

Current Approaches to Diagnosis and Management of Rhinitis

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Abstract: Rhinitis affects >20% of the population and is a common reason patients visit their primary care physician. Proper therapeutic intervention initially requires differentiating rhinitis from acute and chronic rhinosinusitis. After establishing rhinitis as the etiology of a patient's symptoms, a careful, thoughtful history and physical examination aids the cause. Rhinitis can be allergic, nonallergic, or mixed (having features of both allergic and nonallergic rhinitis). Therapeutic interventions vary, depending on the etiology of rhinitis. Symptoms that are refractory to avoidance and pharmacotherapy warrant referral to an allergist or otolaryngologist for consideration of immunotherapy or surgical intervention. In many cases, adhering to an evidence-based therapeutic treatment algorithm will allow physicians to effectively manage rhinitis.

Key Words: allergic rhinitis, infectious rhinitis, nasal airway obstruction, nonallergic rhinitis, nonallergic rhinitis with eosinophilia syndrome, rhinitis, vasomotor rhinitis

Rhinitis is defined as inflammation of the nose and nasal cavity. Differentiating rhinitis from acute and chronic rhinosinusitis can be challenging. All three diagnoses are extremely common in the primary care and emergency department setting. There is also significant overlap in the presenting constellation of symptoms. Rhinitis alone is estimated to affect >20% of the adult population in the United States and cost

billions in healthcare spending annually.¹ Rhinitis is further separated into subclassifications that ultimately direct therapeutic planning. A systematic approach with careful attention to subtle differences in symptoms and physical findings allows one to differentiate rhinitis from acute or chronic rhinosinusitis and determine when and whether consultant referral is needed.

Rhinitis encompasses three primary entities: allergic rhinitis (AR), nonallergic rhinitis (NAR), and mixed rhinitis (MR), which involves elements of both AR and NAR. In addition, less common forms of rhinitis, including neoplastic and obstructive rhinitis, should be on the differential. AR is the most common form, affecting >32 million Americans. NAR is estimated to affect >19 million Americans, and MR affects >26 million Americans.²

Rhinitis is a disease affecting all ages and races, with patient complaints of rhinorrhea, sneezing, and nasal congestion. Decreased quality of life, increased missed work hours, and increased healthcare utilization contribute to the broad economic burden of rhinitis.³ Considerable overlap in rhinitis types (Fig. 1) can make diagnosis and management challenging. The impact and prevalence of the various forms of rhinitis change with age; older adult populations have a higher frequency of NAR, whereas pediatric and young adult populations have an increased frequency of AR.⁴ No matter the age or specific subtype of rhinitis, accurate diagnosis and treatment are critical to improve quality of life for this population.

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Key Points

- Allergic rhinitis (AR) and nonallergic rhinitis (NAR) are treated differently and require close attention to history and clinical examination findings to pursue an optimal treatment course. One-third of the time, the patient will have mixed rhinitis, having features of both AR and NAR.
- AR treatment initially focuses on avoidance and removal of triggers, followed by more aggressive therapies, including pharmacological intervention, allergy testing, and, potentially, immunotherapy.
- NAR results from perturbation of nasal homeostasis. Therapies initially are directed at correcting this perturbation.
- Following a treatment algorithm for rhinitis will help with thorough management and determine when specialist referral is indicated.

Diagnosing Rhinitis

AR

Numerous guidelines outline the diagnosis and management of AR. Untreated AR can progress to asthma, the so-called “atopic march.”⁵ Ker and Hartert and Zheng et al have both reviewed and outlined cross-sectional and longitudinal studies demonstrating the progression of atopic dermatitis in infants to AR and then asthma later in childhood, the triad defining the atopic march; however, the underlying mechanism of how the atopic march progresses remains debatable.^{6,7} Patients with AR may link their symptoms to seasonal or perennial environmental allergens or exposure to animals. Presenting symptoms may include sneezing, clear rhinorrhea, nasal congestion, ocular pruritus and matting, nasal pruritus, epiphora, headache, or olfactory disorders. Associated allergen exposure history and increased symptom intensity during specific seasons suggest seasonal AR. Perennial allergens such as dust, pets, or mold, however, can cause symptoms throughout the year.

An understanding of the pathophysiology behind AR provides a foundation for understanding current treatment concepts. Most often, AR results from a type I, immunoglobulin (Ig) E-mediated hypersensitivity reaction; however, chronic AR also has been linked to type IV hypersensitivity reactions.⁸ In the type I reaction, inhaled allergens adhere to the mucus secreted by the nasal mucosa and stimulate mast cells located in the subepithelial layers (Fig. 2). Upon repeated exposure to an antigen, activated mast cells release numerous cytokines, leukotrienes, and histamine, creating local edema in the early phase leading to nasal airway obstruction, pruritus, and rhinorrhea. The mast cell mediators recruit eosinophils that amplify the late-phase inflammatory response.⁸ In the setting of chronic allergic rhinitis, activated Th2 lymphocytes are recruited to the inflamed nasal mucosa and drive local and systemic production

of IgE and mast cell proliferation.⁹ Interrupting these inflammatory responses remains the foundation of AR therapy.

In patients in whom AR is suspected, allergy testing can be helpful to identify specific allergens. Two broad classifications of allergy testing exist: in vitro and in vivo testing. In vitro testing relies on a blood sample to conduct an immunofluorescence test for a panel of potential allergens. It is important to select an allergen panel that is representative of the local ecology and patient exposures because allergens vary with climate, geography, and occupation. The in vitro assay uses established levels of IgE for specific allergens in the patient sera to establish sensitivity. In vivo testing directly measures the patient's physical response to an antigen challenge. Several methods have been attempted, including intranasal, intraocular, and intraoral testing. Each of these methods has been discarded from common use for reasons of patient comfort or safety. Skin testing has been the dominant testing method during the past several decades because of the accessibility and safety of testing this organ. The selection of allergy testing technique should be based upon local practice standards, availability of testing techniques, and ability to handle associated complications (eg, anaphylaxis). Eczema, dermatographism, or other skin conditions may preclude patients from undergoing allergy skin testing.^{19–23}

Treatment of AR should focus on alleviating the symptoms that most bother the patient. A staged treatment strategy is shown in Table 1. It is often appropriate to begin with minimizing exposure to identified allergens.¹⁰ In situations in which complete avoidance is not possible, decreasing allergen load can improve symptoms. Although the evidence remains weak, a Cochrane review of clinical trials by Nurmatov et al found support for weekly bedding changes and washing/drying bedclothes on high heat settings to kill dust mites.¹¹ Keeping pets outdoors or, at minimum, out of sleeping areas is important for patients with pet dander allergy. For patients with environmental allergies, conducting yard maintenance with a mask of an appropriate filter size helps decrease allergen load. O'Meara et al performed a small double-blind randomized controlled trial on nasal filters, generating preliminary data on their potential efficacy in reducing rhinitis symptoms in subjects with AR.¹² Taivainen et al found decreased cow-barn rhinitis in subjects wearing a powered dust respirator helmet.¹³ Nasal saline douching with a high-volume/low-pressure system allows for mechanical removal of allergens from the nasal cavity.¹⁴ When these conservative measures do not adequately improve a patient's symptoms, pharmacotherapy should be considered. Nasal corticosteroids are extremely effective at reducing the inflammatory response.¹⁵ These require up to 6 weeks of consistent use to establish maximum efficacy for a patient. Patients should be urged to maintain therapy for at least this length of time before reevaluation. It is noteworthy that a subset of patients will be unresponsive to steroid therapy. Nonsedating second-generation H1 receptor antagonists such as loratadine, cetirizine, or fexofenadine are effective in combination with intranasal

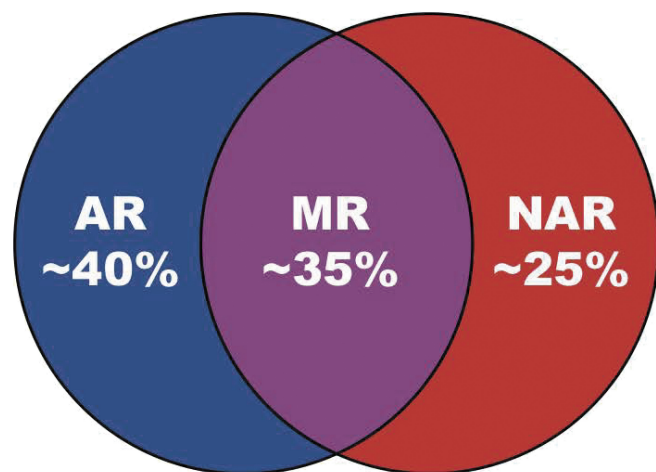


Fig. 1. Overlap in rhinitis types can make diagnosis and management challenging. AR, allergic rhinitis; MR, mixed rhinitis; NAR, nonallergic rhinitis.

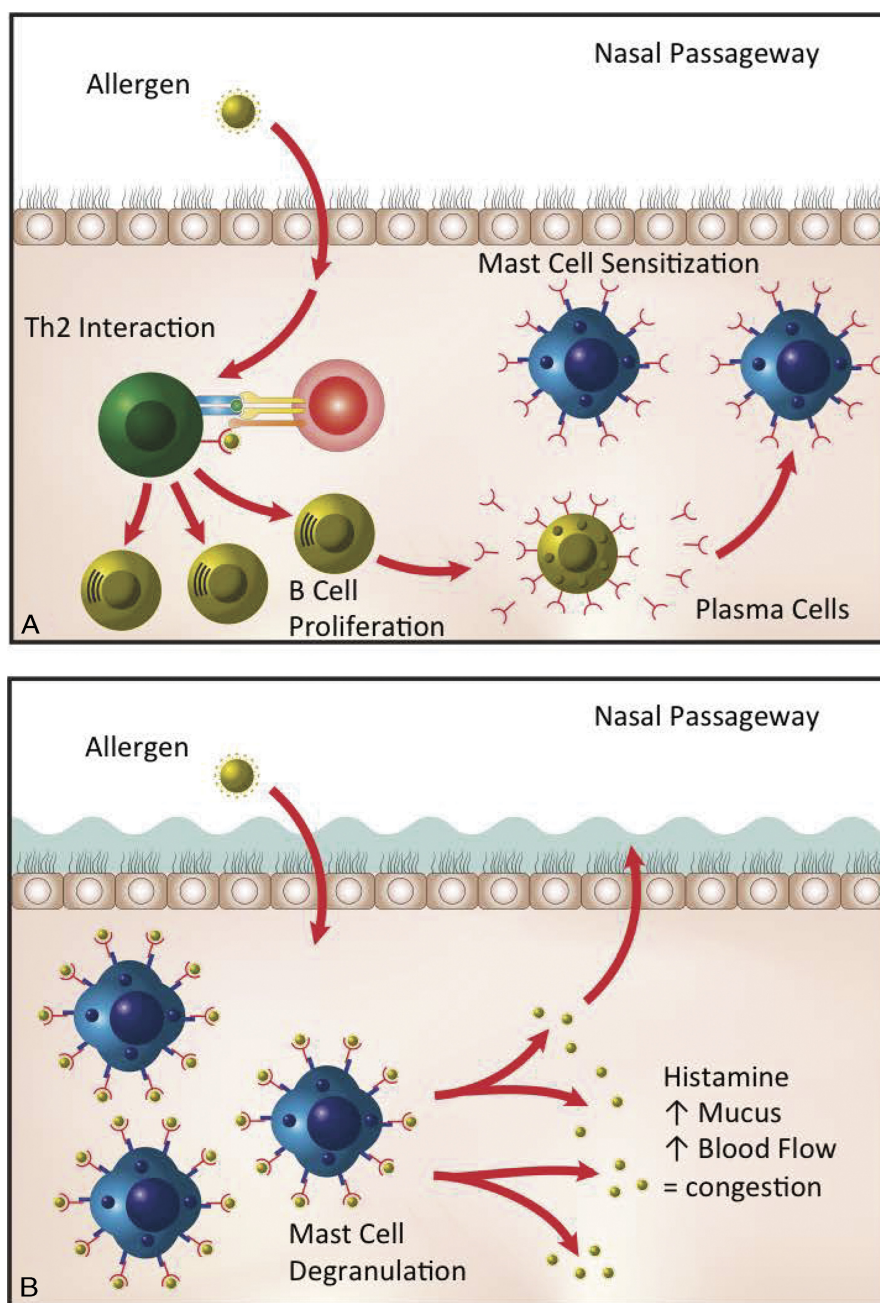


Fig. 2. Pathophysiology behind AR. A, Sensitization to allergen resulting in clonal expansion, specific antibody production, and mast cells with immunoglobulin E specific to allergen. B, Activation of mast cells in response to reexposure to allergen resulting in symptoms.

corticosteroids or as solo therapy.¹⁵ Leukotriene inhibitors have been shown to be as effective at reducing symptoms as loratadine when used as monotherapy; however, they are less effective alone than are intranasal corticosteroids.¹⁶ Horak and Zieglmayer determined that azelastine, a topical H1 antagonist, is as effective as topical fluticasone propionate and can be combined with intranasal corticosteroid therapy for even greater effectiveness.¹⁷ In patients who are refractory to medical therapy for AR, MR also should be considered. Referral for immunotherapy also may be considered. Given the potential for pediatric

patients to progress from AR to asthma as part of the atopic march, early referral for allergy testing and potential immunotherapy is appropriate.¹⁸

Immunotherapy is most commonly delivered by subcutaneous or sublingual routes. Subcutaneous immunotherapy predominates in the United States. Sublingual immunotherapy is more common in Europe and is becoming increasingly popular in the United States.^{19–21} The goal of immunotherapy by both delivery methods is to reduce a patient's response to allergens. Although data are mixed on the equivalency of these methods, when administered

Table 1. Rhinitis therapy strategies

Diagnosis	Treatment approach
AR	Primary
	Minimize allergen exposure
	Bedding changes/high-heat washing and drying
	Wear filtered mask during yard work
	± Allergy testing (blood or skin)
	Secondary
	Nasal corticosteroids
	± Second-generation H1 receptor antagonist or leukotriene inhibitor
	± Azelastine
	± Allergy testing (if not already done)
NAR	Tertiary
	Immunotherapy (SCIT vs SLIT) with completed allergy testing
	Consider MR—evaluate for NAR
	Specialty referral (allergy/otolaryngology)
	Primary
	Trigger avoidance (eg, medications, occupation)
	Nasal douching
	Secondary
	Azelastine
	± Fluticasone/beclomethasone
Other forms of rhinitis	± Ipratropium nasal spray
	Tertiary
	Consider MR—evaluate for NAR
	Specialty referral (allergy/otolaryngology)
	Correct any obstruction, infection, neoplasm
	Consider specialty referral

AR, allergic rhinitis; MR, mixed rhinitis; NAR, nonallergic rhinitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

appropriately, both methods have demonstrated superiority over placebo. Literature reviews on subcutaneous immunotherapy and sublingual immunotherapy point out that comparative clinical trials are lacking, and variations in primary and secondary outcome parameters in existing studies preclude effective comparison between the two immunotherapy methods.^{22,23}

For patients whose nasal airway obstruction is refractory to other therapies, referral to an otolaryngologist for surgical correction is appropriate. If a septal deviation or enlarged inferior turbinates are present, then septoplasty and turbinate reduction have been proven effective at improving nasal airway obstruction symptoms.^{24–26} Surgical reduction of the inferior turbinates was found to be more effective at resolving nasal airway obstruction in subjects with AR compared with intranasal corticosteroids in a randomized controlled trial by Gunhan et al.²⁷

NAR

NAR is a broader diagnostic category than AR and requires additional questioning to narrow a differential. Patients with NAR often present with the same symptoms found in

patients with AR but typically have subtle differences in their histories. Many etiologies exist for NAR, which are broadly categorized into infectious, hormonal, medication-induced, irritant, NAR with eosinophilia syndrome, autoimmune, occupational, or atrophic origin (Table 2).^{28,29} The cause of rhinitis for each category stems from its impact on nasal homeostasis.

Homeostatic perturbation in the nasal cavity may occur through disruption of sensation, the parasympathetic–sympathetic axis, humidification, moisture, temperature control, or non-IgE-mediated mast cell degranulation. Sensation to the nose is complex, but it primarily involves the olfactory and trigeminal nerves. The olfactory nerve provides sensations that are perceived as smell. The trigeminal nerve provides pain, pressure, and temperature feedback from the nasal cavity. The first division, V1, supplies the anterior ethmoid region and the second division, V2, supplies the remainder of the nasal cavity. Any exposure or insult to any of these processes should be examined further as a source of rhinitis.

Infectious etiologies, ranging from viral upper respiratory infection to rare pathogens, can cause rhinitis.²⁹ Commonly, infectious rhinitis is identifiable by history and associated symptoms of infection.

Hormonal alterations, as seen with thyroid dysfunction, puberty, menstruation, menopause, or pregnancy, have been linked to NAR.^{28,30–32} The hormonal alterations affect nasal homeostasis through disruption of the normal sympathetic–parasympathetic axis. In the setting of a relative increase in sympathetic tone, turbinates engorge because of constricted nasal outflow vessels. These engorged vessels yield a sensation of nasal congestion and obstruction, as is common during pregnancy.

Many medications have been linked to symptoms of rhinitis. Mechanisms of medication effects include local

Table 2. Forms of NAR

Classification	Examples
Infectious	Upper respiratory infections
Hormonal	Pregnancy
	Menopause
	Thyroid dysfunction
Medication-induced	ACE inhibitors
	β-Adrenergic agonists
	Phosphodiesterase inhibitors
Irritant	Cold air
	Spicy foods
NARES	Suggested chronic nasal inflammation
Autoimmune	Churg-Strauss
	Lupus
	Wegener granulomatosis
Occupational	Chemical exposure at work (eg, toluene)
Atrophic	<i>Klebsiella ozenae</i>
	History of extensive sinus surgery

NAR, nonallergic rhinitis; NARES, nonallergic rhinitis with eosinophilia syndrome.

inflammatory, neurogenic, or idiopathic forms.³³ Neurogenic drugs initiate rhinitis in a similar fashion to hormones, altering the parasympathetic-sympathetic axis. Examples include angiotensin-converting enzyme inhibitors or phosphodiesterase type 5 inhibitors.^{34,35} Inflammatory drugs act as chemical irritants to stimulate local inflammation. One form of this phenomenon is known as rhinitis medicamentosa and is most often linked to overuse of nasal decongestants. Inflammation also can result from overuse of other medications such as antihypertensives, antipsychotics, β -adrenergic antagonists, or oral contraceptives.^{36,37} Much remains unknown about the specific mechanism by which various drugs cause rhinitis, but careful evaluation of current medications and their temporal relationship with symptoms of NAR is warranted.

Irritant-induced rhinitis reflects both the chemical irritants found in occupational exposures and the changes in temperature, humidity, and barometric pressure. Cold air alters nasal homeostasis by increasing the release of tryptase and other mast cell-activation factors.³⁸ Alteration in the ability to maintain a steady temperature and humidity in the nasal cavity can cause vasoconstriction or vasodilation, resulting in subsequent edema, obstruction, and rhinorrhea. Dry, desert environments may challenge the ability of the nasal cavity to maintain adequate humidity. Irritants encountered at work or in the home environment also can initiate inflammatory responses. These responses range from gustatory rhinitis, typically experienced with spicy foods, to chemical inhalation, by toluene or other industrial products.³⁹⁻⁴² In cases of chemical and food exposure, nasal homeostasis is altered by significant activation and disruption of the olfactory and trigeminal nerve systems. Recreational activities such as swimming and running can produce rhinitis as well.⁴³ A study of British swimmers by Gelardi et al found that subjects with NAR or AR experienced improvement in nasal obstruction complaints after using a nose clip to prevent direct irritation by chlorinated water.⁴⁴ Consideration of a patient's living environment, hobbies, and occupation are, therefore, important components of a comprehensive rhinitis evaluation.

NAR with eosinophilia syndrome describes a patient with negative allergy testing but significant eosinophilia on nasal cytology. This syndrome most often involves an unknown trigger.⁴⁵ It is proposed that these patients have a chronic underlying nasal inflammation creating the eosinophilia and rhinitis symptoms. These patients have a higher risk of nasal polyposis and aspirin sensitivity.⁴⁶

It is important always to consider systemic diseases manifesting as rhinitis. Churg-Strauss disease, Graves disease, systemic lupus erythematosus, and Wegener granulomatosis have been associated with nonallergic rhinitis.^{29,47,48} Each is categorized as an autoimmune or immune-dysfunction rhinitis. Often, a thorough history and physical examination reveal other complaints or symptoms that are consistent with one of these or other forms of autoimmune diseases. If autoimmune disease is suspected, then screening blood work should be performed.

AR classically occurs in the context of extensive sinus resection and involves the triad of foul-smelling odor emanating from the nasal cavity with mucus membrane atrophy and bloody nasal crusts.⁴⁹ Nasal cultures frequently return *Klebsiella ozenae*.⁵⁰ AR is important to consider in patients from areas with little access to regular health care and in patients who have had extensive sinus surgery.

Treatment of NAR closely echoes that of AR. Initially, providers should determine whether AR has been identified and treated. Avoidance of triggers should be the mainstay of therapy whenever possible. For medication-induced rhinitis, identifying a substitute medication with a more favorable adverse effect profile should be considered. Nasal douching helps restore normal physiology by mechanical cleansing and providing moisture to the nasal cavity. This intervention also is safe and effective in pregnant patients.^{14,51,52} Although intranasal corticosteroids are used frequently for NAR, fluticasone and beclomethasone are the only nasal steroids with an indication for NAR in patients 4 years old or older.⁵³ Azelastine nasal spray has been proven effective in randomized controlled trials and carries an indication for NAR in patients 12 years or older.^{17,54} The anticholinergic effects of ipratropium nasal spray can be helpful in treating rhinorrhea caused by NAR. Surgical treatment may be considered for extensive crusting, nasal airway obstruction, or rhinorrhea that did not respond to more conservative treatment.⁵⁵

Other Forms of Rhinitis

Although the majority of rhinitis cases fits into either the AR or NAR variety, there are miscellaneous origins of rhinitis worth considering. Mechanical impingement on laminar airflow from polyps, deviated nasal septum, or trauma-induced bony fractures can incite rhinitis symptoms.³² Most often, these are identifiable on anterior rhinoscopy; however, posterior or superior obstruction may escape initial detection, requiring endoscopic evaluation. More important, rhinitis may originate from a neoplastic origin that either causes mechanical obstruction or alters metabolism within the nasal cavity. Lymphoma is the most frequently described neoplastic cause of rhinitis.⁵⁶ Treatment for these forms of rhinitis targets correcting the obstruction, infection, or neoplasm with appropriate specialist involvement.

Conclusions

AR and NAR are common maladies affecting large portions of the population. Careful attention and a thoughtful history and physical examination allow physicians to systematically investigate and accurately diagnose the patient. Successful treatment of each patient hinges on identification and treatment of the specific type of rhinitis involved.

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