Chapter 11
Sinusitis, Rhinitis, Asthma, and the Single Airway Hypothesis

Christopher C. Chang

Introduction

Diseases of the sinuses are frequently a result of a dysregulation of immunologic function that may range from infection to allergic or autoimmune diseases. Sinus disease may be a part of multisystem or systemic conditions that frequently also involve the nasal passages, eyes, upper and lower airways, and even the gastrointestinal tract. It has been proposed that parts of the human airway from top to bottom, including the nasal passages, sinuses, pharynx, bronchi, and bronchioles, are all of the same histomorphological makeup. The corollary of this theory is that a common airway will be uniformly susceptible to any insults or disease processes. Diseases of the lower and upper respiratory tract, therefore, are all intricately linked. The truth is, as always, not that simple. The reason for the interrelationships between these diseases may not be simply based on a single airway theory, but on systemic changes in immunologic paradigms of the individual during his or her lifetime. For example, immunologic and autoimmune conditions that affect both the sinuses and the lower airway are well known, as in the case of aspirin-exacerbated respiratory disease and granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis). The immunologic basis that leads to the susceptibility of both sinuses and lower airways in these diseases is a subject of ongoing research.

Epidemiological evidence for a connection between the upper and lower airways is abundant. For example, treatment of diseases of the upper airway often leads to clinical improvement in lower airway symptoms. The impact of upper airway inflammation on lower airway diseases such as asthma has been clearly demonstrated, but the mechanisms of this interaction are not entirely clear. It may not be simply explained by a similar epithelial lining of the two structures [1].

Allergic Rhinitis, Sinusitis, and Asthma

Historical Evidence for a Relationship Between Allergic Rhinitis, Sinusitis, and Asthma

The idea that there are common features in upper and lower inflammatory airway disease was described in some of the earliest recorded histories of medicine. Conditions consistent with asthma had been described in Egyptian recorded medical history over 2,400 years ago. The term "asthma" first appeared in the Greek epic work "The Iliad" by Homer. In the twelfth century, Maimonides, in his "Treatise of Asthma," actually described a patient whose asthma symptoms frequently started as a common cold.

In 1819, J Bostock describes his own affliction in his paper, "A Periodical Affection of the Eyes and Chest," in which he describes a condition that includes "the sneezings" and "a farther sensation of tightness in the chest, and a difficulty of breathing, with a general irritation of the fauces and trachea," thus linking lower and upper airways.

C.C. Chang, MD, PhD, MBA, FAAAAI, FACAAI
Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: cchang@nemours.org

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In 1873, Charles Blackley, one of the fathers of allergology, described nasal and bronchial symptoms after exposure to pollen grains [2]. In 1883, it was proposed, but not proven, that aspiration of nasal secretions could lead to asthma exacerbation. This theory has in fact never been proven, and modern studies have revealed that radiolabeled allergen introduced into the nose found its way not to the lower respiratory system, but to the digestive system [3, 4]. This does not, on the other hand, discount the possibility of upper airway pathology influencing lower airway symptoms. Even in the absence of direct contact or direct transmission of the inciting agent, other mechanisms may be in play.

In 1886, F.H. Bosworth published an article entitled, "Hay Fever, Asthma, and Allied Affections," in which he describes the function of the nose in keeping tissues moist and mucous hydrated. He also addresses both "hay fever" and "hay asthma," thereby also forging a link between upper and lower airways.

Epidemiological Evidence of a One Airway Disease

Evidence of a relationship between the upper and lower airways can be deemed from examination of epidemiological studies of three conditions, rhinitis, sinusitis, and asthma. It should be noted that these comparisons do not necessarily reflect a role for atopy by itself, although many studies have specifically addressed the association of "allergic" rhinitis and asthma or sinusitis. In fact, it will be seen that these relationships may also exist when atopy is not involved, as in the case of nonallergic asthma, chronic obstructive pulmonary disease, or chronic rhinitis, to name a few conditions in which atopy may be irrelevant. Thus, the unified airway concept extends beyond the borders of allergy [5].

Rhinitis and Asthma

It has long been known that patients with allergic rhinitis have a higher incidence of asthma, and vice versa [6]. The rates vary from region to region, but a comprehensive review of the literature presented by Cruz et al. in their ARIA report describes coexistence of these two conditions in almost all regions of the world [7]. One of the exceptions was in certain areas in China, where only 6.2 % of asthmatic patients described concurrent nasal rhinitis symptoms. The rates of asthma in rhinitis patients and vice versa are presented in Table 11.1. Much of the available data on the impact of allergic rhinitis on asthma is derived from the International Study of Asthma and Allergies in Childhood (ISAAC). Perennial rhinitis is considered to be a risk factor for nonatopic asthma [20, 21]. In the European Community Respiratory Health Survey, evaluation of 20–44-year-old subjects revealed that asthma is more common in patients with both atopic and nonatopic individuals. Moreover, even in nonasthmatic patients, those with symptoms of rhinitis were more likely to have concurrent bronchial hyperresponsiveness. In a study in Rochester, Minnesota, health-care costs for patients with concurrent asthma and allergic rhinitis were found to be higher than for patients with asthma alone [22].

Further supporting the common airway principle is the fact that there are nonallergic respiratory diseases that demonstrate an association between the lower and upper airways. Disease processes such as bronchiectasis, cystic fibrosis, primary cilia dyskinesia, α1-antitrypsin deficiency, smoking, and Young's syndrome all have concurrent upper and lower airway symptoms [23].

In general, the increase in the rates of asthma in the past 30 years has been accompanied by an increase in the incidence of allergic rhinitis [24–26]. In "modern" Asian countries such as Japan, the prevalence of allergic rhinitis increased from 3.8 % in 1984 to 32 % as reported in an AIRA update in 2008. The prevalence of asthma similarly increased from 4.6 % in 1992 to 9.1 % in 2008 [25]. In "poorer" countries, the rates are still much lower, an example being Tibet, in which the rates of allergic rhinitis, current wheezing, and asthma were 5.2, 0.8, and 1.1 %, respectively [27]. In developing countries within Asia, the rates have already started to rise, mimicking the trend that has already occurred in developed countries. Between 1995 and 2008, the prevalence of asthma in Thailand increased from 12.2 to 14.5 %, while the prevalence of allergic rhinitis increased from 37.9 to 50.6 % [28].

A study of 22 grass allergic patients and 10 controls investigated the existence of bronchial hyperresponsiveness (BHR) and airway inflammation in those with allergic rhinitis. In this study, the authors used bronchoprovocation with histamine and measurements of exhaled nitric oxide and exhaled breath concentrate levels of NO and pH to evaluate the presence of airway inflammation. In allergic patients with BHR, they found that BHR and FeNO levels increased during the pollen season [29]. Further evidence of the link between rhinitis and asthma is presented in a study on 20 grass allergic patients, in whom a number of functional and inflammatory parameters including nasal airflow, FEV1, eosinophils, IL4, and interferon-γ levels were measured. A Th2 cytokine profile correlated with airway flow and was present in both the upper and lower airways [30]. Studies such as these establish a link that supports the unified airway concept.

Table 11.1 Rates of asthma in allergic rhinitis patients

	Place where research was done	Number of subjects in research	Population chosen in research	Asthma in allergic rhinitis patient	Asthma parameters	Allergy rhinitis parameters	Comments
1	Sweden (nested case controlled study) [8]	$N=15{,}813$ Doctor-diagnosed asthma ($n=235$) Controls ($n=2{,}044$)	Random sample from general population aged 21–51 years	Adult-onset doctor-diagnosed asthma was associated with occurrence of noninfectious asthma (OR: 5.4)	Doctor-diagnosed asthma	Comprehensive respiratory questionnaire	Chronic rhinitis is associated with increased risk for adult-onset asthma
2	Arizona, USA (nested case controlled study) [9]	Doctor confirmed asthma ($n=173$) Controls who reported no asthma or shortness of breath with wheezing ($n=2{,}177$)	Random sample from general population	Rhinitis was found to be significant risk factor Crude (OR = 4.13) Adjusted OR = 3.21 (adjusted for years of follow-up, age, sex, atopic status, smoking status, and presence of COPD)	Doctor-diagnosed asthma	Presence of rhinitis by questionnaire	1. Rhinitis increased the risk development of asthma both by about three times among atopic nonatopic patients and by more than 5 times among patients with highest IgE titers 2. Patients with rhinitis with persistent and severe nasal symptoms and a personal history of doctor confirmed sinusitis had an additional increased risk of asthma development
3	Sweden (multivariate logistic regression analysis, cross-sectional study) [10]	$N=1{,}370$	Random sample of adults aged 20–44 years	Onset of asthma was associated with AR (OR = 4.9), sensitization to pets (OR:2.4), and smoking (OR:3.0) Asthma was strongly associated with AR among atopics (OR = 5.7), but asthma and rhinitis also tended to be related among nonatopic (OR = 3.5)	Postal questionnaires were used as follow-up after skin tests	Skin prick tests were conducted. Onset of AR was associated with sensitization to birch (OR:6.5), parietaria (OR:7.4), and pets (OR:3)	Onset of asthma is strongly associated with atopics They tend to be associated in nonasthmatics as well
4	Sao Paulo, Brazil [11]	6–7-year-old ($n=3{,}033$) 13–14-year-old ($n=3{,}487$)	School children living in Sao Paulo			ISAAC questionnaire	Prevalence of severe asthma was higher among children and adolescents with asthma, rhinitis, and eczema combined, and each one had a higher risk individually for asthma

(continued)

Table 1.1 (continued)

	Place where research was done	Number of subjects in research	Population chosen in research	Asthma in allergic rhinitis patient	Asthma parameters	Allergy rhinitis parameters	Comments
5	Pelotas, Brazil (birth cohort study followed up to 90 years, multivariate analysis) [12]	$n=494$	Children born in the year 1993	The prevalence of asthma was found to be 12.8 % (95 % CI:10–15.9 %) In the multivariate analysis, risk factors such as nonwhite skin color were found to be associated with a relative risk (RR) of 1.9 (95 % CI1.1–3.3 %); family history of asthma, RR:2.8 (95 % CI:1.5–5.1); AR, RR:2.6 (95 % CI:1.5–4.4); and maternal smoking during pregnancy, RR:1.7 (95 % CI:1–2.9)	Standardized and validated asthma questionnaire, based on ISAAC, was applied		Rhinitis is demonstrated as a risk factor for asthma
6	Denmark (12-year follow-up study) [13]	$n=281$	Random population sample of individuals aged 7–17 years without asthma	At follow-up, 37.9 % of individuals with BHR to histamine and 30 % of individuals with EIB had developed current asthma, compared with only 5 % of individuals in whom these test results were negative In patients with BHR to histamine, parental asthma, OR:12.6 (95 % CI:1.5–108.5); furred pet ownership, OR:6.0 (95 % CI:1.2–19.6); and dermatitis and/or rhinitis in childhood, OR:2.2 (95 % CI:1.1–5.1), predicted the subsequent development of asthma	BHR to histamine, EIB		Rhinitis is a risk factor for asthma
7	Arizona, USA (large longitudinal cohort study, Tucson Children's Respiratory Study) [14]	Among $n=1,246$ originally enrolled $n=1,024$ children who completed questionnaire were included	Children between the ages of 6 and 18 were included	After adjusting for sex, skin test reactivity, and parental asthma, both rhinitis, OR:2.47 (CI:1.84–3.30), and sinusitis, OR:1.54 (CI:1.11–2.14), were associated with an increased risk of cough and wheezing	Cough or wheezing or both by questionnaire		Rhinitis is significantly associated with cough and wheezing

8	Pisa (cohort study with a follow-up of 5 years) [15]	$N=1,670$	Subjects were greater than or equal to 15 years old and had no positive history of cough apart from the colds at the baseline survey; among them, 299 (18 %) had rhinitis at baseline	16 % of the subjects with rhinitis had developed any cough apart from colds, when compared to only 10 % of the subjects without rhinitis, OR:1.7 (95 % CI:1.2–2.5)	Information on cough rhinitis was obtained by standardized questionnaire		Rhinitis remains significantly associated with an increased risk of cough after adjusting for age, gender, smoking, and occupational exposure
9	Italy (7-year follow-up study) [16]	$n=28$	Homogenous population of nonasthmatic children with AR (6–15 years)	After 7 years, none of the children with negative methacholine test developed asthma, but only 2 out 13 hyperreactive to methacholine reported asthma symptoms			
9	Europe (ECRHS, international cross-sectional study) [17]	$N=90,478$ adults		The risk of asthma increased from 2.0 % in subjects without rhinitis to 6.7 % in subjects with rhinitis only when exposed to pollen, 11.9 % in subjects when exposed to animals, and 18.8 % in subjects with rhinitis when exposed to either pollen or animal	Pulmonary function tests, detailed ECRHS questionnaire	IgE measurements	In all countries, rhinitis was significantly associated with asthma after adjustment for IgE, parental history of asthma
10	Brescia, Italy (follow-up study up to 10 years) [18]	$N=99$ allergic patients 44 suffered from AR alone, 12 from allergic asthma alone, 43 from both AR and asthma		31.8 % of the AR patients developed allergic asthma, and 50 % of the patients with allergic asthma developed allergic rhinitis			
11	Sweden (follow-up study for 7 years) [19]	$N=94$ with atopic dermatitis		43 % developed asthma and 45 % developed AR			

It is important to appreciate that rhinitis, itself, is a risk factor for asthma, whether or not the rhinitis is allergic in nature. In other words, the commonality between the upper and lower airway responsiveness cannot simply be attributed to a state of "atopy" [31]. This is an important consideration in our discussion on the pathogenesis of the one airway, one disease concept below.

Rhinosinusitis and Asthma

The association between rhinosinusitis and asthma has been studied, and results have been varied. In one series of 590 patients, the prevalence of asthma in allergic rhinitis, chronic sinusitis, and nonallergic rhinitis patients was 33, 42, and 8.7 %, respectively [32]. Other sources estimate that between 60 and 90 % of patients with chronic rhinosinusitis may have evidence of asthma [33, 34]. The converse is also true, as up to 80 % of asthma patients may have evidence of chronic rhinosinusitis [34]. Morphological abnormalities of the sinuses have also been reported to occur more frequently in asthmatics [35].

A Swedish study investigated the relationship between symptoms of asthma and chronic rhinosinusitis. The group utilized data extracted from the West Sweden Asthma Study and found that 2.1 % of the general population had "multi-symptom" asthma. They determined that symptoms of chronic rhinosinusitis were associated with a higher risk of having multi-symptom asthma rather than fewer-symptom asthma. Moreover, they found that the incidence of allergic rhinitis was no different between the multi- and fewer-symptom asthma groups but that rhinorrhea and nasal congestion were higher in the multisystem group [36].

A study of 35 subjects with severe steroid-dependent asthma and 34 subjects with mild-to-moderate asthma revealed that 74 % of the former group and 70 % of the latter group also had symptoms of sinonasal disease. It was also noted that 100 % of the severe asthmatics and 88 % of mild-to-moderate asthmatics had abnormal CT scans. The CT scan and clinical scores appeared to be more severe in the severe asthma group [37]. This finding was further confirmed by Brinke et al., who discovered that the frequency of abnormal CT scans in severe asthma patients was 84 %. They also noted that there was a correlation between sinusitis in severe asthma patients and sputum eosinophilia, providing an additional link between the upper and lower airways [38]. A correlation has also been described between markers of airway inflammation such as exhaled nitric oxide (eNO) and sinus CT scores and between eNO levels and nasal polyps [39].

Rhinosinusitis and Rhinitis

It has been estimated that allergic rhinitis may play a role in up to 30 % of cases of acute sinusitis and may be significantly greater in cases of chronic sinusitis [40]. Twenty-six percent of patients with rhinosinusitis have been found to have concomitant allergic rhinitis [41]. Another study of 40 allergic rhinitis patients and 30 controls showed that 67.5 % of perennial allergic rhinitis patients had evidence of sinusitis on CT scan, whereas these findings were present in only 33.4 % of controls [42]. It has also been found that most patients with chronic rhinosinusitis are more likely to be sensitized to perennial allergens over seasonal allergens. On the other hand, in examining the relationship between in vitro IgE sensitization to allergens (atopy) and the degree of severity of rhinosinusitis, there appeared to be no significant correlation [43].

Rhinosinusitis and Upper and Lower Airway Infection

Chronic rhinosinusitis describes a persistent inflammatory state in the sinuses that may or may not be a result of an infectious process. Both bacteria and viruses can infect the sinuses, and common bacteria found in sinusitis among immunocompetent hosts include *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*, and *Staphylococcus aureus*. Viruses frequently involve the sinuses in common upper respiratory tract infections and may play a pivotal role in the overlap between sinusitis and asthma. Although previous studies have failed to detect the presence of viruses in biopsy samples from the sinus mucosa in patients with chronic rhinosinusitis, the possibility still remains that a viral infection may have provided an initial inflammatory stimulus [44].

Pathogenic Pathways That Link the Upper and Lower Airways

The pathogenic links between upper and lower airways have been attributed to various systems, including the nervous, cardiac, and pulmonary systems. The physical proximity and contiguous nature of the upper and lower airways can lead to common disease mechanisms. Similarities in the histomorphology of the two parts of the airway may also contribute to the comorbidity

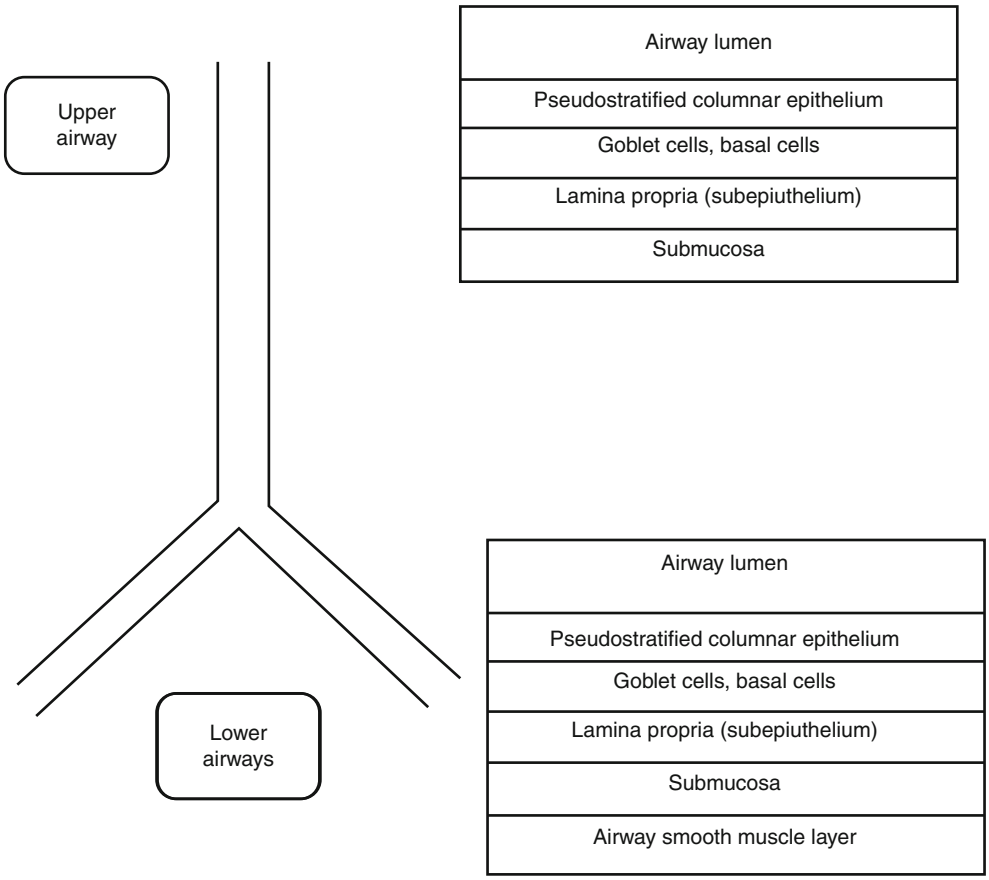

Fig. 11.1 Histopathologic and immunologic parallels between the upper and lower airways: a schematic representation

between sinus disease, upper airway allergies and infections, and lower airway disease such as asthma and bronchiolitis. In addition, immune mechanisms, both local and systemic, may play a role in the unified airway hypothesis (Fig. 11.1).

Functions of the Nose

The nose possesses several normal functions that may explain a relationship between nasal disease and lower airway disease (Table 11.2) [45]. Cilia in the nose are important in filtering out foreign particulate material, including allergens and adjuvants that may potentiate allergenic effects. Moreover, air that passes through the nose and around the nasal turbinates becomes "air-conditioned," so as to reduce its ability to trigger a hypersensitivity reaction [45]. The nose also serves to humidify inhaled air. Slowing down the flow of air through the generation of turbinate air by nasal turbulence helps to keep the mucosa surfaces hydrated for subsequent breaths.

Normal breathing draws air in through the nose. If the nose is not patent, then we become mouth breathers. When we become mouth breathers, all of the normal functions of the nose are not utilized fully. Cold, dry, unfiltered air has the potential to lead to asthma symptoms [46, 47]. Rhinitis sicca, a form of dry nose syndrome or atrophic rhinitis, is an example whereby the normal air-conditioning function is compromised which could exacerbate or serve as a nidus for sinusitis and/or asthma [48]. The nose also provides us with a sense of smell, which can serve as a protective mechanism to avoid areas of potentially harmful inhalants [49].

Anatomical and Histomorphological Comparison of the Upper and Lower Airways

The mucosal surfaces of the lower and upper airways demonstrate significant similarities. Both the lower and upper airway mucosae consist of a pseudostratified columnar ciliated epithelium which covers a reticular basement membrane. Ciliated cells predominate over goblet cells, and triangular basal cells also populate the tracheal and bronchial epithelium [50]. The

Table 11.2 Functions of the nose and upper airway

Warming	Prevents cold-air-induced bronchospasm
Filtering	Limits access of allergens and irritants to the lower airway
Humidification	Prevents dry-air-induced bronchial hyperresponsiveness (especially in EIB)
Smell	Helps us avoid danger signals
Creating turbulence	Turbinates reduce laminar flow for facilitation of other functions listed
Expulsion	Sneezing helps to expel dangerous material from the airways
Moisture recovery	Recover water from exhaled air

EIB exercise-induced bronchospasm

Table 11.3 Similarities and differences in the cellular and histological characteristics in the upper and lower airways

Similarities
Pseudostratified columnar ciliated epithelium over a reticular basement membrane
Goblet cells
Triangular basal cells
Lamina propria
Differences
Lower airway has airway smooth muscle cells in a helical pattern
Upper airway has more subepithelial capillaries and venous cavernous sinusoids
Clara cells are more important in lower airway
Cartilage in upper airway becomes less prominent in the lung

basal cells are small cells which attach to the basement membrane [51, 52]. Under the basal cells lies the subepithelium or lamina propria. Blood vessels populated the submucosa, along with nerves, mucous glands, inflammatory cell infiltrates, and other vascular elements. The bronchioles of the lower airway also possess airway smooth muscle cells arranged in a helical pattern, while the nasal mucosa has more subepithelial capillaries and venous cavernous sinusoids. Clara cells are more unique to the lower airway and predominately exist in the membranous bronchioles. Clara cell-specific protein may have a role in the generation of local inflammatory responses in the airway (Table 11.3) [53]. In the trachea, bronchi and bronchioles are cartilage that starts in the upper airway and gradually becomes less prominent toward the periphery of the lung. The 18–20 C-shaped rings in the trachea become even less complete rings in the bronchi and disappear by a bronchiolar diameter of about 1 mm.

When we review the gross anatomy of the upper and lower airways, specifically when comparing the nose and bronchi, the differences appear more significant than the similarities. The upper airway passages within the nose are surrounded by a rigid framework consisting of bony parts, whereas the lower airway is an elastic, easily pliable tube within a relatively flexible environment. This may explain the effectiveness of β-agonists in the treatment of lower airway conditions such as asthma. This part of the airway, with its smooth airway muscle outside layer, is pliable enough to respond to these bronchodilator drugs, whereas the upper airway is relatively unmovable [54].

Inflammatory Changes in the Upper and Lower Airways

The medical evaluation of the upper and lower airways is generally initiated by rigid or flexible nasal rhinolaryngoscopy of the nose and upper airway and/or bronchoscopy for the lower airway. In general, rhinolaryngoscopy is performed by otolaryngologists or allergists, while pulmonologists usually perform bronchoscopy. Inflammation of the nose can be evaluated by obtaining nasal washings, biopsies, or smears for examination of the cellular infiltrate. Samples obtained during bronchoscopy may include biopsies, bronchial brushings, bronchoalveolar lavage, and culture specimens. Expressed sputum can be generated under varying conditions including hypertonic saline. Tests performed on these samples may include cytology and histology of mucosal surface to identify inflammatory cells such as eosinophils, presence of proinflammatory Th1 and Th2 cytokine profiles, and secreted mediators of inflammation such as eosinophilic cationic protein, leukotrienes, or prostaglandins.

Fiber-optic rhinolaryngoscopy is simple to perform and presents fewer limitations compared to bronchoscopy. Limitations of fiber-optic rhinolaryngoscopy include the inability of the scope to penetrate into the sinuses unless there has been previous sinus surgery and the lack of biopsy sampling during most office procedures. Rigid rhinoscopy however allows the user to biopsy a specific site and directly samples with localized suction any suspicious secretions from the sinus cavities. Limitations of bronchoscopy include the inability of the scope to penetrate into the distal or terminal bronchioles, thus the evaluation being limited to larger lower airways.

An emerging measure of inflammation among more and more medical practitioners is the measurement of fractional exhaled nitric oxide (FeNO). Like peripheral blood eosinophilia and IgE, FeNO measurements are indicative of a systemic eosinophilic inflammatory response. At the present time, fractional exhaled nitric oxide has been utilized as a diagnostic and monitoring tool for lower airway disease such as asthma [55, 56]. Its role in upper airway disease and other eosinophilic disorders is not yet elucidated.

The inflammatory changes that occur in the lower and upper airway as a result of the atopic state were investigated in a study of 19 subjects with allergic asthma and rhinitis, 18 subjects with allergic rhinitis but no asthma, 8 atopic subjects with neither allergic rhinitis nor allergic asthma, and 16 nonatopic controls [57]. The authors found that the number of eosinophils was elevated in patients with rhinitis, whether or not they had asthma, when compared with the atopic non-symptomatic group and the control group. Thickening of the reticular basement membrane in both the upper and lower airways was also detected in the former two groups in a manner similar to the eosinophilia findings. In all groups of atopic individuals, there was significantly increased epithelial desquamation. Airway remodeling, defined as a change in structure of the mucosa and submucosa of the airway, specifically epithelial fragility, thickening of the reticular basement membrane, airway smooth muscle mass increase, and fibrosis [58], was detectable in the lower airway but not in the nasal mucosa. The reverse is also true whereby evidence of inflammatory markers in upper airways has been detected in patients with lower airway disease, including nonallergic asthma and chronic obstructive pulmonary disease (COPD) [5]. Nitric oxide, a marker of inflammation, has been attributed to both lower airway inflammation and nasal polyposis. A study of surgical tissue from 15 patients with nasal polyps demonstrated an increase in all three isoforms of nitric oxide synthetase in leukocytes from nasal polyp tissue which contrasts from normal middle turbinate tissue [59].

The parallels between the upper and lower airway patency were also studied in 221 children aged 6 years in the Copenhagen Prospective Study on Asthma in Childhood. An association was found between decongested nasal airway patency and post-bronchodilator FEV1, after correction for confounding variables, including sex, FVC, body size, and atopic disease. The authors proposed that this association reflected a common physiologic basis for comorbidities of the lower and upper airways [60].

Systemic and Lower Airway Effects of Allergen Exposure in the Nose

One of the mechanisms proposed for the linkage of the upper and lower airways is the systemic effect generated by allergen exposure in the nasal passages. As described above, the nose functions as a regulator of bronchial homeostasis. Besides the physical effects on air characteristics the nose imparts, it also functions as a filtration device. Allergenic particles are one of the primary entities that are filtered by the nose. In doing so, the nose is subject to the inflammatory effects triggered by the exposure to allergen in a hypersensitive host.

Although inflammatory effects are first localized to the nose, additional studies have also revealed evidence of systemic effects. A systemic effect has been shown to occur in mouse models following the induction of a nasal allergic response. The exposure of *Staphylococcus aureus* endotoxin B in the nose has been shown to lead to a systemic release of Th2 cytokines including IL-4, IL-5, and IL-13 in a mouse model. In addition, an increase in bronchial eosinophilia was also detected [61]. Immunologic unity has also been demonstrated in human studies. A correlation between IL-4, interferon-γ, eosinophilia in nasal cytology specimens, nasal airflow, and airway function (FEV1) was detected in a study of 20 patients with seasonal allergic rhinitis and asthma [30]. A nasal allergen provocation study showed that out of season nasal introduction of grass pollen leads to the infiltration of eosinophils into the epithelium and lamina propria of both the nasal and bronchial mucosae 24 h after nasal provocation. In addition, increased levels of ICAM-1 and an increase in the percentage of CD31 vascular endothelial expression of ICAM1, E-selectin, and VCAM1 were detected in the nasal and bronchial mucosae. The authors concluded that out of season nasal provocation in patients with grass allergy leads to inflammatory infiltrates and cytokine and chemokine expression in both the upper and lower airways [62].

Clinical markers of lower airway inflammation following dust mite nasal challenge have been described. In a study of 10 nonallergic children, 16 children with rhinitis alone, and 15 children with rhinitis and asthma, ages 6–10 years, Marcucci et al. studied bronchial symptoms, nasal-specific IgE, nasal and sputum eosinophilic cationic protein (ECP) and tryptase, spirometry, and exhaled nitric oxide (eNO) [63]. The authors conducted the nasal challenge at the beginning of the study in July (considered a low exposure time) and at the end of the study (during the winter which was considered a high exposure season). The results showed that baseline nasal IgE levels were higher in the summertime compared to winter. Also elevated from baseline in allergic or asthmatic subjects compared to controls were sputum ECP and exhaled nitric oxide eNO levels. The response to nasal challenge in asthmatics was mixed, with 3/15 asthmatics experiencing an increase in ECP in summer but 11/15 experiencing the increase in the wintertime. A similar result was seen in the rhinitis patients. Again, a more frequent response in eNO to nasal challenge was seen in the winter compared to the summer. The link between lower airway

and upper airway is perhaps best illustrated in this study from the observed increase in sputum ECP and eNO levels in asthmatic children in winter upon nasal challenge with dust mite allergen. However, in rhinitis patients, only the increase in eNO was detected after challenge in winter.

An increase in sputum ECP has also been detected after nasal allergen challenge with grass or birch pollen in 16 nonasthmatic seasonal allergic rhinitis patients between the ages of 22 and 33 [64].

Other cytokines studied included IL-5, sICAM (soluble intracellular adhesion molecule), and IL-10. The authors noted that in peripheral blood or sputum, there was no change in eosinophils after placebo or allergen challenge, but the plasma levels of IL-5 did increase after challenge. The increase in IL-5 correlated with an increase in sputum ECP and sICAM after nasal allergen challenge. However, sputum IL-10 levels decreased after nasal allergen provocation compared to challenge with placebo.

Bronchoprovocation Effects in the Upper Airway

The united airway theory proposes that the effects between the lower and upper airways should be bidirectional. A study in eight nonasthmatic grass pollen allergic patients and eight healthy controls compared the effects of bronchoprovocation with grass pollen extract [65]. Nasal and bronchial biopsy was performed in all cases at three time points, baseline, 1 h after challenge, and at 24 h after challenge. At 24 h following segmental bronchial provocation (SBP), there was an increase in blood eosinophil levels only in allergic patients compared to controls, suggesting a systemic effect of bronchial allergen challenge in sensitized patients. Bronchial biopsy results revealed that BMK13+ cells, or eosinophils, increased in allergic rhinitis patients in the bronchial segments challenged by allergen or saline, suggesting a local effect. IL-5-positive cells were increased in locally challenged epithelium in allergic rhinitis patients as well. At 24 h post bronchial challenge, nasal biopsies revealed that the number of BMK13+ cells detected in the nasal lamina propria and the number of IL-5-positive cells in the nasal epithelium were both increased in allergic rhinitis patients. Eotaxin-positive cells were also increased in the nasal subepithelium as well as the nasal lamina propria in allergic patients.

Braunstahl studied the effects of bronchoprovocation (SBP) on mast cell and basophil numbers in the nasal and bronchial mucosa of allergic rhinitis patients [66]. In this study, the authors found an increase in basophils in the bronchial mucosa following SBP. In contrast, the numbers of chymase mast cells (MC_C) and chymase/tryptase (MC_{TC}) mast cells were decreased in the nasal mucosa of allergic patients, whereas the numbers of basophils actually increased. The authors also noted an increase in the levels of interleukin-5 in the blood of allergic patients after SBP. Together, these studies support the induction of an inflammatory response in the upper airway in response to provocation with allergen in the lower airway.

The Role of Viral Respiratory Diseases in the Pathogenesis of Rhinitis, Sinusitis, and Asthma

It is well known that one of the main triggers of an asthma exacerbation, especially in children, is a viral respiratory infection. Studies have shown that viruses may be associated with up to 80 % of all asthma exacerbations in children and up to 50 % in adults [67]. It has also been demonstrated that objective measurements of asthma exacerbation, such as a decrease in forced expiratory volume in 1 s (FEV_1), result after infection with rhinovirus in an experimental setting [68]. Changes in other measures of airway hyperresponsiveness and inflammatory cell infiltration have also been described [69].

The most common upper respiratory viral infection is caused by rhinovirus. Other viruses incriminated in upper respiratory tract infections include metapneumonia virus, enterovirus, adenovirus, respiratory syncytial virus (RSV), coronavirus, and picornavirus. Viral infectious diseases that affect the upper airway can lead to lower airway disease by virtue of the resultant interference with normal function of the nose. However, there may be other mechanisms by which upper respiratory infections can affect lower airway function. Whether or not these are direct effects of the virus reaching the lower airways, or systemic inflammatory effects that impact the lower airway, is not clear. Various mechanisms have been proposed. Rhinovirus has, in fact, been isolated in bronchial specimens of individuals infected in the upper airway [70, 71]. Other mechanisms may be related to inflammatory changes mediated by cytokines and chemokines triggered by viral interaction within cellular elements of the upper respiratory tract.

The immunologic mechanisms that link rhinovirus upper respiratory infections with lower respiratory symptoms may involve activation of the nuclear factor κB (NFκB) pathway, a critical mechanism for the activation of multiple proinflammatory genes [72]. It is known that rhinovirus binds to an intracellular adhesion molecule, leading to infection of airway

epithelial cells. Included among the many functions that are mediated by activation of NFκB is the upregulation of an adhesion molecule known as intracellular adhesion molecule (ICAM)-1. Binding of rhinovirus to ICAM-1 allows rhinovirus to enter airway epithelial cells and leads to further activation of other proinflammatory mediators, which subsequently leads to recruitment of other proinflammatory cells such as neutrophils, monocytes, lymphocytes, and eosinophils. This positive feedback loop involving upregulation of the expression of ICAM-1 opens the door for further infection by rhinovirus. What results is the induction of an inflammatory state that is enhanced by the expression of multiple proinflammatory cytokines, including IL-1, IL-6, IL-8, RANTES, and IL-16. Further recruitment of inflammatory cells to the bronchial tree can ultimately lead to lower airway inflammatory symptoms, including cough, wheezing, and dyspnea [70].

Since asthma subjects tend to have a cytokine profile skewed toward a Th2 paradigm, a rhinovirus infection of the upper airway may result in lower production of interferon-γ. A reduction of interferon-γ may accentuate a lower airway involvement in asthma. It has also been shown that granulocyte colony-stimulating factor (G-CSF) levels are increased both locally (in the nose) and systemically (in the circulation) of allergic subjects subjected to experimental rhinovirus-16 infection. Increased G-CSF levels lead to higher neutrophil counts and activity and may play a role in the increased inflammatory state at sites distant from the upper airway. Other cells that may be stimulated and infiltrate to the lower airway include eosinophils, lymphocytes, monocytes, and macrophages [73]. The effects of viral infections extend to selected nonasthmatic subjects with respiratory disease as well [68]. In adults, more than 40 % of exacerbations of COPD can be linked to an upper respiratory infection [74].

Chronic Rhinosinusitis and Asthma

Chronic rhinosinusitis with and without nasal polyps is associated with an inflammatory state that involves increased serum IL-5 and an increased eosinophilia within the bone marrow. Immunologically, this pattern is similar to that seen in asthma. There are also parallels between the cytokine profiles in the sinus tissue of patients with chronic rhinosinusitis and in the bronchial tissue of patients with asthma. Histological findings in chronic rhinosinusitis include epithelial shedding and thickening of the basement membrane, which are hallmarks of asthmatic bronchitis. Eosinophilic degranulation and release of mediators such as eosinophilic cationic protein have been demonstrated to occur in the nose and in the lower airway in patients with sinusitis and asthma.

Interleukin-17 is a cytokine with known effects in asthma. It is a proinflammatory cytokine released by Th17 cells, which is thought to be involved in neutrophilic infiltration of the bronchial tissue in patients with asthma. Saitoh et al. demonstrated that IL-17 is increased in nasal polyps compared to normal sinus tissue and correlated this with an increase in eosinophils and CD4+ T lymphocytes. They were also able to correlate the extent of basement membrane thickening with IL-17 levels [75]. These observations suggest a common role of IL-17 in both the upper and lower airways.

Fungi as a Model for Unifying Lower Airway and Upper Airway Disease

An interesting observation of the ability of fungi to generate an inflammatory airway disease, such as allergic bronchopulmonary aspergillosis in the lungs and allergic fungal sinusitis in the sinuses, further supports the concept of a unified upper and lower respiratory tract. Pakdaman et al. have reviewed the possible role of fungi as superantigens or as adjuncts that enhance the inflammatory response, suggesting that the similarities in the histomorphology of the upper and lower airways present a common target for fungi. In their reviews, they discuss how fungi may be the initial inflammatory insult that leads to chronic airway inflammation [76–78].

Nasal Polyps and Asthma

A Japanese study investigated the cytokine profile of 19 patients with chronic rhinosinusitis with nasal polyps compared to 9 patients without nasal polyps and 14 normal controls [79]. They found elevated levels of eosinophil cationic protein (ECP), *Staphylococcal* enterotoxin-IgE (SAE-IgE), IgE, and IL-5 only in the group with rhinosinusitis with nasal polyps. The polyp group demonstrated a skewing toward a Th2 cytokine profile with relatively lower TGF-β levels, while the group with

rhinosinusitis without nasal polyps demonstrated higher TGF-β levels suggesting a Th1 profile. A very interesting component of this small study was the fact that 31.6 % of the patients with rhinosinusitis with nasal polyps had asthma, while none in the group without polyps had asthma.

A paper comparing the histological and morphological differences between nasal polyps and asthma raised an interesting question concerning the unique infrequency of polyps in the lung compared to the upper airway mucosa and other organ systems with a mucosal surface such as the gastrointestinal and urinary tracts [80]. So what is it about lung mucosa that renders it less prone to the development of polyps? The authors suggest that this observation could be explained by comparing differing mucosal characteristics of the nose and the lung. One factor that stands out is TGF-β which plays an important role in the remodeling process. Epithelial injury results from increased TGF-β, which is upregulated in asthmatics and downregulated in nasal polyposis. On the other hand, the presence of TGF-β in the lung prevents the development of polyps. In the nose, the nasal reticular basement membrane becomes less thickened which is a feature of nasal polyposis. Incidentally, TGF-β also plays a protective role in the development of benign polyps in the large intestine as well, in that a mutation of SMAD4 disrupts TGF-β signaling pathways in juvenile polyposis syndrome.

The Nasobronchial and Nasopharyngeal Reflex

Nasobronchial and nasopharyngeal reflex mechanisms have been mentioned in support of a unified airway in health and disease. Bucca has reported that increased lower airway hyperresponsiveness occurs in patients with sinusitis. In some of these patients, the increased airway hyperresponsiveness also included extrathoracic airway hyperresponsiveness, as measured by MIF_{50}. The authors suggested that the mechanism by which this occurs is through activation of a nasopharyngeal-bronchial reflex. A study of 24 nonasthmatic patients with sinusitis investigated the relationship between pharyngeal mucosal changes and bronchial hyperresponsiveness. The authors used histamine PC_{20} as a threshold for bronchial responsiveness and $PC_{25}MIF_{50}$ as a threshold for extrathoracic airway hyperresponsiveness. In these patients, they found that the epithelial thinning, representing pharyngeal mucosa damage, correlated with extrathoracic airway hyperresponsiveness. Bronchial hyperresponsiveness was also associated with long-standing sinusitis, increased submucosal nerve density, increased eosinophils in the nasal lavage fluid, and a lower $PC_{25}MIF_{50}$. The authors interpreted these results as an indication that pharyngeal damage contributes to airway dysfunction through the stimulation of mucosal nerve endings to activate constrictive reflexes leading to increased extrathoracic airway hyperresponsiveness. They also postulated that it is pharyngeal damage and the failure of normal physiologic filtering functions that grant access of irritants and allergens to submucosal nerve endings [81].

Gravitational Factors and Postnasal Drainage

Whether or not nasal secretions can stimulate lower airway inflammatory response by direct contact is a matter of great debate [82]. Intuitively, it seems to make sense that postnasal drip, facilitated by gravity, will end up in the lower airway. If the mucous contains allergic or inflammatory mediators, then an inflammatory response in the lower airways is expected. However, in two separate studies, nasal application of radioactive-labeled allergen only showed deposition in the digestive tract and not in the lower respiratory tract [3, 4]. In contrast, there have been studies to support the concept that a cough can be associated with postnasal drip [83–85], suggesting an alternative mechanism for the effect of upper airway secretions on lower airway inflammation. It is possible that aspiration of stomach contents may be responsible for a cough in these patients or that the stimulation of pharyngolaryngeal receptors by inflammatory mediators emanating may be the key mechanism for postnasal drip-related cough [86].

A summary of the potential pathogenic mechanisms behind the link between the upper and lower airways is illustrated in Fig. 11.2.

Other Clinical Associations

Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease (AERD), also known previously as Samter's triad, describes a perennial condition comprised of three components, namely, aspirin sensitivity, asthma, and chronic rhinosinusitis with nasal polyposis. The rhinitis/nasal polyposis symptoms include rhinorrhea, nasal congestion, sneezing, and anosmia. Both asthma and the chronic rhinosinusitis in AERD are characterized by eosinophilic infiltrates in the mucosa of the corresponding tissues.

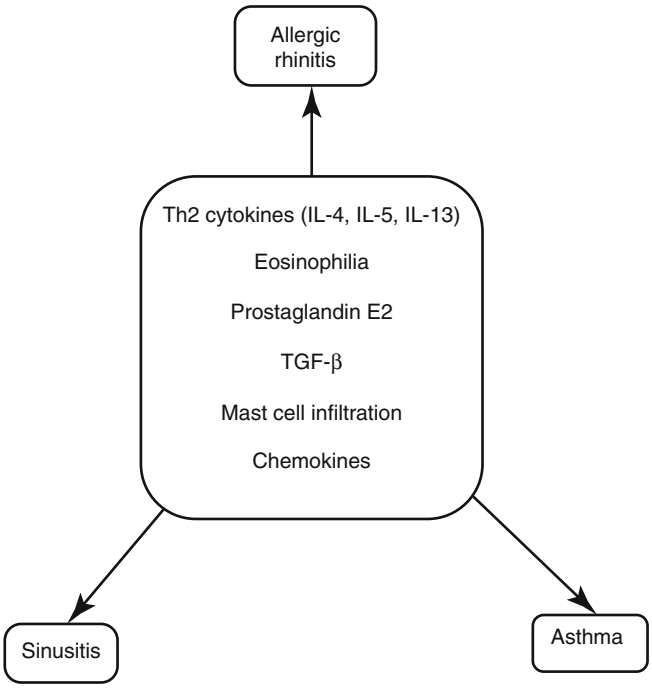

Fig. 11.2 Links between the upper and lower airways: mechanisms of the one airway, one disease hypothesis

Aspirin-induced asthma is a surprisingly common phenomenon [87]. Data has suggested that the prevalence of aspirin-induced asthma is much higher in adults than in children (21 % vs. 5 %). Asthma is usually diagnosed 2–3 years after the onset of upper airway symptoms and is commonly difficult to treat. Nasal polyps are recurrent and frequently require multiple surgeries. The aspirin sensitivity usually occurs in these patients who were previously able to tolerate aspirin. Aspirin is a nonsteroidal anti-inflammatory drug (NSAID), and its mode of action is through inhibition of cyclooxygenase 1. The result of this inhibition is an increase in the substrate arachidonic acid, leading to increased activity of the lipoxygenase pathway and the release of leukotrienes into the circulation and surrounding tissue. Leukotrienes are potent mediators of inflammation. The details of aspirin-exacerbated respiratory disease are discussed in other chapters of this book. This discussion will focus only on why this mechanism predisposes patients to disease of both the upper and lower airways, in the context of a unified airway disease.

In the respiratory tract, mast cells and other secretory cells of the respiratory tract can release leukotrienes upon stimulation. LTC4 synthase is the key enzyme catalyzing the synthesis of leukotriene C4, which binds to the leukotriene receptor, CysLTR1, to trigger inflammatory mediator release. It has been found that CysLTR1 is upregulated in patients with AERD, and CysLTR1-positive cells are reduced after intranasal desensitization with aspirin. The high cysteinyl leukotriene level is accompanied by a low production of prostaglandin E2 [88]. Cyclooxygenase-2 is downregulated in the nasal polyps of aspirin-sensitive patients. Eosinophils from nasal polyps in AERD patients show increased expression of LTC4 synthase [89].

In the airway, excessive production of cysteinyl leukotrienes leads to induction of airway smooth muscle contraction, increased vascular permeability, and airway remodeling. Abnormalities in the arachidonic acid pathway are the mechanism for induction of these effects, as occurs in nasal polyp tissue. Levels of prostaglandin E2 receptor expression are reduced in airway leukocytes in asthmatic patients with aspirin sensitivity [90]. Eosinophils from the bronchial biopsies in patients with asthma also demonstrated increased LTC4 synthase [91]. Together, these observations of common pathologic features in both the mucosa of nasal polyps and asthma support a common susceptibility in distant parts of the airway.

An Autoinflammatory Link Between Sinuses and Lung

Several autoimmune diseases involve the upper and lower airways, specifically the sinuses and the lungs. These include Wegener's granulomatosis and Churg-Strauss syndrome. The types of autoimmune diseases that affect the lung are thought to be related to small-vessel vasculitides. Whether involvement of the lung and sinuses in these conditions is strictly a function of vascular pathology or other mechanisms that would impact both parts of the airway is not known.

Sinuses and the GI Tract

Gastroesophageal reflux has been shown to be a comorbid condition of asthma. As early as the 1,800 s, William Osler had identified a link between the gastrointestinal and respiratory systems, noting that overeating can induce coughing paroxysms in asthmatics [92]. In general, the majority of asthmatic subjects will describe having symptoms of reflux. Similarly, many patients with asthma will complain of respiratory symptoms related to reflux. Even to this day, it is not yet clear if asthma causes reflux or vice versa. A study on upper airway obstruction and gastroesophageal reflux performed in dogs suggested that it is the upper airway obstruction that causes gastroesophageal reflux by generation of a negative inspiratory pressure. Temporally, they showed that it was induction of the airway obstruction that led to gastroesophageal reflux about 1 week after creation of the obstruction [93]. Why abnormal pressures on the esophagus in airway obstruction can predispose patients to reflux can be explained by Bernoulli's principle [94]. Bernoulli's principle states that there is an inverse relationship between the velocity of a fluid through a tube and the pressure exerted perpendicularly by that fluid. On the other hand, it has been suggested that gastroesophageal reflux can trigger asthma through aspiration-induced inflammation resulting in hyperresponsiveness of the airway. In support of this concept, a review of the literature suggests that treatment of symptomatic gastroesophageal reflux improves asthma symptoms [95]. However, this has not been valid in the case of silent or asymptomatic gastroesophageal reflux. The effects of reflux on asthma thus remain unclear. It is probable that putting these two events together produces a vicious cycle, where one disease exacerbates the other. Treatment of either disease will break the cycle and improve symptoms.

A critical review of the literature focused on analyzing three concepts as supporting evidence for a role of GER in sinusitis. Firstly, the authors noted that a higher prevalence of gastroesophageal reflux exists in patients with hard-to-treat sinusitis. Secondly, they reviewed the pathogenic mechanisms for GER and sinusitis and were able to formulate a plausible explanation for a relationship. Part of this evidence included the observation that gastric acid contents can be found in the middle ear of patients with otitis media with effusion [96]. Additionally, Wong et al. showed that a hyperactive reflux can induce autonomic nervous system and lead to sinonasal edema, a compromise in normal drainage, and chronic rhinosinusitis [98]. This was previously described by Pinto et al. [97]. Thirdly, patients who had successful treatment of gastroesophageal reflux experienced a higher degree of resolution of sinus symptoms and global well-being [98, 99]. The authors present an algorithm that involves using acid-lowering drugs like proton pump inhibitors in the treatment of sinusitis [100].

The independent relationships between gastroesophageal reflux and asthma and sinusitis suggest a common susceptibility throughout the entire respiratory tract to contents of the stomach. While the exact mechanism for these effects is unknown, the correlation seems to support a one airway, one disease model.

Upper Airway Disease and Laryngitis

An interesting extension of the one airway, one disease concept is related to the link between rhinitis and laryngitis. A study of 134 allergic rhinitis patients, 54 nonallergic rhinitis patients, and 62 normal controls demonstrated that those patients with either allergic or nonallergic rhinitis had a markedly significant higher rate of dysphonia than patients without rhinitis (32.8, 26.9, and 8.1 %, respectively). The presence of asthma and the use of inhaled corticosteroids were confounding variables that were controlled for in the study. Curiously, however, the use of intranasal corticosteroids, while presumed to be either an exclusion criteria or a variable that would be controlled for, was not specifically mentioned in the paper [101]. Earlier reports have also noted that allergic rhinitis patients who may benefit from immunotherapy were at least three times more likely to have dysphonia than normal controls [102]. Other investigators have also proposed a link between vocal cord problems and allergic rhinitis symptoms that may or may not be simply attributed to postnasal drainage [103, 104]. The relationship between sinusitis and voice abnormalities has also been proposed, and parameters necessary to evaluate vocal characteristics in sinusitis patients were established, although no differences in these parameters were detected in this pilot study of 10 chronic sinusitis and 9 control subjects. The authors proposed that at least 126 patients would be needed to conduct a study that would demonstrate reliable and statistically valid results [105].

Table 11.4 Comparison of the classification systems and treatment of allergic rhinitis and asthma

	Allergic rhinitis		Asthma	
	Controller med	Rescue med	Controller med	Rescue med
Mild intermittent	None	Antihistamines	None	β-agonist
Mild persistent	Intranasal steroid	Antihistamine	Inhaled steroid	β-agonist
Moderate persistent	Intranasal steroid, leukotriene receptor antagonist	Antihistamine	Inhaled steroid, leukotriene receptor antagonist	β-agonist
Severe persistent	Intranasal steroid, leukotriene receptor antagonist, immunotherapy	Antihistamine	Inhaled steroid, leukotriene receptor antagonist	β-agonist, oral or parenteral steroids

How Treatment of One Disease Affects the Other

The Effect of Treatment of Sinusitis on Asthma

Pharmacotherapy of Allergic Rhinitis, Sinusitis, and Asthma

The treatment of allergic rhinitis with medications led to interesting observations regarding the effectiveness of these drugs to also treat asthma [106, 107]. Effective treatment of allergic rhinitis has been associated with a reduced frequency of emergency department visits for asthma and a reduced risk for hospitalization for asthma [108]. Antihistamines used to treat allergic rhinitis may have some benefit in asthma. Glucocorticoids, of course, will treat both areas of the respiratory tract, when applied "topically" to that region. Perhaps more interesting is the effect of immunotherapy on asthma. Because it is believed that immunotherapy works on a systemic basis to modulate the immune system, then one might infer that immunotherapy used to treat allergic rhinitis should help with allergic asthma as well. In fact, numerous studies have supported the role of immunotherapy in asthma [109]. An illustration of the parallel strategies in treatment of allergic rhinitis and asthma is shown in Table 11.4.

Numerous studies in the pediatric population have suggested that treatment of sinusitis in patients with concurrent asthma leads to a more rapid resolution of their exacerbation [110].

A discussion of the role of leukotriene pathway medications is important because of the existence of disease complex known as Samter's triad, which consists of nasal polyposis, aspirin sensitivity, and severe asthma and is now referred to as aspirin-exacerbated respiratory disease (AERD). The role of aspirin in sinusitis is discussed in the chapter on aspirin-induced sinus disease. Leukotriene receptor antagonists such as montelukast have been found to have efficacy in the treatment of both allergic rhinitis and asthma [111, 112]. Leukotriene receptor antagonists have also been found to play a role in the treatment of chronic sinusitis. These conclusions have mostly been established through the study of leukotriene receptor antagonists in the treatment of AERD whereby both asthma (the intended indication) and chronic sinusitis (unintended consequence) have shown improvement [113].

In chronic sinusitis, the eosinophil and the mast cell have been the most commonly implicated cell types. Inhibiting the proinflammatory activity of eosinophils has been shown to reduce IL-4 and IL-5 levels. Anti-IL5 has been found to be effective in the treatment of nasal polyps [114]. Anti-IL4 has been proposed as a therapy for asthma, by virtue of its potential effect on decreasing IL-4 levels. IL-4 has been shown to be able to increase CysLT1 and CysLT2 receptor levels in eosinophils and lymphocytes. Thus, targeting of cytokine pathways may be a means to reduce the effects of leukotrienes. A pilot study of mepolizumab for treatment sinusitis in Churg-Strauss syndrome led to improvement in all seven patients after 4 months of treatment [115]. Withdrawal of the drug led to a reversal of the beneficial effects of mepolizumab.

In addition to targeting cytokines generated by eosinophils and mast cells, imatinib, a tyrosine kinase inhibitor, has also been found to directly inhibit activation and function of these cell lines. A study of eight patients with chronic hypereosinophilic sinusitis showed that imatinib could lead to decreased eosinophils in the blood in most subjects and symptom improvement in about half of the subjects [116].

Immunotherapy in Allergic Rhinitis and Asthma

One of the risk factors for adverse reactions to immunotherapy is asthma. However, immunotherapy has also been associated with improvements in asthma. In fact, this observation may further support the existence of a one airway, one disease paradigm, since the benefit of this mode of therapy extends to both upper and lower airways [72].

Anti-IgE Therapy in Allergic Rhinitis and Asthma

Omalizumab is a recombinant humanized monoclonal antibody (primarily IgG1 class) directed against IgE [117]. Omalizumab was first developed for the treatment of moderate to severe persistent asthma. However, it has also been studied for the treatment of upper airway allergic rhinitis as well. A randomized controlled trial studying the effect of omalizumab on allergic rhinitis symptoms was conducted on 536 patients between the ages of 12 and 75 years [118]. Outcome measures included self-assessment of daily nasal symptom scores, antihistamine use, and quality-of-life assessments. Free IgE levels were also measured. The results indicated that omalizumab was an effective mode of therapy with improvements in all three outcome measures. No increase in adverse side effects was noted in the treatment group compared with the placebo group. Similar results were found in studies on the use of omalizumab in birch pollen- [119] and cedar pollen-induced seasonal allergic rhinitis [120]. In the lower airway, Holgate et al. showed that omalizumab has similar beneficial effects in asthma, and patients were more likely to be able to reduce their inhaled corticosteroid usage with an accompanying reduction in asthma-related hospitalizations and emergency room visits [121]. Quality-of-life improvements were also detected in the INNOVATE study, one of the earlier studies on the effectiveness of omalizumab in allergic asthma [122]. The beneficial effects seen that are common throughout the respiratory tract, in both the upper and lower airways, suggest a common mechanism that can be targeted by a single agent.

Parallel Management of Allergic Rhinitis and Asthma

Classification of asthma into various categories based on risk and control has been an ongoing project since the early 1990s. There have been several iterations of these guidelines with the most recent version focusing on impairment and risk. Controller medications and rescue medications have been relatively clearly delineated, and treatment and management algorithms have been introduced to assist physicians and other caregivers. More recently, a similar set of classification and guidelines have also been introduced for the treatment of allergic rhinitis as well [21, 123]. The most recent version of these guidelines was introduced in 2008 and was put forth by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group and the Allergic Rhinitis and Its Impact on Asthma (ARIA) guideline panel, by review of systemic reviews and best available evidence [124].

The approaches to classifying allergic rhinitis and asthma have been remarkably similar, and probably by design, to reflect the similarities between the two diseases. Both are first categorized into intermittent and persistent, then the persistent form is divided into mild, moderate, and severe groups. The first-line treatment is with topical (either inhaled or intranasal) corticosteroids, reflecting the need to provide anti-inflammatory control that is based on pathologic observations already discussed above. Other maintenance medications include the leukotriene receptor antagonists, montelukast, zafirlukast, and pranlukast, which, as a class effect, may be variably effective in treating symptoms of both the lower and upper respiratory tract. Antihistamines are useful in allergic rhinitis, and their role in allergic asthma is not quite so clear. But the overall parallels in the current recommendations for treatment of upper and lower airway allergic disease are nearly identical, as illustrated in Table 11.3, given more prudence to the one airway, one disease theory.

The Effect of Surgical Treatment of Sinus Disease on Asthma

A prospective study of 68 asthma patients who also had nasal polyposis was conducted to investigate whether or not surgical treatment of the nasal disease led to improvement in asthma [125]. The study lasted 21 weeks, and various asthma-related parameters were evaluated as therapeutic endpoints. Upper airway parameters include both subjective measures such as nasal congestion and rhinorrhea and objective measures such as peak nasal inspiratory flow. Lower airway parameters included symptoms of asthma such as cough and dyspnea along with objective tests including peak expiratory flow rate measurements

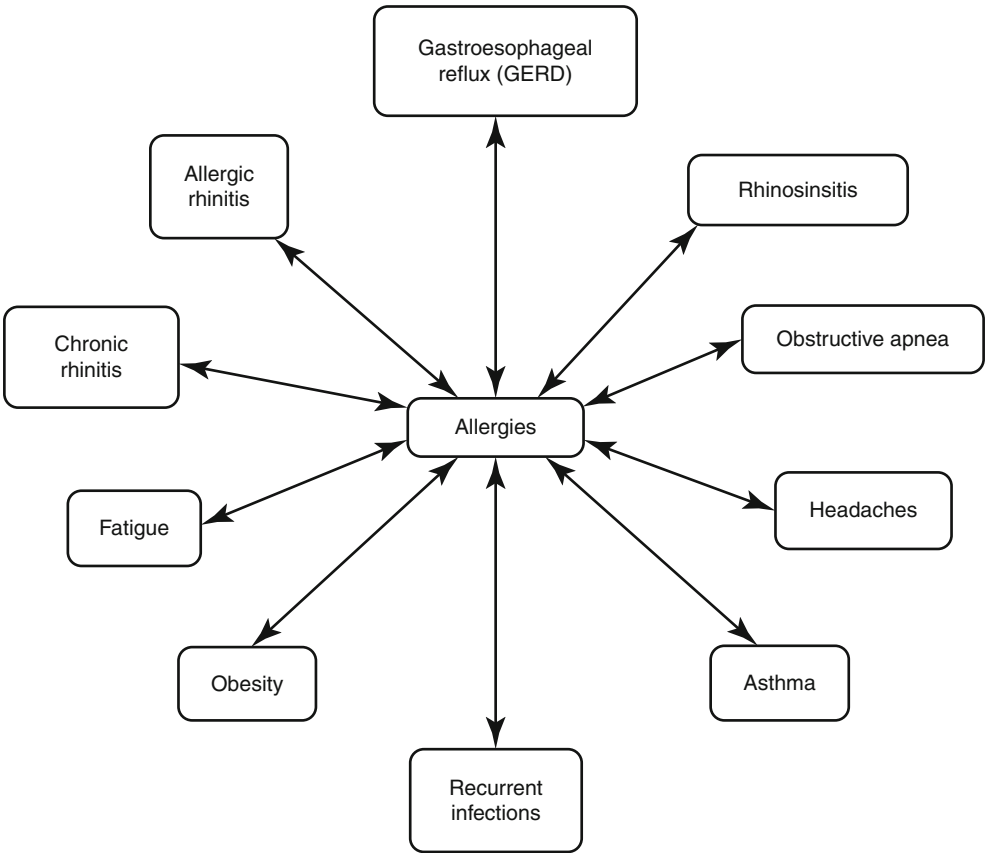

Fig. 11.3 Comorbid conditions associated with asthma

and lung function tests. The study included adult patients and also evaluated the use of fluticasone propionate nasal spray prior to surgery in a double-blind randomized controlled format. The results of the study indicated that functional endoscopic sinus surgery led to a significant improvement in both upper and lower airway symptoms, as well as improvements in objective measurements in both parts of the airway. The inclusion of a double-blind randomized controlled trial of presurgical fluticasone confounds the data somewhat and does not answer the question the investigators had regarding the effectiveness of presurgical use of nasal steroids to improve surgical outcome.

A more recent study evaluated whether or not improvements in asthma were sustained after functional endoscopic sinus surgery. Fifty-one adult patients with both nasal polyposis and asthma underwent functional endoscopic surgery. The improvements in subjective and objective lower and upper airway parameters that occurred immediately after surgery were maintained 1 year post surgery [126]. Another study provided long-term data (average 6.5 years) on 30 patients with asthma who underwent functional endoscopic sinus surgery. Subjective and objective parameters of asthma severity were recorded, including utilization of hospital visits, medication use, and clinical symptoms. A sustained improvement was noted in all parameters [127].

A corollary of these noted benefits of sinus surgery in improving asthma was demonstrated in a study of 510 patients with chronic rhinosinusitis, of whom 68 underwent revision endoscopic sinus surgery. This study showed that biofilm-forming bacteria and asthma were independently associated with a risk for refractory chronic rhinosinusitis requiring revision endoscopic surgery. This would suggest that treatment of asthma may be an important factor in determining the efficacy of surgical treatment of sinus disease, illustrating the bidirectional nature of the association between asthma and sinus disease.

Difficult-to-treat asthma may result from a failure to recognize and treat comorbid conditions associated with asthma. These may include allergic rhinitis, perennial rhinitis, nonallergic rhinitis with eosinophilia, viral bronchitis, pneumonia, atelectasis, chronic postnasal drip, gastroesophageal reflux, obstructive sleep apnea, and rhinosinusitis. These relationships are illustrated in Fig. 11.3. An algorithm depicting an approach to the treatment of difficult asthma is shown in Fig. 11.4.

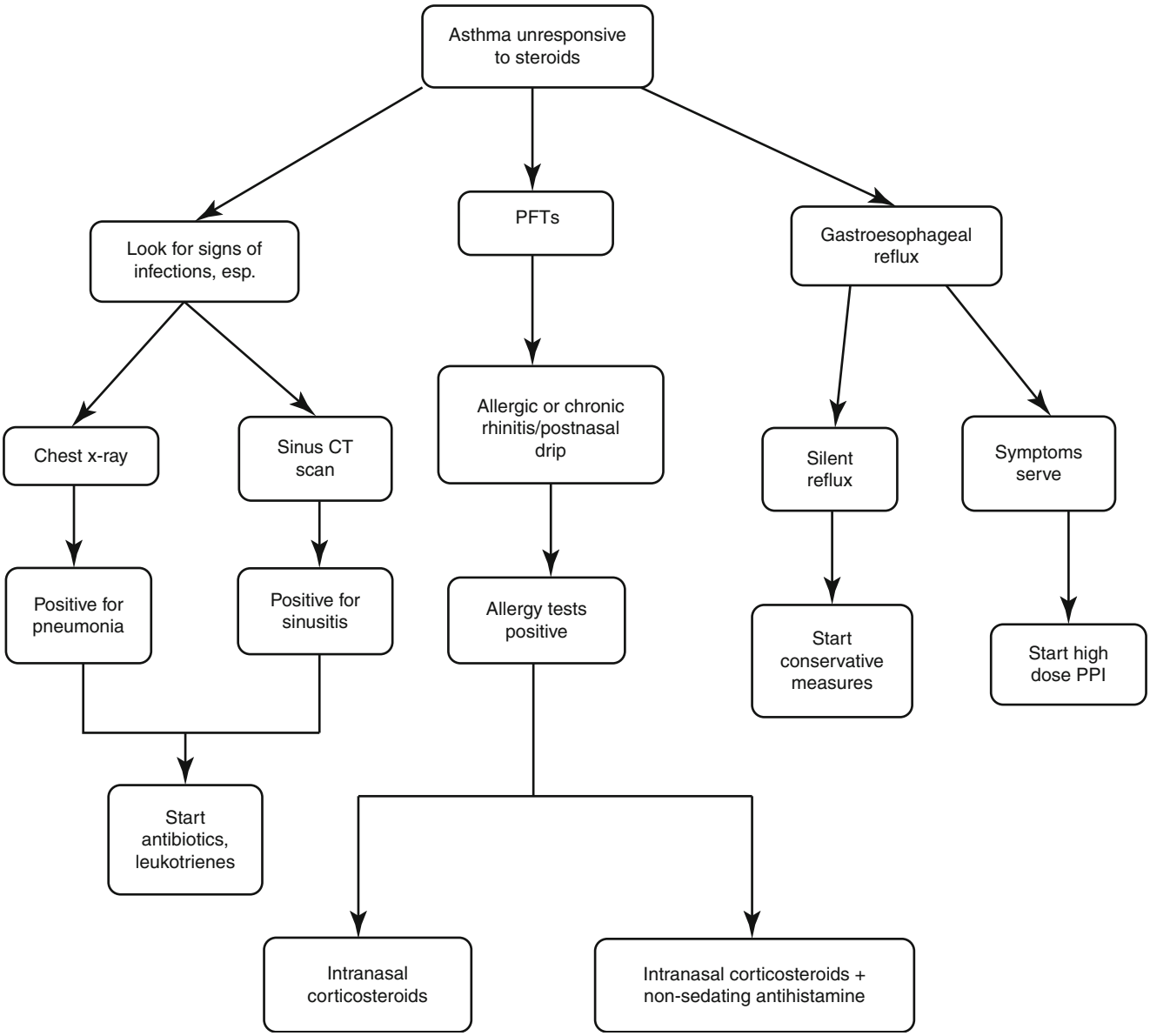

Fig. 11.4 Difficult-to-treat asthma: an algorithm

Conclusions

From ancient times, physicians have appreciated the connection between the upper airway and lower airway. Throughout history, the link has been consolidated, and our understanding of the pathogenic mechanisms behind this link has been cultivated, and now it is no longer simply an intuitive or presumed relationship. Several mechanisms are in play, and these involve neural, vascular, immunologic, and physical pathways. It is now known that there are anatomical and histomorphological similarities between the upper and lower airways that would lead one to believe that effects on one part of the airway should be duplicated in other parts. However, there are also differences between the upper and lower airways. The relationship between the upper and lower airways may in fact be mediated by a multitude of factors. Nasobronchial reflexes may trigger vascular changes between the two parts of the airway. Allergen challenge to one part of the airway may trigger local changes that can lead to similar changes in other parts of the airway but may also mediate inflammatory effects by a systemic inflammatory response, leading to infiltration of inflammatory cells and generation of inflammatory cytokines in distant sites. It has been shown that this may involve the action of Th2 cytokines such as IL-4, IL-5, and IL-13, and that Th1 cytokines

such as TGF-β may actually provide a protective effect. There are similar cytological changes in nasal polyp tissue and lower airway tissue, but polyps themselves are not often seen in the lower airway. Further research on the pathologic mechanisms of upper and lower airway inflammation will bring about a better understanding of the similarities and differences of inflammation in these two areas of a contiguous organ and hopefully lead to better and safer therapeutic modalities.

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