

Asthma and Rhinitis: Comorbidities

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The connection between asthma and rhinitis is not a new discovery. Significant progress has been made in understanding this relationship, however, and the implications of the asthma–rhinitis link make it increasingly important. For example, patients who have asthma and rhinitis tend to have more severe disease with higher treatment costs [1,2]. Treatment of rhinitis may improve asthma control [3–6], and early treatment of allergies may prevent the development of asthma [4–6]. The new clinical practice guidelines for asthma, entitled *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*, developed by the National Asthma Education and Prevention Program of the National Heart, Lung, and Blood Institute and released in August 2007 state:

“The Expert Panel recommends that clinicians evaluate patients who have asthma regarding the presence of rhinitis/sinusitis diagnosis or symptoms..... it is important for clinicians to appreciate the connection between upper and lower airway conditions and the part the connection plays in asthma management” [7].

The corollary also holds true; that is, clinicians treating rhinitis or sinusitis should consider that patients may have undiagnosed asthma, or asthma that can be controlled better by aggressively treating upper airway disease. A recent study from Denmark found that 50% of asthmatics were undiagnosed, and 76% were undertreated according to guideline recommendations [8]. Otolaryngologists who treat rhinosinusitis patients will encounter individuals whose asthma is undiagnosed or undertreated. Increased recognition of the link between upper and lower airway inflammation has led to various new terms for respiratory inflammatory disease, including “the united airway,” the “chronic allergic respiratory syndrome,” [9] and “allergic inflammatory airway syndrome” [10]. This article more fully explores the

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epidemiological, pathophysiological, and clinical evidence that supports the linkage between asthma and rhinitis.

Epidemiologic links

Various epidemiologic studies have shown allergic rhinitis to be a common disorder in the United States. Prevalence rates of allergic rhinitis range from 15% to 40% [11]. The variability in the many epidemiologic studies available may be because of sampling issues and differences in case definition. But regardless, allergic rhinitis is a common disorder that is encountered frequently by the practicing otolaryngologist. Similarly, asthma is a prevalent disorder that affects approximately 7% of the United States population [11]. Asthma and allergic rhinitis, however, occur together at rates that greatly exceed what would be expected from the baseline prevalence of each disorder alone (Fig. 1). Between 19% and 38% of patients who have allergic rhinitis also have asthma [11]. In patients who have asthma, rhinitis is extremely common; the vast majority of patients who have asthma have rhinitis. Multiple studies have shown rhinitis to be present in 50% to 85% of asthmatic subjects, with the differences between studies likely caused by differences in methodology. Relying on patient self-reporting of symptoms may be insensitive considering that many patients with asthma may be more bothered by their asthma than any rhinitis symptoms [9]. In a chart review-based study of 1245 asthmatic subjects in Olmstead County, Minnesota, 52% of asthmatic subjects were found to have allergic rhinitis, and 6% had nonallergic rhinitis [1]. In the Copenhagen Allergy Study, which relied on direct questioning and examination of study subjects, 100% of subjects who had allergic asthma induced by pollen had allergic rhinitis from pollen. Eighty-nine percent of subjects who had allergic asthma caused by animals had allergic rhinitis from animals, and 95% of subjects who had allergic asthma caused by mites had allergic rhinitis from mites [12]. The fact that the vast majority of asthma patients suffer from rhinitis has therapeutic implications that will be discussed later.

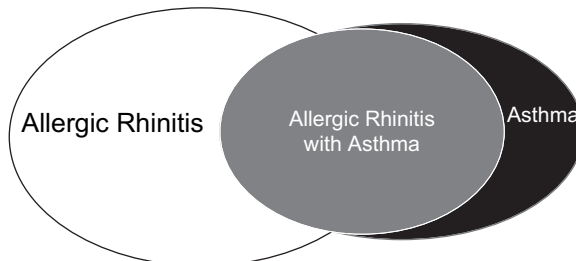


Fig. 1. Venn diagram showing the relative populations with asthma, allergic rhinitis, or a combination of the two.

Allergic rhinitis is a risk factor for the development of asthma; it is much more than just an associated condition. This assertion has been corroborated by multiple studies [13–16]. In the Finnish Twin Cohort Study [17], over 11,000 subjects were administered questionnaires in 1975, 1981, and 1990. The study found that men who reported hay fever in 1975 had a four-fold increased risk of reporting asthma in 1990. In women, the effect was even more pronounced, with a sixfold increased risk of developing asthma after reporting hay fever in the earlier survey. Looking at this longitudinal data, the authors also noted that rhinitis nearly always was diagnosed before asthma. This trend, where allergic rhinitis precedes the development of asthma, has been noted by other authors [13,16], and sometimes has been referred to as the allergic march. But the natural history of rhinitis and asthma are quite variable between individuals, and asthma sometimes becomes manifest before rhinitis. It is now accepted, however, that rhinitis is an independent risk factor for the development of asthma [9,16,18].

There are multiple variables that influence the linkage between asthma and rhinitis. The association of rhinitis and asthma depends upon the atopic status of the patient, the age of onset of atopy, and the severity of symptoms. Subjects who develop atopy at an earlier age appear more likely to develop asthma. It should be noted that atopy is not required for this relationship [19]. In a nested case-control study of data acquired as part of the Tucson Epidemiologic Study of Obstructive Lung Diseases, Guerra and colleagues [16] showed that both allergic and nonallergic rhinitis increased the risk of developing asthma threefold, and only in allergic rhinitis subjects with the highest IgE levels did atopy strengthen this risk of developing asthma. The association of rhinitis and asthma is independent of allergy, but in allergic patients it is dependent to some extent on the severity and persistence of rhinitis symptoms. The pathophysiological explanation for these observations remains a matter of investigation.

Perennial, nonallergic rhinitis also has been established as an independent risk factor for asthma. Data from young adults participating in the European Community Respiratory Health Survey showed that nonallergic rhinitis was associated strongly with asthma. In this large, multicenter study, 1412 young adults who had perennial rhinitis symptoms were compared with 5198 control subjects by means of a questionnaire, total and specific IgE testing, and spirometric testing with methacholine bronchoprovocation [19]. The odds ratio for current asthma among nonatopic perennial rhinitis subjects was 11.6 (95% CI, 6.2 to 21.9) after multiple logistic regression analysis. Additionally, in this study, nonallergic individuals who had rhinitis but no asthma were found to have increased bronchial hyper-responsiveness to methacholine challenge. (The phenomenon of bronchial hyper-responsiveness in non-asthmatic rhinitics will be discussed later in the article.) So the connection between rhinitis and asthma is not merely a result of atopy.

The presence of rhinitis appears to be associated with more severe asthma. In a study of hospital admissions in 2961 children from Norway,

even when correcting for severity of asthma, children who had allergic rhinitis had a higher risk of hospital readmission and more hospital days per year when compared with asthmatic patients without rhinitis [2]. Similar findings have been noted from the United Kingdom. Using a general practice database, Thomas and colleagues [20] found that asthmatic children who had a recorded diagnosis of allergic rhinitis had more general practitioner visits and were more likely to be hospitalized during the 12-month follow-up period of the study compared with children who had asthma alone. In addition to increased severity of disease, increased costs are seen when asthma and rhinitis are concomitant disorders. In the study of 1245 asthmatic subjects in Olmstead County, Minnesota, yearly medical care charges were 46% higher in those patients who had concomitant asthma and rhinitis [1]. Halpern and colleagues [21] studied a medical claims database, and found when analyzing all patients who had a claim of asthma ($n = 27,398$), that the presence of allergic rhinitis was associated with more asthma medication prescriptions and higher asthma prescription costs. These studies suggest that clinically diagnosed allergic rhinitis may be more common in individuals who have severe asthma, or that individuals who manifest both rhinitis and asthma symptoms have a more severe disease complex than those who have only upper or lower airway symptoms.

Although the epidemiologic linkage between asthma and rhinitis is now clear, the exact reason for this connection remains under investigation. Rhinitis, which leads to nasal obstruction, may cause inspiration of unfiltered and unconditioned air that theoretically could exacerbate any underlying lung disease. Although experimental data are lacking to support this assertion, there does appear to be some connection between nasal obstruction and asthma symptoms. In fact, improving nasal breathing in asthmatics with a simple nostril dilating device has been shown to reduce nocturnal asthma symptoms [22]. There is also a putative nasobronchial reflex wherein nasal irritation provokes bronchoconstriction. In a study of normal individuals, Fontanari and colleagues [23] showed that nasal, but not oral inhalation of cold dry air increased airway resistance, and this increased resistance could be blocked by nasal anesthesia, nasal anticholinergic treatment, or bronchial anticholinergic treatment. In animal experiments, mechanical or chemical stimulation of the nose may induce bronchoconstriction, and this same phenomenon has been demonstrated in nonasthmatic people [24]. Milqvist performed warm and cold nasal air challenges in cold-sensitive asthmatic patients and normal control subjects. He found that nasal insufflation of cold air (confined to the nose) caused a decrease in specific airway conductance and forced expiratory volume in 1 second (FEV_1) in the asthmatic patients, but not in normal controls, suggesting an interplay between the nose and the remainder of the airways that is present in cold-sensitive asthmatics, and may represent a trigeminal reflex. Interestingly, warm air insufflation had an opposite effect, increasing the specific airway conductance and FEV_1 [24]. So potentially there are reflex-like linkages

that explain how nasal disease may trigger changes in the pulmonary airways.

Aspiration of infected or inflammatory sinonasal secretions has been invoked to explain the connection between rhinosinusitis and asthma. This mechanistic explanation never has found convincing evidence for its role, and seems highly unlikely in neurologically intact patients. Additionally, studies have been conducted that argue against this phenomenon. In one study, patients taken to the operating room for sinus surgery had radionuclide tracers placed within their maxillary sinuses. They then were followed with scintigraphy for any evidence of pulmonary aspiration of secretions. Two of four patients who had depressed consciousness had evidence of aspiration. None of the neurologically intact individuals who had a history of sinusitis and asthma, or sinusitis alone had any radiotracer localize to the thoracic cavity [25]. Although there is obvious anatomic contiguity between the nose and lower airways, it seems unlikely that direct transfer of inflamed or infected secretions from the upper to lower airways plays a significant role in the connection between asthma and rhinitis.

A potentially very important connection that exists between the lung and nose is the bloodstream. Systemic propagation of nasal or bronchial inflammation, by means of the bloodstream, may be the most important connection that exists between the upper and lower airways. This connection has been investigated in experimental clinical studies, and the findings of these studies are discussed later in this article.

The inflammation in rhinitis and asthma are similar

The pathologic similarity of rhinitis and asthma begins with similar tissues. The nasal and bronchial mucosa are histologically similar. Both nasal and bronchial mucosa have ciliated pseudostratified columnar epithelium. Underlying a basement membrane within the submucosa are mucus glands, vessels, inflammatory cells, and nerves. The nasal submucosa contains numerous capacitance vessels: arteries, venous sinusoids, and capillaries. Changes in this vasculature can lead to nasal obstruction. The bronchial airways, in contrast, do not have such an extensive blood supply or capacitance vessels, but do contain smooth muscle that strongly influences the luminal area of the lower airways [26].

The inflammation in rhinitis is similar to that seen in the bronchial mucosa of subjects who have asthma. The inflammatory cell infiltrate of mononuclear cells, lymphocytes, and eosinophils in both diseases demonstrates marked pathologic similarity in both the bronchial and nasal mucosa [26]. Additionally, the cytokines, adhesion molecules, and other inflammatory mediators are the same in both diseases [26–29]. These include a preponderance of the so-called TH2 cytokines, interleukin (IL)-5, regulated upon activation, normal T-cell expressed, and secreted (RANTES), eotaxin, and the cysteinyl leukotrienes. There are differences of course. For example,

the nasal obstruction from rhinitis is largely caused by engorged capacitance vessels in the nose and mucosal edema, while in asthma, epithelial disruption, basement thickening, and smooth muscle hypertrophy are pathologic developments [26]. The similarity of histologic features, inflammatory cell infiltrates, and soluble inflammatory mediators suggests that the basic underlying pathogenic factors in asthma and rhinitis are the same. The same triggers, whether viral, irritant, or allergen can trigger both rhinitis and asthma. These common features suggest that asthma and rhinitis are intimately linked disorders, and it is becoming increasingly obvious that practitioners are dealing with one airway disease that has various end-organ manifestations.

Patients who have asthma or rhinitis have eosinophilic inflammation in the other uninvolved site

Interestingly, patients who have asthma but no nasal symptoms have eosinophilic inflammation in the nose [30]. So not only is the pathology of rhinitis and asthma similar, but the inflammation present in the lungs also can be identified in the nose, even in those without clinical rhinitis. A similar phenomenon, of bronchial inflammation in the nonasthmatic rhinitis patient also has been observed. Djukanovic and colleagues [31] performed bronchial biopsies on atopic asthmatics, atopic nonasthmatics, and normal subjects. They found that atopic nonasthmatics had basement membrane thickening and eosinophilic inflammation with degranulation—features of asthma. When comparing the subject groups, they found a continuum of severity, with atopic nonasthmatics having milder inflammation and basement membrane thickening compared with atopic asthmatics. Another study analyzed bronchoscopic biopsies of seasonal allergic rhinitis patients without asthma. Subjects were biopsied in and out of pollen season. The study found that natural pollen exposure leads to increased IL-5 expression, increased lymphocyte numbers, and eosinophil recruitment to the bronchial mucosa in nonasthmatic subjects who have allergic rhinitis. Additionally these subjects showed heightened sensitivity to methacholine challenge when tested during the pollen season [32]. These results suggest that atopy in general is associated with pulmonary inflammation and that the clinical picture is determined by the severity of inflammation at different airway sites.

Allergic rhinitis patients prone to bronchial hyper-reactivity

Patients who have allergic rhinitis, but without a clinical diagnosis of asthma, may be predisposed to developing bronchospasm or have evidence of hyper-reactivity to bronchoconstricting agents on challenge testing [33]. This phenomenon was demonstrated over 30 years ago and has been corroborated by multiple studies. Madonini and colleagues [34] found that patients with allergic rhinitis had greater sensitivity to methacholine bronchial

provocation when tested during their allergy season, with 48% of subjects showing reactivity in the asthmatic range. These results are similar to those described by Chakir and colleagues [32]. In the European Community Respiratory Health Survey, self-reported nasal allergies were an independent predictor of bronchial hyper-reactivity (odds ratio [OR] 1.9 to 6.1). Similarly, even absent any rhinitis complaints, positive allergy skin tests were an independent predictor of bronchial hyper-reactivity (OR 2.2 to 6.7) [35].

Different allergen sensitivities may determine the degree of lower airway hyper-reactivity. In a study comparing patients who had allergic rhinitis with pollen or dust mite allergy but no clinical diagnosis of asthma, the patients who had dust mite allergy had lower methacholine threshold values on bronchial provocation testing, indicating a greater degree of bronchial hyper-reactivity [36]. The finding that patients who have rhinitis without an asthma diagnosis or asthma symptoms have bronchial reactivity lends further support to the notion that asthma and rhinitis are different manifestations of a single respiratory system disease.

The nasal and pulmonary compartments immunopathologically linked by means of the bloodstream

The bone marrow and bloodstream serve as source and conduit for inflammatory-type progenitor cells that are involved in allergic inflammation. It now is recognized that certain inflammatory cells are able to home to sites of mucosal inflammation and that these peripheral end-organ sites have the capability to induce differentiation and expansion of progenitor cell lineages. Inflammation at peripheral sites may spill over into the circulation and influence the bone marrow and other peripheral end organs [37]. The allergic rhinitis–asthma linkage by means of the bloodstream has been demonstrated by studies from Braunstahl and colleagues [38]. In one study, nine subjects who had grass pollen allergy, but no asthma, were compared with nine nonallergic nonasthmatic subjects. Both groups were subjected to nasal provocation with grass pollen antigen, and in both groups, bronchial and nasal mucosa biopsies were obtained at baseline and at 24 hours after exposure. Nasal and pulmonary symptom scores were obtained using a visual analog scale and peak nasal inspiratory flow and peak expiratory flow (a measure of pulmonary obstruction). The findings from this study were that in allergic patients, but not in controls, nasal provocation stimulated eosinophilia in the bronchial mucosa and resulted in elevated expression of important cell adhesion molecules (ICAM-1, VCAM-1, and E-selectin). In addition to the histologic changes noted in the lungs after challenging the nose, decreases in peak expiratory flow were noted in the first 24 hours, and pulmonary symptoms were noted by subjects in the first few hours after provocation. This study demonstrated a hematogenous dissemination of allergic inflammation in the nose to the lungs. In another study with a corollary design [39], segmental bronchial provocation with allergen led to

increased IL-5, eotaxin, and eosinophils in both unchallenged bronchial mucosa and the nasal mucosa. Taken together, these studies demonstrate the connection between bronchial and nasal inflammation, and that the inflammation at one site provokes inflammation at another site, likely through the hematogenous dissemination of inflammatory mediators and cells.

Treatment of rhinitis impacts asthma outcomes, and vice versa

Just as nasal provocation may trigger pulmonary inflammation and symptoms, treatment of nasal disease can improve parameters in asthma. This phenomenon has been demonstrated in multiple studies [3,40], although results have been inconsistent, and more studies are needed [41,42]. In one example, Watson and colleagues [3], in a double blind, placebo-controlled crossover trial, showed that intranasal beclomethasone could improve asthma symptoms and reduce bronchial hyper-reactivity. They studied 21 subjects who had perennial allergic rhinitis with asthma and documented methacholine hyper-responsiveness. Subjects received either placebo or beclomethasone dipropionate nasal spray 100 µg in each nostril twice a day for 4 weeks, and then switched over into the other arm for another 4 weeks. Global assessments of rhinitis and asthma symptoms were scored at the beginning and end of each 4-week cycle. Methacholine challenge was performed at the beginning and end of each 4-week period. In the nasal steroid group, methacholine hyper-responsiveness (as measured by geometric mean of the PC₂₀) was decreased compared with the placebo group. Evening asthma scores were decreased significantly in weeks 2 and 3 in the treatment group, but other global parameters of asthma symptoms and peak expiratory flow were not significantly different between the two groups. These results suggest that although nasal steroids may not completely alleviate the clinical manifestations of asthma, they do have a measurable beneficial effect, and this effect might be more noticeable in a larger study. Corren and colleagues [43] studied 18 subjects who had ragweed allergic rhinitis and asthma with documented bronchial hyper-responsiveness to inhaled methacholine. Subjects were randomized to either placebo or beclomethasone dipropionate nasal spray for the entire ragweed season. Subjects recorded daily nasal and chest symptoms, nasal blockage index, oral peak expiratory flow rates, and supplemental medication use. Treatment with beclomethasone prevented the increase in bronchial hyper-reactivity seen in the placebo group at the end of the ragweed season. There were no significant differences in daily asthma symptom scores, oral peak expiratory flow, or asthma medication use, but the small sample size limited the power of this study. In another randomized, double-blind study, Stelmach and colleagues [40] showed that intranasal beclomethasone controlled asthma symptoms as well as inhaled and combination intranasal-inhaled applications of the drug, and that combined use of intranasal and inhaled beclomethasone reduced emergency department visits, lost work days, and sleep problems. A recent

Cochrane review [42] performed a meta-analysis of 14 studies that met inclusion criteria. Although this systematic review found a trend suggesting that intranasal corticosteroids improve asthma symptoms and FEV₁, the result was not statistically significant with their methodology. The authors recommended that further research be performed to evaluate the effects of intranasal corticosteroids on asthma control, and that a combination of intranasal and intrabronchial corticosteroids should remain the clinical practice until more research is done. This inconclusive meta-analysis does not dampen the profound implication of the previous studies; it is possible that asthma control may be improved by treating rhinitis.

Population-based studies suggest that this is indeed the case. Using a medical managed care database, Adams showed that treatment of asthmatic patients with nasal steroids confers protection against emergency department visits for asthma exacerbations [44]. A similar retrospective cohort, again using claims data for 4944 patients who had allergic asthma, showed a significant reduction in asthma-related emergency department visits or hospitalizations for patients who had treatment for rhinitis [45]. Although there are limitations to the conclusions that can be drawn from these sorts of population-based studies, they do support the notion that asthma control may be improved by treatment of concomitant rhinitis.

Conversely, treatment of asthma may improve rhinitis symptoms. Grieff and colleagues [46] performed a double-blind randomized placebo controlled trial in patients who had allergic rhinitis and birch pollen sensitivity, but no asthma, using orally inhaled budesonide (600 µg twice daily) or placebo. Nasal and bronchial symptoms, nasal and peripheral eosinophilia, and bronchial response to methacholine challenge were monitored before and during the birch pollen season. Patients receiving bronchial budesonide treatment had lower nasal symptom scores during the pollen season. Nasal lavage eosinophilic cationic protein levels during the pollen season were lower in those taking orally inhaled budesonide. Nasal eosinophils increased during the allergy season in those receiving placebo, but not those receiving orally inhaled budesonide. Similarly, blood eosinophils increased in the placebo group, but not in the budesonide group during the pollen season. Symptoms of chest congestion increased in these nonasthmatic patients during the pollen season, and this increase was attenuated in the budesonide treatment group. Methacholine bronchial provocation before and during the pollen season showed a decrease in FEV₁ during the pollen season in these nonasthmatic patients, and this decrease was attenuated in the orally inhaled budesonide group. These data suggest that nonasthmatic patients who have allergic rhinitis have some degree of bronchial inflammation when they are naturally exposed to allergens. Additionally, treatment of the pulmonary compartment had a measurable impact on measures of nasal allergic inflammation (symptoms scores, eosinophil numbers, ECP levels in nasal lavage fluid). Bronchial budesonide inhibits the seasonal increase in nasal and blood eosinophils, and nasal lavage levels of ECP [46].

These results must be interpreted with some caution, because distant effects after local treatment of one end-organ may be caused by systemic medication absorption. Additionally, orally inhaled steroids may have local and systemic effects. Airway inflammation requires circulating immune cells, bone marrow production of precursor cells, cytokines such as IL-5, granulocyte-macrophage colony stimulating factor, and eotaxin, and lymphocyte trafficking to airway mucosa. It is possible that application of corticosteroid at one site alters the molecular and cellular interplay between the treated site, other airway sites, the circulation, and the bone marrow, such that bronchial treatment with corticosteroid is a useful adjunctive measure for nasal inflammation, and vice versa.

Specific immunotherapy can prevent asthma in rhinitis patients

Another important clinical relationship that deserves mention is the potential that treatment of allergic rhinitis with immunotherapy can prevent the development of asthma. As noted previously, allergic rhinitis frequently becomes manifest before the development of asthma. Given the significant morbidity and mortality of asthma, any intervention that may prevent its development should be considered.

The potential of specific immunotherapy to prevent the subsequent development of asthma was described as early as 1968. Johnstone and Dutton [5] reported on a single-blinded, saline placebo-controlled study of 210 children who had perennial bronchial asthma with allergies. Of 130 children still under observation at their 16th birthday, 72% of the treated children were symptomatically free from asthma, while only 22% of the placebo children were symptomatically free from asthma. This study makes interesting reading not only because it analyzed the efficacy of different dosages of immunotherapy, but also because it was performed without the knowledge of parent or child. Modern research ethics make repetition of this sort of study impossible. Subsequent work has further solidified the notion that immunotherapy can prevent asthma [6]. The most convincing data come from a prospective multicenter study from Europe [4]. Two hundred and five children who had allergic rhinoconjunctivitis to grass and/or birch pollen were randomized to specific immunotherapy or an open control group and followed over 4 years. Immunotherapy was continued for 3 years. During the study period, bronchial hyper-reactivity declined in the immunotherapy group. Additionally, children without asthma at the start of the study ($N = 151$) were evaluated for the development of asthma at the end of the 3-year treatment period. At 3 years, 29 of 69 children (42%) in the control group developed asthma versus 19 of 79 children (24%) in the immunotherapy group. This same cohort was re-evaluated 2 years after completion of immunotherapy [47]. Subjects in the immunotherapy treatment group had a persistent clinical effect of immunotherapy for rhinitis and conjunctivitis symptoms and conjunctival sensitivity, but also

a persistent reduction in asthma. At 5-year follow-up (2 years after completion of immunotherapy), 15 of 75 children (20%) in the immunotherapy group had asthma, versus 29 of 67 children (43%) in the control group. Further investigation is needed to confirm the role of specific immunotherapy to prevent the development of asthma, but the potential to intervene early in the course of disease to alter outcomes is promising.

Summary

The connection between asthma and rhinitis should be recognized by otolaryngologists. Consideration of the asthma–rhinitis link may impact treatment decisions, as it is likely that asthma and rhinitis are different manifestations of a single respiratory system disease. Rhinitis patients are at increased risk for the development of asthma or may have unrecognized asthma. About a third of rhinitis patients will have asthma, and most patients who have asthma also have rhinitis. An attentive evaluation may uncover a previously unrecognized condition, leading to early intervention, which in turn can improve patient outcomes. Treating rhinitis may improve the control of asthma, thus decreasing the cost, morbidity, and potential mortality of this condition.

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