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Global Airway Disease Beyond Allergy

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Abstract Besides the anatomic continuity of the upper and lower airways, inflammation in one part of the airway influences the homeostasis of the other. The mechanisms underlying this interaction have been studied primarily in allergic disease, showing systemic immune activation, induction of inflammation at a distance, and a negative impact of nasal inflammation on bronchial homeostasis. In addition to allergy, other inflammatory conditions of the upper airways are associated with lower airway disease. Rhinosinusitis is frequently associated with asthma and chronic obstructive pulmonary disease. The impairment of purification, humidification, and warming up of the inspired air by the nose in rhinosinusitis may be responsible in part for bronchial pathology. The resolution of sinonasal inflammation via medical and/or surgical treatment is responsible for the beneficial effect of the treatment on bronchial disease. This article provides a comprehensive overview of the current knowledge of upper and lower airway communication beyond allergic disease.

Keywords Rhinitis · Sinusitis · Asthma · COPD · United airways

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Introduction

The nose plays a crucial role in bronchial homeostasis due to its anatomic position at the entry of the airway (Fig. 1) [1]. By warming up, humidifying, and filtering the incoming air, the nose is essential to the protection of the lower airways from exposure to continuous inflammatory and other triggers. The nose and bronchi are anatomically connected, lined with a pseudostratified respiratory epithelium, and equipped with an array of innate and acquired immune defense mechanisms. It is believed that nasal conditions causing nasal obstruction, stasis of nasal secretions, and/or infectious disease of the sinonasal mucosa may contribute or even induce lower airway pathology in susceptible individuals [2•]. Acute respiratory infections such as the common cold and acute, nonviral rhinosinusitis are associated with nasal congestion and/or secretions in the sinonasal cavities that impair the protective function the nose provides for the lower airways [3••]. In chronic sinus disease with nasal polyps, total blockage of the nasal passages may occur, hence bypassing the protective function of the nose with regard to the lower airways. However, no nasobronchial interaction in inflammatory conditions such as allergic rhinitis is limited to the bronchial effects of impaired nasal breathing. Besides direct anatomic pathways, the nose and bronchi seem to communicate via indirect mechanisms. Allergen contact in patients with allergic rhinitis gives rise to IgE production with a systemic increase in allergen-specific IgE levels and raised blood eosinophilia. Like allergic rhinitis, rhinosinusitis is associated with a well-known systemic inflammation contributing to the inflammatory link between nose and bronchi. The inflammation seen in chronic rhinosinusitis (CRS) with and without nasal polyps (NP) shows systemic signs of inflammation, such as elevated levels of interleukin (IL)-5 in the blood and increased bone marrow eosinopoiesis [4].

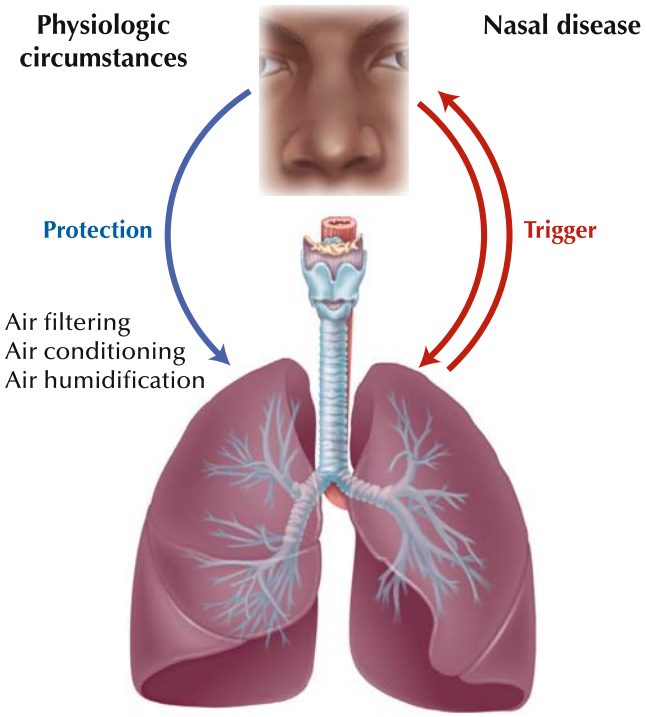

Fig. 1 Scheme depicting the dual role of the nose. Under physiologic conditions, the nose maintains the bronchial homeostasis via its multiple functions for optimizing the quality of inspired air. In the presence of sinonasal inflammation, the inflammation in the upper airways contributes directly or indirectly to bronchial disease

In recent years, the interplay between upper and lower airway inflammation has been the subject of two state-of-the-art documents: ARIA (Allergic Rhinitis and its Impact on Asthma) [5] and EP3OS (European Position Paper on Rhinosinusitis and Nasal Polyps 2007) [3••] for allergic rhinitis and rhinosinusitis, respectively. Both documents provide an overview of the current knowledge on the nasobronchial interaction in allergic rhinitis and rhinosinusitis (Fig. 2). Based on the novel insights into the close relationship between nasal and bronchial inflammation, diagnostic and therapeutic strategies are offered for the optimal medical approach in these patients. Among those with chronic upper airway disease, a substantial group presents with severe chronic upper airway disease and symptoms that are inadequately controlled despite adequate pharmacologic treatment based on guidelines [6•]. Patients with severe chronic upper airway disease may have underlying allergic rhinitis, nonallergic rhinitis, occupational rhinitis, and rhinosinusitis with/without NP. In these patients, the full appreciation of sinonasal pathology with an evaluation of bronchial symptoms is warranted for an optimal diagnosis and successful therapy. We aim to provide a comprehensive overview of the current knowledge of nasobronchial communication in acute rhinosinusitis and CRS.

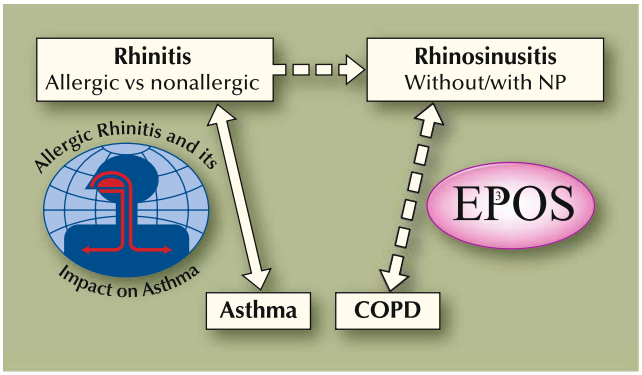

Fig. 2 Scheme depicting the transition from rhinitis to rhinosinusitis in relation to bronchial pathology. The two state-of-the art documents (ARIA [Allergic Rhinitis and its Impact on Asthma] and EP3OS [European Position Paper on Rhinosinusitis and Nasal Polyps 2007]) are listed, as they contain overviews of current knowledge on nasobronchial interaction. COPD—chronic obstructive pulmonary disease; NP—nasal polyps

Common Cold and Lower Airway Disease

The common cold, or acute (viral) rhinosinusitis, is defined as the sudden onset of two or more symptoms, one of which should be nasal congestion/obstruction or nasal secretions (rhinorrhea or postnasal drip), with or without facial pain or smell disorder [3••]. Common colds account for about 50% of all illnesses and occur more frequently in young infants [7]. Besides inducing sinonasal symptoms, common colds cause exacerbations of preexisting lower airways diseases such as asthma and chronic obstructive pulmonary disease (COPD). Most asthma exacerbations are precipitated by respiratory virus infections in all age groups. When sensitive methods such as reverse transcription polymerase chain reaction are used, viruses are found in 80% of wheezing episodes in school-aged children and in almost 50% of asthma exacerbations in adults. Rhinovirus (RV) is the most frequently detected pathogen [8]. The causal relationship between RV infection and asthma exacerbations has been proven by experimental infection models. After nebulization of an RV-16 suspension, asthma patients develop rhinitis symptoms together with worsening of their asthma state [9]. Moreover, a decrease in forced expiratory volume in 1 s (FEV_1), increased airway hyperresponsiveness, and augmented eosinophilic bronchial inflammation are found following experimental RV infection [9]. Even in non-asthmatic patients with atopic rhinitis, RV inoculation increases airway hyperreactivity and causes a drop in FEV_1 [10]. In addition to causing most wheezing episodes in asthmatic patients, common colds are also associated with more than 40% of COPD exacerbations, with RV being the most common viral pathogen [11].

The mechanisms of virus-induced exacerbations of asthma and COPD are not completely understood. One

primary issue is whether RVs reach and replicate in the lower airways, causing lower airways symptoms by direct infection, or if indirect mechanisms cause exacerbations of lower airways diseases. Recent evidence supports the first hypothesis. The presence of RV in bronchial biopsy specimens after an experimental upper respiratory RV infection in human volunteers was confirmed by in situ hybridization and immunohistochemistry [12, 13]. By using the latter methods, the investigators avoided contamination from the upper airways, which could not be excluded in studies in which RV was detected in bronchoalveolar lavage or sputum. However, the importance of bronchial penetration and replication of RV during natural infection is still uncertain. About 90% of RVs infect airway epithelial cells via binding to the receptor intercellular adhesion molecule-1 (ICAM-1), followed by intracellular penetration and replication. RVs upregulate the expression of ICAM-1 via nuclear factor-κB (NF-κB)–dependent mechanisms, thereby enhancing their own infectivity and promoting inflammatory cell infiltration. In bronchial epithelial cell cultures, RV infection induces a variety of proinflammatory cytokines and chemokines, such as interleukin (IL)-6, IL-8, IL-16, and RANTES (regulated on activation, normal T-cell expressed and secreted), which may lead to the chemotaxis and activation of neutrophils, lymphocytes, monocytes, and eosinophils, thereby enhancing lower airway inflammation [12]. In addition to a direct effect of RV on bronchial epithelial cells, indirect mechanisms could play a role in increasing lower airway inflammation during a common cold. Following experimental RV-16 infection in allergic individuals, granulocyte-macrophage colony-stimulating factor (GM-CSF) levels increase not only in nasal secretions but also in the circulation. GM-CSF levels in serum correlate with the blood neutrophilia, suggesting that GM-CSF acts on the bone marrow to increase the neutrophilia in blood [14]. Besides the proinflammatory effect of RV on airway epithelium, host factors also play an important role in the development of acute exacerbations. Several risk factors for experiencing more severe viral exacerbations of lower airway disease are described, including age (being an infant or older adult), smoking, and having low neutralizing antibody titers to RV [14]. Moreover, atopic asthmatic individuals are more prone to virus-induced wheezing, possibly via less interferon-γ production in response to RV, which reflects a defective T-helper type 1 immune response. However, Avila et al. [15] showed a delayed onset of cold symptoms and a shortening of their duration when inoculation with RV was preceded by allergen challenge in individuals with allergic rhinitis. In this experimental setting, allergic inflammation may be protective for RV infection, likely depending on the timing and intensity of antigen exposure.

Although acute viral exacerbations account for a large part of the burden associated with asthma and COPD, currently available treatments are unsatisfactory. Upper airway symptoms are not life-threatening but are self-limiting. Therefore, treatment of upper airway symptoms is based on symptoms (eg, nasal decongestants, rinsing of the nasal cavity, and oral analgesics if necessary) [3••]. To treat viral-induced asthma and COPD exacerbations, one can target the virus itself or the host immune response. No RV vaccination exists because of the wide variety of serotypes of human RV. A range of antiviral agents have been tested in preclinical or clinical trials without consistent effects on asthma demonstrated. Another therapeutic strategy is to prevent the inflammatory reaction caused by RV infection. Glucocorticosteroids are the cornerstone of current asthma and COPD maintenance therapy. However, they disappoint in the treatment of acute exacerbations. In persistent asthma, daily administration of inhaled corticosteroids has only a limited effect in reducing the number of wheezing episodes in adults and children. Corticosteroids have no major therapeutic efficacy in the treatment of COPD exacerbations, as they reduce the absolute treatment failure rate by only 10%, increase FEV_1 by only 100 mL, and shorten the hospital stay by 1 to 2 days. Inhibiting NF-κB signaling may also represent an interesting therapeutic option, as NF-κB is involved in the virus-induced upregulation of ICAM-1 as well as in the transcriptional activation of a large number of the proinflammatory mediators involved in RV infection [16]. However, NF-κB inhibitors are in an experimental stage of development, and it has yet to be determined if the anti-inflammatory properties of these agents will be counterbalanced by the simultaneous inhibition of protective antiviral mediators such as interferon.

Noninfectious, Nonallergic Rhinitis and Asthma

It is estimated that more than 50% of patients with nasal symptoms related to nasal inflammation present without signs of infection or evidence of allergy [17]. This group of patients with so-called noninfectious, nonallergic rhinitis have chronic nasal symptoms that are not evidently caused by IgE-dependent mechanisms or specifically related to structural deformity. Several subgroups have been recognized in these patients: hormonal rhinitis, rhinitis medicamentosa, chemical-induced or occupational rhinitis, and hidden allergic rhinitis characterized by local IgE production and positive allergen provocation test [18••]. After evaluation of the latter diagnoses, a group of patients is labeled with the diagnosis of idiopathic rhinitis. Because of the heterogeneity and the ill-defined pathophysiology of patients with noninfectious, nonallergic rhinitis, current knowledge on the epidemiologic

and pathophysiologic link to lower airway inflammation is limited.

Rhinosinusitis and Asthma

Bronchial asthma is considered a comorbidity of rhinosinusitis [3••]. Up to 50% of patients with CRS have been reported to present with clinical asthma [1]. Interestingly, most patients with CRS who do not report having asthma show bronchial hyperreactivity when given a methacholine challenge test [19]. In this way, Ponikau et al. [19] concluded that 91% of patients with CRS had asthma or increased bronchial hyperreactivity. Others reported that 60% of patients with CRS had lower airway involvement as assessed by history, pulmonary function, and histamine provocation tests [3••]. Alternatively, sinonasal symptoms are frequently reported in asthmatic patients, ranging up to 80% in some studies. Radiologic imaging of the sinuses has demonstrated mucosal thickening of the sinus mucosa in up to 84% of patients with severe asthma. However, these epidemiologic and radiologic data should be interpreted with caution because they may reflect a large reference bias [3••].

CRS is currently thought to have a multifactorial etiology in which host factors (eg, anatomic, local defense, and immunologic factors) act in synergy with microbial and environmental factors [3••]. Histopathologic features of CRS and asthma largely overlap [3••]. Heterogeneous eosinophilic inflammation and features of airway remodeling (eg, epithelial shedding and basement membrane thickening) are found in the mucosa of patients with CRS and asthma. Cytokine patterns in the sinus tissue of patients with CRS highly resemble those of bronchial tissue in asthma, which would explain the presence of eosinophils in both conditions. Therefore, eosinophil degranulation proteins may cause damage to the surrounding structures and induce symptoms at their location in the airway. Finally, lavages from CRS patients showed that eosinophils were the dominant cell type in nasal and bronchoalveolar lavages in the subgroup of patients with CRS with asthma [20]. In addition to the similarities in pathophysiology, sinusitis has been etiologically linked to bronchial asthma and vice versa. As is the case in allergic airway inflammation, sinusitis and asthma can affect each other via the systemic route, involving IL-5 and the bone marrow. In both CRS and allergic asthma, similar proinflammatory markers are found in the blood. Recently, nasal application of *Staphylococcus aureus* enterotoxin B was shown to aggravate the allergen-induced bronchial eosinophilia in a murine model [21]. Here, mucosal contact with enterotoxin B induced the systemic release of IL-4, IL-5, and IL-13, leading to aggravation of experimental asthma. However, the interaction between rhinosinusitis and asthma is not always clinically present, and no consistent correlation exists among CT scan abnormalities, sputum eosinophilia, and pulmonary function [3••].

Endoscopic sinus surgery (ESS) for CRS is most often successful for sinonasal symptoms but may also improve bronchial symptoms and reduce medication use for bronchial asthma [1]. After a mean follow-up period of 6.5 years, 90% of asthmatic patients reported that their asthma was improved over what it had been before the ESS, with a reduction in the number of asthma attacks and in medication used for asthma [22]. Also, in children with sinusitis and asthma, sinus surgery improves the clinical course of asthma, as reflected by a reduced number of asthma hospitalizations and school days missed [23]. Lung function in asthma patients with CRS was reported by some authors as benefiting from ESS but was denied by others [1]. Of note, not all studies show beneficial effects of ESS on asthma. The reason for the inconsistency in results between studies relates to the heterogeneity and small number of patients included in these studies, and the difference in outcome parameters studied. Interestingly, the presence of lower airway disease may have a negative impact on the outcome after ESS. Outcomes after ESS were significantly worse in the asthma group compared with the nonasthma group [1]. Poor outcomes after ESS also have been reported in patients with aspirin-intolerant asthma [23, 24]. However, other authors reported that asthma does not represent a predictor of poor symptomatic outcome after primary or revision ESS. In a series of 120 patients undergoing ESS, Kennedy [25] reported that asthma did not affect the outcome after ESS when comparing patients with equally severe sinus disease, except for the worst patients, in whom asthma did adversely affect the outcome.

Until recently, no well-conducted clinical trials had been carried out showing beneficial effects of medical therapy for CRS on bronchial asthma. Ragab et al. [26] published the first prospective study of surgical versus medical therapy in 43 patients with CRS with/without NP and asthma. Medical therapy consisted of a 12-week course of erythromycin, alkaline nasal douches, and intranasal corticosteroid preparation followed by intranasal corticosteroid preparation tailored to the patients' clinical course. The surgical treatment group underwent ESS followed by a 2-week course of erythromycin, alkaline nasal douches, and intranasal corticosteroid preparation; 3 months of alkaline nasal douches and intranasal corticosteroid; and, finally, intranasal corticosteroid preparation tailored to the patients' clinical course. Medical and surgical treatment regimens for CRS were associated with subjective and objective improvements in asthma state. Interestingly, improvement in upper airway symptoms correlated with improvement in asthma symptoms and control.

Nasal Polyp Disease and Asthma

A total of 7% of asthma patients have NP [1]. In nonatopic asthma and late-onset asthma, NP are diagnosed more frequently (10%–15%). Aspirin-induced asthma is a distinct clinical syndrome characterized by the triad of aspirin sensitivity, asthma, and nasal polyposis and has an estimated prevalence of 1% in the general population and 10% among asthmatics [1].

At present, the etiology of NP remains obscure [3••]. As NP represent a chronic inflammatory disease affecting the mucosa of ethmoidal sinus cavities in susceptible individuals, one may speculate that airborne microorganisms can induce or aggravate the inflammation seen in NP. Recently, new light was shed on the pathology of NP by showing increased colonization of NP by *Staphylococcus aureus* and the presence of specific IgE directed against *S. aureus* enterotoxins in NP tissue [27]. Interestingly, rates of colonization and IgE presence in NP tissue were increased in patients with NP and comorbid asthma or aspirin sensitivity. By their superantigenic activity, enterotoxins may activate inflammatory cells in an antigen-unspecific manner. Hellings et al. [21] recently demonstrated that nasal application of *S. aureus* enterotoxin B is capable of aggravating experimental allergic rhinitis and asthma, with an increase in bronchial and systemic T-helper type 2 cytokine levels [21]. Besides bacterial enterotoxins, Ponikau et al. [28] reported on the potentially important role of fungi, especially *Alternaria*, in the generation of NP. By their capacity to induce eosinophil degranulation, *Alternaria* may contribute to the inflammatory spectrum of CRS with/without NP. Thus far, we have no idea whether microbial stimuli may represent the etiology of NP formation or whether colonization with microorganisms is favored in the presence of NP.

At present, no trials have studied the effects of medical therapy for NP patients on asthma. Therefore, well-designed trials on antibiotic use, vaccination therapy, or antileukotriene treatment in patients with NP and asthma are warranted. After ESS for NP in patients with concomitant asthma, a significant improvement in lung function and a reduction in systemic steroid use were noted, although this was not the case in aspirin-intolerant asthma patients [29].

Rhinosinusitis and Chronic Obstructive Pulmonary Disease

Up to 88% of patients with COPD presenting at an academic unit of respiratory disease may experience nasal symptoms, most commonly rhinorrhea [2•]. Nasal symptoms in COPD patients correlate well with an overall impairment in quality of life. Thus far, there is only one study on patients with COPD showing rhinosinusitis symptoms and inflammatory mediators in the nasal cavity [2•]. Interestingly, patients with stable COPD show increased levels of eotaxin and GM-CSF in nasal lavage fluid compared with controls [2•]. Guilemany et al. [30••] recently reported an association between CRS and idiopathic and postinfectious bronchiectasis. Interestingly, patients with CRS showed a higher bronchiectasis severity score on CT scans of the chest. It has yet to be elucidated to what extent treatment of the sinonasal disease is beneficial to the bronchial pathology.

Clinical Implications and Unmet Needs

Several medical specialties are involved in the medical care of patients with chronic airway disease. In asthmatic and COPD patients, physicians need to inquire routinely about the existence of rhinitis and rhinosinusitis symptoms (Fig. 3). To this purpose, the use of a simple questionnaire for the presence of sinonasal symptoms may be helpful to the clinician. In case of positive history of upper airway symptoms, anterior rhinoscopy, nasal endoscopy, and/or CT scan of the sinonasal cavity may help in making a correct estimation of upper airway involvement in asthma and COPD. Alternatively, bronchial symptoms need to be assessed in patients presenting with rhinitis/rhinosinusitis. When lung function tests are carried out in this patient population, most of them will show bronchial hyperresponsiveness, thus alerting us to the global airway impact of the upper airway disease. However, several clues to help us fully understand the nasobronchial interaction are still missing, thus complicating our clinical approach to individuals with upper and/or lower airway disease. For example, for each individual patient with

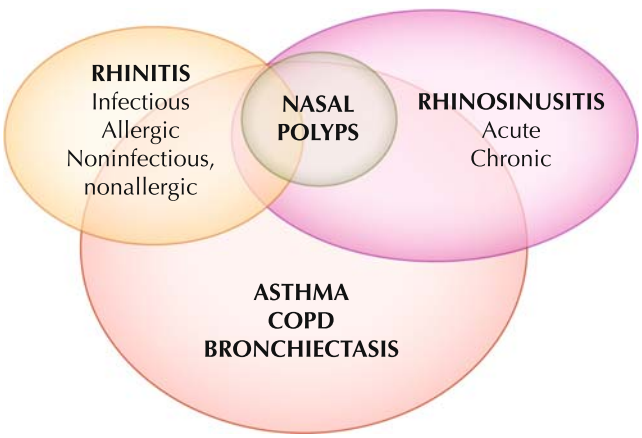

Fig. 3 Scheme representing the close interrelationships among rhinitis, rhinosinusitis, and bronchial pathology (eg, asthma, chronic obstructive pulmonary disease [COPD], and bronchiectasis)

rhinitis, we cannot predict if or when rhinitis will progress to the development of bronchial symptoms. Therefore, it may be important to evaluate bronchial function in all patients with persistent rhinitis symptoms. In patients with NP and concomitant asthma/COPD, we do not know whether sinus surgery or any other medical treatment for rhinosinusitis will have beneficial effects on lower airway pathology. Therefore, prospective clinical trials on the outcomes of upper airway therapy should not only concentrate on parameters of upper airway disease but should also take into account the effects of treatment on the lower airways. Alternatively, the impact of asthma or COPD on rhinosinusitis remains obscure. As upper airway inflammation may be induced by bronchial inflammation [31], rhinologists need to collaborate closely with pneumologists to design a therapeutic strategy that aims to obtain the optimal condition for both parts of the airway.

A minority of CRS and asthma patients are refractory to standard medical therapy and sinus surgery procedures. In these patients, disease development remains incompletely understood. Therefore, one of the tasks remaining is to delineate factors that contribute to severe CRS and asthma, such as exposure to environmental or occupational agents, underlying gastroesophageal reflux, and/or infection or colonization with microorganisms. Recently, fungal extracts and bacterial enterotoxins were linked to the etiology of NP. Research in the field of microbial triggers and their interplay with airway biology should be extended to viruses and atypical bacteria such as *Mycoplasma* and *Chlamydia*. In addition, the cellular source as well as the mechanisms of systemic release of proinflammatory mediators (eg, IL-5 and eotaxin by allergen inhalation) are still unknown. Whether the systemic release of these mediators represents diffusion of locally produced molecules or rather systemic release by circulating cells remains to be explored. After full comprehension of the mechanisms of systemic mediator release, novel treatment strategies can be designed aiming at reducing the systemic immune response with its impact on global airway disease.

For clinical practice, a need exists for noninvasive markers of inflammation in the upper and lower airways. Among noninvasive biologic markers of inflammation, nasal and bronchial nitric oxide (NO) measurement may represent a novel tool for diagnostic purposes as well as for the prediction of success of therapy. In spite of the validity of NO measurements in exhaled air in asthma patients [32], their role in upper airway inflammation needs to be studied further. Induced sputum, another noninvasive tool for research, may provide us with relevant information on the involvement of bronchial inflammation in patients with upper airway disease. Further studies are needed to delineate its validity in rhinologic practice.

Conclusions

Upper and lower airway inflammation share common pathophysiologic pathways, frequently coexist, and communicate via the systemic circulation. The threshold for developing symptoms in upper and lower airways relates to intrinsic and extrinsic factors. Genetic predisposition, organ susceptibility, and breathing patterns are likely to be involved in the development of bronchial symptoms in patients with rhinosinusitis. Extrinsic factors such as exposure to allergens in atopic patients, the microbial environment, and occupational factors all may contribute to the complex picture of global airway disease. Many unanswered questions relate to the generation of symptoms in patients with airway inflammation. However, the awareness of bronchial symptoms in patients with upper airway inflammation and vice versa may at this stage represent a major step forward in the diagnostic and therapeutic approach. The full appreciation of involvement of upper and lower airway disease in one patient can only be executed in a multidisciplinary clinical setting that allows physicians to examine and interpret clinical abnormalities of upper and lower airways. Anterior rhinoscopy and nasal endoscopy should be combined with lung function tests in patients with any chronic upper airway disorder. The validation of noninvasive parameters of airway inflammation, such as NO measurement, and the optimization of combined treatment strategies for patients with upper and/or lower airway disease will be one of our major tasks for the upcoming decade.

Disclosure No potential conflicts of interest relevant to this article were reported.

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