

The Unified Airway—Conceptual Framework

John H. Krouse, MD, PhD

*Department of Otolaryngology, Wayne State University, 540 East Canfield,
5E-UHC, Detroit, MI 48201, USA*

Over the past decade there has been an increasing awareness of the inter-relationship between inflammatory diseases of the upper and lower airway. Both epidemiological and physiological data suggest that the respiratory tract, from the middle ear mucosa, through the nose and sinuses, and into the pulmonary tree, behave as an integrated unit. Pathophysiological processes that affect one component of this integrated system often concurrently impact other portions of the airway, and over time, isolated disease in one area can expand to involve other areas also. This interdependence of the upper and lower respiratory tracts has been explored in numerous studies and clinical reviews, and has led to the concept of the unified airway, a model for understanding and framing inflammatory processes that affect the respiratory system.

In this unified airway model, the respiratory tract is considered to be an integrated system and to behave as an organized, functional unit (Fig. 1). Both local inflammatory processes and systemic mediators promote reactions throughout this system, and pathophysiological mechanisms activated by this inflammation can stimulate effects in all components of this unified airway. The presence and severity of disease processes within the upper and lower airways are linked closely, and exacerbations of disease in one component of the airway are likely to encourage worsening of airway disease diffusely [1].

The discussion of the relationship between the upper and lower airways has historical roots that go back almost a century. In 1920, Keller [2] noted that among patients who had lower respiratory disease, 86% of those individuals also reported concurrent nasal symptoms. He observed that among patients who had nasal congestion, the decreased ability of the nasal airway to appropriately condition inspired air could lead to increased asthma

E-mail address: jkrouse@med.wayne.edu

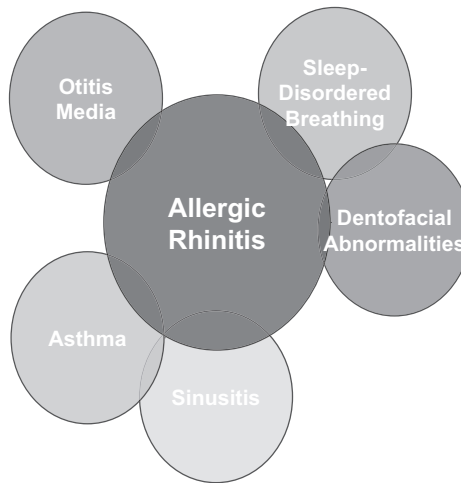


Fig. 1. Interrelationship of airway diseases with allergic rhinitis.

symptoms such as wheezing and cough. From the 1920s through the 1980s, however, little was written on the relationship of nasal function and asthma, and certainly not in an attempt to integrate the behavior of these two components of the respiratory system.

The interest in the integrated function of the upper and lower respiratory tracts has increased in the past decade. In one recent international multidisciplinary consensus meeting, the interrelationship between the diseases of allergic rhinitis and asthma was examined thoroughly, and numerous epidemiological and pathophysiological links were found tying these two common conditions. In fact, the coexistence of these two processes was felt to be so frequent that this panel recommended that “when considering a diagnosis of rhinitis or asthma, an evaluation of both the upper and lower airways should be made” [3].

In examining the relationship between various disease processes, and in exploring the interrelationship between those processes, three criteria have been proposed that should be satisfied in order support this relationship [4,5]. This model has been used in exploring both the relationship between chronic rhinosinusitis and gastroesophageal reflux disease [4], and the relationship between allergic rhinitis and chronic rhinosinusitis [5]. This model also can be adapted to explore the relationship between upper and lower airway diseases. Three criteria in support of a unified airway would be:

1. Patients with upper airway diseases such as rhinitis and rhinosinusitis should have a higher prevalence of lower respiratory diseases such as asthma; the corollary, increased prevalence of upper respiratory diseases among patients with lower respiratory diseases, also should be present.

2. Interrelated pathophysiological mechanisms between upper and lower airway diseases should exist to explain the interaction of these two disease processes.
3. Treatment of one portion of the unified airway should improve symptoms in a separate portion of the respiratory system.

These three principles will be explored throughout this issue, and can be used to evaluate the relevance of the unified airway model to otolaryngologists and other physicians. Some introductory comments will place the discussion into perspective, and will begin to examine these three principles in the integration of upper and lower airway disease.

Epidemiological relationships

Corren [6] published a landmark paper examining the relationship between rhinitis and asthma. In this article, he not only looked at the coexistence of these two common respiratory diseases, but also discussed the temporal relationship of the onset of asthma, frequently preceded by the presence of allergic rhinitis. Corren noted that 78% of patients who have asthma are bothered with symptoms of rhinitis, both allergic and nonallergic. In addition, 38% of patients who have rhinitis have asthma, with the true prevalence perhaps being even higher. Corren [7] emphasized this relationship again in a recent review, pointing out that recognition of the relationship between these two processes allows improved opportunities for treatment and prevention of respiratory disease.

A large-scale epidemiological study was conducted using a Danish general practice database to examine the temporal relationship between asthma and allergic rhinitis among patients presenting to primary physicians over a 1-year period [8]. In this study, the history of almost 8000 patients who presented with one or both of these diseases was reviewed for the coexistence or preceding presence of upper and lower respiratory symptoms. Among this group of patients, both allergic rhinitis and asthma first developed within the same year in 25% of the sample. In addition, in more than 75% of these patients, the two diseases developed within 2 years of each other. This study would suggest that the development of respiratory symptoms in one part of the unified airway is linked closely with the expression of symptoms in another part of the airway, at least temporally.

Numerous examples of this epidemiological relationship can be cited. A Finnish twin cohort study examined 11,000 patients to evaluate whether the presence of allergic rhinitis would predispose patients to the development of asthma [9]. In this 15-year study, patients who had allergic rhinitis had a fourfold increase of developing asthma when compared with a control population that was not allergic. Similar findings also were reported by Guerra in a large Tucson database [10] and by Settiple with Brown University undergraduates [11]. In each of these studies, individuals who had

allergic rhinitis demonstrated a threefold increase in the development of asthma over a 20-year period when compared with their nonallergic counterparts. These longitudinal investigations all support the concept that inflammation in the upper airway can be a predisposing factor in the development of lower airway disease, and that the respiratory tract as a whole functions as a unified mechanism.

Pathophysiological mechanisms

Several mechanisms have been postulated to explain the observed relationship between diseases of the upper and lower airway. Several of these mechanisms are more of historical interest, although a growing body of evidence suggests that common inflammatory processes appear to be involved in diffuse airway inflammation. Three of these potential mechanisms include (1) the nasobronchial reflex, (2) the loss of nasal protection of the lower airway, and (3) shared inflammation throughout the respiratory tract.

The nasobronchial reflex

Argument for the presence of a nasobronchial reflex dates back almost a century, when Sluder [12] proposed that nasal irritation could cause bronchospasm and lead to the development of bronchial asthma. This hypothesis led to a series of studies beginning in the 1960s that attempted to demonstrate the existence of this purported reflex. The study that often has been cited as providing primary support for this mechanism was conducted by Kaufman and Wright [13], and was reported in 1970. In this study, silica particles were applied directly to the nasal mucosa in subjects without asthma. Measurement of pulmonary function in these subjects was reported to demonstrate rapid and significant increases in lower airway resistance, leading to the speculation that a direct reflex was stimulated between the nose and the lungs. Subsequent studies showed that this effect could be blocked through the administration of atropine [13] or with resection of the trigeminal nerve [14].

Since these experiments in the late 1960s, additional support for this presumed nasobronchial reflex has not been demonstrated. In fact, a series of studies cited in Corren's [6] 1997 review of the unified airway failed to replicate the effects of nasal stimulation in causing rapid bronchoconstriction. In addition, in animal models in which nasal stimulation has been conducted with thermal, chemical, and mechanical stimuli, no reflex changes in ventilation or oxygenation have been demonstrated [15]. Although delayed changes can be seen in the lung from 30 minutes to four hours after antigen challenge of the nose [16], immediate reflex changes in pulmonary function cannot be demonstrated consistently. These findings suggest that mechanisms other than a direct reflex arc may be responsible for the observed relationship between upper and lower airway disease.

Loss of nasal protection of the lower airway

Another proposed mechanism that has been offered to explain changes in pulmonary function with nasal disease has been the loss of the protective function of the nose in situations of mouth breathing. The study often cited to support this hypothesis was reported by Shturman-Ellstein and colleagues [17] in 1978. In this trial, patients who had exercise-induced asthma were allowed to exercise under three conditions: spontaneous breathing, nasal breathing, and mouth breathing. Results of this study demonstrated that not only did mouth breathing worsen bronchospasm among this group of subjects, nasal breathing appeared to have a protective effect. The conclusions would appear to suggest that nasal breathing can have a beneficial effect on the lower airway through conditioning inspired air for delivery to the lungs.

Despite the conclusions reported in this study, confirmation of this relationship has not been reported. In fact, recent studies suggest that stimulation of the nose with noxious challenges, such as cold, dry air, can improve the ability of the nasal mucosa to warm and humidify inspired air [18]. In addition, occluding the nose in subjects with cat allergy was not shown to increase bronchospasm among these individuals [19]. Again, the observed relationship between the upper and lower airways does not appear to be explained through a mechanism of nasal airway protection.

Shared inflammation

The primary hypothesis that links the upper and lower airways mechanistically employs a model of shared airway inflammation throughout the respiratory system. The respiratory mucosa in the middle ear, the nose and sinuses, and the lower respiratory tract is structurally and physiologically uniform, having a pseudostratified columnar epithelium that is involved in active transport of mucus and particulate matter. Disorders of the respiratory mucosa present with a similar inflammatory response, common to diverse diseases such as rhinitis, rhinosinusitis, and asthma [20]. Inflammatory mediators released in diseases throughout this respiratory system are identical, and involve T cell cytokines such as interleukin (IL)-4, IL-5, and IL-13, and cellular populations, particularly eosinophils [21].

Studies by Braunstahl and colleagues [22] have shown that stimulation of one portion of the airway mucosa with antigen will result in system-wide inflammatory changes within a matter of hours. Placement of antigen directly onto the bronchial mucosa using bronchoscopy has been shown to induce nasal inflammation in patients who have allergic rhinitis. In addition, reciprocal induction of bronchial inflammation with careful nasal antigen stimulation has been demonstrated using a similar model [23]. These studies suggest that inflammatory crosstalk, or immune communication through the respiratory tract, is responsible for system-wide changes that induce an up-regulation of airway inflammation. Braunstahl discusses the concept as nasobronchial interaction [24].

Other studies confirm the interplay of inflammatory processes in the upper and lower airways. Inflammation throughout the respiratory system appears to be present in patients who have disease even isolated to one portion of the system. Significantly higher numbers of eosinophils can be seen in the nasal mucosa of asthmatic patients, even those who do not have any symptoms of rhinitis [25]. Furthermore, nasal antigen challenge can increase bronchial hyper-responsiveness to methacholine challenge, even without the presence of unstimulated changes in pulmonary function [16]. Ongoing antigenic stimulation of the respiratory tract therefore could provide a cumulative augmentation of airway inflammation, resulting in the observed progression of airway inflammation from allergic rhinitis to asthma.

Because both allergic rhinitis and asthma are inflammatory conditions of the airway, and because common pathophysiological processes appear to be involved in these two processes, it would appear that mechanistic support for the unified airway model is found in the observation of system-wide inflammatory airway effects. Inflammation appears to be the hallmark of chronic airway disease, and this inflammation does not appear to be limited to any one specific component of the respiratory system.

Treatment effects in the unified airway

Numerous studies have focused on the efficacy of treating inflammatory diseases of the upper airway and its impact on asthma. Several papers have shown that treating allergic rhinitis with intranasal corticosteroid sprays can improve both asthma symptoms [16,26] and objective indices of pulmonary function [27]. Both oral antihistamines and oral leukotriene receptor antagonists have shown similar effects, although the direct systemic effects of these medications on the lungs cannot be discounted [28]. In addition, these treatment effects can be translated into direct societal impact, in that patients with concurrent allergic rhinitis and asthma who have treatment for their nasal disease demonstrate decreased incidence of hospitalizations and emergency department visits for asthma when compared with patients not receiving or not adherent to rhinitis treatment [29]. Numerous studies confirm that successful treatment of allergic rhinitis can improve asthma symptoms significantly and decrease their impact.

Similar effects on the lower respiratory system have been demonstrated with treatment of chronic rhinosinusitis. Successful management of chronic sinus disease has been demonstrated to result in the decreased need for asthma medications, improved pulmonary function, and fewer asthma exacerbations [30,31]. These findings have been noted in both adult and pediatric patients with chronic rhinosinusitis [32]. In addition, effective medical management of chronic sinus disease has been demonstrated to improve asthma symptoms and markers of inflammation [33]. Numerous studies confirm that effective management of sinus disease can play a significant role in reducing the symptomatic burden of lower airway inflammation.

Finally, evidence of concurrent benefit to both the upper and lower airways with immunotherapy further strengthens the observation that system-wide airway effects can be noted with proper therapeutic interventions. Reduction in both rhinitis and asthma symptoms has been shown in placebo-controlled trials with immunotherapy, suggesting that a down-regulation of inflammation occurs throughout the respiratory tract with treatment [34,35]. Even more intriguing is the reported decrease in the development of asthma among children who have rhinitis treated preventatively with immunotherapy [36]. It appears that modulation of the immune system with immunotherapy can exert effects in the management of patients who have concurrent upper and lower respiratory diseases, and in the potential prevention of more widespread airway inflammation.

The impact of these various treatment studies supports the hypothesis that treatment of airway inflammation can have benefit in the management of the unified airway as a systemic whole. Treatment of one component of this airway can have widespread effect, and can decrease symptoms, improve objective function, and decrease the burden of respiratory disease on a system-wide basis. The future potential for prevention of respiratory disease through early identification and immune modulatory therapy is intriguing and certainly bears future investigation.

Summary

The model of the unified airway provides a conceptual framework for understanding and managing patients who have both upper and lower airway inflammatory diseases. Through appreciating the relationships that exist among diseases such as otitis media, allergic rhinitis, acute and chronic rhinosinusitis, and asthma, physicians can be more thorough in their diagnosis and treatment of patients who have airway disorders and can implement effective treatment strategies to decrease the burden and symptomatic expression of disease.

Sufficient evidence of epidemiological, mechanistic, and outcome-related support for the presence and operation of this unified airway exists to permit the use of this model as a therapeutic guide for physician practice and patient care. Epidemiological data confirm the strong relationship between airway diseases, and demonstrate the increased prevalence of system-wide airway disease among patients who have complaints of single symptoms such as rhinitis or asthma. It would appear that the presentation of symptoms in one portion of the respiratory tract is a marker of diffuse airway inflammation, and is representative of the presence of concurrent disease elsewhere in the respiratory tract. Even when concurrent disease is not present, there is an increased likelihood that it will develop subsequently over time. Compartmentalization of airway inflammation would appear to be the exception rather than the rule.

Mechanistic support for shared inflammation throughout the respiratory tract continues to accumulate. The ability of the airway to communicate on a system-wide basis through both humoral and cellular mediators has been demonstrated, and additional research continues to validate this concept of inflammatory crosstalk. Future research that examines how this diffuse respiratory inflammation is regulated will be essential in driving therapeutic models for management of patients who have respiratory disease.

Finally, the benefit of treating one portion of the unified airway and its secondary effect elsewhere in the respiratory tract has been demonstrated. Effective medical and surgical management of allergic rhinitis and rhinosinusitis can decrease the expression of asthma symptoms, and can improve pulmonary function and quality of life. Treating the unified airway as an integrated whole, as with the use of immunotherapy, can have additional benefit in both managing the symptoms of active disease and in potentially decreasing the advance of disease throughout the respiratory tract.

The three principles set out at the beginning of this discussion have been shown to have significant support in confirming the validity and utility of the unified airway model. Throughout the remainder of this issue, this model will be explored and applied in a systematic way, and the principles discussed here will be examined in greater detail.

Otolaryngologists frequently treat individuals who have upper airway diseases such as allergic rhinitis and acute and chronic rhinosinusitis, and therefore are positioned uniquely to identify patients currently symptomatic from or at risk of developing other respiratory illnesses such as asthma. In addition, related diseases of the respiratory system such as otitis media and chronic laryngitis may be seen more frequently among this population. An understanding of the concept of the unified airway and the ability to translate its principles into successful diagnostic and treatment strategies can enhance the practice of otolaryngology and can lead to improved patient outcomes and quality of life.

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