

TITLE: Non-allergic Rhinitis, Allergic Rhinitis and Immunotherapy: Advances in the Last Decade

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Abbreviations, Acronyms:

ACAAI: American College of Allergy Asthma and Immunology

AAAAI: American Academy of Allergy Asthma and Immunology

AIT: Allergen Immunotherapy

AR: Allergic Rhinitis

ARIA: Allergic Rhinitis and its Impact on Asthma

EAACI: European Academy of Allergy and Clinical Immunology

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

IFN: Interferon

Ig: Immunoglobulin

IL: Interleukin

ILIT: Intralymphatic Immunotherapy

MASK: Mobile Airways Sentinel Network

MeDALL: Mechanisms for the Development of ALLergy

mHealth: mobile Health

NAR: Non-allergic rhinitis

NARES: Non-Allergic Rhinitis with Eosinophilia Syndrome

NHR: Nasal Hyperresponsiveness

SCIT: Subcutaneous Immunotherapy

sIgE: Specific Immunoglobulin E

SLIT: Sublingual Immunotherapy

TNF: Tumor Necrosis Factor

Tregs: Regulatory T cells

T_F: Follicular T cells

TRPV1: Transient Receptor Potential Cation Channel Subfamily V Member 1

VMR: Vasomotor Rhinitis

ABSTRACT:

Chronic rhinitis encompassing both allergic and non-allergic rhinitis affects a significant portion of the population worldwide, having a great impact on patient quality of life, and associated comorbid conditions, with an important societal economic burden. Allergists are often the first to evaluate and treat allergic and non-allergic rhinitis, addressing the individual triggers of the disease as well as the patient specific responses to these triggers. This review focuses on the advances that have been made in the diagnosis, management and treatment of non-allergic and allergic rhinitis over the past 10 years, including specific allergen immunotherapy, care pathways and digital health.

Allergic and non-allergic rhinitis are two of the most common disorders seen by allergists, and immunotherapy is likely one of the most common procedures practiced by allergists. In honor of the 10th anniversary of the *Journal of Allergy and Clinical Immunology: In Practice*, this review aims to highlight the recent advances that impact clinical care of patients with non-allergic rhinitis and allergic rhinitis, including diagnostics, therapeutics, including allergen immunotherapy and integration of global and digital health strategies.

NON-ALLERGIC RHINITIS

Non-allergic rhinitis (NAR), in contrast to allergic rhinitis (AR), is characterized by rhinitis in the absence of specific immunoglobulin E(IgE)-mediated hypersensitivity, or due to non-IgE mechanisms. The two major expert guideline updates addressing NAR in the past decade

include a Position Paper from the European Academy of Allergy and Clinical Immunology (EAACI) published in 2017¹ and a 2020 Practice Parameter Update from the Joint Task Force of the American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology². Both documents acknowledge the significant burden of NAR and call for improved understanding of this disease. In this section, we will emphasize recent advances and the state of the field in NAR.

Epidemiology of Non-allergic Rhinitis

The worldwide prevalence of nonallergic rhinitis in adults varies widely across populations and by definition - for example, if there is the presence of rhinitis without specific IgE, or if there are symptoms suggesting irritant triggers. It is estimated, however, that NAR affects more than 200 million people worldwide¹. A systematic review by Savouré *et al.* recently documented that using a rigorous definition of NAR, the median prevalence of NAR was 16.4% using a symptoms-based definition, and 31.4% based on a definition accounting for serum or skin testing for specific IgE. In adults, NAR was reported in 24.4%–67.1% of participants with rhinitis³. In children, NAR may be more prevalent in early life, with prevalence decreasing in older children compared to allergic rhinitis⁴. Reported prevalence of NAR in school aged children ranges from 6-8% in a Swedish population⁴ to 25% in a Singaporean cohort⁵. Variability in prevalence estimates likely reflect the type of definition used for the study. However, the extent of specific IgE testing may also influence the published ranges. Importantly, very little is understood about the influence of environmental exposures, such as rural vs urban environment, microbial diversity, lifestyle factors on prevalence of NAR.

Despite the lack of allergic sensitization, multiple papers have examined the relation between NAR and asthma, and have found that NAR is indeed related to asthma risk. Shaaban *et al.* showed in 2008 that in a longitudinal study of adult patients in Western Europe, NAR was

associated with a 2.71 fold relative risk of asthma compared to those without rhinitis.⁶ Using the Tucson Children's Respiratory Study, Carr *et al.* showed that NAR in childhood at age 6 was associated with a hazard ratio of 2.1 for subsequent development of asthma through age 32 when compared with those without rhinitis⁷. However, using data from the Asthma Phenotypes in the Inner City study, Toggias *et al.* showed that asthma associated with NAR in children may indeed be less severe⁸.

Classification of phenotypes

As has been the case for other allergic and immunologic diseases over the past decade, emphasis in NAR has included classifying NAR into phenotypes, providing a framework to better understand the pathophysiology and treatment of this heterogeneous group of diseases. Multiple phenotypes of NAR have been described, with the classification describing the exposure thought to drive the disease. These include senile, gustatory, hormonal, occupational, medication-induced, non-allergic rhinitis with eosinophilia syndrome (NARES) and vasomotor or "idiopathic" and are well reviewed in the aforementioned expert reviews^{1,2}. More recently, these phenotypes are being categorized by suspected physiologic mechanisms, inflammatory or neurogenic, which may ultimately determine the best treatment for the disease (Table 1). Fortunately, research efforts continue to attempt to understand this heterogeneous group of disorders toward improving patient care.

Inflammatory rhinitis phenotypes

The archetypal phenotype for inflammatory nonallergic rhinitis is Non-Allergic Rhinitis with Eosinophilia Syndrome (NARES). In this disorder, patients suffer from profuse rhinorrhea, sneezing, and nonspecific reactivity. Despite the absence of specific IgE to aeroallergens, nasal samples show significant eosinophilia, often >20%². In some cohorts, patients with NARES have high rates of asthma, and others develop chronic rhinosinusitis with nasal polyps,

suggesting that NARES may represent an early form of this disease. NARES is particularly responsive to the use of intranasal steroids, perhaps due to the underlying type 2 inflammation in this disease⁹. De Corso et al recently reviewed this evidence, identifying increased local expression of chemotactic factors such as eotaxin 2, eotaxin 3, other non-selective chemokines, like monocyte chemoattractant protein (MCP)-1, MCP-3, and regulated on activation normal T cell expressed and secreted (RANTES) in patients with NARES. However, additional immunologic characteristics are not well described.

Occupational rhinitis can be caused by IgE-mediated sensitization to high molecular weight antigens, such as in allergic occupational rhinitis. Occupational symptoms can also be nonallergic, driven by exposure to low molecular weight chemical substances, such as cleaning products with noxious odors, and triggered by other irritant exposures like cold dry air and particulates. In a 2017 paper, Castano *et al.* studied protein expression after antigen challenge in patients with rhinitis to both low and high molecular weight products.¹⁰ Participants with low molecular weight triggers had high baseline neutrophils in nasal lavage, and saw increase in those levels after challenge. In contrast to those with high molecular weight triggers, a panel of inflammatory proteins were not significantly induced.

Atrophic rhinitis is characterized by dysfunctional, atrophic nasal mucosa, paradoxical sense of nasal congestion, thick crusts and foul odor. Primary forms may be related to dry climate, and mucosal colonization with *Klebsiella ozaenae* or other pathogenic bacteria. Secondary forms can occur after irradiation, nasal surgery, or chronic granulomatous inflammation in the nose.¹¹ In addition to antibiotic therapy and moisturization techniques currently used, researchers are studying potential novel therapeutics including platelet rich plasma injections¹² and topical vitamin E¹³ to improve airflow mechanics and restore normal mucociliary function.

Neurogenic Rhinitis Phenotypes

Vasomotor rhinitis (VMR), sometimes called idiopathic rhinitis, is characterized by nasal hyperresponsiveness (NHR)¹⁴ and accounts for approximately half of the cases of NAR^{1,15}. NHR is the development of rhinitis symptoms- rhinorrhea, congestion, cough etc- upon exposure to nonspecific environmental stimuli such as changes in temperature, smoke, odors, and particulates. Cold dry air challenges may be useful to identify or quantify NHR in VMR¹⁶.

The transient receptor potential cation channel subfamily V member 1 (TRPV1), also known as capsaicin receptor or vanilloid receptor, is found in c-fiber sensory neurons, including those from the trigeminal nerve in the nasal cavity. It detects physical and chemical stimuli such as high temperature, acidic conditions, and capsaicin. TRPV1 expression is upregulated in the nasal mucosa of patients with VMR, suggesting this may be one pathway of neurogenic inflammation in VMR. Upon stimulation through TRP receptors, the peptidergic c fibers can release neuropeptides such as substance P, that can cause vasodilation, serum extravasation and mucus hypersecretion¹⁷ and thus contribute to VMR symptoms¹⁸. Interestingly, topical capsaicin may actually improve VMR symptoms through downregulation or reduced activity of the TRPV1 receptor¹⁷. Singh *et al.* showed in a murine model that continuous use of azelastine, a topical antihistamine used for treatment of NAR, may desensitize TRPV1 channels, providing one potential mechanism through which this drug could improve VMR symptoms in humans¹⁹.

In summary, NAR is a heterogeneous group of conditions, from which many patients suffer worldwide. Preventative and therapeutic interventions are lacking overall. Future research toward understanding pathophysiology and treatment should emphasize carefully selecting patients by phenotype.

ALLERGIC RHINITIS

Disease burden

An updated 2015 survey of individuals suffering from seasonal allergic rhinoconjunctivitis in the US found that 75-80% rated their symptoms as moderate-to-severe ²⁰. The most bothersome symptom, as in previous surveys, was nasal congestion, and the top 5 effects of allergic rhinoconjunctivitis were on feeling irritable, tired, and frustrated, and being unable to perform at their best and having reduced productivity. Most respondents agree that the current medications they were using for allergic rhino-conjunctivitis were effective, gave consistent relief, and had few side effects.

Etiology and risk factors for allergic rhinitis

Inheritance of allergic rhinitis is about 65%, suggesting that genes are an important reason why some people have allergic rhinitis and others do not. In a meta-analysis of genome-wide association studies using both discovery and replication phases in people with allergic rhinitis and controls, 41 risk loci for allergic rhinitis were identified including 20 loci not previously known to be linked to allergic rhinitis. ²¹ Fine mapping of HLA regions suggested amino acid variants pertinent to antigen binding. Shared genetic loci between allergic rhinitis, allergic sensitization, and nonallergic rhinitis suggest overlapping mechanisms. An important limitation of the meta-analysis is that most of the samples were from people of European ancestry. Longitudinal studies suggest there may be race based differences in the trajectory of atopic diseases.[insert references]

Environmental factors are the other main reason why some people have allergic rhinitis. Outdoor air pollution, indoor exposures, and climate change all can affect the development and aggravation of allergic rhinitis ²². Over 90% of the world population live in areas where air quality does not meet the standards of the World Health Organization. Indoor air pollutants include tobacco smoke, nitric oxide from gas-fueled cooking and heating, and allergens (furry pets, house dust mites, and molds). Climate change can impact allergic rhinitis through

temperature changes, seasonal growth patterns of allergens, altering respiratory infection patterns, and through extreme weather events such as flooding (mold) and thunderstorms. The environment also influences the microbiome of individuals; dysbiosis is linked to many disease states including emerging information about the nasal microbiome in allergic rhinitis.

Specifically, the genera of *Pseudoflavonifractor* dominated in well or partially controlled disease; notably, viral or fungal biome were not considered in this review. α diversity of the nasal microbiome is lower in allergic rhinitis compared to healthy controls, and the evenness and richness of the microbiota is related to asthma control²³. Finally, the SARS-CoV-2 pandemic, and physical efforts to limit virus spread, offer some lessons about symptom control in allergic rhinitis. Wearing either surgical or N95 masks reduced nasal but not ocular allergy symptoms in a study of nurses from Israel²⁴. Surgical and N95 masks filter particles larger than 3 μM and 0.04 μM , respectively, suggesting that pollens of typical sizes between 10-100 μM are likely to be filtered. In addition, the impact of wearing a mask on temperature and humidity also could influence nasal symptoms.

Allergic rhinitis disease mechanism

A clearer understanding of epithelial barrier function may lead to new treatment options for allergic rhinitis. Nasal secretions taken from patients with allergic rhinitis decrease epithelial barrier integrity using an air-liquid interface nasal epithelial cell *in vitro* model²⁵. The more specific factors found to influence the epithelial barrier function included histamine, TNF- α , interleukin(IL)-4, IL-13, and interferon(IFN)- γ ; antagonism of histamine receptor-1, TNF- α , and IL-4 stabilized epithelial barrier function. Histone deacetylase activity is higher in nasal epithelial cells from people with allergic rhinitis and blocking histone deacetylase activity *in vitro* and *in vivo* (in mouse model) restores epithelial integrity²⁶.

Mechanisms for the Development of ALLergy (MeDALL) studies have shed light on allergic diseases including allergic rhinitis at the clinical and mechanistic levels using data from several European birth cohorts. One study using integrated transcriptomics, replicated in the Epigenetic Variation and Childhood Asthma in Puerto Ricans cohort (RNA sequencing) found that multimorbid allergic disease may be different than rhinitis alone.²⁷ This has also been suggested in some birth cohorts²⁸ and in a case-control study in asthma.²⁹ These differences are likely to have symptom and treatment implications.

Diagnosis of allergic rhinitis

Symptoms suggestive of allergic rhinitis and demonstration of sensitization to allergens likely to be clinically relevant is a typical approach to diagnosing allergic rhinitis. Additional considerations for diagnosis of allergic rhinitis include the possibility of local but not systemic sensitization and testing for sensitization using tools that take advantage of knowledge about allergenic molecules. Local allergic rhinitis describes a subset of patients who have negative systemic sensitization for environmental allergens but have a positive nasal allergen provocation test and usually positive specific IgE tests for basal activation tests from nasal secretions³⁰. It is potentially important because some studies suggest that people with local allergic rhinitis improve with allergen immunotherapy. Understanding sensitization patterns to allergenic molecules can lead to advice that allows for successful allergen avoidance, as in the example of dog allergen. Can f 5 is one of several allergenic molecules responsible for dog dander allergy and is found in the prostate gland and therefore only in male dogs. A randomized study design challenging children to male and female dog allergens confirmed that children who are monosensitized to Can f 5 are likely to be tolerant to female dogs³¹.

Allergic rhinitis medical treatment

Selecting outcomes for treatment studies of allergic rhinitis has been advanced through multiple outcome validation studies. A systematic review of the validation of outcomes for allergic rhinitis studies found strengths and weaknesses of outcomes measures³². Specifically, validation was extensive for disease control and quality of life scores. Limitations for using disease control and quality of life scores include a relatively long administration time. Total symptom scores, nasal congestion symptom scores, and medication scores can be rapidly measured but are not extensively validated.

Biologics are approved for treatment of multiple diseases managed by Allergist-Immunologists, including asthma, chronic spontaneous urticaria, atopic dermatitis, chronic rhinosinusitis with nasal polyposis, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and eosinophilic esophagitis. Recent advances in understanding the pathophysiology of allergic rhinitis and new clinical trial data are likely to pave the way for studies of these or other biologics for allergic rhinitis. A systematic review and meta-analysis of using omalizumab for inadequately controlled allergic rhinitis found that omalizumab was statistically significantly associated with symptom relief, decreased medication use, and improvement in quality of life³³. A limitation of the analysis is that it is not clear if these statistical differences are likely to be clinically significant for these outcomes. However, a trial of omalizumab for allergic rhinitis published after the systematic review found that nasal and ocular symptoms were clinically improved compared to standard of care³⁴. A trial of dupilumab for asthma found that some but not all patients with perennial allergic rhinitis had reductions in nasal blockage, runny nose, sneezing, and postnasal discharge³⁵. However, biologics are only approved for allergic rhinitis in Japan and Russia..

IMMUNOTHERAPY

Allergen-specific Immunotherapy (AIT) has been practiced for more than a hundred years and is the only available disease-modifying treatment for allergic rhinitis. Many studies,^{36, 37} clinical trials,^{38,39} and meta analyses⁴⁰ have supported the efficacy of AIT and several organizations recommend its use for the treatment of allergic rhinitis and asthma.^{2,41} AIT is also effective in the prevention of progression of allergic sensitization to allergic asthma, improving quality of life and in lowering medication use in asthma³⁷ as well as AR.⁴² AIT for at least three years has shown sustained immunological responses at least two years after termination of treatment.^{43,44} Clinically, improvements in patient reported symptom scores, and nasal allergen challenge are seen, with a greater likelihood of clinical response occurring with increased exposure to AIT.⁴⁵ Improvements in medication use, quality of life and the long term cost effectiveness of AIT are also expected.^{37,46}

Novel Forms of Allergen Immunotherapy

Subcutaneous immunotherapy (SCIT) has been indicated for treatment of allergic rhinitis for over a century, and sublingual immunotherapy (SLIT) for three decades.⁴⁷ SLIT has been approved by the European Medicines Agency, the Food and Drug administration, and other agencies. However, over the last decade there has been growing evidence of the efficacy of intralymphatic AIT (ILIT), which is accomplished with a much shorter treatment protocol than conventional AIT. Initial studies with a modular antigen transporter (MAT) vaccine using Fel d 1 showed immunological efficacy and was tolerated well.⁴⁸ Other studies have similarly shown efficacy and safety when using birch or grass pollen allergens for ILIT.⁴⁹ Although not all studies support the use of ILIT,⁵⁰ information on the long term outcomes and more safety data is needed when considering ILIT in the context of other AIT options.

Mechanisms of Allergen Immunotherapy

The allergic response begins with the endocytosis of allergens by dendritic cells followed by presentation at secondary lymphoid organs and subsequent Th2 proliferation with the production of IL-4, 5, and 13.^{51,52} In addition, the role of follicular helper T (T_{FH}) cells have been shown to be critical in the B cell response and the production of allergen specific high affinity IgE antibodies in allergic rhinitis.^{53,54} AIT is known to induce tolerance through induction of regulatory T cells (Tregs), production of blocking IgG₄ antibodies and increases in IL-10, TGF- β , and IFN- γ which interferes with the production of Th2 cytokines⁵⁵. Recently, it has also been shown that AIT increased regulatory B cells.⁵¹ and follicular regulatory T (CXCR5⁺ FOXP3⁺) cells which regulate the aberrant T_{FH} cells in allergic rhinitis.^{56,57}

Patient Selection

An appropriate history upon exposure to the allergen, along with evidence of allergen IgE sensitization via skin testing or serum specific IgE (sIgE) remain the accepted gold standard for patient selection for AIT. Nevertheless, some recent studies have suggested sIgE or the sIgE to total IgE ratio (sIgE/tIgE) as potential biomarkers to predict response to AIT. One study found the sIgE/tIgE to be sensitive and specific in predicting successful clinical outcome of AIT,⁵⁸ but other larger studies could not replicate those results.⁵⁹ Increases in allergen specific IgG₄ in the same individual do correlate with clinical response to AIT⁶⁰ although the absolute numbers especially for patient selection prior to AIT may not be as helpful. Similarly, functional *in-vitro* assays such as basophil activation test may have a role in assessing response to treatment but may not be as helpful in patient selection. Studies have also preliminarily considered IL-35-producing Tregs as well as group 3 innate lymphoid cells as possible biomarkers for AIT response, but more robust data is needed.⁶⁰ Although mHealth (mobile health) biomarkers have shown promise⁴¹ and have been used in an AIT study,⁶¹ the search for predictive biomarkers for patient selection continues.

Component resolved diagnostics (CRD) which identifies IgE to specific molecular targets rather than the traditional use of whole allergen extracts for *in vivo* or *vitro* testing can improve the accuracy of diagnostic evaluation especially for allergen such as furry pet allergen. This increased specificity allows the identification of primary poly-sensitization versus cross-reactive sensitization within allergen families. This has implications for prediction of asthma risk and hence the utility of AIT.⁶² When presented with this additional diagnostic information from CRD, the clinical decision to prescribe AIT and contents of the prescription were often affected.⁶³ A growing body of evidence considers the additional use of CRD when considering AIT for pollen, dust mite, pet, and venom allergens.⁶⁴

Safety of Allergen Immunotherapy

Many studies on the safety of SCIT and SLIT have been reported, including an ongoing SCIT surveillance study.⁶⁵ The studies establish that AIT can be administered safely and effectively, although severe adverse events such as anaphylaxis are possible and require appropriate monitoring. Systematic reviews have shown increased risks of adverse events with any forms of AIT.⁴⁰ Some factors increasing risks of systemic reactions include uncontrolled or severe asthma, and accelerated build up schedules.⁶⁵ Similarly, increased risk from AIT in children has also been noted to be associated with uncontrolled asthma.⁶⁶

Immunogenicity of Allergen Extracts

Ideally, allergen extracts would be highly specific, stable, relevant antigenic epitopes that induce safe, robust, and long lasting immune responses. While current commercially available extracts or tablets for AIT are widely used and effective, multiple methods to improve AIT by manipulating the allergenicity of extracts have shown promise over the past decade.

Allergen Modification:

Modification of allergens via chemical polymerization with formaldehyde or glutaraldehyde, carbamylation of lysines, or other methods can render them more immunogenic. These properties have been used to improve immunogenicity of grass pollen extracts, house dust mite extracts and birch pollen extracts with good efficacy and safety.⁶⁷⁻⁶⁹ Long term efficacy and thorough study of adverse effects remains to be determined.

Adjuvants:

Adjuvants are molecules that enhance immunological responses to allergens by physical or chemical interactions. Several adjuvants including aluminum, calcium phosphate, virus like particles, toll like receptor agonists, microcrystalline tyrosine and liposomes have been studied and show various degrees of efficacy and safety, although some (particularly aluminum containing adjuvants) have been sidelined due to reports of adverse effects.^{56,70} The future widespread utility of adjuvant remains to be determined.

Peptide and Recombinant Allergens:

Peptide allergens present short peptides that together make up the T cell epitopes without the conformational structures required to elicit an IgE response, and recombinant allergens are designed to resemble the native allergens with specific changes leading to a decreased IgE response, enhance stability or efficacy. Recombinant cat extract has been studied, and in the last decade, recombinant birch and grass pollen have shown clinical utility for AIT.⁵⁶ Although the efficacy of peptide allergen immunotherapy may be allergen specific with some safety concerns in patients with asthma,⁷¹ recombinant allergens are likely to have a role in the future use of AIT.

Clinical guidelines, practice parameters and care pathways on allergic rhinitis

From 2017 to 2021, several clinical guidelines, practice parameters and care pathways have been published. ARIA (Allergic Rhinitis and its Impact on Asthma) ⁷² and the AAAAI/ACAAI Practice Parameters ^{73,74} used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for strength of recommendation, whereas the UK guidelines used another evidence-based system.² The two updated guidelines using GRADE made similar recommendations, and the AAAAI/ACAAI Practice Parameters adopted the ARIA classification of severity for the first time. This harmonization of recommendations will serve to clarify the evidence base for clinicians to apply these available clinical data.

One important and innovative approach utilized by ARIA was to embed GRADE-based recommendations into real-world data assessing the patient's preferences, goals, and disease severity for treatment of allergic rhinitis. To this end, ARIA proposed next-generation guidelines incorporating real-world data and the speed of onset of medications.⁷⁵ This guideline was based on a consensus and it is important to revise it using real clinical data from trials which particularly need to study and document the importance of on demand, or as-needed, treatment.

In addition, several guidelines on AIT have been proposed by the EAACI. They cover the entire field,⁷⁶⁻⁸⁰ but only the "asthma" guideline was based on GRADE.⁸¹ These papers give a global overview of AIT efficacy, indications, and risks.

Integrated Care Pathways are structured multi-disciplinary care plans detailing the key steps of patient care in order to promote the translation of guideline recommendations into their application to clinical practice. They may be particularly useful toward management of patients with multimorbidities, since clinical trials often exclude these more complex patients from studies, and therefore they are not adequately represented in guidelines. Care pathways should be carried out by a multidisciplinary team including physicians, pharmacists and other health

care professionals. ARIA has proposed care pathways for allergic diseases⁸² and allergen immunotherapy⁸³ including engagement of pharmacists.⁴³

The past five years have seen a harmonization of guidelines and advances toward considering applications to real world patient needs and complexities of care. There is an urgent need to further develop care pathways, to improve shared-decision making between physicians and patients, and to study outcomes in complex or real-world settings.

Digital health in allergic rhinitis

In all societies, the burden and cost of allergic diseases are increasing rapidly. Most economies are struggling to deliver modern health care effectively. There is a need to support the transformation of the health care system into integrated care with organizational health literacy.^{84,85} As an example for chronic disease care, MASK (Mobile Airways Sentinel Network), a new project of the ARIA initiative in collaboration with professional and patient organizations in the field of allergy and airway diseases, are proposing real-life care pathways centered around the patient.⁸⁶⁻⁹¹ MASK is an information and communication technology system freely available through app stores, meant to be utilized by adolescent and adult patients to support treatment of allergic rhinitis symptoms. MASK has been recognized by DG Santé as a Good Practice in the field of digitally-enabled, integrated, person-centered care. Apps such as the AllergyMonitor® and the Vienna app⁹²⁻⁹⁴ which are available in Europe can record symptoms, integrate information like pollen data and utilize physician-endorsed, locally available treatment recommendations. . Future use of electronically captured real world patient experience is expected to transform healthcare and is well under way in the European Union with impact anticipated in the United States.⁹⁵⁻⁹⁷

Conclusions

Advances in allergic rhinitis, nonallergic rhinitis, and immunotherapy in the past ten years encompass understanding disease and therapeutic mechanisms, improving treatment pathways, and utilizing novel technology toward optimizing patient care.

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INFLAMMATORY		NEUROGENIC DYSREGULATION	
Phenotype	Characteristics	Phenotype	Characteristics
NARES	Local & systemic eosinophilia with evidence of T2 inflammation	Rhinorrhea of the elderly	Affecting >65 years of age, clear watery rhinorrhea improved with anti-cholinergic therapy
Atrophic	Loss of normal mucosal function and tissue destruction; bacterial colonization and granulomatous inflammation	Vasomotor/Idiopathic	Nasal hyperresponsiveness to irritant stimuli (cold air, particulates, strong odors) due to upregulated sensory signaling
Occupational	Variable inflammation with hypersensitivity to irritants in the workplace	Rhinitis medicamentosa	Alpha receptor tachyphylaxis in the setting of continuous intranasal decongestant use (ie cocaine, oxymetazoline)
Hormonal	Estrogen contributes to vascular congestion; evidence of H1-receptor upregulation	Gustatory	Clear rhinorrhea while eating, due to neurologic reflex of the noncholinergic, nonadrenergic system
Drug-induced	NSAID/ASA use in NERD	Drug-induced	Disruption in sympathetic/ parasympathetic tone through use of alpha blockers, beta blockers, vasodilators