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Allergic Rhinitis (J Maspero, Section Editor)

A Precision Medicine Approach to Rhinitis Evaluation and Management

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Abstract

Purpose of Review Precision medicine (PM) represents a new paradigm in disease diagnosis, prevention, and treatment. The PM approach focuses on the characterization of different phenotypes and pathogenic pathways in order to allow the selection of specific biomarkers that will be useful in disease management. Rhinitis is a highly prevalent and heterogeneous disease, both in terms of underlying endotypes and clinical presentations. Therefore, to apply the PM principles to the various rhinitis subtypes rise as a meaningful strategy to improve evaluation and treatment.

Recent Findings The technology of recombinant allergens has allowed molecular characterization of IgE reactivity of specific individual components of allergenic extracts. Recently published and ongoing clinical trials based on component resolved diagnosis (CRD) bring more precision to allergen immunotherapy for allergic rhinitis. Monoclonal antibodies against various cytokines involved in inflammatory allergic and nonallergic rhinitis endotypes show promissory results.

Summary Better understanding of pathogenic pathways together with an accurate phenotype classification of patients presented with rhinitis symptoms contributes to point out clinical usefulness of biomarkers and other diagnostic tools, which leads to more accurate environmental control measures, personalized pharmacologic options, and new biological therapy developments.

Introduction

Precision medicine (PM) is a growing up new paradigm in disease management [1•]. PM draws on recent advances in omics sciences, and molecular biology, and bioinformatics, applying them to the evaluation and treatment of health disorders. Based on the knowledge of the pathophysiological mechanisms (endotypes) and the various clinical expressions (phenotypes) of a disease, PM seeks to identify the best management strategies that allow arriving at an accurate diagnosis, which in turns facilitates a predictive, preventive, and therapeutic approach adjusted to the characteristics and needs of the patient, promoting his or her active participation in decision-making [2].

The three steps of PM are (1) pathophysiology: identification of molecular mechanisms of the disease and its variants, (2) prediction/diagnosis: identification of biomarkers and specific diagnostic tools, and (3) management: blocking/interfere those mechanisms for prevention and/or treatment [3].

In multifactorial chronic inflammatory disorders of the upper airway, such as the multiple variants of rhinitis, those endotypes and phenotypes are usually overlapping and dynamic, rendering clear-cut differentiations difficult. To apply a PM approach to this heterogeneous group of diseases acquires potentially greater relevance.

In this article, we will discuss present knowledge and incoming developments for each step in PM approach to rhinitis evaluation and management.

Rhinitis subtypes, phenotypes, endotypes, and biomarkers

Chronic rhinitis is one of the most prevalent pathologic conditions of the upper airways, and is usually presented with frequent comorbid conditions, and associated to considerable impact both in quality of life and in financial burden on health care systems [4].

Rhinitis is characterized by nasal congestion/obstruction, anterior or posterior rhinorrhea, sneezing, and itching [5]. However, there is a high variability in both underlying pathophysiologic mechanisms and clinical phenotypes. The three most widely accepted rhinitis subgroups thus far are allergic rhinitis (AR), infectious rhinitis, and nonallergic noninfectious rhinitis (NAR) [6], the last one recognizing a wide range of underlying pathophysiologic mechanisms [7]. Most relevant pathophysiologic mechanism involved in those types and subtypes of rhinitis (Table 1), as well as potential biomarkers for each endotype, will be briefly discussed.

Allergic rhinitis

AR is among the most common diseases worldwide and usually persists throughout life [8]. The prevalence of AR has been estimated to be approximately 5 to 25% in children [9] and more than 40% in adults [8]. Common symptoms of allergic rhinitis include sneezing, a runny, stuffy, itchy nose, coughing, a sore or scratchy throat, itchy watery eyes, frequent headaches, and excessive fatigue [10]. From a clinical perspective, AR has been classified according to disease severity, and symptom pattern/frequency or seasonality [11•, 12•].

AR is an inflammatory condition caused by an IgE-mediated response to environmental allergens [10]. Nasally inhaled indoor or outdoor allergens, including dust mite, cockroach, animal dander, molds, and pollens, are

Table 1. Classification of rhinitis phenotypes and endotypes

Types	Phenotypes	Pathophysiologic mechanisms				
		IgE-mediated inflammation	Non IgE-mediated inflammation	Infectious	Neurogenic	Unknown
Allergic	• Allergic Rhinitis • Local Allergic Rhinitis	■				
Infectious	• Acute Rhinosinusitis • Chronic Rhinosinusitis ○ CRSsNP ○ CRSwNP			■		
Nonallergic noninfectious	NARES		■			■
	Idiopathic rhinitis		■		■	■
	Age-related rhinitis				■	■
	Gustatory rhinitis				■	■
	Drug-induced rhinitis		■		■	■
	Rhinitis medicamentosa				■	■
	Hormonal rhinitis				■	■
	Occupational rhinitis	■	■		■	■
	Irritant-induced rhinitis		■		■	■
	Atrophic rhinitis					■
	Systemic disease		■			

CRSsNP: Chronic rhinosinusitis without nasal polyps; CRSwNP Chronic rhinosinusitis with nasal polyps; NARES: Nonallergic rhinitis with eosinophilia syndrome.

processed by antigen-presenting cells in the nasal mucosa and presented to T lymphocytes initiating a sensitization response characterized by interleukin (IL)-3, Il-4, IL-5, and IL-13 production [13]. These cytokines induce the differentiation of B lymphocytes into plasma cells leading to the production of allergen-specific IgE which in turn binds to high-affinity IgE receptors on the surface of mast cells and basophils [14].

On aeroallergen re-exposure, the cross-linking of specific IgE molecules by allergenic peptides leads to mast cells or basophil degranulation of preformed (i.e., histamine) and newly formed mediators (i.e., leukotrienes, prostaglandins, platelet-activating factor) [15] that are the main responsible of the immediate (within 30 min) allergic symptoms. In many cases, a late-phase reaction took place 4 to 12 h later, due to the release of chemokines and other chemoattractants that induce Th2 cells, activated eosinophils, and mast cell migration into the nasal epithelium where they release additional cytokines, mediators, and enzymes causing delayed allergic symptoms and perpetuating allergic inflammation [16].

Despite the IgE-mediated inflammatory endotype of AR seems to be sufficiently clear, the resulting phenotypes show multiple expressions. ARIA

guidelines [11] have categorized AR by duration, either as intermittent (< 4 days per week or < 4 weeks) or persistent (> 4 days per week and > 4 weeks) and by severity as mild, characterized by normal sleep, neither impairment of daily activities nor troublesome symptoms, and moderate/severe, associated with impairment of work, leisure, sport, school daily activities, or troublesome symptoms. Although ARIA classification could be certainly useful in terms of AR management by general practitioners, it does not consider the relevance of the allergen or allergens responsible for the sensitization and the triggering of symptoms in each patient, which might be meaningful for a PM approach in terms of diagnostic precision, secondary prevention, and personalized treatment. Following this, molecular characterization of IgE reactivity of specific individual components of allergenic extracts is now possible due to the technology of recombinant allergens. The identification of immunoreactivity to single allergenic components in allergic individuals allows to specifically define patients' allergic profile and to obtain the so-termed component resolved diagnosis (CRD) [17].

Local allergic rhinitis

Local allergic rhinitis, also called entopic rhinitis, is a distinct phenotype characterized by the presence of nasal symptoms of AR in nonatopic patients with negative skin prick test (SPT), undetectable serum-specific IgE against inhalant allergens, but with positive nasal allergen provocation test (NAPT) [18••]. Local allergic rhinitis (LAR) is a form of chronic rhinitis with localized antigen-specific IgE production to common aeroallergens such as house dust mite and grass pollen [19, 20]. The mechanism for LAR implies allergen exposure, nasal

Table 2. Potential biomarkers for immune-mediated inflammatory endotypes in rhinitis and chronic rhinosinusitis

Endotypes	Source	AR	LAR	NARES	CRSwNP	CRSsNP
Type 2 inflammation	Serum	Eosinophils Total IgE Specific IgE ECP			Eosinophils Total IgE SE-IgE ECP	
	Nasal fluids	Eosinophils IL-5 IL-4 IL-13	Eosinophils Specific IgE BAT NAPT	Eosinophils IL-4 IL.17 IL-10	Total IgE IL-5 IL-14 ECP	
	Nasal biopsy	Eosinophils ECP		Eosinophils	Eosinophils SE-IgE ECP	
	Nasal exhale	nNO ↑			nNO ↓	nNO ↑
Non-type 2 inflammation	Nasal fluids Nasal biopsy					IL-6, IL-8, MPO Neutrophils

AR allergic rhinitis, *LAR* local allergic rhinitis, *CRSsNP* chronic rhinosinusitis without nasal polyps, *CRSwNP* chronic rhinosinusitis with nasal polyps, *NARES* nonallergic rhinitis with eosinophilia syndrome, *SE-IgE* specific IgE to *S. aureus* enterotoxin E, *BAT* basophil activation test, *NAPT* nasal allergen provocation test, *nNO* nasal nitric oxide, *ECP* eosinophilic cationic protein, *MPO* myeloperoxidase

mucosal production of specific IgE, and a localized Th2 inflammatory response [21].

Nowadays, in clinical practice, efforts in endotyping patients with rhinitis are mainly limited to measuring total and allergen-specific IgE levels, eosinophilic cationic protein (ECP), and blood and nasal eosinophil counts [22, 23••]. Sensitization tests for AR are based on the demonstration of allergen-specific IgE. A positive SPT with allergens provides indirect evidence of allergen-specific IgE on cutaneous mast cells. SPTs are robust and easy-to-use screening instruments for common allergen sources [24]. Serologic in vitro diagnostic tests are an alternative option to provide a direct assessment of circulating allergen-specific IgE.

More recently, it has been suggested that the detection of serum IgE to specific molecules such as Phl p 1, Phl p 5, Bet v 1, and Pru p 3 may be also useful as biomarkers to predict seasonal allergic rhinitis persistence and future onset of comorbidities, such as asthma and/or oral allergy syndrome [25].

In the case of extremely low total serum IgE levels, the basophil activation test (BAT) allows a highly sensitive indirect demonstration of allergen-specific IgE on the surface of human effector cells from fresh blood [26, 27]. Both BAT and nasal-specific IgE quantification are useful tests for the diagnosis of LAR [28]. Nasal allergen provocation test (NAPT) has the capability of differentiating between allergic (AR and LAR) and nonallergic individuals (healthy controls and NAR), as well as between relevant and nonrelevant allergen sensitization in atopic subjects [29].

Nitric oxide (NO) has been found to be involved in inflammation and to induce regulatory, protective, and defensive tissue-damaging effects. Chemiluminescence represents the gold standard for nasal NO (nNO) measurements as these have a nasal device [30]. Increased levels of exhaled nNO have been found in patients with AR compared with normal subjects [31].

Infectious rhinitis

Rhinitis frequently coexists with sinusitis because the nose and sinuses share vascular, neuronal, and anatomic pathways.

Acute rhinosinusitis

Acute rhinosinusitis is predominantly of viral origin, with the usual causes being rhinovirus, coronavirus, adenovirus, parainfluenza virus, respiratory syncytial virus, or enterovirus [32, 33]. Viral rhinosinusitis may be complicated by secondary bacterial superinfection (i.e., *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*) that establishes a bacterial rhinosinusitis endotype [34].

Chronic rhinosinusitis

Chronic rhinosinusitis is characterized by nasal congestion, purulent discharge, and facial pain which last longer than 12 weeks. The presence or absence of nasal polyps allows further phenotypic classification into chronic rhinosinusitis with or without nasal polyps [22].

Chronic rhinosinusitis without nasal polyps (CRSsNP) seems to involve Th1 mucosal inflammation and overexpression of transforming growth factor beta

resulting in tissue remodeling [35, 36]. Neutrophils infiltrating nasal biopsy samples as well as nasal fluids IL-6, IL-8, and MPO might be considered as potential biomarkers [28].

In contrast, the endotype for chronic rhinosinusitis with nasal polyps (CRSwNP) seems to be Th2 driven and characterized by increased levels of IL-4, IL-5, and IL-13 manifested as significant mucosal eosinophilia and increased levels of total and specific IgE [37••]. Microbial superantigens such as *Staphylococcus aureus* toxins might also play a role throughout basophil degranulation, interaction with the T cell receptor, and specific IgE to *S, aureus* enterotoxin E (SE), the latter one that has been considered as a specific biomarker for CRSwNP [38]. On the other hand, reduction in nNO levels was demonstrated in patients with CRSwNP compared with patients with CRSsNP [39] (Table 2).

Noninfectious nonallergic rhinitis

Although it is questionable to define something for what is not, NAR comprises a heterogeneous group of nasal conditions affecting more than 200 million individuals worldwide [40]. In this review, we will focus on those subtypes in which PM can provide greater benefits.

Nonallergic rhinitis with eosinophilia syndrome

Nonallergic rhinitis with eosinophilia syndrome (NARES) was originally defined by the presence of more than 20% eosinophils in nasal smears without any evidence of IgE-mediated sensitization. Anosmia is a distinctive characteristic not present in AR patients [41, 42]. NARES is also a risk factor for the development of nasal polyposis, aspirin sensitivity, bronchial hyperreactivity, and nonallergic asthma [43]. The pathophysiology is poorly understood, but a key component involves a self-perpetuating, chronic eosinophilic nasal inflammation which contributes to direct mucosal damage, protracted mucociliary clearance, and nasal hyperresponsiveness. Granules of eosinophils contain toxic basic proteins, the majority of which are eosinophilic cationic protein (ECP), which constitutes a well-standardized marker for tissue eosinophilia and activation [44]. ECP levels in nasal secretions can be used to monitor eosinophilic inflammation in different kinds of rhinitis with eosinophilic involvement, and they constitute an indicator of the efficacy of treatment [44]. NARES is not associated with local allergy (entopy) nor with a local inflammation driven by *Staphylococcus aureus* enterotoxin [45].

Idiopathic rhinitis/vasomotor rhinitis

Idiopathic rhinitis (IR) is the most prevalent subtype of the NAR group, and is also a diagnosis requiring exclusion of AR, nasal eosinophilia, structural defects, or underlying systemic disease [46]. In the absence of any cellular inflammatory pattern, the pathophysiologic mechanism in IR is likely to be neurogenically mediated [37]. Most common triggers of symptoms include chemical irritants, as tobacco smoke, perfumes, and cleaning agents, but also changes in temperature, humidity, and barometric pressure, as well as alcohol ingestion. A neural/vascular pathophysiologic mechanism has been initially proposed to explain the effect of nonspecific irritants and alcohol, by inducing tachykinin release and inhibition of sympathetic mediators, enhancing the parasympathetic

response therefore ending in nasal congestion and/or rhinorrhea [47].

Another group of evidences suggests that IR may be disorders of the nonadrenergic noncholinergic or peptidergic neural system [48]. Nasal peptidergic neurons (mainly sensory C fibers) activated by these nonspecific stimuli resulted in antidromic and orthodromic release of inflammatory neuropeptides, which can exert effects on the blood vasculature and mucus-secreting glands, leading to symptoms of IR.

The neurogenic rhinitis endotype could also help to explain gustatory rhinitis and rhinitis of the elderly as well as some features of acute viral rhinitis (cold air responsiveness) and even AR (which have neural inflammation that leads to nonspecific hyperreactivity [49]. *Rhinitis of the elderly*, commonly presents with profuse rhinorrhea, is attributed to nasal hyperresponsiveness of the parasympathetic system [50]. *Gustatory rhinitis* defined by the acute onset of profuse watery rhinorrhea immediately after ingestion of certain spicy foods or after any act of eating is also associated with overstimulation of the parasympathetic system [51].

Several biomarkers might be used, mainly in research settings, such as substance P and neurokinin 1 [52••]. Staining of mucosal biopsy specimens for transient receptor potential cation channel subfamily V member 1 (TrpV1), also known as the capsaicin receptor, zonula occludens 1, or occluding has been used for similar purposes [53].

Hormonal rhinitis

Hormonal rhinitis subtypes include rhinitis of pregnancy and menstrual cycle–related rhinitis. Rhinitis of pregnancy typically begins after 34 weeks of gestation and resolves spontaneously within 2 weeks postpartum [54], whereas menstrual cycle–related rhinitis consists of symptoms appearing in the last few days of the menstrual cycle. The subjacent endotype might be primarily mediated either through increased levels of estrogen, which cause nasal congestion through vascular engorgement or by a vasodilating effect of progesterone [55]. Other mechanisms have also been suggested, including increased production of human growth hormone, enhanced production of a placental growth hormone variant, or of prolactin.

Drug-induced rhinitis

From a pathophysiologic perspective, systemic drug-induced rhinitis may be classified into three subtypes: local inflammatory, neurogenic, and idiopathic types.

The prototype of the inflammatory endotype is represented by aspirin-exacerbated respiratory disease (AERD). This condition is characterized by hypersensitivity to aspirin and other nonsteroidal antiinflammatory drugs leading to upper and lower airway inflammation, and resulting in severe rhinosinusitis and asthma symptoms [56]. Inhibition of cyclooxygenase-1 shifts the metabolism of arachidonic acid to the lipooxygenase pathway, resulting in increased cysteinyl leukotriene release precipitating local inflammation. 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. In the absence of atopy and

negative SPT, increased nasal eosinophil counts and higher baseline levels of urinary LTE_4 would be considered a specific biomarker for AERD [56].

Alpha-adrenergic and beta-adrenergic antagonists (clonidine, methyldopa) could mediate symptoms of rhinitis throughout a neurogenic endotype. Downregulation of the sympathetic tone leads to vascular engorgement, nasal congestion, and rhinorrhea. Phosphodiesterase-5 selective inhibitors such as sildenafil, tadalafil, and vardenafil, which act through their vasodilating properties on the erectile tissue of the nasal turbinates, are other examples of this neurogenic endotype. ACE inhibitors resulting in increased release of bradykinin, which is a potent vasodilator, might be also included in this subtype [57].

Other drugs (e.g., beta-blockers, calcium channel blockers, antipsychotics) [46] could induce rhinitis by still unknown pathophysiologic mechanisms (idiopathic endotype).

Rhinitis medicamentosa

Rhinitis medicamentosa is defined as rebound nasal congestion following excessive local use of decongestant sprays. Nasal vasoconstrictors like sympathomimetics and imidazolines, but also coacaine, are the main responsible drugs [58].

As the diagnosis lies on clinical history and physical examination (swollen, red nasal mucous membranes with minimal discharge), and management seems obvious, then pathophysiological mechanism merits not further discussion.

Occupational rhinitis

Work-related rhinitis includes the development of nasal symptoms caused by factors in the work environment as well as work-exacerbated rhinitis, in which a preexisting or concurrent rhinitis is worsened by occupational factors. The nature of the workplace airborne agent exposure and the pathophysiological mechanisms involved may distinguish between allergic and nonallergic endotypes [59].

High-molecular-weight agents such as animal (rodents) proteins and some low-molecular-weight agents (platinum salts) are complete antigens capable to elicit a specific IgE-mediated response by itself. Others low-molecular-weight agents (diisocyanates, trimellitic acid) act as haptens, which need to bind endogenous proteins in order to initiate a specific IgE-mediated response.

On the other hand, a single exposure to high chemical irritant concentrations or multiple exposures to lower chemical irritant concentrations over time (chlorine, sulfur dioxide, and ammonia) [60] can lead to significant inflammation and even structural damage. Such irritant-mediated nonallergic endotype has been termed as reactive upper airway dysfunction syndrome, irritant-induced rhinitis, or corrosive rhinitis depending on the severity and long lasting of the process [61].

The scarcity of specific biomarkers for NAR reinforces the need to implement other complementary evaluation tools, such as nasal flow measurement (to confirm nasal obstruction), cold dry air provocation (to search for nasal hyperreactivity), nNO measurement (to evaluate nasal inflammation), and test for

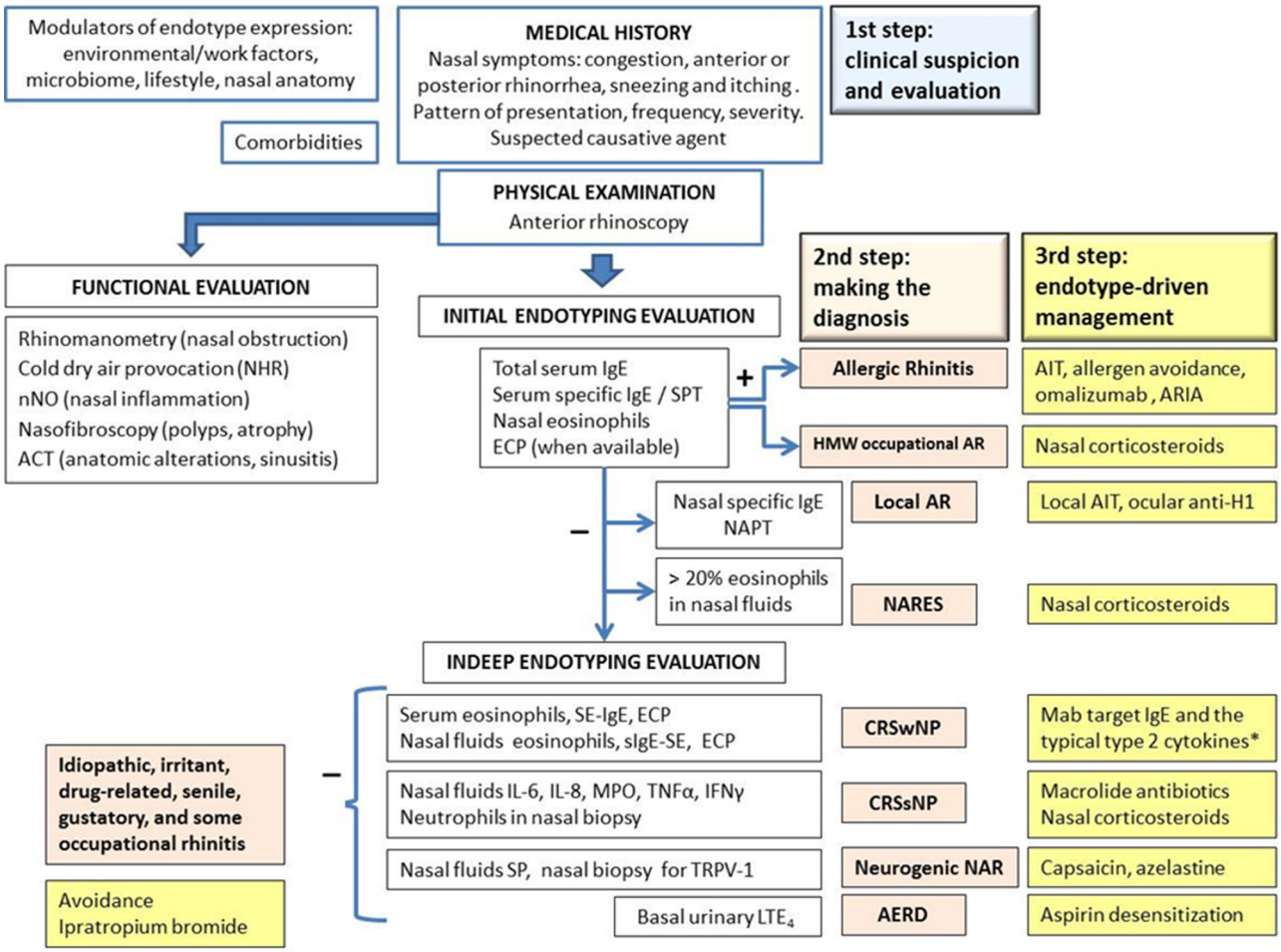

Fig. 1. A precision medicine approach to rhinitis evaluation and management. NHR nasal hyperreactivity, nNO nasal nitric oxide, ACT axial computed tomography, SPT skin prick test, ECP eosinophylic cationic protein, HMW high molecular weight, AR allergic rhinitis, ARIA allergic rhinitis and its impact on asthma guide, NAPT nasal allergen provocation test, AIT allergen immunotherapy, NAR nonallergic rhinitis, NARES nonallergic rhinitis with eosinophilia syndrome, CRSwNP chronic rhinosinusitis with nasal polyps, CRSsNP chronic rhinosinusitis without nasal polyps, sIgE-SE specific IgE against to *S. aureus* enterotoxin E, MPO myeloperoxidase, SP substance P, TRPV-1 transient receptor potential cation channel subfamily V member 1, LTE4 leukotriene E4, AERD aspirin-exacerbated respiratory disease, Mab monoclonal antibody. Asterisk indicates Mab target cytokines IL-4/IL-13 (dupilumab) via blocking the IL-4 receptor alpha, IL-5 (mepolizumab), and IL-5 receptor alpha (benralizumab) as well as IgE (omalizumab).

smell performance (in NARES and other patients mentioning reduced smell capacity). Nasofibroscopy and axial computed tomography will help to evaluate anatomical alterations or the presence of chronic rhinosinusitis with or without polyps, or any evidence of atrophic rhinitis [62].

Treatment of rhinitis subtypes following PM principles

Patients with moderate-to-severe rhinitis who are inadequately controlled despite treatment according to current rhinitis management guidelines have a

negative impact on daily functioning and are at risk of developing serious comorbidities, such as asthma and chronic rhinosinusitis. PM strategies, based on endotype-driven management, represent the future of rhinitis care in patients whose symptoms are not fully controlled despite evidence-based treatment.

Current definition of rhinitis relies on the combination of history, physical examination, and allergy diagnostic testing, which allows the distinction of the previously stated three major subgroups: allergic, infectious, and nonallergic noninfectious rhinitis.

The first step in the implementation of PM in patients with rhinitis, that is to characterize the endotype, will be a guide to a tailored management approach. Furthermore, we have to keep in mind that there are several modulators of endotype expression, such as the environment, microbiome, lifestyle, and nasal anatomy.

The best example of an endotype-driven treatment in AR is the use of allergen-specific immunotherapy in patients in whom an allergen-induced type 2 immune response endotype leads to a clinically relevant exposure-symptom relation. Other examples aiming to interfere with type 2 immune response include biological treatments with monoclonal antibodies targeting either IL-5 or IL4 receptor in CRSwNP. On the other hand, NAR phenotypes warrant different treatment strategies depending on the known or suspected underlying etiology, being it inflammation, neurogenic dysfunction, environmental exposure, and/or medication use.

Allergen immunotherapy

Allergen immunotherapy (AIT) represents an important intervention, currently adjunctive to pharmacological treatment, which confers specific advantages over conventional management.

The decision to prescribe AIT for the patient should be individualized and based on the clinical relevance of the allergens, the persistence of symptoms despite appropriate medications according to guidelines as well as on the availability of good-quality and efficacious extracts. Until now, there are no currently available validated biomarkers that can predict AIT success [63].

The first premise for the prescription of immunotherapy based on CRD is the assessment of IgE positivity to genuine versus cross-reactive allergens. Precise identification of relevant sensitizers in the case of pollen-allergic patient's monosensitized or oligosensitized to pollens with no overlapping pollen season can be achieved by conventional diagnosis with complete pollen extracts. In most cases, patients are sensitized to major pollen allergens, but this may not be the case in areas with high pollen loads. When prescribing AIT in areas with high frequency of sensitization to "minor allergens," molecular diagnosis may be of special interest, since commercial extracts for immunotherapy are well standardized only for major allergens [64]. Thus, patients with sensitization to minor allergens alone may likely not receive sufficient amounts of antigen to achieve a successful outcome from AIT, or even worse will experience adverse reactions when the concentrations of this minor allergens present in the extract are high [65].

In addition, AIT would be appropriately prescribed if sensitization to the species-specific allergens is confirmed in pollen allergies, while in the case of selective recognition of cross-reactive allergens, like profilins and polcalcin, called "pan-allergens" because the highly conserved structure and ubiquitous distribution of these molecules among plant species or cross-reactive carbohydrate determinants presents in the glycoproteins of virtually all pollen, the indication of AIT is arguable. Cross-reactive allergens seem to have limited clinical relevance and besides their content in AIT extracts is usually not quantified [66].

Biological agents

Although biological agents have been studied for the treatment of patients with AR, none of them is currently approved for the treatment of AR alone.

Omalizumab is a humanized anti-IgE monoclonal antibody that binds free IgE, preventing binding to receptors on mast cells and basophils. This agent can also decrease IgE receptors on effector cells. A meta-analysis of randomized clinical trials (RCTs) to assess the efficacy and safety of omalizumab in poorly controlled allergic rhinitis, which included 11 studies and 2870 patients, concluded that omalizumab is significantly associated with symptom relief, decreased rescue medication use, and improvement of quality of life [67•].

It is probably that due to its high cost, omalizumab should not be used as monotherapy in the treatment of AR but may be considered in combination with AIT for highly sensitive poly-allergic rhinitis patients with increased risk of anaphylaxis [68].

Monoclonal antibodies have been proposed as a novel therapy in patients suffering from CRSwNP. In two recent meta-analyses [69•, 70], anti-IgE therapy with omalizumab was assessed in two studies, anti-interleukin IL-5 therapy in three studies (one reslizumab, two mepolizumab), and anti-IL-4 and anti-IL-13 (dupilumbab) therapy in three studies. Biologic therapy was proved to be effective in reducing total nasal endoscopic polyp score and improving several other outcomes, such as opacification in computed tomography, quality of life measures, nasal airflow, and olfaction and type 2 associated biomarkers. Very recently, add-on dupilumab to inhaled corticosteroids resulted in significant and clinically meaningful improvements in endoscopic, radiologic, clinical, patient-reported sino-nasal, and asthma outcomes in patients with CRSwNP [71]. Other biological agents targeting Siglec-8 and IL-33 appear promissory [72].

Macrolide antibiotics have demonstrated great benefit in CRSsNP when used for their antiinflammatory or immunomodulatory properties, which include the blockage of pro-inflammatory cytokines, such as IL-8 and tumor necrosis factor-α (TNF-α) [73].

Environmental control

The prevalence of AR as well as other allergic diseases has been increasing for at least five decades. A possible cause of this increase could be the exposure of genetically predisposed individuals to a constantly changing indoor and outdoor environment. Two of these changes

strongly implicated in the sensitization process and in the triggering of symptoms of allergic diseases are air pollution and global warming induced by climate change, factors which are closely related to each other [74].

Experimental and epidemiological studies have shown a positive correlation between climate change, air pollution, and the incidence of respiratory allergic diseases [75–77]. Therefore, it is expected that any intervention that can be done to improve the environment would benefit the general population at large, and patients with AR. It could reduce the possibility of developing allergic diseases, facilitate treatment, and improve the quality of life of these patients [74].

Home environmental interventions (acaricides and bedroom control programs) may be of some benefit in reducing dust mite load and rhinitis symptoms [78]. One of the main problems to achieve an effective eradication of allergens lies in the adherence or compliance with the recommendations of these measures, since it may require modifications of the house, control of moisture sources, control of pets and insects, and improvements in the ventilation of the house, among others [79].

Regarding the general external environment, it is clear that it depends mainly on state policies tending to modify behaviors and actions both of the individual (recycling of organic material, use of biodegradable products, etc.) and of the general population (emission control of gases, promote the development of nonpolluting energies, active control of both the construction of "healthy" homes, the use of pesticides, the emission of gases by industrial activity, etc.). These holistic changes in lifestyle will have an impact on the global health of the human being and not only on patients with AR.

PM treatment approach for NAR

Avoidance of the etiological agent is the preferred management option in many patients with neurogenic inflammation-driven endotype (occupational rhinitis, gustatory rhinitis) and neuronal imbalance (rhinitis medicamentosa). Irritant avoidance and smoking stop should be advised to all rhinitis patients [80•]. In the same way, treatment of the drug-induced phenotypes of NAR primarily will consist of avoidance of the drug, but aspirin-intolerant individuals may benefit from aspirin desensitization [81].

The inflammatory group (occupational rhinitis and drug-induced rhinitis) may benefit from antiinflammatory treatment such as nasal corticosteroids and nasal antihistamines.

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 [82].

Another example of endotype-driven treatment is the highly successful intervention with capsaicin for the neurogenic noninflammatory endotype. Capsaicin treatment in patients with IR produced symptomatic relief and reduced the expression of transient receptor potential cation channel subfamily V, receptor 1 (TRPV1). Capsaicin did not alter nasal

epithelial morphology nor did it induce apoptosis or necrosis in cultured human nasal epithelial cells and mast cells [53]. Since many years, the use of azelastine has been found to be effective in NAR patients, but only recently, azelastine has been demonstrated to exhibit TRPV1 channel activity through the modulation of Ca2+ signaling on sensory neurons and in nasal epithelial cells [83].

Conclusions

Precision medicine implies the incorporation of a wide array of individual data, including clinical, lifestyle, genetic, and further biomarker information.

PM focuses on the stratification of patients beyond the classical "signs-and-symptoms" approach, identifying modifiable traits that can be treated in a better way because of more precise and validated phenotypic recognition or due to a better understanding of the critical causal pathways.

Although often underestimated, rhinitis is one of the most common chronic diseases worldwide, with increasing prevalence, morbidity, and greater impact in quality of life. Very recently, a new initiative has been launched in the field of PM with the aim of promoting the circulation of knowledge in the field of personalized, predictive, preventive, and participatory medicine in the field of allergic diseases and respiratory medicine (IMPERA) [84].

The three most widely accepted rhinitis subgroups thus far are infectious rhinitis, AR, and NAR. Underlying mechanisms are as numerous and diverse as the disease's phenotypes and are largely overlapping, making a clear demarcation challenging.

A PM approach to rhinitis evaluation and management is schematically summarized in Fig. 1. The first step is based on medical history and physical examination, and search for environmental exposure and lifestyle. The second step includes basic laboratory tests and nasal structural and functional evaluation. To further characterization, in deep evaluation requires identification of specific biomarkers, mainly available in research settings. The third step consists on the implementation of specific preventive measures and endotype-driven therapeutic options. The greatest advances have been made in the field of AIT and in the inhibition or blockade of some of the molecules associated with the immune mediated endotype. However, more studies are still mandatory for those phenotypes associated to neurogenic and idiopathic endotypes.

Compliance with Ethical Standards

Conflict of Interest

Carlos Crisci declares that he has no conflict of interest. Ledit Ardusso declares that he has no conflict 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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- •• Of major importance

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