



ALLERGIC RHINITIS FROM DISEASE DISCOVERY TO PATIENT MANAGEMENT

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Abstract

Allergic rhinitis (AR) is a clinically defined disorder of the nose characterized by symptoms triggered by allergen exposure, leading to an IgE-mediated inflammation. It is a global health problem affecting up to 50% of the world's population, with symptoms extending beyond nasal obstruction, rhinorrhea, sneezing, and itching, impacting productivity, school performance, sleep, and quality of life (QoL). Untreated AR can result in multimorbidity, linking with conditions such as asthma, rhinosinusitis, adenoid hypertrophy, otitis media, dysphonia, laryngopharyngeal reflux, OSA, and migraine. ARIA classifies AR into intermittent or persistent and mild or moderate-severe, recommending management approaches including allergen avoidance, antihistamines, intranasal steroids, immunotherapy, and surgical interventions. This presentation focuses on nasal irrigation and rupatadine, a non-sedating antihistamine with antiplatelet activating factor properties, aiming to improve QoL and safety for AR patients.

Keywords: allergic rhinitis, nasal irrigation, rupatadine, anti platelet-activating factor (PAF), Quality of Life

Introduction

Allergic rhinitis (AR) is a symptomatic condition that affects the nasal passages and is characterized by inflammation triggered by an immune response mediated by immunoglobulin E (IgE) when exposed to allergens. This prevalent condition poses a significant global health challenge, impacting a considerable portion of the world's population, with estimates suggesting a prevalence rate of up to 50%. However, the specific prevalence data for the Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine Universitas Padjadjaran, Dr. Hasan Sadikin Hospital in Bandung, Indonesia, is currently unavailable. Despite the lack of precise local figures, AR remains a pressing concern globally, demanding attention and effective management strategies.

Nevertheless, it is essential to emphasize that in this presentation, our focus is on addressing the aspects that truly matter to individuals affected by allergies, particularly their quality of life (QoL). AR symptoms, such as nasal congestion, sneezing, itching, and rhinorrhea, can significantly impact daily activities, sleep patterns, work productivity, and overall well-being. Therefore, it becomes crucial to explore interventions that not only alleviate symptoms but also enhance the QoL of allergic patients.

One of the potential strategies for managing AR symptoms is nasal irrigation, also known as nasal rinsing or nasal lavage. Nasal irrigation involves the gentle cleansing of the nasal passages with a saline solution to remove allergens, irritants, and mucus. This technique aims to reduce nasal inflammation, alleviate congestion, and improve nasal airflow. Numerous studies have investigated the efficacy of nasal irrigation in AR management, with promising results. By clearing the nasal passages, nasal irrigation can provide symptom relief, improve nasal breathing, and potentially decrease the need for medication. It is worth exploring the benefits and limitations of nasal irrigation as a complementary treatment option for AR.

Pathophysiology and Classification

AR is an integral component of a systemic disease complex, wherein sensitized mast cells promptly release mediators upon allergen exposure, leading to both early and late phase reactions. The manifestation of typical allergic rhinitis (AR) symptoms, including sneezing, rhinorrhea, and nasal congestion, is intricately linked to the actions of various mediators. These mediators, which encompass cysteinyl leukotrienes, prostaglandins, thromboxane A₂, histamine, cytokines, and platelet activating factor (PAF), play a vital role in initiating and perpetuating the characteristic symptoms experienced by individuals with AR. During the early phase response, an immediate release of these mediators occurs, and it has been identified as the primary underlying cause of AR symptoms. Understanding the intricate interplay between these mediators and their involvement in the pathogenesis of AR is essential for developing effective management strategies for this condition. Notably, PAF contributes to nasal mucosa swelling by inducing interstitial edema and congestion within the nasal mucosal vessels, resulting in nasal mucosa congestion and plasma leakage. Furthermore, cysteinyl leukotrienes serve as vital mediators in the inflammatory process among AR patients. In addition to promoting nasal congestion and rhinorrhea, they act as chemoattractants for inflammatory cells, particularly eosinophils. Activated eosinophils release additional inflammatory mediators, including cysteinyl leukotrienes, exacerbating inflammation, congestion, and sleep disruption. It is worth mentioning that cysteinyl leukotrienes contribute to both the early and late phases of allergic reactions, promoting eosinophil adhesion and inhibiting eosinophil apoptosis.

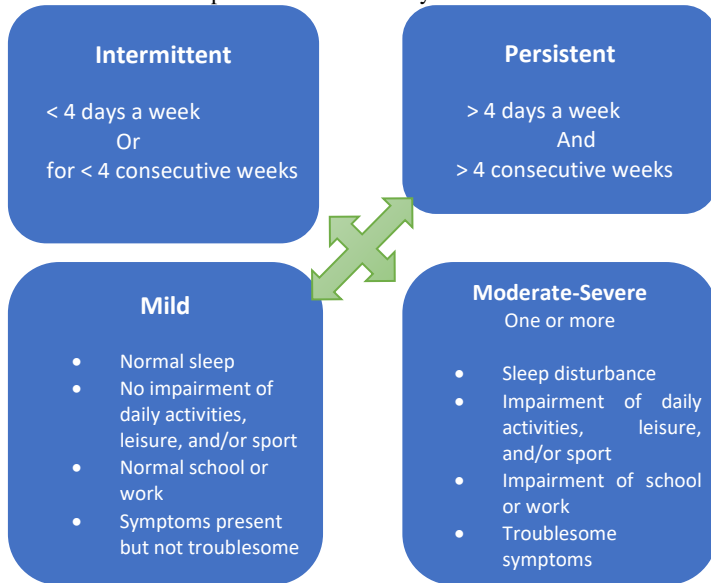


Figure 1 Classification of Allergic Rhinitis According to ARIA-WHO 2008 ¹

Allergic rhinitis (AR) can be assessed and categorized based on two primary dimensions, namely intermittent versus persistent and mild versus moderate-severe. This classification framework offers a comprehensive approach to understanding the impact of the disease and aids in making informed decisions regarding treatment strategies. When referring to intermittent AR, we are describing symptoms that manifest for fewer than four days per week or less than four weeks within a year. In contrast, persistent AR involves symptoms that endure for four or more days per week and beyond four weeks annually. Moving on to the mild versus moderate-severe classification, it considers the intensity and overall influence of symptoms on daily functioning and quality of life. Mild AR refers to symptoms that do not significantly hinder or impair regular activities, sleep patterns, or performance at school or work. Conversely, moderate-severe AR entails more pronounced symptoms that interfere with day-to-day functioning, disrupt sleep, and negatively impact productivity. By recognizing and understanding the severity of AR through these dimensions, healthcare professionals can better tailor treatment approaches to address the specific needs and challenges faced by individuals with allergic rhinitis. This classification system allows healthcare professionals to tailor treatment strategies according to the severity of the disease, ensuring optimal management and improved patient outcomes.¹ [Figure 1]

Management

Diagnosis of AR involves a combination of clinical history, physical examination, and diagnostic tests such as allergen skin testing or serum-specific IgE antibody testing. These methods help healthcare professionals identify AR and determine the specific allergens causing the allergic response. The ARIA-WHO 2008 guidelines provide comprehensive management strategies for AR, including environmental control, nasal irrigation, antihistamines, chromones, vasoconstrictors, intranasal steroids, allergen-specific immunotherapy, biologic agents, and surgical reduction of inferior turbinates in certain cases. The primary goal of treatment is to relieve symptoms and improve the quality of life.

Now, let's focus on the benefits of isotonic and hypertonic nasal irrigation enriched with manganese and copper salts, as well as the use of rupatadine. Nasal irrigation, a common technique for managing AR, involves rinsing the nasal passages with a solution

to remove allergens, irritants, and excess mucus. In this case, the irrigation solution contains manganese and copper salts, which are believed to offer additional therapeutic advantages. These minerals may possess anti-inflammatory properties, soothing nasal tissues and promoting nasal health. By incorporating these salts into nasal irrigation, individuals with AR may experience enhanced relief from their symptoms.

Another treatment option worth considering is rupatadine, a medication with dual affinity for histamine receptors and platelet-activating factor (PAF). Histamine is a key contributor to allergic reactions, causing symptoms such as sneezing, itching, and nasal congestion. Rupatadine effectively blocks histamine receptors, providing relief from these symptoms. Additionally, rupatadine's affinity for PAF receptors is advantageous, as PAF plays a role in inflammation and the allergic response. By targeting both histamine receptors and PAF, rupatadine offers a comprehensive approach to managing AR symptoms, potentially leading to improved outcomes for individuals with this condition.

In conclusion, the diagnosis of AR involves a thorough assessment and various tests, enabling healthcare professionals to determine appropriate treatment strategies. AR management encompasses a wide range of interventions, with the aim of relieving symptoms and improving the overall quality of life for individuals affected by the condition. Isotonic and hypertonic nasal irrigation enriched with manganese and copper salts, along with the use of rupatadine, present promising options for symptom relief and management in AR. These approaches target key pathways involved in allergic reactions, providing patients with potential benefits and a more comprehensive approach to their treatment.

Nasal Irrigation

ARIA guidelines and multiple international consensus statements recommend the inclusion of nasal irrigation as an adjuvant therapy for the management of allergic rhinitis (AR). Nasal irrigation operates through various mechanisms to provide therapeutic benefits. Firstly, it promotes mucociliary clearance, which refers to the process by which mucus and debris are effectively cleared from the nasal passages through the coordinated movement of cilia. This clearance mechanism helps reduce the contact time of air contaminants with the nasal mucosa, allowing for the cleansing of mucus, crusts, cell debris, and local concentrations of pro-inflammatory mediators. Additionally, nasal irrigation contributes to the humidification of the nasal mucosa, which is crucial for maintaining optimal nasal function and health.

In recent years, there has been growing interest in non-pharmacological treatment options for allergic rhinitis (AR), a common condition characterized by inflammation of the nasal passages due to an allergic reaction. Nasal saline irrigation, also known as nasal lavage or nasal douching, involves the rinsing of the nasal passages with a saline solution to remove allergens, irritants, and mucus.

The meta-analysis conducted by Wang et al. in 2020 aimed to provide a comprehensive evaluation of the efficacy of nasal saline irrigation in the treatment of AR. The researchers collected data from various randomized controlled trials (RCTs) and analyzed the outcomes to determine the overall effectiveness of this intervention.

The results of the meta-analysis indicated that nasal saline irrigation had a significant positive impact on relieving local AR symptoms in both adults and children. When comparing the outcomes of adults who used nasal saline irrigation alongside medication (such as steroid nasal spray or oral antihistamine) with those who solely relied on medication, the former group experienced more substantial improvements in symptom relief.

This suggests that combining nasal saline irrigation with medication may yield better results for adult patients.

Another important finding from the meta-analysis was the superiority of hypertonic saline irrigation over isotonic nasal saline irrigation in alleviating local AR symptoms. Hypertonic saline solutions have a higher salt concentration than the normal saline used in isotonic solutions. The increased salt concentration in hypertonic solutions can help reduce nasal congestion and improve mucociliary clearance, leading to better symptom relief.

The findings from this meta-analysis contribute valuable insights into the potential benefits and limitations of nasal saline irrigation as a treatment option for AR. The results suggest that nasal saline irrigation, when used in combination with medication, may offer enhanced symptom relief for adult patients. However, it is crucial to note that further research is needed to better understand the optimal application and potential variations in treatment responses across different age groups.

In conclusion, nasal saline irrigation has shown significant efficacy in improving local AR symptoms in both adults and children. While it may be more beneficial when used in conjunction with medication for adult patients, medication alone appears to be more effective in children. Additionally, hypertonic saline irrigation has demonstrated superior effectiveness over isotonic solutions. These findings highlight the potential of nasal saline irrigation as a complementary treatment for AR, but further research is necessary to establish its optimal use and effectiveness across different populations.

Significantly, the use of hypertonic seawater nasal solution has proven to be highly effective in alleviating nasal symptoms, particularly nasal obstruction, which often leads to sleep disturbances and a decreased quality of life. The airway epithelium, which acts as the primary defense line and physical barrier, also functions as a regulator of immune response by releasing interleukin-8 (IL-8). The proper functioning of CBF is crucial for MCC, as higher rates of CBF and MCC facilitate the removal of debris, chemicals, foreign particles, allergens, viruses, bacteria, and other potential irritants from the nasal epithelium.

Moreover, it is noteworthy to mention that the hypertonic seawater nasal solution enriched with manganese and copper salts has been found to be non-cytotoxic, as demonstrated by the absence of lactate dehydrogenase (LDH) release. Furthermore, it has exhibited no pro-inflammatory effects, as indicated by the absence of interleukin-8 (IL-8) secretion. These compelling findings provide strong evidence for the safety of this enriched solution when applied to the human nasal epithelium. Consequently, these findings lend further support to the potential of this solution as a viable therapeutic option for nasal conditions.

The advantages of utilizing the hypertonic seawater nasal solution enriched with manganese and copper salts go beyond mere symptom relief. Nasal obstruction, a prevalent symptom associated with various nasal conditions such as allergic rhinitis and sinusitis, can significantly disrupt an individual's sleep patterns and overall well-being. By effectively reducing nasal obstruction, this enriched solution holds the promise of improving sleep quality and enhancing the overall quality of life for individuals suffering from nasal-related conditions. Restoring proper nasal airflow can alleviate sleep disturbances and promote a more restful and rejuvenating sleep, ultimately contributing to a better sense of well-being.

In addition to its role in alleviating nasal symptoms and improving sleep quality, the hypertonic seawater nasal solution enriched with manganese and copper salts showcases intriguing antimicrobial properties. The observed bactericidal effects against *Staphylococcus aureus* and *Pseudomonas aeruginosa* highlight the potential of this solution in combating bacterial infections that may contribute to nasal congestion and inflammation. Bacterial infections can exacerbate nasal symptoms and prolong the duration

of the condition. By targeting and eliminating these harmful bacteria, the enriched solution may not only provide immediate relief but also contribute to the resolution of the underlying infection, promoting long-term nasal health.

The antimicrobial properties of the hypertonic seawater nasal solution enriched with manganese and copper salts are particularly significant in the context of nasal conditions where bacterial infections frequently coexist with allergic inflammation. In such cases, the combined approach of alleviating nasal symptoms and targeting bacteria can offer comprehensive relief and expedite the recovery process. This dual action may result in shorter symptom duration, reduced reliance on antibiotics, and overall improved outcomes for individuals suffering from nasal-related conditions.

As we delve deeper into the potential applications of the hypertonic seawater nasal solution enriched with manganese and copper salts, it becomes evident that this solution holds promise as a multifaceted therapeutic option. Its safety profile, coupled with its ability to alleviate nasal obstruction, exhibit antimicrobial effects, and improve sleep quality, positions it as a compelling choice for individuals seeking effective management of their nasal conditions. Nonetheless, further research is warranted to explore the optimal formulation, dosage, and treatment duration of this enriched solution, as well as its potential in different patient populations.

Its ability to alleviate nasal obstruction, enhance sleep quality, and exhibit antimicrobial effects against common pathogens further solidifies its potential as a therapeutic option for nasal-related conditions. By addressing multiple aspects of nasal health, this enriched solution offers a comprehensive approach to symptom management and improved quality of life for individuals affected by nasal conditions. Continued research and exploration of its therapeutic potential will undoubtedly shed more light on its optimal use and broaden its application in clinical practice.

Furthermore, the enhanced performance of CBF and MCC seen with the enriched solution suggests that it may offer improved clearance of pathogens, allergens, and irritants from the nasal epithelium. By enhancing the natural defense mechanisms of the nasal passages, this solution has the potential to provide a more comprehensive and effective treatment approach.

Furthermore, the enriched solution's remarkable safety profile, as evidenced by the absence of cytotoxic effects and pro-inflammatory responses, further enhances its desirability as a safe and well-tolerated treatment option. The absence of lactate dehydrogenase (LDH) release, indicating the absence of cellular damage, and the absence of interleukin-8 (IL-8) secretion, indicating the absence of an inflammatory reaction, provide reassurance regarding the potential adverse effects on the delicate nasal epithelium.

These findings highlight the significant advantage of the enriched solution, as its use does not pose a risk of causing harm or triggering unwanted inflammatory responses in the nasal tissue. This safety profile is particularly crucial when considering the long-term use of nasal treatments, as repeated exposure to potentially harmful substances can have detrimental effects on the nasal epithelium and overall nasal health. By demonstrating its lack of cytotoxic and pro-inflammatory properties, the enriched solution emerges as a reliable and well-tolerated therapeutic option for individuals seeking relief from nasal conditions.

Additionally, the absence of cytotoxicity and pro-inflammatory effects observed with the enriched solution provides reassurance regarding its potential for long-term use. Chronic nasal conditions such as allergic rhinitis and sinusitis often require ongoing management to alleviate symptoms and maintain nasal health. Consequently, having a treatment option that not only effectively addresses symptoms but also ensures safety over extended periods is paramount. The enriched solution's ability to maintain its safety profile even with prolonged use makes it an

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attractive choice for individuals who require long-term management of their nasal conditions.

Moreover, the absence of cytotoxic effects and pro-inflammatory responses with the enriched solution highlights its potential as a well-tolerated treatment option for a wide range of individuals. Nasal conditions can affect people of all ages, from children to older adults. Therefore, it is crucial to have treatment options that are safe and suitable for various age groups. The enriched solution's demonstrated safety, as indicated by its lack of cytotoxicity and pro-inflammatory effects, positions it as a versatile choice that can be utilized across different age brackets without compromising safety or effectiveness.

Furthermore, the absence of cytotoxicity and pro-inflammatory reactions associated with the enriched solution suggests that it may have a favorable side effect profile compared to other nasal treatments. Many conventional medications used for nasal conditions may have undesirable side effects, such as drowsiness, dryness, or rebound congestion. However, the enriched solution's ability to avoid cytotoxicity and pro-inflammatory responses indicates a reduced likelihood of experiencing such adverse effects. This aspect not only enhances the overall tolerability of the enriched solution but also increases patient compliance and satisfaction with the treatment.

In conclusion, the absence of cytotoxic effects and pro-inflammatory responses observed with the enriched solution reinforces its appeal as a safe and well-tolerated treatment option for nasal conditions. The lack of cytotoxicity, as indicated by the absence of LDH release, and the absence of pro-inflammatory effects, as indicated by the absence of IL-8 secretion, provide reassurance regarding the solution's safety profile and its potential for long-term use. By minimizing the risk of adverse effects and ensuring tolerability across different age groups, the enriched solution emerges as a reliable therapeutic choice that can effectively address nasal symptoms without compromising patient well-being.

In addition to these findings, Enrico et al. conducted a study in 2010 involving 672 children with moderate and severe upper respiratory tract obstruction (URTO) caused by adenoid or adenotonsillar hypertrophy. The study investigated the use of isotonic seawater saline solution enriched with copper as a treatment approach. The results demonstrated significant improvement in disease severity, quality of life, and a reduced need for surgical removal of adenoid or adenotonsillar hypertrophy in the treated children⁹

Antihistamine

Histamine plays a pivotal role in the manifestation of almost all symptoms associated with allergic rhinitis (AR). To counteract the effects of histamine and improve the overall quality of life, oral antihistamines have proven to be effective. Current treatment guidelines for AR emphasize the use of second-generation antihistamines due to their favorable safety and efficacy profiles in both adults and children. ARIA guidelines also endorse second-generation antihistamines as the recommended treatment option for AR, irrespective of the severity and duration of symptoms.

It is important to acknowledge that the severity and duration of symptoms associated with allergic rhinitis (AR) can have a significant impact on an individual's quality of life. These symptoms can lead to sleep disturbances, reduced productivity, and hindered school performance, highlighting the need for effective treatment options.

In addition to histamine, another inflammatory mediator called platelet-activating factor (PAF) plays a role in the allergic response. PAF influences various components of the immune response, including platelet aggregation, mast cell degranulation, macrophage and neutrophil activation, and eosinophil chemotaxis

and activation. Understanding the involvement of PAF in the allergic process has led researchers to explore novel treatment approaches that target both histamine and PAF pathways.

One such treatment option that has gained attention is rupatadine, a second-generation antihistamine. Rupatadine has emerged as an effective therapeutic choice for the management of AR in both adults and children. What sets rupatadine apart is its unique characteristic of having dual affinity for both histamine receptors and PAF receptors. This dual affinity allows rupatadine to provide enhanced control over AR symptoms by targeting multiple inflammatory pathways simultaneously.

By blocking histamine receptors, rupatadine effectively reduces the histamine-mediated allergic response, alleviating symptoms such as sneezing, itching, and nasal congestion. Simultaneously, rupatadine's interaction with PAF receptors helps modulate the activity of PAF, leading to a further reduction in inflammation and associated symptoms. This dual mechanism of action allows rupatadine to offer comprehensive symptom relief and improve the overall management of AR.

The effectiveness of rupatadine in treating AR has been demonstrated in various clinical studies. These studies have shown that rupatadine not only provides significant relief from nasal and ocular symptoms but also improves the overall quality of life for individuals with AR. Its ability to target both histamine and PAF pathways makes rupatadine a valuable option for individuals who may not achieve optimal symptom control with traditional antihistamines alone.

Furthermore, rupatadine has been found to have a favorable safety profile, with minimal adverse effects reported. Common side effects associated with rupatadine are generally mild and include drowsiness, headache, and dry mouth, which are comparable to other antihistamines. Its favorable safety profile further supports its use as a well-tolerated treatment option for AR.

In conclusion, the severity and duration of AR symptoms can significantly impact an individual's quality of life, making effective treatment options crucial. Rupatadine, a second-generation antihistamine with dual affinity for both histamine and PAF receptors, has emerged as a promising therapeutic choice for AR. By targeting multiple inflammatory pathways, rupatadine provides comprehensive symptom relief and improves overall management. Its favorable safety profile further enhances its appeal as a well-tolerated treatment option. As further research continues, rupatadine's role in the management of AR is likely to become even more prominent, offering improved outcomes for individuals affected by this condition.

While histamine is primarily associated with sneezing, rhinorrhea, and nasal itch, PAF plays a significant role in inducing nasal congestion by increasing vascular permeability and mucus secretion. Rupatadine's unique anti-platelet-activating factor effect sets it apart from other antihistamines. Moreover, rupatadine exhibits a broad range of anti-inflammatory and anti-allergic properties, effectively addressing both the early and late phases of the allergic inflammatory response.

Valero et al. conducted a prospective, multicenter, observational, longitudinal study to evaluate the response to rupatadine treatment in patients with AR. The study aimed to assess changes in nasal symptoms, disease severity based on ARIA classification, and health-related quality of life (HRQoL) measured by the EsQ-15 global score. The results indicated significant improvements across all aspects evaluated, including the global score, symptoms, daily activities, sleep disturbance, and psychological impact. These improvements were statistically significant ($p < 0.0001$) and were observed after 4 weeks of rupatadine treatment.

One notable advantage of rupatadine is its fast onset of action and rapid absorption, leading to a significant effect within 2 hours after consumption. The effect peaks at around 6 hours and

remains significant even after 72 hours. This prolonged efficacy allows for once-daily administration, ensuring convenience and adherence to the treatment regimen]. Furthermore, rupatadine demonstrates a favorable safety profile for long-term use and has been shown to improve the quality of life in both adults and children undergoing long-term treatment for AR.^{11,12}

Conclusion

Nasal irrigation is recommended as an additional treatment for allergic rhinitis (AR) and has shown effectiveness for both adults and children. In children, hypertonic nasal solution has been found to be more effective than isotonic nasal solution. Currently, there is a hypertonic nasal solution that contains manganese and copper, which has the potential to provide better therapeutic benefits by enhancing ciliary beat frequency (CBF), mucociliary clearance (MCC), and the ability to kill bacteria. Moreover, this enriched hypertonic nasal solution has been observed to reduce the release of IL-8.

Rupatadine is a safe long-term treatment option that can enhance the quality of life for both adults and children with AR. It has a dual action by targeting both histamine receptors and PAF receptors, leading to better control of AR symptom

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