

# Allergic Rhinitis and the Unified Airway: A Therapeutic Dilemma

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## KEYWORDS

• Allergic rhinitis • Unified airway • Immunotherapy • Asthma

Within evidence-based clinical medicine/surgery, there has been an increased awareness that inflammatory diseases of the upper and lower airways act not as individual entities but more as an integrated unit. The pathophysiologic mechanisms that activate inflammatory cascades and release of systemic mediators stimulate all components of the respiratory tree, that is, nose, sinuses, and lungs—a unified airway (**Fig. 1**).<sup>1,2</sup> The notion of a unified airway suggests that distinct clinical diseases are not mutually exclusive of one another in a vacuum but act as part of a spectrum of respiratory disequilibrium throughout the upper and lower pulmonary tree.<sup>3,4</sup> An international surgical panel convened several years ago and developed a consensus statement, “...when preparing patients for surgery...considering a diagnosis of allergic rhinitis, rhinosinusitis, or asthma, an evaluation of both the upper and lower airways should be made.”<sup>3</sup> Treating the unified airway as an integrated unit may improve overall pulmonary function and health-related quality of life.<sup>3,4</sup>

The oral and maxillofacial surgeon sees patients who present with an array of airway comorbidities concurrently with oral and maxillofacial diseases. Three most frequently seen disease entities are AR, maxillary sinusitis (rhinosinusitis), and asthma. The following scenario is often presented:

*A patient has rhinorrhea, sneezing, nasal congestion, and itchy watery eyes in the spring, similar symptoms have occurred annually. Over-the-counter allergy pills have failed to improve symptoms and, when administered, cause dry mouth and somnolence. On physical examination, conjunctivae are injected and nasal mucous membranes are pale, wet, and*

*boggy, and, on auscultation of lungs, there is significant bronchial hyperactivity.*

The role/pathogenesis of AR in the unified airway is the focus of this article. The author attempts to provide an overview of AR and its association with upper and lower airway diseases in order to provide a further understanding of how AR acts as a catalyst supporting the unified airway concept. Allergic rhinitis (AR) is described in terms of its epidemiology, pathophysiology, and recent options for successful treatment that can be applied in everyday practice. (Rhinosinusitis and asthma are briefly addressed, and the reader is referred to the references throughout this text for further reading.)

## EPIDEMIOLOGY

Within the United States, numerous epidemiologic studies have shown AR to be a significant public health problem.<sup>5</sup> Prevalence rates have ranged between 15% and 40%, and the condition has been estimated to affect 20% of the adult population and 40% of the pediatric population.<sup>5,6</sup> There are approximately 17 million physician office visits annually with prescriptions, either by doctors or over the counter, that cost in excess of \$4.5 billion per year.<sup>7</sup> When health-related quality of life is measured, an estimated 3.8 million lost work and school days have been tallied and there is a statistically diminished quality of life when compared with the control, that is, the normal population.<sup>4,8</sup> It is evident that AR has a significant impact on societal production and everyday health in both adults and children.

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Oral Maxillofacial Surg Clin N Am 24 (2012) 205–217  
doi:[10.1016/j.coms.2012.01.012](https://doi.org/10.1016/j.coms.2012.01.012)

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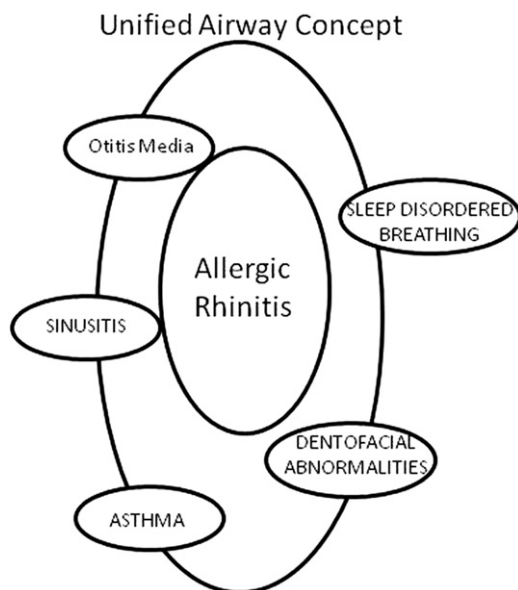


Fig. 1. Unified airway and AR.

There exist epidemiologic links among AR, rhinosinusitis, and asthma—an AR-rhinosinusitis-asthma cascade.<sup>9,10</sup> Rhinosinusitis affects 30 million people in North America. It accounts for an estimated \$2 to \$3 billion in health care costs annually, and patients spend approximately 150 million for products prescribed or recommended.<sup>11</sup> Yet, sinus infections are among the most frequently misdiagnosed and misunderstood diseases in clinical practice. Studies that have measured immune responses to various allergens and subsequent histopathologic sequelae in the nasal and paranasal sinuses hypothesize a model of pathogenesis of rhinosinusitis to be predicated on previous bouts of AR.<sup>12,13</sup>

The correlation of AR and asthma is significant. Asthma affects approximately 7% of the US population.<sup>6</sup> It has a significant economic impact annually of \$16 billion, of which \$11.5 billion are in direct costs, with \$5 billion as prescriptions. Indirect costs due to lost productivity account for greater than \$1.7 billion annually.<sup>14,15</sup> Asthma and AR occur together at a greater rate than each individually. Rates of patients who have both diseases range from 19% to 38%.<sup>11</sup> Multiple clinical studies using retrospective chart reviews have shown that AR is present in 50% to 85% of patients examined with asthma symptoms. In one study of 1245 patients, 52% of patients with asthma also were diagnosed with either seasonal or nonseasonal AR.<sup>9,10</sup> AR as a risk factor for asthma has been further tested within the United States and globally.<sup>16</sup> A study in Finland using questionnaires over 3 decades found that patients

who reported hay fever in 1975 had a 4-fold increased risk for asthma 15 years later. There was a sexual predilection, with women reporting a 6-fold increased risk for developing asthma 15 years after initial diagnosis with hay fever.<sup>17</sup> Halpern and colleagues<sup>18</sup> studied a claims database ( $n = 27,398$ ) of patients with asthma and concomitant AR. The presence of rhinitis was associated with more asthma medication and prescription costs. Dixon and colleagues<sup>19</sup> correlated the relationship among AR, sinusitis, and asthma using a database from the American Lung Association—Asthma Clinical Research Center. The investigators found that AR and rhinosinusitis were the 2 most common comorbid associated sequelae observed in patients with poorly controlled asthma. These 2 disease entities significantly influenced the symptoms of asthma as measured by histopathologic markers that were common to both diseases (see the section "Pathophysiology").

It is being examined if clinically diagnosed AR is more common in patients with asthma or if there is a more severe disease complex with both diseases. Although the epidemiologic databases mentioned earlier suggest compelling evidence linking AR to sinusitis and asthma, more prospective studies are needed to support this premise.

## PATHOPHYSIOLOGY

The pathophysiology of AR is a result of the immunologic response to 1 or more aeroallergens that interact with genetic factors. This may begin in utero and continue throughout the life of the individual. Shinohara and colleagues<sup>20</sup> suggested that symptoms of AR in women during early pregnancy are associated with a higher prevalence of AR in their offspring. Seasonal AR occurs as such during seasons of pollen production, tree blooming, and ragweed growing. This condition is characterized as hay fever. All 3 incite inflammatory cascades, eliciting specific symptoms (see sections on diagnosis and treatment). Nonseasonal AR or perennial AR is the result of exposure to animal dander, cockroaches, mold, and dust mites. This is the more chronic form of AR occurring annually.

Most aeroallergens are sized between 10 and 100  $\mu\text{m}$  and can be captured by the nasal mucosa.<sup>21,22</sup> The nose provides an effective filtering system for aeroallergens whose particles are 10  $\mu\text{m}$  in size. This effectiveness decreases when particles are between 1 and 2  $\mu\text{m}$ . It is not just the deposition of aeroallergens on the mucosa but the cascade of immunologic events that leads to the clinical expression of AR. Allergic sensitization and subsequent steps occur in a specific

cycle. This complex inflammatory cascade occurs in 2 phases, early and late. The allergen first interacts with a specific allergen-presenting cell that presents the allergen to a T-helper cell. The activated T cells then induce B cells to differentiate and produce immunoglobulin class E (IgE). The cornerstone of AR is an IgE-mediated type 1 hypersensitivity reaction to the aeroallergen. The allergen-specific IgE then enters the circulation to initiate the early phase of inflammation.<sup>22</sup> Mast cells and basophils undergo degranulation and release the acute phase inflammatory mediators, such as histamine, cytokines, leukotrienes, and chemokines. There is microvascular leakage, mucosal secretion, and edema and vasodilation. Clinical symptoms include rhinorrhea, lacrimation, sneezing, pruritus, and possible bronchospasm. This early phase occurs 10 to 30 minutes after allergen exposure.

The late phase of AR begins 2 to 6 hours later with the synthesis of new mediators, chemotaxis, and infiltration of eosinophils, neutrophils, basophils, lymphocytes, and macrophages. These cells migrate across the mucosal endothelium into the nasal submucosa. This is clinically expressed as nasal congestion and end organ damage. With repetitive exposure, this condition occurs with a less amount of allergen.<sup>22</sup>

The pathologic similarities of AR, rhinosinusitis, and asthma have their basis in the commonality of the histology of their mucosa. The respiratory lining from the nasal cavity, paranasal cavity, larynx, trachea, and bronchi consists of a pseudostratified ciliated columnar epithelium. The inflammatory infiltrates of mononuclear cells, eosinophils, and other cells appear in both the nasal and bronchial mucosa. The distribution of acute phase reactants, that is, cytokines and other inflammatory mediators, is identical in both AR and asthma, as well as in rhinosinusitis.<sup>23,24</sup> **Box 1** depicts the commonality of histopathology among AR, rhinosinusitis, and asthma.<sup>25</sup> Although these similarities are present, there are morphologic differences on exposures. The vascular engorgement of nasal mucosa is related to changes in capacitance and mucosal edema. The histopathologic condition of asthma is predicated on alterations of the basement membrane and epithelium and hypertrophy of bronchial smooth muscles. A significant similarity between AR and asthma is related to the presence of bronchial hyperactivity in patients with AR who have never been diagnosed with asthma.<sup>26</sup> Forty-eight percent of patients with AR exposed to methacholine during their allergy season exhibited significant bronchial hyperactivity when compared with control groups. A study by the European Community Respiratory health survey

#### Box 1

##### Common histopathologic conditions of AR, rhinosinusitis, and asthma

Eosinophil infiltration

Basement membrane thickening

Lymphocyte infiltration

Epithelial cytoarchitecture changes

Subepithelial edema

RANTES (regulated on activation, normal T cell expressed and secreted)

Presence of inflammatory mediators: cytokines such as IL-4, IL5, IL-13

Goblet cell hyperplasia/excessive mucous production

*Data from Krouse JH, Brown RW, Fineman, et al. Asthma and the unified airway. Otolaryngol Head Neck Surg 2007;136:S75–106.*

showed self-reporting nasal allergies as an independent predictor of bronchial hyperactivity (odds ratio, 2.2–6.7).<sup>27</sup>

Rhinosinusitis and asthma also have identical histopathologic similarities. Given that the lining of the respiratory epithelium is identical, the remodeling with exposure to allergens is quite similar. However, the smooth muscle changes seen with asthma are unique. Aside from this, there are identical histopathologic cascades between both. The hallmark of chronic inflammation seen is an eosinophil-mediated process. Studies have identified the main effector cell as the eosinophil.<sup>28</sup> Numerous eosinophils are found in the nose of asthmatic patients with or without nasal symptoms. Significant numbers of eosinophils, however, are also seen in patients with rhinosinusitis, AR, and asthma when compared with mild cases of rhinosinusitis.<sup>29</sup>

The pathophysiologic connections discussed here lend support for a commonality of disease cascades among AR, rhinosinusitis, and asthma, supporting a unified airway concept. Further clinical investigations, however, are being done to determine whether a single disease is being manifested or not.

#### Samter Triad

Many oral/maxillofacial surgeons have seen patients who present with Samter triad. The historic characteristics of bronchial asthma, nasal polypsis, and intolerance to aspirin and related chemicals, recently designated as Samter syndrome, are an inflammatory condition of unknown etiology

and pathogenesis.<sup>30</sup> The condition is probably acquired, perhaps secondary to a viral infection, but a hereditary factor may be important in some patients.<sup>30</sup> Most patients with this syndrome are adults, with an occasional case being identified in a teenager or an older child. Although not every patient has the fully developed syndrome, the typical patient has all 3 of the classic features.

The clinical presentation begins initially with nasal congestion and rhinorrhea, often mistaken as a recurrent cold. The rhinitis becomes chronic with new onset of sinusitis, followed by the development of chronic rhinosinusitis and the formation of nasal polyps. These symptoms appear within the fourth decade of life. Sensitivity to aspirin occurs within 1 to 5 years after the onset of symptoms with initial acute asthmatic attacks that may be life threatening, profuse rhinorrhea, orbital edema, and facial flushing.<sup>15,31</sup>

Many patients with Samter syndrome also have a marked eosinophilia of both bronchial and nasal secretions as well as the circulating blood. Approximately 10% of the patients have urticaria and/or angioedema, alone or in combination with respiratory inflammation. The histopathologic condition is similar to that seen for chronic asthma, with a 4-fold increase in eosinophils compared with aspirin-tolerant and normal controls.<sup>31</sup>

The pathophysiology of this sensitivity is not an IgE-mediated pathway but an alteration in arachidonic acid metabolism followed by inhibition of cyclooxygenase and lipoxygenase pathways that decrease the levels of antiinflammatory prostaglandins. The latter mechanism results in high levels of leukotriene, leading to severe inflammation.<sup>31,32</sup>

Avoidance of aspirin-containing products is stressed, as well as other nonsurgical and surgical therapy (see section on treatment later).

## DIAGNOSTIC STRATEGIES FOR AR

### *Diagnosis*

As stated earlier, AR poses a significant burden of illness on society. Patients complain of fatigue, headaches, loss of sleep, inability to concentrate, and loss of productivity. The physician must acquire a thorough history of the present illness (HPI).

Important considerations include number of bouts with AR; time of the year, that is, seasonal or perennial; precipitating factors that trigger attacks, whether it occurs at work or in the home; the presence of pets; exposures to new environment; and food.

The HPI should also include a history of contact dermatitis; mucociliary dysfunction, whether acute or associated with systemic manifestations; Kartagener syndrome; or cystic fibrosis in the family.

Autoimmune phenomena should be addressed with conditions such as rheumatoid arthritis, Crohn disease or gastroesophageal reflux disease, adolescent histories of tonsillectomy, adenoidectomy, placement of tubes in the ear, and exacerbations of sinusitis or bronchohyperactivity.<sup>33</sup>

### *Physical Examination*

There are several physical findings associated with AR. **Box 2** depicts the common symptoms/physical findings. The physical examination includes an intranasal examination with a nasal speculum that reveals mucosa with hyperemia. Auscultation may characterize wheezing, suggestive of associated asthma. Spirometry is useful in detecting subclinical asthma and bronchial hyperactivity.<sup>22,34</sup> Additional laboratory work may be helpful if the diagnosis is uncertain. Blood or nasal eosinophilia suggests an allergic cause, whereas neutrophilia points to an infectious cause. Allergic shiners are often seen, as well as sinus tenderness and pressure on palpation. Computed tomography most reliably reveals sinusitis in patients with symptoms of refractory rhinitis. Otoscopic examinations of the tympanic membranes are judicious because there is recurrent otitis media, as well as perforations, clouding, retraction of the eardrums, and cholesteatomas.<sup>22</sup>

Additional testing may be helpful if the diagnosis is uncertain or equivocal (see later). The severity of AR is assessed by assigning numerical values for eyes symptoms, nasal itching, sneezing, rhinorrhea, and nasal congestion (with 0 denoting none; 1, mild; 2, moderate; and 3, severe), taking into account subjective intensity and whether these symptoms interfere with sleep, leisure, and school or work activities or the duration of symptoms each day (with 0 denoting none, 1, <30 minutes; 2, 30 minutes to 2 hours; and 3, >2 hours).<sup>34,35</sup> These criteria are a valuable sedge way to measure antigen sensitivity objectively.

### *Additional Workups/Testing*

The confirmation of the IgE-mediated type1 Gell and Coombs reaction of AR provides the opportunity for efficiency in treatment strategies, that is, pharmacotherapy, immunotherapy, and avoiding offending environmental allergens.<sup>36</sup> Some current tests confirming allergy sensitivities are described.

### *Skin testing*

Since 1873, the use of skin as a test organ has stood the standard test of time. The skin's abundance, visibility, and accessibility afford numerous therapeutic options/treatment strategies.<sup>37</sup> The use of skin as a bioassay can allow for the option

**Box 2**  
**Symptoms and physical findings for AR**

*Symptoms*

**Nasal**

- Sneezing
- Rhinorrhea
- Pruritus
- Impairment of smell
- Congestion
- Eustachian tube dysfunction

**Nonnasal**

- Lacrimation
- Conjunctivitis
- Fatigue
- Depression
- Headaches
- Midface pressure
- Palatal pruritus

*Physical findings*

**Nasal**

- Turbinate hypertrophy/congestion

**Ocular**

- Allergic shiners due to venous stasis from persistent nasal congestion/lower eyelid edema
- Conjunctivitis
- Dennie lines: creases in the lower eyelids from Mueller muscle spasms
- Allergic lashes

**Dental/other**

- Crowded teeth/high arch palates
- Dental tooth pain
- Vocal cord edema
- Adenoid hypertrophy

*Data from Ahmad N, Zacharek MA. Allergic rhinitis and rhinosinusitis. Otolaryngol Clin North Am 2008; 41(2):267–81.*

of immunotherapy because allergen-specific immunotherapy can result in significant improvements for allergic nasal, ocular, and bronchial symptoms. Specifically, the clinician can challenge the patient’s sensitivity using multiple dosing/strengths to improve sensitivity and specificity, which decreases false-negative findings.

Allergens can be identified by skin or in vitro tests for the presence of allergen-specific IgE

antibodies (**Box 3** depicts examples of the most common tests). These allergens that are tested provide the same antigen extracts that will be used in immunotherapy.<sup>36</sup>

**Intradermal testing** Intradermal or intracutaneous testing involves the injection of the liquid allergen at specific dilutions into the dermis. A wheal of 4 mm results, just like a tuberculin test. This dilution contacts subepithelial mast cells that form an IgE-mediated reaction. If the patient was previously sensitized, mast cell degranulation occurs and the wheal expands over a period of 10 to 20 minutes. If the measurement increases from 4 to 7 mm or more, the test result is considered positive. Caution must be exerted while interpreting because there can be false-positives and false-negatives due to cross-reactivity with medications that the patient may be taking; skin sensitivity, such as eczema, urticaria, and other dermatologic problems; and glycerin sensitivity because the dilutions contain glycerin.<sup>38</sup> There are single and multidermal intradermal dilution testing.

The benefits of this technique lie in its ability to be qualitative and quantitatively sensitive/specific. Multiple samplings give greater accuracy and safety when evaluating the degree of allergy sensitivity. More importantly, they provide a methodological pathway for a safe starting dose of immunotherapy.<sup>39</sup>

**Box 3**  
**Tests for IgE-mediated respiratory allergy sensitivity**

*Skin tests*

- Intracutaneous
- Intradermal dilution, single/whole
- Epicutaneous tests, prick/puncture with single or multiple antigens

*End organ provocation*

- Nasal provocation
- Bronchial provocation
- Conjunctival provocation

*In vitro serologic test: measuring aeroallergen-specific IgE*

- Radioisotope labeling
- Enzyme-linked labeling
- Fluorescence labeling

*Data from Haydon RC. Allergic rhinitis—current approaches to skin and in vitro testing. Otolaryngol Clin North Am 2008;41(2):331–46.*

**Epicutaneous testing** These testing methods were the earliest in determining the sensitivity of allergens. The scratch tests involved placing of the allergen on abraded skin surfaces with equivocal results. Patch testing has been a replacement for chemical sensitivity, and both have been largely replaced by prick/puncture testing.<sup>36,39</sup> The latter approach has become the most often choice for the diagnosis of an IgE-mediated sensitivity. Prick/puncture begins with a drop of allergen on the skin, followed by a puncture through the epidermis only. Multiple antigens can be tested at the same time, and the skin responses are read within 20 minutes.<sup>36</sup> Areas of choice for testing vary from the upper back to volar surfaces of the arms and anterior thighs. Each puncture is about 2 cm from the previous and is compared with controls, which are usually 50% glycerin as a negative control and 50% glycerin with histamine as a positive control. The clinician measures the wheals after 20 minutes, and a positive response is 3 mm or more. The prick/puncture technique is quick, easy, and safe, with good sensitivity and specificity.

**In vitro testing** In vitro tests for serum IgE antibody to allergens, including varieties of the radioallergosorbent test and enzyme-linked immunosorbent assay, estimate the amount of allergen-specific IgE antibody in a patient's skin. The sensitivity and specificity are equal to that of skin testing.<sup>34,36</sup> The benefits are a single venipuncture, the safety avoidance of cross-reactivity of other medications that the patient may be on, as well as any skin conditions that may exist that can exacerbate the reactions between antigen and IgE-mediated hypersensitivity. The scoring is determined by the intensity of measurements of labeled IgE antibody complexes in the serum. Classes based on 0 to 5 are then interpreted, with class 5 being the most intense reaction, that is, high antibody titers and therefore high allergic sensitivity.<sup>40</sup> These highly sensitive patients can be managed appropriately to avoid any anaphylactic reactions and allow the choosing of appropriate dilution of immunotherapeutic agents.

## TREATMENT STRATEGIES FOR AR

The goal of treatment strategies depend on an integrated algorithm based on a cascade of immune responses: (1) an early phase, whereby histamine is released with the resultant acute symptoms of sneezing, itching, rhinorrhea, and congestion, and (2) the late phase, which is mediated by T-cell cytokines of interleukins 4 and 5. This occurs up to 2 hours and involves the infiltration of

eosinophils and basophils with more significant rhinorrhea and congestion.<sup>34</sup>

Three main approaches of treatment that are most efficacious against AR are environmental exposure monitoring, pharmacotherapy, and immunotherapy.

### *Environmental Exposure Monitoring*

Environmental control of allergens, both indoors and outdoors, does remain a cornerstone in the preventive therapy for AR. Allergy testing (see earlier) is a valuable place to begin so that both the clinician and the patient can derive a strategy for avoidance/early intervention.<sup>41</sup>

### *Indoor allergens*

Indoor allergens, such as mold, dust mites, and cockroaches, were measured by randomized controlled clinical trials. A trial in 2007 with asthmatic patients showed that eradication of molds significantly reduced attacks.<sup>41</sup> Protocols were developed that included algorithms that were practical and easy to undertake. Limited studies reviewed in a meta-analysis on avoiding house dust mites using high-efficiency particulate air filters (in 1 study), acaricides (in 2 studies), and mattress covers and hot water laundering of bedding (in 1 study) demonstrated that active treatment reduced both levels of house dust mites and rhinitis symptoms.<sup>34,41</sup>

Cockroach sensitization once identified can be eradicated by multiple baits, food monitoring for cleanliness, and traps. Although ventilation is a good way to eradicate indoor allergens, cockroach antigens are not airborne but are heavy and settle into areas that are difficult to keep clean.<sup>41</sup>

### *Outdoor allergens*

It is difficult to perform randomized controlled trials for outdoor allergens, and so a practical approach from wearing protective clothing when gardening to not mowing the lawn during heavy pollen seasons should be adopted. Warm days are associated with high pollen counts, and so outdoor activities need to be monitored.

### *Pharmacotherapy*

Certain classes of drugs have preferential effects against both early- and late-phase symptoms of AR (**Tables 1** and **2**).

### *Antihistamines*

Antihistamines were introduced more than 40 to 50 years ago for the treatment of AR. Their mechanism was to decrease the release of histamine by functioning as a competitive antagonist for the histamine 1 receptor on the target cells of the

**Table 1**  
Pharmacologic agents and their effect on the symptoms of AR

| Agent                      | Sneezing | Itching | Congestion | Rhinorrhea | Ocular Symptoms |
|----------------------------|----------|---------|------------|------------|-----------------|
| Oral antihistamines        | +++      | +++     | ±          | ++         | +++             |
| Nasal antihistamines       | ++       | ++      | ++         | +          | —               |
| Intranasal corticosteroids | ++       | ++      | +++        | ++         | +               |
| Leukotriene modifiers      | +        | +       | +          | +          | +               |
| Oral decongestants         | —        | —       | +++        | —          | —               |
| Nasal decongestants        | —        | —       | +++        | —          | —               |
| Mast cell stabilizers      | +        | +       | ±          | +          | —               |
| Topical anticholinergics   | —        | —       | —          | +++        | —               |

+++ , marked benefit; ++ , substantial benefit; + , some mild benefit; ± , questionable benefit; — , no benefit.

Adapted from Krouse JH. Allergic rhinitis—pharmacotherapy. Otolaryngol Clin North Am 2008;41(2):357; with permission.

mucosa of nose, conjunctiva, and lung. The ability to act as a competitive antagonist allowed a decrease in histamine-driven symptoms, that is, rhinorrhea.<sup>34,42</sup> Although clinically effective, antihistamine use was limited by adverse anticholinergic and sedative effects because of the ability of antihistamines to cross the blood-brain barrier, leading to impaired task performance

secondary to psychomotor and cognitive impairment. Furthermore, these first-generation agents had significant anticholinergic effects such as xerostomia and blurred vision.

Over the past 30 years, second-generation antihistamines have been developed with better safety profiles. These newer agents do not readily cross the blood-brain barrier and, therefore, lack the

**Table 2**  
Pharmacological agents categorized by their generic and brand names

| Agent                             | Generic Drug Name                                                                                           | Brand Name <sup>R</sup>                                                        |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| <i>Oral Antihistamines</i>        | Diphenhydramine<br>Hydroxyzine<br>Chlorpheniramine<br>Loratadine <sup>*</sup><br>Fexofenadine<br>Cetirizine | Benadryl<br>Atarax<br>Chlor-Trimetron<br>Claritin/Alavert<br>Allegra<br>Zyrtec |
| <i>Nasal Antihistamines/</i>      | Azelastine                                                                                                  | Astelin/Optovar                                                                |
| <i>Ophthalmic Antihistamine</i>   | Olopatadine                                                                                                 | Pataday/Patanol                                                                |
| <i>Intranasal corticosteroids</i> | Beclomethasone dipropionate<br>Budesonide<br>Flunisolide<br>Fluticasone                                     | Vancenase<br>Pulmocort<br>Nasalide<br>Flonase                                  |
| <i>Leukotriene modifiers</i>      | Zileuton<br>Montelukast<br>Zafirlukast                                                                      | Zyflo<br>Singulair<br>Accolate                                                 |
| <i>Oral decongestants</i>         | Pseudoephedrine<br>Phenylpropanolamine                                                                      | Sudafe/Novafed<br>Accutrim/Propalin                                            |
| <i>Nasal decongestants</i>        | Oxymetazoline                                                                                               | Afrin/Sudafed OM                                                               |
| <i>Mast Cell Stabilizers</i>      | Cromolyn sodium                                                                                             | Nasal crom                                                                     |
| <i>Topical anti-cholinergics</i>  | Ipratropium bromide<br>Ipratropium + Albuterol                                                              | Atrovent/Aeopvent<br>Combivent                                                 |
| <i>Mucolytics</i>                 | Guaifenisin                                                                                                 | Mucinex/Humibid                                                                |

Abbreviation: R, reserved patent drug company.

substantial sedative capability of first-generation drugs. The ability of these agents to significantly interact with central histamine 1 receptors provides for excellent efficacy of the mucosa barrier, which reduces symptoms of nasal itching and watery eyes without impairment of psychomotor function.<sup>42</sup> Terfenadine was the first antihistamine used, although it was withdrawn from the market because of its liver toxicity.<sup>42</sup> Loratadine has been used since the mid-1990s. It is available both as a prescription and an over-the-counter drug. Loratadine is nonsedating at low doses and does not impede liver enzyme activity. Fexofenadine is another agent that has grown in favor since 2005. Although its parent was terfenadine, fexofenadine lacks cardiotoxic capabilities and impediment of liver enzymes. Clinical studies that compared second-generation antihistamines demonstrated equivalence in the reduction of symptoms, with only a small degree of equivocal relationships.<sup>34,42</sup>

The third-generation drugs have been in use since the mid-1990s. Cetirizine, a metabolite of hydroxyzine, has excellent efficacy in allergy-driven symptoms. It has been recently released as an over-the-counter medication safe in doses of 10 mg/d. Over the past few years, desloratadine and levocetirizine have gained favor for the treatment of nasal congestion associated with AR. Clinical studies have shown levocetirizine to have a great efficacy in treating all symptoms of AR, including nasal congestion with minimal sedating effects.<sup>43</sup>

Topical antihistamines, such as azelastine, in conjunction with a topical nasal corticosteroid (see later) are beneficial, rapid, and efficacious in reducing nasal and eye symptoms when compared with oral cetirizine.<sup>44</sup> More studies on the efficaciousness of nasal antihistamines are being evaluated.<sup>34</sup>

### ***Intranasal corticosteroids***

Corticosteroids are well known as antiinflammatory medications affecting a variety of cellular mediators in the inflammatory cascade. Topical intranasal corticosteroids are very efficacious in the treatment of moderate to severe AR.<sup>34</sup> The safety profiles of these agents have been evaluated with respect to their systemic effects on growth. A 1-year prospective clinical trial with intranasal mometasone furoate and fluticasone showed no suppression of growth in patients.<sup>34</sup> The bioavailability of nasal corticosteroids is minimal because the amount that is absorbed from the nasal mucosa to the circulation is miniscule.<sup>45</sup> The mechanism of action of nasal corticosteroids occurs mostly during the late phase of AR by acting on T-cell cytokines and eosinophils

as well as during the early phase. Symptoms, including nasal congestion, are better relieved by nasal and oral antihistamines and nasal corticosteroids with respect to symptoms of AR. There was a clinically and statistically significant benefit to nasal corticosteroids over antihistamines for nasal congestion and sneezing.<sup>34,45,46</sup>

Nasal corticosteroids have relatively few adverse effects. The most common effect is epistaxis, which occurs in 10% of cases. Caution is taken when using these agents in terms of timing of doses. They are usually prescribed for 1 to 2 times per day depending on the circumstance. The Food and Drug Administration (FDA) has approved 8 types of medications, beclomethasone, which has grown out of favor because of issues of growth suppression; fluticasone propionate; and mometasone. Increased intraocular pressure and posterior subcapsular cataracts have been reported in adults. However, these complications are less likely with doses administered intranasally.<sup>34,46,47</sup>

### ***Decongestants***

Decongestants are used both topically and orally to decrease nasal vascular congestion and improve nasal airflow. Their mechanism of action is based on  $\alpha_1$ -adrenergic and  $\alpha_2$ -adrenergic pathways that reduce blood flow within venous capillaries of the nasal and inferior turbinate mucosa. The most commonly prescribed decongestant is pseudoephedrine, which is now restricted because of its ability to be transformed into methamphetamine. The addition of phenylephrine to the formula has helped. In 2001, phenylpropanolamine was also taken off the counter because of the risk of stroke in women. As such, caution must be rendered when prescribing oral decongestants. Even in nonsusceptible patients, side effects such as jitteriness, insomnia, restlessness, and tremulousness must be addressed. Patients who have hypertension and urinary retention are at risk. Topical decongestants are available over the counter, but care must be rendered regarding their efficacy. Hypoxic injury of the nasal mucosa is seen occasionally; rhinitis medicamentosa causes a dependency on nasal medication. These effects may be reversed with nasal corticosteroids if monitored carefully.<sup>42</sup>

### ***Leukotriene receptor antagonists***

This group of drugs antagonizes the potent antiinflammatory mediators for the late-phase allergic responses. These antagonists consist of cysteinyl leukotrienes that are released by basophils and mast cells when exposed to antigens, causing an increase in 5-OH-lipoxygenase and the synthesis of active metabolites such as leukotriene D<sub>4</sub>, E<sub>4</sub>,

and C4. There are a limited number of medications available that are approved by the FDA. Zileuton is used off label for AR and nasal polyps.<sup>42</sup> Another antagonist being used extensively for AR is montelukast. It has been shown to be superior to placebo in relieving nasal symptoms in patients with AR.<sup>48</sup> A meta-analysis demonstrated that, compared with placebo, montelukast induced a moderate but significant reduction in scores for daily symptoms of rhinitis, whereas nasal corticosteroids induced a significant and substantial reduction in symptom scores. This suggests that the role of montelukast is generally as an adjunct in the treatment of a patient who does not have an adequate response to an antihistamine, a nasal corticosteroid, or both.<sup>34,42,48</sup> It can therefore be used in combination therapy.

### **Mast cell stabilizers, topical anticholinergic, and mucolytics**

**Mast cell stabilizers** Cromolyn sodium is an over-the-counter nasal medication whose mechanism is to decrease calcium influx to mast cells when they bind to antigen. This prevents the degranulation of cells to release histamine. Cromolyn may be more effective when administered just before exposure to an allergen and so is valuable as a prophylactic medication when patients are anticipating an exposure to an antigen.

**Topical anticholinergic** The one topical agent used is ipratropium bromide. It is used nasally in patients with AR. The drug acts on the parasympathetic tone of the mucosa, with a concomitant decrease in rhinorrhea. It is used with other medications to

decrease the nasal discharge when exposed to allergen.

**Mucolytics** Mucolytics act to decrease the tenacity of nasal secretions. Guaifenesin has been shown to be efficacious because it acts as a vagal stimulant at doses of 2400 mg/d.<sup>49</sup> There is equivocal evidence to support significant improvement in patients with AR, although results may be beneficial for pulmonary secretions.<sup>42</sup>

### **Monoclonal antibody therapy**

There has been much research on the use of monoclonal antibodies for pulmonary diseases refractory to the medications stated earlier. Anti-IgE antibody, omalizumab, has been used to treat asthma refractory to corticosteroids. The mechanism interferes with antigen binding to the mast cell. Although clinical trials show success, it is not a cost-effective treatment (\$10,000 annually) of refractory AR.<sup>50</sup>

The various pharmacotherapeutic options mentioned are predicated on their physiologic ability to alter the mechanisms of action during the early and late phases of AR. **Fig. 2** and see **Table 1** depict the complexity of each phase and the importance of an integrated approach for the most effective management strategies. These options only serve as an adjunct with other treatments to maximize relief from AR.

### **Immunotherapy for AR**

The use of immunotherapy is predicated on patients who are refractory to both environmental control and pharmacotherapy, who require systemic

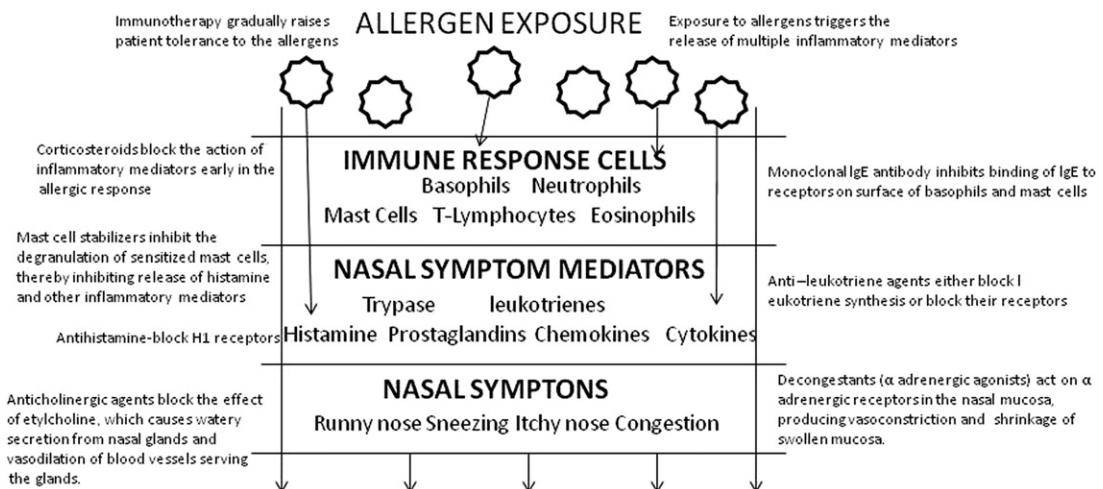


**Fig. 2.** Mechanisms/cascades of AR and medicine action at each level. (Adapted from Marple BF, Fornadley JA, Patel AA, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg* 2007;136:S112; with permission.)

corticosteroids, who are refractory to the recommended doses of nasal corticosteroids, or who have coexisting conditions such as sinusitis, asthma, or both. This section is divided into 3 units: immunologic mechanisms of immunotherapy, injection immunotherapy, and sublingual immunotherapy (SLIT).

### ***Immunologic mechanisms***

A common parameter for investigating how immunotherapy affects immune function is the measurement of serum antibody levels. The predominant class of immunoglobulin is IgG, and, with immunotherapy, there are increases in allergen-specific IgG antibodies. These proteins act as blocking antibodies to prevent allergens from binding to IgE on both mast cells and basophils. Anti-IgG prevents transmembrane signal transduction and degranulation of histamine from mast cells/basophils.<sup>51</sup> The main subset of IgG is IgG1, the levels of which increase rapidly at first when therapy begins but taper off in the first few months of immunotherapy. IgG also inhibits antigen presentation, so a higher concentration of antigen is necessary to induce T-cell proliferation and cytokine release.<sup>52</sup>

Although IgE levels increase in the serum over the first few months of immunotherapy, they decrease to suboptimal levels by 2 years. Symptom change seen in AR seems to be correlated with this increase and decrease. Immunotherapy can also stimulate B cells to increase production of immunoglobulin classes A and M, causing an increase in tolerance to allergen exposure by patients.<sup>51</sup>

The next 2 sections describe the vehicles of immunotherapeutic administration: injection and SLIT.

### ***Injection immunotherapy for AR***

Subcutaneous allergen immunotherapy consists of an open-ended schedule of weekly doses of a solution containing the culpable allergens that gradually increase to an optimal maintenance dose.<sup>34,52,53</sup> Maintenance doses are often given at intervals ranging from 2 to 6 weeks; data are lacking to compare various dosing frequencies. Numerous meta-analyses and systematic reviews have been written that support the efficacious effect of subcutaneous injection immunotherapy.<sup>51</sup> A Cochrane systematic review was recently published that scrutinized 51 studies for seasonal allergies. In 15 studies, there were 1645 participants receiving immunotherapy and 1226 receiving placebo. The meta-analyses showed an overall significant reduction in symptom scores as measured by a standard mean difference in all 15 studies after completion of subcutaneous immunotherapy

( $P < .0001$ ).<sup>53</sup> The same systematic review was analyzed for bronchial and ocular symptoms, as well as rhinosinusitis quality-of-life measurements. The results were again significant with reduction in symptom scores.

These reviews support the premise that allergen-specific immunotherapy can decrease allergen symptoms. A systematic review by Calderon and colleagues<sup>53</sup> supports this premise, although, the data lacked samples from pediatric population. This finding suggests that caution must be rendered when applying immunotherapy within this population until more definitive clinical trials are evaluated.<sup>34,44,51,52</sup> Immunotherapy, however, may also confer long-term benefits for AR in that it alters the natural history of the disease. The reviews mentioned reported adverse reactions as local or systemic. The local reactions were analyzed in 30 studies, with approximately 10% requiring treatment: 208 in active treatment and 186 in the placebo group.<sup>51–53</sup>

The systemic reaction was reviewed in 33 studies and graded based on a consensus paper. Reactions are graded from 1 to 4, with 1 being mild to 4 being anaphylactic shock. Although the majority in the sample had mild reactions, the rate of systemic reactions can range for 0.05% to 2.9%, with 1 fatality per 2 million injections.<sup>51,54</sup> Approximately 5% to 10% of patients who receive allergen immunotherapy have systemic reactions, which are moderately to severe in 1% to 3% of patients; rarely, patients have even died of anaphylaxis.<sup>34,51,53</sup>

### ***SLIT for AR***

The use of SLIT in the treatment of AR has been researched over the last 2 decades. Meta-analyses on the efficacy/safety of SLIT have been mostly from studies in Europe. Wilson and colleagues<sup>55</sup> published a large meta-analysis on the efficacy of SLIT in AR. Symptom severity scores were measured, and results showed a significant decrease in rhinitis and need for any medications. A meta-analysis done by Penagos and colleagues<sup>56</sup> revealed a significant reduction in symptom severity with SLIT in the pediatric population. The period to 18 months showed the greatest efficacy, suggesting longer treatment of AR when it involves seasons, that is, pollen versus dust mites. The former study by Wilson and colleagues, however, did not see such significance and suggested that it is because of smaller pediatric sample size.<sup>51,56</sup> Although SLIT seems to be very effective as a method for immunotherapy in children and adults, more studies with larger sample sizes are needed.

**Box 4****Treatment guidelines for patients with AR**

1. Verify the cause of allergic symptoms with the use of history and tests
2. Reduce exposure to allergens
3. Start an inhaled nasal corticosteroid, an oral second-generation antihistamine, or both
4. For resistant nasal symptoms, add a leukotriene receptor antagonist; for resistant itching or tearing eyes, add an ocular antihistamine, mast cell stabilizer, or nonsteroidal antiinflammatory drug
5. Consider immunotherapy if quality of relief with medication is inadequate to forestall progression of disease or if patient is affected by allergy-induced complications, such as sinusitis and asthma

*Adapted from Plaut M, Valentine MD. Allergic rhinitis. N Engl J Med 2005;353:1934–44; with permission.*

SLIT has been shown to have a good safety profile. Although mild oral and sublingual itching occurs, there have been no reports of systemic reactions to this therapy. The rarity of systemic reactions suggests that this therapy is safer than subcutaneous immunotherapy. There were a few trials that showed adverse events on oral and gastrointestinal sequelae, but none were characterized as anaphylactic.<sup>51</sup> With respect to the pediatric population, SLIT is safer than injection therapy.<sup>51,56</sup> With the evidence presented, it seems that there is a significant role for immunotherapy in preventing the progression of allergen damage. Further studies are being developed to determine whether there is a place for prophylactic immunotherapy in the treatment of AR. In addition, further work is underway to evaluate the efficacy and safety of such therapies and to determine whether the preparation of large numbers of anti-immunoallergens is feasible.<sup>34,56</sup>

## SUMMARY/FUTURE DIRECTIONS

Five sets of guidelines for treatment of AR have been developed from expert panels, 2 in the United States and 3 in Europe (**Box 4**). This approach has been used with some success.<sup>57,58</sup> AR, however, only represents one link/catalyst in the spectrum of inflammatory diseases involved in the unified airway. It is an illness of great health expenditure, significantly affecting the health and well-being of those who are susceptible. The clinician must carefully evaluate the symptoms of AR, as well as associated comorbidities throughout the upper and lower airway, to avoid inappropriate

management. There are risk-to-benefit ratios to be weighed when considering therapeutic intervention. The pursuit of further evidence relating to the clinical application of immunotherapy should be a future priority in evidence-based clinical decisions.

## REFERENCES

1. Krouse JH. The unified airway—conceptual framework. *Otolaryngol Clin North Am* 2008;41(2):257–66.
2. Passalacqua G, Ciprandi G, Canonica GW. United airway diseases: therapeutic aspects. *Thorax* 2000;55:26–7.
3. Bousquet J, van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma (ARIA); executive summary of the workshop report. *Allergy* 2002;57:841–55.
4. Ahmad N, Zacharek MA. Allergic rhinitis and rhinosinusitis. *Otolaryngol Clin North Am* 2008;41:267–81.
5. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines for the joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998;81:478–518.
6. Meltzer EO. The relationship of rhinitis to asthma. *Allergy Asthma Proc* 2005;26:336–40.
7. Summary of health statistics for US adults: National Health Interview Survey, 2002. Available at: <http://www.cdc.gov/nchc/fastats/allergies.htm>. Accessed August, 2008.
8. Kremer B. Quality of life scales in allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2004;4:171–6.
9. Yawn BP, Yunginger JW, Wollan PC, et al. Allergic rhinitis in Rochester, Minnesota, residents with asthma: frequency and impact on health care changes. *J Allergy Clin Immunol* 1999;103:54–9.
10. Ryan MW. Asthma and rhinitis: comorbidities. *Otolaryngol Clin North Am* 2008;41:283–95.
11. Halpern LR, Martin RA, Carter JB. Pharmacotherapeutics of rhinosinusitis: treatment protocols in the adult and pediatric population. *Oral and Maxillofacial Surgery Clinics of North America*. Philadelphia: W. B. Saunders; 2000.
12. Yaritkas M, Doner F, Demirci M. Rhinosinusitis among the patients with perennial or seasonal allergic rhinitis. *Asian Pac J Allergy Immunol* 2003;21:75–8.
13. Zacharek M, Krouse J. The role of allergy in chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2003;11:196–200.
14. Weiss KB, Sullivan SD, Lyttle CS. Trends in the cost of illness for asthma in the United States, 1985–1994. *J Allergy Clin Immunol* 2000;106(3):493–9.
15. Joe SA, Thakkar K. Chronic rhinosinusitis and asthma. *Otolaryngol Clin North Am* 2008;41(2):297–309.

16. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003; 111:1171–83.
17. Huovinen E, Kaprio J, Laitinen LA, et al. Incidence and prevalence of asthma among adult Finnish men and women of the Finnish twin cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest* 1999;115(4):928–36.
18. Halpern MT, Schmier JK, Richner R, et al. Allergic rhinitis: a potential cause of increased asthmatic medication use, costs, and morbidity. *J Asthma* 2004;41(1):117–26.
19. Dixon AD, Kaminsky DA, Holbrook JT, et al. Allergic rhinitis and sinusitis in asthma. *Chest* 2006;130(2): 429–35.
20. Shinohara M, Wakiguchi H, Saito H, et al. Symptoms of allergic rhinitis in women during early pregnancy are associated with higher prevalence of allergic rhinitis in their offspring. *Allergol Int* 2007;56(4):1–7.
21. Norman P, et al. Allergic rhinitis. In: Frank M, Austen KF, Claman HN, et al, editors. *Samter's immunologic diseases*, vol. 2, 5th edition. Boston: Little Brown; 1995. p. 1279–82.
22. Eapen RJ, Ebert CS, Pillsbury HC. Allergic rhinitis—history and presentation. *Otolaryngol Clin North Am* 2008;41(2):325–30.
23. Bachert PG, Vignola AM, Gevaert P, et al. Allergic rhinitis, rhinosinusitis, and asthma: one airway disease. *Immunol Allergy Clin North Am* 2004;24: 19–43.
24. Pawankar R. Allergic rhinitis and asthma: are they manifestations of one syndrome? *Clin Exp Allergy* 2006;36:1–4.
25. Krouse JH, Brown RW, Fineman SM, et al. Asthma and the unified airway. *Otolaryngol Head Neck Surg* 2007;136:S75–106.
26. Townley RG, Ryu UY, Kolotkin BM, et al. Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. *J Allergy Clin Immunol* 1975;56:429–42.
27. The European Community Respiratory Health Survey Steering Committee. The European Community Respiratory Health Survey II. *Eur Respir J* 2002; 20:1071–9.
28. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 2003;129(Suppl 3):S1–32.
29. Harlin S, Ansel D, Lane S, et al. A clinical and pathologic study of chronic sinusitis: the role of the eosinophil. *J Allergy Clin Immunol* 1988;81(5 Pt 1):867–75.
30. Zeitz HJ. Bronchial asthma, nasal polyps and aspirin sensitivity: Samter's syndrome. *Clin Chest Med* 1988;9(4):567–76.
31. Szczeklik A, Stevenson D. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2003;127(3):316–21.
32. Sousa A, Parikh A, Scadding G, et al. Leukotriene receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med* 2002;347(19):592–8.
33. Du Buske LS, Sheffer AL. Allergic rhinitis and other disease of the nose. In: Branch W, editor. *Office practice of medicine*. 3rd edition. Philadelphia: W.B. Saunders; 1994. p. 176–85.
34. Plaut M, Valentine MD. Allergic rhinitis. *N Engl J Med* 2005;353:1934–44.
35. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(Suppl 5):S147–334.
36. Haydon RC. Allergic rhinitis—current approaches to skin and in-vitro testing. *Otolaryngol Clin North Am* 2008;41(2):331–46.
37. Blackley CH. *Experimental researches on the causes and nature of catarrhus aestivus*. London: Balliere, Trindall, Cox; 1873.
38. Mabry RL. Whealing responses. In: Mabry RL, editor. *Skin endpoint titration*. 2nd edition. New York: Thieme Medical Publishers; 1994. p. 19–25.
39. Smith TF. Allergy testing in clinical practice. *Ann Allergy Asthma Immunol* 1992;68:293–302.
40. Lockey RF. “ARIA”: global guidelines and new forms of allergen immunotherapy. *J Allergy Clin Immunol* 2001;108(4):497–9.
41. Ferguson BJ. Environmental control of allergies. *Otolaryngol Clin North Am* 2008;41:411–7.
42. Krouse JH. Allergic rhinitis—current pharmacotherapy. *Otolaryngol Clin North Am* 2008;41(2): 347–58.
43. Bachert C, Bousquet J, Canonica GW, et al. Levocetirizine improves quality of life and reduces cost in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol* 2004;114:838–44.
44. Berger W, Hampel F Jr, Bernstein J, et al. Impact of azelastine nasal spray on symptoms and quality of life compared with cetirizine oral tablets in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;97:375–81.
45. Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 1997; 79:237–45.
46. Nielsen LP, Dahl R. Comparison of intranasal corticosteroids and antihistamines in allergic rhinitis: a review of randomized, controlled trials. *Am J Respir Med* 2003;2:55–65.
47. Juniper EF, Stahl E, Doty RL, et al. Clinical outcomes and adverse effect monitoring in allergic rhinitis. *J Allergy Clin Immunol* 2005;115:S390–413.
48. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;116:338–45.

49. Yuta A, Baraniuk JN. Therapeutic approaches to mucus hypersecretion. *Curr Allergy Asthma Rep* 2005;5:243–51.
50. Berger WE. Treatment of allergic rhinitis and other immunoglobulin E-mediated diseases with anti-immunoglobulin E antibody. *Allergy Asthma Proc* 2006;27:S29–32.
51. Leatherman B. Injection and sublingual immunotherapy in the management of allergies affecting the unified airway. *Otolaryngol Clin North Am* 2008; 41(2):359–74.
52. van Neerven RJ, Wikborg T, Lund G, et al. Blocking antibodies induced by specific allergy vaccination prevent the activation of CD4+ T cells by inhibiting serum Ig-E facilitated allergen presentation. *J Immunol* 1999;163:2944–52.
53. Calderon MA, Alves B, Jacobson M, et al. Allergen injection immunotherapy for seasonal allergic rhinitis [see comment]. *Cochrane Database Syst Rev* 2007;1:CD001936.
54. Tinkelman DG, Cole WQ 3rd, Tunno J. Immunotherapy: a one year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol* 1995;95:8–14.
55. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis [see comment]. *Allergy* 2005;60:4–12.
56. Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta- analysis of randomized, placebo controlled, double blinded-trials. *Ann Allergy Asthma Immunol* 2006;97:141–8.
57. American Academy of Allergy, Asthma, and Immunology. The allergy report. Available at: <http://www.theallergyreport.org>. Accessed October 7, 2005.
58. van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis: European Academy of Allergology and Clinical Immunology. *Allergy* 2000;55:116–34.