

Allergic rhinitis and inflammatory airway disease: Interactions within the unified airspace

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ABSTRACT

Background: Allergic rhinitis (AR), the most common chronic allergic condition in outpatient medicine, is associated with immense health care costs and socioeconomic consequences. AR's impact may be partly from interacting of respiratory conditions via allergic inflammation. This study was designed to review potential interactive mechanisms of AR and associated conditions and consider the relevance of a bidirectional "unified airway" respiratory inflammation model on diagnosis and treatment of inflammatory airway disease.

Methods: MEDLINE was searched for pathophysiology and pathophysiological and epidemiologic links between AR and diseases of the sinuses, lungs, middle ear, and nasopharynx.

Results: Allergic-related inflammatory responses or neural and systemic processes fostering inflammatory changes distant from initial allergen provocation may link AR and comorbidities. Treating AR may benefit associated respiratory tract comorbidities. Besides improving AR outcomes, treatment inhibiting eosinophil recruitment and migration, normalizing cytokine profiles, and reducing asthma-associated health care use in atopic subjects would likely ameliorate other upper airway diseases such as acute rhinosinusitis, chronic rhinosinusitis (CRS) with nasal polyposis (NP), adenoidal hypertrophy, and otitis media with effusion.

Conclusion: Epidemiological concordance of AR with several airway diseases conforms to a bidirectional "unified airway" respiratory inflammation model based on anatomic and histological upper and lower airway connections. Epidemiology and current understanding of inflammatory, humoral, and neural processes make links between AR and disorders including asthma, otitis media, NP, and CRS plausible. Combining AR with associated conditions increases disease burden; worsened associated illness may accompany worsened AR. AR pharmacotherapies include antihistamines, leukotriene antagonists, intranasal corticosteroids, and immunotherapy; treatments attenuating proinflammatory responses may also benefit associated conditions.

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Potential mechanisms by which allergic rhinitis (AR) and its principal associated conditions interact have attracted intense interest recently. It has been proposed that the relationships are consistent with a bidirectional "unified airway" model of respiratory disease.^{1,2} In this model, the respiratory tract is considered an integrated system in which both local inflammatory processes and systemic mediators promote reactions throughout the system. In this context, pathophysiological mechanisms of allergic respiratory disease can affect the entire airspace (*i.e.*, nasal mucosa, sinuses, lungs, middle ear, and nasopharynx), thereby promoting the established or likely concordance of AR with other respiratory disease states. Practical corollaries are that patients with upper airway disease should show a higher prevalence of lower respiratory disease, such as asthma, versus the general population; patients with lower-tract disease should have an increased prevalence of upper airway involvement; and interventions directed at one portion of the unified space should influence symptoms in another.¹

EPIDEMIOLOGICAL ASSOCIATIONS

Epidemiological data support the unified airway model and its clinical implications. Nearly 80% of patients with asthma have rhinitis and 10–14% of patients with rhinitis have asthma—prevalence rates far in excess of the general population—and the coexistence of rhinitis with asthma impairs asthma control.^{3,4} AR is present in essentially 100% of

atopic patients with acute asthma exacerbation.^{5,6} The presence of AR has been recently shown in a longitudinal, population-based study to increase the risk for subsequent asthma nearly fourfold.⁷ When AR is present as comorbidity of asthma, it serves as a marker of more severe lower respiratory disease and increased cost to the health care system. Conversely, effective treatment of AR is associated with improved asthma control.^{4,6,8}

AR and nonallergic rhinitis are established risk factors for chronic rhinosinusitis (CRS), and CRS, especially a clinical subset with nasal polyps, is strongly associated with asthma.^{9–11} The prevalence of allergy among patients most seriously afflicted by refractory CRS was noted in one study to be >60% and may be beyond 80% among patients for whom endoscopic surgery is indicated, figures considerably higher than the prevalence of CRS in the general population.^{11,12} Major histopathological findings of CRS are also found in asthma, including evidence of airway remodeling.¹³ Similar to the benefits of AR treatment on comorbid asthma control, successful CRS management may positively affect associated lower airway disease.⁹

The unified airway model can be extended to the middle ear cleft,^{14,15} essentially, a "fifth sinus" in which the ear resides.¹⁶ Studies indicate that the ear is a susceptible target for allergic phenomena, and that allergy is a risk factor for recurrent or chronic otitis media with effusion (OME).^{14,15,17} OME is characterized by the presence of fluid in the middle ear in absence of the signs and symptoms of acute infection.¹⁸ Although large-scale data are limited, a study of unselected children showed that 50% of patients identified with OME were atopic, testing positive to at least two of the following allergy tests: eosinophilia in nasal secretion smears and peripheral blood, skin test, and nasal provocation test and serum IgE level.¹⁹ Another study assessing 209 children with intractable OME showed AR in 89%.²⁰ Tests to determine atopy included medical history, nasal smears, and skin-prick test. In a subset of patients, blood eosinophil counts and total IgE levels were also measured. Highly sensitive *in vitro* testing of 97 preschool, school-age, and adult subjects with refractory OME found 79 (81%) to be atopic.¹⁶ Among those with available medical records, 48% had been previously diagnosed with AR.¹⁶

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Data suggesting a direct epidemiological link between nasal polypoid disease (NP) and nasal allergy are lacking,²¹ but allergy may contribute to exacerbated polypoid disease. A chronic persistent inflammatory process is believed to be a major factor in the etiology of NP, and CRS (for which allergy is a risk factor) appears to be required for the development of NP in many cases. Nasal polyps have long been associated with rhinitis and asthma and tend to develop exclusively from a limited, profoundly inflamed area of nasal mucosa.²¹ NP is one of five diagnostic criteria for allergic fungal rhinosinusitis.²² Aspirin-sensitive respiratory disease indicates another association between nasal polyps, rhinosinusitis, and asthma. It is characterized by this triad, intractable inflammation of upper and lower respiratory tracts, and exacerbations of rhinosinusitis and asthma from ingestion of aspirin or other nonsteroidal anti-inflammatory drugs.²³ The association of upper and lower airway disease in this context is further illustrated by a retrospective study in which patients with aspirin-intolerant asthma had statistically superior asthma outcomes versus aspirin-tolerant asthma patients after endoscopic sinus surgery for CRS.²⁴ Despite these suggestive associations, the prevalence of nasal polyps in allergic individuals is similar to that in the general population.²¹

Small studies have found a greater risk of adenoidal hypertrophy (AH) in children with AR, particularly among those with inhalant sensitivity to mold spores.^{25,26} Limited data also suggest higher association of AH with otitis media in children.²⁷ Cross-talk between inflammatory processes in the adenoids and the middle ear is suggested by research indicating that the population of adenoid mast cells in children with OME is significantly greater than that in children without OME.²⁸ Among adults with AH, tissue histopathology also suggests chronic inflammatory cell infiltration.²⁷

AR AND COMORBID RESPIRATORY DISEASE: POSSIBLE MECHANISMS OF LINKAGE

Inflammatory Mechanisms

As an IgE-mediated, type 1 hypersensitivity reaction to an inhaled antigen, AR is characterized by an immunologic cascade. Upper and lower airway pathology in patients with AR may be linked through up-regulated systemwide inflammatory responses enacted over the uniform pseudostratified columnar epithelium comprising the respiratory mucosa.^{1,29}

In the early phase allergic response, degranulation of sensitized mast cells leads to the release of preformed mediators, including histamine, kinins, and proteases. Chemotaxis and migration of degranulating mast cells, neutrophils, basophils, eosinophils, T-lymphocytes, and macrophages across the mucosal endothelium into the nasal epithelium and submucosa produces vascular leakage and interstitial edema, nasal pruritus, rhinorrhea, nasal congestion, and sneezing.²⁹ The late-phase allergic response occurs several hours after antigen exposure and has a prolonged nature that may foster chronicity, as well as an inflammatory cell influx in which the eosinophil shows its greatest proportionate rise.^{29,30}

Eosinophils, along with mast cells and basophils, are relatively abundant at sites of allergic inflammation, and their activation and release of preformed or newly synthesized cationic proteins (major basic protein, eosinophil cationic protein [ECP], peroxidase, and eosinophil-derived neurotoxin) is considered central to allergy pathophysiology.^{31,32} Tissue eosinophilia is a cardinal feature of allergic airway disease, and eosinophil expansion, priming, recruitment, and prolonged tissue survival in response to allergic stimuli are mediated by the TH2 cytokine IL-5.³³ Working in synergy with IL-4, IL-13, and the eosinophil-specific chemokines known as eotaxins, IL-5 promotes a range of eosinophil-mediated inflammatory responses.³³ Transit of eosinophil populations to tissues is mediated *via* cell surface selectins, integrins (such as vascular cell adhesion molecule [VCAM] 1), and their associated ligands.^{33,34} Migration of eosinophils from bone mar-

row to bloodstream to tissue, and their activation, is shown in the Fig. 1.

Allergy and eosinophilia represent an established thread in inflammatory airway disease. Eosinophilic infiltration of nasal and bronchial sites has been well described for atopic patients with AR and asthma. Eosinophil-mediated inflammation is the key component perpetuating many forms of CRS.⁹ The influx of eosinophils in severe CRS is comparable between allergic and nonallergic patients, but absent in healthy controls.¹³ Histopathological studies of sinus mucosa from most adult patients with CRS show high-grade tissue infiltration by eosinophils and markedly elevated levels of IL-5, granulocyte-macrophage colony-stimulating factor, IL-3, and RANTES, all of which support a role for eosinophil-mediated inflammatory responses.^{32,35} Additionally, highly active eosinophil-derived products that contribute to inflammatory CRS pathology are shown in mucus at the outermost aspects of epithelial surfaces.³⁶

The middle ear mucosal lining shares a histological homology with upper and lower airways, and acute inflammatory changes identified within the otic mucosa are similar to features in the lower airways during an asthma exacerbation.^{16,37} In atopic patients with middle ear effusion, the presence of ECP is highly correlated with allergy but is unrelated to serum levels of ECP, suggesting a predominantly localized process.³⁸ Eustachian tube dysfunction, the most common etiological risk factor for otitis media, may be caused by local effects of inflammatory mediators and resultant edema.¹⁷ Middle ear effusions from children with AR contain significantly higher levels of mast cells and tryptase, a specific mediator of mast cell activity, indicating an underlying TH2-driven immune response also reflected in distinctly different eosinophil and neutrophil profiles between atopic and nonatopic subjects with chronic OME.^{16,39}

Despite the lack of a direct link with atopy, eosinophilic infiltration of the nasal mucosa is a defining characteristic of NP. This eosinophilia is associated with increased levels of IL-5 and other mediators, cytokines, mast cells, immune cell colony-stimulating factors, eotaxin, and other inflammatory messengers and intermediaries.⁴⁰⁻⁴³ Atopy in a patient with NP has a significant negative impact on physical function level and pain.⁴⁴

Systemic and Neural Mechanisms

Evidence strongly supports the systemic distribution of inflammatory mediators from the initial inflammation site to lymphoid tissue and marrow,⁴⁵ contributing to amplified inflammatory responses across the nasal passages, sinuses, and lower airways. Even a single nasal allergen challenge administered to nonasthmatic subjects with seasonal allergy leads to increased blood eosinophil levels and IL-5 in both upper and lower airways, independent of the amount of allergen administered.⁴⁶

Nasal allergen challenge of atopic subjects with both AR and asthma increases bronchial hyperresponsiveness.⁴⁷ Nasal challenge in nonasthmatic subjects with AR has been shown to promote increased bronchial expression of adhesion molecules (VCAM-1, intercellular adhesion molecule 1, and endothelial-leukocyte adhesion molecule 1), facilitating eosinophil influx from the circulation into bronchial mucosa, causing reduced peak expiratory flow.⁴⁸ The nasobronchial interaction is bidirectional; direct bronchial allergen challenge in nonasthmatic AR patients induced a robust nasal inflammatory reaction characterized by immune-cell degranulation, as well as increased IL-5 levels, in peripheral blood.⁴⁹

The neurological, immunologic, and allergic responses involved in inflammation are interrelated.⁵⁰ Neural signals contribute to sneezing, rhinorrhea, mucosal vasodilation, and other cardinal signs of nasal inflammation.⁵¹ A naso-ocular reflex mediates the frequent conjunctival symptoms associated with AR.⁵² Nasal provocation with grass or ragweed extract leads to ipsilateral maxillary sinus inflammation without evidence of passage of pollen into the sinus cavity, strongly suggesting a reflex nasosinal path or systemic distribution of a proinflammatory mediator.⁵³ Consistent with a nasonasal reflex, single-

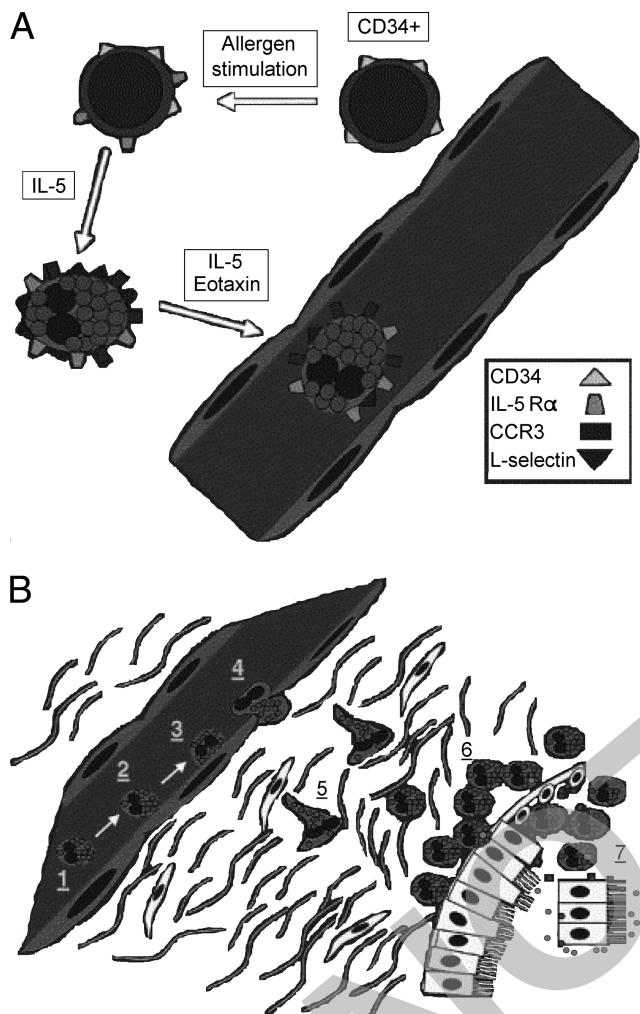


Figure 1. The role of eosinophils in allergic inflammation. (A) Eosinophil maturation in bone marrow. After allergen-induced late-phase reaction, CD34⁺ cells express IL-5 receptor α -chain. IL-5 drives the CD34⁺ and IL-5 receptor α -chain + cells to eosinophil maturation. Under the stimulus of IL-5 or eotaxin, these mature cells shed L-selectin and migrate from the bone marrow to the blood. (B) Schematic summary of eosinophil recruitment to and activation in bronchial tissues. At 1, the eosinophil is moving in the peripheral blood. At 2, the eosinophil has tethered to the vessel wall by adhesion molecules (e.g., endothelial P-selectin and eosinophil very late activation antigen [VLA]-4 with endothelial vascular cell adhesion molecule [VCAM] 1) and rolls along the endothelium. At 3, the eosinophil has more firmly adhered to the endothelium (by the eosinophil β 1- and β 2-integrins and the endothelial intercellular cell adhesion [ICAM] molecules) and has flattened on the surface. At 4, the eosinophil is undergoing transmigration between endothelial cells into the connective tissues. At 5, the eosinophils (with use of VLA-4 and VLA-6) interact with connective tissue matrix proteins (e.g., fibronectin and laminin), become "primed" and partially activated under the influence of various factors (e.g., cytokines such as IL-5, chemokines such as RANTES and eotaxin, and lipid mediators such as PAF), and migrate toward their eventual destination. At 6, eosinophils become fully activated (by interactions with cytokines, lipid mediators, Ig, complement fragments, and β 2-integrins) and start to degranulate. Finally, at 7, the eosinophils have degranulated, releasing toxic mediators (e.g., granule proteins, lipid mediators, oxygen metabolites, proteases, and cytokines) and disrupting cells in the bronchial epithelium. (Reprinted with permission from Ref. 87.)

nostril antigen challenge in atopic individuals leads to immediate increases in nasal secretion weight and nasal symptoms in both nostrils, sustained for up to 20 minutes.⁵⁴ Unilateral allergen challenge in atopic subjects has also been associated with significant and prolonged increases in bilateral nasal resistance.⁵⁵ A nasosnasal reflex may also foster bilateral nasal hyperresponsiveness persisting beyond the resolution of an acute challenge.⁵⁶

TREATMENT CONSIDERATIONS

Crucial to the clinical relevance of an integrated airway model is therapeutic interdependence of the upper and lower airways, such that treatment of one portion of the continuous airspace results in symptom improvement elsewhere in the respiratory system.¹ Given the enormous population of pediatric and adult subjects at risk for seasonal and perennial AR, of whom a subset will have associated or comorbid airway disease, therapeutic interdependence of AR with another respiratory condition could confer major practical benefits.

Myriad interventions have been used to manage AR, including topical intranasal corticosteroids (INs), antihistamines, leukotriene antagonists, and immunotherapy. Despite extensive clinical use, there are only limited data evaluating the response of associated respiratory conditions when these medications are deployed specifically for short- or long-term management of AR.

Evidence implicates histamine as a driver of numerous proinflammatory and immune responses.⁵⁷ Histamine H₁-receptors are expressed on mast cells, basophils, and endothelial cells, as well as smooth muscle cells within the bronchial tree, where they mediate vasodilation and bronchoconstriction.⁵⁷ Despite the ubiquity of H₁-receptors across respiratory tract tissues, meta-analysis of well-designed trials using antihistamines as adjunctive asthma treatment in adults found little difference versus placebo in their effects on asthma control.⁵⁸ However, there may be a role in bronchial allergy for novel histamine receptors (*i.e.*, the H₄-receptor) that are not ligands for current antihistamines, and much higher doses of H₁-antihistamines than those known to be effective for AR may have some benefit.⁵⁷ In contrast, a recent analysis has shown that long-term (6 month), standard-dose antihistamine administration to patients with persistent AR reduced self-reported lost workdays because of AR, asthma, sinusitis, otitis, or upper respiratory infection, reducing costs versus nontreatment, and suggesting some benefit relevant to the few comorbid conditions selected for the primary analysis.⁵⁹ Clinical severity was unreported. Workplace absenteeism and measured costs may be unreliable markers for clinical burden of illness, or for the symptomatology of a comorbid respiratory condition.

Leukotriene antagonists are unlikely to replace current mainstays of allergy treatment, but may be valuable adjuncts to first-line care in difficult-to-treat subjects. Their primary effectiveness is in managing aspirin-induced, exercise-induced, or allergic bronchoconstriction.⁶⁰ They are well tolerated and effective in patients with comorbid rhinitis and asthma.⁴ Used as adjunctive therapy with oral or inhaled corticosteroids for NP treatment, leukotriene antagonists have shown only transient benefits.⁶¹

Allergen immunotherapy by the subcutaneous route (subcutaneous immunotherapy [SCIT]) in appropriate patients with AR significantly reduces symptom scores and medication use. It is associated with a relatively low risk of severe adverse events and no long-term consequences.⁶² SCIT has an established role in the management of allergic asthma,⁶³ and recent investigation suggests that multiallergen SCIT may improve clinical benefits for patients with rhinitis and asthma.⁶⁴ Only limited data exist supporting a role for immunotherapy in managing atopic patients with CRS or acute recurrent sinusitis.⁶⁵ No available information supports a conclusion regarding the role of immunotherapy in NP or OME.

Sublingual immunotherapy (SLIT) is not approved for use in the United States but is used extensively in Europe and has shown efficacy in several meta-analyses in AR in adults and asthma and

rhinitis in children.⁶⁶⁻⁶⁹ SLIT appears to be better tolerated than SCIT.⁷⁰ The Allergic Rhinitis and Its Impact on Asthma 2008 guidelines support using SLIT in selected patients with AR, conjunctivitis, and/or asthma caused by pollen and mite allergy.⁴

INS Therapy for Inflammatory Airway Disease

Topical INSs are the most effective available first-line medications in AR patients with congestion, achieving improvement of symptoms with very low risk of significant adverse reactions. The therapeutic advantages of INSs arise through modulating the activation and repression of genes regulating components of the inflammatory cascade, mitigating TH2 expression and transformation, inhibiting the influx of immune cell populations and a range of cytokines, chemokines, adhesion molecules, histamine, leukotrienes, and allergen-specific IgE.^{4,71-74} Long-term use of newer-generation INSs lacks the safety concerns associated with prolonged exposure to systemic glucocorticoids.^{4,71,72} Control of comorbid asthma and AR with INS treatment and associated beneficial effects on lower airway disease control has been documented.^{4,75}

Additionally, INSs show consistently good therapeutic efficacy for other inflammatory respiratory conditions affecting the sinuses, middle ear, and nasopharynx.⁷⁶ Retrospective and nested, case-control studies of claims data indicate that patients with rhinitis, sinusitis, or otitis media and asthma receiving INSs have a lower risk of emergency care or hospitalization versus patients using prescription antihistamines^{8,77}; for atopic patients with AR and asthma, risks are at least reduced for those who receive both.⁸ These findings give support to the notion of “treating the nose to treat the lung.”⁷⁵

INS in Acute Rhinosinusitis (ARS)

ARS is a general complication of nasal inflammation, typically attributed to impaired sinus drainage and inadequate gas exchange secondary to occlusion of the ostiomeatal complex by edema. Although viral respiratory tract infections are the most common cause of acute sinus inflammation, AR is implicated in ~25–30% of cases of young adults presenting with acute maxillary sinusitis.^{78,79} Recent studies have indicated that adults and children with ARS can be treated initially with INS monotherapy without adverse outcomes or compromised patient safety. In a randomized, double-blind trial enrolling 240 adults with acute sinusitis diagnosed by clinical criteria, patients with less severe baseline symptom scores trended toward significantly greater clinical benefit with topical budesonide monotherapy. In more intensely symptomatic patients, combinations of an INS plus amoxicillin, or either drug alone, offered no benefit over placebo. The authors note that less severely symptomatic patients may benefit from INS therapy early in the course of their illness when processes favoring ostial occlusion are reversible through anti-inflammatory actions.⁸⁰ In a pediatric trial enrolling 981 patients with mild-to-moderate disease, once- or twice-daily mometasone monotherapy was superior to amoxicillin (500 mg three times daily) or placebo in improving symptoms. Benefits were noted by day 2 of therapy. No patient randomized to INS treatment alone experienced disease recurrence or bacterial infection, suggesting that antibiotic therapy is unnecessary and may be safely withheld during an initial phase of INS-based symptomatic care.⁸¹

INS for CRS with or without NP

A recent meta-analysis has established that INSs are beneficial in treating CRS with polyposis.⁸² Treatment (with budesonide [$n = 478$], mometasone [$n = 664$], or fluticasone [$n = 142$] once- or twice-daily for 6–16 weeks) was associated with measurable reductions in polyp size at even the most conservative estimate of treatment effect, with the true effect likely greater. Inconsistencies among studies in symptom assessment precluded statistical evaluation of this end point in the meta-analysis.⁸²

In a recent meta-analysis of 9 randomized studies involving 657 patients, treatment with INS (fluticasone propionate, budesonide, beclomethasone dipropionate, dexamethasone, or triamcinolone) for CRS without polyps showed no clear overall benefit.⁸³ However, a standardized mean difference favoring INS obtained from three trials reporting the mean change in total symptom score provides evidence of symptomatic benefit (RR, 0.63; 95% CI, 0.16–1.09; $p = 0.009$).

INS for AH

Evidence from a small number of well-designed studies indicates that INS therapy significantly improves symptoms in children with moderate or severe AH, and that improvement is associated with a reduction in adenoid tissue. In a recent systematic review of five randomized trials encompassing 349 patients ≤ 12 years of age, all but one study documented significant efficacy of INS treatment. Notable findings extracted from beclomethasone studies were that treatment significantly improved symptom scores versus placebo, reduced the mean adenoid/choana ratio by at least 14% bilaterally, and decreased symptom scores by at least 50% in nearly 40% of patients. Mometasone furoate nasal spray administered for ~2.5 months reduced adenoid size sufficient to preclude operation in 77% of treated patients; no such improvement was reported with placebo. Mometasone furoate nasal spray treatment achieved a significant mean overall symptom score reduction from 11 to 3 versus 10 to 9 for placebo and significantly greater decreases in the principal individual symptom scores (nasal obstruction, rhinorrhea, obstructive sleep apnea, cough, and snoring).⁸⁴

INS for OME

Very limited evidence suggests that topical INSs administered alone or in combination with an antibiotic are associated with more rapid short-term resolution of OME, with treatment responses that are similar between atopic and nonatopic subjects.^{85,86} Children with OME were randomized to treatment with prophylactic antibiotics alone, prophylactic antibiotics plus intranasal beclomethasone (336 $\mu\text{g/day}$), or prophylactic antibiotics plus intranasal placebo. Otoscopic extent of disease, symptom scores, and middle ear pressures improved in all treatment arms, but those receiving INS showed more rapid improvement over 8 weeks, and only INS significantly improved middle ear pressures over 12 weeks.⁸⁶

CONCLUSIONS

The interrelationships between AR and its principal comorbid respiratory conditions are consistent with a bidirectional “unified airway” model of respiratory inflammation, in which pathological activity at one site results in disease expression at another. Implications of this model have great clinical relevance for diagnosis and management of inflammatory airway disease. The presence of AR may be reflective of an inflammatory process unfolding at another locale, but—more crucially—if processes central to the pathophysiology of AR have a role in disease activity elsewhere in the respiratory tract, then competent management of AR may be expected to impact comorbid disease activity and improve overall health status.

Although asthma is the most well-characterized comorbidity of AR, other upper airway disorders that often coincide with allergic airway disease are otitis media, NP, and CRS. The role of allergy in these and other associated conditions, such as AH, is not fully established, but the relationship is intriguing and reasonably likely considering the range of inflammatory, humoral, neural, and systemic processes that are plausible common pathways.

Available pharmacologic options for AR management include antihistamines, leukotriene antagonists, INSs, and immunotherapy. Given the purported role of inflammatory processes in symptom generation, treatment options that attenuate the proinflammatory response may also have advantages for a comorbid or associated

airway condition. Physicians should maintain a treatment approach targeted toward the pathophysiology of allergy, taking into consideration symptom severity, comorbid disease, and individual patient needs.

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REFERENCES

- Krouse JH. The unified airway—Conceptual framework. *Otolaryngol Clin North Am* 41:257–266, v, 2008.
- Braunstaal G-J, and Hellings PW. Nasobronchial interaction mechanisms in allergic airways disease. *Curr Opin Otolaryngol Head Neck Surg* 14:176–182, 2006.
- Corren J. Allergic rhinitis and asthma: How important is the link? *J Allergy Clin Immunol* 99:S781–S786, 1997.
- Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63(suppl 86):8–160, 2008.
- Linneberg A, Henrik Nielsen N, Frølund L, et al. The link between allergic rhinitis and allergic asthma: A prospective population-based study. The Copenhagen Allergy Study. *Allergy* 57:1048–1052, 2002.
- Thomas M. Allergic rhinitis: Evidence for impact on asthma. *BMC Pulm Med* 6(suppl 1):S4, 2006.
- Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: A longitudinal population-based study. *Lancet* 372:1049–1057, 2008.
- Corren J, Manning BE, Thompson SF, et al. Rhinitis therapy and the prevention of hospital care for asthma: A case-control study. *J Allergy Clin Immunol* 113:415–419, 2004.
- Joe SA, and Thakkar K. Chronic rhinosinusitis and asthma. *Otolaryngol Clin North Am* 41:297–309, vi, 2008.
- Gelincik A, Büyüköztürk S, Aslan I, et al. Allergic vs nonallergic rhinitis: Which is more predisposing to chronic rhinosinusitis? *Ann Allergy Asthma Immunol* 101:18–22, 2008.
- Gutman M, Torres A, Keen KJ, and Houser SM. Prevalence of allergy in patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 130:545–552, 2004.
- Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 129(suppl):S1–S32, 2003.
- Ponikau JU, Sherris DA, Kephart GM, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: Is the histopathology similar to asthma? *J Allergy Clin Immunol* 112:877–882, 2003.
- Luong A, and Roland PS. The link between allergic rhinitis and chronic otitis media with effusion in atopic patients. *Otolaryngol Clin North Am* 41:311–323, vi, 2008.
- Nguyen LHP, Manoukian JJ, Sobol SE, et al. Similar allergic inflammation in the middle ear and the upper airway: Evidence linking otitis media with effusion to the united airways concept. *J Allergy Clin Immunol* 114:1110–1115, 2004.
- Hurst DS, and Venge P. Evidence of eosinophil, neutrophil, and mast-cell mediators in the effusion of OME patients with and without atopy. *Allergy* 55:435–441, 2000.
- Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 122(suppl):S1–S84, 2008.
- Stool SE, Berg AO, Berman S, et al. Otitis media with effusion in young children. Clinical Practice Guideline, No. 12, AHCPR Publication No. 94-0622. Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, Rockville, MD, July 1994.
- Tomonaga K, Kurono Y, and Mogi G. The role of nasal allergy in otitis media with effusion: A clinical study. *Acta Otolaryngol (Stockh)* 458(suppl):41–47, 1988.
- Alles R, Parikh A, Hawk L, et al. The prevalence of atopic disorders in children with chronic otitis media with effusion. *Pediatr Allergy Immunol* 12:102–106, 2001.
- Mygind N, Dahl R, and Bachert C. Nasal polyposis, eosinophil dominated inflammation, and allergy. *Thorax* 55(suppl 2):S79–S83, 2000.
- Kuhn FA, and Swain R Jr. Allergic fungal sinusitis: Diagnosis and treatment. *Curr Opin Otolaryngol Head Neck Surg* 11:1–5, 2003.
- Farooque SP, and Lee TH. Aspirin-sensitive respiratory disease. *Annu Rev Physiol* 71:465–487, 2009.
- Awad OG, Fasano MB, Lee JH, et al. Asthma outcomes after endoscopic sinus surgery in aspirin-tolerant versus aspirin-induced asthmatic patients. *Am J Rhinol* 22:197–203, 2008.
- Modrzynski M, and Zawisza E. An analysis of the incidence of adenoid hypertrophy in allergic children. *Int J Pediatr Otorhinolaryngol* 71:713–719, 2007.
- Huang S-W, and Giannoni C. The risk of adenoid hypertrophy in children with allergic rhinitis. *Ann Allergy Asthma Immunol* 87:350–355, 2001.
- Yildirim N, Sahan M, and Karslioglu Y. Adenoid hypertrophy in adults: Clinical and morphological characteristics. *J Int Med Res* 36:157–162, 2008.
- Abdullah B, Hassan S, Sidek D, and Jaafar H. Adenoid mast cells and their role in the pathogenesis of otitis media with effusion. *J Laryngol Otol* 120:556–560, 2006.
- Ahmad N, and Zacharek MA. Allergic rhinitis and rhinosinusitis. *Otolaryngol Clin North Am* 41:267–281, v, 2008.
- Bascom R, Pipkorn U, Proud D, et al. Major basic protein and eosinophil-derived neurotoxin concentrations in nasal-lavage fluid after antigen challenge: Effect of systemic corticosteroids and relationship to eosinophil influx. *J Allergy Clin Immunol* 84:338–346, 1989.
- Bochner BS, and Schleimer RP. Mast cells, basophils, and eosinophils: Distinct but overlapping pathways for recruitment. *Immunol Rev* 179:5–15, 2001.
- Eliashar R, and Levi-Schaffer F. The role of the eosinophil in nasal diseases. *Curr Opin Otolaryngol Head Neck Surg* 13:171–175, 2005.
- Rosenberg HF, Phipps S, and Foster PS. Eosinophil trafficking in allergy and asthma. *J Allergy Clin Immunol* 119:1303–1310, 2007.
- Wardlaw AJ. Molecular basis for selective eosinophil trafficking in asthma: A multistep paradigm. *J Allergy Clin Immunol* 104:917–926, 1999.
- Chan KH, Abzug MJ, Coffinet L, et al. Chronic rhinosinusitis in young children differs from adults: A histopathology study. *J Pediatr* 144:206–212, 2004.
- Ponikau JU, Sherris DA, Kephart GM, et al. Striking deposition of toxic eosinophil major basic protein in mucus: Implications for chronic rhinosinusitis. *J Allergy Clin Immunol* 116:362–369, 2005.
- Iino Y, Nagamine H, Yabe T, and Matsutani S. Eosinophils are activated in middle ear mucosa and middle ear effusion of patients with intractable otitis media associated with bronchial asthma. *Clin Exp Allergy* 31:1135–1143, 2001.
- Hurst DS, and Venge P. The presence of eosinophil cationic protein in middle ear effusion. *Otolaryngol Head Neck Surg* 108:711–722, 1993.
- Hurst DS, Amin K, Sevéus L, and Venge P. Evidence of mast cell activity in the middle ears of children with otitis media with effusion. *Laryngoscope* 109:471–477, 1999.
- Bachert C, Vignola AM, Gevaert P, et al. Allergic rhinitis, rhinosinusitis, and asthma: one airway disease. *Immunol Allergy Clin North Am* 24:19–43, 2004.
- Bachert C, Wagenmann M, Hauser U, and Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. *J Allergy Clin Immunol* 99:837–842, 1997.
- Simon H-U, Yousefi S, Schranz C, et al. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. *J Immunol* 158:3902–3908, 1997.
- Bachert C, Gevaert P, Holtappels G, et al. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol* 107:607–614, 2001.
- Alobid I, Benítez P, Valero A, et al. The impact of atopy, sinus opacification, and nasal patency on quality of life in patients with severe nasal polyposis. *Otolaryngol Head Neck Surg* 134:609–612, 2006.
- Braunstaal GJ. The unified immune system: Respiratory tract–nasobronchial interaction mechanisms in allergic airway disease. *J Allergy Clin Immunol* 115:142–148, 2005.
- Beeh KM, Beier J, Kornmann O, et al. A single nasal allergen challenge increases induced sputum inflammatory markers in non-asthmatic subjects with seasonal allergic rhinitis: Correlation with plasma interleukin-5. *Clin Exp Allergy* 33:475–482, 2003.

47. Corren J, Adinoff AD, and Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* 89:611–618, 1992.
48. Braunstahl G-J, Overbeek SE, KleinJan A, et al. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 107:469–476, 2001.
49. Braunstahl G-J, Overbeek SE, Fokkens WJ, et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med* 164:858–865, 2001.
50. Frieri M. Neuroimmunology and inflammation: Implications for therapy of allergic and autoimmune diseases. *Ann Allergy Asthma Immunol* 90(suppl 3):34–40, 2003.
51. Sarin S, Undem B, Sanico A, and Togias A. The role of the nervous system in rhinitis. *J Allergy Clin Immunol* 118:999–1014, 2006.
52. Naclerio RM, Pinto J, deTineo M, and Baroody FM. Elucidating the mechanism underlying the ocular symptoms associated with allergic rhinitis. *Allergy Asthma Proc* 29:24–28, 2008.
53. Baroody FM, Mucha SM, deTineo M, and Naclerio RM. Nasal challenge with allergen leads to maxillary sinus inflammation. *J Allergy Clin Immunol* 121:1126–1132, 2008.
54. Baroody FM, Ford S, Proud D, et al. Relationship between histamine and physiological changes during the early response to nasal antigen provocation. *J Appl Physiol* 86:659–668, 1999.
55. Wagenmann M, Baroody FM, Cheng C-C, et al. Bilateral increases in histamine after unilateral nasal allergen challenge. *Am J Respir Crit Care Med* 155:426–431, 1997.
56. Sheahan P, Walsh RM, Walsh MA, and Costello RW. Induction of nasal hyper-responsiveness by allergen challenge in allergic rhinitis: The role of afferent and efferent nerves. *Clin Exp Allergy* 35:45–51, 2005.
57. Thurmond RL, Gelfand EW, and Dunford PJ. The role of histamine H1 and H4 receptors in allergic inflammation: The search for new antihistamines. *Nat Rev Drug Discov* 7:41–53, 2008.
58. Van Ganse E, Kaufman L, Derde MP, et al. Effects of antihistamines in adult asthma: A meta-analysis of clinical trials. *Eur Respir J* 10: 2216–2224, 1997.
59. Bousquet J, Demarteau N, Mullol J, et al. Costs associated with persistent allergic rhinitis are reduced by levocetirizine. *Allergy* 60: 788–794, 2005.
60. Busse WW. The role of leukotrienes in asthma and allergic rhinitis. *Clin Exp Allergy* 26:868–879, 1996.
61. Stewart RA, Ram B, Hamilton G, et al. Montelukast as an adjunct to oral and inhaled steroid therapy in chronic nasal polyposis. *Otolaryngol Head Neck Surg* 139:682–687, 2008.
62. Calderon MA, Alves B, Jacobson M, et al. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 1:CD001936, 2007.
63. Passalacqua G, and Durham SR. Allergic rhinitis and its impact on asthma update: Allergen immunotherapy. *J Allergy Clin Immunol* 119:881–891, 2007.
64. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. *J Allergy Clin Immunol* 123:763–769, 2009.
65. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: Adult sinusitis. *Otolaryngol Head Neck Surg* 137(suppl): S1–S31, 2007.
66. Calamita Z, Saconato H, Bronhara Pela A, and Atallah AN. Efficacy of Sublingual immunotherapy in asthma. Systematic review of randomized clinical trials. *Allergy* 61:1162–1172, 2006.
67. Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in children. Meta analysis of randomized controlled trials. *Ann Allergy Asthma Immunol* 97:141–148, 2006.
68. Penagos M, Passalacqua G, Compalati E, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 133:599–609, 2008.
69. Wilson DR, Torres L, and Durham SR. Sublingual immunotherapy for allergic rhinitis. *Allergy* 60:4–12, 2005.
70. Bousquet P, Cox LS, Durham SR, et al. Sub-Lingual Immunotherapy: World Allergy Organization Position Paper 2009. *World Allergy Organiz J* 2:233–281, 2009.
71. Marple BF, Fornadley JA, Patel AA, et al, and the American Academy of Otolaryngic Allergy Working Group on Allergic Rhinitis. Keys to successful management of patients with allergic rhinitis: Focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg* 136(suppl):S107–S124, 2007.
72. Mygind N, and Andersson M. Topical glucocorticosteroids in rhinitis: Clinical aspects. *Acta Otolaryngol* 126:1022–1029, 2006.
73. Naclerio RM, Adkinson NF Jr, Creticos PS, et al. Intranasal steroids inhibit seasonal increases in ragweed-specific immunoglobulin E antibodies. *J Allergy Clin Immunol* 92:717–721, 1993.
74. Marple BF. Targeting congestion in allergic rhinitis: The importance of intranasal corticosteroids. *Allergy Asthma Proc* 29:232–240, 2008.
75. Greenberger PA. Allergic rhinitis and asthma connection: Treatment implications. *Allergy Asthma Proc* 29:557–564, 2008.
76. Crystal-Peters J, Neslusan C, Crown WH, and Torres A. Treating allergic rhinitis in patients with comorbid asthma: The risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 109:57–62, 2002.
77. Adams RJ, Fuhlbrigge AL, Finkelstein JA, and Weiss ST. Intranasal steroids and the risk of emergency department visits for asthma. *J Allergy Clin Immunol* 109:636–642, 2002.
78. Fokkens W, Lund V, and Mullol J, on behalf of the European Position Paper on Rhinosinusitis and Nasal Polyps Group. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007: A summary for otorhinolaryngologists. *Rhinology* 45:97–101, 2007.
79. Slavin RG, Spector SL, Bernstein IL, et al. The diagnosis and management of sinusitis: A practice parameter update. *J Allergy Clin Immunol* 116(suppl):S13–S47, 2005.
80. Williamson IG, Rumsby K, Bengt S, et al. Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: A randomized controlled trial. *JAMA* 298:2487–2496, 2007.
81. Meltzer EO, Bachert C, and Staudinger H. Treating acute rhinosinusitis: Comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol* 116:1289–1295, 2005.
82. Joe SA, Thambi R, and Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 139:340–347, 2008.
83. Kalish L, Arendts G, Sacks R, and Craig JC. Topical steroids in chronic rhinosinusitis without polyps: A systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 141:674–683, 2009.
84. Zhang L, Mendoza-Sassi RA, César JA, and Chadka NK. Intranasal corticosteroids for nasal airway obstruction in children with moderate to severe adenoidal hypertrophy. *Cochrane Database Syst Rev* 3:CD006286, 2008.
85. Thomas CL, Simpson S, Butler CC, and van der Voort J. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. *Cochrane Database Syst Rev* 3:CD001935, 2006.
86. Tracy JM, Demain JG, Hoffman KM, and Goetz DW. Intranasal beclomethasone as an adjunct to treatment of chronic middle ear effusion. *Ann Allergy Asthma Immunol* 80:198–206, 1998.
87. Gleich GJ. Mechanisms of eosinophil-associated inflammation. *J Allergy Clin Immunol* 105:651–663, 2000. □

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