

Persistent Nonallergic Rhinosinusitis

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Nonallergic rhinitis is a complex of syndromes that are united by the absence of atopic, T_H2 lymphocyte, immunoglobulin E (IgE)-mediated mechanisms. We propose a classification system based on the presence or absence of inflammatory granulocytes. Eosinophilic nonallergic rhinosinusitis may also be called chronic eosinophilic sinusitis syndromes (CESS) to help classify these disorders in which diverse mechanisms of eosinophil chemoattraction and survival predominate. Allergic fungal sinusitis, eosinophilic nasal polyps, aspirin sensitivity, and related disorders would fit in this category. Accumulation of neutrophils occurs in chronic infectious rhinosinusitis, foreign body reactions, and immunodeficiencies. More complex and variable combinations of leukocytes are found in Wegner's granulomatosis and related syndromes, and during the evolution of viral infections. The noninflammatory disorders can be divided by mechanism into hormonal; sympathetic dysfunction (including antihypertensive adrenergic drug therapy); cholinergic rhinitis; and nociceptive syndromes with hyperalgesia and other features (eg, the nonallergic rhinitis of chronic fatigue syndrome). Therapy based on the most likely pathophysiologic mechanism is anticipated to have the most success, but requires acceptance of the wide differential diagnosis of nonallergic rhinitis and rejection of the obsolete term of "vasomotor rhinitis."

Introduction

Nonallergic rhinitis (NAR) is a diverse syndrome that encompasses a complex and broad variety of disorders [1,2••]. In the past, NAR was considered a single diagnosis of exclusion, with allergic rhinitis and nonallergic sinusitis as the major competing diagnoses. Vasomotor rhinitis (VMR) was a misnomer. However, this "garbage can" approach is now severely outdated, and obstructs investigation, understanding, and diagnosis of the many causes of NAR. The misdiagnosis of VMR can have a negative impact on the care and prognosis of NAR subjects [3••]. The syndrome of NAR can result from dysfunction in non-

atopic inflammatory, eosinophilic, neural, iatrogenic, and idiopathic mechanisms. Proper diagnosis and treatment depends on appropriate classification according to the inflammatory (Table 1); non-inflammatory (no specific granulocytic or other cellular infiltrate) (Table 2); and neural mechanisms (Table 3) responsible for the symptoms and signs [1,4,5••].

Physiologic Approach to the Differential Diagnosis of Nonallergic Rhinitis

Nonallergic rhinitis is suggested by nasal congestion and fullness and mucoid rhinorrhea complaints. Many of these symptoms are more consistent with irritant effects, including dry mucosa and crusted mucoid secretions; inability to tolerate exposure to irritants such as tobacco smoke, changes in weather, humidity, and air conditioning; pollution; and other odors. Inhalant chemicals can directly stimulate nociceptive trigeminal neurons, leading to local axon response-mediated release of glandular products and conscious appreciation of nasal mucosal irritation.

Studies in anosmic patients suggest that there are a series of discrete chemical families that may stimulate trigeminal, but not olfactory, sensory neurons. An example is the capsaicin receptor. Capsaicin, the hot, spicy essence of chili peppers, stimulates vanilloid receptor 1 (VR1) on nonmyelinated type C trigeminal neurons and leads to sensations of pain. VR1 is a multimodal, nonselective cationic ion channel whose function is regulated by many factors. Capsaicin, its analogs, heat ($>43^\circ\text{C}$), and acid (H^+) each interact with distinct domains of this protein. VR1 is now recognized as part of a larger superfamily of transient receptor potential (TRP) proteins, and is classified as TRP-vanilloid-1 (TRPV1) [6]. These receptors are expressed on keratinocytes [7]. By analogy, they may be expressed on airway epithelial cells as well.

Cold, dry air and hyperosmotic stimuli can also activate local mucosal responses and depolarize specific trigeminal nociceptive nerve populations. "Cold" is a relative term. Passage of dry air over the mucosal epithelial lining fluid leads to evaporation of water. This is an endothermic reaction that decreases the enthalpy of the water remaining on the mucosal surface. As a result, the temperature of this 5 to 10 μm thick fluid reservoir decreases within milliseconds. "Cold"–L-menthol responsive protein on nerve fibers becomes activated and rapidly conveys afferent information to the brainstem via trigeminal nerve tracts [8]. These rapidly adapting receptors (RAR) cease functioning and return to their basal state in time to

Table 1. Differential diagnosis of inflammatory rhinosinusitis based on potential pathogenic mechanisms and the predominant infiltrating cellular components

Eosinophil-predominant	Neutrophil-predominant	Complex infiltrates
Allergic rhinitis	Infectious rhinitis	Common cold syndromes
Intermittent	Acute bacterial rhinosinusitis	Basophilic/metachromatic
Perennial	Acute infectious exacerbations of	nonallergic rhinitis
Food allergy with rhinitis	chronic sinusitis	Granulomatous and vasculitic diseases
Occupational rhinitis with eosinophilia	Dentogenic sinusitis	Wegener's granulomatosis if eosinophils
IgE-mediated	Nasal polyps in cystic fibrosis	are absent
Non-IgE-mediated	HIV/AIDS-related infectious	Malignant midline granuloma
Nonallergic rhinitis with eosinophilia	rhinosinusitis	Sarcoidosis
syndrome (NARES)	Humoral immunodeficiency	Granulomatous infections
Blood eosinophilia with nonallergic	IgA, IgE, IgG subclass and	Tuberculosis
rhinitis with eosinophilia	other deficiencies	Leprosy
syndrome (BENARES)	Common variable	Syphilis
Chronic eosinophilic sinusitis	hypogammaglobulinemia	Autoimmune disorders
syndromes (CESS)	Young's syndrome of sinopulmonary	Relapsing polychondritis
Nasal polyps with eosinophilia	disease, azoospermia, and nasal polyps	Systemic lupus erythematosus
Aspirin / NSAID sensitivity	Kartagener's syndrome of bronchiectasis,	Sjögren's syndrome
Triad asthma	chronic sinusitis, nasal polyps, and	Atrophic rhinitis
Asthma	immotile cilia	Postoperative
Sinusitis and/or nasal polyps	Foreign body with infection	Senile rhinitis
NSAID sensitivity	Corrosive occupational rhinitis	Ozena
Allergic fungal sinusitis		
Nonallergic fungal sinusitis		
Churg-Strauss syndrome with		
eosinophilic granuloma		
Eosinophilic granuloma		

respond to exhaled air and the next nasal breath. This function may become inactivated when the nostrils are totally occluded by structural (*eg*, polyps) or severe disease (allergic rhinitis, common cold). We speculate that these neurons may still respond to other stimuli and provide afferent information that is interpreted as nasal obstruction or "congestion/fullness." This subpopulation of Aδ neurons innervate central respiratory centers that regulate severe cold-induced apnea and the physical effort required to inhale each breath (work of breathing).

Evaporation of water leaves nonvolatile solutes behind, and thus increases the osmolarity of the epithelial lining fluid. Specific osmoreceptor systems play an important role in generating sensations of nasal pain (irritation); obstruction to nasal airflow; "congestion" or "fullness," as portrayed on the homunculus of upper airway structures in the insula; perceived rhinorrhea; and the induction of local mucosal type C axon responses that lead to glandular secretion [9]. These responses act within minutes to increase glandular exocytosis of mucins and serous cell antimicrobial proteins that act to neutralize a broad array of potential pathogenic insults. The molecular basis for these hyperosmolar-induced responses are not understood. An example of a nonallergic, hyperosmotic stimuli would be the landing of dry pollen grains on the nasal mucosa [10]. Dry pollen grains hydrate immediately in the epithelial lining fluid. The flux of water into the pollen grain and its extruded solutes leads to local hyperosmolar conditions that can then stimulate the osmoreceptive noci-

ceptive nerves. This offers an explanation for the nasal complaints of NAR subjects during heavy pollen days, days with heavy airborne fine particulate material burdens, and exposures to dry, dusty conditions.

Non-IgE-mediated responses of other airway receptors to oxidants; natural (*eg*, terpenes [11]) and airborne pollutant volatile organic compounds (VOCs); and fine particulate matter (*eg*, fly ash, diesel fuel particles, inert dusts, heavy doses of spores or pollen, acidic fog, volcanic emissions [VOG], and smog) represent important irritant stimuli. Occupational exposures may be complicated by toxicologic effects of silicon-based crystals, lanthanides, actinides, and other heavy metals, monomeric or polymeric solvents (*eg*, isocyanates), and Western red cedar plitic acid.

Historical features that favor allergic rhinitis include seasonal or perennial allergen exposure-related symptoms of itching, watery lacrimation, and rhinorrhea (allergic rhinoconjunctivitis); local and systemic nociceptive nerve-induced reflexes such as sneezing; beneficial effects of oral antihistamines to reduce histamine H1 receptor-mediated vascular permeability and nociceptive nerve stimulation (itch, sneezing); and nasal cytology showing increased eosinophils and mucosal metachromatic cells [1,12]. Positive allergy skin tests or calibrated serum radioallergosorbent stimulation tests (RAST) with geographically significant inhalants such as seasonal pollens, dust mites, and danders that match the patient's periods of symptoms are essential inclusion criteria for the diagnosis of allergic

Table 2. Differential diagnosis of noninflammatory rhinosinusitis based on potential pathogenic mechanisms: Structural anomalies and hormonal and drug-related

Structural anomalies	Hormonal and drug-related
Deviated septum Hypertrophic turbinates (mechanism undefined) Ostiomeatal complex (OMC) anatomic variants Concha bullosa Haller's cells Paradoxical curvature of the middle turbinate Choanal atresia Tumors Benign Neoplastic Adenoidal hypertrophy with potential recurrent infections Complications of excessive surgical excision of mucosa Strictures Fracture of cribriform plate Cerebrospinal rhinorrhea (high glucose) Hypertrophy of fleshy components of the anterior nasal valve Rhinophyma Foreign body	Pregnancy (estrogen and progesterone) Hypothyroidism Acromegaly Adrenergic dysfunction Antihypertensive agents β-adrenergic antagonists α-adrenergic antagonists (reserpine, α-methyldopa, guanethedine, phentolamine, prazosin) Rhinitis medicamentosa Chronic topical α-adrenergic agonist abuse Cocaine abuse Chlorpromazine (neuroleptic) Side effects of eye drops delivered via nasolacrimal ducts Glaucoma medications

rhinitis. IgE concentrations may be elevated, although allergic rhinitis can occur with relatively normal serum IgE. Similarly, modest plasma eosinophilia (4% to 20%) may occur, but is not always present.

The sensation of itch and its recruitment of systemic reflexes such as the allergic salute and sneeze strongly support the diagnosis of allergic rhinitis. Sensations of pain or irritation with congestion are most typical of nonallergic rhinitis, but may also occur in perennial nonallergic rhinitis. Itch and pain are mediated by two distinct subsets of type C neurons [13]. Itch nerves are depolarized by histamine-induced activation of H1 receptors. This population has the most narrow diameter of all neurons, and, therefore, the slowest nerve conduction velocity [14•]. The primary afferents synapse in a distinct region of the substantia gelatinosa of the dorsal horn of the spinal cord. The secondary relay interneurons cross the midline, travel in the lateral spinothalamic tract in a region distinct from pain and temperature afferents, and terminate on separate thalamic nuclei. Thus, the itch nervous system forms a distinct topographic neurologic tract that is independent of the capsaicin and heat-sensitive type C nervous system. In the skin, histamine-sensitive itch neurons are highly branched and innervate a large area of the dermis that contains the arteriolar vessels that regulate blood flow between the deep and superficial plexus of vessels. Stimulation of these neurons leads to the release of calcitonin gene-related peptide (CGRP), which causes vasodilation of the arterioles, an increased influx of highly oxygenated arterial blood into the superficial plexus of subepidermal postcapillary venules, and the clinical signs of redness (erythema, rubor), and heat (calor).

Acute sinusitis is marked by the sudden onset of unilateral maxillary, frontal, or retro-orbital pain, copious neutro-

phil-rich mucopurulent anterior and posterior nasal discharge, throat-clearing or hacking cough, and tenderness (hyperalgesia) over the affected sinuses [4,5••,15]. Similar symptoms can occur with common cold syndromes due to rhinovirus, parainfluenza, and related viruses. However, these viral syndromes typically respond within 4 days of rest, oral and/or topical α1- and α2-adrenergic agonist decongestants, and nasal saline sprays or nostril irrigation.

Chronic sinusitis is designated when symptoms last longer than 12 weeks, and do not remit despite appropriate antibiotic therapy [4,5••]. The differential diagnosis of chronic sinusitis is also large, and may result from occlusion of the ostiomeatal complex (OMC) by anatomical variants such as deviated nasal septum, mucosal thickening due to viral or allergic inflammation, nasal polyps, or novel nonallergic, eosinophilic inflammatory mechanisms [16••]. Staphyococcal enterotoxin superantigens, fungi, *Helicobacter pylori*, and aspirin/nonsteroidal anti-inflammatory drug (NSAID) sensitivity may contribute to these inflammatory mechanisms in nasal polyposis and chronic sinusitis. A history of recurrent sinopulmonary infections should raise the possibility of the humoral immunodeficiency with hypogammaglobulinemia, such as IgA, IgE, or IgG subclass deficiencies, common variable hypogammaglobulinemia, and HIV infection with AIDS (especially if unusual opportunistic infectious agents are identified). Measurement of serum antibody concentrations and HIV titer are indicated under these circumstances.

Physical Examination

Physical examination is useful in distinguishing between these major forms of rhinosinusitis. Nonallergic rhinitis may have a normal or dry, atrophic appearance. Desiccated

Table 3. Differential diagnosis of noninflammatory rhinosinusitis based on potential pathogenic mechanisms: Neural dysfunction and other conditions

Neural dysfunction	Other conditions
Absent sympathetic function (absent vasoconstriction) Horner's syndrome Stellate ganglion resection or block	Nasal hyperresponsiveness to mediators (eg, in untreated allergic rhinitis) Histamine Methacholine
Hyperactive cholinergic parasympathetic function (excessive mucus exocytosis) Cholinergic rhinitis Trigeminal neuralgia	Endothelin Bradykinin Toxicologic epithelial metaplasia
Food/nocifer-activated cholinergic reflex-mediated rhinitis Gustatory rhinitis, "salsa sniffles" Cold, dry air-induced rhinorrhea, "ski-bunny rhinitis"	Post-exposure syndromes (workers at World Trade Center, NYC) Solvent exposure Pollution
Nociceptive rhinitis/irritant rhinitis Increased nociceptive nerve sensitivity to weather changes, perfume, tobacco smoke, and other inhalants	Occupational exposures Olfactory mucosal disruption
Nonallergic rhinitis of chronic fatigue syndrome (CFS), fibromyalgia, and allied syndromes Hyperalgesia and dysfunctional mucosal secretory mechanisms (eg, axon responses)	Postviral Alzheimer's disease Parkinson's disease
Bright light-induced nasal congestion Vidian neurectomy side effects Loss of parasympathetic and sympathetic innervation	Idiopathic "vasomotor rhinitis" that does not fit any other criteria

patches of gel phase mucus may adhere to the mucosa. Pallor to pink coloration may be present.

Bright-red mucosa may signal aggressive use of nasal steroids or decongestants. The latter may lead to rhinitis medicamentosa if the decongestants are used topically for more than 30 days, or in some subjects who may have a phenotypic predisposition for development of vasoconstrictor-induced reactive vasodilation and nasal airway occlusion, or physiologic dependence on the α -adrenergic agonist.

Significantly increased secretion volume may follow exposure to nonallergic irritants, such as eating capsaicin-containing foods (gustatory rhinitis), smelling foul odors, weather changes, or even exposure to bright lights [13]. These represent forms of cholinergic rhinitis in which the afferent limbs of the parasympathetic reflex arc are overactive or too easily activated, and the cholinergic efferent limb has the capacity to cause copious glandular exocytosis.

Sympathetic hypofunction following stroke (eg, Horner's syndrome), or damage to the sympathetic trunks or superior cervical ganglion (eg, anterior surgical approach for cervical discectomy) can lead to unremitting vasodilation. Excessive swelling of the nasal venous sinusoids thickens the mucosa, expands the turbinates, reduces the nostril airspace volume, and thus increases nasal airflow resistance and decreases nasal inspiratory and expiratory airflow. Catecholamine receptor dysfunction with a loss of vasoconstrictor functions can also occur due to thyroxine deficiency in hypothyroidism. Unremitting nasal congestion in a person with increasing weight, slowing mentation, myxedema, or signs suggestive of other autoimmune disorders should be assessed for hypothyroidism, and its cause should be diagnosed. Acromegalics develop abnor-

mal facial bone structure with anatomical nasal obstruction. It is unclear if excessive growth hormone adds to the detrimental rhinitis. Blockade of adrenergic receptors or vasodilation caused by antihypertensive drugs leads to sensations of nasal obstruction to airflow, fullness, and possibly rhinorrhea, and the appearance of a swollen, congested mucosa with increased turbinate size. It is unclear if other drugs such as angiotensin-converting enzyme inhibitors or angiotensin-receptor antagonists can cause similar vascular swelling and rhinitis.

Pregnancy is associated with thickening of mucosal linings and increased mucosal secretion [17]. Approximately one third of pregnant women develop rhinitis severe enough to warrant treatment. Their complaints include a combination of allergic rhinitis and nonallergic mechanisms. Estrogen and progesterone can enhance histamine H1-receptor expression on nasal epithelial and endothelial cells in vitro. This suggests that the hormonal milieu of pregnancy combined with "spontaneous" histamine release from mast cells or bacteria such as *Moraxella catarrhalis* and *Hemophilus influenzae* may increase nasal irritation (via nociceptive nerves), vasodilation, and vascular leak from superficial postcapillary venules. This suggests that antihistamines can be beneficial in this form of nonallergic rhinitis. However, definitive studies of either oral or topical antihistamines in pregnancy have not been performed. Anecdotal experience suggests that saline nasal sprays can be highly effective. The saline may dilute irritants, dissolve thick gelatinous disulfide-bonded mucins, and thus reduce mucus viscosity and improve normal posterior mucus flow toward the stomach, or even alter ion channel activities on epithelial and neural cells due to effects of the Cl⁻. In addi-

Table 4. Diagnostic and treatment algorithm for rhinosinusitis

History: Symptom complex			
Itch, sneeze, watery rhinorrhea	Congestion, fullness, irritant sensitivity	Facial pain, mucopurulent discharge	Unilateral fullness or pain, systemic complaints
Examination			
Turbinate pallor to bluish tinge edema	Spectrum from mucus hypersecretion, normal to atrophic	Tenderness over sinuses	Nasal mass, mucosal lesion
Watery to clear mucoid discharge, conjunctival injection, wheezing		Mucopurulent sinus ostial discharge	CT scan with mass or bone erosion
		Confirmatory CT scan with mucosal occlusion ± air-fluid levels	
Nasal cellular examination (scrapings)			
Eosinophilic	Variable with eosinophils, neutrophils, or normal cells	Neutrophil-rich mucopurulent discharge	Variable
Allergy skin tests			
Positive skin tests relevant to season and exposure history	Positive skin tests may not be relevant to symptoms	Positive skin tests may not be relevant to symptoms	Positive skin tests may not be relevant to symptoms
Most probable diagnosis			
Allergic rhinitis	Nonallergic rhinitis syndromes	Acute sinusitis, chronic sinusitis	Tumor, nasal polyps, vasculitis
Symptom-oriented treatment			
Intermittent	Avoid irritants	Rest	Nasal polyps
Nonsedating antihistamine	Nasal saline spray or irrigation	Fluids	Oral steroids and intranasal steroids
Intranasal antihistamine and/or decongestant ± Conjunctival antiallergy treatment	Vaseline/glycerol gels	Chicken soup (Ziment)	Treat other underlying pathology
	Anti-occlusion strips (Breathe Right)	Oral ± topical α -agonist decongestants	Mass or mucosal lesions
Persistent	If inflammatory signs:	Nasal saline sprays or irrigation	ENT evaluations for biopsy
Oral nonsedating antihistamine	Intranasal steroid	If symptoms persist > 4 to 10 days:	
Intranasal antihistamine ± α -adrenergic agonist (decongestant)	Azelastine	Amoxicillin	
Intranasal steroid	If copious mucus discharge:	Other antibiotics	
± Conjunctival antiallergy treatment	Topical ipratropium (anticholinergic)	If chronic:	
Allergy shots	If excessive congestion	Rigid or flexible endoscopic sinus surgery (FESS)	
	Oral α -adrenergic decongestants, 3 days of nasal α -agonist spray	Treat underlying disorders	
	If intractably enlarged turbinates	Chronic topical antibiotics?	
	Turbinectomy		
	Assess systemic hyperalgesia (CFS, fibromyalgia)		

CFS—chronic fatigue syndrome; ENT—ear, nose, throat. Breathe Right, CNS, Inc., Whippany, NJ.

tion, the benzalkonium chloride preservative in many saline nasal sprays may have toxic effects on neutrophils and other cells that unwittingly contribute to the rhinitis complaints. Recent reclassification of cetirizine, loratidine, and budesonide to Class B pregnancy status has also increased the pharmacologic repertoire of oxymetazoline, pseudoephedrine, diphenhydramine, chlorpheniramine, and beclomethasone dipropionate.

Physical examination is of paramount importance when other forms of inflammation or masses cause obstruction. Occupational rhinitis may demonstrate signs of IgE-mediated allergic inflammation (*eg*, baker's nose with flour mite allergy), mucosal destruction (*eg*, toxic gases), or eschar (*eg*, smoke inhalation). Localized ulcerat-

ing papules or other lesions may indicate granulomatous diseases such as Wegener's granulomatosis, malignant midline granuloma, sarcoidosis, syphilitic gummas, and leprosy-related or tuberculoid granulomas. Masses causing unilateral or bilateral nasal obstruction also include choanal atresia, juvenile inverted papillomas, smoking-related squamous carcinomas, Epstein-Barr virus-related nasopharyngeal carcinoma, and adenoidal hypertrophy. Nasal biopsy and histologic evaluation are required for diagnosis in each case. Unilateral lesions must be aggressively investigated, as they are more likely to have neoplastic origins.

The most commonly recognized masses are the nasal polyps. Pediatric nasal polyps are nearly universal in cystic fibrosis, where they have a neutrophilic infiltrate. Most nasal

polyps have an opalescent appearance, soft consistency, ethmoid origin, and tissue eosinophilia. Although they may protrude through the nares, small polypoid swellings along the lateral middle turbinate and ethmoid region may require rhinoscopy for identification [18]. Rhinoscopic demonstration of a mucopurulent sinus discharge is pathognomonic of acute sinusitis. However, culture of the nasal discharge is unlikely to reveal the pathogenic organism responsible for the sinus infection, particularly in chronic sinusitis where inflammatory and other mucosal changes will alter the nasal and sinus mucosal ecologic niches available for microbial colonization. Sinus puncture and aspiration remain the "gold standard" for microbial identification of the single or multiple bacterial or fungal species that may inhabit the affected sinus.

Anatomical variants that predispose to sinusitis may also contribute to rhinitis complaints. One reason is that mucosal contact between adjacent surfaces activates mucosal nociceptive neurons, leading to sensations of "friction" [19] that may be interpreted at the cerebral level as fullness, congestion, headache, obstruction, or rhinorrhea. Septal deviation is an excellent example. Although most septal deformations are innocuous, the greater the angle to deviation, the greater the likelihood that the septum will impact the middle or inferior turbinates, and the greater the likelihood of sinusitis. Septal perforation from cocaine-induced vasoconstriction and loss of viability of septal chondrocytes may lead to unusual patterns of airflow and altered sensations of air cooling or hydration during normal breathing. Expansion of turbinates by allergic inflammation, engorgement of venous sinusoids (*eg*, sympathetic dysfunction), glandular hypertrophy, cellular infiltration, and other undefined mechanisms may also increase areas of mucosal contact and irritation. These lesions, plus concha bullosa, paradoxically turned middle turbinates, and ethmoid air cell variants may respond to conservative medical treatment, but may eventually require surgical intervention for relief of symptoms. Medical treatment would be aimed at the most suspect pathogenic mechanism, and could include nasal steroids to reduce inflammation, oral or short courses of topical α -adrenergic decongestants, nasal capsaicin for denervation of the nociceptive endings [20••], or lubricants such as nasal saline sprays, petroleum jelly (Vaseline), or glycerol suspensions (*eg*, Nose Better Gel [Lee Pharmaceuticals, South El Monte, CA]) to provide symptomatic improvement. If unsuccessful, correction of septal deviation; electrical, radio frequency, laser, or liquid nitrogen cauterization and ablation; fiberoptic or rigid endoscope-directed inferior or middle turbinectomy; and ostiomeatal reconstruction, including maxillary and ethmoid ostiotomies, may be indicated. Similar procedures can be used for polypectomy. However, subjects with chronic nonallergic sinusitis, allergic rhinitis, chronic fatigue syndrome (CFS), and allied disorders may not benefit from these procedures, unless there is long-term, continuing treatment of the underlying disorder with nasal steroids, allergy shots, or other appropriate therapies. In fact, iatrogenic harm may

result in the chronic fatigue syndrome group because of the nociceptive dysfunction and hyperalgesia that plays an important pathogenic role in these disorders.

The chronic nonallergic rhinitis of CFS has several distinguishing features [9,21] that have not yet been examined in other subsets of nonallergic rhinitis or subjects with systemic hyperalgesia. These subjects complain of pain affecting many organs with syndromes such as fibromyalgia, noninflammatory arthralgia ("rheumatism"), chronic nonmigranous headaches, noncardiac chest pain due to esophageal spasm, irritable bowel syndrome, irritable bladder syndrome, severe premenstrual symptoms, vulvodynia, and dyspareunia. Many of these subjects have excessive fatigue, problems in cognition and short-term memory, and autonomic instability, indicating central nervous system dysfunction. The diffuse symptomatology has led to the rubric "chronic multisymptom illness" to include these disorders, CFS, fibromyalgia, and potentially the complaints suffered by many veterans of the Persian Gulf and other wars. Chronic rhinitis characterized by fullness and congestion often without nasal pathologic changes is present in approximately 70% of these subjects, and can occur in addition to legitimate allergic rhinitis [21]. Some may present as chronic sinusitis with normal CT scans. Sensations of chronic nasal irritation, pain, obstruction to nasal airflow without evidence of increased nasal airflow resistance ("blockage"), nasal drip with or without increased discharge (rhinorrhea), post-nasal drip, and irritation are comparable with subjects with acute sinusitis and active, untreated allergic rhinitis. The CFS population is distinct because they have increased pressure-induced hyperalgesia over their sinus regions that are significantly more severe than in acute and chronic sinusitis [15]. The CFS/fibromyalgia population can be differentiated from chronic sinusitis by the presence of systemic hyperalgesia that is absent in control subjects. Treatment is based on recognition of the syndrome; education of the patient regarding its potential etiologies and treatments as part of an honest and trustful relationship; graded initiation of aerobic exercise; cognitive-behavioral therapy; and selected use of selective serotonin reuptake inhibitors, low doses of doxepin, cyclobenzaprine, and other, older tricyclic drugs; assessment of thyroid status; and symptomatic treatment of their noninflammatory rhinitis with nasal saline sprays, lubricant gels, steroids, and ipratropium, as indicated.

Ancillary Testing

Negative allergy skin tests, RAST tests, and low IgE levels are to be anticipated in NAR syndromes. However, the clinician may incorrectly interpret isolated positive skin test or RAST results as indicative of allergic rhinitis, when, in fact, the study may be a false-positive. This is a common finding in food allergy, including food-related rhinitis. It may be necessary to perform nasal provocations with aqueous solutions of specific atypical allergens to determine if a

true-positive allergic or false-positive nonallergic reaction is responsible for a patient's nasal symptoms.

The presence of clear rhinorrhea in a patient with recent sinus surgery or head trauma should lead to suspicion of cerebrospinal fluid leak. This can be identified by glucose testing or dipstick, which will indicate a high glucose level nearing that of plasma. Glucose is not normally present in nasal secretion in the levels that are detectable by dipstick. The carbohydrates in normal nasal mucus are present in the oligosaccharide sidechains of mucins.

If performed properly, nasal cytology can be very helpful in differentiating inflammatory from noninflammatory rhinitis. Eosinophils are normally rare in nasal scrapings. Allergic rhinitis will typically have greater than 4% eosinophils, although the absolute percentages are used only for research purposes. Eosinophil markers, such as eosinophil cationic protein, major basic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase are elevated in allergic rhinitis. Elevations are also found in the nonallergic eosinophilic disorders, such as nonallergic rhinitis with eosinophilia syndrome (NARES), where 20% to 100% of the nasal smear or rhinoprobe sample may be eosinophils [4,5••,16••]. A variant is blood eosinophilia with nonallergic rhinitis eosinophilia syndrome (BENARES). Diagnosis of NARES requires negative allergy skin tests, and may be a precursor for the chronic eosinophilic sinus syndromes (CESS). This acronym is used as a general term to encompass the very broad series of eosinophilic disorders, and presumably a wide range of eosinophilic chemoattractant processes, such as nasal polyposis, aspirin sensitivity, triad asthma (Samter's syndrome), chronic noninfectious sinusitis, allergic fungal sinusitis, nonallergic fungal sinusitis, and other noninvasive fungal syndromes (*eg*, mycetoma) [4,5••]. Each is an inflammatory mucosal condition that should be treated as an inflammatory disorder.

Neutrophilia is highly suggestive of bacterial infection because microbial cell wall components can activate complement leading to C3b formation, epithelium and neutrophils can release interleukin (IL)-8, and neutrophils can release leukotriene B₄ (LTB₄). These three mediators are the most important neutrophil chemoattractants *in vivo*. Current treatment to reduce these mediators is limited to Zileuton, a 5-lipoxygenase inhibitor indicated for asthma (Zyflo, Abbott Laboratories, Abbott Park, IL) that decreases LTB₄ production, and steroids that downregulate IL-8 expression.

Epithelial cell metaplasia is related to the severity of chronic sinusitis [22]. Ciliated cells predominate in the healthy nose. Minor changes, such as narrowing of the OMC (May CT scan grade I) and ethmoid mucosal disease (grade II), are associated with a transition to goblet-cell predominance. This implies a decrease in cilia and mucociliary activity. Bilateral sinus disease (grade III) is associated with the predominance of poorly characterized microvillous cells. Pansinusitis (grade IV) is generally associated with polyposis [23] and squamous cell metaplasia with desquamation and bleeding with intact erythrocytes present above the basement

membrane. These changes are reversible with successful sinusitis treatment. The presence of blood suggests that the sinuses may become inoculated with gingival and fecal organisms due the transient bacteremias that follow brushing of the teeth and bowel movements. Malekzadeh *et al.* [23] have shown two types of chronic sinusitis histology: polyposis and glandular hyperplasia. This suggests that fundamentally different mechanisms lead to each type, and that different treatments may be required.

The presence of anatomical variants, masses, and sinus discharges can be identified by flexible and rigid rhinoscopy. These changes are also apparent on CT scans, which also identify the presence of sinus-bone osteitis, and MRI, which yields soft tissue contours without imaging the bone.

If only the nasal cavity is of interest, acoustic rhinometry is available to measure the cross-sectional area of the cavity as a function of distance from the nasal vestibule. The volume of each cavity can be integrated from this area function to assess asymmetries that may occur during the normal nasal cycle or due to unilateral masses. Anterior and posterior rhinomanometry is predominantly a research tool for measuring nasal airflow resistance. It has not been replaced by the nasal inspiratory flow, or maximal nasal inspiratory and expiratory flow-volume loops.

Mucociliary function can be assessed by placing a saccharine tablet on the nasal septum and timing how long it takes for the patient to taste the sweet substance. Care must be taken in placement, because the most anterior cilia sweep mucus anteriorly. Times longer than 15 minutes are considered abnormal. Nasal biopsy with electron microscopy is useful in identifying ciliary disarray in Kartagener's syndrome. However, ciliary dysfunction is common as allergic rhinitis, chronic sinusitis, and nasal polyposis worsen. This dysfunction may be reversible with clearing of the underlying inflammatory disease. Olfactory testing is useful in cases of nasal polyposis, cerebrospinal fluid rhinorrhea, and other conditions, but is rarely used clinically in other allergic or nonallergic syndromes.

Treatment Approaches

As described earlier, history and physical examination will give many clues regarding the appropriate NAR diagnosis, its underlying pathophysiology, and optimal treatment options (Table 4). Negative allergy skin tests or RAST results, or positive skin tests that do not corroborate a patient's history of rhinitis, suggest the presence of NAR [12]. Nasal scrapings or other evaluations may reveal eosinophilia, neutrophilia, or a normal cellular pattern. Visual nasal examination should follow to investigate unilateral or bilateral airflow obstruction, anatomical deviation of the septum, turbinates and other normal structures, mucopurulent sinus discharges, nasal polyps, or more sinister mucosal lesions that would require biopsy for diagnosis. Limited coronal CT scans may be

required to confirm the presence and extent of involvement of chronic sinusitis, nasal polyposis, vasculitis, and granulomatous and fungal diseases. CT scan may not be necessary in non-inflammatory NAR, because history, examination, skin tests, and nasal scrapings are likely to point to the specific diagnosis.

Brief summaries for treatment of AR, NAR, sinusitis, and nasal masses are given in Table 4. The remainder of this discussion is focused on the symptomatic treatment of other NAR syndromes.

Avoidance of known provocative stimuli is the mainstay of treatment. This includes avoidance of irritant gases (ozone, nitrogen oxides, vapor phase of tobacco smoke, sulfur dioxide, and its dissolved chemical form—sulfites); fine particulate materials (*eg*, diesel fuel particulate, dusts, particulate phase of tobacco smoke); cleaning materials (*eg*, bleaches); perfumes and other powerful odorants; cold, dry air; and other stimuli. However, this avoidance regimen is incompatible with a satisfying social life, and would be appropriate only for agoraphobics. Modification of lifestyle to avoid or reduce the impact of the most severe triggers is a more practical approach. Reduction of inhaled irritants can be effective with bedroom, home, office, face-mask, and personal (necklace-mounted) high-efficiency particulate air (HEPA) filters. Iatrogenic rhinitis due to NSAIDs, antihypertensive medication, or glaucoma drugs respond to alteration of the drug class.

Eosinophilic disorders such as NARES, BENARES, CESS, and nasal polyps should be treated with intranasal steroids. Oral steroids may be required to initiate a reduction in nasal polyp volume or improvement of chronic sinusitis. US Food and Drug Administration (FDA)-approved nasal steroids are beclomethasone, fluticasone, and budesonide for NAR and mometasone for sinusitis. Short courses of oral steroids are often beneficial for at least temporary relief of hyposmia or anosmia. These drugs may also be beneficial in noninflammatory NAR, because steroids can reduce nociceptive nerve sensitivity and activity, possibly by reducing the production of neurotrophic factors such as nerve growth factor.

Intranasal azelastine has benefited subjects without major inflammatory disease. The mechanism is unclear, but suggests an increase in nasal histamine release from metachromatic or bacterial cells, or a mechanism not involving histamine receptor antagonism. It is difficult to assess efficacy, however, because 82% to 85% of subjects respond to azelastine, and 73% to nasal saline. Saline is not a true placebo because it can actively dissolve irritants into the gel phase of epithelial lining fluid, and reduce the viscosity of the mucous gel phase. These effects would promote ciliary clearance of thick mucoid secretion and irritants. A parallel, no-treatment control group may be necessary for these studies. Nasal lavage with forceful irrigation of saline (*eg*, Water-Pik [Teledyne Waterpik, Fort Collins, CO] with Grossan nasal adapter [HydroMed, Los Angeles, CA]) of the nasal cavity, and

particularly sinus cavities, after sinus surgery can effectively improve cleansing of mucin-fibrinogen-plasma protein clots that adhere to sinus mucosal surfaces and may harbor infectious agents. The combination of a topical steroid and azelastine is a compelling, but scientifically untested treatment option.

First-generation, sedating antihistamines are often used for NAR. Their benefit may come from the anticholinergic properties of these drugs and their ability to reduce rhinorrhea. Ipratropium bromide nasal spray is a better option because it specifically blocks the cholinergically induced mucous exocytosis that can follow stimulation of nociceptive nerves by hot, spicy foods such as capsaicin (gustatory rhinitis); cold, dry air (Ski Bunny rhinitis); or other irritant exposures. This treatment is effective for prophylaxis before eating or other exposure, or to reduce mucus hypersecretion once it has begun. Injections of anticholinergic botulinum toxin have also been used experimentally. Anticholinergic therapy is an excellent adjunct for "runners" who have excessive mucoid discharge.

Ablation of nociceptive sensory nerves that may induce local mucosal axon responses and recruit parasympathetic reflexes have been tried using topical application of capsaicin. The putative normal human axon response to an irritant such as hypertonic saline is thought to be mediated by the mucosal release of substance P and other neuropeptides that cause glandular exocytosis without vascular permeability. Substance P antagonists have not been studied in rhinitis. Capsaicin has been effective at reducing sensations of irritation, congestion, and nasal blockage in NAR [20••]. However, this remains an experimental therapy because of the need for experimental provocation protocols, follow-up to observe for side effects an efficacy, co-administration of lidocaine to prevent severe nasal pain, and lack of an FDA-approved medication. Topical silver nitrate-induced mucosal necrosis has also been attempted, but is not advocated. Psychotropic drugs that alter nociception have not been adequately tested in neurogenic rhinitis.

α 1- and α 2-adrenergic agonists are excellent decongestants because they reduce the swelling of the deep venous sinusoids and superficial blood flow to reduce the thickness of the mucosa. Oral decongestants with greater α 1 than α 2 activities are limited by their vasoconstrictor effects in hypertension, and central nervous system effects of irritability, anxiety, and nightmares. These agents may regulate arteriolar blood flow to the most superficial fenestrated capillaries and postcapillary venules. Topical nasal decongestants tend to have greater α 2 than α 1 activities, and may have greater effects on the arteriovenous anastomotic vessels that regulate blood flow into the deep venous sinusoids. The engorgement of these vessels determines the mucosal thickness, the cross-sectional area of the nasal airspace within the bony box of the facial bones, and, thus,

nasal patency. These drugs are well tolerated for up to 3-day periods. Some studies suggest no rebound effects after 30 days of treatment. However, treatment for more than 30 days is associated with intense rebound hyperemia (rhinitis medicamentosa). It is unclear if all subjects will develop this syndrome, or if some subjects are predisposed. Specific agonists directed toward the most specific vasoconstricting $\alpha 1A/D$, $\alpha 1B$, $\alpha 1C$, $\alpha 2C10$, $\alpha 2C2$, or $\alpha 2C4$ receptors may be much more selective decongestants with fewer side effects.

Destruction of the parasympathetic innervation has had beneficial short-term effects in NAR. Vidian neurectomy is the classic procedure, but this cuts both parasympathetic and sympathetic tracts to the nasal mucosa. Thus, long-term effects have been unsatisfactory.

Anatomical defects may require bracing or surgery. Devices to prop open the fleshy alae nasi can increase the minimum cross-sectional area of the anterior nasal valve, decrease the work of nasal breathing, and improve subjective complaints. If significant contact of adjacent mucosal surfaces can be demonstrated by rhinoscopy or CT scan, then correction of septal deviation or partial resection of the inferior or potentially middle turbinate may be beneficial. Several surgical approaches have been advocated, ranging from resection to laser, cryosurgery, and submucosal diathermy [24,25]. Despite the frequency of turbinate hypertrophy and its use as a comparator to nasal polyposis in scientific investigations, there is surprisingly little known about the histology and pathology of this condition. It is important to remember that surgery will have no benefit, or may even worsen symptoms if neurologic, drug, or other types of rhinosinusitis are responsible for the complaints [3••,25].

Conclusions

The illusion that "nonallergic rhinitis" is "vasomotor rhinitis" should be shattered by this review of the predominant mechanisms that lead to the complex differential diagnoses of rhinitis with negative allergy skin tests (Tables 1–4). Improvements in treatment options will only occur as we classify our patients more discretely, and recognize the subsets of patients who are well-accommodated by current therapies, and those who have no responses. We can anticipate that our understanding of nasal pathogenic mechanisms will, in turn, be echoed by similar, discrete syndromes in the lower airways.

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