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Practical guideline for the management of allergic rhinitis in Japan 2024

Mitsuhiro Okano [a,*], Kimihiro Okubo [b], Minoru Gotoh [b], Mikiya Asako [c], Nobuo Ohta [d], Atsushi Kamijo [e], Kayoko Kawashima [f], Masafumi Sakashita [g], Daiju Sakurai [h], Tetsuya Terada [i], Yuji Nakamaru [j], Takechiyo Yamada [k], Shuji Yonekura [l], Aiko Oka [a], Marie Yamada [a], Tomokazu Yoshizaki [m]

[a] Department of Otorhinolaryngology, International University of Health and Welfare School of Medicine, Narita, Japan
[b] Department of Otorhinolaryngology, Nippon Medical School, Tokyo, Japan
[c] Department of Otolaryngology, Head and Neck Surgery, Kansai Medical University, Osaka, Japan
[d] Department of Otorhinolaryngology, Tohoku Medical and Pharmaceutical University, Sendai, Japan
[e] Kamijo Allergy & ENT Clinic, Nagano, Japan
[f] Department of Otorhinolaryngology, Head and Neck Surgery, Osaka Habikino Medical Center, Habikino, Japan
[g] Division of Otorhinolaryngology Head and Neck Surgery, Department of Sensory and Locomotor Medicine, University of Fukui, Fukui, Japan
[h] Department of Otorhinolaryngology, Head and Neck Surgery, Interdisciplinary Graduate School of Medicine, University of Yamanashi, Yamanashi, Japan
[i] Department of Otorhinolaryngology-Head and Neck Surgery, Osaka Medical and Pharmaceutical University, Osaka, Japan
[j] Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan
[k] Department of Otorhinolaryngology, Head and Neck Surgery, Akita University, Graduate School of Medicine, Akita, Japan
[l] Department of Otolaryngology Head and Neck Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan
[m] Department of Otolaryngology - Head and Neck Surgery, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan

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ABSTRACT

The Practical Guideline for the Management of Allergic Rhinitis in Japan was first published in 1993. After the COVID-19 pandemic, the current 10th edition was published in 2024. The most recent collection of evidence from the literature, such as the sustained post-treatment effect of sublingual immunotherapy on Japanese cedar pollinosis, was added to the revised guideline, which incorporates evidence-based medicine. In this revised guideline, a diagram illustrating the pathogenesis of allergic rhinitis and the mechanisms of action of various pharmacological treatments has been added. Also included is a diagram that shows the mechanism of action of allergen immunotherapy and a more detailed description of the oral allergy syndrome. The clinical question and answer section was also revised along with the introduction of new questions, such as: Does anti-IgE antibody treatment effectively reduce the symptoms of severe seasonal allergic rhinitis? Also updated was the evidence-based step-by-step strategy for treatment.

1. Definition and classification

1.1. Definition and terminology

Allergic rhinitis constitutes a type I allergic affliction of the nasal mucosa, which is primarily characterized by paroxysmal and recurrent sneezing, watery nasal discharge, and nasal congestion.

A novel disease concept known as local allergic rhinitis (LAR) has been proposed, wherein localized production of IgE in the nasal mucosa triggers a local reaction, despite negative results for skin tests and serum-specific IgE tests. It has been observed that some LAR patients may later develop allergic rhinitis or bronchial asthma, underscoring the importance of early therapeutic intervention [1].

1.2. Classification of rhinitis

Rhinitis broadly refers to inflammation of the nasal mucosa [2].

1. Infectious Rhinitis: Viral, bacterial, and other infectious causes classified as acute (commonly known as a cold) and chronic rhinitis based on the symptom duration.

* Corresponding author.
E-mail address: mokano@iuhw.ac.jp (M. Okano).

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2. Allergic Rhinitis: A non-infectious hypersensitive form categorized as perennial or seasonal, which is characterized by sneezing, rhinorrhea, nasal obstruction, or fullness depending on the seasonal occurrence. House dust mites commonly trigger perennial cases, while pollinosis predominates in seasonal instances.
3. Non-infectious, Non-allergic Rhinitis: Encompasses various forms:
   a) Vasomotor Rhinitis: Often attributed to autonomic nerve abnormalities in the nasal mucosa, though internationally it is termed idiopathic rhinitis due to its unknown cause.
   b) Eosinophilic Rhinitis (Non-Allergic Rhinitis with Eosinophilia Syndrome: NARES): Characterized by increased eosinophils in nasal secretions despite negative allergy tests, with potential links to chronic rhinosinusitis with nasal polyps.
   c) Drug-induced Rhinitis (Rhinitis Medicamentosa): Resulting from prolonged use of sympatholytic antihypertensives, vasodilator antihypertensives, bronchodilators, antidepressants, NSAIDs, and oral contraceptives. However, the most common cause is the overuse and overdose of intranasal vasoconstrictors for nasal blockage.
   d) Occupational Rhinitis: Developed and exacerbated by workplace inhalation of substances. Occupational rhinitis can be divided into allergic and non-allergic rhinitis. The non-allergic occupational rhinitis is caused by the exposure to substances such as chemicals acting as an irritant.
   e) Senile Rhinitis: Nasal discharge prevalent in the elderly due to mucosal atrophy.
   f) Gustatory Rhinitis: Triggered by consumption of spicy foods, stimulating increased nasal secretions via nervous reflex.
   g) Atrophic Rhinitis: Now rare, characterized by mucosal atrophy leading to foul-smelling nasal secretions, and specific granulomatous rhinitis associated with tuberculosis, syphilis, sarcoidosis, or granulomatosis with polyangiitis.
   h) Pregnancy Rhinitis: Onset occurring from mid-pregnancy, likely due to hormonal influences on nasal mucosa blood vessels and autonomic nerve receptors.

2. Epidemiology

The prevalence of allergic rhinitis has been on the increase in Japan since the late 1960s. The initial increase was perennial allergic rhinitis caused by house dust mites; however, seasonal allergic rhinitis has increased markedly in urban areas, with Japanese cedar pollinosis (JC pollinosis) also becoming a social problem due to its high prevalence [3]. Although the exact cause of the increase in allergic rhinitis is still unclear, it is known that one of the important causes is that there is increased antigen exposure.

Results from studies that have measured house dust mite allergens in bedrooms underscore Japan's heightened risk, with house dust mite antigen (Der 1) levels at 14.9 μg/g of dust, which is approximately 10 times higher than that found in the United States and 25 times higher than that in Europe [4]. Research indicates significant increases in sensitization and rhinitis risk when the Der 1 levels exceed 2 μg/g of dust, along with elevated risks of bronchial asthma when the levels surpass 10 μg/g of dust. This issue is even more pronounced in other Asian countries.

The escalation in JC pollen allergy can largely be attributed to increased pollen dispersion. Initially, pollinosis cases associated with native Japanese plants were reported by Saito et al. in the Nikko region of Tochigi Prefecture in 1964 [3]. While annual variations occur, there has been a significant increase in pollen dispersion since around 1995.

While Okuda's 2001 survey on cedar pollinosis is well known as a nationwide epidemiological survey of allergic rhinitis, another nationwide survey is the epidemiological survey of otorhinolaryngologists and their families that has tracked significant increases in allergic rhinitis and pollinosis over two decades [5]. Accumulated data have shown that allergic rhinitis increased from 29.8 % to 49.2 %, and pollinosis increased from 19.6 % to 42.5 %. Notably, perennial allergic rhinitis rose to 18.7 %, JC pollinosis to 38.8 %, and non-JC pollinosis to 25.1 % over the same period. Age-specific prevalence rates further reveal sharp increases in younger age groups, which underscore a trend of earlier disease onset.

Accurate sensitization and prevalence rates can be determined through serum-specific IgE measurements and questionnaire surveys within specific populations. In an initial cross-sectional study at Fukui University Hospital of health checkups in 2006, which involved 1540 individuals aged 20–49 years old, the study reported on the sensitization and prevalence rates. A subsequent 2016 study enrolled 1472 individuals aged 20–59 years old, and revealed updated results [6,7]. Notably, in a study that was conducted primarily among younger adults, the prevalence of JC pollinosis increased by 8.1 % to 43.3 % in subjects in their 20 s, and by 6.9 % to 43.7 % in subjects who were in their 30 s. Tracking changes in the remission rates over a 10-year period in a cohort group (334 participants, age from 20 s to 40 s), found that 12.7 % of the JC pollinosis cases saw their symptoms disappear or there was a restoration of their sensitization. Conversely, in allergic rhinitis for house dust mites, the remission rate was higher at 36.2 %.

There have been several reports using the International Study of Asthma and Allergies in Childhood (ISSAC) questionnaire. Sasaki et al. conducted a survey of approximately 130,000 elementary school children in 47 prefectures in 2005 and 2015, using the ISSAC questionnaire [8]. Allergic rhinitis increased from 14.8 % to 18.7 % in elementary school students, and from 20.5 % to 26.7 % in junior high school students. In contrast, wheezing and eczema remained unchanged. Regarding high school students, Tokunaga et al. conducted a survey of 95 % of high school students (about 20,000 students) in Fukui Prefecture in December 2012 [9], and found that the number of high school students who actually exhibited allergic rhinitis symptoms was 19.2 %.

Yonekura et al. conducted a 10-year cohort study of approximately 700 residents in their 40 s to 70 s in Chiba Prefecture and found that although sensitization and prevalence to house dust mites decreased with age, the IgE production to JC pollen was affected by the amount of pollen in the area [10]. Furthermore, even though IgE production to JC pollen was affected by the amount of pollen in the air, an increase in the sensitization and prevalence that was observed in the years found to have high pollen counts. In this middle-aged and elderly group, 19.2 % of the patients had remission of cedar pollinosis after 10 years of follow-up, while 3.4 % had new onset of the disease.

3. Mechanisms

Genetic predisposition plays a significant role in allergic rhinitis. Among the Japanese population, genetic variations associated with IgE production, such as CD14, IL-33, and TYRO3, are known to contribute to susceptibility [11].

Antigens trigger IgE production in the nasal mucosa and associated lymphoid tissues upon penetration. Upon inhalation of an antigen in a sensitized individual, the antigen-IgE reaction triggers the release of various chemical mediators, predominantly histamine and leukotrienes (LTs), from mast cells. Sensory nerve endings and blood vessels in the nasal mucosa respond to these mediators, resulting in symptoms like sneezing, nasal discharge, and mucosal swelling, collectively known as the early phase reaction.

Moreover, mucosal swelling occurs due to the actions of secondary inflammatory cells, particularly LTs and type 2 cytokines produced by eosinophils, Th2 cells and group 2 innate lymphoid cells (ILC2s), marking the late phase reaction [12,13]. This phase typically manifests 6 to 10 h post-antigen exposure. In natural settings, continual antigen exposure results in a complex interplay of early and late phase reactions, which contribute to the experienced varied nasal symptoms.

1. Sneezing

Among various chemical mediators, only histamine induces a significant sneeze reflex. The sneezing observed during antigen induction primarily stems from a respiratory reflex triggered by histamine stimulation of the sensory nerve endings. The sensory stimulation effect is thought to be amplified by nasal mucosa hypersensitivity where minimal persistent inflammation (MPI) and priming effects are involved. MPI involves the induction of allergic inflammation, including eosinophil infiltration, in the nasal mucosa even with antigen exposure that does not cause overt symptoms [14]. The priming effect refers to the reduced antigen exposure threshold required for symptom manifestation, which is 10–100 times, once the symptoms have developed.

2. Rhinorrhea

Nasal discharge primarily consists of secretions from nasal glands, which are stimulated by histamine acting on sensory nerve endings. This stimulation, amplified by nasal mucosal hypersensitivity, is transmitted to the central nervous system, leading to the release of acetylcholine through a parasympathetic reflex. Chemical mediators like histamine, LTs, and platelet-activating factor (PAF), directly act on nasal mucosal blood vessels, causing plasma leakage, which forms part of the nasal discharge. However, the albumin concentration accounts for only 4 to 15 % of the total nasal discharge, which suggests that most rhinorrhea arises from the nasal glands.

3. Nasal Obstruction

The initial swelling of the nasal mucosa during antigen exposure as an early phase reaction is predominantly caused by histamine, LTs, PAF, prostaglandin D_2 (PGD_2), and other chemical mediators that directly affect the nasal mucosal vasculature, which leads to interstitial edema. During the late phase, nasal mucosal swelling is attributed to inflammatory cells that infiltrate the nasal mucosa, especially LTs derived from eosinophils, thromboxane A_2 (TXA_2), and PAF. IgE-mast cell interactions lead to basophil, neutrophil, eosinophil, and lymphocyte infiltration, which is triggered by chemotactic factors.

4. Examination and diagnosis

4.1. Examination

Allergy assessments involve patient interviews, nasal examinations (rhinoscopy, endoscopy), eosinophil staining of nasal secretions, nasal sinus X-rays, blood tests including eosinophil counts, and quantification of total serum IgE levels. Potential causative allergens could be identified based on skin tests, allergen-specific IgE antibody measurements, or nasal provocation tests.

Skin tests are cost-effective and allow patients to promptly ascertain results. Intradermal, scratch, and prick tests are available, with prick tests gaining popularity due to their safety, painlessness, and having a strong correlation with the clinical symptoms. Prior to testing, medications that might influence the results should be discontinued [15,16].

Serum-specific IgE antibody measurements offer advantages such as the simplicity of requesting post-blood sampling, feasibility of use irrespective of the skin condition, and the lack of any requirement for discontinuing currently prescribed medications. Nevertheless, these tests are relatively expensive, and the results typically require several days with the exception for the rapid test kits. Moreover, this test tends to exhibit a slightly lower sensitivity and specificity as compared to that seen for skin tests. In cases of elevated total IgE levels, a positive specific IgE result may not always hold clinical significance. Although component-resolved diagnostics (CRDs) that utilize allergen components for specific IgE testing are now feasible, the coverage by medical insurance is limited to only a few allergens including food allergens in Japan. Identification of the causative antigen is crucial, and there is a need to be able to discern between perennial and seasonal conditions through the use of medical interviews. In addition, for seasonal cases, knowledge of local pollen flora and dispersal periods is essential [17].

The nasal provocation test holds clinical significance as it evaluates nasal mucosal reactions in allergic rhinitis. It is also pivotal for diagnosing LAR. Unfortunately, provocation disks or devices are currently not available for sale in Japan.

4.2. Diagnosis

When typical nasal mucosal findings and symptoms indicative of allergic rhinitis (sneezing, watery rhinorrhea, and/or nasal blockade) are present, it is possible to establish a clinical diagnosis of allergic rhinitis. However, in instances where the clinical diagnosis is challenging, insufficient response to medical treatment is observed, or the patient is being considered for allergen immunotherapy, antigen identification tests are warranted. A definitive diagnosis is made based on typical nasal symptoms (sneezing and nasal itch, watery rhinorrhea and nasal blockade) in conjunction with two or more of the following tests; eosinophil staining of nasal secretions, skin test (or specific IgE assay), and nasal provocation test.

It is imperative that patient examinations are able to initially differentiate allergic rhinitis from rhinitis caused by other factors. Early stages of a cold that present with sneezing and nasal discharge pose challenges with regard to differentiation. During a cold, nasal discharge typically becomes mucopurulent within a few days and resolves within 1 to 2 weeks. The nasal mucosa appears red, and is accompanied by general fatigue, muscle pain, fever, sore throat, cough, and phlegm. Currently, one of the most significant issues is being able to distinguish between the novel coronavirus (SARS-CoV-2) infection and pollinosis. Although nasal itching and eye symptoms are characteristic of pollinosis, differentiation is not always straightforward. Therefore, it is advisable to implement adequate infection control measures and conduct antigen and PCR tests for COVID-19, if necessary. As acute rhinosinusitis and chronic non-eosinophilic rhinosinusitis do not present with sneezing, nasal discharge with viscous or mucopurulent neutrophil increase and edematous middle turbinates are the observable symptoms. Differential diagnosis can be facilitated by X-ray and CT images. Furthermore, diagnosis should not rely solely on symptoms such as nasal discharge and congestion without confirming intranasal findings.

- Key points to consider in the diagnosis
  1. In young children, nasal congestion often results from adenoid hypertrophy or chronic rhinosinusitis.
  2. During periods spent outside throughout the pollen season, pollinosis shows normal nasal mucosa findings and negative nasal eosinophil tests.
  3. Positive skin test results and serum specific IgE antibody measurements do not necessarily implicate the antigen as the cause, thereby necessitating a comprehensive diagnosis.
  4. Clinical diagnosis of allergic rhinitis is feasible in symptomatic individuals with typical nasal mucosal findings. In cases of an inadequate response to medication, allergy diagnosis or antigen identification tests are warranted.
  5. Discrepancies between medical history and results of skin tests or serum specific IgE tests may necessitate performing both tests for an accurate diagnosis.
  6. In cases where skin tests, nasal provocation tests, and serum specific IgE tests yield negative results, retesting should be considered, in conjunction with factoring in antigen selection and test sensitivity.
  7. Regional variations exist in positive antigens, which necessitate an awareness of local specificities [18]. Allergies to pets (particularly cats and dogs) and insects (particularly moths) have recently become more prevalent.
  8. Rhinitis with nonspecific hypersensitivity that requires differentiation includes eosinophilic rhinitis, vasomotor rhinitis, and local

allergic rhinitis (LAR). Eosinophilic rhinitis presents with increased eosinophils in nasal secretions despite negative skin tests and serum specific IgE tests. Similarly, LAR features negative skin tests and serum specific IgE tests, but positive nasal provocation tests and detection of antigen-specific IgE in nasal secretions [1,19,20]. However, at the present time, LAR prevalence in Japan remains uncertain [21]. Vasomotor rhinitis, which is also known as idiopathic rhinitis internationally, is characterized by negative nasal eosinophil tests, skin tests, and serum specific IgE tests, and can be attributed to autonomic nervous system imbalance.

4.3. Classification of allergic rhinitis

The classification based on the causative antigen, onset time, disease type, and severity of symptoms is outlined as follows:

1. Route of entry of causative allergen

Allergens enter through inhalation, food (oral ingestion), contact (skin contact), and hematogenous (intravenous) routes. Inhalation is most common, with pollen, house dust mites, insects, animal dander, and fungi being predominant allergens. Food antigens and hematogenous injections, though not commonly associated with nasal symptoms, can still induce mild symptoms.

2. Predilection time

Allergic rhinitis is classified into seasonal and perennial. Perennial allergic rhinitis can be caused by various pollens.

3. Disease types

Sneezing and rhinorrhea are closely correlated with a shared underlying mechanism, and thus are categorized as the “sneezing/rhinorrhea type”. When nasal congestion predominates over other symptoms, it is classified as the “nasal blockage type”. Symptomatology that combines both types equally is termed the “combined type”.

4. Severity

Symptom severity is graded based on the frequency of sneezing attacks/nasal discharge frequency, and duration of mouth breathing due to nasal congestion. Scores range from 0 to 4 points, with categories ranging from mild to most severe [3,22].

4.4. Assessment based on QOL

Allergic rhinitis is manageable when treated, but resists cure. Thus, treatments are aimed at improving the quality of life (QOL). A QOL questionnaire for Japanese patients with allergic rhinitis was developed in 2002 [23].

5. Treatment

5.1. Treatment goals

The goal of treatment is to achieve the following results for the patient:

1. Achieving an absence of symptoms or very mild symptoms, thereby allowing for an uninterrupted daily routine without the need for medication.
2. Maintaining stable and persistent symptoms, with only rare and brief acute exacerbations.
3. Avoidance of antigen-induced reactions altogether or the experiencing of only mild reactions.

Although it can be difficult to precisely define symptom stability, for perennial allergies, stability can be inferred if the symptoms only worsen for <2 weeks several times a year. Negative results in nasal challenge tests are specific indicators of remission.

5.2. Treatment options

Treatment options for allergic rhinitis encompass patient education, antigen elimination and avoidance, pharmacotherapy, allergen immunotherapy, and surgery.

Antigen elimination and avoidance are critical for empowering patients to learn how to manage their condition. However, when complete elimination is impractical, efforts should focus on minimizing exposure.

Recent advancements in treatment include the introduction of new medications targeting allergic rhinitis. However, current drug therapies primarily address symptoms or prevent acute attacks, and lack a definitive curative effect. Discontinuation often results in symptom recurrence shortly thereafter. Unlike pediatric asthma, prolonged administration of medications without clear antigen testing is not advisable while awaiting remission, particularly in cases of pollinosis.

Allergen immunotherapy remains the only approach capable of achieving clinical remission or long-term cure. The effects of allergen immunotherapy last for a long time after the completion of treatment. In Japan, subcutaneous immunotherapy (SCIT) is not widely used due to difficulties in obtaining antigens and concerns about safety, including side effects. In contrast, sublingual immunotherapy (SLIT) allows for home administration under careful supervision and has been shown to be highly effective, although not without side effects.

Surgical intervention is indicated when nasal mucosal changes are irreversible despite continued pharmacologic therapy. Although palliation is achieved, recurrence is expected and thus, ongoing allergy management is necessary.

5.3. Communicating with patients

Allergic rhinitis is a chronic condition that requires long-term management. Symptoms of allergic rhinitis might not always prompt immediate consultation, and in some cases, patients may seek medical help only after symptoms become severe. Establishing empathy and building a collaborative partnership with the patient is crucial.

Encourage patients to understand the treatment plan and collaboratively set treatment goals from the outset. Patient education plays a pivotal role in reinforcing treatment adherence during outpatient visits, thereby enabling long-term management. To enhance adherence, encourage patients to engage in activities such as maintaining a nasal allergy diary, regular hospital visits, lifestyle improvements, and self-identification and avoidance of allergens [24].

The use of a questionnaire during consultations aids in comprehensively assessing the patient’s condition. Recently, a mobile application has emerged as a next-generation Allergic Rhinitis and its Impact on Asthma (ARIA) care pathway for allergic rhinitis and bronchial asthma, and which has proved to be valuable in the monitoring of the patient conditions [2]. Healthcare professionals should acquire effective communication skills to manage diverse patient situations. Patient education involving various healthcare professionals beyond physicians, including nurses and pharmacists is effective [2].

5.4. Antigen elimination and avoidance

Remission rates for allergic rhinitis, including pollinosis, are significantly lower than for bronchial asthma, with JC pollinosis having a remission rate of approximately between 10 and 20 %. Effective elimination and avoidance of antigens are crucial strategies in the

management of allergic rhinitis.

To mitigate exposure, it is essential to eliminate allergens through meticulous cleaning and washing of bedding. In Japan, where high temperatures and humidity prevail, employing dehumidifiers to maintain indoor humidity levels is effective in reducing dust mite populations. However, research on predicting the therapeutic outcomes of these antigen avoidance measures remains limited.

Controlling cedar pollen dispersion poses a significant challenge, and complete avoidance of exposure is nearly impossible for patients. However, it is important to avoid exposure to pollen and to remove it outdoors. The verification of the prediction of the therapeutic effect by the avoidance of the antigen is still not sufficient.

For pet allergies, the first recommendation is to discontinue keeping pets that trigger allergic reactions. When dogs and cats are kept indoors, it is necessary to rigorously maintain cleanliness and consider spatial separation within the living areas [25].

5.5. Pharmacotherapy

Therapeutic drugs for allergic rhinitis fall into several categories: chemical mediator release inhibitors, receptor antagonists, Th2 cytokine inhibitors, corticosteroids, biological agents, and others. The onset mechanisms of allergic rhinitis and the mode of actions of each drug are illustrated in Fig. 1.

1) Chemical Mediator Release Inhibitor (Mast Cell Stabilizer)

Since the introduction of disodium cromoglycate (DSCG, cromolyn sodium) in 1967 as a drug that inhibits the release of chemical mediators from mast cells, various types of topical (eye drops, nasal sprays) and oral chemical mediator release inhibitors have been developed. Its efficacy in the inhibition of the release of chemical mediators involved in allergic rhinitis, particularly from mucosal mast cells, which is crucial in its development, is limited. Other chemical mediator release inhibitors, such as tranilast, amlexanox, and pemirolast potassium, were developed in Japan and are available on the market. Because these medicines do not have side effects like sleepiness or dry mouth, they are easy to use for the initial treatment of pollinosis.

Caution is necessary as oral formulations may lead to gastrointestinal disorders and liver dysfunction, particularly with tranilast, which can occasionally cause liver dysfunction and symptoms resembling cystitis.

2) Chemical Mediator Receptor Antagonist

Chemical mediator receptor antagonists act at the target tissue, which is the final stage of the allergic rhinitis onset mechanism. Besides histamine, other chemical mediators implicated in allergies include LTs, PGs, TXA_2, PAF, and kinins. The specific roles of these mediators in allergic pathology, except for histamine, leukotrienes, and PAF, have not been fully elucidated.

a) Histamine H1 Receptor Antagonist

Histamine H1 receptor antagonists, commonly known as antihistamines, have been used to treat allergic rhinitis since the 1940s. Early developments included first-generation antihistamines such as diphenhydramine and promethazine hydrochloride. These drugs were fast-acting but had short-lived effects, causing sedation, cognitive

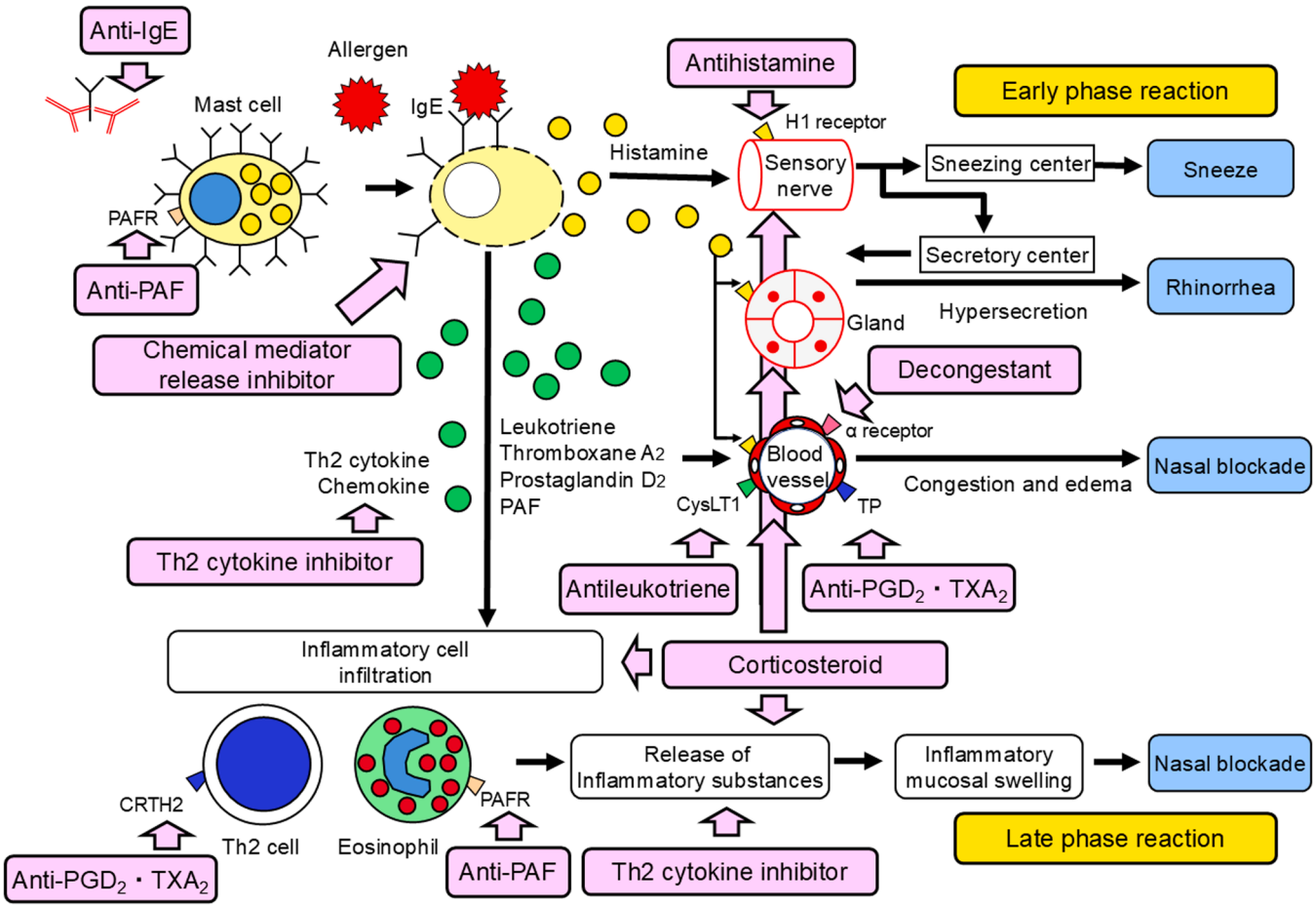

Fig. 1. The mechanism of action of pharmacotherapy for allergic rhinitis.

impairment, drowsiness due to central nervous system depression, and anticholinergic effects leading to dry mouth, urinary retention, and constipation.

Subsequently, mequitazine, epinastine hydrochloride, ebastine, cetirizine hydrochloride, bepotastine besilate, fexofenadine hydrochloride, olopatadine hydrochloride, loratadine, levocetirizine hydrochloride, bilastine, desloratadine, and rupatadine fumarate were introduced, providing longer-lasting effects with significantly improved side effect profiles. Second-generation antihistamines are preferred for overall symptom improvement and nasal congestion relief. Recent developments in second-generation antihistamines significantly reduce central depressive effects like drowsiness (non-sedating antihistamines). Yanai's classification based on H1 receptor occupancy rates in the brain has categorized the non-sedating antihistamines as blocking <20 % [26].

Ideal antihistamine characteristics include rapid onset, prolonged efficacy, minimal side effects (e.g., drowsiness, reduced work efficiency), long-term safety, and good compliance with once or twice daily dosing. Combined therapy using second-generation non-sedating antihistamines with pseudoephedrine hydrochloride, possessing vasoconstrictive effects, is increasingly utilized for congestion or combined type. Administration routes extend beyond oral ingestion to nasal sprays and patches, the latter achieving more stable blood concentrations than oral forms, thereby enhancing compliance.

a) Leukotriene Receptor Antagonist (antileukotriene)

Leukotrienes, synthesized by mast cells, eosinophils, and macrophages within the nasal mucosa, exert their effects on vascular endothelial cells and eosinophils through specific receptors. They induce vasodilation of the nasal mucosa, increase vascular permeability, and facilitate eosinophil migration. Consequently, leukotriene receptor antagonists such as pranlukast hydrate and montelukast sodium are able to mitigate nasal congestion during both the immediate and delayed phases, thus exhibiting superior efficacy as compared to the second-generation antihistamines. These antileukotrienes also diminish nasal mucosal hypersensitivity by inhibiting eosinophil infiltration and reducing nasal secretions induced by leukotriene D_4. Adverse effects include diarrhea, abdominal pain, elevated bilirubin levels, nausea, decreased white blood cell count, thrombocytopenia, and liver dysfunction.

a) PGD_2 and TXA_2 Receptor Antagonist

PGD_2 and TXA_2 receptor antagonists (anti-PGD_2 and TXA_2 drugs; ramatroban) obstruct thromboxane receptors, thereby reducing increased vascular permeability and nasal resistance, and thus, ameliorating nasal congestion. They suppress eosinophil migration induced by PGD_2 and nasal mucosal hypersensitivity by blocking CRTH2 (chemoattractant receptor homologous molecule expressed on Th2 cells), a receptor for PGD_2, thereby improving symptoms of sneezing and rhinorrhea [27]. Due to its antiplatelet properties, caution is advised when combining these with antiplatelet drugs, thrombolytics, or anticoagulants.

3) Th2 cytokine inhibitor

Suplatast tosilate represents a unique approach by inhibiting the production of cytokines IL-4, IL-5, and IL-13 from Th2 cells. This mechanism suppresses allergic symptoms by reducing IgE production, eosinophil infiltration, and histamine release from mast cells [28]. By suppressing late-phase inflammation, suplatast is more effective for nasal congestion than for sneezing and runny nose. The combined use with other drugs that have different mechanisms of action enhances the effect more than using it alone.

4) Corticosteroid

a) Intranasal corticosteroid (INS)

Among current treatments for allergic rhinitis, INS are the most efficacious with regard to symptom improvement due to their potent anti-inflammatory properties. The mechanisms involved include: 1) inhibition of local infiltration of mucosal mast cells, eosinophils, and lymphocytes in the nasal mucosa; 2) suppression of type 2 cytokine production and release; 3) reduction of vascular permeability and glandular secretion; and 4) inhibition of leukotriene and prostaglandin synthesis through blocking of the arachidonic acid metabolism. INS exert potent local effects in small doses, are minimally absorbed, and are rapidly metabolized, thus minimizing systemic side effects except for beclomethasone propionate. Early initiation during MPI has been demonstrated to mitigate symptom exacerbation during peak pollen dispersion, underscoring their role in early intervention.

a) Systemic corticosteroid

In cases where INS are inadequate (severe, most severe, or refractory cases), oral corticosteroids may be prescribed. In Japan, Celestamine®, which is a combination of an antihistamine (d-chlorpheniramine maleate) and betamethasone, is widely used. Furthermore, single intramuscular depot corticosteroid injections administered prophylactically before the pollen season effectively alleviate nasal congestion but show limited efficacy against sneezing or rhinorrhea. Given the risk of side effects such as facial swelling, skin and menstrual irregularities, injection site complications like muscle atrophy and scarring, and adrenal insufficiency, cautious consideration is advised against routine use.

5) Biologic

Omalizumab, a humanized monoclonal antibody that targets the Cε3 domain of IgE, inhibits IgE binding to mast cells, thereby suppressing mast cell activation. Its efficacy for allergic rhinitis as a standalone therapy has been proved in Europe, the United States, and Japan, where it has previously been used for the treatment of bronchial asthma and idiopathic chronic urticaria [29].

Okubo et al. demonstrated that omalizumab reduced nasal symptoms by approximately 40 % and eye symptoms by 50 % during the pollen season as compared to the placebo [30]. Furthermore, 25 % of patients achieved asymptomatic or mild symptoms (nasal symptom score ≤ 1). The addition of omalizumab to patients who inadequately respond to antihistamines or INS significantly reduced peak nasal symptom scores and alleviated impaired work and study performance [31]. Thereafter, omalizumab was approved for the treatment of severe seasonal allergic rhinitis in Japan.

Omalizumab should be prescribed according to the Optimal Clinical Usage Guideline, which consists of the following criteria:

1. Seasonal allergic rhinitis induced by JC pollen.
2. Serum specific IgE against JC pollen $\geq$ class 3 (e.g., 3.5 UA/mL in the fluorescence enzyme immunoassay).
3. Severe symptoms persisting for more than one week despite treatments with chemical mediator receptor antagonists and INS, in addition to allergen avoidance and elimination.
4. Age $\geq$ 12 years.
5. Body weight and total serum IgE level consistent with the requirements for omalizumab administration.

The serum total IgE levels should be in the range of 30–1500 IU/mL, with the patient's body weight between 20 and 150 kg. The recommended dosage is 0.008 mg/kg/IgE/mL or higher, administered

subcutaneously every two weeks. Alternatively, a dosage of 0.016 mg/kg/IgE/mL or more can be administered every four weeks, based on the efficacy of omalizumab.

6) Nasal vasoconstrictor (α-sympathetic stimulant)

Patients with allergic rhinitis experience not only acute attacks but also persistent nasal congestion during intermittent periods. This congestion is not merely a source of discomfort; it also gives rise to a number of secondary complications, including neurological symptoms, sleep disturbances, mouth breathing and impaired mental focus. The underlying causes of this distressing symptom are congestion, edema and excessive connective tissue growth of the nasal mucosa.

These medications activate α1 and α2 adrenergic receptors, resulting in the contraction of blood vessels within the nasal mucosa and the provision of temporary relief from congestion. In order to mitigate the risks associated with these medications, it is recommended that nasal sprays be administered on a daily basis only, and that they only be used for brief periods.

7) Others

a) Non-specific immunotherapy

The use of commercially available allergy therapy drugs, such as histamine-added gamma globulin and bacterial vaccines, has been demonstrated to have limited efficacy in the treatment of allergic rhinitis. However, the use of histamine-added gamma globulin has shown the potential for the limited utilization within this context. The available evidence indicates that it regulates parasympathetic receptors in the nasal mucosa and inhibits eosinophil infiltration.

a) Chinese medicine

Herbal medicines such as shoseiryuto and kakkonto are employed in the treatment of allergic rhinitis. A diagnosis entails a comprehensive assessment of the symptoms, an accurate classification of the disease stage, and a thorough understanding of the underlying etiology. This information serves as the foundation for the selection of an appropriate herbal medicine, guided by empirical principles. Of these, only shoseiryuto has undergone placebo-controlled trials, thereby confirming its efficacy.

8) Adverse effects and interactions of drugs for allergic rhinitis

a) Antihistamines

Serious adverse effects include liver dysfunction, jaundice, shock, and anaphylaxis, which necessitate close monitoring and immediate discontinuation if abnormalities arise. First-generation antihistamines, due to their low H1 receptor selectivity and high penetration of the blood-brain barrier, frequently result in central nervous system depression, gastrointestinal disturbances, and circulatory issues. Furthermore, they display anticholinergic effects and are contraindicated in patients with angle-closure glaucoma and prostatic hyperplasia. It is advisable to exercise caution when administering this medication to children, as they may experience adverse effects such as convulsions, restlessness, insomnia, and tremors. Second-generation antihistamines, distinguished by their high H1 receptor selectivity and

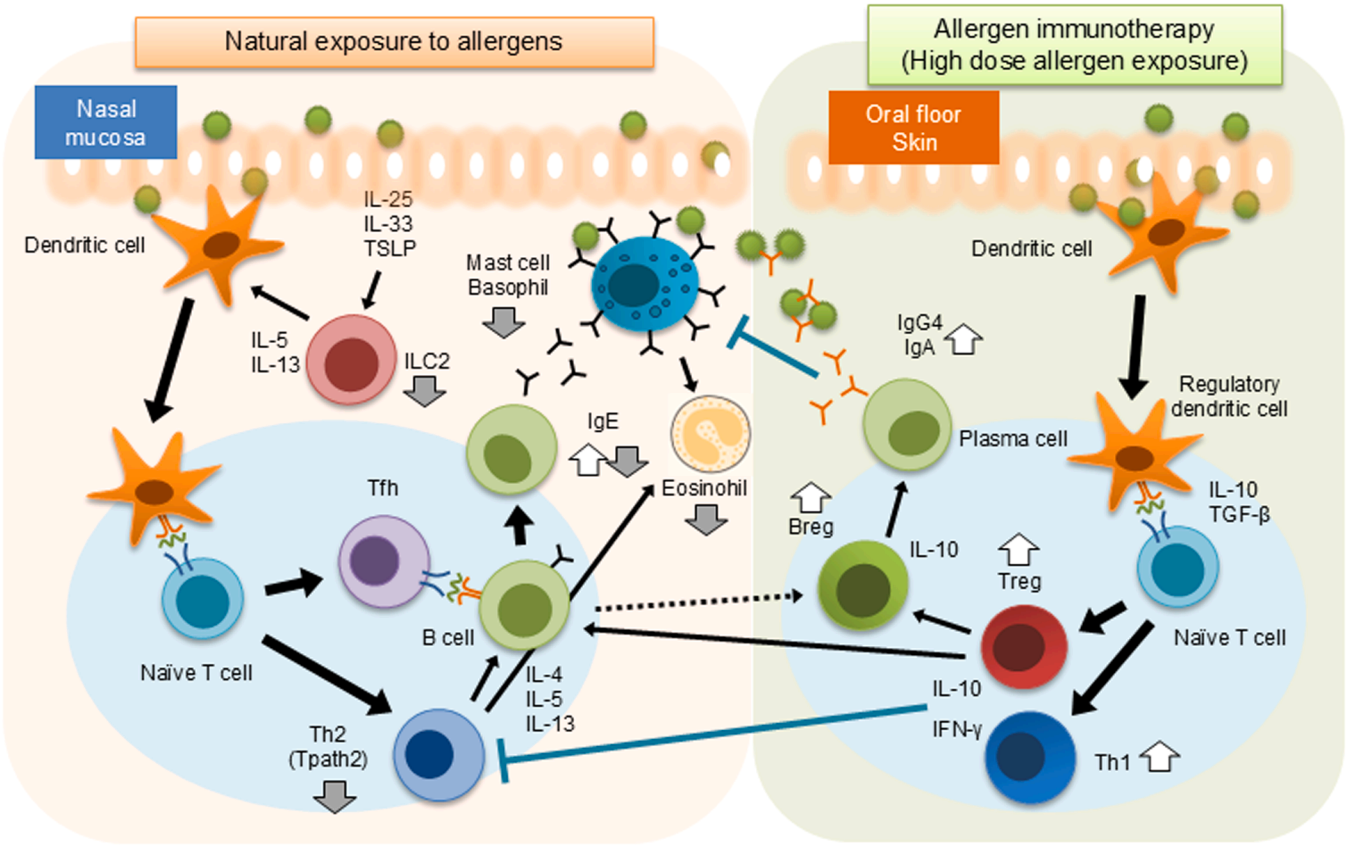

Fig. 2. The mechanism of action of allergen immunotherapy for allergic rhinitis. ⇧ increase. ⇩: decrease. →:promotion. ⊣:suppression. Treg: regulatory T cell. Breg: regulatory B cell. Tpath2: pathogenic Th2 cell. Tfh: follicular helper T cell.

low blood-brain barrier penetration, are associated with a reduced incidence of adverse effects [32]. These medications are classified as sedative if the H1 receptor occupancy exceeds 50 %, as mildly sedative at 20–50 %, and as non-sedative if the occupancy is below 20 % (Fig. 2). Despite the fact that these later-developed second-generation antihistamines are predominantly non-sedative and have reduced central nervous system depressant effects, some patients may still experience sedation.

a) Other Allergic Rhinitis Drugs

Liver dysfunction represents a significant concern with ramatroban, pranlukast hydrate, montelukast sodium, tranilast, and suplatast tosilate, which necessitates regular monitoring of liver function. Pranlukast hydrate has been associated with serious adverse effects, including leukopenia, interstitial pneumonia, eosinophilic pneumonia, and rhabdomyolysis. Montelukast sodium has been linked to the development of severe skin disorders, such as anaphylaxis, angioedema, and toxic epidermal necrolysis. Tranilast has been linked to the development of cystitis-like symptoms, while suplatast tosilate has been associated with the onset of nephrotic syndrome. Although these occurrences are rare, it is imperative that patients are monitored closely throughout the course of their treatment.

There is a documented association between antileukotrienes and the development of vasculitis that resembles eosinophilic granulomatosis, particularly when oral corticosteroids are tapered or discontinued. This necessitates close observation of the eosinophil counts. Although the teratogenicity of allergic rhinitis medications has not been established in humans, animal studies indicate that tranilast and pemirolast potassium may pose risks during pregnancy and are contraindicated in pregnant women.

Systemic corticosteroids are highly effective in suppressing nasal inflammation, but they have numerous side effects and contraindications. In contrast, INS like fluticasone propionate and fluticasone furoate are generally well-tolerated, and rarely cause nasal symptoms such as epistaxis and unpleasant odors.

5.6. Allergen immunotherapy

Allergen immunotherapy is a treatment that aims to alter the natural course of allergic diseases, with SCIT and SLIT the two primary therapies. Although SCIT is effective, it carries the risk of severe systemic side effects and requires frequent visits to the hospital for injections. SLIT, on the other hand, is considered safer and its indications are being expanded to children. Recent placebo-controlled double-blind studies have provided evidence that supports the efficacy of SLIT for allergic rhinitis. It is expected to improve symptoms and QOL in patients with perennial and seasonal allergic rhinitis [33–37]. Additionally, if symptoms recur after treatment, reinitiating treatment may improve the conditions in the patients once again. Allergen immunotherapy for allergic rhinitis may also prevent the onset of bronchial asthma.

1) Mechanism of action of allergen immunotherapy

The assumed mechanism of the allergen immunotherapy is that a large amount of allergen administered subcutaneously or sublingually is taken up by dendritic cells, which then induce phenotypic changes. Th1 cells and regulatory T cells are induced from specific naive T cells that receive antigen presentation from dendritic cells. These suppress the function of specific Th2 cells, as well as suppress IgE production from B cells and induce IgG4 antibody production. These suppress the activation of mast cells, basophils, and eosinophils, thereby suppressing allergic symptoms upon allergen exposure. In recent years, it has been suggested that the suppression of ILC2s and pathogenic Th2 cells by allergen immunotherapy may be involved in the efficacy [38] (Fig. 2).

2) Indications

Allergen immunotherapy is indicated for patients with a confirmed diagnosis of the causative allergen. It is indicated for mild to severe allergic rhinitis, especially for patients who are not responsive to conventional symptomatic treatments or who experience side effects from pharmacotherapy. Safety has not been established for children under the age of 5 years. In principle, it is indicated for patients who do not have serious systemic diseases and who are not taking systemic corticosteroids or immunomodulatory drugs. It should be administered with caution to patients who are using nonselective beta-blockers for diseases such as hypertension. Severe bronchial asthma is contraindicated. Continuing allergen immunotherapy during pregnancy is generally considered safe, but careful consideration should be given when starting new treatment. Currently, in Japan, SCIT formulations are approved for allergic rhinitis caused by JC pollen, house dust mites, and ragweed. SLIT is approved for the treatment of allergic rhinitis caused by JC pollen and house dust mites.

To reduce the side effects and increase the effectiveness of allergen immunotherapy, the following points should be taken into consideration.

1. When administering SCIT, a physician with expertise and experience in the field of allergy must determine the type and dosage of the antigen extract and be able to deal with systemic reactions such as anaphylactic shock.
2. A treatment period of at least 3 years is recommended.
3. Before starting SLIT, physicians should complete e-learning courses provided by the pharmaceutical companies for each drug.
4. SLIT combination treatment for house dust mites and JC pollen is as safe as monotherapy when started with a 4-week interval [39].

5.7. Surgery

Surgical intervention does not constitute a cure for allergic rhinitis; rather, it serves to significantly mitigate its symptomatic manifestations. It is advocated particularly for severe cases that have been unresponsive to conventional therapies and for those presenting with anatomical nasal malformations [40]. A diverse array of surgical techniques has been employed for allergic rhinitis, which necessitates a comprehensive understanding of each approach to ensure optimal patient selection.

Surgical procedures can be categorized into the following three main types based on their therapeutic objectives: nasal mucosa degeneration surgery, nasal cavity corrective surgery and rhinorrhea improvement surgery. Various techniques are depicted, with these methods often combined depending on the case. The spectrum ranges broadly, encompassing invasive approaches such as submucosal resection of the inferior turbinate and posterior nasal nerve resection, to less invasive methods like laser surgery. Tailoring the surgical approach to each individual case is essential.

Although surgeries aimed at nasal mucosal degeneration are minimally invasive and typically outpatient procedures, their efficacy is limited in cases of nasal obstruction accompanied by morphological abnormalities. Thus, a combined approach with procedures targeting nasal obstruction, such as inferior turbinate and nasal septum correction, is often necessary. Notably, nasal septal correction surgery may include external nasal septal rhinoplasty for cases of lordosis or nasal deviation.

Variants of surgery targeting the inferior turbinate include resection or outward fracture of the inferior turbinate bone for irreversibly thickened tissues, or reduction of mucosal volume from the surface or the posterior aspects [41]. Preservation of the physiological function of the inferior turbinate mucosa is essential, advocating against extensive resection or widespread mucosal removal.

To address rhinorrhea, current surgical techniques involve severing the posterior nasal nerve, a terminal branch of the pterygoid nerve

running from the sphenopalatine foramen to the nasal cavity alongside the sphenopalatine artery [42]. Common methods include severing peripheral branches within the sphenopalatine foramen or inferior turbinate mucosa [43]. While previous techniques such as vidian nerve resection via the maxillary sinus have fallen out of favor due to associated complications, cryosurgery has regained attention [44], particularly in the United States, for its potential in neurodegenerative ablation.

Surgical management has been generally effective for perennial allergic rhinitis, with reported effectiveness in seasonal pollinosis as well [45]. Surgical treatment in Japan has been shown to alleviate allergic rhinitis symptoms during pollen seasons, enhance QOL, reduce medication reliance, and exhibit equivalent effects to immunotherapy.

5.8. Treatment strategy and stepwise approach

The National Health Insurance (NHI) system in Japan is a universal healthcare system designed to ensure that all citizens have access to medical services. This system is characterized by universal coverage, income-based premiums, partial copayment, and comprehensive coverage, and it also applies to the diagnosis and treatment of allergic rhinitis [46].

1) Perennial allergic rhinitis

Select a therapy based on severity and disease type..

Mild symptoms: For mild symptoms, one of second-generation antihistamine, mast cell stabilizer, a Th2 cytokine inhibitor, or INS is the first-line agent.

Moderate symptoms: For moderate symptoms of sneezing and rhinorrhea type, choose one of the following: (i) second-generation antihistamine, or (ii) INS. Add (i) with (ii) as needed. For symptoms of nasal blockage or combined type, choose an agent from (i) antileukotriene (ii) PGD_2/TXA_2 receptor antagonist, (iii) second-generation antihistamine with oral decongestant (vasoconstrictor), or (iv) INS. Combine (i) or (ii) with (iv) as needed.

Severe and most severe symptoms: For symptoms with sneezing and rhinorrhea type, combine second-generation antihistamine added on INS. For symptoms of nasal blockage or combined type, add INS with antileukotriene or PGD_2/TXA_2 receptor antagonist or add on INS with second-generation antihistamine with oral decongestant, with the short-term administration of topical decongestants as needed.

For all cases, eliminate and avoid antigens. For cases in which treatment can be continued, specific immunotherapy can also be chosen. For cases of nasal blockage type, in which the effects of pharmacotherapy are insufficient, surgical treatment can also be chosen.

2) Pollinosis

Therapy is chosen based on severity and disease type. However, the severity of pollinosis markedly changes with the amount of pollen dispersal. Therefore, before starting treatment, determine the severity based on symptoms at a hospital visit, symptoms at peak pollen dispersal, and amounts of pollen dispersal.

Initial treatment (early interventional and prophylactic treatment): The aim of initial treatment is to suppress allergic inflammation and nasal mucosal hypersensitivity, which are aggravated by repeated exposure to small amounts of antigen. For patients who suffer from even mild symptoms simultaneously with or before pollen dispersal, start pharmacotherapy when symptoms develop. Administer the choice of second-generation antihistamine, mast cell stabilizer, antileukotriene, PGD_2/TXA_2 receptor antagonist, Th2 cytokine inhibitor, or INS. If symptoms are exacerbated as pollen dispersal increases, use the combination of oral medication and INS early.

Mild symptoms: For mild symptoms, administer one of second-generation antihistamine, antileukotriene, PGD_2/TXA_2 receptor antagonist, or INS.

Moderate symptoms: For symptoms of sneezing and rhinorrhea type, start treatment by the combination of second-generation antihistamine and INS. For symptoms of nasal blockage or combined type, use a combination of adding INS with antileukotriene or PGD_2/TXA_2 receptor antagonist and second-generation antihistamine, or adding on INS with second-generation antihistamine with an oral decongestant.

For the severe and most severe symptoms: Use a combination of INS and second-generation antihistamine for symptoms of sneezing and the rhinorrhea type. For symptoms of the nasal blockage combined type, use a combination of added INS with antileukotriene or PGD_2/TXA_2 receptor antagonists and second-generation antihistamine. In addition, use of a combination drug containing an antihistamine and an oral decongestant for this type with INS are suitable in these cases.

For cases with severe nasal blockade, concomitantly administer a nasal topical decongestant to start the treatment. For cases with severe nasal mucosal swelling and severe pharyngeal and laryngeal symptoms at a hospital visit, administer oral corticosteroids for up to 4-7 days.

6. Specific considerations

6.1. Complications

1) Chronic rhinosinusitis

Chronic rhinosinusitis denotes inflammation of the maxillary and ethmoid sinuses persisting for 12 weeks or longer. Allergic rhinitis plays a significant role in the persistence of chronic rhinosinusitis. Among these conditions, allergic sinusitis, allergic fungal rhinosinusitis, and eosinophilic chronic rhinosinusitis are specifically associated with allergic rhinitis.

a) Allergic sinusitis

In patients with allergic rhinitis, radiological tests may reveal shadows in the paranasal sinuses even in the absence of infection, a condition known as allergic sinusitis. Typically, this condition is mild, characterized by watery or mucous rhinorrhea, and nasal congestion due to intranasal inflammation from allergic rhinitis. The sinus mucosal lesions in allergic sinusitis are believed to be triggered by an allergic reaction to antigens that have infiltrated and deposited in the paranasal sinuses, though this cannot be directly proven. Other hypothesized mechanisms include the obstruction of the natural orifice due to a severe type I allergic reaction in the nasal cavity and the extension of type I allergic inflammation from the nasal cavity to the paranasal sinuses [47].

a) Allergic fungal rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a form of chronic rhinosinusitis linked to an allergic reaction to fungi and is marked by local eosinophil infiltration. It is known to be prone to recurrence, and is frequently associated with eosinophilic nasal polyps. Although its pathology resembles that of eosinophilic chronic rhinosinusitis, allergic fungal rhinosinusitis is distinguished by lesions that may show laterality, and exhibit positive sensitization to fungi. This condition is characterized by the accumulation of a glue-like, viscous secretion, which facilitates the detection of fungi. AFRS is less prevalent in Japan than in Western nations [48].

a) Eosinophilic chronic rhinosinusitis

There has been a notable rise in cases of eosinophilic chronic rhinosinusitis (ECRS), which is marked by significant eosinophil infiltration in both nasal polyps and the mucosa of the nasal sinuses, making it prone to intractable. This condition often develops in adults and is frequently associated with bronchial asthma, including aspirin-

exacerbated respiratory disease. The disease typically presents with multiple edematous nasal polyps, predominantly in the ethmoid sinuses on both sides, and severe lesions around the middle turbinate, including the middle nasal meatus and olfactory cleft. Consequently, olfactory impairment is observed from an early stage. Intranasal examination reveals the presence of viscous, glue-like secretions rich in eosinophils. Diagnosis of ECRS is based on the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score [49].

2) Bronchial asthma

Epidemiological studies have revealed that allergic rhinitis and allergic bronchial asthma frequently co-occur in the same individual, particularly in children. Allergic rhinitis serves as a significant risk factor for the development of bronchial asthma, with the two conditions exacerbating one another. This exacerbation of allergic rhinitis can precipitate a worsening of the bronchial asthma [50]. Effective management of allergic rhinitis can notably improve the bronchial asthma symptoms. In contrast, adult-onset bronchial asthma is often non-atopic.

Although pollen grains are large and typically remain in the nasal cavity rather than reaching the lower respiratory tract, these have led to the belief that cedar pollen inhalation does not induce bronchial asthma, although there are exceptions. Cedar pollen-induced asthma occurs when orbicules released from cedar pollen reach the lower respiratory tract directly, triggering asthma onset. Another mechanism by which allergic rhinitis exacerbates bronchial asthma is thought to involve nasal congestion that shifts breathing from nasal to oral, disrupting the regulation of air purification, warming, and humidification. This shift allows nasal secretions to flow into the lower respiratory tract, potentially causing coughing and asthma attacks. Additionally, chemical mediators and cytokines such as IL-5, released due to allergic inflammation in the nasal cavity, are believed to promote eosinophil production and infiltration into the lower respiratory tract, thereby worsening bronchial asthma.

3) Allergic conjunctivitis

Allergic conjunctivitis is characterized as an inflammatory disorder of the conjunctiva involving a type I hypersensitivity reaction [51]. The spectrum of allergic conjunctival diseases includes allergic conjunctivitis and vernal keratoconjunctivitis, the latter being a proliferative form. Allergic rhinitis commonly presents with congestive allergic conjunctivitis, with a particularly high complication rate observed in pollinosis patients. Severe cases may involve eyelid swelling, and in children, persistent rubbing of the eyes can lead to dark circles beneath the eyes.

6.2. Pregnant women and lactating mothers

Nasal congestion often worsens during pregnancy. Pregnant and lactating women require careful consideration when administering medications due to potential effects on the fetus and infant. Teratogenicity is typically a concern between the second and fourth months of pregnancy, a critical period for fetal organ development. Around the second month, the fetus's central nervous system, heart, digestive system, and limbs are forming and differentiating, necessitating the avoidance of medication where possible.

Beyond the fourth month of pregnancy, medications may cross the placenta and affect fetal functional development. Drugs also pass into breast milk. Therefore, topical treatments are preferred. If medication is necessary, minimal use of topical drugs is recommended. Medications should adhere to the Australian Drug Evaluation Committee Birth Defects Division criteria for pregnant women [52] and the Medications and Mothers' Milk 2021 criteria for lactating women [53].

Allergen immunotherapy carries a low but present risk of systemic side effects, including anaphylaxis, particularly during the induction phase. Initiating allergen immunotherapy or increasing allergen doses in pregnant women is contraindicated.

6.3. Children

The onset of allergic rhinitis in children is occurring at increasingly younger ages [54]. Although allergic rhinitis can manifest in very young children, it is frequently complicated by other pediatric allergic diseases. Allergic dermatitis and bronchial asthma often show improvement or remission by the upper grades of elementary school; however, allergic rhinitis tends to persist with a lower rate of remission. Allergic rhinitis often coexists with otitis media with effusion, sinusitis, and tonsillar hypertrophy. House dust mites and JC pollen are the most common triggers.

Diagnosing children can be challenging due to their limited ability to articulate symptoms. A thorough assessment should include detailed interviews with both the parents and, if feasible, the child. Typical symptoms of allergic rhinitis include sneezing, nasal congestion, and rhinorrhea. Nasal itching in children often manifests as habitual rubbing of the nose (allergic salute), frequent touching of the nostrils, leading to nosebleeds, or the development of horizontal lines across the tip of the nose (allergic crease). Dark circles around the eyes (allergic shiner) may also be noted due to the associated skin changes. The selection of allergy testing must be adapted to the child's age and developmental stage. Serum-specific IgE tests are used to identify sensitizing antigens, enabling a comprehensive diagnostic evaluation.

Communication between healthcare providers and parents is crucial. For children in the upper grades of elementary school and beyond, it is essential to ensure that the child comprehends and is aware of their condition. Perennial allergic rhinitis generally resolves as children mature, but pediatric cases are typically challenging to manage and require prolonged treatment. Consequently, frequent hospital visits should be minimized. Given the prevalence of dust mite allergies in children, it is imperative to instruct them on eliminating and avoiding dust mites and to refrain from contact with pets. Pharmacological treatment for allergic rhinitis is akin to that for adults; however, some medications are not approved for pediatric use, and certain formulations are not suitable for children. The standard dosage for children in upper elementary and junior high school is generally half that of adults. SCIT is suitable for children aged 5 and older, with careful adjustment of antigen dosage in those with bronchial asthma. SLIT for cedar pollen and perennial mite allergies has no age restriction, but safety for children under 5 remains has yet to be established due to limited experience. Surgical interventions for nasal ventilation are considered with the child's growth in mind.

6.4. Elderly patients

1) Age-Related Changes in Nasal Function

Even with normal aging, the anatomy and physiology of the nose undergo various changes that impact nasal function. Histological alterations with age include a reduction in the volume of nasal glands, although the number of goblet cells and ciliated cells remains unchanged. Furthermore, the height of the mucosal epithelium and the number of basal cells decline, while fibrosis of the lamina propria progresses, leading to atrophic mucosa. In the elderly, this atrophy of the mucosa and reduced blood flow to the nasal lining diminish the nasal cavity's ability to humidify and warm incoming air [55,56].

2) Diagnosis and Treatment

The diagnosis of allergic rhinitis in the elderly parallels that in younger individuals. Although the sensitivity of skin tests and serum-specific IgE may be somewhat diminished in the elderly, these diagnostic tests retain their value and are not markedly less effective than in

younger populations [56]. Given that the elderly are more prone to conditions with symptoms akin to allergic rhinitis, such as nonallergic rhinitis and senile rhinitis, careful differentiation is essential. It is crucial to consider the possibility of concurrent allergic and nonallergic rhinitis when diagnosing and treating these patients.

Treatment approaches for elderly patients are largely similar to those for younger and middle-aged individuals [56]. However, older adults often exhibit altered responses to medications due to age-related declines in organ function. Elderly patients are also more likely to have multiple underlying conditions and take a greater number of medications, increasing the risk of drug interactions. Specific concerns include the prevalence of glaucoma, prostatic hyperplasia, and geriatric syndromes such as cognitive decline, falls, and incontinence. Thus, when prescribing antihistamines, a thorough review of the patient's medical history is essential.

6.5. Oral allergy syndrome (OAS)

OAS is an IgE-associated immediate-type food allergy that occurs mainly on the oral and pharyngeal mucosa when food is ingested [57]. It is also called pollen-food allergy syndrome (PFAS). Most OAS cases are classified as Class 2 food allergies, where patients previously sensitized to inhaled or contact allergens exhibit oral symptoms upon ingesting foods containing cross-reactive allergens. In this case, the sensitizing and triggering antigens are different and are caused by incomplete food allergens that are unstable to heat treatment or digestive enzymes.

OAS occurs in patients with various types of pollinosis, but it is known to predominate in patients with birch and alder pollinosis. The foods that cause OAS differ according to the type of pollinosis. The most common OAS-causing foods in latex-allergic patients are avocados, chestnuts, bananas, and kiwis [58]. Clinical symptoms of OAS begin immediately after food ingestion. These symptoms usually gradually subside. The diagnosis of OAS is based on the history and the demonstration of IgE or other allergenic components by prick test using fresh food or allergen components such as Bet v1 [59].

Treatment is based on avoidance of the causative food, although heat treatment often enables oral intake. Since anaphylaxis rarely leads to severe symptoms, patients with a history of anaphylaxis should have a portable adrenaline injection kit, oral antihistamines, and oral corticosteroids with their medical certificates in case of an emergency. Allergen immunotherapy for pollinosis has been reported to improve OAS to pollen and related foods; however, there are conflicting results regarding this effect [59].

6.6. Anaphylaxis

1) Definition

Anaphylaxis is a severe, systemic hypersensitivity reaction that typically develops swiftly and can be life-threatening. Severe anaphylaxis is marked by potentially fatal symptoms affecting the airway, respiratory system, and cardiovascular system, and may occur without the usual skin manifestations or circulatory shock [60].

2) Diagnostic Criteria

Anaphylaxis is highly likely if either of the following criteria is met [60]:

a. Rapid onset (within minutes to hours) of skin or mucosal symptoms, such as generalized urticaria, itching or flushing, or swelling of the lips, tongue, or uvula.
b. Rapid onset (within minutes to hours) of hypotension, bronchospasm, or laryngeal symptoms following exposure to a known or highly likely allergen, even in the absence of typical skin symptoms.

The first criterion—"Rapid onset of skin, mucous membranes, or both"—must be accompanied by at least one of the following:

a. Airway/Respiration: Severe respiratory issues such as dyspnea, wheezing or bronchospasm, stridor, decreased peak expiratory flow (PEF), or hypoxemia.
b. Cardiovascular: Symptoms related to low blood pressure or organ failure, including hypotonia (collapse), syncope, or incontinence.
c. Other: Severe gastrointestinal symptoms such as intense abdominal cramping or recurrent vomiting, particularly following exposure to non-food allergens.

3) Severity

Anaphylaxis is not diagnosed solely on the basis of multiple symptoms classified as grade 1 (mild). The diagnosis of anaphylaxis is confirmed if there are symptoms affecting multiple organs, including those classified as grade 3 (severe), or if there are multiple symptoms of grade 2 (moderate) or higher. The severity (grade) is determined by assessing the most severe organ symptoms. An appropriate evaluation of severity is essential, and treatment should be tailored to the severity of each affected organ [60]. Although various grading methods exist, the severity can differ depending on the evaluation approach, thus a more straightforward grading method is preferred.

4) Treatment

a. Initial response

If anaphylaxis is suspected by either the patient or medical staff, immediate action should be taken. Given that sudden postural changes can precipitate abrupt alterations in the patient's condition (e.g., empty vena cava syndrome), avoid abrupt sitting or standing. As a general guideline, position the patient supinely rather than upright. Should the patient experience breathing difficulties, place them in a sitting position; if pregnant, position them semi-supine with the left side lower; and if unconscious, arrange them in the recovery position. Activate the hospital's emergency system for immediate assistance.

a. Indications for adrenaline

Intramuscular injection of adrenaline is warranted for symptoms categorized as grade 3 (severe) in the severity assessment of anaphylaxis previously outlined, including arrhythmias, hypotension, cardiac arrest, loss of consciousness, hoarseness, barking cough, dysphagia, dyspnea, wheezing, cyanosis, persistent and intolerable abdominal pain, recurrent vomiting, among others.

In cases of past severe anaphylaxis or rapidly progressing symptoms, administration may be considered even for grade 2 (moderate) symptoms. Additionally, adrenaline intramuscular injection is indicated for respiratory symptoms unresponsive to inhaled bronchodilators and for pregnant patients experiencing anaphylaxis. Upon diagnosis or strong suspicion of anaphylaxis, administer 0.01 mg/kg of 0.1 % adrenaline (1:1000; 1 mg/mL) immediately via intramuscular injection into the anterolateral aspect of the thigh. The maximum dose is 0.5 mg for adults and 0.3 mg for children. While intravenous administration is required in cases of cardiac arrest or near-arrest, it is generally discouraged due to the risk of adverse effects such as arrhythmias and hypertension. Adrenaline reaches the peak blood concentration approximately 10 min after intramuscular injection, with a half-life of around 40 min. Due to

the transient effect of adrenaline, it should be administered every 5 to 15 min if symptoms persist despite initial treatment. Patients unresponsive to basic anaphylaxis management should be urgently referred to emergency medical services, critical care, or resuscitation teams as needed.

6.7. Introduction to otorhinolaryngologists

Otorhinolaryngologists are not only knowledgeable about allergies, but can also evaluate nasal findings and provide appropriate local and surgical treatment. In patients with allergic rhinitis who have severe nasal congestion or who do not respond to conservative treatment, observation and evaluation of the nasal cavity is recommended to identify the presence or absence of potential complications such as sinusitis, nasal polyps, nasal septum deviation, hypertrophic rhinitis, and tumors. Patients who require allergen immunotherapy or who wish to receive treatment are also candidates for referral. Since surgical or local treatment is selected depending on the complications, referral to an otolaryngologist at the appropriate time is recommended.

7. Clinical questions & answers

Clinical Question 1

Does anti-IgE antibody treatment effectively reduce the symptoms of severe seasonal allergic rhinitis.

Answer

The administration of anti-IgE antibody is strongly recommended when the optimal use guideline is satisfied.

"Summary of Evidence"

Omalizumab (*XOLAIR* ®) is a humanized monoclonal antibody targeting the mast cell binding site Cε3 of IgE. A randomized, double-blind, placebo-controlled trial for JC pollen allergy, revealed significantly lower nasal and ocular symptom medication scores in the omalizumab group compared to the placebo group ($p < 0.01$), thereby demonstrating its efficacy and safety [30]. Another randomized, double-blind, placebo-controlled study examined the adjunctive effect of omalizumab with antihistamines and INS in 337 adult and adolescent patients with severe cedar pollen allergy inadequately controlled by standard treatments. The active drug group exhibited significant improvements in sneezing, rhinorrhea, nasal congestion, lacrimation, ocular pruritus, nasal symptom score (-1.03, $p < 0.001$), eye symptom score (-0.87, $p < 0.001$), and QOL compared to the placebo group [31]. Questionnaire results from a clinical trial of omalizumab indicated that it could reduce work productivity loss by nearly one-third in patients with severe cedar pollen allergy, potentially offering substantial benefits in work activity [61]. Omalizumab is generally safe, but it can rarely cause anaphylaxis or shock, such as dyspnea or low blood pressure. Other side effects include redness and swelling at the injection site.

Clinical Question 2

Is the use of a nasal vasoconstrictor in conjunction with INS effective for allergic rhinitis.

Answer

Nasal vasoconstrictors should be used for a limited duration. When combined with INS, they effectively prevent rebound nasal symptoms. It is weakly recommended to administer nasal vasoconstrictors alongside INS.

"Summary of Evidence"

Short-term use of nasal vasoconstrictors effectively alleviates nasal congestion in patients with allergic rhinitis. Prolonged use of nasal vasoconstrictors can lead to a major cause of drug-induced rhinitis. To manage this, discontinuation of nasal vasoconstrictors and treatment with INS for several weeks are required. When used once daily in conjunction with INS for a month, nasal vasoconstrictors have shown high efficacy in managing nasal symptoms and preventing rebound symptoms [62]. Similarly, in children with allergic rhinitis and sleep apnea, the combined daily use of a nasal vasoconstrictor and INS for two months was highly effective in treating nasal symptoms without causing rebound effects [63]. If used, nasal vasoconstrictors should be limited to short durations and are contraindicated for infants and children under the age of two.

Clinical Question 3

Are antihistamines effective in alleviating symptoms of allergic rhinitis, such as sneezing, rhinorrhea, and nasal congestion.

Answer

It is effective in mitigating sneezing and rhinorrhea. Some second-generation antihistamines also address nasal congestion. It is weakly recommended for nasal congestion.

"Summary of Evidence"

Second-generation antihistamines are effective in alleviating sneezing and rhinorrhea, and they have also been shown to relieve nasal congestion. The randomized, placebo-controlled, double-blind study for JC pollinosis conducted across multiple centers in Japan demonstrated that the active drug group experienced significant improvements in sneezing, rhinorrhea, nasal congestion, nasal itching, itchy eyes, and watery eyes compared to the placebo group [64]. Further evidence and meta-analyses support the effectiveness of certain second-generation antihistamines for managing these symptoms.

Concurrent use of antihistamines with other central nervous system depressants and alcohol may enhance sedative effects, with increased caution advised, particularly in the elderly. Instructions should be tailored according to the specific drug's package insert and individual patient metabolism.

Clinical Question 4

Are antileukotriene, and PGD_2 *and* TXA_2 *receptor antagonist effective in alleviating nasal congestion associated with allergic rhinitis.*

Answer

In cases of perennial allergic rhinitis and pollinosis, antileukotriene, as well as PGD_2 and TXA_2 receptor antagonist, are strongly recommended due to their significant improvement in nasal congestion symptom scores.

"Summary of Evidence"

Regarding the efficacy of anti-leukotriene drugs for nasal congestion in perennial allergic rhinitis, multicenter double-blind comparative studies and long-term administration trials have demonstrated that pranlukast hydrate offers comparable benefits to antihistamines for all nasal symptoms, with a notably superior improvement rate for nasal congestion. Similarly, montelukast sodium has shown increased therapeutic effectiveness with prolonged use, benefiting all nasal symptoms, including congestion. For pollinosis, pranlukast hydrate significantly enhances nasal cavity volume, and montelukast sodium exhibits similar clinical efficacy. In a pollen exposure chamber, the montelukast sodium group exhibited significant improvements in nasal congestion symptom scores compared to the placebo group. Furthermore, significant improvements in nasal congestion in perennial allergic rhinitis patients were observed after 4 weeks of PGD_2 and TXA_2 receptor antagonist (ramatroban) administration, with its efficacy against pollen-induced nasal congestion confirmed through a placebo-controlled double-blind comparative study in a pollen exposure chamber.

Clinical Question 5

Are Chinese medicines effective in treating allergic rhinitis.

Answer

Shouseiryuto demonstrates a notable efficacy in alleviating sneezing, nasal discharge, and nasal congestion in patients with perennial allergic rhinitis and is weakly recommended.

"Summary of Evidence"

In a double-blind randomized controlled trial involving 220 patients with perennial allergic rhinitis across 61 otorhinolaryngology departments nationwide, shoseiryuto demonstrated significantly superior results in overall improvement, as well as in reducing sneezing, nasal discharge, and nasal congestion scores. Shoseiryuto is utilized in Kampo medicine for symptoms such as foamy watery phlegm, watery nasal discharge, and sneezing, which align with those of allergic rhinitis. When prescribing Kampo medicines, treatment is tailored to the

patient's specific symptoms. Ephedra-containing drugs are typically fast-acting and particularly effective for nasal congestion but are not intended for long-term use. The quasi-randomized comparative study which compared shoseiryuto with other Kampo medicines, daiseiryuto exhibited a significantly greater overall improvement. Although Kampo medicines can be used alone, the prevailing consensus is that they should serve as adjunctive rescue treatments alongside basic therapies like INS.

Clinical Question 6

Is the combination of multiple medications effective in treating allergic rhinitis.

Answer

Combining an antihistamine with pseudoephedrine hydrochloride is more effective in alleviating nasal congestion in patients with JC pollinosis than using an antihistamine alone, and their combined use is weakly recommended.

"Summary of Evidence"

In a clinical trial involving patients with JC pollinosis, initial administration of an antileukotriene, followed by the combination of antihistamines and placebo during peak pollen dispersal, resulted in significant improvements in nasal discharge, sneezing, and pharyngeal and laryngeal symptom scores compared to the placebo group. In a double-blind, randomized, placebo-controlled study during the JC pollen season, the combination of INS with intranasal antihistamine resulted in a notable reduction in total nasal symptom scores [65]. Additionally, combining antihistamine with pseudoephedrine hydrochloride proved more effective in alleviating nasal congestion in JC pollinosis than antihistamines alone. The combination of oral antihistamines with INS is more effective for nasal symptoms compared to oral antihistamines alone, though a meta-analysis indicates no significant difference compared to INS alone.

As a disadvantage, additional costs and the risk of side effects can be mentioned. However, the combination of INS with intranasal antihistamine had side effects equivalent to the use of INS alone [65]. Regarding the combination of oral fexofenadine with pseudoephedrine hydrochloride, serious side effects such as seizures and acute generalized exanthematous pustulosis have been reported.

Clinical Question 7

Is treatment for JC pollinosis effective when administered before the onset of pollen dispersal.

Answer

Initial treatment with INS significantly improved mean nasal symptom scores throughout the season and proved cost-effective. We weakly recommend this approach.

"Summary of Evidence"

A randomized, placebo-controlled, double-blind study demonstrated that initial treatment with INS significantly reduced mean symptom scores throughout the season and proved more cost-effective when initiated four weeks before pollen dispersion, compared to treatment started after pollen dispersion [66]. The one-week early treatment group also showed greater cost-effectiveness. A clinical study using an exposure chamber during the off-season found that taking a second-generation antihistamine immediately after pollen dispersion effectively suppressed symptoms compared to a placebo, with no significant difference observed between continuous initial treatment for one week and initiation at the time of pollen dispersion. Given that 10–20 % of cases may develop symptoms with minimal pollen exposure before full dispersion, it is essential to tailor symptom management strategies according to the drug used and individual patient needs during the peak of pollen dispersion.

Clinical Question 8

Does the effect of allergen immunotherapy for allergic rhinitis endure over time.

Answer

JC pollen SLIT tablets show sustained clinical efficacy during 3 years of treatment and sustained effects for 2 years after treatment in JC pollinosis. For cases of house dust mite monosensitization, SLIT administered for 3 to 5 years remains effective for 7 to 8 years.

"Summary of Evidence"

A randomized, double-blind, controlled study assessed the disease-modifying effects of JC pollen SLIT tablets over 5 years, comprising a 3-year treatment period and a 2-year follow-up, in Japanese patients with JC pollinosis. The active treatment groups exhibited significantly reduced total nasal symptoms and medication scores both during the treatment period (third season, 46.3 % vs. the placebo group, $P < 0.001$) and during the 2-year follow-up period (fourth and fifth seasons, 45.3 % and 34.0 % vs. placebo, respectively; $P < 0.001$) [37].

In an open-label study comparing SLIT with house dust mites with a drug-controlled treatment group over 15 years for house dust mite monosensitization, symptoms were suppressed for 7 years in the 3-year SLIT with house dust mites group and for 8 years in the 4-year and 5-year SLIT groups. Even if symptoms worsened, they remained milder than before treatment, and rapid improvement was noted upon resuming SLIT.

Clinical Question 9

Is SLIT effective in treating allergic rhinitis in children.

Answer

The effectiveness of SLIT for pediatric allergic rhinitis has been demonstrated in a meta-analysis of randomized, placebo-controlled, double-blind comparative studies, and its use is strongly recommended.

"Summary of Evidence"

Symptoms in children include nasal congestion, runny nose, nasal itching, and sneezing, which can impact school performance and sleep. When the causative antigen is known, sublingual immunotherapy (SLIT) is actively pursued, as drug therapy alone may be insufficient. Nasal vasoconstrictors can help with nasal obstruction but should be used sparingly and are contraindicated in children under the age of 2 years. Combination drugs of second-generation antihistamine and vasoconstrictor are suitable for those aged 12 and older.

Moreover, efficacy was evident 12 weeks after commencing SLIT [34], marked by increases in serum-specific IgG4 and serum-specific IgE, aligning with immunological changes observed at 12 weeks. In children aged 5 to 17 years undergoing SLIT, the active drug group experienced a notable reduction in drug scores compared to the placebo group [35]. A meta-analysis of international randomized, placebo-controlled, double-blind studies of SLIT for pediatric allergic rhinitis also revealed significant improvements in both symptom and drug scores in the active drug group compared to the placebo group.

Clinical Question 10

Is allergen immunotherapy safe for pregnant women.

Answer

Although initiation of both SCIT and SLIT are generally contraindicated during pregnancy, evidence suggests that continuing allergen immunotherapy during pregnancy may be safe. Therefore, its use is weakly recommended during pregnancy.

"Summary of Evidence"

Pregnant and breastfeeding women should use medications with caution, considering their effects on the fetus and infant.

Medications for pregnant women should be chosen according to the Australian Criteria set by the Australian Drug Evaluation Committee (ADEC) Congenital Anomalies Division, and those for breastfeeding women should follow the Medication and Mothers' Milk 2021 evaluation criteria. Allergen immunotherapy, including both SCIT and SLIT, has been demonstrated to be safe for continuation during pregnancy [67–69]. Surveys of patients who continued allergen immunotherapy have shown no significant differences in the incidence of premature birth, hypertension/proteinuria, congenital malformations, or maternal and fetal complications. While some reports indicate that initiating SLIT during pregnancy is safe, the safety of starting allergen immunotherapy during pregnancy has not been fully established.

Clinical Question 11

Is serum-specific IgE testing beneficial for diagnosing occupational allergic

rhinitis.

Answer

Immunological tests for low molecular weight antigens exhibit a low positive rate and prove to be of limited utility. We cautiously advise against their use.

"Summary of Evidence"

Occupational allergic rhinitis is a form of occupational rhinitis where allergens such as animals, plants, chemicals, medicines, metals, and other substances present in the workplace trigger symptoms. Certain professions are particularly susceptible to this condition due to the specific antigens involved.

Diagnosing occupational allergic rhinitis begins with a thorough medical history. Symptoms typically arise or worsen during work hours and improve after leaving the workplace or taking days off. It is crucial to inquire whether the symptoms exacerbate at work and if they alleviate upon leaving.

The diagnostic approach for occupational allergic rhinitis mirrors that of standard allergic rhinitis. This involves performing immunological tests based on the patient's history and conducting nasal provocation tests for confirmation. Immunological tests, such as skin tests and blood tests, are employed to detect sensitization by identifying serum specific IgE, especially in response to high molecular weight antigens like those from animals and plants. However, for low molecular weight antigens such as metals and dyes, which act as haptens and are not antigenic on their own, the positive rate of these tests is generally low, rendering serum specific IgE tests less effective, with exceptions for some antigens like isocyanates [70].

Clinical Question 12

Do probiotics prove effective in ameliorating the symptoms of allergic rhinitis.

Answer

There exist probiotics that can significantly alleviate the symptoms of allergic rhinitis. Although their use is weakly recommended, conventional treatments are presently preferred.

"Summary of Evidence"

Probiotics are defined as live microorganisms that positively impact host health by enhancing the balance of intestinal flora, in contrast to antibiotics. These include strains such as lactobacilli and bifidobacteria. Research, including randomized, double-blind, placebo-controlled trials, has investigated the efficacy of probiotics in ameliorating allergic rhinitis symptoms. Certain combinations of probiotic strains may offer symptomatic relief. For instance, administration of *Bifidobacterium longum* BB536 has been shown to alleviate symptoms of JC pollinosis. In a randomized, double-blind, placebo-controlled crossover study using BB536 powder, subjects took the powder twice daily for four weeks before being exposed to JC pollen for four hours. BB536 significantly reduced eye symptom scores, lifestyle interference scores, and medication scores during the treatment period [71]. Similar results were seen in supplements or foods containing *Lactobacillus gasseri* KS-13, *Bifidobacterium bifidum* G9–1, *B. longum* MM-2, *Lactobacillus plantarum* YIT 0132 (LP0132), and *Lactobacillus helveticus* SBT2171 (LH2171) [72–74]. Although the effectiveness is modest, certain probiotics do show promise in alleviating allergic rhinitis symptoms.

CRediT authorship contribution statement

Mitsuhiro Okano: Conceptualization. **Kimihiro Okubo:** Conceptualization. **Minoru Gotoh:** Writing – review & editing. **Mikiya Asako:** Writing – review & editing. **Nobuo Ohta:** Writing – review & editing. **Atsushi Kamijo:** Writing – review & editing. **Kayoko Kawashima:** Writing – review & editing. **Masafumi Sakashita:** Writing – review & editing. **Daiju Sakurai:** Writing – review & editing. **Tetsuya Terada:** Writing – review & editing. **Yuji Nakamaru:** Writing – review & editing. **Takechiyo Yamada:** Writing – review & editing. **Shuji Yonekura:** Writing – review & editing. **Aiko Oka:** Writing – review & editing. **Marie Yamada:** Writing – review & editing. **Tomokazu Yoshizaki:** Supervision.

Declaration of competing interest

MO received honoraria from Taiho Pharmaceutical, Mitsubishi Tanabe Pharma, Novartis Pharma, Kyorin Pharma, Meiji Seika Pharma, and Sanofi. KO received honoraria from Torii Pharmaceutical, Taiho Pharmaceutical, Mitsubishi Tanabe Pharma, Kyorin Pharma, and Novartis, and received a manuscript fee from Torii Pharmaceutical and Mitsubishi Tanabe Pharma. MG received honoraria from Taiho Pharmaceutical, Novartis Pharma, Torii Pharmaceutical, Kyorin Pharma, and Meiji Seika Pharma. MA received honoraria from Sanofi, GSK, Kyorin Pharma, and Taiho Pharmaceutical. NO received honoraria from Mitsubishi Tanabe Pharma, Kyorin Pharma, and Sanofi. AK received honoraria from Novartis Pharma and Sanofi. KK received honoraria from Mitsubishi Tanabe Pharma, Meiji Seika Pharma, and Sanofi. MS received honoraria from Kyorin Pharma, Meiji Seika Pharma, and Sanofi. DS received honoraria from Taiho Pharmaceutical. TT received honoraria from Mitsubishi Tanabe Pharma, Kyorin Pharma, and Sanofi. YN received honoraria from Sanofi. TY received honoraria from Taiho Pharmaceutical, Mitsubishi Tanabe Pharma, Novartis Pharma, Kyorin Pharma, Meiji Seika Pharma, and Sanofi. The other authors have no conflict of interest.

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