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Non-IgE-Mediated Rhinitis

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Abstract Patients with chronic rhinitis symptoms frequently present in physicians' offices. The best-studied form of chronic rhinitis is IgE-mediated allergic rhinitis; however, the prevalence of non-allergic, non-IgE-mediated rhinitis among the chronic rhinitis population is high, and the disorder is an important cause of widespread morbidity. Despite this fact, almost no diagnostic tests or adjusted treatment schedules are established for this patient group. Chronic non-IgE-mediated rhinitis covers an extensive range of different diagnoses and comprises drug-induced, hormonal, occupational, gustatory, senile, and idiopathic rhinitis. The etiology as well as pathophysiology is only defined for some of these forms. This review summarizes the causes of non-IgE-mediated rhinitis as well as the available options for diagnostic work-up and treatment strategies. It aims at providing a tool for a more individual approach of non-allergic rhinitis patients in order to obtain an improvement of their quality of life.

Keywords Idiopathic rhinitis · Non-allergic rhinitis · Capsaicin · Provocation tests

Abbreviations

ARM	Acoustic rhinometry
CDA	Cold dry air
CF	Cystic fibrosis
CGRP	Calcitonin gene-related peptide
CSS	Churg–Strauss syndrome
eNO	Exhaled nitric oxide
GPA	Granulomatosis with polyangiitis; previously Wegener'granulomatosis
HMW	High molecular weight
IB	Ipratropium bromide
IR	Idiopathic rhinitis
LAR	Local allergic rhinitis
LMW	Low molecular weight
NANC	Non-adrenergic non-cholinergic
NAR	Non-allergic rhinitis
NHR	Nasal hyperreactivity
nNO	Nasal nitric oxide
PCD	Primary ciliary dyskinesia
PNIF	Peak nasal inspiratory flow
RMM	Rhinomanometry
RUDS	Reactive upper airway dysfunction syndrome
SP	Substance P
SPT	Skin prick tests
TRPA	Transient receptor potential channel subfamily A
TRPV	Transient receptor potential channel subfamily V

Introduction

The prevalence of chronic rhinitis is estimated to be as high as 30 % of the total population and is a significant cause of widespread morbidity, medical treatment costs, and reduced work productivity [1]. Chronic rhinitis is defined as a symptomatic inflammation of the inner lining of the nose, leading to nasal obstruction, rhinorrhea, sneezing, or nasal/ocular itch. Two of these nasal symptoms should be present for at least 1 h daily for a minimum of 12 weeks to

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define chronic rhinitis [1]. Although sometimes mistakenly viewed as a trivial disease, symptoms of rhinitis may significantly impact a patient's quality of life, by causing fatigue, headache, cognitive impairment, and other debilitating systemic symptoms [2].

In chronic rhinitis patients, allergy is the best-characterized causal factor of rhinitis. In atopic individuals, inhaled allergens are taken up by antigen-presenting cells that cause naive $CD4^+$ cells to shift towards the Th2-subtype with production of Th2 cytokines such as IL-4, IL-5, and IL-13. These cytokines induce the production of antigen-specific IgE, which binds to mast cells and induces degranulation upon renewed contact with the allergen [3]. IgE-mediated allergic rhinitis is relatively easy to diagnose by the combination of typical symptoms with positive skin prick tests (SPT) or IgE-detecting serum tests for the suspected allergen [4•]. However, in a large group of patients suffering from chronic rhinitis, antigen-specific IgEs are not systemically detected, and they are classified as having non-allergic or non-IgE-mediated rhinitis. This group of patients forms a diagnostic and therapeutic challenge and probably accounts for about half of the total chronic rhinitis population [5]. In contrast to large-scale and well-conducted epidemiologic and immunologic studies on IgE-mediated allergic rhinitis, little is known on the exact prevalence and pathophysiological mechanisms underlying non-IgE-mediated rhinitis. Currently, it is believed to comprise a heterogeneous patient population suffering from symptoms that are often indistinguishable from those present in allergic rhinitis patients. This review summarizes the currently known etiologies of non-IgE-mediated rhinitis and makes a proposition for a more accurate diagnostic work-up and treatment options.

Subtypes of Non-IgE-Mediated Rhinitis

Infectious Rhinitis

One of the most prevalent causes of acute non-IgE-mediated rhinitis is infectious rhinitis. Everybody experiences an acute viral rhinitis—also known as common cold—several times during a lifetime and these are typically acute and self-limiting. It is estimated that 0.5–2 % of viral upper respiratory tract infections are complicated by a bacterial super-infection, almost always resulting in bacterial rhinosinusitis [6]. Taken together, infectious rhinitis is rarely a cause of chronic rhinitis.

Although technically nasal vestibulitis is not a form of rhinitis, bacterial infection of the nasal vestibule skin, typically with Staphylococcus Aureus, can give rise to a chronic infection in (often immune-compromized) subjects [7]. It can occur secondary to nose picking and excessive nose blowing and causes bleeding and crusts in the nasal vestibule. Local antibiotic treatment with intranasal mupirocin calcium ointment applied topically is the treatment of choice [8].

Drug-Induced Rhinitis

The best known form of drug-induced rhinitis is 'rhinitis medicamentosa' that describes the nasal congestion occurring with overuse of topical nasal vasoconstrictors [9]. The exact mechanism is poorly understood. It is suggested that recurrent nasal tissue hypoxia and negative neural feedback with chronic decreased α2-receptor responsiveness are involved [9, 10].

Also aspirin and NSAID's can induce symptoms of rhinitis as a consequence of hypersensitivity to the drug, either isolated or as a part of Samter's triad, in combination with nasal polyps and asthma [11]. In aspirin-intolerant patients, an underlying disorder in the eicosanoid synthesis is involved, shifting arachidonic acid metabolism through the lipoxygenase pathway, thus resulting in increased amounts of pro-inflammatory leukotrienes [10].

Additionally, vasoactive drugs such as antihypertensive medication (methyldopa, hydralazine, guanethidine, ACE-inhibitors, and the α- and β-receptor antagonists) down-regulate the activity of the sympathetic nervous system, that in the nasal airways leads to congestion [10]. Also immunosuppressives, oral contraceptives, and psychotropic agents can be associated with nasal symptoms [10].

Rhinitis Linked to Systemic Vasculitic Disease

Systemic autoimmune diseases such as lupus erythematosus, relapsing polychondritis, and Sjögren syndrome may present with difficult-to-threat rhinitis and rhinosinusitis in addition to other organ involvement. The systemic diseases presenting most frequently with upper airway involvement are the vasculitic diseases Churg–Strauss syndrome (CSS) and granulomatosis with polyangiitis (GPA; previously Wegener's granulomatosis) [12, 13] with over 75 % of patients suffering from rhin(osinus)itis symptoms, usually nasal obstruction and chronic recurrent infections [14]. In GPA patients, this is commonly associated with crusting and bloody discharge; in CSS patients, symptoms are typically non-erosive [15]. Also, a small percentage of sarcoidosis patients can develop sarcoid of the nose causing symptoms of nasal obstruction, rhinorrhea, or crusting [16].

Rhinitis Linked to Hormonal Disease

A large multicenter study has indicated that the cumulative incidence of pregnancy rhinitis was 22 %, making it the

most prevalent form of hormonal rhinitis [17]. Pregnancy rhinitis typically starts during the second month of pregnancy, usually disappearing rapidly after delivery. But nasal congestion can even present in conjunction with the rise in serum estrogens that occur in the normal menstrual cycle [18, 19]. The pathogenesis remains largely unexplained, but estrogen has been shown to increase vasodilation and vascular leakage by stimulating nitric oxide production [20] in addition to its' general pro-inflammatory effects [21].

Evidence linking thyroid disease directly with nasal pathology is limited. Increased nasal secretion in hypothyroidism has been reported on an anecdotal basis [18].

It has been proposed that rhinitis occurs in acromegaly. However, a Swedish study could not show the induction of nasal congestion in response to a treatment with recombinant growth hormone [22].

Rhinitis Linked to Defective Mucociliary Clearance Function

Cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are both congenital diseases characterized by defects in the mucociliary transport system. Especially in patients with PCD, rhinitis is a lifetime problem often with an early onset during first days of life [23]. This regularly leads to impaired breast-feeding due to nasal blockage, which should be an alarm sign to investigate ciliary dysfunction. 97 % of CF patients suffer from severe upper airway problems, generally leading to chronic rhinosinusitis with nasal polyps [24].

Occupational Rhinitis

Occupational rhinitis is defined as an inflammation of the nasal mucosa due to causes attributable to a particular work environment [25].

Agents that can cause occupational rhinitis are classified as either high or low molecular weight (HMW or LMW) agents, and the most common ones are listed in Table 1. HMW agents are proteins present in biological substances that induce a classic IgE-mediated allergic inflammation [26•].

In contrast, the mechanisms via which LMW agents induce airway symptoms are less well understood. The group referred to as 'LMW sensitizers' can also sensitize the adaptive immune system by acting as haptens and can induce nasal symptoms after a latency phase of months to years [26•]. These 'LMW sensitizers' are mostly chemicals; but also several drugs, metallic agents, and wood types own this sensitizing capacity and only a minority of these agents induce detectable antigen-specific IgE, thus complicating diagnosis.

A second group of LMW agents is the 'LMW irritants.' A single exposure to high concentrations of irritant (often during spilling accidents) induces an acute toxic effect on the respiratory mucosa that can lead to persistent nasal symptoms. This phenomenon is referred to as reactive upper airway dysfunction syndrome (RUDS) [27]. But recently, there is increasing evidence that also long-term exposure to lower concentrations of irritants can induce a more chronic dysfunction of the nasal mucosa. For example, people who are chronically exposed to chlorination products, such as cleaners [28], swimming pool workers [29], and competitive swimmers [30], suffer from more upper airway symptoms than controls. Mechanisms responsible for irritant-induced rhinitis are not well known and are thought to involve epithelial damage [31] and

Table 1 Common occupational agents, listed by molecular weight class. *HMW* high molecular weight, *LMW* low molecular weight

HMW agents		
Flour	Mites	Latex
Laboratory animals	Sea food	Plants
Enzymes	Guar gum	Insects
Tobacco	Soya	Cattle
LMW sensitizers (LMW agents with latency phase)		
Isocyanates	Persulfate salts	Anhydrides
Aldehydes	Resins	Plastic
Polyurethane	Polyester	Polyamides
Acrylates	Amines	Plicatic acid
Metals: platinum, nickel, aluminum, cobalt, chromium		
Trees: mansonia, cedar, pine		
Drugs: piperacillin, morphine, tylosin, spiramycin		
Irritants (LMW agents without latency phase)		
Aluminum phosphide	Formalin	Phthalic anhydride
Ammonia	Fire/Smoke	Sulfur dioxide
Bleaching agents	Hydrazine	Sulfuric acid
Calcium oxide	Hydrochloric acid	Tear gas
Carbon monoxide	Hydrofluoric acid	Trichloroethylene
Chlorine	Lithium hydride	Uranium hexafluoride
Chloropicrin	Metal fumes	Urea fumes
Diesel exhaust fumes	Metam sodium	
Diethylaminoethanol	Mustard gas	
Dinitrogen tetroxide	Nitrogen oxide	
Epichlorohydrin	Ozone	
Ethylene oxide	Perchloroethylene	
Hydrocarbons	Phosgene Gas	

neurokinin release [32]. Recently, the transient receptor potential (TRP) A1 channel that is expressed on the sensory nerve endings from the non-adrenergic, non-cholinergic (NANC) nervous system in the nasal mucosa has emerged as being a major irritant detector [32, 33].

Smoking-Related Rhinitis

Unlike its' effect on lower airway physiology, the impact of tobacco smoke on the nasal mucosa is less well studied. Still, there is growing evidence that such exposure can have a significant impact on nasal function. Smokers show a higher prevalence of chronic rhinitis compared to non-smokers [34•], and Benninger and coworkers reported that tobacco smoke exposure overall is associated with acute and chronic nasal symptoms [35]. Nasal mucosa of smokers shows infiltration of $CD8^+$ T lymphocytes [36] and a decreased cilia beat frequency [37], and components of cigarette smoke such as formaldehyde and acrolein act as a local irritant on the nasal mucosa [38].

Senile Rhinitis

Senile rhinitis or rhinitis of the elderly is the characteristic clinical picture of patients above 65 years of age, suffering from a persistent rhinorrhea, often in the absence of other nasal symptoms [39]. Senile rhinitis is caused by a deregulation between the sympathetic and parasympathetic nervous systems that innervate the nasal mucosa, causing a cholinergic hyperactivity, leading to a reduced functional reserve for homeostasis, which is called upon to compensate for stressful situation [40].

Gustatory Rhinitis

Gustatory rhinitis is characterized by watery rhinorrhea after ingestion of hot and spicy food. It is believed to be triggered via a gustatory reflex, involving sensory nerve fibers of the NANC neural system. These nerves express TRP channels that are both activated by certain food components, such as mustard and garlic (TRPA1) and capsaicin, the hot component of red peppers (TRPV1) as well as by temperature changes [41]. Why certain people experience more symptoms than others is currently unclear, but it is likely that a hyperactivity of the sensory nerves is involved.

Idiopathic Rhinitis

After the exclusion of the above-mentioned causes, the etiology of chronic rhinitis remains obscure in about 50 % of patients with negative IgE testing, in whom the disease is classified as idiopathic rhinitis (IR), formerly known as vasomotor rhinitis [42].

Although the subjects have traditionally been classified as either 'runners' (predominantly rhinorrhea symptoms) or 'blockers' (predominantly nasal blockage symptoms), many patients suffer from both symptoms. IR patients often report nasal hyperreactivity (NHR) as a key feature [43•]. NHR is defined as the induction of nasal symptoms in response to contact with unspecific stimuli, such as temperature changes, strong odors, nose blowing, cigarette smoke, and other respiratory irritants [44, 45•].

Several mechanisms have been postulated to explain the pathophysiology of IR. The two most plausible hypotheses are non-IgE-mediated inflammation and/or neurogenic responses [45•]. Van Rijswijk et al. studied the presence of inflammatory cells in nasal biopsies and did not find significant differences between IR patients and controls [46]. On the other hand, the group of Powe showed that the both allergic rhinitis and IR patients showed an inflammatory infiltrate consisting of mast cells and IgE^+ cells [47]. An explanation for this discrepancy might be that Van Rijswijk investigated steroid-resistant patients as it was a group of referred patients. In these patients, neural dysfunction emerges as the most probable cause for the development of symptoms and NHR [45•]. Again, the NANC nervous system is believed to be responsible for nasal symptoms. These symptoms are evoked by local release of neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) upon stimulation of the sensory nerves of the NANC system. A recent study showed an upregulation of the TRPV1-SP signaling pathway in the nasal mucosa of steroid-unresponsive IR patients in comparison to healthy controls [48•].

Local Allergic Rhinitis

Over the last years, several studies from Rondon and others suggest that a subgroup of chronic rhinitis patients with negative SPT or serum IgE suffer from an entity referred to as local allergic rhinitis (LAR). These patients are often initially classified as non-allergic rhinitis; however, nasal lavage points towards a local production of antigen-specific IgE in the nasal mucosa. Moreover, these patients show a Th2-pattern of mucosal cell infiltration during exposure to respiratory allergens with release of the inflammatory mediators tryptase and eosinophil cationic protein [49•, 50]. Further studies are needed to establish this new entity, but these findings suggest that some chronic rhinitis patients with negative SPT and serum testing might be wrongly classified as non-IgE-mediated rhinitis patients. Technically, this makes local allergic rhinitis not a subtype of, but a differential diagnosis for non-IgE-mediated rhinitis.

Diagnosis of Non-IgE-Mediated Rhinitis

Allergic rhinitis is diagnosed when a patient's rhinitis symptoms correlate with a positive reaction on SPT or serum IgE for the suspected allergen. When both of these tests remain negative, the problem is addressed as non-allergic or non-IgE-mediated rhinitis, and further differential diagnosis is needed.

History

Chronic rhinitis in general is diagnosed on patients' complaints. Especially for the diagnosis of certain phenotypes of non-IgE-mediated rhinitis (senile rhinitis, occupational rhinitis, hormonal rhinitis, gustatory rhinitis, and drug-induced rhinitis), medical history is the key factor for diagnosis. Full evaluation should always include a determination of the pattern, chronicity, response to medications, the presence of co-existing conditions, smoking in previous 6 months, occupational exposure, exposure to irritants or occurrence of accidental spills, a detailed environmental history, and identification of precipitating factors.

Anterior Rhinoscopy

Besides history, anterior rhinoscopy should be used to check for signs of infection, endonasal crust formation, and/or significant anatomical deformities. Result of nasal exam should be interpreted within the clinical context.

Nasal Endoscopy

Nasal endoscopy is carried out at least once in all rhinitis patients with chronic symptoms, mainly for exclusion of chronic rhinosinusitis with/without nasal polyps, tumors, foreign bodies, or septal pathology. Nasal endoscopy may explain why patients with rhinitis do not respond well to recommended treatment.

Nasal Patency Measurements

Rhinomanometry (RMM), acoustic rhinometry (ARM), and peak nasal inspiratory flow (PNIF) meters objectively measure nasal flow and pressure, allowing the calculation of nasal airway resistance. All techniques correlate well with subjective sensation of nasal blockage [4•, 51], but disadvantages of RMM and ARM are that the probes can distort the nasal valves, tactile sensation may result in reflex changes, and results are affected by nasal cycling. Therefore, it is mainly a useful tool in rhinitis patients for quantification of nasal resistance before and after provocation with a certain stimulus as described below.

Nasal Sampling

Nasal sampling (cytology and nasal biopsies) is not recommended in diagnosing non-IgE-mediated rhinitis, but may help to distinguish between an inflammatory or neurogenic etiology of symptoms. The inflammatory cells collected by nasal lavage or counted on biopsy can provide information on the level and type of inflammation and cell contents in the nasal cavity [4•]. To check for inflammatory/neurogenic mediators released into the nasal fluid, samples are best collected by means of sinus packings or filter paper [4•]. This information could be directive in choosing a therapy; when inflammation is present, especially eosinophilic inflammation, steroids are more likely to have a beneficial effect [52], although there is no strict correlation between reduction of nasal inflammatory cells and nasal symptoms [53]. If there is no or little inflammation present, other therapeutic options will be more appropriate.

Nasal Provocation Tests

During nasal provocation tests, the nasal mucosa of the rhinitis patient is exposed to the agent that is suspected to trigger symptoms [4•, 26•]. At both early and late time points after provocation, outcomes of nasal patency changes, weight of nasal secretions, symptom and visual analog scoring and in some cases nasal sampling determine the positivity of the test.

In case of a typical history of allergic rhinitis in the absence of detectable systemic IgE, nasal provocation with the suspected allergen is the technique of choice to diagnose local allergy. In this setting, it is important to compare responses to those after provocation with a vehicle control and use appropriate concentrations of allergen in order to avoid a hyperreactivity response.

Because most LMW occupational agents can induce rhinitis symptoms in the absence of (detectable) IgE-production, nasal provocation testing with the suspected occupational agent—either naturally in the workplace or in a medical setting—is the golden standard for diagnosing occupational rhinitis [26•].

Nasal challenge with aspirin is used to diagnose aspirin intolerance with respiratory symptoms in patients with severe asthma in whom oral or bronchial aspirin challenges are contraindicated [54].

Nasal Hyperreactivity Measurements

Although NHR measurements are technically also provocation tests, we discuss them in a separate paragraph, thus emphasizing their importance in the diagnosis of IR. Analogous to bronchial testing, histamine and

methacholine are the most widely used provocation tests for measuring the degree of NHR. However, it has been shown that both of these substances are ineffective in discriminating IR patients from healthy controls [55, 56]. In 1998, the group from Amsterdam showed that intranasal exposure to cold dry air (CDA) was the most reliable method for measuring NHR symptoms in patients with IR [55]. Recently, these results were confirmed by Van Gerven et al. who demonstrated that even a short protocol with CDA-exposure during 15 min has a high sensitivity and specificity for the detection of NHR [43•].

Nasal NO Measurements

As for exhaled nitric oxide (eNO), nasal (nNO) can be measured by chemiluminescence and represents a biomarker for the NO synthase activity in the sino-nasal mucosa that is generally found to be increased under inflammatory conditions [57].

However, there is a high degree of inter- and intra-individual variability [58], and since nNO is highly subject to environmental factors, it has not yet a place in the diagnostic pathway of rhinitis patients. Of note, PCD patients typically show low levels of nNO [59], making NO measurement a potential screening tool for defective mucociliary function.

Treatment Options for Non-IgE-Mediated Rhinitis

Treatment strategies of non-IgE-mediated rhinitis have traditionally involved avoidance of environmental factors or triggers that initiate rhinitis symptoms, topical steroid treatment, and surgery [60]. However there is evidence that other pharmacological resources can bring relief in these patients.

Avoidance of Triggers

If there is evidence for drug-induced rhinitis, discontinuation or change of medication should be considered [61] and is mandatory in the case of rhinitis medicamentosa.

In case of occupational rhinitis, environmental control is the mainstay of therapy, not only to improve the rhinitis symptoms, but also to avoid progression of symptoms to the lower airways. This is achieved by either removing the etiologic agent, improving ventilation, wearing protective masks, or changing the work site [26•].

If a hormonal or vasculitic disorder lies at the base of the nasal problems, treatment of this underlying disease is the key step in dealing with the rhinitis. The major principle underlying treatment of rhinitis in pregnancy is caution with medication use [18].

Because of the characteristic problem of NHR in IR patients, it is recommended to avoid exposure to unspecific triggering agents like cold dry air, smoke, excessive nose blowing, strong odors, exhaust particles, cleaning agents, and other irritants.

Nasal Saline Lavage

In most placebo-controlled studies investigating therapeutic options in rhinitis, nasal saline is used as a placebo. This way it has been shown that this placebo often appeared to be efficacious in the treatment of non-IgE-mediated rhinitis and consequently can be considered an ‘active placebo’ [62]. In addition, it is a cheap and safe treatment option.

Intranasal Corticosteroids

Topical steroids appear to be useful particularly for treatment of patients suffering from non-IgE-mediated rhinitis in whom an inflammatory pathogenesis is a prominent feature of their disease, such as vasculitic-induced rhinitis. Also in occupational rhinitis, strategies to prevent or reduce symptoms may include the daily use of intranasal steroids in case of rhinitis due to HMW agents and LMW sensitizers, although there are no studies available to prove their beneficial effect [63].

Inconsistent results have been reported on the efficacy of intranasal steroids in the treatment of IR patients. A randomized, placebo-controlled double-blind study from Lundblad et al. showed an improvement rate of 56 % of mometasone furoate spray in over three-hundred IR patients [62]. Dockhorn also proved that topical steroid use significantly reduced severity of rhinorrhea, congestion, and sneezing in non-allergics compared to placebo [64]. However, they also showed that steroid treatment was not as effective in controlling rhinorrhea in those patients whose previous response to nasal steroids was unsatisfying. A similar study by Blom et al. tested the efficacy of fluticasone propionate in 65 non-allergic rhinitis patients, but found only a small decrease in nasal symptoms, which only reached significance for sneezing [53].

Currently, in IR patients with no information on nasal inflammatory markers, a consistent trial with intranasal steroids for at least 6 weeks is still the first therapy of choice, also because corticosteroids are able to influence neuropeptide activity [65, 66].

Ipratropium Bromide

In cases where disease is caused by an overactive parasympathetic system of the nasal mucosa, cholinergic

antagonists such as ipratropium bromide (IB) are effective. The parasympathetic nervous system is mainly responsible for mediating glandular secretion, and therefore, IB has been shown to be effective in reducing both the severity and the duration of rhinorrhea in non-allergic rhinitis [67, 68]. It is the first therapy of choice in senile rhinitis, and it can be beneficial for rhinorrhea symptoms in patients suffering from other types of non-IgE-mediated rhinitis [64].

Antihistamines

Antihistamines, the classical treatment option for allergic rhinitis, have also been studied in the context of non-allergic rhinitis. Two double-blind, placebo-controlled studies showed a beneficial effect of azelastine topical spray in IR patients [69, 70]. Application of this local antihistamine reduced nasal symptoms including nasal obstruction, rhinorrhea, sneezing, postnasal drip, nasal congestion, and anosmia with a response rate between 82 and 85 % in over two-hundred IR patients [69, 70]. The mechanism of action has not been unraveled, but might involve anti-inflammatory characteristics [70] and reduction of substance P release [71] in addition to it's histamine 1 receptor antagonism [60]. The older antihistamines have some anticholinergic side effects that might contribute to a therapeutic effect in non-allergic rhinitis; however, the majority of other antihistamines are thought to be of little or no benefit in the treatment of non-allergic rhinitis [60].

Capsaicin and TRPV1-Antagonists

Since 1991 several clinical trials, including double-blind, placebo-controlled studies, have proven that repeated intranasal application of capsaicin reduces symptoms and NHR in IR patients [72–76]. No adverse side effects were noted when the nasal airway was anesthetized to avoid burning sensation in the nose [73, 76]. However, up till today, this therapeutic option is used in only a few centers over the world. The mechanism is not fully elucidated, but the therapeutic effects are most likely caused by a decrease in nasal mucosal innervation and a downregulation of the TRPV1-SP nociceptive signaling pathway [48•]. Since capsaicin clearly targets the nervous system and has no anti-inflammatory actions, it is the therapy of choice in IR patients in whom a minimum period of 6 weeks of intranasal steroid treatment has proven to be ineffective. When patients were selected in this manner, rhinitis symptoms improved in 80 % of IR patients [48•]. Re-innervation about 6 months after capsaicin therapy can be responsible for relapse of symptoms in a certain percentage of IR patients. When the symptoms return after a symptom-free period upon capsaicin therapy, it is worthwhile to treat these patients for a second time with capsaicin.

The concept that selective blockade of TRPV1 stimulation in the nose can reduce NHR and development of rhinitis symptoms triggered by exogenous agents acting on the sensory nerves lead to development of a local TRPV1 antagonist SB-705498, that already showed its potential [77].

Surgical Intervention

Most authors feel that surgical therapy should only be considered for those patients who fail to obtain symptomatic relief with medical therapy. Both subjective and objective symptoms significantly decrease after laser turbinectomy in non-IgE-mediated rhinitis patients [78, 79] but do not deal with the cause of the rhinitis.

Vidian neurectomy that interrupts both sympathetic and parasympathetic fibers innervating the nasal mucosa seems to be effective in dealing with the rhinorrhea associated with IR, but resulted in little improvement of nasal congestion [80].

Unmet Needs for Non-IgE-Mediated Rhinitis

Although it is estimated that about 200 million people suffer from non-IgE-mediated rhinitis worldwide [5], proper epidemiological studies, diagnostic pathways, and therapeutic strategies are scarce or even lacking.

First of all, there is an urgent need for more large-scale observational trials to map the exact prevalence of non-IgE-mediated rhinitis as well as the subgroups within this heterogeneous patient population.

Furthermore, there is a need for better diagnostic work-up of the non-IgE rhinitis patient. When a chronic rhinitis patient presents with undetectable systemic IgE, too often insufficient effort is made to further explore possible causes for the nasal complaints. Therefore, it is mandatory that the ENT practitioner is aware of the different diagnostic entities within the chronic rhinitis group and broadens his/her history in order to pick up possible causes for the disease. The development of validated questionnaires might be a possibility to overcome this issue.

Also, more mechanistic studies are needed to investigate the pathophysiology of non-IgE-mediated rhinitis and IR more in depth. These studies might lead to the discovery of specific clinical, immunologic, or other biological markers that can diversify the heterogeneous group of non-allergic rhinitis patients and make us able to offer an individualized treatment strategy to each rhinitis patient. Additionally, these studies are needed to find new therapeutic targets for non-allergic rhinitis patients and NHR symptoms.

Conclusions

In this review, we aimed at emphasizing the diagnostic and therapeutic challenge of non-IgE-mediated rhinitis. We conclude that there is a great need for consensus on categorization, diagnostic work-up, and treatment for the patients affected. Defining the etiology of rhinitis in a symptomatic patient is important for choosing the most appropriate therapeutic approach, especially in the light of more treatment options becoming available nowadays. This is the only way to achieve an optimization of the quality of life in the chronic rhinitis patient.

Compliance with Ethics Guidelines

Conflict of Interest K Van Gool and V Hox declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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