

The effect of treatment of allergic rhinitis on asthma morbidity, including emergency department visits

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Purpose of review

It has been hypothesized that asthma and allergic rhinitis are both manifestations of a single inflammatory process present throughout the airway and that control of the inflammatory response associated with allergic rhinitis may help to reduce inflammation throughout the airway and improve control of asthma. Although previous evidence has documented that therapy directed at allergic rhinitis can improve asthma symptoms and bronchial responsiveness, until recently, there was no evidence that the use of medication targeted at the upper airway can also reduce utilization of acute health care services due to asthma.

Recent findings

We identified studies published between August 2001 and July 2002 that examined the therapeutic link between allergic rhinitis and asthma. In particular, we concentrated on investigations that evaluated whether, among patients diagnosed with allergic rhinitis and asthma, treatment of the former resulted in significantly fewer asthma-related emergency department visits or inpatient hospitalizations. Two such studies were identified. Using observational study designs, both investigations established that among a population with asthma and allergic rhinitis, treatment for allergic rhinitis was associated with a decrease in the risk of subsequent asthma-related events by one-third to one-half compared with persons who did not receive treatment for this disorder.

Summary

Effective management of allergic rhinitis with nasal steroids and possibly oral antihistamines reduces utilization of acute health care services due to asthma among persons with co-existent asthma.

Keywords

asthma, allergic rhinitis, outcome assessment, inhaled corticosteroids, therapeutics

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Abbreviation

ICS inhaled corticosteroid

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Introduction

Asthma and allergic rhinitis are common conditions that have been linked epidemiologically, pathologically, and physiologically. It has been suggested that 'upper respiratory allergic disorders and asthma may represent facets of a single inflammatory airway syndrome' [1], with some advocating use of the names 'rhino-conjunctivo-sino-pharyngo-oto-bronchitis' [2] or 'allergic rhino-bronchitis' [3]. In collaboration with the World Health Organization, a recent workshop was convened to discuss allergic rhinitis and its impact on asthma (ARIA). The reader is referred to this publication for an exhaustive review of the complex relationship between allergic rhinitis and asthma [4•].

Several mechanisms have been postulated for the close association between nasal and airway inflammation, including aspiration of infected or inflamed secretions, a nasobronchial reflex, and the mechanical effect of nasal blockage that leads to mouth breathing and exposure to cold or dry air and an increase in allergens in the lower respiratory tract [5]. Another mechanism is inflammation of the airways via systemic absorption of inflammatory mediators [3]. Allergic subjects have a systemic response to allergen [6]. Absorption of mediators generated within the nasal mucosa into the systemic circulation can result in an inflammatory response within the entire respiratory tract and not just in the nasal mucosa [7]. According to this concept of disease, controlling the overall inflammatory load with effective treatment of nasal tract inflammation serves to reduce inflammation in the lung and hence to control asthma.

Allergic rhinitis as a risk factor for development of asthma

Allergic rhinitis frequently precedes asthma and may constitute a risk factor for the occurrence of asthma [8,9]. Rhinitis was found to be an independent risk factor for onset of asthma among a subgroup of Swedish participants with stage 1 asthma in the European Community Respiratory Health Survey [10]. In addition, early treatment of allergic rhinitis may help to prevent the occurrence of asthma [11] and sensitization to new allergens in children [12].

Guerra *et al.* [13•] recently published a nested case-control study from longitudinal data collected as part of the Tucson Epidemiologic Study of Obstructive Lung Diseases that supports this temporal relationship. After

adjustment for years of follow-up, age, sex, atopy, smoking, and presence of chronic obstructive pulmonary disease, subjects with allergic rhinitis had more than a threefold greater risk of subsequent development of asthma (OR, 3.21; 95% CI, 2.19–4.71). However, subclinical asthma can be present before the diagnosis, and a true assessment of the temporal relationship between rhinitis and asthma in adults is difficult. Importantly, previous studies have shown that recall bias of disease during childhood can cause inappropriate interpretation of subsequent recrudescence of disease as incident disease [14]. Nonetheless, Guerra *et al.* observed a linear dose relationship between the duration and severity of nasal symptoms and the risk of developing asthma. Such a dose response should be insensitive to any recall bias.

Use of nasal steroids in persons with asthma and allergic rhinitis

Topical steroids are a class of medications that play an important role in the treatment of upper and lower airways disease. Topical steroids decrease the inflammatory response associated with these disorders, including the release of mediators central to the pathogenesis of both diseases [15]. In addition, the use of nasal steroids in patients with both allergic rhinitis and asthma is associated with a reduction in both nasal [16] and asthma symptoms [7,17,18]. Topical nasal steroids can also reduce airway responsiveness [19–22].

Until recently, however, there was no evidence that the use of medication targeted at the upper airway could also reduce utilization of acute healthcare services, such as emergency department visits or hospitalizations due to asthma. Using an observational study design, two recent investigations tested the hypothesis that treatment of allergic rhinitis, among patients diagnosed with allergic rhinitis and asthma results in significantly fewer asthma-related emergency department visits or inpatient hospitalizations.

Adams *et al.* [23••] performed a retrospective cohort analysis of members of a large managed care organization. Over a 3-year period from October 1991 to September 1994, they identified 13 844 subjects aged 5 years and older with a diagnosis of asthma. They observed an association between treatment for upper airways disease with nasal steroids and oral antihistamines and events requiring acute healthcare utilization. The rate of asthma-related emergency department visits was lower in subjects dispensed nasal steroids or oral antihistamines than in individuals not treated for allergic rhinitis. This effect was seen among children and adults, among all three upper airway diagnoses (rhinitis, sinusitis, and otitis media) and was independent of the use of oral inhaled steroids.

Crystal Peters *et al.* [24••] also utilized a retrospective cohort design to examine the relation between treatment of nasal symptoms and acute healthcare utilization for asthma. They identified a cohort of 31 728 persons aged 12–60 years with asthma, of whom 12 208 had a diagnosis of both asthma and allergic rhinitis. Subjects with a diagnosis of chronic obstructive pulmonary disease and those with missing values for analytic variables were excluded, limiting the final study population to 4944 subjects. Treatment of allergic rhinitis was defined as a prescription for a nasal inhaled steroid, a sedating antihistamine, or a nonsedating antihistamine. Using a multivariate Poisson regression model, the authors observed that the risk of an asthma-related event for persons treated for rhinitis was about half that for the untreated group (incidence density ratio for treatment group 0.49; $P = 0.001$).

In both studies, infrequent use of nasal treatment had a protective effect. Many patients experience nasal symptoms only seasonally and thus there may be skepticism as to whether this frequency of nasal treatment is sufficient to produce any clinically significant effect. However, evidence suggests that nasal steroids are highly effective in improving symptoms, quality of life, and levels of nasal eosinophil in patients with seasonal allergies when used on as-needed, less-than-daily basis during the allergy season [25]. In addition, a similar pattern has been reported for the use of orally inhaled corticosteroids for asthma among adults and children, with infrequent use having been associated with a significantly decreased risk for hospitalizations [26,27].

Of interest, Crystal Peters *et al.* noted that persons who received treatment for allergic rhinitis also received a significantly higher number of prescriptions for asthma medications. The allergic rhinitis treated group had a higher rate of prescription of orally inhaled steroids (48%) than the untreated group (42.2%). Similarly the use of oral steroids was higher in the rhinitis treated group than in the untreated group. Although a trend towards increased use of β -agonists, theophylline, and cromolyn were also noted, these differences were not significant. This is consistent with previous work that suggests the presence of AR is associated with asthma severity [28,29].

Crystal Peters also reported that 73% of their study population had received treatment with either nasal steroids or antihistamines for allergic rhinitis. In contrast, Adams *et al.* noted that the majority of patients with a diagnosis of asthma and an upper airways disease were not dispensed either nasal corticosteroids or prescription antihistamines and that very few were using these medications regularly. The two analyses used data from similar time periods. Trends in the use of these medications over time do not adequately explain the

disparate results. However, Crystal Peters *et al.* identified a more restricted population. After the application of exclusion criteria, 40% of the subjects identified with both asthma and allergic rhinitis and only 15.6% of those identified with asthma were available for analysis. Therefore, differences in how the two populations were defined may explain the inconsistency in the results. Additional evidence supports the existence of under recognition and under treatment of allergic rhinitis [30].

Despite minor differences in methodology, both studies demonstrate that among a population with asthma and allergic rhinitis, persons who receive treatment for allergic rhinitis have a significantly lower risk of subsequent asthma-related events than persons who do not receive treatment for rhinitis. The similarity of the effect estimates between the two studies suggests the findings are robust. The small difference in the magnitude of the effect estimate observed in the individual studies may represent differences in the definitions utilized for upper airway disease. Adams *et al.* combined all three upper airway diagnoses into a single category of upper-airway disease. In addition, Crystal Peters *et al.* defined asthma-related events differently among the treated and untreated subgroups, which may have inflated the effect estimate observed. Among the allergic rhinitis treated subpopulation, only events that occurred within 31 days of a prescription for an allergic rhinitis medication were included. Therefore, additional events occurring in the treated cohort but more than 31 days from the dispensing of a rhinitis medication would not have been included in the analysis.

Treatment with nasal steroids or antihistamines could be a marker of better quality of asthma care. Adams *et al.* attempted to control for this in the multivariate models by including the frequency of routine ambulatory and unscheduled urgent care visits as markers of asthma management. Although the nonpharmacological aspects of asthma management guidelines are important [31] there is little evidence suggesting that they alone are effective in reducing morbidity in the absence of appropriate medication. Recognition of upper airways disease and appropriate treatment may indicate that the patient is receiving good-quality care; yet, the correct use of medication is a mechanism of higher-quality care that is responsible for reducing morbidity.

The association between treatment for allergic rhinitis and asthma morbidity may be confounded by the greater likelihood that patients who receive appropriate treatment for upper airway conditions also receive appropriate asthma controller medications. To address this, both Crystal Peters *et al.* and Adams *et al.* adjusted for the simultaneous use of oral inhaled corticosteroids

(ICSs) with nasal steroids. Crystal Peters *et al.* controlled for oral ICSs in their multivariate models, and the protective effect of allergic rhinitis treatment on asthma morbidity persisted. Adams *et al.* also stratified their analysis on the basis of oral ICS use and documented that the effect of allergic rhinitis treatment on the risk of asthma-related events was similar among persons who did and did not receive oral ICSs during the same treatment period. The protection against the risk of asthma-related events attributed to treatment of rhinitis in these populations does not appear to be only a marker for better and more comprehensive care.

Nasal steroids and antihistamines may not provide equal protection against asthma-related events. Adams *et al.* carried out separate analyses for each type of allergic rhinitis treatment and found that the absolute reduction in events was greater for nasal steroids than antihistamines in almost all categories. In multivariate models controlling for age, sex, frequency of orally inhaled steroids, the dispensing of β -agonists, upper airway diagnosis, and amount and type of ambulatory care, the use of nasal steroids conferred protection against exacerbations of asthma leading to emergency department visits (OR, 0.7; 95% CI, 0.59–0.94). However, among persons receiving oral antihistamines, a significant reduction in the risk of asthma-related emergency department visits did not persist in multivariable models (OR, 0.9; 95% CI, 0.78–1.11). Crystal Peters *et al.* did not distinguish between treatment with antihistamines and treatment with nasal steroids.

The use of computerized databases has limitations. Reliance on medication dispensing as a surrogate for actual medication may underestimate their effect. Diagnostic misclassification may occur secondary to overlap in the spectrum of upper airway disease, errors in the transcription of medical records, or the possible influence of reimbursement incentive on coding. However, the ability to assess the effectiveness of medications under conditions of actual use in the setting of clinical practice, the elimination of the risk of recall bias for drug exposure, and most importantly, the availability of large populations to enable assessment of relatively rare events (asthma-related emergency department visits and hospitalizations) are significant advantages of the use of such databases.

Conclusion

The evidence increasingly suggests that benefits can be provided for people with asthma by more effective management of co-existent rhinitis. Nasal steroids and possibly oral antihistamines may be beneficial in this regard. However, a number of questions remain unanswered. These include the best strategies for using treatment for allergic rhinitis, for example, singly or in

combination: whether specific subgroups of people with asthma derive more benefit than others and what frequency of use of nasal steroids is necessary to be of benefit. The issue of whether side effects are increased from a higher overall dosage of corticosteroids also needs to be considered. It may now be time to consider the merits of organizing and funding a prospective clinical trial of sufficient statistical power to address the question of the magnitude of benefit for asthma morbidity from treatment of allergic rhinitis and some of these other important issues.

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