

Allergic Rhinitis



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KEYWORDS

- Allergic rhinitis • Type 1 hypersensitivity • Vasomotor rhinitis • Skin prick testing
- Serum-specific Ig E • Allergen immunotherapy • Chronic rhinosinusitis
- Nasal polyps

KEY POINTS

- Allergic rhinitis affects up to 1 in 6 individuals, with health care costs estimated in the billions of dollars.
- Allergic rhinitis is a type 1 IgE-mediated hypersensitivity reaction and usually presents with typical symptomatology.
- Allergic rhinitis can be diagnosed by history and physical examination, with testing reserved for treatment of nonresponders or when identification of the specific cause is necessary to guide treatment.
- There are many therapeutic options, with intranasal corticosteroids the single most effective agent.

INTRODUCTION

Rhinitis is defined as inflammation of the nasal mucosa and affects up to 40% of the population. Among all causes of mucosal inflammation, allergic rhinitis (AR) is the most common, affecting 1 in 6 individuals. Symptoms of AR interfere with all facets of daily life and are associated with reduced quality of sleep and work performance.¹ Previously thought of as a disease restricted to the nasal passages, AR is now viewed as a manifestation of systemic airway disease and is often comorbid in patients with asthma. As a type 1 IgE-mediated hypersensitivity process, symptoms of AR are triggered by allergens; thus, minimizing allergen exposure should be an essential component of any treatment plan. AR often goes undetected by clinicians due to its nature as a long-standing condition. Patients suffering from AR may not seek medical treatment because they often fail to recognize its impact on their daily lives. As such, physicians should routinely screen for this widespread and debilitating condition with a focused history and physical examination.

EPIDEMIOLOGY

Approximately 10% to 20% of the global population suffers from AR, the most common cause of reversible nasal congestion. The reported prevalence of AR has

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Prim Care Clin Office Pract 43 (2016) 465–475

<http://dx.doi.org/10.1016/j.pop.2016.04.009>

primarycare.theclinics.com

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been steadily increasing. The true incidence likely remains underestimated, however, because data collection hinges on physician diagnosis and misses those who are undiagnosed or self-medicate. In the United States, AR is the most common atopic condition, affecting between 9% and 16% of the population. Of patients with AR, 80% develop symptoms before the age of 20.² Further highlighting the significance of AR in the pediatric population, in the United States from 1994 to 2002, the prevalence of AR in more than 2000 children ages 13 to 14 years increased from 13% to 19%.³

The direct health-related cost expenditure of AR is estimated to be between \$2 billion and \$5 billion per year with an additional \$2 billion to \$4 billion lost in annual productivity.⁴ A 2007 cohort of more than 8000 US workers revealed that AR caused greater loss of productivity than any other illness, including hypertension, diabetes, and heart disease, and accounted for approximately one-quarter of all lost productivity.⁵ In 2006, AR accounted for more than 12 million office visits in the United States, making it the 16th most common primary diagnosis for outpatient office visits.⁴ The prevalence and burden of AR obligates primary care providers to be able to readily and cost-effectively diagnose and manage this chronic condition.

CLINICAL PRESENTATION

The clinical presentation of AR is a consequence of its pathophysiology as a classic allergen response. Inflammatory mediators, including mast cells, macrophages, eosinophils, and lymphocytes, enter the nasal mucosa after introduction of the inciting allergen. The most common allergens include dust mite fecal particles, animal dander, molds, and pollens.⁶ Identification of the inciting agent is not always necessary to effectively treat AR.

The structure and histology of the nose is designed to allow it to function as a wet filter. Its main purpose is to humidify inhaled air. To accomplish this, the nose must maintain an extensive vascular network allowing it to produce copious amount of mucous, which in the average adult nose averages 2 cups of mucous daily.⁷ The mucous captures inhaled particles, gases, and vapors at which point ciliated cells direct them to the back of the throat, allowing them to be swallowed thus diverting them from the lower respiratory tract.⁸ This postnasal drip is actually a normal physiologic process. Its consequences, however, such as pharyngitis, vocal cord dysfunction, and cough, indicate potential pathology.⁷ When the captured particles incite the IgE-mediated allergy cascade, symptoms soon follow.

As a mucosal antibody, IgE is found in the lining of the eyes, nose, and lower airways. Basophils and mast cells are activated when an allergen bridges 2 specific IgE molecules. The principal vasoactive elements, including histamine, leukotrienes, and prostaglandins, are responsible for the initial phase of symptoms. Inflammatory cells, such as eosinophils, macrophages, and neutrophils, are then recruited, and their arrival leads to further release of vasoactive mediators, producing a delayed-phase inflammatory response. This second wave of symptoms occurs 4 to 6 hours after exposure to the inciting allergen.⁹

The classic symptoms of AR are nasal congestion, nasal itching, sneezing, and rhinorrhea. Allergic conjunctivitis presents as itchy, watery eyes resulting from the same pathophysiology as AR and is not surprisingly a common comorbid condition. Patients may not attribute their symptoms to seasonality or surrounding environments and present with what they believe to be a viral-related illness. Patients' degrees of atopy vary from minimal to severe and symptoms of AR exhibit a similar pattern. For many patients, AR-induced nasal congestion is not merely a trivial stuffy nose but a debilitating problem. A 2007 prospective, cross-sectional survey, identifying

symptom perception among patients and providers, revealed that AR-related symptoms had a significant impact on work or school performance in 74% of patients. Sleep patterns were affected for approximately 50% of patients, whereas 61% of patients reported feeling tired, 38% reported feeling irritable, and 23.5% reported a general malaise.¹⁰

Clinical manifestations depend heavily on age of presentation. Adults and older children suffering from rhinorrhea report blowing their noses constantly during the day. Younger children who have not yet learned this technique will snort, sniff, or cough in an effort to expel secretions. Some children may demonstrate an audible palatal click as the tongue scratches the hard palate. Repeated manipulation or rubbing of the nose due to persistent congestion or drainage can cause excoriations of the external nares and a permanent crease at the juncture of the middle and lower thirds of the nasal bridge.¹¹ Due to the constant inflammation and subsequent increase in blood flow, venous engorgement in the periorbital region may produce allergic shiners. Other manifestations in the head involve changes consistent with allergic facies seen in children as a consequence of mouth breathing from nasal obstruction: open mouth with receding chin and overbite, elongation of the face, and high arching palate.⁹

As an allergen-mediated disorder of the nasal passage, AR shares several similarities with another allergic disease of the lower respiratory tract: asthma. Not surprisingly, the 2 conditions are often comorbid; 85% of patients with asthma have AR whereas 40% of patients suffering from AR have or will develop asthma. Consequently, the Allergic Rhinitis and its Impact in Asthma guidelines recommend evaluating patients with one condition for the presence of the other.¹² It is now widely accepted that the upper and lower airways represent a continuum of the respiratory tract because they share several physiologic and morphologic features. Allergen cross-linking of IgE receptors results in nasal obstruction in the heavily vascularized nasal passage whereas the same process produces bronchoconstriction in the smooth muscle lined bronchi. AR may promote or exacerbate asthma via different mechanisms. Excessive postnasal drip irritates the lower respiratory tract while the preferential mouth breathing allows cold, dry air to enter the lungs and potentiate bronchial hyper-reactivity. In addition to this, the rhinobronchial reflex, a vagal-mediated response, can cause bronchial constriction as a result of nasal stimulation.¹²

It is important to distinguish AR from other forms of nasal inflammation, namely non-AR. Non-AR can be classified into 9 subtypes, including infectious, gustatory, vasomotor, drug induced, and hormone induced. Hormonal-induced rhinitis includes pregnancy-related rhinitis that can affect 20% to 30% of pregnancies at any gestational age¹³ and usually resolves spontaneously within 2 weeks of delivery.¹⁴

Vasomotor rhinitis (VMR), also known as idiopathic rhinitis, compromises the majority of non-AR causes.¹⁴ The pathophysiology of VMR is poorly understood and may involve increased cholinergic activity, dysfunctional nociceptive receptors that are stimulated in response to innocuous stimuli.¹⁵ Environmental factors trigger symptoms and common causes include inhalation of cold air, changes in temperature, humidity, or barometric pressure, and even strong emotions. Typical symptoms of VMR are rhinorrhea, congestion, postnasal drip, headaches, throat clearing, and coughing. Sneezing and nasal itching are generally mild or absent, a key differentiating feature between VMR and AR. Ocular symptoms also tend to be minimal in VMR because the dysfunction is confined to the nasal mucosa and not representative of an underlying allergy-mediated response.¹⁴

It is important to remember that many symptoms involving the nose or nasal passages may be due to other disease states and the red flag symptoms, discussed

later, should prompt clinicians to seek an alternate diagnosis: unilateral obstruction with or without pain, recurrent epistaxis, mucopurulent rhinorrhea, or anosmia.¹¹

DIAGNOSIS

A history marked by typical allergy symptoms forms the basis for diagnosing AR. The diagnosis is likely when 2 or more of the classic AR symptoms of nasal congestion, rhinorrhea, sneezing, and itching are present for more than 1 hour on most days.¹⁶

Clinicians should try to identify a patient's allergic trigger through the history. Common allergens that should be evaluated for include pollen, mites, molds, animal fur, textile flooring, and smoke. A family history of atopic disease increases the probability of AR as the causative condition. Medications, including nonsteroidal anti-inflammatory drugs, aspirin,⁶ antihypertensives, and topical nasal decongestants,⁴ can precipitate or worsen symptoms. A review of systems should focus on identifying other comorbid conditions that suggest a diagnosis of AR, including asthma, conjunctivitis, sleep disorder, and otitis media. Often patients cannot distinguish symptoms caused by AR from the common cold, and the frequency and severity of these colds should be firmly established.

Although an accurate history is paramount in diagnosing AR, the physical examination is useful to help rule out other conditions or even concomitant pathology. Nasal mucosal swelling can lead to eustachian tube dysfunction, which manifests as a retracted immobile tympanic membrane with pneumatic otoscopy, although an ear examination is typically normal in patients with AR.⁶

Findings on anterior rhinoscopy may reveal an erythematous mucosa with swollen turbinates. The turbinates may appear to have the traditional bluish mother-of-pearl hue; however, this may be seen in non-AR as well.⁹ Rhinoscopy is useful for determining the presence of a nasal polyp (NP) or deviated septum, both of which can cause airflow obstruction that patients may perceive as persistent congestion.

According to guidelines published by the American Academy of Otolaryngology - Head and Neck Surgery, allergy testing should be reserved for patients who (1) have a clinical diagnosis of AR but do not respond to empiric treatment or (2) require identification of the specific allergen to target therapy.⁴ Allergy testing may be performed as a skin test or serum-specific IgE (SSIgE) level.

Clinical skin prick testing (SPT) has been in use for more than 100 years to aid in the diagnosis of atopic, IgE-mediated conditions and is considered the gold standard to which other diagnostic modalities are compared.

SPT has been validated as a safe and efficient means to diagnose allergy. With results available in 15 to 20 minutes, SPT allows for the evaluation of multiple allergens in a single session. SPT lancets are designed to penetrate the stratum corneum, exposing the underlying epidermis to the allergen in question. Multiple site devices allow for testing of up to 10 different allergens in a single testing session. There are several variables that can affect the outcome of SPT. Controllable patient-dependent variables include anatomic testing site and distance between sites, whereas operator-dependent factors include technique affecting the angle and depth of penetration. Uncontrollable patient-related factors include age, race, or sun-damaged skin. Underlying comorbidities, such as an immunodeficiency, diabetes, or hypertension, can inhibit the immunologic response to SPT.¹⁷

Intradermal testing (IDT) involves the same principles as SPT; however, the allergen is introduced into the dermal skin layer using a standard hypodermic needle and syringe. IDT, although generally more sensitive and reproducible than SPT, is less well tolerated, takes longer to perform, and is associated with more false positive

results. There is also a greater risk of systemic reactions with IDT as opposed to SPT. IDT is usually performed after a negative SPT.

The only absolute contraindications to SPT and IDT are recent anaphylaxis, pregnancy, certain medications that cannot be discontinued, and any form of extensive skin disease.

An alternative to in vivo skin testing is SSIgE levels. One advantage of SSIgE testing is the lack of interference from antihistamines or other medications. Disadvantages include the need to obtain blood, cost, and delays in test results.¹⁸ A prospective study comparing SPT to SSIgE for 53 different inhalant allergens in patients with chronic rhinitis concluded that serum testing should be viewed as complementary and not equivalent to SPT.¹⁹

Once a diagnosis of AR is confirmed using a combination of history and physical and diagnostic testing, it is vital to properly stage the extent of disease because this helps guide treatment. AR was previously categorized as either seasonal (occurring during a particular time of year) or perennial (present throughout the entire year); however, this has been abandoned in favor of a classification similar to that used in asthma, which, as discussed previously, shares many features with AR. Symptoms are classified by duration as either intermittent (less than 6 weeks) or persistent and by symptom severity as either mild or moderate to severe. Mild symptoms do not interfere with sleep or daily activities whereas moderate to severe symptoms result in sleep derangements and in work/life impairment⁶ (Fig. 1).

MANAGEMENT AND TREATMENT

There is an extensive armamentarium available to treat the symptoms of AR. Unfortunately, as a type 1 hypersensitivity-mediated process, there is no known cure. A majority of symptoms can be managed by a primary care provider, but

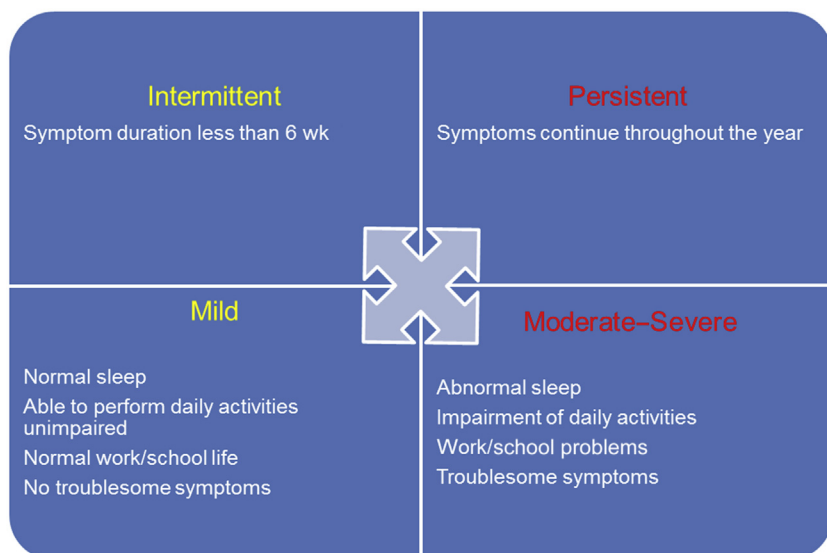


Fig. 1. Classification of AR according to symptom duration and severity. (Adapted from Small P, Kim H. Allergic rhinitis. *Allergy Asthma Clin Immunol* 2011;7(Suppl 1):S3.)

clinicians must remain vigilant for unusual presentations and red flag symptoms, prompting referral to an appropriate specialist.²⁰

An overview of the stepwise treatment of AR is available in [Fig. 2](#).⁶ In general, management involves allergen avoidance, oral antihistamines, intranasal corticosteroids, leukotriene receptor antagonists, and, lastly, allergen immunotherapy with intranasal corticosteroids as the mainstay of treatment.

Exposure to relevant allergens and irritants, such as dust mites, molds, pollens, pets, and tobacco smoke, should be minimized. Effective strategies include allergen-impermeable bedding covers and keeping indoor relative humidity below 50% to inhibit mite growth. Pollen exposure can be minimized by limiting time spent outdoors and by keeping windows closed. Removing pets from the home can reduce symptoms within 4 to 6 months for patients who are allergic to animal dander.⁶ Commercially available high-efficiency particulate air filters have been shown to reduce indoor levels of common asthma and allergy triggers.²¹ Early studies suggested no improvement in symptoms, but multiple studies since 2000 have shown symptomatic benefit in both AR and asthma. Further research is needed to clearly define the effect of air filtration on AR-related disease outcomes.²²

Nasal irrigation with isotonic saline has been shown effective according to a 2012 systematic review. Nasal symptoms decreased by an average of 27.66% and medicine consumption decreased by an average of 2.99%. Both saline nasal spray and high-volume (200–400 mL) irrigation showed symptomatic benefit.²³

Oral antihistamines have years of proved efficacy in the treatment of AR. First-generation antihistamines include diphenhydramine and chlorpheniramine and are commonly used, both over the counter and through prescriptions. These older agents are not selective for the H₁-receptor. They cross the blood-brain barrier and have effects on dopamine, serotonin, and acetylcholine receptors. As such they

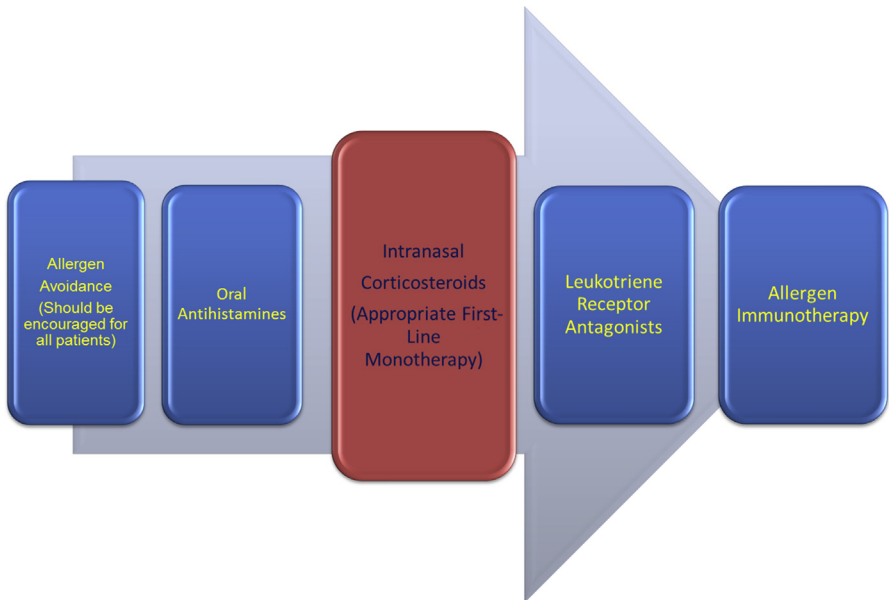


Fig. 2. A simplified, stepwise algorithm for the treatment of AR. Treatments can be used individually or in any combination. (Adapted from Small P, Kim H. Allergic rhinitis. *Allergy Asthma Clin Immunol* 2011;7(Suppl 1):S3.)

may cause a host of wanted side effects, including some that affect the central nervous system (CNS).

Newer-generation antihistamines include cetirizine, desloratadine, and fexofenadine. They are similar in efficacy to first-generation medications.²⁴ These agents have the benefit of an improved safety profile with reduced CNS effects as well as decreased incidence of cardiovascular side effects, such as prolonged QT. Placebo-controlled and head-to-head trials with these newer antihistamines have shown that they are statistically significantly better than placebo at reducing symptoms and have similar efficacy among themselves. Even these newer agents, however, can cause CNS effects at recommended doses. One study showed the combined incidence of drowsiness and fatigue was significantly greater in patients treated with cetirizine than in those treated with fexofenadine.²⁵ It has also been reported that up to 7% of the general population and 20% of the African American population may be slow metabolizers of desloratadine, increasing their risk of unwanted side effects. Among the newer-generation antihistamines, fexofenadine has the lowest risk of side effects, specifically sedation/impairment, even at a higher than recommended dose (Table 1).²⁴

Intranasal corticosteroids are the single best therapy for AR and are recommended as first-line treatment of patients with mild to moderate persistent symptoms. They function by decreasing the inflammatory cellular response, thus inhibiting cytokine release, reducing mucus production, and decreasing leukotriene and prostaglandin response.²⁶ With an onset of action of 30 minutes, their effects can last for up to several hours. There are many available formulations, both prescription and over the counter, and no single one has been shown superior in either safety or efficacy. As a class, intranasal corticosteroids have the benefit of improving ocular symptoms related to allergic conjunctivitis.²⁶ Budesonide is the sole agent that carries an FDA pregnancy category B rating.²⁷ Despite their universally accepted efficacy, inhaled steroids do pose risks for patients. The most commonly reported adverse effects are headache, throat irritation, epistaxis, stinging, burning, and nasal dryness.²⁸ The rate of skeletal growth was unaffected in children treated using mometasone for

Table 1 Sedation associated with first-generation and second-generation antihistamines		
Agent	Sedation/Impairment Effect	
	Recommended Dose	Above Recommended Dose
Diphenhydramine (first generation)		
Clemastine (first generation)		
Chlorpheniramine (first generation)		
Cetirizine (second generation)		
Desloratadine (second generation)		
Fexofenadine (second generation)		

Adapted from Spangler DL, Brunton S. Efficacy and central nervous system impairment of newer-generation prescription antihistamines in seasonal allergic rhinitis. South Med J 2006;99(6):594; with permission.

1 year in 1 randomized placebo-controlled trial.²⁹ A 2015 placebo-controlled study did reveal, however, a small yet statistically significant difference in growth velocity in children treated with 110 µg of intranasal triamcinolone (5.65 cm/y vs 6.09 cm/y). At 2-month follow-up, the growth velocity in the treatment group approached baseline growth rate, indicating a catch-up period on treatment cessation.³⁰

Although FDA-approved treatment options for AR, the leukotriene receptor antagonists montelukast and zafirlukast offer only minimal improvement in nasal congestion. This was evidenced by a systematic review of 20 trials involving adults treated with montelukast.³¹ Leukotriene receptor antagonists, although better than placebo, are inferior to intranasal corticosteroids and antihistamines and should be used as a second-line or third-line option.

Allergen immunotherapy is a proved long-term treatment option for AR. The risk of potentially life-threatening consequences of allergen immunotherapy is very low; nonetheless, it should only be prescribed by physicians who are adequately trained in allergy treatment and capable of managing anaphylaxis.⁶ A patient's triggering allergens are administered either by subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). Doses are slowly increased every week for 6 to 8 months until immunologic tolerance is reached. Maintenance injections are then given every 3 to 4 weeks for 3 to 5 years at the maximum tolerated dose. Evidence supports use of immunotherapy for allergy to pollens and dust mites; mold and animal dander allergies are less responsive.⁶ A 2009 Cochrane review of SCIT confirmed its efficacy and low side-effect profile; 0.56% of participants had events categorized as early systemic reaction grade 4, which refers to either respiratory failure with or without loss of consciousness or hypotension with or without loss of consciousness, with 1 of 4 of those events occurring after placebo administration. There were no fatalities reported.³² SLIT is an alternative approach in providing allergen immunotherapy. It has been found better tolerated with lower dropout rates than SCIT due to its lower cost, ease of administration, and favorable side-effect profile. These factors, combined with its similar efficacy to SCIT, are making SLIT a more attractive option for patients and providers alike.³³

Alternative therapeutic modalities include acupuncture, nasal air filters, intranasal carbon dioxide, intranasal cellulose, and homeopathy. Although many of these have shown positive results in small trials, they have not been adopted as recommended treatment strategies.³⁴

CHRONIC RHINOSINUSITIS AND NASAL POLYPS

Chronic rhinosinusitis (CRS) with nasal polyposis or CRS without nasal polyposis is a clinical syndrome distinct from AR and is marked by nasal and paranasal inflammation with symptoms lasting longer than 3 months. Rhinosinusitis in adults is characterized by 2 or more symptoms, 1 of which should be either nasal blockage/congestion or nasal discharge, which can be anterior or posterior. Additional diagnostic symptoms include facial pain or pressure and reduction or loss of smell. This should be accompanied by endoscopic or CT changes of mucosal inflammation or polyposis.³⁵ Radiographic findings on CT include ostiomeatal complex or sinus mucosal changes. On endoscopy, NPs, mucopurulent discharge, edema, and mucosal obstruction may be seen.³⁶

The most common category of CRS in Western countries is eosinophilic CRS, which encompasses several eosinophilic processes, including allergic fungal rhinosinusitis, eosinophilic mucin rhinosinusitis, eosinophilic fungal rhinosinusitis, and aspirin-exacerbated respiratory disease. Allergic fungal rhinosinusitis is an

IgE-mediated response to mold whereas there is no specific IgE response in eosinophilic mucin rhinosinusitis or eosinophilic fungal rhinosinusitis.³⁷

NPs form as a result of chronic inflammation of the paranasal sinus mucosa. Typically benign, they usually develop bilaterally in adulthood. NPs found in children may be the presenting sign for cystic fibrosis whereas unilateral NPs should be evaluated for malignancy.³⁸ The prevalence of NP is approximately 4% with a 2:1 male-to-female ratio.³⁸ A majority of cases of nasal polyposis are idiopathic, but rare causes, such as Wegener granulomatosis and sarcoidosis, should be considered.³⁶

Therapy for NP involves observation, medical therapies, and surgical interventions. The goals of medical treatment are to reduce nasal obstruction, improve sinus drainage, and restore olfaction and taste.³⁹ These can be accomplished with a combination of topical and/or systemic steroids, nasal saline irrigation, and long-term antibiotics. Surgery should be reserved for those patients who remain symptomatic despite maximum medical treatment.³⁶

SUMMARY

As the most prevalent atopic condition affecting 10% to 20% of the population, AR deserves a thorough understanding of its manifestations, diagnosis, and treatment. Dismissed as trivial by many, AR is a source of profound distress for millions across the world, resulting in billions of dollars of lost productivity. Primary care providers should routinely screen for this condition because patients may view their symptoms as unavoidable and neglect to mention it.

A thorough history and physical examination are often sufficient to make the diagnosis. Further testing is available in the form of SPT and SSIgE measurements. These modalities are typically used when patients do not respond to initial treatment or if identification of a specific allergen is important to guide therapy.

Unfortunately, there is no cure for AR. Many treatment options are available, including oral medications, topical sprays, and SCIT or SLIT. Intranasal corticosteroids are the mainstay of treatment. Regardless of the therapeutic approach, allergen avoidance remains a vital component of any treatment plan.

CRS is a distinct clinical entity from AR but may also involve an atopic component depending on the subtype. The etiology of polyp formation in CRS remains unknown. Treatment CRS with or without NPs should focus on symptom relief, with surgery as an option for patients who have failed maximum medical therapy.

REFERENCES

1. Dykewicz MS, Hamilos DL. Rhinitis and sinusitis. *J Allergy Clin Immunol* 2010; 125:S103–15.
2. Stewart M, Ferguson BJ, Fromer L. Epidemiology and burden of nasal congestion. *Int J Gen Med* 2010;3:37–45.
3. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phase One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–43.
4. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg* 2015;152(2):197–206.
5. Lamb CE, Ratner PH, Johnson CE, et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. *Curr Med Res Opin* 2006;22:1203–10.
6. Small P, Kim H. Allergic rhinitis. *Allergy Asthma Clin Immunol* 2011;7(Suppl 1):S3.

7. Macy E. A rhinitis primer for family medicine. *Perm J* 2012;16(4):61–6.
8. Harkema JR, Carey SA, Wagner JG. The nose revisited: a brief review of the comparative structure, function, and toxicologic pathology of the nasal epithelium. *Toxicol Pathol* 2006;34(3):252–69.
9. Weber RW. Allergic rhinitis. *Prim Care* 2008;35(1):1–10.
10. Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy* 2007;62(Suppl 85):9–16.
11. Lakhani N, North M, Ellis AK. Clinical manifestations of allergic rhinitis. *Journal Allergy Therapy* 2012;S5:007.
12. Nathan RA. Management of patients with allergic rhinitis and asthma: literature review. *South Med J* 2009;102(9):935–41.
13. Ellegard EK. Clinical and pathogenetic characteristics of pregnancy rhinitis. *Clin Rev Allergy Immunol* 2004;26(3):149–59.
14. Scarupa MD, Kaliner MA. Nonallergic rhinitis, with a focus on vasomotor rhinitis: clinical importance, differential diagnosis, and effective treatment recommendations. *World Allergy Organ J* 2009;2(3):20–5.
15. Wheeler PW, Wheeler SF. Vasomotor rhinitis. *Am Fam Physician* 2005;72(6):1057–62.
16. Min YG. The pathophysiology, diagnosis and treatment of allergic rhinitis. *Allergy Asthma Immunol Res* 2010;2(2):65–76.
17. Fatteh S, Rekkerth DJ, Hadley JA. Skin prick/puncture testing in North America: a call for standards and consistency. *Allergy Asthma Clin Immunol* 2014;10(1):44.
18. Sicherer SH, Wood RA. Allergy testing in childhood: using allergen-specific IgE tests. *Pediatrics* 2012;129(1):193–7.
19. Calabria CW, Dietrich J, Hagan L. Comparison of serum-specific IgE (ImmunoCAP) and skin-prick test results for 53 inhalant allergens in patients with chronic rhinitis. *Allergy Asthma Proc* 2009;30(4):386–96.
20. Angier E, Willington J, Scadding G, et al. Management of allergic and non-allergic rhinitis: a primary care summary of the BSACI guideline. *Prim Care Respir J* 2010;19(3):217–22.
21. Brown KW, Minegishi T, Allen JG, et al. Reducing patients' exposures to asthma and allergy triggers in their homes: an evaluation of effectiveness of grades of forced air ventilation filters. *J Asthma* 2014;51(6):585–94.
22. Sublett JL, Seltzer J, Burkhead R, et al. Air filters and air cleaners: rostrum by the American Academy of Allergy, Asthma & Immunology Indoor Allergen Committee. *J Allergy Clin Immunol* 2010;125(1):32–8.
23. Hermelingmeier KE, Weber RK, Hellmich M, et al. Nasal irrigation as an adjunctive treatment in allergic rhinitis: a systematic review and meta-analysis. *Am J Rhinol Allergy* 2012;26(5):e119–25.
24. Spangler DL, Brunton S. Efficacy and central nervous system impairment of newer-generation prescription antihistamines in seasonal allergic rhinitis. *South Med J* 2006;99(6):593–9.
25. Howarth PH, Stern MA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 mg and 180 mg once-daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;104:927–33.
26. Okano M. Mechanisms and clinical implications of glucocorticosteroids in the treatment of allergic rhinitis. *Clin Exp Immunol* 2009;158(2):164–73.
27. Sur DK, Scandale S. Treatment of Allergic Rhinitis. *Am Fam Physician* 2010;81(12):1440–6.

28. Demoly P. Safety of intranasal corticosteroids in acute rhinosinusitis. *Am J Otolaryngol* 2008;29(6):403–13.
29. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics* 2000;105(2):E22.
30. Skoner DP, Berger WE, Gawchik SM, et al. Intranasal triamcinolone and growth velocity. *Pediatrics* 2015;135:e348.
31. Grainger J, Drake-Lee A. Montelukast in allergic rhinitis: a systematic review and meta-analysis. *Clin Otolaryngol* 2006;31(5):360–7.
32. Calderon MA, Alves B, Jacobson M, et al. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007;(1):CD001936.
33. Aboshady OA, Elghanam KM. Sublingual immunotherapy in allergic rhinitis: efficacy, safety, adherence and guidelines. *Clin Exp Otorhinolaryngol* 2014;7(4):241–9.
34. Solelhac G, Charpin D. Management of allergic rhinitis. *F1000prime Rep* 2014;6:94.
35. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;50:1–12.
36. Piromchai P, Kasemsiri P, Laohasiriwong S, et al. Chronic rhinosinusitis and emerging treatment options. *Int J Gen Med* 2013;6:453–64.
37. Chaaban MR, Walsh EM, Woodworth BA. Epidemiology and differential diagnosis of nasal polyps. *Am J Rhinol Allergy* 2013;27(6):473–8.
38. Stevens WW, Schleimer RP, Chandra RK. Biology of nasal polyposis. *J Allergy Clin Immunol* 2014;133(5):1503, 1503.e1–4.
39. Newton JR, Ah-See KW. A review of nasal polyposis. *Ther Clin Risk Manag* 2008;4(2):507–12.