

Update on nonallergic rhinitis

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Background: Although nonallergic rhinitis is a well recognized entity, its incidence and therapy have not been definitively studied. Recent epidemiologic studies and treatment trials have furthered our knowledge regarding the frequency of occurrence of this disorder and effective treatment modalities.

Objective: To review and put into perspective recent advances in our knowledge regarding the incidence and significance as well as therapy of chronic nonallergic rhinitis. In addition, based upon these data, to propose a classification of this disorder.

Data Sources: The MEDLINE database and the results of a national survey of allergists (National Rhinitis Task Force) conducted in 15 allergy practices involving 975 patients.

Conclusions: Nonallergic rhinitis is a common disease that probably affects as many as 17 million Americans. Of equal importance is that, based on available data, approximately 22 million people suffer with a combination of nonallergic rhinitis and allergic diseases (mixed rhinitis). Both nonallergic and mixed rhinitis occur more frequently in adults than in children, may be more common in female patients than in male patients, and are more likely to be perennial than seasonal. Agents demonstrating efficacy (based on controlled trials or having approval by the FDA) for the therapy of nonallergic rhinitis are azelastine and topical nasal steroids.

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INTRODUCTION

Rhinitis is defined as inflammation of the membranes lining the nose, characterized by nasal symptoms, including itching, rhinorrhea, and/or nasal congestion. Chronic nasal symptoms without allergic causation are a broad classification of nasal diseases known as nonallergic rhinitis. As many as half of the patients presenting with nasal symptoms may have this disorder. Nasal symptoms characteristic of nonallergic rhinitis are often indistinguishable from those that occur in allergic rhinitis, and, therefore, negative testing for IgE-mediated sensitivity to relevant aeroallergens is necessary to confirm this diagnosis. However, it is

children.³ In contrast, the frequency of nonallergic rhinitis and the different syndromes that comprise this disorder are poorly defined and no true data have existed regarding prevalence. However, the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology points out that whereas allergic rhinitis is very common, approximately 50% of patients presenting with rhinitis do not have allergic rhinitis.³ Several studies have helped to establish the frequency of occurrence of allergic versus nonallergic rhinitis as seen in the allergist's office (Table 4). Mullarkey et al⁴ found that 52% of 142 rhinitis patients seen in an allergy clinic could be classified as having nonallergic rhinitis. Enberg⁵ evaluated 152 consecutive adults with nasal symptoms and found a 30% frequency of perennial nonallergic rhinitis. This frequency would increase to 46% if these subjects had been more precisely classified with positive skin tests, without clinical correlation, as having nonallergic rhinitis. The European Community Respiratory Health Survey (ECRHS)⁶ reported a 25% frequency of nonallergic rhinitis among 1,412 subjects selected for having a history that suggested allergic rhinitis. Togias⁷ found that 17% of 362 rhinitis patients at an academic allergy clinic had nonallergic rhinitis. These studies, however, may be skewed toward the allergic rhinitis because these patients are seen most often in the allergy practice.

Table 4. Frequency of Occurrence: Allergic vs Nonallergic Rhinitis

Study	Year	Patients	Allergic Rhinitis (%)	Nonallergic Rhinitis (%)
Mullarkey et al ⁴	1991	142	48	52
Enberg ⁵	1991	152	70	30
Togias ⁷	1991	362	83	17

Rough data from large population surveys indicate the prevalence of chronic sinusitis to be 13.5%⁸ and chronic rhinitis to be 20.4%.⁹ Presumably, a substantial portion of subjects surveyed would be more precisely labeled as having nonallergic rhinitis if skin testing and sinus imaging had been performed.

The Joint Task Force notes that data regarding the true prevalence of rhinitis are difficult to interpret. Physician-diagnosed rhinitis is the basis for most of the population surveys and may lead to a lower reporting of rhinitis whereas epidemiologic studies lean toward seasonal allergic rhinitis or hay fever, because identification of seasonal symptom exacerbation is easier to identify.³

Settipane and Klein¹⁰ looked at the frequency of occurrence of nonallergic rhinitis subtypes in 78 patients and determined that nonallergic rhinitis with eosinophilia syndrome (NARES) was found in 33%, blood eosinophilia nonallergic rhinitis syndrome (BENARS) in 4%, VMR in 61%, sinusitis in 16%, elevated I ϵ E in 12%, and

hypothyroidism in 2%. In his series of nonallergic rhinitis patients, Enberg⁵ found that 10% had NARES.

Three additional observations of note have been reported regarding the clinical presentation of nonallergic rhinitis. These include associations with age, sex, and seasonal occurrence/variation. Togias⁷ has observed that 70% of patients diagnosed with nonallergic nasal disease developed their condition in adult life (age >20 years), whereas approximately 70% of patients diagnosed with allergic rhinitis developed their condition in childhood (age <20 years). However, a causal relationship between aging and nonallergic rhinitis has not been confirmed by other investigators.¹¹

Sex may be a risk factor for the development of nonallergic rhinitis. In the series of Settipane and Klein,¹¹ 58% of the nonallergic rhinitis patients were female. Enberg⁵ found 74% of nonallergic rhinitis patients to be female. However, these two studies lacked a control group. The National Rhinitis Classification Task Force (NRCTF) study found that 71% of patients with nonallergic rhinitis were female compared with 55% in the allergic rhinitis group.¹²

Sibbald and Rink¹¹ found that patients with nonallergic rhinitis were more likely to experience perennial, rather than seasonal, symptoms. They reported the following frequencies of negative skin testing: 50% in patients with perennial rhinitis, 32% in patients with combined perennial/seasonal rhinitis, and 22% in patients with purely seasonal allergic rhinitis.

Although these epidemiologic data are interesting, consideration must be given to the fact that most of these studies classify patients as having only allergic or nonallergic disease while failing to accurately capture the significant number of patients with co-existing allergic/nonallergic rhinitis or "mixed rhinitis."

The NRCTF recently conducted a retrospective analysis of 975 patients in approximately 15 allergy practices with the goal of determining the prevalence of "pure" allergic, "pure" nonallergic, and mixed rhinitis in the allergy practice (Table 5).¹² Forty-three percent of patients were classified as having pure allergic rhinitis, 23% pure nonallergic rhinitis, and 34% mixed rhinitis. Of all patients presenting with chronic rhinitis, 57% were classified as having nonallergic rhinitis, either pure or mixed. (Table 6) Clearly, this relatively high incidence of nonallergic rhinitis and the similar symptomatic presentation of allergic rhinitis dictates that a definitive diagnosis be made before treatment is initiated.

Table 5. National Rhinitis Classification Task Force Survey of Nonallergic Rhinitis 1999 (N = 975)

Characteristic	No.	%
Male	500	51.3
Female	475	48.7
Age (yr)		
<18	10	1.0
18-30	100	10.3
31-45	200	20.6
46-60	300	30.8
>60	365	37.3

Table 6. National Rhinitis Classification Task Force Survey of Nonallergic Rhinitis 1999 (N = 975)

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Type of Rhinitis		
Pure Allergic	Mixed	Pure Nonallergic
43%	34%	23%
	37%	

CLINICAL PRESENTATION, DIAGNOSIS, PATHOPHYSIOLOGY, AND TREATMENT OF INDIVIDUAL NONALLERGIC RHINITIS SYNDROMES

Syndromes of Unknown Etiology

Vasomotor rhinitis (VMR). Vasomotor rhinitis is unrelated to allergy, infection, structural lesions, systemic disease, or drug abuse.³ It is a diagnosis of exclusion (eg, negative allergen testing) and is likely to result from many different etiologies. For the purposes of this review, the term VMR will be used to designate idiopathic, perennial nonallergic rhinitis associated with negative allergy skin tests to relevant allergens, normal serum IgE levels, and a lack of identifiable inflammation on nasal cytology.

The symptoms of VMR range from obstructive/congestive to secretory/rhinorrhea; sneezing and nasal pruritus are less common. In a survey of 678 rhinitis patients,¹³ nasal blockage was the predominant symptom in patients with VMR, whereas allergic rhinitis patients were more likely to suffer from eye irritation, some sneezing, and rhinorrhea. Concomitant asthma was more common in the allergic rhinitis group. Togias⁷ reported nonallergic rhinitis to be associated with fewer sneezes and conjunctival symptoms but, with regard to rhinorrhea or congestion, could not differentiate this disorder from perennial allergic rhinitis.

In terms of pathophysiology, little is known about VMR except that nonspecific nasal hyperreactivity occurs on exposure to nonimmunologic stimuli such as changes in temperature or relative humidity, alcohol ingestion, strong odors, and other airborne irritants. Hyperreactivity of the nasal mucosa to methacholine,¹⁴ capsaicin,¹⁵ and histamine¹⁶ has been demonstrated in the laboratory, but its cause remains unexplained.

Recent studies show an increased number of mast cells but not goblet cells in patients with perennial nonallergic rhinitis. No significant difference has been found between the number of mast cells in allergic and nonallergic patients. [17,18](#)

Options in the treatment of VMR include either nonspecific, "broad-based" therapy aimed at multiple symptoms or alternatively, therapy tailored to treat specific symptoms. Nonspecific treatment may be more advantageous because symptoms of VMR are often variable, alternating from obstructive/congestive to secretory/rhinorrhea. Examples of broad-based treatment include topical steroids and the topical antihistamine, azelastine.

Budesonide aerosol preparation, beclomethasone aqueous preparation, and fluticasone aqueous preparation are topical corticosteroids that have an FDA indication for the treatment of nonallergic rhinitis. The benefit derived from topical nasal steroids impact overall rhinitis symptoms rather than being limited to any one particular symptom. Because of their anti-inflammatory nature, it has been proposed that nasal steroids may have greater benefit when nasal mucosal inflammation is present. The pharmacologic effects of fluticasone nasal spray in nonallergic rhinitis have been studied. Unilaterally administered fluticasone nasal spray has been shown to have a beneficial effect on nasal inflammatory cells and cytokine profile in both allergic and nonallergic rhinitis patients. [19](#) The number of CD3, major basophil protein, and tryptase positive cells was significantly less in allergic and nonallergic treated patients as compared with controls, and IL-4 and IL-5 mRNA were downregulated on the treated side. Based on this information, a 2- to 4-week trial of a topical nasal steroid is a therapeutic consideration in VMR. [20,21,22](#)

Azelastine nasal spray was recently approved by the FDA for the treatment of the symptoms of VMR such as rhinorrhea, nasal congestion, and postnasal drip. Azelastine has been shown, in clinical trials, to be effective across the total symptom complex, ie, rhinorrhea, sneezing, and nasal discharge, without discrimination as to the type of nasal symptoms that respond. [23](#) Two multicenter, placebo-controlled trials, using identical protocols for the use of azelastine nasal spray in VMR patients, have demonstrated significant improvement in postnasal drip, rhinorrhea, sneezing, and congestion ([Table 7](#)). These studies had a fairly high response rate to azelastine; between 82% and 85% of more than 200 subjects with VMR were shown to respond favorably to azelastine nasal spray treatment. The response rate in the placebo group was 73%. It is not uncommon to see such a high placebo response when placebo consists of a nasal saline spray, as was the case in this study. In fact, nasal saline can be considered an "active placebo" because it is

often efficacious in nonallergic rhinitis. Clinical and preclinical studies suggest that the mechanism of azelastine effects may involve anti-inflammatory actions. ^{24,25,26,27,28} These include azelastine's ability to reduce the effects of neurokinins such as substance P and vasointestinal peptide, ²⁰ prevent histamine release in vitro and in vivo, ²¹ diminish eosinophil activation and the expression of adhesion molecules, ²² suppress the synthesis of inflammatory cytokines and nitric oxide via an inhibitory effect on nuclear factor- κ B (NF- κ B),²⁵ and reduce vascular permeability. ²⁴ These studies suggest that azelastine has significant effects on transcription of inflammatory factors, thus azelastine seems to have unique combination of anti-inflammatory effects in addition to those that have been traditionally cited, such as inhibition of histamine release, calcium transport, and the influx of inflammatory cells into the site of an allergic reaction. It is perhaps through a combination of all these activities, especially those involving decreased production of cytokines, that azelastine exerts its activity in VMR.

Table 7. Relative Contribution of Individual Symptoms to Overall Response

Although there are no direct comparison studies between azelastine and topical nasal steroids in perennial nonallergic (vasomotor) rhinitis, there is information which suggests that azelastine nasal spray has a more rapid onset of action than intranasal corticosteroids. This information consists of clinical studies of these individual therapies in allergic rhinitis as well as a review of their FDA-approved product information. In dose-ranging trials, azelastine nasal administration resulted in a decrease in symptoms which reached statistical significance from saline placebo within 3 hours after initial dosing. In comparison, a decrease in allergic rhinitis symptoms after fluticasone or budesonide may be seen in 12 to 24 hours and may even occur within 7 hours of the latter. Of further note, azelastine nasal spray is the only therapy shown in nonallergic rhinitis to improve all individual symptoms (congestion, rhinorrhea, postnasal drip, and sneezing) that are usually combined in a total symptom score for VMR. This may be because, in part, of the antihistaminic and anti-inflammatory activities of azelastine.

As mentioned previously, an alternate treatment plan for VMR is to target a specific symptom. For example, patients whose symptoms are primarily obstruction/congestion may be treated with decongestants as first-line agents. These can be administered topically on a short-term

basis, but for longer term use, they should be administered systemically because of the frequent adverse effect of rebound nasal congestion. Patients with predominantly secretory/rhinorrhea symptoms may be best treated with the anticholinergic agent ipratropium bromide in a nasal spray.²⁹ This is effective because of its ability to inhibit the parasympathetic (cholinergic) nervous system, which innervates the serous and seromucous glands of the nasal mucosa. Intranasal ipratropium bromide is well tolerated because there is little systemic absorption; no systemic anticholinergic drug-related adverse effects have been associated with its use.^{30,31} Topical side effects include infrequent episodes of nasal dryness and minor epistaxis.

Another treatment which may be useful for hypersecretion symptoms because of their anticholinergic, drying effect on nasal mucosa is first-generation antihistamines. However, there are no clinical data demonstrating the efficacy of this therapy in VMR. Further, first-generation oral antihistamines may be limited by frequently associated sedation and tachyphylaxis. The cost of treatment as well as the clinical implications suggest that oral antihistamines may not be the ideal approach to the treatment of rhinitis without a definitive diagnosis of allergic disease. Oral antihistamines would not be expected to be effective in pure nonallergic rhinitis and only partially or intermittently effective in mixed rhinitis.

Another therapy for VMR is topical saline in the form of a spray or irrigation device. Nasal saline may result in reduction of postnasal drip, sneezing, and congestion.³¹ In some cases, using the above therapies in various combinations may give added benefit. Experimental treatments for VMR include topical use of capsaicin intranasally.¹⁵ This is a pungent substance derived from pepper that acts to desensitize sensory neural fibers in the nose, reducing nasal hyperreactivity. Beneficial effects are delayed in onset with 63% and 69% reduction of nasal blockage and nasal discharge respectively, after 1 month of therapy. Topical application of 15% to 20% silver nitrate might also be effective.^{32,33} Surgical approaches to therapy include endoscopic vidian nerve section and/or electrocoagulation of the anterior ethmoidal nerve.^{34,35} In both surgical approaches, the parasympathetic supply to the nasal mucosa is divided, resulting in reduced nasal secretion. Although there may be recurrence of symptoms secondary to re-innervation, recent studies report long-term benefits.³⁶ Although sphenopalatine ganglion block has also been reported to relieve symptoms of VMR, the number of blocks required for complete relief range from 2 to 4.³⁷ In cases where congestion is the predominant symptom, turbinectomy is another treatment option. A variety of surgical procedures can be performed for the treatment of hypertrophic inferior turbinates. There is some concern about the extent to which the nasal mucosa return to a normal

functioning state after radical turbinectomy. However, laser turbinectomy has been reported to result in preservation of normal nasal cytology and saccharin time. ³⁸

Nonallergic rhinitis with eosinophilia syndrome (NARES). First described in 1981, Jacobs and colleagues ³⁹ presented a series of 52 patients with perennial symptoms of sneezing paroxysms, profuse watery rhinorrhea, and nasal pruritus. Nasal smears showed marked eosinophilia, but allergic disease could not be identified by skin testing or by RAST. This condition may represent approximately 15% to 33% of adults with nonallergic rhinitis. ^{4,10} In these patients, NARES usually occurs as an isolated disorder. However, it may be associated with non-IgE-mediated asthma, aspirin intolerance, and nasal polyps. BENARS seems to be a subtype of NARES. ¹⁰ Defined as having characteristics similar to NARES, BENARS is also associated with elevated numbers of blood eosinophils (average 957/mm³ in three patients). In a study of 78 consecutive patients with nonallergic rhinitis ([Table 8](#)), NARES was found in 33% and BENARS in 4% ([Table 9](#)). Rare nonallergic disorders associated with nasal eosinophilia include phaeohyphomycosis of the maxilloethmoid sinus ⁴⁰ and Churg-Strauss syndrome. ⁴¹

Table 8. Characteristics of Nonallergic Rhinitis Cases

Characteristic	Number	%
Male	33	42.3
Female	45	57.7
Age (years)		
< 10	1	1.3
10-20	12	15.4
20-30	18	23.1
30-40	15	19.2
40-50	10	12.8
> 50	12	15.4
Diagnosis		
NARES	26	33.3
BENARS	3	3.8
Other	49	62.7

Table 9. Diagnosis of 78 Patients with Nonallergic Rhinitis

Diagnosis	Number	%
NARES	26	33.3
BENARS	3	3.8
Other	49	62.7

NARES patients tend to have more intense nasal symptoms than patients with either VMR or allergic rhinitis. ⁴² Additionally, the presence of anosmia is common. The nasal cytology of NARES is characterized by eosinophilic infiltration, which may range from mild to massive, and is frequently associated with basophilic/metachromatic cell infiltration. ² The pathophysiology of NARES syndrome is not understood. Eosinophilia may contribute to nasal mucosal dysfunction. This may occur as a result of the release of toxic substances, such as major basic protein and eosinophil cationic protein contained in eosinophil granules. These toxic proteins may damage nasal ciliated epithelium and prolong mucociliary clearance. ^{43,44,45,46,47,48} In 1992, Davidson et al ⁴⁹ reported on 56 nonallergic rhinitis patients and found a significant correlation between nasal eosinophilia and prolonged nasal ciliary clearance time (as measured by saccharin clearance). Delayed mucociliary clearance

may result in an increased propensity toward infection. Recurrent infections may be a factor predisposing to the development of nasal polyps. Because nasal polyps are frequently associated with nasal eosinophils, there is some concern that nasal eosinophilia may be a precursor for nasal polyps or aspirin intolerance.⁴² In cases where aspirin intolerance exists, the aspirin reaction is not the etiology of the eosinophilic rhinosinusitis but mainly a marker of a severe form of NARES that is often associated with asthma, sinusitis, and nasal polyps. The presence of nasal eosinophilia in patients with nonallergic rhinitis is generally regarded as a good prognostic indicator for response to treatment with topical steroid therapy. Where eosinophilic infiltration is massive, which is often the case in aspirin sensitivity syndrome, intermittent to frequent use of oral glucocorticoid may be required to control symptomatology.

Basophilic/metachromatic nasal disease. Basophilic/metachromatic cell nasal disease, or nasal mastocytosis, is a subcategory of nonallergic rhinitis that, such as NARES, is a histologic diagnosis.^{50,51} Mast cell infiltration (frequently $>2,000/\text{mm}^3$) without nasal eosinophilia is the hallmark of this syndrome. Nasal symptoms are more likely to be secretion/rhinorrhea and congestion/blockage without significant sneezing/pruritus. Physical examination reveals an especially pale nasal mucosa. Unlike patients with NARES, patients with this condition are not predisposed to develop aspirin sensitivity, nasal polyps, asthma, or sinusitis. The etiology of this condition is unknown. Because it is an inflammatory condition, treatment should include a trial of topical anti-inflammatories; some patients benefit from intranasal cromolyn or intranasal corticosteroids, whereas others may require oral corticosteroids.

Syndromes of Suggested Etiology

Chronic sinusitis. Chronic rhinitis symptoms may be associated with or result from chronic infection and/or inflammation of the paranasal sinuses. According to a 1975 health interview survey, chronic infectious rhinosinusitis was experienced by 4% of the population.⁵² In 1985 the U.S. National Health Interview Survey ranked chronic sinusitis first among the most common chronic diseases, with a prevalence of 13.5%.⁸

Chronic sinusitis in adults has been recently defined⁵³ as persistent symptoms and signs of sinusitis lasting >8 weeks, or four episodes per year of acute sinusitis, each lasting at least 10 days in association with persistent changes documented by computed tomography (CT). CT of the sinuses should be performed 4 weeks after medical therapy without intervening acute infection. In children, the respective figures are 12 weeks of symptoms or more than six episodes of sinusitis per year. The symptoms and signs of chronic sinusitis are nasal congestion, discharge,

headache, facial pain or pressure, and olfactory disturbance, with fever and halitosis as minor symptoms, and cough and irritability as possible symptoms in children.

The etiology of chronic sinusitis often involves an infectious origin, but the extent to which chronic infection is important in the perpetuation of the disease is unclear. Further, it is not clear to what extent anaerobic bacteria are present in chronic sinusitis as a result of dysfunctional sinus clearance or whether, in some cases, anaerobes may be a primary cause of the condition.⁵⁴ It is important to note that bacteria found in cultures of nasal secretions are not representative of those found in the infected sinus cavity. The frequent failure of prolonged and intensive antimicrobial therapy suggests that bacterial infection is not the cause of the persistence of chronic sinusitis. It is more likely that chronic sinusitis represents chronic mucosal inflammation, which is multifactorial in etiology.

The inflammatory nature of chronic sinusitis has been well documented. In the sinus fluid of chronic sinusitis patients undergoing surgery, inflammatory cells are mainly the neutrophils normally observed in acute sinusitis, but a low percentage of eosinophils, mast cells, and basophils may also be observed.^{55,56} High concentrations of histamine, leukotrienes C₄, D₄, and E₄, and prostaglandin D₂ have been found, suggesting mast-cell/basophil activation in chronically inflamed sinuses.

The diagnosis of chronic sinusitis in a nonallergic population necessitates a workup for an underlying etiology (Table 10). With proper diagnosis and treatment of the underlying disorder, chronic sinusitis is optimally controlled. One example is osteomeatal complex obstruction, which when identified and treated, first medically and, if that is unsuccessful, then by endoscopic surgery, may reverse the infectious process, at least temporarily. Another example is antibody deficiency syndromes that usually respond well to intravenous replacement therapy.

Table 10. Conditions That May Underlie Chronic Sinusitis

Table 10. Conditions That May Underlie Chronic Sinusitis
Anatomical
Rhinitis
Nasal polyps
Ciliary dyskinesia, Kartagener syndrome
Cystic fibrosis
Granulomatous disease
Neoplasms
Immunodeficiency

There are, however, many patients with chronic sinusitis in whom no underlying disorder can be identified. An underlying inflammatory process is often present and can contribute to inadequate sinus ventilation and drainage. These patients, who often respond poorly to therapy, present a therapeutic dilemma. Scarce data exist on the efficacy

of treatment for chronic sinusitis. Intuitively, maintenance of sinus osteal patency is important for proper drainage of retained secretions. Treatment should include a long-term trial of a topical steroid nasal spray in an attempt to reduce tissue inflammation and edema in the region of the osteomeatal complex obstruction. Additional therapeutic modalities that may be beneficial include guaifenesin, decongestants, steam inhalation, and saline spray or irrigation, and for acute flares, intermittent 3-week courses of antibiotics sometimes combined with systemic glucocorticoids. However, treatment will not be successful until a more complete understanding of the pathomechanisms of inflammation in chronic sinusitis is achieved.

Metabolic conditions. Pregnancy, oral contraceptives, other estrogens, hypothyroidism, and acromegaly can contribute to rhinitis symptoms. In pregnancy rhinitis, it often turns out that rhinitis symptoms, usually of less severity, have been present since before conception, and often these symptoms can be attributed to causes unrelated to the pregnancy.⁵⁷ The extent to which pregnancy is a causal factor is unknown; it may be more of an aggravating factor. During pregnancy, physiologic changes may contribute to increased nasal congestion/obstruction. Among these changes are a massive expansion of circulating blood volume, which contributes to an increase in nasal vascular pooling, and possible progesterone-induced, vascular smooth muscle relaxation. Further, pregnancy-associated hormones may have a direct effect on the nasal mucosa, resulting in increased nasal secretion/rhinorrhea secondary to increased nasal mucous gland hyperactivity.⁵⁸ Additionally, episodes of bacterial rhinosinusitis have been noted to be more common during pregnancy.⁵⁹ A complete discussion of the treatment of rhinitis during pregnancy is beyond the scope of this review.⁶⁰ However, the major principle underlying the treatment of rhinitis in pregnancy is caution with medication use. First-line treatment should include the safest therapies such as steam inhalation, nasal saline sprays, and an avoidance of irritants. Topical medical therapy is preferred to systemic. The FDA classification system for the safety of medications in pregnancy provides additional guidance.

Vasculitides/autoimmune and granulomatous diseases. Systemic autoimmune/vasculitis diseases such as Churg-Strauss vasculitis,⁴¹ systemic lupus erythematosus,⁶¹ relapsing polychondritis,⁶² and Sjögren syndrome⁶³ can also result in rhinitis. Additionally, granulomatous diseases such as sarcoidosis⁶⁴ and, more commonly, Wegener granulomatosis⁶⁵ can produce nasal manifestations in a large proportion of affected patients.

Rhinitis sicca is a related syndrome that commonly occurs in Sjögren syndrome. It may also occur as a normal consequence of aging.

Nasal polyps. Nasal polyps, which occur in approximately 1% of the general population, are not any more frequent in patients with allergic rhinitis.⁶⁷ Nasal polyps are frequently associated with aspirin intolerance and aspirin tetrad syndrome (aspirin intolerance, nasal polyps, sinusitis, and asthma), intrinsic asthma, chronic sinusitis, Young syndrome, cystic fibrosis, Kartagener syndrome, Churg-Strauss syndrome, and allergic fungal sinusitis (Table 13). Children 16 years or younger with nasal polyps should be evaluated for cystic fibrosis. Nasal polyps are often bilateral, multiple, freely movable, and pale gray, and arise from the middle meatus of the nose. Polyps in the paranasal sinuses can lead to bone erosion of the sinus walls (Woakes syndrome).⁶⁸ Histologically, nasal polyps classically have a pseudostratified ciliated columnar epithelium, thickening of the epithelial basement membrane, a high stromal eosinophil count, mucin with neutral pH, few glands, and essentially no nerve endings.⁶⁹ Cells usually consist of a mixture of lymphocytes, plasma cells, and eosinophils. The majority of nasal polyps are associated with an eosinophilic inflammatory mechanism. However, in polyps from cystic fibrosis patients, neutrophils predominate with insignificant eosinophils.⁷⁰ Chemical mediators found in nasal polyps are as follows: histamine, serotonin, leukotrienes (LTB₄, LTC₄, LTD₄, LTE₄), IL-5, norepinephrine, kinins, TAME-esterase, and possibly prostaglandin D₂.^{71,72} There is a higher concentration of histamine in nasal polyps than in normal nasal mucosa, and norepinephrine is present in greater concentration at the base of nasal polyps than in normal nasal mucosa.⁷³ The concentrations of IgA, IgE, and in some cases, IgG and IgM, are greater in polyp fluid than in serum.⁷⁴ At the present time, the pathogenesis of polyp formation is unknown. IgE-mediated disease is not the cause of nasal polyps. In fact, nasal polyps may be associated with a loss of susceptibility to potential additional effects of inhaled allergens.⁷⁵ Upper respiratory infections may contribute to the exacerbation of nasal polyps. Despite medical and surgical management, nasal polyps are frequently recurrent. Topical corticosteroids alone can often control symptoms.⁷⁶ If topical therapy is not effective, it is often worthwhile to try systemic corticosteroids before surgical polypectomy. A commonly used regimen starts with prednisone at 60 mg and tapers by 5 mg daily over a 12-day course. Beclomethasone has been approved by the FDA for the prevention of nasal polyp reoccurrence after surgical removal. Polypectomy does not increase the risk of developing asthma or making asthma worse.⁷⁷

Table 13. Etiology of Nasal Polyps

Aspirin intolerance
Aspergillus sinusitis
Intrinsic asthma
Chronic sinusitis
Young syndrome
Cystic fibrosis
Kartagener syndrome
Churg-Strauss syndrome
Allergic fungal sinusitis

Structurally related rhinitis. Common anatomical causes of nasal obstruction include deviated septum, enlarged turbinates, dysfunctional nasal valve, and in children, adenoid hypertrophy. Anatomical abnormalities account for approximately 5% to 10% of chronic nasal disorders. Nasal septal deviation is fairly common but usually mild and well tolerated. In cases where deviation is moderate to severe, particularly when there is concomitant nasal mucosal edema secondary to underlying rhinitis, symptoms of blockage will result and may be complicated by sinusitis, snoring, sleep apnea, and fatigue. Enlarged turbinates and nasal valve disease are also aggravated by concomitant rhinitis. Therefore whenever there is any question about the extent of anatomical cause, and before the physician embarks on a surgical procedure to reduce the bulk of nasal turbinates, straighten the septum, or correct a dysfunctional nasal valve, workup and treatment of associated rhinitis should be pursued.

Common structural causes of rhinitis symptoms were mentioned previously, but rare causes of obstruction/congestion deserve mention. The differential diagnosis includes tumors and neoplasms such as chordoma, chemodectoma, neurofibroma, angiofibroma, inverting papilloma, squamous cell carcinoma, sarcoma, and encephaloceles or meningocele.

Structural defects may also result in rhinorrhea. A rare cause of rhinorrhea is cerebral spinal fluid (CSF) leak, occurring most commonly as a result of trauma, but also either spontaneously or as a complication of surgery.⁷⁸ Although traumatic CSF leaks usually present within 48 hours of trauma, delayed onset can be seen. However, 95% of cases present within 3 months. Because CSF contains sugar and nasal mucous does not, testing for the presence of glucose is helpful in making the diagnosis. Quantitative glucose measurements accurately identify the fluid as CSF if it contains more than 30 mg/100 mL glucose. A more specific test for CSF rhinorrhea is β_2 -transferrin, which has come into common use in recent years.⁷⁹ Additionally, thin coronal CT, radionuclide cisternography, and magnetic resonance cisternography can help to localize the site of CSF leakage.⁸⁰

Atrophic rhinitis. In industrialized countries, atrophic rhinitis is usually only seen as a rare complication of radical nasal tissue removal by surgery aimed to relieve obstruction.^{81,82} In undeveloped countries, symptoms of epistaxis, severe crusting, and stuffiness are associated

with a foul or fetid odor and *Klebsiella* colonization. Presumably, greater use of antibiotics has reduced the occurrence of this syndrome in developed countries. Atrophic rhinitis is resistant to treatment. The standard modality is antibiotic treatment of bacterial overgrowth and aggressive nasal saline irrigation. One suggested form of saline therapy is the use of a dental water-pick attached to a nasal irrigator nozzle. An alternative therapy is the implantation of bone chips, which reportedly reduces nasal stuffiness.

Physical/chemical/irritant-induced rhinitis. Physical triggers of rhinitis symptoms include cold and dry air, ingestion of spicy food, and exposure to bright light. These common triggers are most often markers of increased nasal hyperreactivity because of an underlying nasal disorder. However, patients without an underlying disorder, particularly those who work outdoors in the cold, occasionally present complaining chiefly of excessive nasal symptomatology in response to the above stimuli. Some insight into the pathophysiology of this disorder has been gained by reproducing the conditions in the laboratory. Studies with cold, dry air have demonstrated the involvement of both mast cell degranulation and an increased neuronal reflex mechanism.^{83,84} The underlying defect seems to be an inability of the nasal mucosa to humidify inhaled air at extreme atmospheric conditions. This results in increased osmolality of nasal secretions and nasal epithelial desiccation and detachment, leading to mast cell degranulation and activation of irritant sensory nerves. Studies with spicy food ingestion have suggested the pathophysiology involves a purely neurogenic reflex mechanism, with the efferent pathway being parasympathetic nerve fibers.⁸⁵ This condition is called gustatory rhinitis. Why some patients may have a more responsive reflex mechanism is unknown. Effective treatment for both these conditions is prophylaxis with topical ipratropium bromide before cold air exposure or eating spicy food.

An increasing array of indoor and outdoor air pollutants is recognized as affecting the nose. Among these are dust, ozone, sulfur dioxide, formaldehyde, volatile organic compounds, wood smoke, and environmental tobacco smoke.⁸⁶ The relationship between frequency of exposure and the development of acute or chronic rhinitis syndromes is unknown. Nor has associated rhinitis been well characterized. Most of these triggers are nasal irritants causing dryness and reduced nasal airflow, rhinorrhea, and sneezing.⁸⁶ Chronic cigarette smoke exposure results in decreased cilia beat frequency, ineffective movement, and frank deciliation in experimental models.⁸⁷ Ciliostasis has been demonstrated in wood workers exposed to dust.⁸⁸ Neutrophils' influx has been shown to occur with ozone exposure and exposure to volatile organic compounds.^{86,89} Chronic exposure to formaldehyde vapors may result in nasal histologic abnormalities.⁹⁰ Prolonged occupational

associated with sneezing episodes and conjunctival complaints. Frequently, however, nonallergic rhinitis occurs in tandem with allergic disease and presents as mixed rhinitis. Approximately 22 million people suffer with a combination of allergic and nonallergic disease. Nonallergic rhinitis, pure and mixed, occurs more frequently in adults than in children, may be more common in women, and is more likely to be perennial than seasonal. Common causes of nonallergic rhinitis are VMR, chronic sinusitis, nasal septal deviation, NARES/BENARES, nasal polyps, and aspirin sensitivity; nonallergic rhinitis may also be drug-induced, estrogen-related, or physical/chemical/irritant-induced. Infrequent causes include hypothyroidism, atrophic mucosa, systemic immunologic disorders, CSF rhinorrhea, ciliary dyskinesia, and nasal mastocytosis. Frequency ranges from 2% for hypothyroidism to 61% for VMR. At least, in some cases, the pathophysiology of VMR seems to involve proinflammatory chemical mediators. Given the often indistinguishable symptoms and high incidence of pure nonallergic and mixed rhinitis, treatment should ideally be based on a differential diagnosis that includes skin testing for allergens. However, rhinitis is often treated empirically and oral antihistamines, most often chosen for empirical treatment, have not been shown to be effective for nonallergic rhinitis and would only be partially or intermittently effective for mixed rhinitis. If empirical treatment is chosen, treatment options should be limited to those which have been demonstrated to be effective in allergic and nonallergic disease. For long-term control of symptoms, topical medications are preferred to systemic and treatment should address all symptoms whether allergic or nonallergic in etiology. Azelastine nasal spray and intranasal corticosteroids should be considered as first-line therapy if empirical treatment is chosen. Additionally, it is sometimes worthwhile to use nasal lavage (saline washing). Experimental treatment includes capsaicin and silver nitrate application. Experimental surgical treatment includes vidian nerve section, electrocoagulation of the anterior ethmoidal nerve, sphenopalatine ganglion block, and turbinectomy. As knowledge grows of the pathophysiology of nonallergic rhinitis subtypes, physicians will be better able to treat this common disorder.

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