

NONALLERGIC RHINITIS

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Patients with chronic rhinitis frequently ask, "Isn't everybody allergic?", and physicians tend to label all patients with chronic rhinitis as allergic. However, epidemiologic studies indicate that 15% to 20% of individuals are atopic, and yet the prevalence of chronic rhinitis is much higher, with nearly 40% of individuals having some rhinitis symptoms.^{22, 49} This difference suggests that approximately 50% of patients with chronic rhinitis are not allergic⁸, and studies of patients from allergy and otolaryngology clinics demonstrate that 28% to 60% of patients with chronic rhinitis are skin test negative.^{35, 38, 42, 56}

Patients with nonallergic rhinitis comprise a heterogeneous group with variable presentations. Similar to patients with allergic rhinitis, these individuals often have nasal obstruction, increased secretions, and sneezing. Patients, however, tend to present at an older age, have less pruritus—either nasal or ocular—and have symptoms that are perennial or sporadic without clear seasonality and are exacerbated by nonspecific triggers. Often these patients complain of sinus headaches and postnasal drip. Because the repertoire of nasal symptoms is limited, it may be difficult by clinical criteria to differentiate between allergic rhinitis and nonallergic rhinitis, let alone to differentiate the nonallergic rhinitis syndromes into subsets. For this reason, ancillary testing may be necessary.

The focus of this article is to discuss the primary nonallergic rhinitis syndromes (Box 1). The categories of nonallergic rhinitis are based on a descriptive nomenclature rather than specific causation and, as such, may be subject to future modifications. For practical purposes, it is worth separating chronic nonallergic rhinitis into subgroups because there are differences in presentation, physical examination, laboratory findings, and most importantly, treatment response.

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Box 1. Classification of Chronic Rhinitis**Allergic Rhinitis**

- Seasonal
- Perennial

Nonallergic Rhinitis

Primary

- Nonallergic, noneosinophilic rhinitis (vasomotor rhinitis)
- Nonallergic, eosinophilic rhinitis (NARES)
 - Without polyps
 - With polyps
- Atrophic rhinitis (ozena)

Secondary

Hormonal

- Pregnancy
- Hypothyroidism
- Acromegaly

Drug-Induced

Oral Agents

- Estrogen
- Antihypertensives
- Phenothiazines
- Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs)

Topical Agents

- α -Adrenergic (rhinitis medicamentosa)
- Cocaine

Granulomatous

- Sarcoidosis
- Wegener's granulomatosis
- Midline granuloma
- Relapsing polychondritis
- Rhinoscleromatosis

NONALLERGIC, NONEOSINOPHILIC RHINITIS OR VASOMOTOR RHINITIS

Although the term *vasomotor* implies increased neural traffic to the blood vessels supplying the nasal mucosa, this has never been proven.⁸ The descriptive term of *nonallergic, noneosinophilic rhinitis* may be preferred; however, the term *vasomotor rhinitis* (VMR) is used in this article. VMR is defined by negatives and is a diagnosis of exclusion because no clear origin is known. To make this diagnosis, causes due to infection, allergy, anatomic abnormalities, and eosinophilia must be ruled out. Despite the shortcomings of this exclusionary mode of diagnosis, there is a presentation that is reasonably typical. Patients who suffer from VMR usually present in the middle adult years. VMR is the most common cause of rhinitis for patients more than age 50. If a patient presents at this older age with a new onset of rhinitis, the presumptive diagnosis should be VMR until proven otherwise. Symptoms cover the

spectrum from copious nasal dripping to marked congestion. Often, the patients note aggravations of their symptoms with exposure to odors, irritants, cold air, and weather changes. Pathophysiologic studies suggest increased neural reflexes with exposure to these agents.

Epidemiology of VMR

The epidemiology of chronic rhinitis is fragmentary, at best. Because there is no universally accepted definition of nonallergic rhinitis, comparison of the epidemiologic studies is difficult. Another issue is that the clinical differentiation between normal and disease in VMR is based on the patient's subjective complaints. This is an important issue because VMR can be considered a normal development as one ages. Estimates indicate that nearly 50% of patients with chronic rhinitis have nonallergic rhinitis,^{8, 35, 38, 42, 49, 53, 56} with most diagnosed with VMR. In a study of 78 consecutive patients with perennial nonallergic rhinitis, 61% were diagnosed with VMR.⁴⁷ To complicate issues, patients may have more than one syndrome contributing to their nasal symptoms. It is common to have patients that have predominately allergic symptoms (and skin test positivity) early in their lives develop VMR as they grow older, with a "burning out" of their allergic symptoms. Until a specific diagnostic test is available, VMR will continue to be a syndrome rather than a distinct nosologic entity. Despite this status, future pathophysiologic studies may lead to specific criteria for diagnosis and may make good epidemiologic studies possible.

Pathophysiology of VMR

An understanding of the possible pathologic mechanisms in chronic nonallergic rhinitis requires an understanding of the normal mechanisms in nasal physiology. Nasal responses to exogenous stimuli are primarily mucosal in origin. There are four major symptoms that are seen in nasal reactions: airflow obstruction, increased secretions, pruritus, and sneezing.⁸ It is worth reviewing each of these responses in detail to understand possible pathologic mechanisms, including recent information on the nasal epithelium as an effector organ.

Air Flow Obstruction

Nasal air flow obstruction primarily is a result of increased blood flow in the capacitance vessels of the submucosa. The control of blood flow is largely a function of autonomic sympathetic fibers, with the parasympathetic system having little effect.⁵ The sympathetic input originates in the hypothalamus, synapses in the superior cervical ganglion, traverses the carotid plexus, and joins the parasympathetic fibers to form the vidian nerve³⁷ (Fig. 1). The combined sympathetic and parasympathetic fibers pass through the sphenopalatine ganglion to innervate the

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Figure 1. Three main sources of innervation of the nasal mucosa, excluding neurons of the olfactory nerve. Shown are sensory fibers, which are derived primarily from branches of the trigeminal nerve, and autonomic nerves, which belong to the parasympathetic and sympathetic divisions. SP = substance P; NPK = neuropeptide K; CGRP = calcitonin gene-related peptide; NPY = neuropeptide Y; VIP = vasoactive intestinal peptide; PHM = peptide, histidine, methionine. (From Raphael GD, Meredith SD, Baraniuk JN, et al: Nasal reflexes. In Setticone GA (ed): Rhinitis. Providence, RI, Oceanside Publications, 1991, pp 135–142; with permission.)

nasal mucosa. Most of these fibers innervate the vascular smooth muscle, with the remainder innervating the serous and mucous glands. A complex vascular structure is encountered in the nasal cavity with five groups of blood vessels. The arterioles, capillaries, and arteriovenous anastomosis (AVA) comprise the resistance vessels, whereas the veins and venous erectile tissue (sinusoids) comprise the capacitance vessels.^{10, 37} The function of the nasal AVA is presumably to control temperature and heat loss.^{10, 58} The sympathetic tone of the resistance vessels regulates regional blood flow, whereas the tone of the capacitance vessels determines nasal patency.⁸ The venous sinusoids mainly are on

Table 1. PHARMACOLOGY OF NASAL BLOOD VESSELS

	Vasodilation	Vasoconstriction
Resistance vessels	Prostaglandin E ₂ Histamine Bradykinin Substance P VIP	Adrenaline Noradrenaline
Capacitance vessels	Histamine	Adrenaline Noradrenaline Prostaglandin E ₂

From Eccles R, Bende M, Widdicombe JG: Nasal blood vessels. In Mygind N, Pipcorn U (eds): Allergic and Vasomotor Rhinitis: Pathophysiologic Aspects. Copenhagen, Munksgaard, 1987, p 70; with permission.

the anterior inferior turbinate and adjacent nasal septum. This area of the nose has the greatest effect on nasal air flow, and, hence, when engorged, causes the most resistance. Although not totally understood, the vascular tone of the capacitance vessels is influenced by local metabolic and vasoactive substances, temperature, and neurotransmitters¹³ (Table 1). Sympathetic autonomic control varies in its input. When the sympathetic tone is removed (as in cervical sympathectomy), nasal resistance and congestion increase.¹⁰ Cyclic reciprocal changes in sympathetic tone result in a nasal cycle that occurs in normal individuals but is more noticeable when one has nasal congestion. Every 2 to 4 hours, air flows unequally between the two nasal passages.^{13, 31}

Increased Secretions

Increased mucus production occurs when nasal serous and mucous glands are stimulated. Mucous production and secretion are mediated by parasympathetic fibers arising from the superior salivatory nucleus of the brain stem. These join sympathetic fibers to form the vidian nerve, and then relay in the sphenopalatine ganglion (Fig. 1).³⁷ The postganglionic parasympathetic fibers innervate the blood vessels and serous and mucous glands but not the goblet cells of the respiratory epithelium.⁷ Parasympathetic stimulation largely affects glandular secretions with little effect on blood flow. Autoradiographic studies suggest that M3 muscarinic receptors, and to a lesser extent M1 muscarinic receptors, are involved in glandular secretion.³⁷ Intranasal challenge with methacholine produces hypersecretion by these receptors in normal, allergic, and nonallergic subjects.^{16, 42}

The serous glands of the submucosa produce 50 times more secretions than the goblet cells.⁷ The fluid is less viscous and forms the bulk of the sol layer. Serous secretions contain the antibacterial proteins lactoferrin and lysozyme, and the secretory component for the transport of IgA and IgM (Box 2). The mucous glands of the submucosa secrete mucoglycoproteins that form the gel phase of nasal mucus. On the mucosal surface, the mucous gel phase floats on the serous sol phase.

Box 2. Major Constituents of Nasal Secretion

Plasma proteins

Albumin
Immunoglobulins IgA, IgG, IgM
Carboxypeptidase N
Angiotensin-converting enzyme
Kallikrein

Serous cell products

Lactoferrin
Lysozyme
Secretory IgA and secretory component
Neutral endopeptidase
Aminopeptidase
Uric acid
Glandulin
Peroxidase

Mucous cell products

Mucous glycoproteins

Undetermined sources

Calcitonin gene-related peptide
Urea

Inflammatory mediators

Histamine
TAME esterase
PGD₂
Bradykinin
LTC₄
Tryptase
Major basic protein
Eosinophil derived neurotoxin

Cells

Macrophages
Mast cells
Eosinophils
Neutrophils
PGD₂ = prostaglandin D₂; LTC₄ = leukotriene C₄

From Druce HM: Allergic and non-allergic rhinitis. In Middleton EJ, Reed CE, Ellis EF, et al (eds): Allergy Principles and Practice, ed 5. St. Louis, Mosby-Year Book, 1998, pp 1005-1016; with permission.

The epithelial cilia beat in the sol layer, propelling the mucous layer, which results in the removal of particulates, infectious agents, and other debris.

Plasma extravasation also creates fluid, which contributes to interstitial swelling and nasal secretions.^{10, 41} These fluids flush the interstitial space and epithelium during normal nasal function, and are increased during inflammatory hypersecretory states. The flux of plasma is a function of the transmitted arteriolar and venous pressures with fluid flow primarily through fenestrated capillaries.¹⁰ With the release of inflammatory mediators, such as substance P, histamine, kinins, and leukotrienes, there is also a separation of endothelial cells in the microvascular walls of the postcapillary venules, further promoting plasma extravasation and edema.⁴¹ The tight junctions between epithelial cells regulate the amount of interstitial fluid that can flow into the nasal cavity, and these junctions are affected by inflammatory and hydrostatic factors. The epithelium functions as a semipermeable membrane with the ability to exude fluid and absorb macromolecules, including drugs and antigens. The extravasated plasma contains albumin, immunoglobulins, and factors of the kinin, complement, coagulation, and fibrinolytic systems (Table 3). The bulk flow of plasma fluids flushes nociceptive stimuli

from the tissues and mucosa. This vascular leakage is responsible for the boggy appearance of the mucosal edema in disease states. Abundant elastic fibers also are present in the interstitial spaces, furnishing a static-recoil force that retracts the nasal mucosa and decreases mucosal blood flow, helping to offset vascular engorgement and edema when present.

Pruritus and Sneezing (Nociceptive Responses)

Pruritus and the sneeze reflex are mediated primarily by stimulation of irritant sensory nerve endings and central neural reflexes.^{4, 5} The sensory innervation comes to the nasal mucosa by way of the ophthalmic and maxillary divisions of the fifth cranial nerve (Table 2). The afferent neurons, called the nociceptive fibers, are small diameter, type C unmyelinated fibers (also known as nonadrenergic, noncholinergic [NANC] neurons). They convey sensation from the nasal mucosa to the brain stem and the cerebral cortex. Heat, mechanical injury, osmolar changes, vascular distention, and specific chemical stimuli—such as histamine and capsaicin—can lead to neural depolarization. Sensations range from pricking to pruritus to pain. Reflexes from parasympathetic nerves may ensue within seconds, resulting in sneezing and increased nasal secretions. The type C sensory neurons also contain neuropeptides, such as calcitonin gene-related peptide (CGRP), substance P (SP), and neurokinin A (NKA), and the classic neurotransmitter acetylcholine.^{4, 5, 31} With stimulation of the nerve, depolarization occurs, sending an afferent stimulus to the central nervous system. At the same time, there may be local release of CGRP, SP, and NKA. The release is believed to be by way of an axon reflex (antidromic) mechanism, although this has not been proven in human nasal mucosa.¹⁰ In turn, the neuropeptides produce local inflammatory effects (neurogenic inflammation) by directly affecting blood flow and glandular secretion.^{4, 44} Sensory neuropeptides

Table 2. INNERVATION OF HUMAN NASAL MUCOSA

	Sensory	Parasympathetic	Sympathetic
Nerves	I, V, XIII	VII	Thoracic
Ganglia	Trigeminal	Sphenopalatine	Stellate
Transmitters	Substance P	Acetylcholine	Norepinephrine
	Neurokinin A	VIP	Neuropeptide Y
	CGRP	PHM	
	GRP		
Structures innervated	Arterial and venous vessels	Arterial and venous vessels	Arterial and venous vessels
	Glands	Glands	Anastomoses
	Epithelium		Glands
Predominant functions	Afferent limb of reflexes	Reflex gland secretion and dilation	Constriction
	Axon response		

GRP = gastrin-releasing peptide

From Baraniuk JN, Kaliner MA: Functional activity of upper airway nerves. In Busse WW, Holgate ST (eds): *Asthma and Rhinitis*. Cambridge, MA, Blackwell Sciences, 1995, p 653; with permission.

act at the endothelial junctions, opening them and allowing plasma to escape.^{4, 41, 58} Receptors for these neuropeptides are present on the secretory glands.^{4, 57} Neuropeptides also play a role in the function of parasympathetic and sympathetic nerve functions. The efferent system (orthodromic) of parasympathetic nerves contains vasoactive intestinal peptide (VIP) and the related peptides, peptidine histidine methionine (PHM) and peptidine histidine isoleucine (PHI), which are released with nerve depolarization. VIP-binding sites are present on nasal epithelium, glands, and vessels. In vivo, VIP binds to these sites, functioning as a potent vasodilator and a secretagogue.^{5, 31} The postganglionic sympathetic nerves also may contain neuropeptide Y (NPY). The sympathetic tone of the vessels seems to be a function of the short-acting norepinephrine and slow-onset, long-lasting NPY.⁵

The neuropeptides released by sensory neural fibers and parasympathetic and sympathetic systems are degraded by proteases. The predominant protease is neutral endopeptidase (NEP), which is present in epithelial cells and submucosal glands.⁵ NEP levels are reduced with viral infections and are destroyed by cigarette smoke¹¹ and ozone.³⁹ Reduction of NEP levels may potentiate the proinflammatory effects of neuropeptides.

Nasal Epithelial Function

Recent studies suggest that nasal epithelial cells play a greater role than just being a physical barrier in health and disease.⁷ Under normal circumstances, the ciliated epithelium promotes mucociliary clearance, defends the airway, and maintains physiochemical homeostasis. Perturbation of the epithelium can affect ciliary function and normal secretion. Airway epithelial cells have been shown to generate inflammatory compounds including leukocyte chemoattractants and activators. Specific cytokines produced by these cells can affect the growth, differentiation, migration, and activation of inflammatory cells. Epithelial cells express specific-cell adhesion molecules and MHC class II antigens that can promote antigen presentation and T-cell activation.

Studies on the Pathophysiology of VMR

As can be surmised from this brief discussion of normal nasal function there are numerous pathologic events that could lead to the symptoms of VMR (or other rhinitic syndromes), including alterations in blood flow, increased nasal secretions, epithelial cell dysfunction, and an imbalance of neuropeptide function. Although it has not clearly been shown that a vasomotor reflex is increased in individuals with this syndrome, there are studies suggesting that patients with VMR are more reactive to irritant stimuli or that there is an imbalance in neural control of nasal reflexes. Nasal patency is affected by several neural reflexes. In patients with VMR, the nasal patency response to axillary pressure is

less than the response in normal individuals (Table 3).^{8, 26} The normal decrease in nasal resistance in response to standing is abrogated, and there is an increase in nasal resistance with isometric exercises and the cold pressor test as compared with normal individuals.^{26, 43}

Sanico and Togias⁴³ examined the possible role of age-related changes in nasal mucosal function as a possible contributor to VMR. Examination of the nasal mucosa of older individuals revealed increased metaplasia of the ciliated epithelium to stratified squamous epithelium, fewer goblet cells, and reduced vascularity of the cavernous spaces. Unstimulated nasal secretions and IgA were decreased. Olfactory neuroepithelium was replaced, but odor-detection thresholds were 11 times higher than those found in younger adults. Nasal secretory ability to intranasal provocation with histamine and methacholine was reduced in elderly subjects as compared with younger individuals. Sneezing in response to histamine, however, was similar in both groups. Although the elderly patients were less efficient in reducing the osmolality of hyperosmolar stimuli, they did not have an exaggerated response to cold air. These findings suggest altered functionality of the nasal mucosa in older individuals, but do not explain clearly the vasomotor syndrome.

Intranasal provocative challenges with methacholine have given contradictory results between healthy and nonallergic rhinitis patients. Two studies found increased methacholine sensitivity manifested as a hypersecretory response,^{16, 42} whereas Togias et al found no differences.⁵⁵

Table 3. FACTORS AFFECTING NASAL AIRWAY RESISTANCE IN NORMAL SUBJECTS THROUGH THE SYMPATHETIC NERVOUS SYSTEM

	Nasal Airway Resistance	
	Increased (↑)	Decreased (↓)
Nasal cycle (2–6 h)	↑	↓
Posture		
Erect to supine	↑ Ipsilateral side	
Lateral recumbency	↑ Dependent side	↓ Upper side
Skin pressure (axilla or side of chest)	↑ Ipsilateral side	
Temperature		
Skin	↑ On warming	↓ On cooling
Nasal inspiration of cold air	↑	
Respiration		
Breath-hold TLC		↓
Deep inspiration (mouth)		↓
Forced expiration (mouth)	↑	
Hyperventilation	↑	↓
Hypoxia/asphyxia		↓
Hypercapnea		↓
Exercise		↓
Other reflexes		
Sexual stimulation	↑	
Stress	↑ (Chronic)	↓ (Acute),
Ocular stimulation	↑	

From Eiser N: The hitch-hiker's guide to nasal airway patency. *Respir Medicine* 84:179–183, 1990; with permission.

When nonallergic patients have been selected for dominant symptoms of rhinorrhea ("runners") or congestion ("blockers"), the runners displayed an increased secretory response compared with the blockers. Using neurogenic stimuli (e.g., capsaicin), the symptom of itching has been found to be similar in healthy controls and patients with nonallergic rhinitis.⁴² Using topical nicotine as a nociceptive stimulus, Greiff et al¹⁷ showed a dose-dependent rise in fucose levels (a mucous gland product), but were unable to induce a plasma exudative response, suggesting increased secretory activity but not an inflammatory response. A possible neuropeptide mechanism has been suggested by a report that showed increased immunoreactive VIP in biopsy specimens of patients with VMR.²⁸ VIP has potent vasodilatory and secretory effects that could explain VMR symptoms. A decrease in NEP, the major enzyme destroying nociceptive neuropeptides, may contribute to the effects of cigarette smoke¹¹ and ozone³⁹ resulting in increased neurogenic inflammation.

Although the role of inflammatory cells, such as mast cells, basophils, eosinophils, neutrophils, and lymphocytes, in allergic disease is extensive and complex, their contribution to VMR is less clear. Nasal secretions and biopsies of nasal mucosa reveal either a paucity of inflammatory cells or primarily neutrophils, a finding similar to normal individuals. This suggests that VMR is noninflammatory with regard to cellular infiltration.^{6, 15, 27} Despite these findings, studies suggest that mast cells may contribute to some symptoms. Togias et al⁵⁵ showed that inhalation of cold air can induce a nonimmunologic degranulation of mast cells with the release of chemical mediators including histamine, TAME esterase, and prostaglandin D₂. A subsequent study showed that this same method of challenge produced a late-phase clinical reaction

Table 4. CLINICAL FEATURES OF CHRONIC RHINITIS SYNDROMES

Clinical Feature	Allergic	VMR	NARES
Age of onset	<30	>30	>30
Exacerbators	Allergens	Irritants, weather changes	ASA, NSAIDs
Symptoms			
Sneezing	Frequent	Occasional	Occasional
Anosmia	Rare	Rare	Common
Ocular itching	Common	Rare	Occasional
Asthma	Common	Rare	Occasional
Aspirin idiosyncrasy	Rare	Rare	Common
Physical findings: polyps	Rare	Rare	Common
Laboratory findings: nasal cytology	Many Eos	No Eos	Many Eos
Skin tests (or specific IgE RAST)	Positive	Negative	Negative
Total IgE	Elevated	Normal	Normal
Sinus CT	Usually normal	Normal	Abnormal (polypoid changes)

NARES = nonallergic rhinitis with eosinophilia syndrome; ASA = acetylsalicylic acid

reflected by mediator release.²⁰ These responses suggest that nonimmunologic mast cell activation may contribute to the VMR response. These mediators could lead to heightened sensitivity of nerve endings, increased vascular permeability, and cellular recruitment as seen in patients with allergic rhinitis.

Diagnosis/Laboratory Evaluation of VMR

The symptoms of VMR may resemble those of allergic rhinitis, but often there are clues that help separate the two syndromes (Table 4). VMR typically presents later in life, and has a lower prevalence of pruritus, conjunctival symptoms, and sneezing. Symptoms usually are perennial or sporadic without a clear association to allergen exposure. Those patients with VMR tend to be more sensitive to irritants such as cigarette smoke and strong odors, exposure to cold air, and weather changes. Many workers with occupational rhinitis have this syndrome with exposure to irritants in the workplace. As stated earlier, VMR steadily increases with age and accounts for more than 60% of chronic rhinitis beyond age 50 years. Rhinitis with eating, especially of hot, spicy foods, is a variant of this syndrome and is called gustatory rhinitis. These patients often drip dramatically from their nose with eating. Although nasal discharge may be copious in patients with VMR, congestion may be even a bigger problem, mediated in part by increased blood flow in nasal tissues. Often individuals feel they have "sinus problems," especially if headache and postnasal drip are present.⁹ They often are treated inappropriately with antibiotics. A low threshold for obtaining sinus CT scans should be the rule in older patients presumed to have sinusitis because often they do not. A strong clue to the presence of VMR is a poor response to antiallergy treatment. A reasonable practice is to give nasal corticosteroids to patients with chronic rhinitis. If they do not respond well, then there is a good chance that they have VMR. This diagnosis is made by default, and a thorough examination is needed to rule out other causes of rhinitis. Examination of the nasal mucosa in patients with VMR is nonspecific and is done primarily to rule out other contributors to rhinitis. Skin testing or specific IgE radioallergosorbent tests (RAST) are typically negative (although one can be allergic and also have VMR). Nasal cytology is necessary to rule out eosinophilic rhinitis, and a CT scan of the sinuses may be necessary to rule out sinusitis or underlying anatomic abnormalities. Typically, when all these studies are negative or noncontributory, the diagnosis of VMR is appropriate. Although VMR is usually noninflammatory, one can see neutrophils on nasal smears from these individuals.^{25, 32} Nasal cytology, which shows neutrophils, is nonspecific; one should not rely on the presence of these cells to make a diagnosis of sinusitis, unless other clinical parameters suggest the diagnosis and, ideally, there is a confirmatory

sinus CT scan. Relying on the presence of neutrophils in nasal smears to make a diagnosis of sinusitis is not supported by the literature.^{9, 25}

Treatment of VMR

The treatment of VMR is often unsatisfactory, especially compared with that of allergic rhinitis, which is almost always effective. Whether the cause is autonomic imbalance, hyper-reactivity, or the effect of aging on the nasal mucosa, patients should be told that VMR is often difficult to control. As with allergic rhinitis, if one has exogenous factors that make it worse—such as irritants and odors—then these should be avoided. Medications that have been used include those used for allergic rhinitis, although they are generally not as effective as they are for allergic rhinitis.

If congestion is the major complaint, oral decongestants are probably the most effective agents (Table 5). Unfortunately, patients, especially elderly individuals, are often intolerant of their side effects, especially central nervous system (CNS) stimulation, or have disorders, such as heart disease and hypertension, which make these drugs less attractive. For those patients in whom the predominant symptom is rhinorrhea, anticholinergic agents, such as an ipratropium nasal spray, may be effective. Anterior nasal drainage is more responsive than postnasal drainage. Certainly, there are patients who respond to antihistamines, and, if used, the nonsedating antihistamines are preferable. Intranasal azelastine is occasionally effective, and its use is supported by a recent study.² Saline irrigation also may be effective. Similarly, there are studies that support the use of intranasal corticosteroids, but response to this class of drug is sporadic at best.

Recently, topical capsaicin, the active neurotoxin found in chili peppers, has been touted for recalcitrant VMR. The proposed mechanism of action is neuropeptide depletion and specific degeneration of the sensory C-fibers of the nasal mucosa.^{6, 28} The beneficial clinical response seen supports the theory that neurogenic mechanisms are important in VMR. In resistant cases, surgical treatment may be required. Turbinectomies

Table 5. RESPONSE OF CHRONIC RHINITIS SYNDROMES TO VARIOUS MEDICATIONS

Drug	VMR		NARES	Allergic Rhinitis
	Drippers	Blockers		
Antihistamines	Fair	Poor	Fair	Good
Decongestants	Poor	Good	Fair	Good
Topical steroids	Poor	Poor	Excellent	Excellent
Ipratropium bromide	Good	Poor	Fair	Fair
Cromolyn	Poor	Poor	Poor	Good
Azelastine	Fair	Poor	?	Good

NARES = nonallergic rhinitis with eosinophilia syndrome

and septoplasties frequently are performed for marked congestion.³² Although removing the obstructing turbinates makes rational sense in theory, there is often little benefit.

Treatment with anterior ethmoidal glycerol rhizotomy has been performed to reduce nasal hypersecretion. In one study, 78 patients who underwent surgery were followed postoperatively for 12 to 15 months. Approximately 75% reported complete relief of symptoms, and only 12% had poor results.⁵⁹ Nineteen patients required a second treatment because of suboptimal response. Although it apparently offers an option for some patients with severe nasal discharge owing to VMR, there are questions about the long-term efficacy of the procedure because of the short-lived effects of previously reported rhizotomy procedures.^{8, 32}

NONALLERGIC EOSINOPHILIC RHINITIS

Although it was known for years that there were patients with nasal eosinophilia with negative skin tests, few data were collected or published until 1980, when Mullarkey et al³⁸ described 142 patients with chronic rhinitis. Twenty-one of the patients in this report had marked nasal eosinophilia (> 25%) on nasal smear and lacked evidence of allergy based on skin tests and IgE levels (Table 6).³⁸ They labeled the syndrome eosinophilic nonallergic rhinitis (ENAR) and noted that approximately one third had associated nasal polyps and an excellent response to treatment, especially with intranasal corticosteroids sprays. They speculated that the ENAR was a precursor of the triad of asthma, polyps, and aspirin sensitivity. In 1981, Jacobs et al²² described 52 more patients with perennial symptoms of rhinorrhea, obstruction and sneezing, with nasal eosinophilia and negative studies for allergy. Jacobs et al²² labeled these patients with nonallergic rhinitis with eosinophilia syndrome (NARES). They found neither elevated total IgE nor evidence of specific IgE to inhaled allergens, arguing against a missed allergen. These two studies and subsequent studies further solidified the existence of a distinct syndrome of chronic rhinitis starting later in life, sporadic or perennial, typically without a clear association to precipitating factors, and strongly associated with asthma, nasal polyps, and responding favorably to nasal corticosteroids.

Epidemiology of NARES

Although NARES is reasonably common in clinical practice, the prevalence in the general population is not well defined. In the study by Mullarkey et al,³⁸ 15% of the patients with chronic rhinitis had NARES, 37% had VMR, and the remaining had allergic or "probably allergic rhinitis." Another study by Settupane et al⁴⁷ suggests the common nature of this syndrome. These investigators examined 78 consecutive patients with perennial nonallergic rhinitis without polyps or asthma

and found 33% had nasal eosinophilia consistent with NARES syndrome, whereas 61% were diagnosed with VMR.

Although the epidemiology of NARES may not be defined fully, that of nasal polyposis has been examined more thoroughly. Because more than 80% of polyps are eosinophilic and most of these patients are not allergic,^{44, 46} the prevalence of this condition presumably reflects the epidemiology of more severe NARES. The frequency of nasal polyps in allergic rhinitis is only 1.5%, reflecting the lack of an association.⁴⁴ It also has been observed that positive skin tests are seen with the same frequency in nasal polyp populations as in the general population, indicating that allergic mechanisms are not the cause of NARES.⁵⁰ In patients with asthma, polyps are found in 13% of those with nonallergic diseases and in 5% of those with allergy ($P > 0.01$).⁴⁴ Eosinophilic polyps increase with age and peak at over 50 years of age, similar to the age profile of patients with NARES.

The triad of nasal polyps, aspirin intolerance, and asthma is a subset of NARES. Although there are triad patients that coincidentally have positive skin tests, it seems that most patients with eosinophilic polyps are *intrinsic*, even if they have positive skin tests. As summarized by Settiple,⁴⁵ "the overwhelming evidence is that polyps are not caused by the allergic or IgE antibody response."

Pathology of NARES

Surgical specimens of eosinophilic polyps are bluish-gray or translucent in appearance, with polyp size generally 2 to 3 cm. Microscopic examination reveals an edematous stroma with extensive eosinophilic infiltrate and mast cells, goblet cell hyperplasia, and a thickened hyalinized basement membrane.¹⁹ Pseudocystic spaces are present, which are fluid-filled areas in the stroma.

Cellular infiltrates of eosinophilic polyps contain more T cells than B cells, and T suppressor ($CD8^+$) cells predominate.³⁰ IgE-producing mast cells are rare. Current research is examining why eosinophils are so common in NARES and polyps. There are data showing that epithelial cells and fibroblasts produce granulocyte-macrophage colony-stimulating factor (GM-CSF), which could result in eosinophilic recruitment (microenvironmental theory).^{23, 40} Eosinophils themselves produce GM-CSF, suggesting a positive feedback mechanism (autocrine theory). Up-regulation of endothelial adhesion molecules, specifically P-selectin⁵² and VCAM-1,²⁴ suggest a mechanism of eosinophilic infiltration, but there is still some controversy in this area.^{18, 24, 52} The chemokines, RANTES and eotaxin, have been proposed as the major eosinophil chemotaxins and activators.^{3, 18, 19}

Studies indicate that the eosinophil mediates tissue injury by releasing toxic products including major basic protein, eosinophil cationic protein, eosinophil peroxidase, and other eosinophil granule products^{1, 3} (Fig. 2). As in any of the eosinophilic syndromes, T cells also are believed to be contributors to the pathogenesis. The T-helper subset, T_H2 , pro-

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Figure 2. Several inflammatory factors can activate eosinophils and attract them to sites of inflammation. Autocrine release of cytokines may promote eosinophilic infiltrates. The eosinophil granule proteins have potent destructive effects that lead to tissue necrosis. Leukotrienes have multiple important effects on glands, vessels, and other cells, whereas cytokines promote local and systemic inflammatory effects. MPB = major basic protein; ECP = eosinophil cationic protein; EDN = eosinophil-derived neurotoxin; EPO = eosinophil peroxidase; LTC₄ = leukotriene C₄. (From Baraniuk JN: Pathogenesis of allergic rhinitis. *J Allergy Clin Immunol* 99:S769, 1997; with permission.)

motes eosinophil production and maturation by way of the lymphocyte-derived cytokines IL-3, IL-5, and GM-CSF.^{3, 19} IL-5 is a specific eosinophil proinflammatory agent affecting differentiation, activation, and maturation.

Diagnosis of NARES

As with other forms of rhinitis, the history can give clues to the diagnosis of NARES and associated eosinophilic nasal polyposis. Congestion and sneezing are present and are characteristically perennial or sporadic without a clear association to allergen exposure. Loss of smell is common in patients with associated nasal polyposis. Ophthalmic symptoms are infrequent, but as previously discussed, there is a strong association with the presence of nonallergic asthma.

In the subset of patients with NARES with triad asthma, a history of aspirin and NSAID-induced exacerbations may be obtained. The

physical examination is helpful if polyps are visualized. Generally, polyps can be seen by a simple speculum examination; but rhinoscopy may be necessary. If polyps are not present, the examination of the nasal mucosa is not different from allergic or other causes of rhinitis. The sine qua non for the diagnosis of NARES is nasal cytology, with the presence of significant eosinophilia and negative skin tests or skin tests results that do not correlate with the history. There is no universal agreement regarding the percentage of eosinophils that is diagnostic, and a range of 4% to 25% of total granulocytes has been proposed as being significant.^{25, 33, 35, 38} Patients may have "burned-out" allergies with positive skin tests and yet develop a picture more typical of NARES later in life. CT scans of the sinuses often show polyposis with coexisting sinusitis. IgE levels are typically low in patients with NARES. Complete blood counts commonly show eosinophilia often higher than that seen in patients with allergic rhinitis.

Treatment of NARES

The treatment of choice for NARES is topical corticosteroids and, if necessary, systemic corticosteroids (Table 5).^{34, 36} Topically applied corticosteroids have been shown in many trials to reduce rhinitis symptoms, decrease obstruction, shrink polyps, and decrease polyp recurrence rate. They may not help improve the sense of smell and may not improve concomitant sinus disease. Systemic corticosteroids can have dramatic effects, but generally are used in short courses because of their well-known side effects. They can affect a temporary *medical polypectomy*, and in most cases, topical corticosteroids can then control symptoms for extended periods once the inflammation has been suppressed by systemic therapy. In patients recalcitrant to medical treatment, surgery may be required and often can have sustained effects. Topical corticosteroids are required postsurgery in most cases of eosinophilic polyposis because of the high recurrence rate.

ATROPHIC RHINITIS

Primary atrophic rhinitis or ozena has been reported primarily from third world countries where hygiene is poor. Congestion is the major complaint associated with foul odor (e.g., ozena) in the nose. Progressive atrophy of the nasal mucosa and underlying concha occurs, associated with thick, dry crusting. Nasal cavities enlarge and microscopic examination reveals squamous metaplasia of the epithelium. Although the cause is still unknown, it is believed that bacteria, especially gram-negative organisms and, in particular, *Klebsiella ozena*, infect the mucosa producing the disease.^{14, 60} Presumably, malnutrition also plays a role. Although nasal secretion cultures generally are discouraged because of lack of specificity for sinus infectivity, this may be a unique situation where a

culture is of value. It is unclear whether antibiotic therapy is of benefit, but, in theory, the organisms should be susceptible to various antibiotics and treatment should be prolonged (6 to 8 weeks). Topical antibiotics and frequent nasal irrigation also have been tried. Surgery may be required for cosmetic reasons because of anatomic changes.⁵⁵

A related syndrome is rhinoscleroma, a chronic granulomatous, destructive process that affects the nasal passages.¹⁴ It is endemic to the same areas of the world as ozena, but can be seen infrequently in the United States. It seems to be caused by another *Klebsiella* species, *K. rhinoscleromatis*. Symptoms include a foul-smelling, purulent discharge; nodules on the nasal mucosa; and nasal obstruction. A characteristic histopathologic feature is the presence in the submucosa of large foamy nonlipid containing histiocytes called Mikulicz cells.

Secondary atrophic rhinitis with crusting of the nasal mucosa and atrophy often is unrecognized. Generally, it is seen in older patients and develops as a result of nasal surgery, trauma, chronic sinus infections, and irradiation.⁴⁸ Atrophy of nasal tissues—including the concha—and nasal crusting are found in these settings, but their presence may require rhinoscopic or CT confirmation. The biopsy shows squamous metaplasia. Whether bacteria play a role in this form of atrophic rhinitis is uncertain. The pathogenesis of secondary and primary atrophic rhinitis remains obscure.

SUMMARY

Although atrophic rhinitis is apparently rare in this country, the syndromes of VMR and NARES are common. As such, clinicians should be familiar with the diagnosis and treatment of these syndromes, a position supported by the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology.¹² Definitive "labeling" of these patients may require referral to an allergist. Clinical history, physical examination, nasal smear results, and response to empiric treatment may help the clinician discern between the various causes of chronic rhinitis. Determining the presence of nasal eosinophilia is a simple office procedure that can predict a good response to nasal corticosteroids. Conversely, a lack of response to empiric nasal corticosteroids may suggest VMR, especially in an older patient. An understanding of the normal physiology of the nose is not only fascinating but can give insight into possible pathophysiologic mechanisms for these poorly defined syndromes. Further research is necessary to determine the origin of these diseases and will lead to more efficacious treatment.

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