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DIAGNOSIS AND MANAGEMENT OF RHINITIS

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The complaint of rhinitis is one of the most frequent reasons why patients seek a physician's evaluation. Rhinitis is an inflammatory response of the nasal mucosa to various stimuli (both allergic or nonallergic). It is characterized by symptoms of nasal congestion, sneezing, nasal pruritis, and rhinorrhea.⁴⁹ The prevalence of rhinitis and the economic impact for both patient and managed care organizations dictate that clinicians carefully consider the medications available to them.

PREVALENCE OF RHINITIS

Rhinitis accounted for an estimated 48.4 million office visits in 1994. Of these, almost 70% were for upper respiratory tract infections.⁴⁹ In London, 16% of patients seen had allergic rhinitis, with 8% having perennial symptoms and 6% having both perennial and seasonal complaints.⁹² The most likely time of onset of allergic symptoms is between age 12 and 15 years.⁴⁴ For allergic rhinitis, students have the highest prevalence (15% to 20%).¹² As the patient ages, the likelihood of development of allergic rhinitis declines.

There are many reasons for the increasing prevalence of allergic rhinitis over the past 100 years. More recently, attention has been drawn to the role of diesel-exhaust particles inducing IgE production.⁷⁷ Increased mRNA for many cytokines that stimulate IgE production, in addition to increased interleukin (IL)-4 protein found in nasal lavage after intranasal challenge with diesel particles,³¹ may be one reason. In children, possible

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PRIMARY CARE

risk factors for developing allergic rhinitis before age 6 years include maternal smoking (at least 1/2 pack per day), parental history of atopy, ingestion of food (other than formula or breast milk) before age 2 months, and the presence of dogs indoors.¹¹²

ECONOMIC IMPACT OF RHINITIS

Estimated costs for allergic rhinitis exceed \$1.2 billion per year for direct (medication and physician) and indirect (time off of work) costs.⁴ Allergic rhinitis alone accounted for 811,000 missed workdays, 824,000 missed school days, and 4,230,000 reduced activity days in 1987.⁶¹ According to physician audits and other database data, estimated 1994 prescription antihistamines accounted for \$460 million, intranasal corticosteroids \$211 million, and prescription cold medicines \$169 million.⁷⁰ In consideration of the profound economic impact that rhinitis has on all patients, it is imperative that all clinicians consider the pathophysiology and differential diagnoses for rhinitis in choosing appropriate therapy.

PATHOPHYSIOLOGY OF RHINITIS

For patients with allergic rhinitis, sensitization occurs by processing foreign antigens by an antigen-presenting cell and presentation to T-helper 2 (T_H2) cells. These T cells produce cytokines, which promote stimulation of B cells to produce IgE specific for that antigen (allergen). When two IgE antibodies are cross-linked by binding to specific epitopes of the allergen, degranulation of the attached (at the Fc receptor) mast cell occurs with resultant mediator release. The allergic reaction exhibits a biphasic response characterized by release of prostaglandin (PG) D₂, tosyl-L-arginine methyl esterase (TAME-esterase), kinins, and histamine immediately from mast cells and the same mediators (except PGD₂) from basophils 3 to 6 hours later.⁷⁵ Cytokines IL-3, IL-5, IL-9, and IL-10 promote IgE and mast cell production.³ Additionally, IL-4 and IL-13 promote production of IgE, whereas {gamma} interferon and IL-12 oppose IgE production.⁷ The mast cell also enhances IgE production by producing IL-4, IL-5, and IL-6.¹¹

Inflammatory cells are recruited into the area by cytokine release also. Monocyte chemoattractant and activating factor (MCAF), monocyte chemoattractant protein-1 (MCP-1), a chemokine known as "RANTES" (regulated and normal T cell expressed and secreted), and macrophage inflammatory protein—1 α (MIP-1 α) activate basophils (MCAF/RANTES) and eosinophils (RANTES/MIP-1 α), whereas IL-8 inhibits MCAF—induced histamine release from basophils.⁵⁵ Increases in CD4 T lymphocytes and CD4-positive, IL-2-receptor-positive activated T cells are seen in the nasal mucosa.¹⁰⁴ A priming effect results in increased mast-cell density during continued (seasonal) allergen challenge.⁵⁹

As a result of histamine release, sneezing with nasal and ocular pruritus result. Pruritus may be felt in the soft palate also, as well as referred

into the ear along the eustachian tube. Nasal congestion results from histamine release acting as a vasodilator on the turbinates and from the effect of leukotrienes and prostaglandins on the nasal mucosa. Other components of nasal secretions include antibodies (especially IgA), macroglobulin, lactoferrin, lysozyme, and mucus cell glycoproteins. Histamine also activates glandular hypersecretion via nociceptive-parasympathetic reflexes to produce mucus.³ Nonallergic stimulation of the afferent pathway from nasal sensory receptors results in cholinergic stimulation via the efferent pathway to the nasal goblet cells resulting in further rhinorrhea. The majority of the resulting rhinorrhea is propelled backwards by cilia in the nasal cavity toward the pharynx (postnasal drip), with the excess secretions draining anteriorly.⁶⁰

DIFFERENTIAL DIAGNOSIS OF RHINITIS

Allergic Rhinitis

Deciphering between allergic and nonallergic reasons for rhinitis can be difficult, especially when viral infections may occur during the height of an allergy season. Many elderly patients are convinced they have allergies because of pseudo-allergic responses (such as gustatory and vasomotor rhinitis). Compounding the confusion that many patients experience are evaluations by practitioners inadequately trained to properly test for immediate (IgE mediated) hypersensitivity that perpetuates the patient's perception of allergies.

The history the patient relates is the most useful tool for suggesting an allergic cause. Symptoms and history that can differentiate allergic from nonallergic causes are summarized in Table 1. Seasonal allergies correspond to pollenosis from wind-pollinated plants, whereas perennial allergies are year-round and caused mostly by indoor allergens. Typically, spring allergens are caused by tree pollen, late-spring and summer symptoms by grass pollen, and fall symptoms by weed pollenosis. Indoor animals, feather pillows containing dust mites, rainfall and humidity-increasing mold exposure, as well as cockroach exposure, all elicit symptoms consistent with perennial allergic rhinitis. Food allergies rarely are a source of allergic rhinitis in adults.

Table 1. DIFFERENCES BETWEEN ALLERGIC AND NONALLERGIC RHINITIS

Allergic Rhinitis	Nonallergic Rhinitis
Onset of symptoms early in life	Symptoms usually after age 30 years
At least one parent affected	No family history of atopy
Seasonal variability common	Symptoms perennial
Suspected allergens identifiable	Symptoms precipitated by irritants/weather changes
Nasal, ocular, throat pruritis	No itching felt by patient
No fever or myalgias	"Flu-like" symptoms with infectious origin
Incidence: one in five patients	Most coworkers, friends, relatives affected by virus
Nasal turbinates moist, slightly blue	Erythematous, irritated, often dry mucosa

Physical findings vary depending on the severity of allergic reaction. The rhinorrhea is typically clear, although occasionally the density of eosinophils and neutrophils imparts a yellow-to-green color to the secretions. The turbinates may appear pale and slightly blue (cyanotic) with clear secretions. A transverse crease may result from a child rubbing the anterior portion of their nose upward (allergic salute). Persistent postnasal drainage may induce lymphoid follicular hyperplasia of the posterior pharynx (cobblestone appearance). Ocular signs vary in intensity from mild conjunctival erythema to marked cobblestoning of the inner eyelids. Edema of the eyelids may occur, especially when the patient rubs the eyes repeatedly. Chemosis occurs as a result of swelling of the limbus around the iris. Finally, "allergic shiners" appear as dark circles under the eyes and are caused by vascular congestion of venous drainage of the nose.

Laboratory evaluation to determine a cause should be limited. Staining the nasal secretion for eosinophils with Hansel's stain can suggest a cause, but it is not specific for allergic rhinitis.⁷³ Irritant rhinitis as well as infectious rhinitis produce neutrophils predominantly. Total IgE levels and complete blood cell counts are insufficient in predicting whether a patient is allergic or not and should not be used as screening tools. Skin testing or radioallergosorbent (RAST) testing should be used to confirm suspicions but should not be relied on to make a diagnosis. Because of the lability of allergens used in skin testing as well as variability in skin test responses and their interpretation, testing should be performed by board-certified allergists who are experienced in recognizing conditions that produce false-positive reactions. Intradermal testing should be limited because of over-interpretation of test results with concentrations that elicit irritant responses.⁸ Likewise, over-reliance on mildly positive RAST results for diagnosis and therapy may erroneously perpetuate the notion of an allergy to a patient. Such false impressions are long-lasting in most patients who desire a diagnosis for their complaints. Finally, provocation-neutralization testing, set end-point titration, and RAST for IgG specific for food antigens or *Candida* are all controversial and have not been shown to provide reliable evidence of allergy.¹⁰⁰

Nonallergic Rhinitis with Eosinophilia Syndrome

The nonallergic rhinitis with eosinophilia syndrome (NARES) is characterized by sneezing paroxysms, nasal pruritis, and copious clear rhinorrhea that stain positive for eosinophils. Although the physical exam may suggest allergies, skin testing is exclusively negative.⁵⁰ In a study evaluating patients with negative skin testing, 33% of patients had NARES (based on nasal smear revealing greater than 5% nasal eosinophils), and 61% had vasomotor rhinitis.⁹⁰ Likewise, patients with nasal polyposis may have nasal eosinophilia, but the majority are not due to allergies.¹⁹

Infectious Rhinitis

Viral upper respiratory tract infections account for the majority of cases of rhinitis reported by patients each year.⁴⁹ Rhinoviruses are impli-

cated most frequently, but others include respiratory syncytial virus and coronaviruses. Within a few days, nasal obstruction, rhinorrhea, sneezing, and a sore ("scratchy") throat predominate.¹⁰³ A clue to viral origin is the serial transmission from person-to-person (as seen in spouses),²⁸ as well as greater incidence of affected patients in the community than expected for allergies (typically one in five patients for the latter). The predominant cells on nasal smears after rhinovirus infection include polymorphonuclear leukocytes and, rarely, desquamated ciliated epithelial cells.¹¹⁰ Although kinins IL-6 and IL-8 are increased in symptomatic patients with rhinovirus infection, there are no significant increases in either histamine or prostaglandin D₂ (PGD₂) in nasal secretions.⁴⁸ It is for this reason that first-generation antihistamines have been shown to have relatively little efficacy in symptom control (except for their anticholinergic side-effects in drying the mucosa). Rhinoviruses bind to cells via a receptor known as the intercellular adhesion molecule 1 (ICAM-1),⁴¹ which plays a prominent role in the inflammatory response. Symptoms of viral infections usually improve within 7 to 10 days, and if not (or if symptoms worsen after initial clearing), then secondary bacterial sinusitis should be considered.

Physical Factors Affecting Congestion ("Vasomotor Rhinitis")

A multitude of physical stimuli can affect nasal symptoms. Increasing nasal resistance is caused by hyperventilation, chronic stress, skin pressure or lateral recumbency on the ipsilateral side, sexual arousal, or warm temperatures. Circadian variation in sneezing, nasal congestion, and rhinitis are worse in early morning (6 AM) compared with other times of the day.⁸⁰ Exercise decreases nasal congestion. Other factors include rapid changes in temperature, humidity, or bright lights that elicit nasal symptoms (vasomotor instability). Gustatory rhinitis occurs when patients report clear rhinorrhea after eating any food (but more likely either hot or spicy foods).⁷⁹ Irritant rhinitis results from stimulation of nasal receptors by odors, dust particles, or smoke, inducing clear rhinorrhea with resultant sneezing and nasal congestion. Both gustatory and irritant rhinitis are mediated by parasympathetic pathways.⁷⁹

Medication-Induced Rhinitis

Several medications have contributed to nasal symptoms. Nasal congestion can be produced by beta-blockers, terazosin, reserpine, methyl-dopa, and oral contraceptives. Aspirin and nonsteroidal anti-inflammatory (NSAIDs) agents promote rhinitis associated with triad asthma (nasal polyposis, aspirin hypersensitivity, and asthma), but are not IgE-mediated. Perhaps the best known side effect is rebound nasal congestion that occurs with abuse of topical nasal decongestants (rhinitis medicamentosa). Exactly when patients are prone to develop rebound congestion is unknown, but typically a patient notices that he or she has to use the topical

decongestant more frequently because of shorter duration of relief. Cocaine abuse also should be considered, especially in patients who present with rhinitis associated with nasal septal perforation.

Medical Conditions Affecting Rhinitis

Among conditions that can contribute to rhinitis and nasal congestion are hypothyroidism, diabetes mellitus, and pregnancy. Pregnancy is particularly a problem for some women because of the effect of progesterone on the vascular bed of the nasal turbinates promoting uncomfortable congestion. Rare conditions that may cause rhinitis include sarcoidosis, Wegener's granulomatosis, rhinoscleroma, and cerebrospinal fluid rhinorrhea.

Obstruction caused by septal deviation as well as foreign bodies and nasal polyps should be considered as a cause for refractory nasal congestion and rhinorrhea. In children, adenoidal hypertrophy plays a role in persistent congestion, snoring, cough, and rhinitis. Elderly patients also are susceptible to rhinitis from thinning of the nasal mucosa (atrophic rhinitis).³⁶

COMPLICATIONS OF RHINITIS

Left untreated, patients with rhinitis can develop other serious medical problems. Patients with asthma who have upper-airway obstruction have significantly greater improvement in airflow limitation with intranasal beclomethasone.¹⁰⁸ Likewise, treatment with intranasal steroids prevented increased airway hyper-responsiveness to methacholine challenge during allergy season.²⁶ Patients with obstructive sleep apnea were found to have increased obstructive apnea indices, obstructive apnea duration, and nasal resistance during ragweed season when their allergic rhinitis was symptomatic.⁶⁴ Infectious complications of otitis media and sinusitis occur with greater frequency because of nonallergic origins for rhinitis. Viral upper-respiratory tract infections also contribute to increased airway hyper-reactivity in not only asthmatics, but also in patients with allergic rhinitis.¹⁷

MEDICATION USAGE FOR RHINITIS

In prescribing medications, physicians should be aware of costs, limitations, and indications. Prescribing a nonsedating antihistamine for a patient with copious rhinorrhea from a viral cause is not effective. In one study, nasal steroids were prescribed for nonallergic rhinitis almost as frequently as for allergic rhinitis.⁵⁷ For the treatment of allergic rhinitis, a step-wise approach should be considered based on symptom scores and the patient's needs.

Antihistamines

Antihistamines (H_1 antagonists) are effective in competitively blocking the effect of histamine on nasal and ocular mucosa and thus controlling pruritis and sneezing. The first-generation antihistamines are lipophilic and cross the blood-brain barrier to induce varying degrees of anti-cholinergic side effects (including sedation and drying of secretions). Extended release preparations are quite effective. In fact, brompheniramine may provide comparable relief of symptoms compared with terfenadine.⁵⁴

The newer, "second-generation" antihistamines provide relief with a minimum of side effects. Because they do not cross the blood-brain barrier, they are less- or nonsedating. The decreased anticholinergic properties allow them to be useful in instances (such as sinus infections occurring with allergies) where excessive drying of the nasal mucosa is undesirable. In suppressing histamine-induced cutaneous responses, they are superior to chlorpheniramine.⁹⁵ They also are well tolerated in asthma.³⁸ Tolerance does not appear to develop with prolonged use.^{62,96}

The majority of second-generation antihistamines have some anti-inflammatory properties.⁷⁴ Terfenadine,¹⁸ loratadine,^{71,23} and cetirizine²³ inhibit histamine release from basophils, and loratadine decreases $\{\alpha\}_2$ macroglobulin from nasal mucosa.⁴⁰ Loratadine⁷² and azelastine hydrochloride⁶³ inhibit the production of leukotriene (LT) C₄ from neutrophils and eosinophils respectively. Cetirizine²¹ and azelastine⁶³ also prevent production of LTB₄. Kinin⁹¹ and superoxide¹⁶ production also are inhibited by azelastine. Cetirizine inhibits the migration of both eosinophils and neutrophils into the skin after skin testing.²⁰ Both early- and late-phase eosinophil and neutrophil numbers were reduced, and ICAM-1/CD54 expression was suppressed by cetirizine after conjunctival challenge with the pollen.²⁴ Cetirizine also reduced the migration of monocytes and T lymphocytes in response to chemotactic factors fMLP and LTB₄.⁵¹

Second-generation antihistamines also have the advantage of less-frequent dosing as well as rapid onset of action. Fexofenadine (Allegra, Hoechst Marian Roussel, Kansas City, MO) and azelastine (Aztelin, Wallace Laboratories, Cranbury, NJ) are effective when used twice a day. Terfenadine (Seldane, Hoechst Marian Roussel, Kansas City, MO) has been targeted for removal by the Food and Drug Administration (FDA) because of its cardiac side effects in patients using medications that interfere with terfenadine's metabolism, congenital QT prolongation, and those with liver dysfunction. Astemizole (Hismanal, Janssen Pharmaceutica, Titusville, NJ) is given once a day and has a similar side-effect profile, but does not have an available, active metabolite (such as fexofenadine for terfenadine). Loratadine (Claritin, Schering Corporation, Kenilworth, NJ) is given once daily and is available with pseudoephedrine as a decongestant. Cetirizine (Zyrtec, Pfizer, Inc., New York, NY) is less sedating than its parent compound hydroxyzine.⁵³ Azelastine (Astelin) is a nasal spray administered twice a day. Another topical antihistamine, levocabastine (Livostin, Ciba Vision Ophthalmics, Atlanta, GA), is available as an eye drop but is effective also intranasally.²⁹

Oral Decongestants

Although antihistamines are useful in suppression of the histamine response, they are ineffective in relief of nasal congestion. Adrenergic receptors such as $\{\alpha\}_1$ act as vasoconstrictors and therefore decrease blood flow in turbinates. Pseudoephedrine, phenylpropanolamine, and phenylephrine are the most commonly used decongestants added to antihistamines. Clinicians should consider drug interactions (tricyclic antidepressants, monoamine oxidase inhibitors), side effects (insomnia, palpitations), and medical conditions that may contraindicate their usage (pregnancy, hypertension) before prescribing combination therapy. Although topical decongestants are very effective in relief of nasal congestion, their use should be limited to no longer than 5 days in order to prevent rhinitis medicamentosa.

Ipratropium Bromide

Intranasal ipratropium bromide (Atrovent, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) has been used for both allergic⁶⁹ and nonallergic rhinitis.¹⁵ Treatment resulted in 30% reduction in rhinorrhea in nonallergic rhinitis, without sedation. Ipratropium bromide also reduced the need for other agents in treating perennial rhinitis.⁴² Ipratropium bromide at 0.06% was effective in controlling the rhinorrhea associated with the common cold.³⁰ It also has been shown to be safe and effective for children older than age 6 years in treating perennial nonallergic rhinitis (42 μg per nostril twice a day).⁶⁸ However, ipratropium has no effect on relieving nasal congestion or modifying the allergic reaction.

Cromolyn Sodium and Nedocromil Sodium

Cromolyn sodium (Nasal crom, Pharmacia and Upjohn, Kalamazoo, MI) is a mast-cell stabilizer that blocks the release of histamine. Although it is now available over-the-counter, it must be used regularly (four times a day) as a pretreatment to prevent both immediate- and late-phase allergic responses. When used regularly, cromolyn sodium 4% decreased symptom scores for rhinorrhea, nasal congestion, and sneezing⁴⁵ and proved superior to terfenadine during the early allergy season.⁵⁸ Intranasal nedocromil has also been shown to decrease mast-cell numbers⁵⁹ and allergy symptoms.⁸²

Corticosteroids

Intranasal corticosteroids are extremely effective in the treatment of allergic inflammation. They promote vasoconstriction (decongestion), decrease capillary permeability and glandular response to cholinergic stimuli (reduce secretions), reduce mediator production and release, and in-

hibit influx of inflammatory cells (eosinophils and basophils) into nasal epithelium.⁶⁵ Intranasal fluticasone propionate (Flonase, Glaxo-Wellcome, Inc., Research Triangle Park, NC) 200 $\mu\text{g}/\text{d}$ significantly decreased the amount of IL-1 β granulocyte macrophage colony stimulating factor (GM-CSF), IL-6, IL-8, MIP-1 α , and RANTES released within a few hours after allergen challenge.¹⁰⁹ Intranasal corticosteroids inhibit the transcription of cytokines, as evident by decreased expression of IL-4, IL-5, and IL-6.¹⁰ When given either prechallenge, or shortly after challenge with allergen intranasally, budesonide (Rhinacort, Rhinocort, Astra USA, Inc., Wayne, PA) was rapidly effective in decreasing immediate hypersensitivity mediator release (TAME activity) and symptoms.² Within 1 week of continued use, intranasal corticosteroids also inhibit early mediator release and symptoms.⁷⁸

Corticosteroids are useful when started while the patient is symptomatic⁷⁶ and provide relief (comparable to loratadine) less than 1 week after starting.⁸⁶ Intranasal fluticasone propionate at 200 $\mu\text{g}/\text{d}$ produced greater relief of nasal congestion and peak inspiratory flow than loratadine⁵² or terfenadine.¹⁴ Also, once-daily administration of triamcinolone acetonide (Nasacort, Rhone-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, PA) 110 $\mu\text{g}/\text{d}$ was superior to astemizole 10 mg/d in relief of nasal congestion, nasal itching, and sneezing.⁵ In contrast to other nasal steroids, mometasone furoate (Nasonex, Schering Pharmaceuticals, Kenilworth, NJ) exhibited a dose response curve, with 200 $\mu\text{g}/\text{d}$ providing the best results.¹³ Studies have demonstrated comparable efficacy of flunisolide (Nasarel, Nasalide, Dura Pharmaceuticals, San Diego, CA) and fluticasone propionate at 200 mcg/day with beclomethasone dipropionate (Vancenase, [Schering Pharmaceuticals, Kenilworth, NJ], Beconase [GlaxoWellcome, Inc., Research Triangle Park, NC]) at 400 $\mu\text{g}/\text{d}$.^{83,84} There do not appear to be significant differences in the effectiveness among the nasal steroids in inhibiting rhinitis.⁵⁶

Nasal steroids have few side effects, with mostly intermittent epistaxis and rarely nasal septal necrosis reported. In long-term studies, beclomethasone dipropionate did not show any evidence of mucosal atrophy.⁴⁷ Inhaled corticosteroids may have an effect on growth rate, as shown by as little as 400 $\mu\text{g}/\text{d}$ budesonide having a similar effect on short-term growth (as measured by knemometry) as 60 mg of methylprednisolone acetate IM.¹¹¹ When used as directed, no increased risk of intraocular pressure was noted with nasal steroids.³⁴ Cataracts were reported in elderly patients after a cumulative dose of at least 1000 mg of beclomethasone in current users (although when controlled for previous systemic corticosteroid use as well as previous, but not current use of inhaled corticosteroids, the trend was not significant).²⁷

Oral steroids and injectable steroids may provide rapid relief of allergic symptoms by reducing late-phase mediator production¹⁰²; however, because of the risk of aseptic necrosis of the hips and cataracts, the frequency of their use should be limited to only those patients who are refractory to other medications used. Oral prednisone, although effective in reducing kinin formation during experimental rhinovirus infection, was

no different from placebo in decreasing nasal secretion volume or symptom scores.⁴³

Allergen Avoidance

Frequently overlooked in the management of allergic and nonallergic rhinitis is avoidance of allergens or irritants. Although common sense dictates that patients should be able to recognize causative factors in their rhinitis, reinforcement by their physician can help in acknowledging avoidance techniques. For instance, cat lovers often accuse a friend's or relative's cat in causing their symptoms, but never their own cat. Likewise, smokers are reluctant to acknowledge the effect of smoke as an irritant. For patients who are pollen allergic, avoiding outdoor activities during peak pollination periods and keeping doors and windows closed during spring and fall pollen periods helps. Patients who are dust-mite allergic benefit by avoiding feather products, zippered vinyl encasements for their mattress and box spring, and laying on carpeted surfaces.

Immunotherapy

Allergy shots should be considered for patients who, despite optimal environmental controls and medication, still have their quality of life compromised by their allergy symptoms. Skin testing should be used to confirm the allergist's impression, not to justify putting patients on immunotherapy. Because of the risk of anaphylaxis and death, immunotherapy should be administered in medical facilities equipped to handle such emergencies.¹

SPECIAL CIRCUMSTANCES

Quality of Life

Patients with allergic rhinitis overall feel that their quality of life is worse compared with the general population. Allergic patients feel they have more fatigue, physical limitations, decreased social functioning, increased pain, and an overall poorer image compared with nonatopic patients, as measured by SF-36 and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) surveys.^{65,67} Patients with rhinitis also experience significant perception of side effects from medications (31%), avoid drugs because of side effects (65.1%), and worry about side effects from medications (48%).⁹⁹ Patients frequently complain about decreased energy, possibly caused by medication side effects (sedation), or insomnia from symptoms or medications interfering with their sleep cycle. Headaches from allergies usually result from hypertrophy of the turbinates or sinus inflammation. Upwards of 46% of patients with rhinitis may have headaches, with referral of the discomfort to the frontal sinus distribution in

84%.⁸⁸ With the exception of sinusitis, food-induced migraines, and discomfort to the frontal sinus distribution, the majority of headaches do not have an allergic origin, and other causes should be sought.⁸⁸

Because of their perception of poor health, some patients with chronic rhinitis may be refractory to standard treatments. Some of these patients may assume a sense of heightened awareness and vigilance in trying to avoid odors from chemicals that they perceive as "threatening."⁸⁷ They may be further convinced of their plight by anecdotal reports obtained by alternative and controversial health care providers or the internet. Many of these patients have underlying psychologic reasons for their complaints.⁹⁸ When patients present with severe symptoms that are out of proportion to objective evidence, last longer than 6 months, and are refractory to optimal medications and environmental controls, a diagnosis of undifferentiated somatoform disorder should be considered.²²

Medication Side Effects

When prescribing medications, keep side effect profiles in mind, especially when considering sedation for patients who require mental alertness. Twenty-five milligrams of hydroxyzine twice a day was shown to significantly prolong reaction times to computer-based eye-hand tests and induce sedation when compared with taking 60 mg of terfenadine twice a day or placebo.³⁷ Binding of dopamine, serotonin, muscarinic, and histamine receptors has been shown to occur with hydroxyzine when compared with binding of only histamine receptors by cetirizine.⁹⁷ Patients taking 25 mg of hydroxyzine made fewer correct responses during a simulated assembly line task compared with subjects taking cetirizine or placebo.¹⁰⁷ Sedation with cetirizine is dose dependent, with no significant sedation at 5 mg³³; however, in comparison with 120 mg of terfenadine⁸¹ and placebo,⁶² 10 mg of cetirizine was not significantly different in inducing somnolence.

Other studies have documented learning problems associated with allergies and sedating medications.⁹³ Children with seasonal allergic rhinitis showed smaller increases in conceptual knowledge and learning when compared with normal controls, an effect that was improved with loratadine yet worsened by the use of diphenhydramine.¹⁰⁶ Similar results also were seen in young adults with acrivastine versus diphenhydramine.¹⁰⁵ In a study of occupational injuries (especially burns, fractures, and wounds), workers were 50% more likely to have taken a sedating antihistamine in the month prior to injury than controls.³⁵ In a driving performance study, subjects taking triprolidine exhibited significantly worse driving skills when compared with those taking terfenadine.⁶ Although second-generation antihistamines may not offer additional antihistamine benefits over older H₁ antagonists (and may be more expensive), they should be considered safer when sedation is a concern.^{66,94}

Astemizole and terfenadine are metabolized by the CYP3A4 isoenzyme of the cytochrome P₄₅₀ enzyme system of the liver. When given with medications that competitively use the same metabolism (macrolide an-

tibiotics, imidazole antifungals, nefazodone, or fluvoxamine), increases in their blood levels occur with resultant risk of torsades de pointes. Despite warnings of drug interactions, combined use of contraindicated drugs with terfenadine has been demonstrated.¹⁰¹ Similar problems may occur in patients with prolonged QT interval, hypokalemia, liver dysfunction, or during overdoses. Fexofenadine (Allegra, Hoechst Marion Roussel, Kansas City, MO), the carboxylic-acid-active metabolite of terfenadine, does not appear to have significant cardiac side effects.³²

Pregnancy

The use of medications during pregnancy poses some risk of fetal malformation. Choosing medications with a safer profile in addition to informing the patient of available alternative options are the most reasonable approaches. Based on the 1977 Collaborative Perinatal Project, medications that were implicated in fetal malformations included brompheniramine, phenylpropanolamine, phenylephrine, and hydroxyzine. Both chlorpheniramine and tripeleminamine have been recommended as antihistamines to be considered during pregnancy.⁸⁵ Although designated as category C medications, inhaled corticosteroids have not been implicated in any increased incidence of fetal malformations in asthmatics.³⁹ Likewise, cromolyn sodium did not increase the risk of fetal malformation in asthmatic patients.

TREATMENT PLAN

Patients with rhinitis can significantly improve the quality of their lives with the use of medications,⁹ environmental controls, and (for allergic causes) immunotherapy. Because of the costs for medications, a stepwise approach similar to that for asthma (National Heart Lung Blood Institute/National Asthma Education and Prevention Program guidelines) can provide an efficient and cost-effective program for management of rhinitis. Table 2 outlines an example of such a plan. Early recognition of the cause for rhinitis, as well as confounding factors contributing to recurrence (allergies versus septal deviation for instance), can help in management or prevention of future episodes.

Whether allergic or nonallergic, rhinitis characterized by copious amounts of clear drainage is best treated initially with an antihistamine that has anticholinergic side effects. For when viral-induced rhinitis is refractory to an antihistamine, intranasal ipratropium bromide 0.06% should be used.³⁰ Nasal saline lavage may provide relief for patients with excessive purulent or dry secretions aggravating nasal congestion, especially in patients with sinusitis.

In the treatment of allergic rhinitis, patients may benefit initially from as-needed antihistamines, especially those that are less- or nonsedating. For allergic rhinitis that has an established pattern of symptoms (perennial or seasonal exacerbations), treatment with intranasal corticosteroids should be considered first and supplemented with antihistamines as

Table 2. THERAPY BASED ON SYMPTOM SCORES FOR ALLERGIC RHINITIS

Symptom Frequency/Intensity	Medication to Add
Rare/Intermittent (<3 times/wk)	antihistamine (prn)
Mild (rare sneezing, mild pruritis)	environmental controls
Mild/Recurrent (>3 times/wk)	Nasal corticosteroid
Usually with minor nasal congestion	environmental controls
For ocular pruritis	add antihistamine (prn)
Moderate Continuous/Recurrent (weekly duration)	Nasal corticosteroid with regular use of antihistamine* (start early or pre-season)
Seasonal predictability	
Severe Continuous/Recurrent	Nasal corticosteroid and antihistamine
Quality of life compromised	Consider immunotherapy especially if oral or parenteral steroids required

*When tolerance develops to antihistamine affect, consider rotation with other antihistamines at 2-week intervals. May add oral decongestant for moderate or severe persistent congestion.

needed for ocular symptoms or those refractory to the corticosteroids. To reduce the inflammatory response, intranasal corticosteroids are superior to antihistamines, but must be used regularly to achieve this effect.⁸⁹ Likewise, intranasal azelastine requires continuous treatment (compared with on-demand) to achieve its anti-inflammatory effect.²⁵ For nasal polyps complicating allergic rhinitis, intranasal fluticasone is beneficial.⁴⁶

CONCLUSION

The treatment of rhinitis is based on consideration of the differential diagnoses as well as the appropriate therapy. Causes for nonallergic rhinitis include infectious, irritant, structural, and vasomotor stimuli. Allergic rhinitis is characterized by pruritis caused by histamine release along with sneezing, clear rhinorrhea, and nasal congestion. Allergic rhinitis typically affects 20% of the population and is associated with a history consistent with immediate hypersensitivity and a familial history. Because of the various release of mediators other than histamine, the medications required for treatment of allergic rhinitis should focus on control of the inflammatory response. Intranasal corticosteroids are the most effective, although the newer less- or non-sedating antihistamines have some anti-inflammatory properties. Side effects of these medications are infrequent but need to be considered when prescribing. Avoidance techniques for allergen exposure also need to be followed. When the patient's quality of life has been compromised despite optimal medications and environmental controls, immunotherapy should be considered. Improvement of the patient's quality of life in decreasing the morbidity associated with chronic rhinitis should be the major consideration in prescribing.

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