REVIEW ARTICLE

Updates in Rhinitis: A Comprehensive Review of Recent Advances

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Abstract

Rhinitis is a common inflammatory condition of the nasal mucosa. It significantly impacts a person's health and quality of life. Traditionally, it is categorized as allergic rhinitis (AR) or nonallergic rhinitis (NAR). Recent advancements have led to a more nuanced understanding of its pathophysiology, classification, and management. This review emphasizes key updates over the last decade. The focus is on evolving concepts in phenotyping and endotyping, novel insights into disease mechanisms, advancements in diagnosis, and emerging therapeutic strategies, including biologics and targeted nerve interventions. The recognition of local allergic rhinitis (LAR), the role of innate immunity and epithelial barrier dysfunction, and the increasing array of precision medicine options underscore a paradigm shift toward personalized management. Despite these newer advances, challenges remain in fully characterizing NAR and optimizing therapeutic guidelines. This review aims to provide an overview of these transformative developments, guiding clinicians and researchers toward more effective and tailored approaches to treat rhinitis.

Keywords: Allergic rhinitis, Biologics, Diagnosis, Endotypes, Immunotherapy, Local allergic rhinitis, Nonallergic rhinitis, Phenotypes, Rhinitis, Treatment.

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Introduction

Rhinitis, characterized by symptoms of sneezing, rhinorrhea, nasal itching, and congestion, affects a substantial portion of the global population, with prevalence estimates varying between 10% and 40%.[1] Beyond its perceived benign nature, rhinitis significantly impacts quality of life, sleep, cognitive function, and productivity, and is frequently comorbid with asthma, conjunctivitis, and chronic rhinosinusitis.[2,3] For decades, rhinitis has been broadly classified into allergic rhinitis (AR), triggered by IgE-mediated reactions to allergens, and nonallergic rhinitis (NAR), encompassing various subtypes without a clear allergic etiology.[4]

The past decade has witnessed a rapid evolution in our understanding of rhinitis, driven by advances in molecular biology, immunology, and therapeutic development. This review aims to consolidate the most significant updates in rhinitis within the last ten years, covering re-evaluation of classification, unraveling of new pathophysiological insights, refinement of diagnostic methods, and the emergence of innovative treatment modalities, including the burgeoning field of biologics and targeted nerve therapies. This synthesis provides a comprehensive overview for healthcare professionals navigating the complexities of modern rhinitis management.

Updates in Classification, Phenotypes, and Endotypes

Traditional classification of rhinitis, primarily differentiating AR from NAR, has been increasingly recognized as insufficient to capture the intricate heterogeneity of the disease. The current trend emphasizes phenotyping (observable characteristics) and endotyping (mechanistic pathways) to guide personalized treatment strategies.[5,6]

Local Allergic Rhinitis

One of the most significant advances in rhinitis classification is the widespread acceptance and characterization of local allergic rhinitis (LAR).[7] LAR presents with classic AR symptoms triggered by allergens, but patients show negative results on standard skin prick tests and serum-specific IgE tests. Diagnosis relies on positive nasal provocation tests (NPT) with relevant allergens, demonstrating local IgE production within the nasal mucosa.[8] Studies have elucidated the local immune response in LAR, involving mast cells, eosinophils, and T-helper 2 (Th2) cytokines, mirroring systemic AR but confined to the nasal cavity. The recognition of LAR is crucial as it accounts for a substantial proportion of patients previously misdiagnosed as NAR, enabling appropriate allergen-specific interventions.[7,8]

Nonallergic Rhinitis Subtypes Refined

Nonallergic rhinitis remains a heterogeneous group, but recent efforts have aimed at a more granular classification with prognostic and therapeutic implications.[9] Key subtypes gaining clearer definition include:

- *Nonallergic rhinitis with eosinophilia syndrome (NARES)/eosinophilic nonallergic rhinitis (ENAR)*: Characterized by significant eosinophilia (typically >20%–25%) in nasal cytology, without systemic IgE sensitivity. ENAR is often associated with nasal polyps, asthma, and aspirin-exacerbated respiratory disease (AERD), suggesting a type 2 inflammatory endotype.[10]
- *Vasomotor rhinitis (VMR)/noneosinophilic nonallergic rhinitis (NENAR)*: This is characterized by prominent congestion and rhinorrhea triggered by nonspecific stimuli (e.g., temperature changes, strong odors) without evidence of inflammation or allergy. Recent research highlights neurogenic inflammation and autonomic dysregulation as key drivers.[9,11]
- *Other NAR forms*: Gustatory rhinitis, drug-induced rhinitis (e.g., from ACE inhibitors), hormonal rhinitis, atrophic rhinitis, and occupational rhinitis continue to be recognized based on specific etiologies.

Advancements in Pathophysiological Insights

The understanding of rhinitis pathophysiology has moved beyond a simple IgE-mast cell paradigm for AR and vague autonomic dysfunction for NAR. Recent research highlights the intricate interplay of genetic, environmental, immunological, and neurological factors.[6]

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Epithelial Barrier Dysfunction

Emerging evidence suggests that impaired epithelial barrier function in the nasal mucosa plays a crucial role in both AR and NAR.[12] Damaged tight junctions can lead to increased permeability, allowing allergens, irritants, and microbial products to penetrate the mucosa, initiating or exacerbating inflammatory responses. This concept has opened new avenues for therapeutic interventions targeting barrier integrity.

Innate Immunity and Alarmins

The role of innate immune responses, particularly through epithelial-derived cytokines known as alarmins (e.g., IL-33, TSLP, IL-25), has gained prominence in type 2 inflammatory rhinitis.[13] These alarmins are released upon epithelial damage and drive the differentiation and activation of type 2 innate lymphoid cells (ILC2s), contributing to the characteristic type 2 immune response (eosinophilia, IgE production). This deeper understanding has directly informed the development of biologic therapies.

Neurogenic Inflammation

For NAR, especially VMR, renewed focus is on the role of neurogenic inflammation.[11] Dysregulation of sensory nerves (trigeminal nerve), release of neuropeptides (e.g., substance P, calcitonin gene-related peptide), and altered autonomic tone contribute to symptoms such as hypersecretion and congestion. This insight underpins the development of targeted nerve interventions.

Microbiome Influence

The nasal microbiome's influence on rhinitis development and progression is an active area of research.[14] Dysbiosis, characterized by an imbalance in bacterial communities, may modulate immune responses, potentially contributing to inflammation and allergen sensitization. While still in early stages, this area holds promise for future diagnostic and therapeutic strategies.

Contemporary Diagnostic Approaches

While clinical history and physical examination remain fundamental, contemporary diagnostic approaches are integrating more refined tools to support phenotyping and guide treatment.

Advanced Allergy Diagnostics

Beyond traditional skin prick tests and serum-specific IgE, molecular allergology (component-resolved diagnostics [CRD]) has become more accessible.[15] CRD allows for the identification of specific allergen molecules (e.g., profilins, PR-10 proteins, storage proteins), providing a more precise risk assessment for cross-reactivity, severity, and the potential efficacy of allergen immunotherapy.

Nasal Provocation Tests

Nasal provocation tests (NPT), particularly with allergens, are increasingly recognized as a vital diagnostic tool for LAR, as previously mentioned.[8] Nonallergen NPTs (e.g., with histamine or methacholine) can assess nasal hyperactivity, aiding in the diagnosis of NAR.

Nasal Cytology

Microscopic examination of nasal secretions for inflammatory cells (eosinophils, neutrophils, mast cells) is gaining traction as a simple, non-invasive tool for phenotyping.[10] Detection of high eosinophil counts can differentiate ENAR from other NAR subtypes and guide the use of intranasal corticosteroids or potentially biologics.

Biomarkers

Research into biomarkers is accelerating, aiming to identify objective measures of disease severity, response to treatment, and specific endotypes.[16] While not routinely used in clinical practice, promising candidates include:

- *Exhaled nitric oxide (eNO)*: Nasal eNO levels can reflect Type 2 inflammation.
- *Tear/nasal fluid cytokines*: Levels of IL-4, IL-5, IL-13, TSLP, IL-33, and eotaxin are under investigation as indicators of type 2 inflammation.
- *Serum biomarkers*: Periostin, IgE, and eosinophil counts provide systemic indicators.

Therapeutic Advancements

The therapeutic landscape for rhinitis has greatly expanded, particularly for severe and refractory cases, with a move toward personalized and targeted interventions.

Pharmacotherapy Updates

Intranasal Corticosteroids (INCS)

Remain the cornerstone of AR and inflammatory NAR treatment, with new formulations offering improved patient adherence and reduced systemic absorption.[17] Combinations of INCS and intranasal antihistamines (e.g., azelastine/fluticasone) have demonstrated superior efficacy for moderate-to-severe AR compared to monotherapy.[18]

Antihistamines

Newer generation oral antihistamines (e.g., rupatadine, bilastine) offer effective symptom control with minimal sedation.[19] Intranasal antihistamines provide rapid onset of action, particularly useful for "on-demand" relief.

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists (LTRAs) continue to be an option, particularly for patients with coexisting asthma, but generally less effective than INCS for nasal symptoms alone.[20]

Allergen Immunotherapy

Allergen immunotherapy (AIT), available as subcutaneous (SCIT) and sublingual (SLIT) routes, remains the only disease-modifying treatment for AR. Recent updates include:

- *Expansion of SLIT indications:* SLIT tablets are now approved for several common allergens (e.g., grass, ragweed, dust mites), offering a convenient home-based option.[21]
- *Improved protocols:* Ultra-rush and modified rush protocols for SCIT aim for faster desensitization while maintaining safety.[22]
- *Real-world evidence:* Numerous studies reinforce the long-term efficacy of AIT in reducing AR symptoms, medication use, and preventing asthma development.[23]

Biologic Therapies

A game changer: The most transformative development in severe rhinitis and its comorbidities has been the advent of biologic agents, primarily targeting type 2 inflammation. While most are approved for comorbid conditions such as severe asthma or chronic rhinosinusitis with nasal polyps (CRSwNP), their beneficial effects on severe AR and NAR with type 2 features are increasingly recognized.

Omalizumab (Anti-IgE): Approved for severe allergic asthma, omalizumab has shown efficacy in reducing symptoms and medication use in patients with severe AR, particularly those with high serum IgE levels.[24] Its role in patients with concurrent severe AR and chronic urticaria is also being explored.

Dupilumab (anti-IL-4Ra): A groundbreaking biologic targeting the common alpha subunit of the IL-4 and IL-13 receptors, dupilumab is approved for severe asthma, atopic dermatitis, and CRSwNP. For CRSwNP patients, dupilumab significantly reduces nasal polyps, improves sense of smell, and alleviates nasal congestion, with concomitant benefits for AR symptoms where present.[25] Its potential role in severe, refractory AR without CRSwNP is under investigation.

Mepolizumab and reslizumab (anti-IL-5): Primarily indicated for severe eosinophilic asthma and CRSwNP with eosinophilia, these anti-IL-5 agents also reduce nasal eosinophilia and improve nasal symptoms in patients with type 2 rhinitis and CRSwNP.[26]

Benralizumab (anti-IL-5Ra): Targets the IL-5 receptor alpha expressed on eosinophils, leading to direct eosinophil depletion. Similar to anti-IL-5 antibodies, it is approved for severe eosinophilic asthma and shows promise in CRSwNP and Type 2 rhinitis.[27]

Tezepelumab (anti-TSLP): A novel biologic targeting thymic stromal lymphopoietin (TSLP), an upstream alarmin crucial for initiating type 2 inflammation. Approved for severe asthma, tezepelumab has shown broad efficacy across various type 2 inflammatory conditions and holds significant promise for patients with severe AR, including those with nontype 2 asthma or AR features.[28]

Targeted Nerve Interventions for Nonallergic Rhinitis

For refractory NAR, particularly VMR with prominent rhinorrhea and congestion, targeted nerve interventions represent a significant advance.

Posterior Nasal Nerve (PNN) Ablation/ Cryoablation

Procedures such as cryotherapy (e.g., RhinAer®) or radiofrequency ablation target the PNN, which supplies secretomotor and vasomotor innervation to the nasal mucosa. By disrupting these nerves, symptoms of chronic rhinorrhea and congestion are significantly reduced, offering a minimally invasive alternative for patients unresponsive to conventional medical therapy.[29]

Vidian Neurectomy

A more invasive surgical procedure that ablates the vidian nerve, historically performed for severe rhinorrhea, is now rarely used due to significant side effects, but its principle informs newer PNN interventions.

Other Emerging Therapies

Nasal Barrier Sprays

Containing cellulose powder or polymers, these sprays aim to create a protective barrier on the nasal mucosa, preventing allergen and irritant penetration.[30]

Probiotics

While still primarily investigational, some studies suggest that oral or intranasal probiotics may modulate immune responses and alleviate AR symptoms, though more robust evidence is needed.[31]

Immunomodulators

Research on compounds modulating specific immune pathways, beyond biologics, continues, but none have reached widespread clinical use for rhinitis.

Conclusion and Future Directions

The landscape of rhinitis diagnosis and management has undergone a remarkable transformation over the past decade. The shift from a binary AR/NAR classification to a more nuanced understanding of phenotypes and endotypes, particularly the recognition of LAR and the refined characterization of NAR subtype, marks a significant step towards precision medicine. Our understanding of pathophysiology has deepened, highlighting the crucial roles of epithelial barrier function, innate immunity, and neurogenic inflammation.

Diagnostic tools are becoming more sophisticated, allowing for better identification of specific patient subsets, while the therapeutic arsenal has expanded dramatically. The introduction of biologic agents, initially for comorbid conditions but increasingly recognized for their broader benefits in severe type 2 rhinitis, represents a paradigm shift for patients with refractory disease. Furthermore, targeted nerve interventions offer new hope for those suffering from chronic, treatment-resistant NAR.

Despite these advances, challenges remain. A clearer understanding of the underlying mechanisms of all NAR subtypes is still needed to develop more targeted therapies. The high cost of biologics necessitates careful patient selection and economic evaluation. Further research is required to identify reliable and accessible biomarkers for routine clinical practice to guide personalized treatment decisions for all forms of rhinitis.

Future directions in rhinitis research will likely focus on:

- Developing more predictive biomarkers for response to specific therapies, especially biologics.
- Exploring novel targets beyond type 2 inflammation for non-responders or nontype 2 endotypes.
- Investigating the role of the nasal microbiome and its manipulation in disease prevention and treatment.
- Refining immunotherapy approaches for broader allergen coverage and improved safety profiles.
- Integrating artificial intelligence and machine learning to analyze complex patient data for personalized management algorithms.
- Ultimately, the goal is to move towards a stratified, patient-centric approach to rhinitis care, optimizing treatment selection based on an individual's specific endotype, thereby improving clinical outcomes and enhancing quality of life for millions affected by this pervasive condition.

Conflict of Interest

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