Allergic rhinitis (AR) is associated with decreased learning, performance and productivity at work and school, as well as a reduced quality of life. With a staggering annual economic impact between $6 billion and $8 billion, AR affects 20% of the adult population and up to 40% of children. Effective therapy for allergic rhinitis requires understanding the pathophysiology of the disease, as well as the role of various inflammatory mechanisms. As such, various classes of medication are at the physicians’ disposal to treat patients with allergic rhinitis. Among these are second-generation antihistamines and anticholinergic agents, intranasal corticosteroids, and mast cell stabilizers. Recently, montelukast, a leukotriene receptor antagonist, has been added to the modes of therapy approved by the US Food and Drug Administration for allergic rhinitis. For patients refractive to standard pharmacologic intervention, immunotherapy is followed by a review of emerging strategies and their rationale use in AR.

Irrespective of its cause, the annual economic impact of this pervasive disease is calculated to be $6.3 billion to $7.9 billion in direct and indirect costs.6,7 This figure, however, does not account for the detrimental effects of AR on quality of life (QOL), which include fatigue, irritability, memory deficits, excessive daytime somnolence, and depression.8,9 Quality of life is reduced in this patient population not only because of the disease symptoms (sneezing, nasal pruritus, rhinorrhea, and congestion), but also because its pathophysiology can disrupt normal sleep.10,11 Therefore, effective therapy for AR must provide symptomatic relief and target the complex underlying inflammatory mechanisms.

This review provides a summary of the pathophysiology of AR, its relationship with asthma, and an analysis of the traditional modes of pharmacotherapy used in its management. This summary is followed by a review of emerging strategies and their rationale use in AR.

Pathophysiology of Allergic Rhinitis

Allergic rhinitis is characterized by a two-phase allergic reaction: an initial sensitization phase where allergen exposure results in IgE formation as well as induction of the humoral response, and subsequent clinical disease after repeated antigen exposure (Figure 1). The clinical phase can also be further subdivided into early- and late-phase responses.

The early-phase inflammatory response is initiated within minutes of allergen exposure and is primarily due to the release by mast cells of mediators, including histamine, tryptase, cysteiny1 leukotrienes (CysLTs), cytokines (interleukin-4 [IL-4], IL-5, IL-6, and tumor necrosis factor-α [TNF-α]), chemotactic factors, and enzymes (Figure 2). The net effect of these mediators is to produce the early symptoms of AR (primarily sneezing, itching, and rhinorrhea) and stimulate the production, adhesion, and infiltration into local tissue of circulating leukocytes, especially eosinophils.

In contrast, the late-phase response begins 2 to 4 hours following allergen exposure and is essentially a cellular event12-14 (Figure 3). Inflammatory cells become activated and release their mediators, promoting local edema and tissue damage and perpetuation of the overall inflammatory process.12,13 Symptomatically, late-phase AR is characterized by nasal congestion and obstruction as opposed to sneezing and rhinorrhea, which are characteristic of the early phase response.15

The role that various agents such as histamine play has been an area of intense study in the past. The role that CysLTs play as mediators of the inflammatory process has been more recently described, particularly as it relates to the
Sensitization

Antigen-presenting cells on various tissues, including mucosal surfaces, endocytose inhaled allergen.

Processing of allergen and copresentation (with HLA class II molecules) to CD4^+ T cells.

Interleukin-4 (IL-4) and IL-13 stimulate T cells, which expand to become IgE-secreting B cells.

Binding of allergen-specific IgE to receptors on mast cells and basophils results in allergen priming.

Allergic Response in Sensitized Patients

Mediators (Figure 2)

Subsequent exposure of sensitized patient induces allergic response.

Allergen binds to IgE molecules on cell surface, activating mast cells.

Mast cells release granules (degranulation) containing preformed mediators.

Within minutes of exposure, activated mast cells begin to synthesize and release new mediators.

Inflammatory Cells (Figure 3)

Inflammatory cells (eosinophils, basophils, monocytes, and lymphocytes) infiltrate nasal mucosa.

Mediators released into nasal mucosa, triggering cellular processes.

Release of leukotrienes, interleukins, and cytokines by mast cells promotes inflammatory processes and recruitment of inflammatory cells, particularly eosinophils.

pathophysiology of AR. Cysteinyl leukotrienes increase nasal airway resistance and airway obstruction and contribute to rhinorrhea via increased vascular permeability and mucus secretion.\textsuperscript{14-17} They also function as chemoattractants for inflammatory cells, especially eosinophils, into the nasal tissues, which are then activated and secrete more inflammatory mediators, including CysLTs. This leads to augmented inflammation and congestion.\textsuperscript{18,19}

Other mediators, including prostaglandins (PGs), kinins, and neuropeptides, have been found to be important in AR. Prostaglandins, primarily PGD\(_2\), cause congestion and rhinorrhea.\textsuperscript{20,21} Kinins are released after allergen challenge; bradykinin elicits congestion, rhinorrhea, and sore throat.\textsuperscript{22,23} Neuropeptides can induce vasodilation, thus causing congestion.\textsuperscript{24-26}

As noted, cytokine secretion is a major feature of the inflammatory process in AR, and these elements may play an important role in cellular adhesion. Cytokine release upregulates the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin on the vascular endothelium, thereby enhancing the state of cell activation and prolonging the survival of eosinophils.\textsuperscript{27-29} In addition, the endothelin-converting enzyme 1, which generates endothelin-1, is upregulated in AR.\textsuperscript{30,31} This evidence points to an important underlying role for airway epithelial cells in initiating or maintaining local inflammation.

Furthermore, inducible nitric oxide (NO) synthase in the nasal mucosa has been shown to be upregulated in persistent AR with a concomitant reduction in the levels of NO after treatment with topical corticosteroids.\textsuperscript{32} Increased levels of exhaled NO have also been demonstrated during nasal and oral breathing in subjects with intermittent rhinitis.\textsuperscript{33} A similar increase in NO has also been shown to accompany eosinophil recruitment during a clinically asymptomatic inflammatory response.\textsuperscript{32}

No clear correlation has yet been demonstrated between the amount of allergen-specific IgE present in serum and the nature or severity of allergic symptoms. This has raised the question of the possible role of non-IgE-mediated types of immune responses in AR, particularly of T-helper 2 (Th2) lymphocytes, which can generate IL-3, IL-4, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNF-\(\alpha\).\textsuperscript{34} After nasal allergen challenge, an increase in IL-4, IL-5, and GM-CSF has been described in association with a mucosal eosinophilia.\textsuperscript{35} Nonetheless, a prerequisite for T-cell activation is the interaction with antigen-presenting cells, and recent evidence suggests that Langerhans’ cells, as well as other dendritic cells, are found in the nasal mucosa, and the incidence of these cells increases during allergen provocation.\textsuperscript{36}

Asthma and Allergic Rhinitis

It is now recognized that asthma and AR do not necessarily constitute distinct disease entities, but rather represent a final common pathway of closely related pathologic processes in the respiratory tract, with variable expression of severity and response to treatment. The onset of
AR and asthma also appear to be temporally related, with upper airway symptoms often preceding or appearing at the same time as asthma. 

Although the prevalence of AR is as high as 89% and 94% in asthmatic adolescents and asthmatic adults, respectively, similarities and differences have been identified between these two conditions with regard to symptomatology, the role of inflammatory cells, T-cell activation, production of cytokines, cellular activity, the role of the airway epithelium, and response to treatment. 

For example, both the nose and lower airways respond to neural stimulation by irritant substances. However, increased mucosal blood flow is the main contributor to exacerbations of nasal obstruction in AR in contrast to smooth muscle constriction as the major cause of lower airway narrowing in asthma. 

And, although eosinophilia is a characteristic feature of both diseases, in AR the mucosal eosinophilic response is strongly related to the antigenic load as opposed to asthma, in which bronchial eosinophilia is prominent even in mild forms of the disease. 

In both asthma and AR, there is evidence of epithelial accumulation of mast cells displaying allergen-induced activation, which results in the production of the pro-inflammatory mediators, including histamine, cytokines, prostaglandins, leukotrienes, tryptase, and kinins in the nose and the lower airways. 

The role of T lymphocytes in the development and maintenance of AR has been previously discussed and recent confirmation of a predominant Th2-type CD4 positive T-cell profile has been obtained in studies of bronchoalveolar lavage in asthmatics. 

And although, there is evidence correlating the degree of T-cell activation with the severity of asthma, this correlation is yet to be convincingly demonstrated in AR. As such, it may be hypothesized that the crucial difference between asthma and AR could be the level of T-cell activation. 

Adhesion mechanisms are also central to the pathogenesis of asthma and AR. Increased amounts of ICAM-1 and VCAM-1 have been demonstrated in chronic forms of both diseases and under conditions of allergenic stimulation, positive staining for adhesion molecules have been shown to increase in both the nose and lungs. Interestingly, ICAM-1 is also a receptor for the vast majority of rhinoviruses, and it has been proposed that the induction of ICAM-1 on epithelial cells could be the primary event leading, through a concomitant rhinovirus infection, to asthma and non-specific airway hyperreactivity.

Traditional Management of Allergic Rhinitis

Allergen avoidance and environmental control remain initial steps in managing AR. These interventions alone commonly provide insufficient relief. Therefore, manipulation of cytokine release from airway epithelial cells constitutes the next step in management. Topical corticosteroid applications and oral antihistamines are currently the two most important types of therapy and constitute the mainstay of the modern management of AR. Other agents in this area include oral and intranasal decongestants, oral corticosteroids, anticholinergic agents, leukotriene

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Symptom Relief</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids (intranasal, oral)</td>
<td>Bind to glucocorticoid receptors, affecting the production of various mediators</td>
<td>Sneezing, rhinorrhea, itching, congestion</td>
<td>Intra nasal: irritation, bleeding. Oral: Effects of long-term steroid use including potential growth suppression in children and osteoporosis</td>
</tr>
<tr>
<td>Mast cell stabilizers (intranasal)</td>
<td>Prevent mast cell degranulation</td>
<td>Sneezing, rhinorrhea, itching</td>
<td>Minimal</td>
</tr>
<tr>
<td>Antihistamine (intranasal, oral)</td>
<td>Antagonize histamine at the H1 receptor</td>
<td>Sneezing, rhinorrhea, itching</td>
<td>First-generation: sedation, dry mouth, dry eyes, urinary retention. Second-generation: minimal likelihood of sedation</td>
</tr>
<tr>
<td>Decongestants (intranasal, oral)</td>
<td>Stimulate α-adrenergic receptors, thereby inducing vasoconstriction</td>
<td>Congestion</td>
<td>Intra nasal: rhinitis medicamentosa. Oral: elevated blood pressure, tremor, tachycardia, loss of appetite, sleep disturbance</td>
</tr>
<tr>
<td>Anticholinergics (intranasal)</td>
<td>Muscarinic receptor blockade</td>
<td>Rhinorrhea</td>
<td>Minimal</td>
</tr>
</tbody>
</table>
receptor antagonists, and mast cell stabilizers (Table).

**Antihistamines**

Antihistamines are the oldest drugs used to treat allergic diseases. First-generation antihistamines (eg, chlorpheniramine maleate, diphenhydramine, promethazine hydrochloride, triprolidine hydrochloride) have an unfavorable risk-benefit ratio in most patients, with poor selectivity and a high rate of anticholinergic and sedative effects. Although these agents may be useful at night and lead to better sleep, during the day, patients may be fatigued or sleepy. Furthermore, these agents have the potential to impair learning, especially in children. They have similar effects to those caused by alcohol, thus making skilled activities more difficult or dangerous.60,61

Low-sedating or non-sedating, second-generation antihistamines (eg, cetirizine hydrochloride, loratadine, fexofenadine hydrochloride, desloratadine) have higher potency with prolonged durations of action. It has been shown that sedative effects of these antihistamines correlate with the level of antihistamine that crosses the blood-brain barrier. For example, fexofenadine, which does not cross the blood-brain barrier, tends to be less sedative than cetirizine, which occupies 30% of the histamine type 1 (H1) receptors in the brain.58 Because the second-generation antihistamines are less sedating or non-sedating, their impact on learning and drowsiness is similar to that of placebo.66,67 These agents effectively reduce itching, sneezing, and watery rhinorrhea; however, nasal obstruction is not reduced significantly.55,59

Topical antihistamines, delivered by nasal spray, avoid or minimize systemic adverse effects. Azelastine hydrochloride used topically has been shown to reduce rhinorrhea but failed to reduce congestion in one study, but not in another.60,61 Thus, the debate on benefits of antihistamines on nasal congestion continues. Because antihistamines are not greatly effective in relieving congestion, they are often combined with a decongestant. However, because of the potential adverse effects of decongestants, caution should be used, especially with other over-the-counter combinations that contain a sedating first-generation antihistamine and a decongestant. Such combinations can cause insomnia and, subsequently, daytime fatigue. According to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines, these combinations should no longer be used.55

**Oral and Intranasal Decongestants**

Intranasal or oral decongestants can effectively reduce nasal obstruction and congestion by their vasoconstrictive action on α-adrenergic receptors. Intranasal formulations act within 10 minutes, and many work up to 12 hours. Adverse effects may include nasal burning, dryness, or mucosal ulceration, and rarely, septal perforation. With oral formulations, activity starts within 30 minutes and lasts up to 6 hours, or for 8 to 24 hours with sustained-release formulas. Systemic effects can include irritability, dizziness, headache, tremor, tachycardia, and insomnia, which, in turn, can result in daytime somnolence. Tachyphylaxis and a rebound of symptoms (rhinitis medicamentosa) can result from prolonged use of a topical decongestant. Thus, long-term use of these agents is not recommended.55

**Oral and Intranasal Corticosteroids**

Intranasal corticosteroids have proven efficacy in patients with AR, compared with placebo. Several studies have demonstrated that corticosteroids can attenuate the expression and release of pro-inflammatory cytokines from airway epithelial cells and that they are effective in reducing the number of epithelial Langerhans’ cells, mast cells, eosinophils, IL-4 immunoreactive cells, and Th2 cells.33,62-68 Clinically, they reduce congestion and improve sleep; furthermore, they reduce daytime sleepiness, daytime fatigue, and sleep problems.69,70 Due to their clinical application and low systemic bioavailability, intranasal corticosteroids are generally considered safe and have a minimal influence on adrenal suppression.71,72 However, in treating concomitant diseases such as asthma, the amounts of nasal, inhaled, or oral steroids should be adjusted to avoid unwanted effects, including adrenal suppression.55 Short courses of oral corticosteroids are particularly effective in severely symptomatic patients and when nasal blockage compromises the effective penetration of corticosteroid nasal sprays or drops.73

**Topical Anticholinergic Drugs**

Parasympathetic stimulation of nasal glands results in vasodilation, resulting in watery secretion. Parasympathetic innervation is mediated through the autonomic transmitter acetylcholine. Therefore, muscarinic receptor blockade through anticholinergic drugs such as ipratropium bromide have antisecretory properties and a high safety profile with minimal crossing of the nasal and gastrointestinal mucosa as well as the blood-brain barrier.74 When delivered locally to the nasal mucosa, anticholinergic drugs inhibit mucus secretion and the subsequent rhinorrhea in both adults and children with perennial AR.55,76

In children with perennial AR, ipratropium given topically significantly improved rhinorrhea, congestion, and sneezing compared with baseline. Responses to QOL questionnaires showed also that after 6 months of treatment, ipratropium improved sleep by almost 50%.77 However, because ipratropium does not relieve nasal congestion or sneezing associated with seasonal AR, the ARIA guidelines recommend it as first-line therapy only when rhinorrhea is the primary symptom.35,74

**Mast Cell Stabilizers**

Sodium cromoglycate, with mast cell-stabilizing properties, is an effective strategy for controlling symptoms of AR with minimal associated adverse effects. However, its clinical effect is only for preventive purposes, and sodium cromoglycate is most likely to be useful if initiated before symptoms become severe.78-81 It is effective in young children, but it has the disadvantage of having to be frequently administered (up to six times daily), with adherence to frequent dosing to achieve adequate prophylaxis.

**New Agents Currently in Use**

Although traditional agents provide relief for a large number of patients, their lim-
lations and adverse effects have prompted further, more targeted research on the medical management of AR. Of particular use has been the ability to understand the similarities between the pathophysiology of asthma and that of AR, as well as the central role played by CysLTs in both diseases.

Leukotriene Inhibitors
As noted previously, CysLTs are key mediators of AR symptoms, and of congestion in particular. Therefore, the use of antileukotrienes to alleviate both daytime and nighttime symptoms is a rational approach. For example, after allergen challenge in patients with AR, zileuton, a leukotriene synthesis inhibitor, significantly reduced congestion.82 Similarly, the leukotriene receptor antagonists provide effective symptomatic relief, compared with placebo. For example, pranlukast significantly reduced nasal mucosal swelling and zafirlukast significantly reduced congestion, rhinorrhea, and sneezing.83,84 Montelukast, the only leukotriene receptor antagonist currently approved for treatment of AR in the United States, significantly improves nighttime symptoms (difficulty going to sleep, nighttime awakenings, and congestion on awakening), as well as daytime symptoms (congestion, rhinorrhea, pruritus, and sneezing), compared with placebo in patients with allergies in the spring and fall.85-87 Furthermore, montelukast significantly reduces the number of peripheral blood eosinophils, suggesting that it reduces allergic inflammation systemically.88 The combination of CysLTs (montelukast) with antihistamines (loratadine), however, has not demonstrated better symptom relief than therapy with single agents alone.86

Immunotherapy
Immunotherapy has been shown to be effective in the treatment of seasonal and perennial rhinitis.89-92 The proposed mechanisms for immunotherapy include blunting of elevations in IgE, decrease in serum neutrophil and eosinophil activity, reduction in the mast cell population as well as associated mediators, and the suppression of allergen-induced T-lymphocyte proliferative responses with an increase in the circulating numbers of allergen-specific CD8+ T lymphocytes93-99 (Figure 4). Some evidence also suggests that these events may be mediated by an effect of immunotherapy on T lymphocytes with an alteration from a predominant “Th2” response to favor an additional “Th1” response, which eventually would lead to the attenuation of tissue eosinophilia and local IgE production.100

Allergen-specific immunotherapy, administered under controlled conditions with immediate access to resuscitative equipment, has a prominent role in the treatment of severely symptomatic patients with allergic rhinitis who have failed to respond to conventional treatment with antihistamines, topical corticosteroids, or LRTAs, administered singly or in combination. The advantage of immunotherapy is that the immune system is modified, and this modification may be permanent or at least persist for years after therapy is terminated.

Comment
Although numerous agents are available for the treatment of AR, it is crucial that allergen avoidance remains the corner-

Figure 4. Omalizumab binds to free IgE, reducing cell-bound IgE. It reduces number of high-affinity receptors on the mast cells and basophils, reducing mediator release. This leads to a reduction in exacerbation of asthma and a reduction in symptoms.
stone of therapy. Understandably, total avoidance may not be feasible or may provide only incomplete relief. As such, pharmacotherapy should be aimed at providing relief for specific symptoms. Recent investigations point to intranasal corticosteroids as the most cost-effective group of agents, but second-generation antihistamines and leukotriene receptor antagonists are also effective.\(^{101-104}\)

Immunotherapy, the only treatment that can modify the diseases, is indicated in patients with moderate to severe refractory AR.

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