional link between the nose & the bronchi: experimental evidence

Common inflammatory mechanisms

The respiratory tract can be considered a single morpho-functional entity. It is lined, until the bronchi of the lower dimension, by a ciliate epithelium and mucinous glands with a dense network of vascularization and innervation. The latter, in particular, appears very similar in the upper and lower compartments, supporting the hypothesis of the so-called nose (sinu)–bronchial reflex as a possible pathogenetic mechanism [28,29]. Although this phenomenon has been extensively observed in animals, some concerns remain regarding its existence in humans, despite the fact that it has been shown that nasal challenge is able to stimulate a contractile bronchial response or increase bronchial responsiveness [30–32].

The respiratory mucosa is rich in mast cells capable of contributing to nose–bronchi connections through the release of mediators and cytokines [33]. Lymphoid tissue forms the mucosal-associated lymphoid tissue (MALT) and is widely represented in the nose and bronchi. The major difference between the two compartments is that the nasal mucosa is located in a rigid structure and contains sinusoid vessels with erectile features, whereas the bronchi are contained in an elastic parenchyma, rich in peribronchial smooth muscle [34,35]. This anatomical diversity explains the different responses to trigger stimuli: rhinorrhoea and obstruction in the nose, and secretions and bronchoconstriction in the lung. It is known that the upper respiratory tract acts as a physical filter, sounding board, heater and humidifier of inhaled air, so it is easy to assume how the impairment of any of these functions results in an alteration of

the lower-tract homeostasis. There is evidence that the hyperventilation of cold air through the mouth in asthmatics facilitates the reduction of parameters of respiratory function and increases nasal resistance [36].

Another potential functional link between the nose and bronchi has been identified in the systemic impact of local inflammation via soluble mediators that involve the bone marrow [37]. This latter responds in a rapid and specific way to nasal challenge, with an increased production of precursors and mature eosinophils [38,39].

Recently, it was shown that in nonasthmatic rhinitics who are allergic to mites, specific bronchial challenge is able to bring the levels of nitric oxide to the same levels as subjects with asthma [40].

The dynamic of the allergic reaction is well known. It involves the early phase, characterized by a rapid release of histamine, vasodilatation, increased permeability and bronchoconstriction. This is followed by a complex network of inflammatory phenomena involving T lymphocytes, cytokines and adhesion molecules (late phase) [41].

During the early phase, some specific adhesion molecules are expressed *ex novo* or enhanced on the epithelial and endothelial surface, leading to rolling, extravasation and migration of inflammatory cells; the molecule ICAM-1 (CD54) appears to be a reliable marker of allergic inflammation [42]. The kinetics of inflammation involve the migration of inflammatory cells into the mucosa, where they appear approximately 30 min after a specific challenge,

continue to increase during the next 24 h and then slowly decline. This phenomenon can be observed and measured at the nasal and conjunctival level, but experimental evidence suggests that it also exists at the bronchial level in asthmatics [43–46].

It is interesting to note that a weak inflammatory infiltrate is also present when the allergenic exposure is too low to elicit symptoms [47]. This phenomenon is called 'minimal persistent inflammation' and involves persistent expression of ICAM-1, the molecule that is the main receptor for human rhinovirus [48,49]. These two events are important because asthma exacerbations in both children and adults are frequently associated with infection of the upper airways by this pathogen, as confirmed by *in vitro* studies [50–53].

Recent studies in humans have demonstrated that local allergen exposure in the nose of patients with AR can rapidly lead to significant allergic inflammation in the lungs, even without a previous history of asthma or BHR [54].

It is hypothesized that airway epithelial cells may act both as inflammatory initiators and as immunopathological feedback regulators between AR and asthma via the release of systemic inflammatory mediators. The importance of the airway epithelial cell in the development of allergic airway disease comes from its role in the innate airway defense against antigens. The activation of epithelial Toll-like receptors represents an important link between innate immunity and allergic disease. In addition,

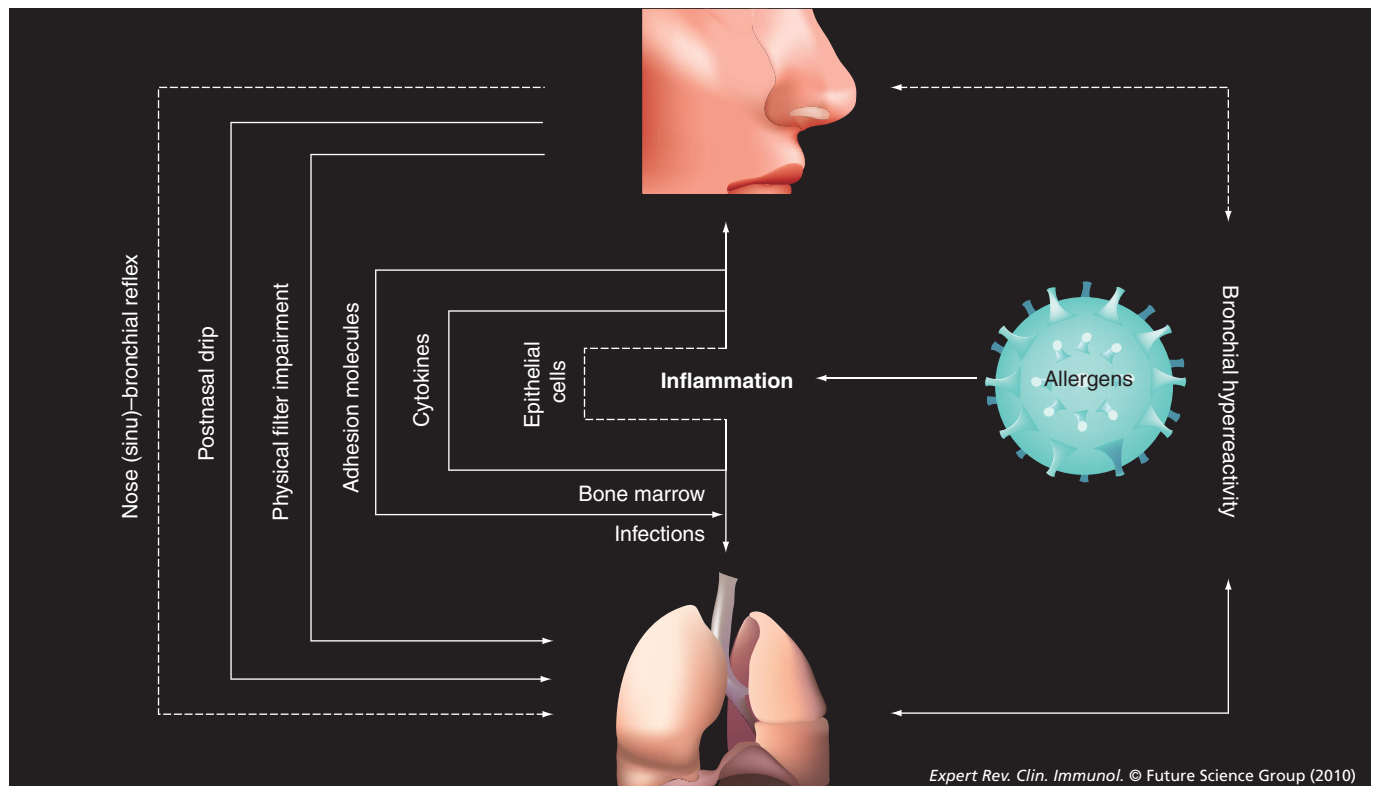


Figure 2. Physiopathological hypotheses explaining the concept of 'one airway disease'.

Solid lines: experimental data confirm the impact of the mechanism mentioned. Dotted lines: some experimental evidence suggests the impact of the mechanism mentioned, but only preliminary or suggestive data are available (sometimes without a full understanding of the mechanism itself).

airway epithelial cells can act as inflammatory promoters capable of directing dendritic cells towards a Th2 response, and also as active producers of several inflammatory/anti-inflammatory mediators. Thus, airway epithelial cells are a possible therapeutic target for the development of new drugs and/or new strategies to treat asthma and AR [55].

Studies have shown that, even in the absence of clinical symptoms of asthma, patients with seasonal AR have an increase in inflammatory cells in their 'in-season' bronchial biopsies. Similarly, patients with asthma but without symptoms of rhinitis have an increased number of eosinophils in their nasal biopsies and secretions. While the former would be explained more easily by the release of inflammatory mediators from the nose to the lung, the latter would suggest a systemic connection via soluble mediators to the bone marrow [56]. The hypothesis of the pathophysiological network sustaining the concept of the 'one airway disease' is summarized in **FIGURE 2**.

Functional aspects

Bronchial hyperreactivity is a paramount feature of asthma and may be considered a strong risk factor for the onset of asthma in patients with AR [19,57]. It is also interesting to note the frequent association between BHR and rhinitis [58]. A possible mechanism of BHR resides in the so-called neurogenic inflammation, involving neuropeptides such as substance P and neurokinine A; the regulation of capacitance vessels is mainly controlled by the neural sensorial apparatus, which would be involved in the phenomena of extravasations and edema [59,60]. The drain-back of nasal secretions, typical in people suffering from rhinosinusitis, may involve this mechanism, as well as the extension of the inflammatory process through the dissemination of proinflammatory elements, facilitating bronchial contractile responses [61].

Patients suffering from AR frequently (in up to 80% of cases) display BHR. When assessing total symptom scores by rhinomanometry, spirometry and methacholine bronchial challenge, early bronchial impairment is often detectable in patients with persistent AR and BHR. Moreover, nasal function is strictly related to bronchial caliber and BHR grade [62].

Impairment of spirometric parameters and BHR can also be observed in patients with AR alone. Thus, a careful evaluation of the lower airways should always be performed in those patients [63]. In a large group of patients (prospectively and consecutively evaluated) with moderate-to-severe persistent AR alone, tree and house dust mite sensitization, rhinitis duration longer than 5 years and a forced expiratory volume in 1 s (FEV_1) of 86% or less of predicted value were significantly associated with severe BHR; 6.4% of patients had severe BHR, 21.6% had mild BHR and 56.2% had borderline BHR; 15.8% of patients had a negative methacholine test. Thus, BHR is frequently present in patients with chronic rhinitis and should be suspected in the presence of defined risk factors [64].

In another large group of patients, the duration and type of sensitization were identified as early prognostic markers of bronchial involvement in patients with moderate-to-severe and persistent AR alone [65].

Small airway disease (SAD), defined as a reduction in forced expiratory flow (FEF) at 25–75% of the pulmonary volume (FEF_{25–75}) and a normal spirometry (normal FEV_1 , forced vital capacity [FVC] and FEV_1 :FVC ratio), is suggested to be a marker of early allergic or inflammatory involvement of the small airways in subjects with allergic diseases and no asthma. In a cross-sectional study involving 58 midshipmen with slight spirometric abnormalities, 20 subjects had a reduced FEF_{25–75}, consistent with the definition of SAD. All the candidate allergic predictors appeared to be strongly associated with a reduced FEF_{25–75}. The proportion of subjects with this impairment appeared to increase with increasing severity of the allergic predictors, and, correspondingly, the mean value of FEF_{25–75} appeared to decrease. This study provides evidence that there is a relationship between SAD and allergic parameters such as nasal symptoms and eosinophils [66].

In another study in patients with AR and without asthma, spirometric parameters were similar in and out of the pollen season but all other parameters were markedly different. The major finding of the study was that FEF_{25–75} was significantly associated with nearly all of the parameters considered, including BHR, and, again, FEF_{25–75} has been proposed as an early marker of bronchial involvement in patients with AR who perceive only nasal symptoms [67].

In a large cohort of patients with moderate-to-severe persistent AR alone and normal baseline FEV_1 , a large percentage (approximately two-thirds) of patients with moderate-to-severe persistent AR showed reversibility to bronchodilation testing (increase greater than 12% in basal FEV_1 values). In this study, reversibility to bronchodilation was associated with early bronchial airflow limitation, despite being in the presence of borderline FEV_1 values. Reversibility was also associated with a longer duration of rhinitis, confirming that spirometric impairment is more common in patients with long-lasting rhinitis [68]. The response to bronchodilation might be considered as further proof of bronchial impairment in AR. The duration of AR is an important factor for the development of bronchial involvement. The possible explanation of this phenomenon might depend on the allergic inflammation that persists for a long time and tends to progress from the nose into the bronchi [2].

Bronchial hyperreactivity in AR might, therefore, represent a prognostic factor for further progression to asthma [69].

Common triggers & effect of provocation tests

Clinical and epidemiological observations suggest that the natural progression of respiratory allergy starts from the upper respiratory tract and spreads to the lower tract [70]. However, it was demonstrated that segmental bronchial challenge can induce nasal symptoms and inflammation in patients suffering from AR; furthermore, there is a direct correlation between the degree of BHR and nasal nonspecific reactivity in rhinitic subjects with asthma [71]. It was noticed that the decline of respiratory function after nasal challenge occurs after 4–6 h, while the effects of bronchial challenge on the nose appear after 24 h [72].

Support for the inflammatory link between the upper and lower airways was found in a study that included 14 children with AR and 15 with AR and asthma. Basal sputum eosinophil

cationic protein (ECP) and exhaled nitric oxide (eNO) values before allergen-specific nasal challenge were significantly higher in both groups compared with healthy controls. The increase in sputum ECP and eNO after allergen-specific nasal challenge in rhinitic children without wheezing could suggest the use of these mediators as positive predictive markers of evolution towards asthma [73].

In children with rhinoconjunctivitis and asthma who were sensitized to house dust mites, experimental nasal allergen exposure is followed by early changes in nasal eosinophilia and is correlated with bronchial reactivity to methacholine [74]. Eosinophils in the nasal smear display the best correlation with all the clinical and immunological parameters in AR and also correlate with methacholine response [75] and FEV₁ in patients with perennial AR associated with asthma. Nasal cytology may be considered a noninvasive tool to assess airway inflammation in mild asthmatics with associated AR [76].

In the occupational field, some agents seem to be relevant in the genesis of AR. Recent data demonstrated that eosinophilic nasal inflammation was present in subjects with occupational asthma caused by persulphate salts, irrespective of the presence of clinical rhinitis [77]. Further studies are needed to elucidate the interaction between upper and lower airway responses to sensitizing and irritant agents in the workplace [6].

Role of infections & rhinosinusitis

Allergens are not always the unique trigger of the inflammatory reaction, since infections and organic dust might also cause exacerbations of rhinitis and associated conditions.

When examining the effects of intranasal lipopolysaccharide (LPS) exposure as a surrogate for upper airway bacterial infections in patients with symptomatic AR, a priming effect of allergen on the nasal response to LPS as well as the presence of a systemic link between airway mucosal sites in the upper and lower airways was observed. This suggests that exogenous signals, such as upper airway infections, can interfere with the initiation, maintenance and progression of asthma [78].

There is a great deal of evidence supporting an association between rhinosinusitis and asthma [79]. However, it is less clear whether rhinosinusitis is a direct trigger for asthma or the two conditions are simply manifestations of a common underlying process. Possible mechanisms for this relationship include naso-pharyngo-bronchial reflexes, postnasal drip, abnormal breathing and the local production of inflammatory mediators that trigger pulmonary inflammation. There are similarities between the histopathological changes in the epithelium in chronic rhinosinusitis (CRS) and asthma. The bone marrow may provide the link between the upper and lower airways in creating a common disease. A second possible mechanism could be the response to staphylococcal enterotoxins, which act as superantigens. In addition, evidence suggests that medical or surgical treatment of rhinosinusitis may improve the coexistent asthma [80]. The current classification of CRS includes disease without and with nasal polyps, the latter being considered a subgroup of CRS. Different patterns of inflammatory and regulatory cytokines (involving distinct T-helper lymphocyte

populations) and of remodeling markers were recently described to differentiate nasal polyposis from CRS, yielding two distinct entities [81]. Current evidence suggests that rhinosinusitis without either polyps or eosinophilic inflammation is a direct trigger for asthma, whereas rhinosinusitis with both polyps and eosinophilic inflammation shares underlying mechanisms with asthma [82].

Endoscopic studies in children with asthma found hyperplastic adenoids or sinusitis in over 50% of the subjects. A characteristic inflammation mediated by cytokines of Th2-lymphocyte polarization was present at both the bronchial and sinus level [82]. In the latter region, the same changes can be seen even in nonallergic patients. In this regard, it is also known that nonallergic asthma phenotypes may show Th2 polarization in the bronchial tree [83]. Moreover, it seems that treatment (with antibiotics and topical steroids) of rhinosinusitis induces a physiological Th1 repolarization and improves nasal symptoms, asthma symptoms and respiratory function parameters, with a reduction of BHR [84]. There is also evidence that markers of bronchial inflammation, typically monitored in asthmatics, correlate with the severity of sinusitis [85].

Th2 cells (secreting IL-4, IL-5, IL-9 and IL-13) are considered to be responsible for the induction and clinical manifestations of atopic diseases. Local overproduction of Th2 cytokines at the site of allergic inflammation and an intrinsic defect in the production of IFN- γ by Th1 cells in atopic individuals have now been reported by several authors. Both IFN- γ and IL-10 have been suggested to play a modulatory role in the induction and maintenance of allergen-specific tolerance in healthy individuals. However, recent studies indicate that Th1 cells secreting IFN- γ might cause severe airway inflammation. On the other hand, 'inflammatory T cells' or Th17 cells producing IL-17 could represent a link between T-cell inflammation and granulocytic influx as observed in allergic airway inflammation [86].

Effects of treatment on rhinitis & asthma

It has been shown that treatment with nasal steroids, combined with inhaled steroids, is able to reduce BHR to methacholine challenge in subjects with asthma and to improve symptoms by reducing visits to the emergency department for exacerbation [87–90].

A Cochrane review performed a meta-analysis of 14 studies and found a trend suggesting that intranasal corticosteroids improve asthma symptoms and FEV₁, but the result was not found to be statistically significant [91]. Later, 863 patients in an open randomized trial with persistent asthma treated with inhaled steroids, plus the addition of antileukotrienes or nasal steroids for the treatment of seasonal AR, experienced no additional improvements in overall asthma control compared with inhaled steroids alone [92]. In other circumstances, the failure to consider the treatment of rhinitis as essential to asthma management impaired clinical control of asthma, suggesting that asthma and rhinitis, in some patients, can be controlled by the exclusive use of nasal medication [93]. Overall, owing to the serious and numerous methodological limitations of the aforementioned systematic review and of the controlled and randomized studies performed in the following years, the definition of a realistic extent of effect of nasal steroids on asthma control appears rather uncertain.

Population-based studies suggest that treatment of asthmatic patients with nasal steroids confers protection against emergency department visits for asthma exacerbations [94] and hospitalizations [95,96]; however, these outcomes need to be explored in more rigorous settings of investigation.

Curiously, the hypothesis that nasal inhalation of a corticosteroid can be effective both for rhinitis and asthma was examined with positive findings in several studies where budesonide had been nasally administered through a special spacer, resulting in both upper and lower airways deposition [97,98]. Alternatively, exhaling a budesonide inhaler through the nose results in a significant reduction in dose requirement of budesonide nasal spray in patients who have asthma with rhinitis [99].

Another study examined the effects of orally inhaled budesonide (avoiding nasal deposition of the drug) on nasal allergic disease in seasonal AR without asthma and found a reduction of nasal and circulating eosinophilia with an attenuation of seasonal nasal symptoms [100]. The treatment of AR with triamcinolone resulted in a decrease of two noninvasive markers of lower airway inflammation, eNO and H_2O_2 , supporting the concept that upper and lower airway inflammation should be seen as a continuum [101].

Conversely, treatment of the pulmonary compartment had a measurable impact on measures of nasal allergic inflammation (i.e., symptoms scores, eosinophil numbers and ECP levels in nasal lavage fluid). Bronchial budesonide inhibits the seasonal increase in nasal and blood eosinophils, and nasal lavage levels of ECP [102]. These observations should be kept in consideration, as the distant effects after local treatment may be caused by systemic medication absorption.

Thus, further research should be performed to evaluate the effects of intranasal corticosteroids on asthma control; a combination of intranasal and intrabronchial corticosteroids should continue to be used in clinical practice until more research is carried out.

Antihistamines at therapeutic doses do not affect asthma, but their beneficial action on the upper airway contributes to improve the overall management of the 'one airway disease' [103,104]. A protective effect of antihistamines on BHR after nasal allergen challenge in patients with AR can be explained either by a direct effect of the drug on the lower airways or, indirectly, by protection related to the control of rhinitis [105]. An effect on systemic inflammation and on nasal and bronchial mucosal inflammation after nasal allergen provocation in subjects with grass-pollen AR and asthma has also been reported [106].

During the pollen season, antihistamine treatment reduces the symptoms of asthma, although concerns exist regarding differences in lung function [107]. The synergistic effect with drugs of other classes (antileukotrienes, α -mimetics) may reduce the use of bronchodilators and improve peak flow in mild asthma [108–110]. In children, the occurrence of respiratory infections and exacerbations of asthma may be reduced by continuous antihistamine treatment [111,112]. The Early Treatment of the Atopic Child study suggested that this therapeutic strategy can reduce the subsequent development of asthma in children with atopic dermatitis [113], but this was not confirmed by the El Paso Asthma and Allergy Coalition study [114].

The impact of antileukotriene (leukotriene receptor antagonist [LTRA]) treatment in patients with both AR and asthma has also been evaluated. Since the pathophysiology of the two diseases involves the inflammatory cascade and eosinophil influx into nasal and bronchial mucosae, these drugs are expected to improve both the conditions. Observational studies and clinical trials showed that LTRAs are effective in treating both the upper and lower airways in patients with asthma and AR [115–117].

The apparent success of specific immunotherapy in children with AR in preventing the development of asthma and BHR, seen in recent longitudinal studies, provides a powerful argument supporting a common pathogenetic mechanism in allergic respiratory disease [118–121]. Compared with placebo, short-term co-seasonal sublingual immunotherapy resulted in lower asthma symptoms and reduced use of medication in the second and third years of therapy, associated with a reduction in asthma development [122]. Similar findings have been reported on the effect of immunotherapy on the degree of nonspecific BHR in patients with allergic bronchial asthma and/or AR [123].

Various studies have provided evidence that treatment of AR with specific immunotherapy, either sublingual or subcutaneous, can reduce BHR and may prevent asthma, but further investigation is needed to confirm the preventative role of specific immunotherapy [124–129]. The potential of an early intervention with the aim to change the natural history of allergic disease remains both attractive and promising [130].

Finally, the appropriate treatment of sinusitis can improve asthma symptoms in those patients also affected by this disease [131–133].

Conclusion

Currently, we have epidemiological data, basic studies and clinical trials suggesting a close structural and functional relationship between the upper and lower airways. The concept of 'one airway disease' is the cornerstone of the ARIA document, and has relevant implications for the diagnostic and therapeutic management of respiratory allergy. In this sense, an integrated and unified approach to both diseases is strongly recommended to optimize the demands of efficacy and safety. A strategy combining the treatment of both compartments appears to be optimal. Intranasal glucocorticosteroids for the treatment of rhinitis may reduce morbidity in asthmatics. Antihistamines and LTRAs have been shown to contribute to asthma control or prevention. Specific immunotherapy of rhinitis may reduce the risk of asthma or improve asthma control.

Since the adequate treatment of AR may positively affect the course of asthma, possible bronchial involvement should be considered in the management of each patient with AR.

The role played by sinus disease in asthma is only partly understood, largely owing to deficits in the clinical classification and in basic knowledge of pathophysiological pathways.

Expert commentary

In the last decade, numerous epidemiological, physiopathological and clinical investigations have confirmed the previous observations of the links existing between the upper and lower airways. However, many aspects still remain unclear, including the role

played by sinus disease and the precise mechanisms of neural inflammation. The importance of epithelial cells as inflammatory initiators and regulators of allergic disease was recently highlighted. Current knowledge suggests an integrated therapeutic approach towards AR and asthma, but the effect of each specific treatment needs further comprehension for the possible favorable implications in terms of cost reduction, better patient compliance and acceptability of a single treatment that can act on two fronts.

Five-year view

In the next few years, new data concerning the inflammatory and functional involvement of small airways in rhinitic patients without clinical asthma, together with further explorations of remodeling phenomena, will hopefully permit a deeper understanding of the

links between the upper and lower airways. The development of new tools of investigation and the fine-tuning of existing ones, such as eNO measurements, sequential sputum induction, high-resolution computed tomography and MRI, to assess ventilation heterogeneity, may be fundamental in the definition of accurate biomarkers and functional parameters that can outline different disease phenotypes.

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Key issues

- Recent epidemiological, pathophysiological, functional and clinical data confirm previous observations, suggesting a bidirectional link between the upper and lower airways.
- New hypotheses involving the role of epithelial cells as initiators and enhancers of respiratory allergic disease deserve further investigation.
- There is a great deal of evidence supporting an association between rhinosinusitis and asthma.
- Allergic rhinitis and asthma may have common triggers.
- The concept of 'one airway disease' has relevant implications for the diagnostic and therapeutic management of respiratory allergy.
- An integrated therapeutic approach may be beneficial for both allergic rhinitis and asthma.

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