

Allergic and nonallergic rhinitis

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ABSTRACT

Rhinitis is characterized by nasal congestion, rhinorrhea, sneezing, and/or posterior nasal drainage. It affects a significant portion of the population and presents a large burden economically and on quality of life. Rhinitis is broadly characterized as allergic and nonallergic, of which nonallergic rhinitis may be divided into inflammatory and noninflammatory etiologies. The inflammatory causes include nonallergic rhinitis with eosinophilia, postinfectious, and rhinitis associated with nasal polyps. The noninflammatory causes include idiopathic nonallergic (vasomotor) rhinitis, medication-induced rhinitis, hormone related (e.g., pregnancy), and systemic disease related. Allergic rhinitis is classified as intermittent or persistent and mild versus moderate-severe. The nasal mucosa is extremely vascular; parasympathetic stimulation promotes an increase in nasal cavity resistance and nasal gland secretion, whereas sympathetic stimulation leads to vasoconstriction. The diagnosis of rhinitis begins with a directed history, particularly noting pattern, chronicity, and triggers of symptoms. Examination of the nasal cavity with attention to appearance of the septum and inferior turbinates is recommended. Skin testing for aeroallergens is helpful in demonstrating the presence or absence of immunoglobulin E antibodies and to differentiate nonallergic from allergic rhinitis. Treatment includes patient education, irritant or allergen avoidance, and pharmacotherapy. Medications used for the treatment of rhinitis include intranasal corticosteroids, oral and intranasal antihistamines, intranasal anticholinergic agents, oral decongestants, and leukotriene receptor antagonists. When used in combination, an intranasal antihistamine spray and nasal steroid provide greater symptomatic relief than monotherapy. Allergen immunotherapy is the only disease-modifying intervention available for allergic rhinitis.

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Rhinitis is a symptomatic disorder usually characterized by inflammation of the nasal mucosa, typified by the presence of one or more of the following: nasal congestion, pruritus, sneezing, rhinorrhea, and posterior nasal drainage. Rhinitis is broadly classified as allergic or nonallergic in etiology. Allergic rhinitis (AR) affects nearly 60 million people in the United States, with approximately 80% of those diagnosed with AR developing symptoms before age 20 years.¹ Boys tend to have an increased incidence of AR in childhood, but women are more commonly affected in adulthood.^{1,2} Moreover, AR has a strong association with asthma and results in reduced quality of life and significant medical expenditures, including indirect costs from missed work and school. Nonallergic rhinitis (NAR) affects > 22 million people in the United States and is present more commonly in women, with an age of onset usually > 40 years.³ Many patients have overlap features of AR and NAR, referred to as mixed rhinitis.

NASAL ANATOMY

The inferior, middle, and superior turbinates, located laterally in each nasal cavity, are lined by pseudostratified columnar epithelium composed mostly of ciliated cells and mucus-secreting goblet cells.⁴ The nasal mucosa regulates temperature and filters and humidifies inspired air. It is extremely vascular, and changes in blood supply can lead to obstruction. The nasal mucosal vasculature is predominantly affected by the autonomic nervous system.⁴ Sympathetic stimulation leads to vasoconstriction and a consequent decrease in nasal cavity resistance. Parasympathetic stimulation, however, promotes nasal gland secretion and an increase in nasal cavity resistance.

PATHOPHYSIOLOGY

AR is an immunoglobulin E (IgE) mediated, eosinophilic inflammatory response to inhaled allergens, including pollens, mold, animal dander, dust mite fecal particles, and cockroach residue in previously sensitized hosts.⁴ The sensitization process begins in the nasal tissues when antigen presenting cells phagocytose and process the inhaled allergen and, subsequently, present the processed antigen to CD4⁺ T cells in local lymph nodes. The allergen stimulated T cells proliferate in a T-helper type 2 (Th2) pathway and release cytokines, including interleukin (IL) 3, IL-4, IL-5, IL-13, among others.¹ These cytokines lead to local and systemic production of IgE antibodies by

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plasma cells. These antibodies bind to the high-affinity receptor (FcεRI) on mast cells and basophils. This process is referred to as sensitization. On allergen re-exposure, cross-linking of IgE-FcεRI complexes facilitates degranulation of mast cells and basophils, which release preformed mediators, including histamine and enzymes (e.g., tryptase).⁴ There also is rapid *de novo* synthesis of other mediators, such as cysteinyl-leukotrienes (leukotriene C4, leukotriene D4, leukotriene E4) and prostaglandin D₂ (PGD₂).⁴

Histamine produces pruritus, rhinorrhea, and sneezing, whereas leukotrienes and PGD₂ are associated more with the development of nasal congestion. This process comprises the early or immediate-phase response. Cytokines released during the immediate-phase response mediate a cascade of events over the next 4–8 hours, referred to as the late-phase response. Clinical symptoms in early and late response are similar, but nasal congestion predominates in the late phase.¹ Mediators released at the postcapillary endothelial cells during the early phase response promote the expression of adhesion molecules, which assist in migration of eosinophils, neutrophils, and basophils, and eventually macrophages and CD4⁺ Th2 cells into the superficial lamina propria of the nasal cavity. These cells become activated and produce more mediators that are similar to those involved in the early phase, except for mast cell–derived tryptase and PGD₂, which suggests basophil-derived histamine release in the late phase.^{2,4}

NAR represents a non-IgE-mediated group of disorders. Although symptoms are similar to AR, there is an absence of skin test reactivity and negative specific IgE skin reactivity to common aeroallergens.¹ The pathogenesis of NAR is incompletely understood. One theory is based on the concept of localized allergy in the nose, without positive skin-prick or allergen-specific serum IgE results.² Nasal nociceptive nerve dysfunction and possible resultant loss of sympathetic activity or increased parasympathetic reflex are suggested to play a role.⁵ Some studies looked at how environmental irritants can precipitate rhinitis by activating transient receptor potential channels on nasal mucosa and initiating release of neuropeptides.⁵

CLASSIFICATION OF AR

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines⁶ classify AR as intermittent (symptoms present for < 4 days per week or < 4 weeks per year) or persistent (>4 days per week and >4 weeks per year). Intermittent and persistent rhinitis are further categorized into mild or moderate-severe disease based on the severity of the symptoms and quality-of-life outcomes. Rhinitis is categorized as mild if the symptoms do not interfere with quality of life, such as impairment of daily activities or school or work per-

formance, and if symptoms are not troublesome.⁷ The disease may be classified as moderate-severe if one or more of the above-mentioned conditions is present. The ARIA guidelines⁶ classification has largely replaced classifying AR by temporal patterns: seasonal for individuals who have symptoms only during particular pollen (tree, grass, weed) or mold seasons, or perennial for those with year-round symptoms typically caused by pet dander, house-dust mite, and cockroach.

SUBTYPES OF NAR

NAR may be divided into two broad etiologies: inflammatory and noninflammatory.^{2,3,8} A differential diagnosis based on this classification is represented in Table 1. Vasomotor rhinitis, also referred to as idiopathic, nonallergic noninfectious rhinitis, is the most common of these disorders and manifests with symptoms of perennial nasal congestion, rhinorrhea, and posterior nasal drainage. Unlike AR, nasal pruritus is rare. Classic “nonallergic” triggers include irritants (e.g., weather or temperature changes), smoke, perfumes, chemicals, and strong odors.² Subclassifications of vasomotor rhinitis include gustatory rhinitis (rhinitis provoked by eating, especially hot or spicy foods) and exercise induced. In NAR with eosinophilia syndrome, eosinophils are found in nasal cytology (>5% to >20%); however, skin testing results for aeroallergens is negative.³ The etiology for this condition is unknown. NAR with eosinophilia syndrome usually manifests in middle-age adults and is uncommon in children. Patients may have sneezing paroxysms, copious amounts of clear rhinorrhea, nasal pruritus, and anosmia.¹

Primary atrophic rhinitis occurs in young-to-middle-age adults who present with nasal congestion and foul smelling, thick, dry crusts in the nares. This disease of unknown etiology is more prevalent in developing countries with tropical climates.⁹ Bacterial infections are common.⁹ Secondary atrophic rhinitis, more common in Western countries, may result from granulomatous disease, nasal irradiation, aggressive nasal surgery, or trauma.⁸ It is less severe and progressive than primary atrophic rhinitis. Infectious rhinitis or rhinosinusitis may present with purulent nasal secretions, fever, and/or headache among other symptoms. Acute viral upper respiratory infections commonly predispose to bacterial sinusitis. Rhinitis also may result from hormonal changes, such as those that occur during pregnancy, puberty, and menstrual cycles. Symptoms associated with pregnancy usually occur in the third trimester and typically resolve within 2 weeks of delivery.¹

Overuse of topical α-adrenergic agents such as phenylephrine and oxymetazoline can result in rhinitis medicamentosa. Use of these medications for >5 to 7 days may result in rebound congestion on stopping the medication. Classically, “beefy red” turbinates are seen on

Table 1 Classification scheme of nonallergic rhinitis

Inflammatory
Infectious rhinosinusitis
Viral
Bacterial
Fungal
Nonallergic rhinitis with eosinophilia
Rhinitis associated with nasal polyposis
Noninflammatory
Idiopathic nonallergic rhinitis or vasomotor rhinitis
Rhinitis medicamentosa or drug-induced rhinitis caused by
Topical drugs
Phenylephrine
Oxymetazoline
Topical illicit agents
Cocaine
Systemic drugs
Angiotensin-converting enzyme inhibitors
β -adrenergic antagonists
α 2-Adrenergic agonists (clonidine, methyldopa)
α -Adrenergic antagonists (prazosin, tamsulosin)
Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil)
Hydralazine
NSAIDs and aspirin (in AERD)
Gabapentin
Psychotropic drugs
Thioridazine
Risperidone
Chlordiazepoxide-amitriptyline
Ovarian hormonal agents
Oral contraceptives (high dose, older generation)
Hormone replacement therapy
Hormone-induced vasomotor instability
Pregnancy
Rhinitis associated with systemic disease
Severe hypothyroidism
Chronic fatigue syndrome
Eosinophilic granulomatosis with polyangiitis
Granulomatosis with polyangiitis (ANCA+ vasculitis)
Midline granuloma
Ciliary dysfunction syndromes, <i>e.g.</i> , cystic fibrosis
Rhinitis associated with structural defects
Deviated septum and/or septal-wall abnormalities
Trauma resulting in cerebrospinal fluid rhinorrhea
Tumors
Foreign bodies

NSAID = Nonsteroidal anti-inflammatory drug; AERD = Aspirin-exacerbated respiratory disease; ANCA+ = Anti-neutrophil cytoplasmic antibodies.

physical examination. Other medications that may cause symptoms of rhinitis include α -receptor antagonists, phosphodiesterase type 5 inhibitors, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs.¹

DIFFERENTIAL DIAGNOSIS

It is important to consider conditions that mimic rhinitis. Anatomic abnormalities, such as a deviated septum, nasal tumors, and foreign bodies, especially in young children, are other causes of nasal obstruction. Cerebrospinal fluid rhinorrhea can present with symptoms of rhinitis, but the drainage usually occurs in the setting of basal skull fracture, trauma, or surgery; a diagnosis can be established by computed tomography or obtaining β 2 transferrin levels from the nasal discharge.² Systemic diseases associated with rhinitis include severe hypothyroidism, chronic fatigue syndrome, ciliary dysfunction syndromes, and granulomatous diseases, *e.g.*, (ANCA+) granulomatosis with polyposis.³

DIAGNOSIS OF RHINITIS

The diagnosis of rhinitis begins with a directed history, particularly noting the pattern, chronicity, triggers of symptoms, response to pharmacotherapy, and effect on quality of life. Examination of the nasal cavity with attention to the appearance of the septum and inferior turbinates is recommended. In AR, the nasal mucosa is commonly pale and boggy, the turbinates are swollen, and clear nasal secretions are often present. Evaluation of the sclera, conjunctivae, ears, and oropharynx is also useful. Skin testing for seasonal and perennial aeroallergens is helpful in demonstrating the presence or absence of IgE antibodies and to help differentiate NAR from AR. Rhinoscopy may be of value if an anatomic or pathologic entity is suspected but not visualized on speculum examination.

TREATMENT

Pharmacotherapy can be used in both NAR and AR treatment. Current guidelines suggest intranasal corticosteroid (INCS) as an initial choice for management, especially for NAR and moderate-severe or persistent symptoms in AR. If a patient's condition is not optimally controlled with INCS, then consider adding an intranasal antihistamine because analysis of data indicates greater symptomatic relief with the combination than with monotherapy, although the rate of adverse effects can be higher than with INCS alone.¹⁰ For intermittent mild AR, an oral or intranasal antihistamine can be used. The leukotriene receptor antagonist, montelukast, also can be used in AR and particularly for individuals with AR and asthma, which may have an allergic component, although leukotriene receptor antagonist monotherapy is not superior to INCS.¹⁰

Oral decongestants, *e.g.*, pseudoephedrine, may help briefly with symptoms of congestion in NAR and AR. It is important to take a thorough history regarding hypertension, arrhythmias, insomnia, prostate hypertrophy, or glaucoma to prevent serious adverse effects associated with pseudoephedrine.¹ Nasal ipratropium bromide, an anticholinergic agent, can help treat rhinorrhea associated with gustatory and with exercise- and cold-induced rhinitis. For ocular symptoms, aside from INCS, an intraocular H₁ receptor antihistamine, sometimes in combination with a mast cell stabilizer, may be used. Patients with rhinitis medicamentosa attributable to overuse of topical α -adrenergic agonist medications should be weaned off these agents over 7–10 days while using an INCS; they may require a short course of oral prednisone during this time.¹ Management of atrophic rhinitis may include nasal saline solution irrigation and antibiotics. Treatment of rhinitis associated with a systemic disease should be directed at the underlying disease process.

Another cornerstone of treatment includes avoidance of aggravating irritants in NAR and allergen control in AR. With house-dust mite allergy, there has been benefit shown to using impermeable covers to encase mattresses, pillows, box springs, and beddings. Some reduction of symptoms has been reported with washing linen in hot water (120°F, 49°C) and replacing carpets with a hard wood floor.¹ Patients allergic to animals with dander benefit from avoidance at home; however, they may encounter these allergens in school, work, and public transportation. Regular washing of the pet and use of high-efficiency particulate air filters in households with pets have been shown to be of some benefit in reducing symptoms in individuals who are sensitized, but removal of the pet from the home is most effective.⁸ It may take, on average, 6 months before allergen concentrations reach levels found in animal-free homes.¹ Moisture control and repair of areas that allow water intrusion in the household may help prevent growth of indoor molds and reduce symptoms. Subcutaneous or sublingual allergen immunotherapy should be considered if symptoms are not adequately controlled by avoidance and pharmacotherapy, or in individuals who cannot tolerate pharmacotherapy or desire a disease-modifying treatment. Allergen immunotherapy has been shown to modify the natural history of allergic diseases, prevent future sensitizations to new environmental allergens, and reduce asthma when initiated early.¹

IMMUNOLOGY

- AR is a Th2-mediated immune response. Synthesis of allergen-specific IgE is dependent on activation of CD4⁺ T-helper cells and their secretion of IL-4 and IL-13.

- Mast cells and basophils are activated by cross-linking of Fc ϵ RI receptors on these cells by binding of multivalent antigens.
- Environmental irritants can activate transient receptor potential channels on nasal mucosa that initiate release of neuropeptides, which play an important role in NAR pathogenesis.

CLINICAL PEARLS

- AR and NAR constitute a heterogeneous group of disorders with a common set of symptoms, including nasal congestion, rhinorrhea, sneezing, and posterior nasal drainage.
- In AR, symptoms consist of an immediate response and a delayed response; nasal blockage is the predominant symptom in a delayed-phase response.
- Classically, vasomotor rhinitis, the most common type of NAR, may be triggered by irritant odors, perfumes, and weather or temperature changes.
- The ARIA guidelines⁶ classify AR into intermittent or persistent and mild versus moderate-severe.
- Aside from patient education, intranasal steroids and intranasal antihistamines are mainstays of treatment. AR management also includes allergen avoidance measures and consideration of allergen immunotherapy.

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