

Nonallergic Rhinitis

Treatment



Phillip L. Lieberman, MD^{a,b,*}, Peter Smith, MD^c

KEYWORDS

- Nonallergic rhinitis • Vasomotor rhinitis • Nonallergic rhinopathy
- Noninfectious nonallergic rhinitis • Idiopathic rhinitis

KEY POINTS

- The therapy for nonallergic rhinitis is best based on the underlying pathology, which typically exists in a form whereby an abnormality of the autonomic nervous system is dominant or a form in which inflammation seems to be the cause of symptoms.
- In general nonallergic rhinitis is less responsive to treatment than its allergic counterpart.
- In most cases combination therapy with an intranasal corticosteroid and a topical nasal antihistamine is the most effective treatment.

DEFINITION

Chronic nonallergic rhinitis (NAR) is a syndrome rather than a specific disease. It is diagnosed by excluding other disorders. A lack of understanding of the pathogenesis of this condition has led to an imprecise terminology with several alternate names for this condition ([Table 1](#)).

NAR is best defined by the chronic presence of one or more symptoms of rhinitis, in the absence of a specific cause.

There is no consensus about how long symptoms should be present to establish chronicity, but many studies have required a minimum duration of more than 1 year.^{1,2}

PATHOGENESIS

In order to understand the mechanisms of action of the medications used in the treatment of NAR, it is important to have some insight into the pathogenesis of this condition.

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^a Division of Allergy and Immunology, Department of Medicine, University of Tennessee, Memphis, TN, USA; ^b Department of Pediatrics, University of Tennessee, Memphis, TN, USA; ^c Qld Allergy Services, Clinical School of Medicine, Griffith University, 17/123 Nerang Street, Southport, Queensland 4215, Australia

* Corresponding author. 7205 Wolf River Boulevard, Suite 200, Germantown, TN 38138.

E-mail address: phillieberman@hotmail.com

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Table 1 Treatment modalities for NAR	
Treatment Modality	Comment
INS	It is the most useful in the inflammatory form of NAR. Not all studies have shown these agents to be effective. Efficacy may depend on triggers, with those patients who exhibit triggers only possibly responding to a lesser degree than those with triggers due to respiratory irritants (see text).
TA sprays	Azelastine is better studied than olopatadine, but one study of the latter indicated efficacy (see text). It is probably more effective in the inflammatory form. Effects are theoretically due to activities of these agents unrelated to their antagonism of H1 receptor stimulation.
Combination therapy with INS and TA	It is probably the most effective therapy to date. At least on a conceptual basis they should be more effective than either agent alone, and studies in allergic rhinitis have confirmed this.
Ipratropium bromide	It is effective only for rhinorrhea. It is of particular benefit in gustatory rhinitis and rhinitis due to exposure to cold.
Capsaicin	It is theoretically useful only in the noninflammatory form and thought to be effective because of desensitization or depletion of mediators. This effect seems to be mediated through TPV1.
Oral decongestants	There is a lack of good evidence of effect, but theoretically it may be helpful for nasal stuffiness only.
Nasal saline irrigation	It seems to have some modest effect in selected patients.
Oral antihistamines	Second-generation antihistamines theoretically should be of no benefit; but first-generation antihistamines, theoretically because of their anticholinergic activity, could be helpful in some patients.
Surgery	Numerous approaches have been studied, but reports are limited to case series. Of course, it is reserved for recalcitrant cases not responding to medical treatment.

Abbreviations: INS, intranasal corticosteroids; TA, topical antihistamine; TPV1, transient receptor potential cation channel subfamily V member 1.

Based on the fact that there seems to be many forms of this syndrome, there may be several different mechanisms underlying its clinical expression.^{3–5} Several investigators have broadly divided NAR into noninflammatory and inflammatory forms.^{6–33} The inflammatory form has been further divided into eosinophilic and noneosinophilic varieties.^{1,2,6–33} With all forms of chronic NAR, there seems to be a component of autonomic dysregulation. In the noninflammatory form, these neurologic abnormalities are predominant.

For the purpose of this article, the authors have arbitrarily decided to use the inflammatory and noninflammatory classification in this brief discussion of NAR pathogenesis.

NONINFLAMMATORY FORMS

With the noninflammatory form, it is postulated that the disease results from abnormalities in the autonomic nervous system, which may include the adrenergic, cholinergic, and/or nonadrenergic, noncholinergic innervation of the nose.^{8–11} Such abnormalities have also been demonstrated in the inflammatory form and, in that context, have been

proposed to be secondary to the primary inflammatory process.^{6,7,11,28} The nature and importance of these abnormalities has been clarified by Bernstein and colleagues³⁴ who evaluated the neurogenic responses to chemical/olfactory stimuli in patients with NAR using functional MRI. Subjects underwent MRI during exposure to different types of odors. They exhibited increased blood flow to several odor-sensitive regions of the brain in response to both pleasant (vanilla) and unpleasant (hickory smoke) odors. The neurologic responses were associated with the production of symptoms on exposure to hickory smoke.

Gustatory rhinitis is perhaps the prototype of noninflammatory NAR. In this condition eating, especially hot or spicy foods, produces profuse, watery rhinorrhea.³⁵ The underlying pathology seems to be a heightened cholinergic response.

Patients with noninflammatory NAR may display a variety of neurologic abnormalities, including heightened responses to cold, methacholine, and other stimuli designed to activate cholinergic responses^{6,9,28} as well as diminished responses to vasoconstrictive stimuli³⁶ and increased concentrations of intranasal neuropeptides.¹⁵

Of growing importance in the pathogenesis of NAR is the recognition that a superfamily of 28 chemical, thermal, and nociceptors transmit the neural stimuli that trigger symptoms. The transient receptor potential (TRP) receptors, TRP vanilloid 1 (TRPV1) and TRP ankyrin 1 (TRPA1), are perhaps of particular note. TRPV1 is the receptor for capsaicin. Several triggers activate TRPA1, including cold dry air as well as dietary isothiocyanates (mustard, wasabi, horseradish), allicin (garlic and onion), environmental isothiocyanates, formalin, toluene, ozone, chlorite, and noxious components of smoke (acrolein, methacrolein, croton aldehyde).^{37–54} TRPV1 and TRPA1 sensitization and activation patterns are summarized in **Fig. 1**.

INFLAMMATORY FORMS

Nasal eosinophilia occurs in a significant number of individuals with NAR. Nasal biopsies from these patients commonly show increased eosinophils as well as increased numbers of mast cells and prominent mast cell degranulation.^{2,18} The cellular inflammatory infiltrate may have dominant cells other than eosinophils. Nasal cytology in some cases shows a predominance of mast cells and neutrophils.^{55,56} These histologic findings may be associated with different clinical manifestations.⁵⁵ For example, eosinophilia can indicate responsiveness to glucocorticoids, whereas when mast cells are the predominant cell type, nasal itching is often a characteristic feature.⁵⁵

The inflammatory cytokine pattern in chronic NAR may differ from that in normal nonrhinitis patients. In a study comparing patients with allergic rhinitis, NAR, and controls (45 included in each group), both the patient groups had increased levels of interleukins 16 and 17 compared with controls.⁵⁷

By definition patients with chronic NAR have negative skin and in vitro tests for allergen-specific immunoglobulin E (IgE) and, thus, lack evidence of systemic production of allergen-specific IgE. However, IgE production has been shown to occur locally in the nasal tissue in some patients with NAR.^{2,58–61} One group has shown that as many as one-half of patients with chronic NAR react to nasal challenge with allergen, especially dust mite allergen, with symptoms and signs similar to those experienced by patients with allergic rhinitis.^{59,62,63} Because of these findings some investigators suggest performing an allergen-specific nasal challenge and measuring nasal-specific IgE levels in addition to standard allergy tests in this subgroup of patients. In addition, they recommend repeating allergy testing “after a time interval” because patients formerly diagnosed with NAR may develop allergic disease.^{64–66}

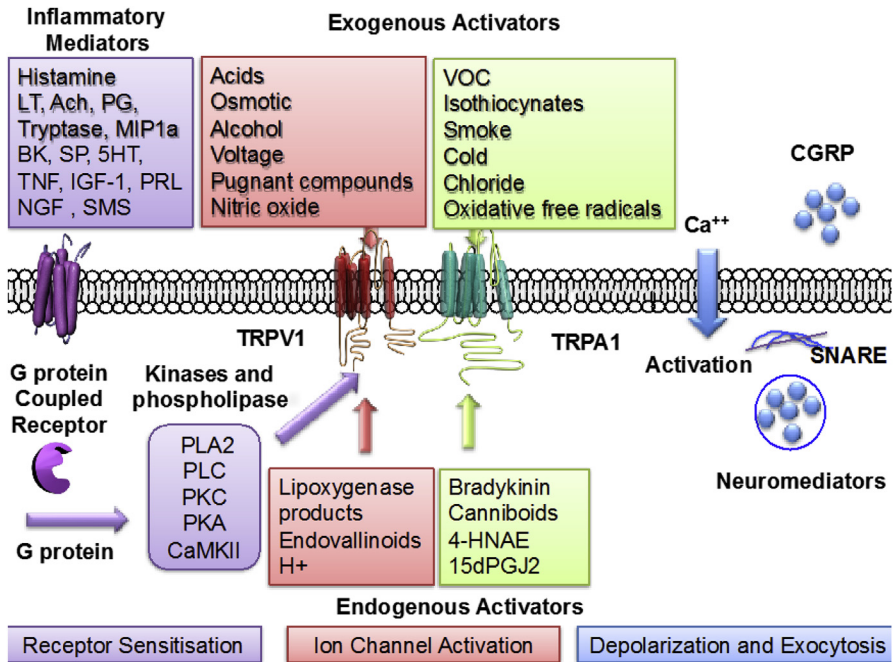


Fig. 1. TRPV1 and TRPA1 sensitization and activation patterns. Inflammatory mediators, neurokinins, hormones including histamine, LT, acetylcholine, prostaglandins, proteases including tryptase, bradykinin, MIP1 alpha, tumor necrosis factor (TNF) alpha, insulin growth factor 1 (IGF-1), prolactin, nerve growth factor (NGF), somatostatin, and calcitonin gene-related peptide (CGRP) act via their receptors to activate kinase and phospholipase systems, which prime TRPV1. Priming of TRPA1 is less defined. Once primed, the receptors become more susceptible to activation by endogenous and exogenous compounds. Activation results in a preferential influx of calcium and, in the case of sensory nerves, depolarization. This process promotes active exocytosis of neuromediators at the peripheral nerve terminals. The later process is reported to comprise the major component of neurogenic inflammation. BK, bradykinin; LT, Leukotriene; MIP1, Macrophage Inflammatory Protein; PC, phospholipase C; PG, prostaglandin; SP, substance P; VOC, volatile organic compound.

These observations have prompted the question as to whether the production of local allergen-specific IgE in patients with symptoms of rhinitis is simply premonitory to the development of the systemic production of these IgE antibodies. In this case one would expect the appearance of positive skin tests and serum-specific IgE in the future. A prospective 10-year follow-up study with initial cohorts of 194 patients with local allergic rhinitis and 130 healthy controls was designed to answer this question. After 5 years of follow-up, skin prick tests and/or serum-specific IgE became positive in 6.81% of patients with local allergic rhinitis and in 4.5% of controls. The investigators interpreted these findings as indicating local allergic rhinitis is a separate condition from classic allergic rhinitis and not simply a premonitory phase of this disorder.⁶⁷

Contrary to these observations, other researchers were unable to demonstrate consistent responses to nasal allergen challenge in patients with NAR,⁶⁸ challenging the concept that NAR results from a localized, IgE-mediated mechanism. Furthermore, localized allergic rhinitis (LAR) patients respond to medications conventionally used to treat allergic rhinitis, which are characteristically not as effective in NAR.

TREATMENT

Overview

The basic medications that we use to treat NAR are similar but not identical to those used for allergic rhinitis. These medications include intranasal glucocorticoids (INS), topical antihistamine (TA) sprays, combination therapy with INS and TA, ipratropium bromide, capsaicin, oral and intranasal decongestants, nasal saline irrigation, first-generation oral antihistamines, and surgery.

As can be seen in [Table 1](#), and as mentioned earlier, knowledge of the pathogenesis of NAR is helpful in the choice of treatment. In the inflammatory form of this disease, INS and TA are probably the most helpful compounds; in the noninflammatory variety, ipratropium bromide and capsaicin play an important role.

Unfortunately patients with chronic NAR are in general less responsive to pharmacologic therapy than those with allergic rhinitis.^{7,69} For example, second-generation oral antihistamines are usually not helpful.^{70,71} In contrast, first-generation antihistamines may be more effective in the noninflammatory form because of their anticholinergic activity, which helps reduce postnasal drainage. The 2 classes of medications most useful in treating the total symptom complex of chronic NAR^{72–83} are intranasal corticosteroids (INS) and topical nasal antihistamines (TA). Additionally ipratropium bromide is specifically effective in the therapy for rhinorrhea.^{84,85} Nasal decongestants, both topically and orally, can be used to treat patients who have continued nasal congestion in spite of the use of intranasal corticosteroids. They can be applied as adjunctive agents in this regard (see later discussion).

Patients with mild disease may be adequately treated with either an INS or TA. There are no comparative studies specifically designed to compare these two agents. Those with moderate to severe disease tend to respond better to the combination of an INS and TA.⁸⁶

Specific Agents

Intranasal corticosteroids

Several INS preparations have been shown to be effective for most patients in multiple randomized controlled studies.^{75,76,78,87} Multiple preparations are available. The largest report demonstrating a treatment effect with INS was a combined analysis of 3 double-blind, randomized, prospective, placebo-controlled studies of 983 patients with NAR. Included in this evaluation were subjects with and without nasal eosinophilia (674 were classified as without nasal eosinophils).⁸⁷ Intranasal fluticasone propionate at doses of 200 or 400 μ g was more effective than placebo in both groups, as assessed by total nasal symptom scores for nasal obstruction, postnasal drip, and rhinorrhea.

However, not all patients with NAR have been shown to respond to INS. A large study showed no significant impact on symptoms.⁷ A subsequent multicenter trial was performed to assess the effects of INS therapy on a subset of patients with symptoms triggered predominantly by weather and temperature changes.⁸⁸ In this randomized study, which excluded patients triggered by respiratory irritants, 699 patients with NAR triggered by weather factors were treated with either fluticasone furoate or placebo for 4 weeks. There were no significant differences between the two groups. Thus, although patients with NAR as a group respond to INS, there may be subgroups of nonresponders that require further study. Specifically, based on this study, those with symptoms triggered by respiratory irritants may respond to a greater extent than those with problems related only to weather conditions.

Topical antihistamine sprays

Two topical antihistamine sprays have been studied in NAR. These sprays are azelastine and olopatadine.

Azelastine is the best studied of the two and the only one to be evaluated in a double-blind, multicenter, placebo-controlled trial.⁷⁷ It is available as Astelin in a 0.1% preparation containing 137 mcg per actuation that is dosed 2 actuations each nostril twice daily in adults and one actuation twice daily in children. It is also available in a 0.15% concentration (Astepro, containing 205 mcg per actuation), one to 2 actuations per nostril twice daily and decreasing the dose as symptoms improve. The 0.15% version contains sucralose as a taste-masking agent. It decreases the incidence of taste perversion (bad taste), which is one of the most common side effects of this drug. Both concentrations are available as generic preparations.

Olopatadine hydrochloride nasal spray (0.06%) is available as Patanase (containing 665 mcg per actuation) that is dosed 2 actuations twice daily in adults and one actuation twice daily for children down to 6 years of age. Patanase has not been approved for use in NAR.

As monotherapy, azelastine has been shown to be effective in randomized controlled studies.^{77,89} In 2 multicenter randomized open-label trials, approximately 80% to 85% of more than 200 subjects with NAR responded favorably to azelastine.⁷⁷ Significant improvement was seen in all symptoms evaluated.

The improvement in symptoms with azelastine is likely in part due to its antiinflammatory properties. These effects are multiple. They include the ability to diminish eosinophil activation and adhesion molecule expression and suppression of inflammatory cytokine generation.^{81,82,90} Azelastine may also reduce neurogenic excitation from olfactory stimuli. In the previously mentioned study in which subjects with NAR were exposed to pleasant and unpleasant odors, the administration of azelastine significantly attenuated exaggerated blood flow to odor-sensitive regions of the brain as assessed by MRI.³⁴ More recently, an in vitro cell study found that azelastine, like capsaicin, can activate TRPV1 receptors and with continuous cell exposure can desensitize these receptors. A similar effect was seen with the antihistamine bepotastine but not with olopatadine or fluticasone.⁹¹

Olopatadine and azelastine (0.1%) were compared for the treatment of NAR in a multicenter, randomized parallel group study lasting 14 days.⁹² Both reduced congestion, rhinorrhea, postnasal drip, and sneezing; there were no statistically significant differences between their effects. In addition, there was no difference in the side-effect profile of the two agents. But this study did not contain a placebo arm and was powered only to assess noninferiority. In another placebo-controlled study, olopatadine reduced the exaggerated response to hyperosmolar challenge in patients with prominent vasomotor symptoms.⁹³ This drug, like azelastine, also seems to have clinically significant antiinflammatory activity unrelated to its antagonism of histamine receptor 1 stimulation.⁹³

Combination therapy with intranasal corticosteroids and azelastine

The most effective treatment of NAR uses the combination of INS and azelastine. Based on several studies in allergic rhinitis the combined treatment is more effective than either agent alone. Combination therapy can be achieved either by using 2 separate nasal sprays or a combination product. A combination spray containing azelastine hydrochloride 137 mcg and fluticasone propionate 50 mcg (Dymista) became available in the United States in 2012 and is approved for children down to age 5 years and adults for seasonal allergic rhinitis. The dose is one actuation per nostril, twice daily. This combination product has been studied in patients with seasonal allergic

rhinitis and has been shown to be superior to single treatment with either agent alone.⁹⁴ Also in a post hoc analysis of a 1-year, randomized, open-label, active-controlled, parallel-group study in 612 subjects aged 12 years and older with perennial allergic rhinitis (424 subjects) or NAR (188 subjects), Dymista was found to be effective in both groups. Efficacy was assessed by change from baseline in PM reflective total nasal symptom score (rTNSS), time to first achieve 100% PM rTNSS reduction from baseline, and percentage of symptom-free days.⁹⁵

The conclusion one draws from these investigations is that combination treatment with azelastine and fluticasone seems to be at this time the treatment of choice in most individuals with NAR.

Ipratropium bromide

When rhinorrhea is the only symptom or the dominant symptom, as in gustatory or skiers/joggers rhinitis, ipratropium bromide (0.03% or 0.06%) nasal spray is recommended and is the treatment of choice.^{35,96} Ipratropium bromide is usually used at a dose of one or 2 sprays each nostril up to 3 times a day. Alternatively, it can also be used as needed or an hour before exposures that cause rhinorrhea, such as cold air or before eating. The concentration of 0.06% is usually intended only for short-term use (eg, treatment of rhinorrhea associated with the common cold). Two multicenter placebo-controlled trials have demonstrated the effectiveness of ipratropium bromide to control rhinorrhea.^{84,85}

The administration of ipratropium bromide nasal spray (0.03%) for 1 year among 285 patients with perennial NAR resulted in significant improvement in rhinorrhea as well as a decreased need for additional medications to control symptoms.⁸⁴ In addition, in a study of 253 patients with perennial NAR, ipratropium nasal spray significantly reduced rhinorrhea versus that observed with placebo.⁸⁵ However, this drug has little if any effect on any manifestation of rhinitis other than anterior rhinorrhea.

Adjunctive therapies

Adjunctive therapies include topical capsaicin, oral or topical decongestants, nasal saline sprays and irrigations, and oral antihistamines. Studies of antileukotriene drugs and intranasal chromones in the treatment of NAR are lacking, but clinical consensus is these medications are relatively ineffective for this condition.

Topical capsaicin

Topical capsaicin has been shown to diminish the symptoms of NAR, but irritation of the nasal mucosa can be a limiting factor.^{97,98} A randomized trial of 42 patients with NAR evaluated the effects of a diluted capsaicin nasal spray to which eucalyptol was added to reduce the burning sensation caused by this agent (Sinus Buster Nasal Spray [Akorn, Incorporated, Lake Forest, IL, USA]).⁹⁹ After 2 weeks of therapy with this preparation (dosed up to 12 actuations daily), patients reported significant improvements in total nasal symptom scores compared with placebo and good tolerability. This preparation is available without a prescription. A recent Cochrane Review of the use of capsaicin concluded "Capsaicin may be an option in the treatment of idiopathic non-allergic rhinitis." It is given in the form of brief treatments, usually during the same day. It seems to have beneficial effects on overall nasal symptoms up to 36 weeks after treatment, based on a few small studies (low-quality evidence). Well-conducted randomized controlled trials are required to further advance our understanding of the effectiveness of capsaicin in NAR, especially in patients with NAR of different types and severity, and using different methods of capsaicin application.¹⁰⁰

Oral and intranasal decongestants

Although there are no specific studies examining the clinical efficacy of decongestants for NAR, they can be used as needed only for congestion not responsive to the use of a nasal glucocorticoid, topical nasal antihistamine, or a combination of both. An oral decongestant, such as pseudoephedrine or phenylephrine, can be added to the treatment regimen. The usual dosing of pseudoephedrine is 30 or 60 mg, up to 3 times daily on symptomatic days. A sustained-release preparation of 120 mg used twice daily is also available. Phenylephrine hydrochloride is less effective and in some studies has not been superior to placebo at the 10-mg dose that is commonly available without prescription.^{101,102} Intranasal decongestants when used as monotherapy for extended periods of time can cause rebound nasal congestion or tolerance (tachyphylaxis). However, several recent studies of perennial and seasonal allergic rhinitis have indicated this agent can be used for longer periods of time without inducing tolerance if used in conjunction with an intranasal corticosteroid. This combination therapy has yet to be investigated in NAR; however, clinical experience indicates it is effective and well tolerated for this condition as well.^{103–105}

Nasal saline irrigation

A large body of observational reports and one prospective controlled clinical study has found that nasal lavage can be helpful in NAR.^{106,107} In the only prospective study the use of nasal irrigation significantly improved nasal symptoms.¹⁰⁷ Intranasal saline sprays have been found effective in relieving postnasal drip, sneezing, and congestion.^{72,108} Saline sprays may be somewhat less effective than larger-volume nasal lavage, although they may be more convenient for some patients.¹⁰⁹ A variety of over-the-counter devices, including bulb syringes and bottle sprayers, are effective, provided the system delivers an adequate volume of solution (>200 mL per side) into the nose.

Oral antihistamines

Clinical experience and limited data suggest that the newer nonsedating H1 antihistamines are not as effective in NAR, compared with allergic rhinitis.^{70,71} Older, first-generation H1 antihistamines (eg, chlorpheniramine) have anticholinergic properties that may be helpful to some patients with persistent and bothersome postnasal drip and/or anterior rhinorrhea despite the use of the aforementioned therapies.¹¹⁰ However, these medications are sedating; but if dosed at night the carryover effect during the day is minimal making these agents well tolerated in most patients.

Role of surgery

Several surgical approaches have been used in patients with severe chronic NAR.^{96,111–114} These approaches have been reported as uncontrolled case series. Such interventions can be considered in patients with recalcitrant symptoms not responding to standard therapies, such as topical nasal steroids in combination with TA and/or decongestants and/or ipratropium bromide. Six to 12 months of medical management should be allowed before surgical options are considered.

A turbinectomy can be performed when congestion is predominant. With this technique there has been concern about the destruction and/or elimination of the mucosal surface. However, laser turbinectomy has been reported to preserve normal nasal cytology as well as normal ciliary activity.¹¹³

Several other surgical procedures have been tried in the past, including vidian nerve resection, electrocoagulation of anterior ethmoidal nerve, sphenopalatine ganglion block, and others.^{114–116} None of these techniques has been shown to have long-term benefits, and the potential risks (eg, persistent pain) have to be considered carefully because they may outweigh any possible benefits.

Other alternative and complementary therapies have been evaluated, such as acupuncture and topical silver nitrate, although these cannot be recommended at this time.

Prognosis

NAR is a persistent condition, usually present lifelong. In one study, 180 patients with NAR were reevaluated 3 to 7 years after the initial diagnosis was made.¹¹⁷ Patients with NAR generally experienced worsening disease (52%), with an increase in the persistence (12%) and severity (9%) of nasal symptoms. In addition, 24% developed new comorbidities over time. Asthma was the most frequently developed comorbidity at the reevaluation, increasing from 32% to 55% of the subjects. There was also an increase in the development of sinusitis. This longitudinal study emphasizes the need for research to further elucidate relevant mechanistic pathways for NAR, which could potentially lead to novel, more effective therapeutic strategies.

REFERENCES

1. Blom HM, Godthelp T, Fokkens WJ, et al. Mast cells, eosinophils and IgE-positive cells in the nasal mucosa of patients with vasomotor rhinitis. An immunohistochemical study. *Eur Arch Otorhinolaryngol* 1995;252(Suppl 1):S33.
2. Powe DG, Huskisson RS, Carney AS, et al. Evidence for an inflammatory pathophysiology in idiopathic rhinitis. *Clin Exp Allergy* 2001;31:864.
3. Bousquet J, Fokkens W, Burney P, et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. *Allergy* 2008;63:842.
4. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122:S1.
5. van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. *Allergy* 2005;60:1471.
6. Numata T, Konno A, Hasegawa S, et al. Pathophysiological features of the nasal mucosa in patients with idiopathic rhinitis compared to allergic rhinitis. *Int Arch Allergy Immunol* 1999;119:304.
7. Blom HM, Godthelp T, Fokkens WJ, et al. The effect of nasal steroid aqueous spray on nasal complaint scores and cellular infiltrates in the nasal mucosa of patients with nonallergic, noninfectious perennial rhinitis. *J Allergy Clin Immunol* 1997;100:739.
8. Malcomson KG. The vasomotor activities of the nasal mucous membrane. *J Laryngol Otol* 1959;73:73.
9. Jones AS, Lancer JM. Vasomotor rhinitis. *Br Med J (Clin Res Ed)* 1987;294:1505.
10. Wilde AD, Cook JA, Jones AS. The nasal response to isometric exercise. *Clin Otolaryngol Allied Sci* 1995;20:345.
11. Wolf G. New aspects in the pathogenesis and therapy of hyperreflexive rhinopathy. *Laryngol Rhinol Otol (Stuttg)* 1988;67:438.
12. Moneret-Vautrin DA, Hsieh V, Wayoff M, et al. Nonallergic rhinitis with eosinophilia syndrome a precursor of the triad: nasal polyposis, intrinsic asthma, and intolerance to aspirin. *Ann Allergy* 1990;64:513.
13. Baraniuk JN. Neural control of human nasal secretion. *Pulm Pharmacol* 1991;4:20.
14. Lundblad L, Hua XY, Lundberg JM. Mechanisms for reflexive hypertension induced by local application of capsaicin and nicotine to the nasal mucosa. *Acta Physiol Scand* 1984;121:277.

15. Lacrois JS, Pochon N, Lundberg JM. Increased concentration of sensory neuropeptide in the nasal mucosa from patients with nonallergic chronic rhinitis. In: Passall D, editor. *The new frontier of otorhinolaryngology in Europe*. Sorrento (Italy): Monduzzi Editore; 1992. p. 59.
16. Borson DB. Roles of neutral endopeptidase in airways. *Am J Physiol* 1991;260:L212.
17. Trotter CM, Hall GH, Salter DM, et al. Histology of mucous membrane of human inferior nasal concha. *Clin Anat* 1990;3:307.
18. Berger G, Goldberg A, Ophir D. The inferior turbinate mast cell population of patients with perennial allergic and nonallergic rhinitis. *Am J Rhinol* 1997;11:63.
19. Bachert C, Prohaska P, Pipkorn U. IgE-positive mast cells on the human nasal mucosal surface in response to allergen exposure. *Rhinology* 1990;28:149.
20. Otsuka H, Inaba M, Fujikura T, et al. Histochemical and functional characteristics of metachromatic cells in the nasal epithelium in allergic rhinitis: studies of nasal scrapings and their dispersed cells. *J Allergy Clin Immunol* 1995;96:528.
21. Fokkens WJ, Godthelp T, Holm AF, et al. Dynamics of mast cells in the nasal mucosa of patients with allergic rhinitis and non-allergic controls: a biopsy study. *Clin Exp Allergy* 1992;22:701.
22. Ying S, Durham SR, Jacobson MR, et al. T lymphocytes and mast cells express messenger RNA for interleukin-4 in the nasal mucosa in allergen-induced rhinitis. *Immunology* 1994;82:200.
23. Varney VA, Jacobson MR, Sudderick RM, et al. Immunohistology of the nasal mucosa following allergen-induced rhinitis. Identification of activated T lymphocytes, eosinophils, and neutrophils. *Am Rev Respir Dis* 1992;146:170.
24. Godthelp T, Holm AF, Fokkens WJ, et al. Dynamics of nasal eosinophils in response to a nonnatural allergen challenge in patients with allergic rhinitis and control subjects: a biopsy and brush study. *J Allergy Clin Immunol* 1996;97:800.
25. Connell JT. Nasal mastocytosis. *J Allergy* 1969;43:182.
26. Drake-Lee AB, Moriarty B, Smallman LA. Mast cell numbers in the mucosa of the inferior turbinate in patients with perennial allergic rhinitis: a light microscopic study. *J Laryngol Otol* 1991;105:736.
27. Ruhno J, Howie K, Anderson M, et al. The increased number of epithelial mast cells in nasal polyps and adjacent turbinates is not allergy-dependent. *Allergy* 1990;45:370.
28. Malm L, Wihl JA, Lamm CJ, et al. Reduction of methacholine-induced nasal secretion by treatment with a new topical steroid in perennial non-allergic rhinitis. *Allergy* 1981;36:209.
29. Humbert M, Menz G, Ying S, et al. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. *Immunol Today* 1999;20:528.
30. Humbert M, Grant JA, Taborda-Barata L, et al. High-affinity IgE receptor (FcεpsilonRI)-bearing cells in bronchial biopsies from atopic and nonatopic asthma. *Am J Respir Crit Care Med* 1996;153:1931.
31. Kroegel C, Jäger L, Walker C. Is there a place for intrinsic asthma as a distinct immunopathological entity? *Eur Respir J* 1997;10:513.
32. Togias AG, Proud D, Lichtenstein LM, et al. The osmolality of nasal secretions increases when inflammatory mediators are released in response to inhalation of cold, dry air. *Am Rev Respir Dis* 1988;137:625.
33. Howarth PH, Salagean M, Dokic D. Allergic rhinitis: not purely a histamine-related disease. *Allergy* 2000;55(Suppl 64):7.

34. Bernstein JA, Hastings L, Boespflug EL, et al. Alteration of brain activation patterns in nonallergic rhinitis patients using functional magnetic resonance imaging before and after treatment with intranasal azelastine. *Ann Allergy Asthma Immunol* 2011;106:527.
35. Raphael G, Raphael MH, Kaliner M. Gustatory rhinitis: a syndrome of food-induced rhinorrhea. *J Allergy Clin Immunol* 1989;83:110.
36. Papon JF, Brugel-Ribere L, Fodil R, et al. Nasal wall compliance in vasomotor rhinitis. *J Appl Physiol* (1985) 2006;100:107.
37. Story GM, Peier AM, Reeve AJ, et al. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell* 2003;112:819–29.
38. Trevisani M, Siemens J, Materazzi S, et al. 4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1. *Proc Natl Acad Sci U S A* 2007;104(33):13519–24.
39. Bautista DM, Jordt SE, Nikai T, et al. TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. *Cell* 2006;124(6):1269–82.
40. Taylor-Clark TE, Undem BJ, Macglashan DW Jr, et al. Prostaglandin-induced activation of nociceptive neurons via direct interaction with transient receptor potential A1 (TRPA1). *Mol Pharmacol* 2008;73(2):274–81.
41. Bandell M, Story GM, Hwang SW, et al. Sensitization of TRPA1: a molecular mechanism of inflammatory pain. *Brain* 2008;131(Pt 5):1241–51.
42. Corey DP, Garcia-Anoveros J, Holt JR, et al. TRPA1 mediates formalin-induced pain. *Proc Natl Acad Sci U S A* 2007;104(33):13525–30.
43. Patapoutian A. Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin. *Neuron* 2004;41(6):849–57.
44. Bautista DM, Movahed P, Hinman A, et al. Pungent products from garlic activate the sensory ion channel TRPA1. *Proc Natl Acad Sci U S A* 2005;102(34):12248–52.
45. Jordt SE, Bautista DM, Chuang HH, et al. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. *Nature* 2004;427:260–5.
46. Macpherson LJ, Geierstanger BH, Viswanath V, et al. The pungency of garlic: activation of TRPA1 and TRPV1 in response to allicin. *Curr Biol* 2005;15(10):929–34.
47. Macpherson LJ, Xiao B, Kwan KY, et al. An ion channel essential for sensing chemical damage. *J Neurosci* 2007;27(42):11412–5.
48. Namer B, Seifert F, Handwerker HO, et al. TRPA1 and TRPM8 activation in humans: effects of cinnamaldehyde and menthol. *Neuroreport* 2005;16(9):955–9.
49. Merrill AW, Cuellar JM, Judd JH, et al. Effects of TRPA1 agonists mustard oil and cinnamaldehyde on lumbar spinal wide-dynamic range neuronal responses to innocuous and noxious cutaneous stimuli in rats. *J Neurophysiol* 2008;99(2):415–25.
50. Puig S, Sorkin LS. Formalin-evoked activity in identified primary afferent fibers: systemic lidocaine suppresses phase-2 activity. *Pain* 1996;64(2):345–55.
51. Koizumi K, Iwasaki Y, Narukawa M, et al. Diallyl sulfides in garlic activate both TRPA1 and TRPV1. *Biochem Biophys Res Commun* 2009;382(3):545–8.
52. Escalera J, von Hehn CA, Bessac BF, et al. TRPA1 mediates the noxious effects of natural sesquiterpene deterrents. *J Biol Chem* 2008;283:24136–44.
53. Bessac BF, Sivula M, von Hehn CA, et al. TRPA1 is a major oxidant sensor in murine airway sensory neurons. *J Clin Invest* 2008;118:1899–910.

54. Andre E, Campi B, Materazzi S, et al. Cigarette smoke-induced neurogenic inflammation is mediated by alpha, beta-unsaturated aldehydes and the TRPA1 receptor in rodents. *J Clin Invest* 2008;118:2574–82.
55. Maselli Del Giudice A, Barbara M, Russo GM, et al. Cell-mediated non-allergic rhinitis in children. *Int J Pediatr Otorhinolaryngol* 2012;76:1741.
56. Gelardi M, Luigi Marseglia G, Licari A, et al. Nasal cytology in children: recent advances. *Ital J Pediatr* 2012;38:51.
57. Cai J, Guan S, Mai Z, et al. Analysis of the level and significance of IL-16 and IL-17 in nasal secretion and in serum of patients with allergic rhinitis and non-allergic rhinitis. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2014;28(11): 821–3 [in Chinese].
58. Klein Jan A, Vinke JG, Severijnen LW, et al. Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J* 2000;15:491.
59. Rondón C, Romero JJ, López S, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol* 2007;119:899.
60. Rondón C, Fernández J, López S, et al. Nasal inflammatory mediators and specific IgE production after nasal challenge with grass pollen in local allergic rhinitis. *J Allergy Clin Immunol* 2009;124:1005.
61. Rondón C, Campo P, Togias A, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol* 2012;129:1460.
62. Rondón C, Campo P, Herrera R, et al. Nasal allergen provocation test with multiple aeroallergens detects polysensitization in local allergic rhinitis. *J Allergy Clin Immunol* 2011;128:1192.
63. Rondón C, Campo P, Galindo L, et al. Prevalence and clinical relevance of local allergic rhinitis. *Allergy* 2012;67:1282.
64. Klimek L, Bardenhewer C, Spielhaupter M, et al. Local allergic rhinitis to *Alternaria alternata*: evidence for local IgE production exclusively in the nasal mucosa. *HNO* 2015;63(5):364–72 [in German].
65. Klimek L, von Bernus L, Pfaar O. Local (exclusive) IgE production in the nasal mucosa. Evidence for local allergic rhinitis. *HNO* 2013;61(3):217–23 [in German].
66. Campo P, Rondón C, Gould HJ, et al. Local IgE in non-allergic rhinitis. *Clin Exp Allergy* 2015;45(5):872–81.
67. Rondón C, Campo P, Zambonino MA, et al. Follow-up study in local allergic rhinitis shows a consistent entity not evolving to systemic allergic rhinitis. *J Allergy Clin Immunol* 2014;133(4):1026–31.
68. Wierzbicki DA, Majmundar AR, Schull DE, et al. Multiallergen nasal challenges in nonallergic rhinitis. *Ann Allergy Asthma Immunol* 2008;100:533.
69. Philip G, Togias AG. Nonallergic rhinitis. Pathophysiology and models for study. *Eur Arch Otorhinolaryngol* 1995;252(Suppl 1):S27.
70. Mullarkey MF. Eosinophilic nonallergic rhinitis. *J Allergy Clin Immunol* 1988;82:941.
71. Rinne J, Simola M, Malmberg H, et al. Early treatment of perennial rhinitis with budesonide or cetirizine and its effect on long-term outcome. *J Allergy Clin Immunol* 2002;109:426.
72. Setticone RA, Lieberman P. Update on nonallergic rhinitis. *Ann Allergy Asthma Immunol* 2001;86:494.
73. Kondo H, Nachtigal D, Frenkiel S, et al. Effect of steroids on nasal inflammatory cells and cytokine profile. *Laryngoscope* 1999;109:91.

74. Malm L, Wihl JA. Intra-nasal beclomethasone dipropionate in vasomotor rhinitis. *Acta Allergol* 1976;31:245.
75. Wight RG, Jones AS, Beckingham E, et al. A double blind comparison of intra-nasal budesonide 400 micrograms and 800 micrograms in perennial rhinitis. *Clin Otolaryngol Allied Sci* 1992;17:354.
76. Small P, Black M, Frenkiel S. Effects of treatment with beclomethasone dipropionate in subpopulations of perennial rhinitis patients. *J Allergy Clin Immunol* 1982;70:178.
77. Banov CH, Lieberman P, Vasomotor Rhinitis Study Groups. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. *Ann Allergy Asthma Immunol* 2001;86:28.
78. Scadding GK, Lund VJ, Jacques LA, et al. A placebo-controlled study of fluticasone propionate aqueous nasal spray and beclomethasone dipropionate in perennial rhinitis: efficacy in allergic and non-allergic perennial rhinitis. *Clin Exp Allergy* 1995;25:737.
79. Pipkorn U, Berge T. Long-term treatment with budesonide in vasomotor rhinitis. *Acta Otolaryngol* 1983;95:167.
80. Takao A, Shimoda T, Matsuse H, et al. Inhibitory effects of azelastine hydrochloride in alcohol-induced asthma. *Ann Allergy Asthma Immunol* 1999;82:390.
81. Ciprandi G, Pronzato C, Passalacqua G, et al. Topical azelastine reduces eosinophil activation and intercellular adhesion molecule-1 expression on nasal epithelial cells: an antiallergic activity. *J Allergy Clin Immunol* 1996;98:1088.
82. Yoneda K, Yamamoto T, Ueta E, et al. Suppression by azelastine hydrochloride of NF-kappa B activation involved in generation of cytokines and nitric oxide. *Jpn J Pharmacol* 1997;73:145.
83. Tamaoki J, Yamawaki I, Tagaya E, et al. Effect of azelastine on platelet-activating factor-induced microvascular leakage in rat airways. *Am J Physiol* 1999;276: L351.
84. Grossman J, Banov C, Boggs P, et al. Use of ipratropium bromide nasal spray in chronic treatment of nonallergic perennial rhinitis, alone and in combination with other perennial rhinitis medications. *J Allergy Clin Immunol* 1995;95:1123.
85. Bronsky EA, Druce H, Findlay SR, et al. A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. *J Allergy Clin Immunol* 1995;95:1117.
86. Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol* 2010;105:168.
87. Webb DR, Meltzer EO, Finn AF Jr, et al. Intranasal fluticasone propionate is effective for perennial nonallergic rhinitis with or without eosinophilia. *Ann Allergy Asthma Immunol* 2002;88:385.
88. Jacobs R, Lieberman P, Kent E, et al. Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. *Allergy Asthma Proc* 2009;30:120.
89. Lieberman P, Kaliner MA, Wheeler WJ. Open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis. *Curr Med Res Opin* 2005;21:611.
90. Lieberman P. Intranasal antihistamines for allergic rhinitis: mechanism of action. *Allergy Asthma Proc* 2009;30:345.
91. Singh U, Bernstein JA, Haar L, et al. Azelastine desensitization of transient receptor potential vanilloid 1: a potential mechanism explaining its therapeutic effect in nonallergic rhinitis. *Am J Rhinol Allergy* 2014;28:215–24.

92. Lieberman P, Meltzer EO, LaForce CF, et al. Two-week comparison study of olopatadine hydrochloride nasal spray 0.6% versus azelastine hydrochloride nasal spray 0.1% in patients with vasomotor rhinitis. *Allergy Asthma Proc* 2011;32:151.
93. Smith PK, Collins J. Olopatadine 0.6% nasal spray protects from vasomotor challenge in patients with severe vasomotor rhinitis. *Am J Rhinol Allergy* 2011; 25:e149.
94. Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol* 2012; 129:1282.
95. Price D, Shah S, Bhatia S, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. *J Investig Allergol Clin Immunol* 2013; 23(7):495–503.
96. Georgalas C, Jovancevic L. Gustatory rhinitis. *Curr Opin Otolaryngol Head Neck Surg* 2012;20:9.
97. Blom HM, Van Rijswijk JB, Garrelds IM, et al. Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. *Clin Exp Allergy* 1997;27:796.
98. Marabini S, Ciabatti PG, Polli G, et al. Beneficial effects of intranasal applications of capsaicin in patients with vasomotor rhinitis. *Eur Arch Otorhinolaryngol* 1991;248:191.
99. Bernstein JA, Davis BP, Picard JK, et al. A randomized, double-blind, parallel trial comparing capsaicin nasal spray with placebo in subjects with a significant component of nonallergic rhinitis. *Ann Allergy Asthma Immunol* 2011;107:171.
100. Gevorgyan A, Segboer C, Gorissen R, et al. Capsaicin for non-allergic rhinitis. *Cochrane Database Syst Rev* 2015;(7):CD010591.
101. Hatton RC, Winterstein AG, McKelvey RP, et al. Efficacy and safety of oral phenylephrine: systematic review and meta-analysis. *Ann Pharmacother* 2007; 41:381.
102. Horak F, Zieglmayer P, Zieglmayer R, et al. A placebo-controlled study of the nasal decongestant effect of phenylephrine and pseudoephedrine in the Vienna Challenge Chamber. *Ann Allergy Asthma Immunol* 2009;102:116.
103. Baroody FM, Brown D, Gavanescu L, et al. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol* 2011;127(4):927–34.
104. Meltzer EO, Bernstein DI, Prenner BM, et al. Mometasone furoate nasal spray plus oxymetazoline nasal spray: short-term efficacy and safety in seasonal allergic rhinitis. *Am J Rhinol Allergy* 2013;27(2):102–8.
105. Vaidyanathan S, Williamson P, Clearie K, et al. Fluticasone reverses oxymetazoline-induced tachyphylaxis of response and rebound congestion. *Am J Respir Crit Care Med* 2010;182(1):19–24.
106. Harvey R, Hannan SA, Badia L, et al. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane Database Syst Rev* 2007;(3):CD006394.
107. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. *Laryngoscope* 2000;110:1189.
108. Spector SL. The placebo effect is nothing to sneeze at. *J Allergy Clin Immunol* 1992;90:1042.
109. Pynnonen MA, Mukerji SS, Kim HM, et al. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. *Arch Otolaryngol Head Neck Surg* 2007;133:1115.

110. Meltzer EO. An overview of current pharmacotherapy in perennial rhinitis. *J Allergy Clin Immunol* 1995;95:1097.
111. el-Guindy A. Endoscopic transseptal vidian neurectomy. *Arch Otolaryngol Head Neck Surg* 1994;120:1347.
112. Dong Z. Anterior ethmoidal electrocoagulation in the treatment of vasomotor rhinitis. *Zhonghua Er Bi Yan Hou Ke Za Zhi* 1991;26:358.
113. Mladina R, Risavi R, Subaric M. CO2 laser anterior turbinectomy in the treatment of non-allergic vasomotor rhinopathia. A prospective study upon 78 patients. *Rhinology* 1991;29:267.
114. Fernandes CM. Bilateral transnasal vidian neurectomy in the management of chronic rhinitis. *J Laryngol Otol* 1994;108:569.
115. Prasanna A, Murthy PS. Vasomotor rhinitis and sphenopalatine ganglion block. *J Pain Symptom Manage* 1997;13:332.
116. Prianikov PD, Svistushkin VM, Egorov VI, et al. The modern approach to the treatment of the patients presenting with vasomotor rhinitis with the use of the electrosurgical technique. *Vestn Otorinolaringol* 2015;2:63–6.
117. Rondón C, Doña I, Torres MJ, et al. Evolution of patients with nonallergic rhinitis supports conversion to allergic rhinitis. *J Allergy Clin Immunol* 2009;123:1098.