





Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology

P. W. Hellings^{1,2} | L. Klimek³ | C. Cingi⁴  | I. Agache⁵ | C. Akdis⁶ | C. Bachert⁷  | J. Bousquet⁸ | P. Demoly⁸ | P. Gevaert⁷ | V. Hox⁹ | C. Hupin^{9,10} | L. Kalogjera¹¹ | F. Manole¹² | R. Mösges¹³  | J. Mullol¹⁴ | N. B. Muluk¹⁵ | A. Muraro¹⁶ | N. Papadopoulos^{17,24} | R. Pawankar¹⁸ | C. Rondon¹⁹ | M. Rundenko²⁰ | S. F. Seys²  | E. Toskala²¹ | L. Van Gerven^{1,2} | L. Zhang²² | N. Zhang⁷ | W. J. Fokkens²³

¹Clinical division of Otorhinolaryngology, Head & Neck Surgery, University Hospitals Leuven, Leuven, Belgium

²Laboratory of Clinical Immunology, Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium

³Center for Rhinology and Allergology, Wiesbaden, Germany

⁴Department of Otorhinolaryngology, Head and Neck Surgery, University of Eskisehir Osmangazi, Eskisehir, Turkey

⁵Department of Allergy and Clinical Immunology, Transylvania University, Brasov, Romania

⁶Swiss Institute of Allergy and Asthma Research, Christine Kuhne-Center for Allergy Research and Education, University of Zurich, Davos, Switzerland

⁷Upper Airway Research Laboratory, Ghent University Hospital, Ghent, Belgium

⁸Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France

⁹Service d'ORL, Cliniques Universitaires St-Luc, Brussels, Belgium

¹⁰Institut de Recherche Expérimentale et Clinique (IREC), Pole de Pneumologie, ORL & Dermatologie, Université catholique de Louvain (UCL), Brussels, Belgium

¹¹Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Sestre milosrdnice, Zagreb, Croatia

¹²ENT Department, Faculty of Medicine, University of Oradea, Oradea, Romania

¹³Institute of Medical Statistics, Informatics, and Epidemiology, Medical Faculty, University of Köln, Cologne, Germany

¹⁴Unitat de Rinologia i Clínica de l'Olfacte, Servei d'Otorinolaringologia, Hospital Clínic, Barcelona, Catalonia, Spain

¹⁵ENT Department, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey

¹⁶The Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, Department of Mother and Child Health, University of Padua, Padua, Italy

¹⁷Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

¹⁸Nippon Medical School, Tokyo, Japan

¹⁹Allergy Service, Carlos Haya Hospital, Malaga, Spain

²⁰London Allergyology and Immunology Center, London, UK

²¹Department of Otorhinolaryngology-Head and Neck Surgery, Temple University, Philadelphia, USA

²²Department of Otolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Beijing, China

²³Department of Otorhinolaryngology, Head & Neck Surgery, Academic Medical Centre (AMC), Amsterdam, The Netherlands

²⁴University of Manchester, Manchester, UK

Correspondence

Peter W. Hellings, Department of Otorhinolaryngology, Head & Neck Surgery, University Hospitals Leuven, Leuven, Belgium.
Email: peter.hellings@uzleuven.be

Edited by: Thomas Bieber

Abstract

This EAACI position paper aims at providing a state-of-the-art overview on nonallergic rhinitis (NAR). A significant number of patients suffering from persistent rhinitis are defined as nonallergic noninfectious rhinitis (NANIR) patients, often denominated in short as having NAR. NAR is defined as a symptomatic inflammation of the nasal mucosa with the presence of a minimum of two nasal symptoms such as nasal obstruction, rhinorrhea, sneezing, and/or itchy nose, without clinical evidence of endonasal infection and without systemic signs of sensitization to inhalant allergens. Symptoms of NAR may have a wide range of severity and be either continuously present and/or induced by exposure to unspecific triggers, also called nasal hyperresponsiveness (NHR). NHR represents a clinical feature of both AR and NAR patients. NAR involves different subgroups: drug-induced rhinitis, (nonallergic) occupational rhinitis, hormonal rhinitis (including pregnancy rhinitis), gustatory rhinitis, senile rhinitis, and idiopathic rhinitis (IR). NAR should be distinguished from those rhinitis patients with an allergic reaction confined to the nasal mucosa, also called “entopy” or local allergic rhinitis (LAR). We here provide an overview of the current consensus on phenotypes of NAR, recommendations for diagnosis, a treatment algorithm, and defining the unmet needs in this neglected area of research.

KEYWORDS

classification, nonallergic rhinitis, rhinitis, treatment

1

1 | INTRODUCTION

The prevalence of chronic rhinitis is estimated to be as high as 30% of the total population.¹ Chronic rhinitis is defined as a symptomatic inflammation of the inner lining of the nose, leading to nasal obstruction, rhinorrhea (anteriorly or posteriorly), sneezing, or nasal/ocular itch. Two nasal symptoms should be present for at least 1 hour daily for a minimum of 12 weeks per year to define chronic rhinitis.¹ By this definition, patients with occasional or physiological nasal symptoms are excluded, as well as those individuals with nasal inflammation beyond the nasal cavities, that is, rhinosinusitis. Chronic rhinitis may have a spectrum of disease severity, ranging from mild to severe disease. Patients with severe chronic rhinitis unresponsive to recommended treatment are defined as having severe chronic upper airway disease (SCUAD)^{2,3} It is important to realize that rhinitis symptoms are present in those individuals with rhinosinusitis. Chronic rhinosinusitis (CRS) is reported in up to 10.9% of the Western population,⁴ and defined as inflammation of the sinonasal cavities, characterized by two or more symptoms such as nasal obstruction, facial pain, pressure or fullness, (thick and/or discolored) secretions, and/or decreased sense of smell.⁵

Based on the knowledge of the major etiologic factor, chronic rhinitis patients are clinically divided into four major subgroups (Figure 1).

Infectious rhinitis is often an acute and self-limiting disease caused by a virus, usually known as common cold⁵ However, infectious rhinitis may have a prolonged disease course with bacterial

infection, especially in those patients with a septal perforation, nose picking, and/or corpus alienum. Discolored secretions and/or crust formation are considered clinical landmarks of infectious rhinitis. It is generally accepted that infection may represent only one of the multiple underlying factors in the pathophysiology of CRS. CRS with/without nasal polyps (CRSwNP/CRSsNP) is found in those individuals with a prolonged inflammation extending beyond the nasal cavities.⁵

Allergic rhinitis is the most prevalent noncommunicable disease¹ and is defined as a symptomatic inflammation of the nose induced by allergen inhalation by sensitized individuals.⁶ The diagnosis is based on the correspondence between the history of induction of symptoms by allergen contact and positive results of skin prick test (SPT) or allergen-specific IgE in the blood. We should recognize that a group of AR patients may have so-called entopy, that is, an allergic reaction confined to the nasal mucosa.⁷ Most likely, LAR patients represent a subgroup of those formerly defined as nonallergic rhinitis with eosinophilia syndrome (NARES).

Nonallergic noninfectious rhinitis (NANIR) involves a heterogeneous group of patients suffering of rhinitis without clinical signs of infection (discolored secretions) and without systemic signs of allergic inflammation (allergen-specific IgE in blood and/or positive SPT results). This group is often defined in short as NAR. Subgroups of NAR are as follows: drug-induced rhinitis,⁸ rhinitis of the elderly,⁹ hormonal rhinitis including pregnancy-induced rhinitis,¹⁰ nonallergic occupational rhinitis,¹¹ gustatory rhinitis,¹² and idiopathic rhinitis.¹³ In reality, a significant portion of chronic rhinitis patients may belong

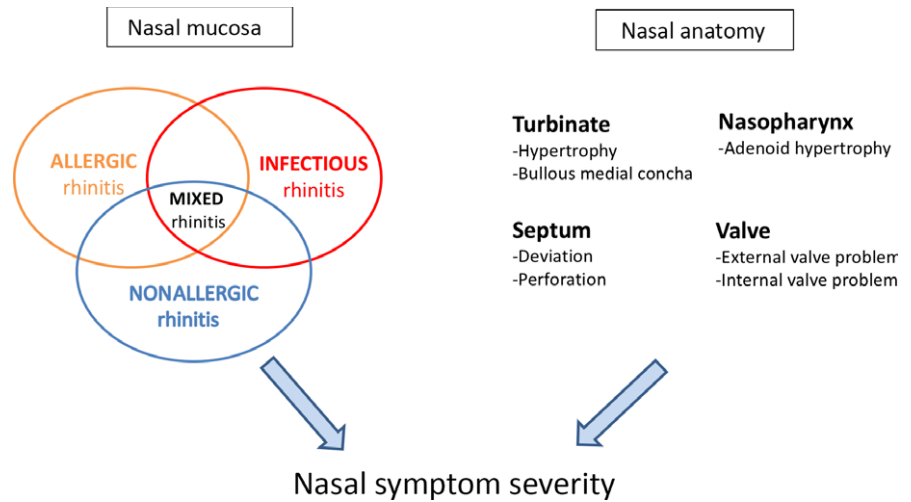


FIGURE 1 Phenotypes of chronic rhinitis

to the group of so-called *mixed rhinitis*.¹⁴ This patient population may have more than one known/unknown etiologic factor, for example, patients with an isolated positive SPT for pollen suffering all year long despite absence of eosinophilia in secretions. It is important to stress the importance of a precise diagnosis in this group, as a nasal endoscopy is warranted to evaluate the endoscopic signs of CRSsNP and CRSwNP that are not always obvious by anterior or posterior rhinoscopy,¹⁵ as well as the anatomic factors that may contribute to the severity of the different nasal symptoms for which the patients seek medical advice (Figure 1).

2 | PREVALENCE OF NAR

Epidemiological data on NAR are limited, as we lack a uniform definition of NAR as well as an international consensus on diagnostic criteria. In addition, epidemiologic data are difficult to interpret as nasal endoscopy excluding rhinosinusitis in adults and adenoid hypertrophy in children has not been performed in the studies conducted. Despite the weakness of epidemiologic studies, it is estimated that more than 200 million people suffer from NAR worldwide.¹⁶ Within the pediatric population, Westman et al.¹⁷ showed an 8.1% prevalence of NAR at the age of 4 and 6.3% prevalence at the age of 8 in a Swedish birth cohort of 2024 children. A similar study performed in Singapore found that NAR was the diagnosis in 24.9% of 6600 children with rhinitis symptoms (mean age of 7.8 years). Chiang et al.¹⁸ reported that NAR was more common in children under 6 years of age compared to AR, while AR diagnosis increased with age, and NAR decreased to 10%-15% in older children.¹⁸ In Belgium, the prevalence of self-declared NAR was 9.6% in a population of 4959 subjects of 15 years or older.¹⁹ Shaaban et al.²⁰ performed a longitudinal population-based study in Western Europe on the cumulative incidence of asthma in 17 716 subjects during a period of 8 years. They found that the adjusted relative risk for asthma development in NAR was 2.71 (95% CI: 1.64-4.46). Asthma is similarly associated with allergic and nonallergic rhinitis, but only children with AR had increased bronchial

responsiveness and elevated FeNO, suggesting different endotypes of asthma associated with allergic and nonallergic rhinitis.²¹

3 | SUBGROUPS OF NAR

NAR patients may have a variety of clinical phenotypes. At present, we recognize the following subgroups to be relevant in clinical practice:

3.1 | Senile rhinitis or rhinitis in elderly

Senile rhinitis is defined as rhinitis in patients above 65 years of age and is an underdiagnosed condition affecting up to 29.8% of the Portuguese population over the age of 65 years.⁹ Apart from the fact that a significant portion of patients with senile rhinitis may have an allergic disease, the diagnosis of senile rhinitis most often refers to those patients with late-onset, bilateral watery nasal secretions without endonasal mucosal and/or anatomic pathology.²² A neurogenic dysregulation is considered the cause of the symptoms as ipratropium bromide, that is, an anticholinergic drug, is effective in reducing the severity and duration of the rhinorrhea in these patients.²³

Senile rhinorrhea is a form of clear anterior rhinorrhea that affects elderly patients much more often than younger adults regardless of gender and older patients reported more drip quantity and more frequent drip, making rhinorrhea more bothersome and individuals more likely to seek treatment.²⁴

3.2 | Gustatory rhinitis

Gustatory rhinitis is characterized by watery rhinorrhea after ingestion of hot and spicy food.¹² It is believed to be induced by a gustatory reflex associated with a hyperactive, nonadrenergic, noncholinergic, or peptidergic neural system.²²

3.3 | Occupational rhinitis

Occupational rhinitis is defined as an inflammation of the nasal mucosa due to exposure to a particular work environment and has

to be distinguished from “work-exacerbated” rhinitis.¹¹ Several agents are reported to be associated with occupational rhinitis, such as high and low molecular weight (HMW and LMW) allergens and irritants. HMW agents may induce a typical IgE-mediated allergic inflammation, giving rise to occupational allergic disease. In contrast, the mechanisms of chronic inflammation induced by most LMW molecules remain speculative.²⁵ The latter group of patients with nonallergic occupational rhinitis represent a subgroup of NAR. In case of prolonged exposure to occupational agents, patients may progress to asthma.²⁶ Therefore, recognition of occupational rhinitis is considered to be crucial in the prevention of occupational asthma. Besides occupational agents, also environmental agents such as pollution and/or tobacco smoke may induce nasal symptoms via largely unknown mechanisms.¹¹ Rhinitis can arise de novo after high-level and/or after prolonged exposure to airborne occupational or environmental irritant chemicals.²⁷ As nonspecific nasal hyperreactivity to occupational triggers can also be found in the absence of mucosal inflammation, some authors refer to this condition as “occupational nonallergic rhinopathy”.^{27,28}

3.4 | Hormonal rhinitis

Hormonal imbalances during menstrual cycle, puberty, pregnancy, menopause, and specific endocrine disorders such as hypothyroidism and acromegaly are often associated with NAR.^{29,30} Estrogens exert a vascular engorgement effect in the nose, which may lead to nasal obstruction and/or nasal hypersecretion. Beta-estradiol and progesterone increase the expression of histamine H1-receptors on human nasal epithelial and microvascular endothelial cells and induce eosinophil migration and/or degranulation. In contrast, testosterone decreases eosinophil activation and viability.³¹ Although hormonal changes have a presumed etiological role especially in gestational rhinitis or pregnancy-induced rhinitis,³² the exact pathophysiology of

hormonal rhinitis remains unclear and smoking appears to be the only agreed identifiable risk factor in pregnancy-induced rhinitis.²⁹

In new-onset allergic rhinitis and asthma after puberty, it was shown that girls with late onset of menarche were less likely to develop allergic rhinitis after puberty compared with those who have menarche at an average age.³³ Late menarche (>13 years of age) was statistically significantly inversely related to allergic rhinitis development. As the use of hormonal contraceptives was inversely associated with new-onset allergic rhinitis, the authors suggested that in addition to endogenous hormones, hormonal contraceptives might protect young women from allergies and asthma after puberty.

3.5 | Drug-induced rhinitis

A variety of drugs may cause nasal symptoms, primarily nasal obstruction.³⁴ Drug-induced rhinitis can be divided into two subgroups: adverse events of systemic treatment and abuse of decongestive nasal therapy, best known as rhinitis medicamentosa. The former category includes prolonged oral intake of aspirin, ibuprofen, and other NSAID,³⁵ beta-blockers, sedatives, antidepressants, oral contraceptives, or drugs used to treat erectile dysfunction.

Peptidergic drugs activate human mast cells through a G-protein-coupled receptor, the Mas-related G-protein-coupled receptor X2 (MRGPRX2), and this interaction could be responsible for some forms of drug-induced rhinitis.³⁶

Rhinitis medicamentosa is induced by prolonged use of potent decongestant sprays, and abrupt arrest of the use of these sprays is recommended.

3.6 | Idiopathic rhinitis

Up to 50% of patients with NAR do not have a clear etiology underlying their symptoms and are so-called idiopathic rhinitis patients.

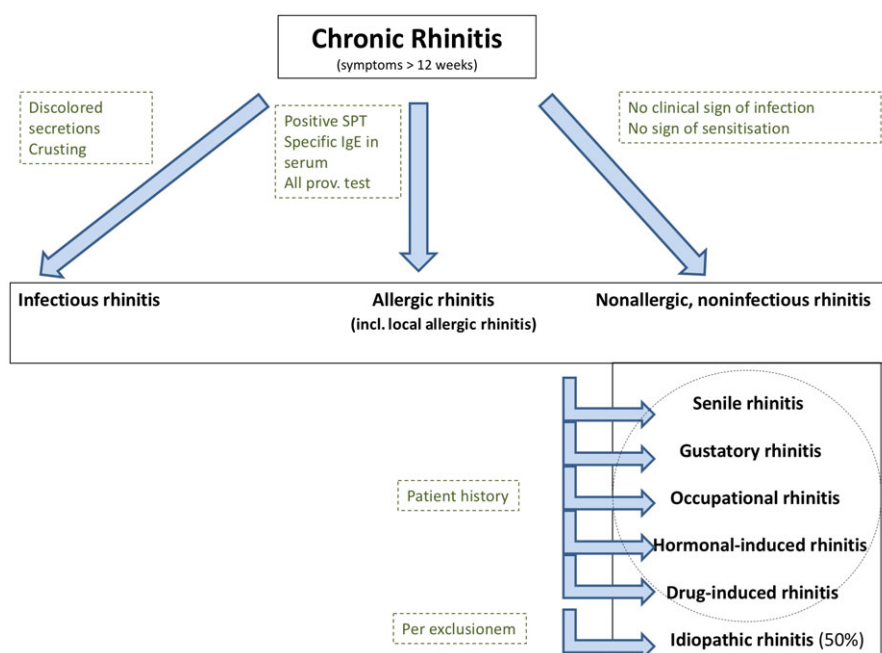


FIGURE 2 Diagnosis of chronic rhinitis

The key feature of IR patients is the presence of NHR.³⁷ Recently, it was shown that the nociceptive TRPV1-substance P (SP) signaling pathway is upregulated in IR patients, most likely to be involved in the pathophysiology.¹³

4 | DIAGNOSIS OF NAR

The diagnosis of NAR is based on a detailed medical history and exclusion of clinically relevant sensitization to airborne allergens, and exclusion of clinical signs of rhinosinusitis (Figure 2).

Medical history is the key for the diagnosis of well-defined phenotypes of NAR, such as senile rhinitis, gestational/hormonal rhinitis, gustatory rhinitis, occupational rhinitis, and drug-induced rhinitis. Therefore, it is recommended to consider the age of the patient, the duration and frequency of symptoms, the hormonal state, the occupational/environmental exposure to a list of triggers leading to nasal symptoms, and the systemic and nasal medication use. All of these items may provide hints toward diagnosing the specific type of rhinitis.

Besides history, *anterior rhinoscopy* should be used to check for signs of infection, endonasal crust formation, and/or significant anatomic deformities. *Nasal endoscopy* is recommended as it allows the evaluation of the whole endonasal cavity including the ostiomeatal complex.⁵ The importance of nasal endoscopy in the diagnosis of prolonged courses of rhinitis cannot be underestimated, as it may reveal the presence of CRSsNP or CRSwNP.

Skin prick testing or determination of *allergen-specific IgE in the blood* is necessary for the diagnosis of AR.³⁸ However, both SPT and determining specific IgE in serum have their limitations. It is impossible to test all possible allergens and only the relevant are selected. On the other hand, evidence of systemic sensitization by SPT or specific IgE does not necessarily mean that nasal symptoms are triggered by allergy. Clinical relevance of detected sensitization may be confirmed by history and/or allergen provocation test.³⁹

Up until now, the following diagnostic tests are *not recommended* in NAR:⁴⁰

- *Allergen provocation* testing can be performed in different ways and is mainly performed to confirm sensitization upon specific indication in AR patients, OR patients, and patients that are likely to have LAR.
- *Microbiological* analysis of the nasal content is not recommended in noninfectious rhinitis, as the presence of any virus, bacteria, or fungus does not necessarily imply infection.⁵
- *Nasal cytology or biopsies* are not recommended in NAR, but may help to distinguish between an inflammatory or neurogenic etiology of symptoms.⁴¹ Detection of eosinophilic inflammation in cytology or biopsy in the absence of systemic allergy may be attributed to LAR, NARES or to intolerance to drugs (such as aspirin), food or preservatives.³⁹
- Measurement of *total IgE* or *allergen-specific IgE in nasal secretions* is performed in a limited number of academic centers for the diagnosis of LAR.

- In contrast to nasal endoscopy to exclude endonasal signs of sinonasal disease, *CT scans* of the sinonasal cavities are not recommended in rhinitis patients.
- Measurement of *nasal hyperreactivity* is only performed in a limited number of academic centers beyond routine clinical practice.
- Measurement of markers of *cerebrospinal fluid leakage* (β -tran sferrin or β -trace) via a skull base defect are only indicated in unilateral watery rhinorrhea.

5 | DIFFERENTIAL DIAGNOSIS OF NAR

5.1 | Local allergic rhinitis

Local allergic rhinitis (LAR) or entopy has been reported as a localized nasal allergic response in patients with negative SPT and absence of detectable specific IgE (sIgE) to inhalant allergens in the blood.⁴² In Southern Europe, almost one-third of the rhinitis patients are classified into the LAR group.⁴³ The pathophysiology is characterized by local production of sIgE, a Th2 cytokine pattern of mucosal cell infiltration (eosinophils, basophils, mast cells, CD3 + T cells, and CD4 + T cells), and a positive nasal allergen provocation test (NAPT) with release of inflammatory mediators (tryptase and eosinophil cationic protein).³⁹ There is evidence of an allergen-specific basophil activation in peripheral blood, suggesting that this cell can be the first or only target for sIgE after its nasal production.⁴⁴ A history of "AR-type" symptoms elicited by natural exposure to aeroallergens is usually present. The diagnosis of LAR can be confirmed by the detection of nasal sIgE, a positive NAPT response, or both.⁴⁵ The NAPT is a key tool for the diagnosis although it is time-consuming. NAPT with multiple aeroallergens (NAPT-M) in one session has proved to be specific, sensitive, reproducible, and less time-consuming (75% reduction in the number of visits for diagnosis of NAR, and a 55% for LAR).⁴⁵ Basophil activation test in peripheral blood⁴⁴ is very specific and less time-consuming and supports the diagnosis of LAR.

Medical management of LAR is similar to AR, with good response to nasal corticosteroids. Due to its cost and complexity, NAPT or detection of specific IgE in nasal secretions is not recommended in clinical practice. As a consequence, a percentage of patients with LAR are still be classified into the NAR group in every day clinic.

5.2 | Conditions mimicking NAR

Among the conditions mimicking NAR, we should acknowledge the rare condition of a post-traumatic or spontaneous skull base defect with leakage of cerebrospinal fluid (CSF), giving rise to (unilateral) watery discharge from the nose. CSF leakage should be considered in those patients with a relevant history and rhinorrhea not responding to nasal corticosteroids, ipratropium bromide, or capsaicin nasal treatment.⁴⁶

CRSsNP and CRSwNP should not be overlooked in patients with NAR, as symptomatology between NAR and CRS patients may

overlap in part. Nasal endoscopy is the preferred means of diagnosis of CRS, and CT scans should be reserved for those patients with suspicion of CRS and without nasal endoscopy available.³

6 | DIAGNOSTIC CHALLENGE OF NASAL HYPERREACTIVITY

The induction of one or more nasal symptoms upon encounter of unspecific environmental stimuli, such as smoke, temperature/humidity changes, strong odors, and other irritants, is called nasal hyperreactivity (NHR). NHR is a key clinical feature of both AR and NAR⁴⁷ and is mainly defined by the history of the patient. Several diagnostic tests have been developed to quantify NHR, such as nasal exposure to hyperosmolar solution,⁴⁸ nasal histamine,⁴⁹ or cold dry air (CDA)^{37,50} CDA represents a physiological, safe, and tolerable stimulus for the nasal mucosa and has been proven to be a good diagnostic tool for NHR.⁵¹ Braat et al.⁵⁰ demonstrated that CDA provocations were superior to nasal histamine provocations in discriminating IR patients from healthy controls, as histamine provocation did not allow the discrimination between IR patients and controls. Sensitivity for CDA was 87% compared with 100% for histamine, but specificity was 71% for CDA and 0% for histamine.⁵⁰ The protocol used in the latter study is time-consuming; therefore, a short protocol of CDA exposure with high sensitivity and specificity for the demonstration of NHR in AR and IR was recently validated.³⁷ At present, more studies on CDA nasal provocation studies are warranted to confirm the validity of this technique and to study NHR in different patient populations and controls. There is now growing consensus about the usefulness of such a technique in daily practice as NHR often remains undiagnosed and cannot be taken into account in trials evaluating the effects of medical treatment for rhinitis.

7 | ENDOTYPES OF NAR

As NAR involves a variety of conditions, the pathophysiology may vary but can roughly be divided into a classic inflammatory pathway, neurogenic pathway, and other (largely unknown) pathways.

The inflammatory pathway is found in a subgroup of NAR patients. A Th2 cytokine inflammatory pattern is found in AR patients, as well as in those with occupational allergic rhinitis induced by high molecular weight (HMW) allergens. These patients do not generally cause a therapeutic challenge as they respond well to nasal corticosteroid treatment, as is the case in LAR patients. However, several patients with NAR do not have an influx of inflammatory cells in the nasal mucosa and are believed to have a neurogenic mechanism involved, including rhinitis of the elderly, gustatory rhinitis, some forms of occupational rhinitis, some forms of drug-induced rhinitis, and IR.^{13,25,52}

The neural regulation of the upper airways is complex and consists of a number of interacting nervous systems.⁴¹ Sensory,

parasympathetic, and sympathetic nerves regulate epithelial, vascular, and glandular processes in the nasal mucosa.⁵² The anatomically defined sensory, parasympathetic, and sympathetic neural systems contain heterogeneous populations of nerve fibers often containing unique combinations of neuropeptides.⁵³ Some phenotypes seem to be based on a relatively simple regulatory disorder, such as rhinitis of the elderly that mostly seems to be a dysregulation of the parasympathetic/sympathetic neural dysbalance and can be treated with the anticholinergic drug ipratropium bromide⁵⁴ or rhinitis medicamentosa, resulting in dysregulation of adrenergic receptors in nasal mucosa and in a relative increase in the parasympathetic drive, leading to significant rhinorrhea and nasal obstruction.³⁴

Solitary chemosensory cells of the nasal cavity are specialized epithelial chemosensors that respond to irritants through the canonical taste transduction cascade stimulating peptidergic trigeminal nociceptive (or pain) nerve fibers.⁵⁵ Activation of these nasal cells can trigger similar local inflammatory responses (mast cell degranulation and plasma leakage) such as direct chemical excitation of trigeminal pain fibers using capsaicin, and this is only by cholinergic neurotransmission and neural activity and not by release of local inflammatory mediators.⁵⁵

IR is thought to be a disorder of the nonadrenergic noncholinergic (NANC) or peptidergic neural system.^{41,56} Perivascular and intra-epithelial nonadrenergic noncholinergic (NANC), sensory nerve fibers contain neuropeptides (including VIP, substance P (SP), and calcitonin gene-related peptide (CGRP)). These neuropeptides are locally released from peptidergic neurons (antidromic release), mainly unmyelinated sensory C-fibers, in the nasal mucosa after activation by unspecific stimuli, and can be responsible for the symptoms of IR.⁵⁶ Stimulation can be induced by inflammatory mediators, such as histamine and bradykinin, but also by a number of inhaled irritants such as nicotine, chlorine, formaldehyde, and capsaicin, mostly via the TRPA1 and TRPV1 receptor. Recently, it was shown that the nociceptive TRPV1-SP signaling pathway is upregulated in IR patients.¹³

8 | THERAPEUTIC ALGORITHM FOR NAR

NAR patients constitute a group of patients with different phenotypes, with variable severity, underlying etiology and type of inflammation. The phenotypes warrant different treatment strategies depending on the etiology. However, most of the studies on treatment for NAR have been performed in unselected NAR patients. It makes sense to link the therapeutic strategy to the known or suspected underlying etiology, being inflammation, neurogenic dysfunction, environmental exposure, and/or medication use (Figure 3).

The inflammatory group (occupational rhinitis and drug-induced rhinitis) may benefit from anti-inflammatory treatment such as nasal/oral corticosteroids and/or nasal/oral antihistamines. However, most RCTs evaluating local corticosteroids in NAR patients showed a lack of efficacy. Only two studies^{57,58} comprising 101 patients showed a positive outcome, whereas all other studies comprising more than

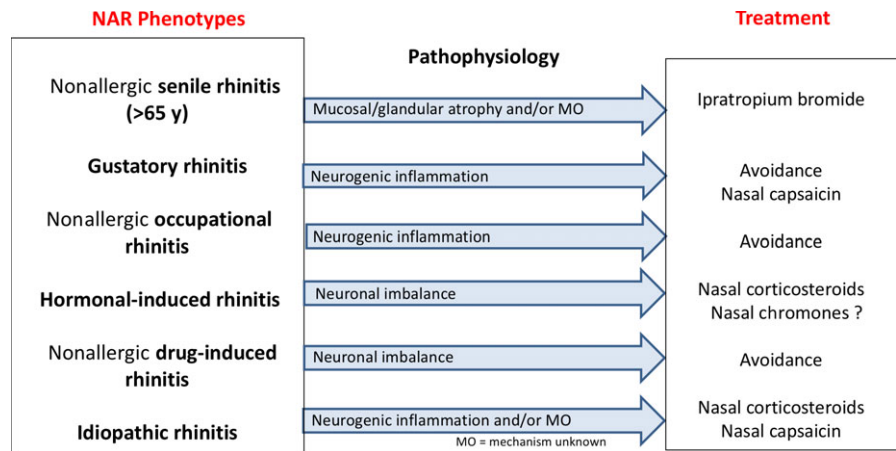


FIGURE 3 Therapeutic strategy of nonallergic rhinitis

1000 patients did not show a major benefit of nasal corticosteroid treatment^{59,60,61} Interestingly, two double-blind, placebo-controlled trials have been published showing a therapeutic effect for azelastine nasal spray in NAR patients^{62,63} The precise mode of action (antihistaminic, anti-inflammatory, or otherwise) remains to be elucidated.

Treatment of the drug-induced phenotypes of NAR primarily will consist of avoidance of the drug. Aspirin-intolerant individuals may benefit from aspirin desensitization.^{64,65,66,67}

Irritant avoidance and smoking stop should be advised to all rhinitis patients, and more specifically in those with occupational and IR.⁶⁸

The treatment of noninflammatory phenotypes of NAR is diverse depending on the presumed pathophysiology. Ipratropium bromide is an anticholinergic drug and the first treatment option in rhinitis in the elderly.²³ Several studies have been published showing that repeated administration of capsaicin in a double-blind, placebo-controlled trial led to a significant long-term reduction in symptoms in patients with IR^{69,70,71} Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the active component of plants of the genus *Capsicum* such as chili peppers. Capsaicin is unique among naturally occurring irritant compounds because the initial neuronal excitation evoked by it is followed by a long-lasting refractory period, during which the previously excited neurons are no longer responsive to a broad range of stimuli.⁷² Recent data provided more insight in the working mechanisms of this beneficial effect of capsaicin.¹³

Capsaicin reduced the density of the innervation of the nasal mucosa and the TRPV1-SP signaling pathway, without affecting the integrity and function of nasal epithelial cells or mast cells, and in this way improved the symptoms in 80% of well-selected IR patients,¹³ but capsaicin has not been shown to be effective in allergic rhinitis nor in other forms of nonallergic rhinitis such as the inflammatory endotypes or other neurogenic endotypes such as rhinitis of the elderly or smoking-induced rhinitis.⁷²

Intranasal administration of a selective intranasal TRPV1 antagonist in patients with IR induced a marked reduction in total symptom scores triggered by nasal capsaicin challenge.⁷³ When medical treatment fails or in case of severe nasal obstruction with hypertrophy of

the inferior turbinates, a surgical intervention such as turbinate reduction⁷⁴ may be considered. Severe IR patients may respond well to a vidian neurectomy,⁷⁵ but this intervention is rarely performed.

In summary, treatment of NAR should be adapted as much as possible to the underlying etiology.

9 | UNMET NEEDS IN NAR

NAR represents a heterogenous group of mucosal pathology of variable severity and with a heterogenous underlying etiology. In spite of the fact that NAR is not life-threatening, patients consulting their doctor mostly suffer from a severe condition. Despite all efforts in listing the unmet needs by the international expert community,¹⁶ the following unmet needs still need to be addressed during the next decade:

- prevalence studies on NAR, including phenotyping and endotyping, with evaluation of the associated conditions and SCUAD among the NAR population
- exploration of the pathophysiology of NHR, with improving the therapeutic approach of NHR
- international consensus on the optimal and most cost-effective diagnostic approach of NAR patients
- properly conducted trials on the efficacy of different medical treatment options in NAR patients with clear diagnostic inclusion and exclusion criteria
- insight into the mechanisms of nasal hyperreactivity in different subgroups of NAR
- endotype-driven treatment for NAR
- positioning the role of turbinate reduction in NAR, with emphasis on the precise indication and expected outcomes after surgery.

10 | CONCLUSION

NAR represents a nasal condition with high prevalence, variable etiology and severity, and a wide array of different treatment options. However, only limited studies are available exploring the real-life epidemiology,

pathophysiology, and therapeutic outcomes of the different subgroups of NAR. The availability of novel tools for measuring NHR as well as the increased insight into the pathophysiology of different types of NAR will lead to a better treatment strategy of this condition.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

- Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8-160.
- Bousquet J, Bachert C, Canonica GW, et al. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol*. 2009;124:428-433.
- Hellings PW, Fokkens WJ, Akdis C, et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? *Allergy*. 2013;68:1-7.
- Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA²LEN study. *Allergy*. 2011;66:1216-1223.
- Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinology*. 2012;50(Suppl 23):1-298.
- Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet*. 2011;378:2112-2122.
- Rondón C, Campo P, Togias A, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol*. 2012;129:1460-1467.
- Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. 2013;68:1219-1232.
- Morais-Almeida M, Pite H, Pereira AM, et al. Prevalence and classification of rhinitis in the elderly: a nationwide survey in Portugal. *Allergy*. 2013;68:1150-1157.
- Orban N, Maughan E, Bleach N. Pregnancy-induced rhinitis. *Rhinology*. 2013;51:111-119.
- Hox V, Steelant B, Fokkens W, Nemery B, Hellings PW. Occupational upper airway disease: how work affects the nose. *Allergy*. 2014;69:282-291.
- Jovancevic L, Georgalas C, Savovic S, Janjevic D. Gustatory rhinitis. *Rhinology*. 2010;48:7-10.
- Van Gerven L, Alpizar YA, Wouters MM, et al. Capsaicin treatment reduces nasal hyperreactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV1) overexpression in patients with idiopathic rhinitis. *J Allergy Clin Immunol*. 2014;133:1332-1339.
- Bernstein JA. Allergic and mixed rhinitis: epidemiology and natural history. *Allergy Asthma Proc*. 2010;31:365-369.
- Hellings PW, Scadding G, Alobid I, et al. Executive summary of European Task Force document on diagnostic tools in rhinology. *Rhinology*. 2012;50:339-352.
- Bousquet J, Fokkens W, Burney P, et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. *Allergy*. 2008;63:842-853.
- Westman M, Stjärne P, Asarnej A, et al. Natural course and comorbidities of allergic and nonallergic rhinitis in children. *J Allergy Clin Immunol*. 2012;129:403-408.
- Chiang WC, Chen YM, Tan HKK, et al. Allergic rhinitis and non-allergic rhinitis in children in the tropics: prevalence and risk associations. *Pediatr Pulmonol*. 2012;47:1026-1033.
- Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. *Allergy*. 2006;61:693-698.
- Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet*. 2008;372:1049-1057.
- Chawes BLK, Bønnelykke K, Kreiner-Møller E, Bisgaard H. Children with allergic and nonallergic rhinitis have a similar risk of asthma. *J Allergy Clin Immunol*. 2010;126:567-573.
- Settipane RA. Other causes of rhinitis: mixed rhinitis, rhinitis medicamentosa, hormonal rhinitis, rhinitis of the elderly, and gustatory rhinitis. *Immunol Allergy Clin North Am*. 2011;31:457-467.
- Malmberg H, Grahne B, Holopainen E, Binder E. Ipratropium (Atrovent) in the treatment of vasomotor rhinitis of elderly patients. *Clin Otolaryngol Allied Sci*. 1983;8:273-276.
- Rodríguez K, Rubinstein E, Ferguson BJ. Clear anterior rhinorrhea in the population. *Int Forum Allergy Rhinol*. 2015;5:1063-1067.
- Hox V, Vanoirbeek JA, Alpizar YA, et al. Crucial role of transient receptor potential ankyrin 1 and mast cells in induction of nonallergic airway hyperreactivity in mice. *Am J Respir Crit Care Med*. 2013;187:486-493.
- Karjalainen A, Martikainen R, Klaukka T, Saarinen K, Uitti J. Risk of asthma among Finnish patients with occupational rhinitis. *Chest*. 2003;123:283-288.
- Shusterman D. Nonallergic rhinitis: environmental determinants. *Immunol Allergy Clin North Am*. 2016;36:379-399.
- Kaliner MA. Classification of nonallergic rhinitis syndromes with a focus on vasomotor rhinitis, proposed to be known henceforth as nonallergic rhinopathy. *World Allergy Organ J*. 2009;2:98-101.
- Ellegård E, Hellgren M, Torén K, Karlsson G. The incidence of pregnancy rhinitis. *Gynecol Obstet Invest*. 2000;49:98-101.
- Navarrete-Palacios E, Hudson R, Reyes-Guerrero G, Guevara-Guzmán R. Correlation between cytological characteristics of the nasal epithelium and the menstrual cycle. *Arch Otolaryngol Head Neck Surg*. 2003;129:460-463.
- Hamano N, Terada N, Maesako K, et al. Expression of histamine receptors in nasal epithelial cells and endothelial cells—the effects of sex hormones. *Int Arch Allergy Immunol*. 1998;115:220-227.
- Caparroz FA, Gregorio LL, Bongiovanni G, Izu SC, Kosugi EM. Rhinitis and pregnancy: literature review. *Braz J Otorhinolaryngol*. 2016;82:105-111.
- Wei J, Gerlich J, Genuneit J, et al. Hormonal factors and incident asthma and allergic rhinitis during puberty in girls. *Ann Allergy Asthma Immunol*. 2015;115:21-27.
- Varghese M, Glaum MC, Lockey RF. Drug-induced rhinitis. *Clin Exp Allergy*. 2010;40:381-384.
- Kirsche H, Klimek L. ASA-intolerance syndrome and persistent rhinosinusitis: differential diagnosis and treatment. *HNO*. 2015;63:357-363.
- Subramanian H, Gupta K, Ali H. Roles of Mas-related G protein-coupled receptor X2 on mast cell-mediated host defense, pseudoallergic drug reactions, and chronic inflammatory diseases. *J Allergy Clin Immunol*. 2016;138:700-710.
- Van Gerven L, Boeckxstaens G, Jorissen M, Fokkens W, Hellings PW. Short-time cold dry air exposure: a useful diagnostic tool for nasal hyperresponsiveness. *Laryngoscope*. 2012;122:2615-2620.
- Jutel M, Papadopoulos NG, Gronlund H, et al. Recommendations for the allergy management in the primary care. *Allergy*. 2014;69:708-718.
- 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;124:1005-1011.
- Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in Rhinology EAACI position paper. *Clin Transl Allergy*. 2011;1:2.

41. Van Gerven L, Boeckxstaens G, Hellings P. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. *Rhinology*. 2012;50:227-235.
42. Powe DG, Jagger C, Kleinjan A, Carney AS, Jenkins D, Jones NS. "Entropy": localized mucosal allergic disease in the absence of systemic responses for atopy. *Clin Exp Allergy*. 2003;33:1374-1379.
43. Rondón C, Campo P, Galindo L, et al. Prevalence and clinical relevance of local allergic rhinitis. *Allergy*. 2012;67:1282-1288.
44. Gómez E, Campo P, Rondón C, et al. Role of the basophil activation test in the diagnosis of local allergic rhinitis. *J Allergy Clin Immunol*. 2013;132:975-976.
45. 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;128:1192-1197.
46. Patel PN, Oyefara B, Aarstad R, Bahna SL. Rhinorrhea not responding to nasal corticosteroids. *Allergy Asthma Proc*. 2007;28:735-738.
47. Segboer CL, Holland CT, Reinartz SM, et al. Nasal hyper-reactivity is a common feature in both allergic and nonallergic rhinitis. *Allergy*. 2013;68:1427-1434.
48. Sanico AM, Philip G, Lai GK, Togias A. Hyperosmolar saline induces reflex nasal secretions, evincing neural hyperresponsiveness in allergic rhinitis. *J Appl Physiol*. 1999;86:1202-1210.
49. Gerth van Wijk R, Dieges PH. Nasal hyper-responsiveness to histamine, methacholine and phenolamine in patients with perennial non-allergic rhinitis and in patients with infectious rhinitis. *Clin Otolaryngol Allied Sci*. 1991;16:133-137.
50. Braat JP, Mulder PG, Fokkens WJ, van Wijk RG, Rijntjes E. Intranasal cold dry air is superior to histamine challenge in determining the presence and degree of nasal hyperreactivity in nonallergic noninfectious perennial rhinitis. *Am J Respir Crit Care Med*. 1998;157(6 Pt 1):1748-1755.
51. Togias AG, Naclerio RM, Proud D, et al. Nasal challenge with cold, dry air results in release of inflammatory mediators. Possible mast cell involvement. *J Clin Invest*. 1985;76:1375-1381.
52. Baroody FM. Nonallergic Rhinitis: mechanism of Action. *Immunol Allergy Clin North Am*. 2016;36:279-287.
53. Baraniuk JN, Merck SJ. Neuroregulation of human nasal mucosa. *Ann N Y Acad Sci*. 2009;1170:604-609.
54. Tan R, Corren J. Optimum treatment of rhinitis in the elderly. *Drugs Aging*. 1995;7:168-175.
55. Saunders CJ, Christensen M, Finger TE, Tizzano M. Cholinergic neurotransmission links solitary chemosensory cells to nasal inflammation. *Proc Natl Acad Sci U S A*. 2014;111:6075-6080.
56. van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. *Allergy*. 2005;60:1471-1481.
57. Varricchio A, Capasso M, De Lucia A, et al. Intranasal flunisolide treatment in patients with non-allergic rhinitis. *Int J Immunopathol Pharmacol*. 2011;24:401-409.
58. Löfkvist T, Svensson G. Treatment of vasomotor rhinitis with intranasal beclomethasone dipropionate (Becotide). Results from a double-blind cross-over study. *Acta Allergol*. 1976;31:227-238.
59. Blom HM, Godthelp T, Fokkens WJ, KleinJan A, Mulder PG, Rijntjes E. 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(6 Pt 1):739-747.
60. Jacobs R, Lieberman P, Kent E, Silvey M, Locantore N, Philpot EE. Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. *Allergy Asthma Proc*. 2009;30:120-127.
61. Lundblad L, Sipilä P, Farstad T, Drozdiewicz D. Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a nordic, multicenter, randomized, double-blind, placebo-controlled study. *Acta Otolaryngol*. 2001;121:505-509.
62. Gehanno P, Deschamps E, Garay E, Baehre M, Garay RP. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. *ORL J Otorhinolaryngol Relat Spec*. 2001;63:76-81.
63. Banov CH, Lieberman P. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. *Ann Allergy Asthma Immunol*. 2001;86:28-35.
64. Xu JJ, Sowerby L, Rotenberg BW. Aspirin desensitization for aspirin-exacerbated respiratory disease (Samter's Triad): a systematic review of the literature. *Int Forum Allergy Rhinol*. 2013;3:915-920.
65. Fruth K, Pogorzelski B, Schmidtmann I, et al. Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy*. 2013;68:659-665.
66. Klimek L, Pfaar O. Aspirin intolerance: does desensitization alter the course of the disease? *Immunol Allergy Clin North Am*. 2009;29:669-675.
67. Klimek L, Dollner R, Pfaar O, Mullol J. Aspirin desensitization: useful treatment for chronic rhinosinusitis with nasal polyps (CRSwNP) in aspirin-exacerbated respiratory disease (AERD)? *Curr Allergy Asthma Rep*. 2014;14:441.
68. Eriksson J, Ekerljung L, Sundblad B-M, et al. Cigarette smoking is associated with high prevalence of chronic rhinitis and low prevalence of allergic rhinitis in men. *Allergy*. 2013;68:347-354.
69. Blom HM, Van Rijswijk JB, Garrelds IM, Mulder PG, Timmermans T, Gerth van Wijk R. Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. *Clin Exp Allergy*. 1997;27:796-801.
70. Ciabatti PG, D'Ascanio L. Intranasal Capsicum spray in idiopathic rhinitis: a randomized prospective application regimen trial. *Acta Otolaryngol*. 2009;129:367-371.
71. Van Rijswijk JB, Boeke EL, Keizer JM, Mulder PGH, Blom HM, Fokkens WJ. Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study. *Allergy*. 2003;58:754-761.
72. Fokkens W, Hellings P, Segboer C. Capsaicin for rhinitis. *Curr Allergy Asthma Rep*. 2016;16:60.
73. Holland C, van Drunen C, Denyer J, et al. Inhibition of capsaicin-driven nasal hyper-reactivity by SB-705498, a TRPV1 antagonist. *Br J Clin Pharmacol*. 2014;77:777-788.
74. Orabi AA, Sen A, Timms MS, Morar P. Patient satisfaction survey of outpatient-based topical local anesthetic KTP laser inferior turbinectomy: a prospective study. *Am J Rhinol*. 2007;21:198-202.
75. Robinson SR, Wormald PJ. Endoscopic vidian neurectomy. *Am J Rhinol*. 2006;20:197-202.

How to cite this article: Hellings PW, Klimek L, Cingi C, et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2017;72:1657-1665. <https://doi.org/10.1111/all.13200>