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REVIEW ARTICLE

Japanese Guideline for Allergic Rhinitis

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ABSTRACT

Like asthma and atopic dermatitis, allergic rhinitis is an allergic disease, but of the three, it is the only type I allergic disease. Allergic rhinitis includes pollinosis, which is intractable and reduces quality of life (QOL) when it becomes severe. A guideline is needed to understand allergic rhinitis and to use this knowledge to develop a treatment plan. In Japan, the first guideline was prepared after a symposium held by the Japanese Society of Allergology in 1993. The current 6th edition was published in 2009, and is widely used today.

To incorporate evidence based medicine (EBM) introduced from abroad, the most recent collection of evidence/literature was supplemented to the Practical Guideline for the Management of Allergic Rhinitis in Japan 2009. The revised guideline includes assessment of diagnosis/treatment and prescriptions for children and pregnant women, for broad clinical applications. An evidence-based step-by-step strategy for treatment is also described. In addition, the QOL concept and cost benefit analyses are also addressed. Along with Allergic Rhinitis and its Impact of Asthma (ARIA), this guideline is widely used for various clinical purposes, such as measures for patients with sinusitis, childhood allergic rhinitis, oral allergy syndrome, and anaphylaxis and for pregnant women.

KEY WORDS

allergen immunotherapy, mechanism, pharmacotherapy, pollinosis, surgery

1. DEFINITION AND DISEASE NAMES

Allergic rhinitis is a type I allergic disease of the nasal mucosa, characterized by paroxysmal repetitive sneezing, watery rhinorrhea, and nasal blockage. The disease names, most commonly used in publications, include allergic rhinitis, nasal allergy, nasal hypersensitivity, and pollinosis. Allergic rhinitis is classified into perennial and seasonal. Pollinosis is seasonal allergic rhinitis caused by pollen antigens, frequently complicated by allergic conjunctivitis.[1]

2. CLASSIFICATION OF RHINITIS

Rhinitis generally indicates nasal mucosal inflammation (Table 1). Histopathologically, nasal mucosal inflammation is an exudative inflammation. Suppurative and allergic inflammation are particularly common. Both are characterized by leakage of serum components from vessels, edema, cell infiltration, and hypersecretion.

Infectious rhinitis is classified into acute and chronic rhinitis. Hyperesthetic non-infectious rhinitis, that is nasal hypersensitivity complicated by sneezing and watery rhinorrhea, or all nasal symptoms including sneezing, watery rhinorrhea, and nasal blockade, is classified into allergic and nonallergic rhinitis. Nonallergic rhinitis includes vasomotor rhinitis and rhinitis with eosinophilia syndrome. Vasomotor rhinitis is symptomatically similar to allergic rhinitis. However, it cannot be identified as an allergy by tests. The major cause of vasomotor rhinitis is dysautonomia of the nasal mucosa. However, this definition is not recognized in international classification and vasomotor rhinitis is classified as idiopathic rhinitis.[2] Rhinitis

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Table 1 Classification of rhinitis

1. Infection
a. Acute b. Chronic
2. Hyperesthetic non-infectious rhinitis
a. Combined type (nasal hypersensitivity):
i) Allergic: perennial rhinitis, seasonal rhinitis
ii) Nonallergic: vasomotor (idiopathic) rhinitis, rhinitis with eosinophilia syndrome
b. Rhinorrhea type: gustatory rhinitis, cold inhalation rhinitis, senile rhinitis
c. Congestive type: medicament rhinitis, psychogenic rhinitis, pregnant rhinopathia, hormonal rhinitis, and cold rhinitis
d. Dry type: dry nose
3. Irritant rhinitis
a. Physical b. Chemical c. Radiation
4. Others
a. Atrophic rhinitis b. Specific granulomatous rhinitis

The hyperesthetic non-infectious rhinitis is characterized by hypersensitivity. However, this is not inflammatory, except for the allergic rhinitis. Thus, this should reasonably be eliminated from the classification of rhinitis and regarded as a disease similar to allergy or hypersensitivity diseases. However, this was placed into this classification in view of potential clinical convenience. Vasomotor rhinitis is called an idiopathic rhinitis in international classification. This term was used according to the practices. The conditions listed in 4a and 4b should be classified under chronic rhinitis in 1b. However, they were separately classified because of the small number of cases.

Adapted from reference 1.

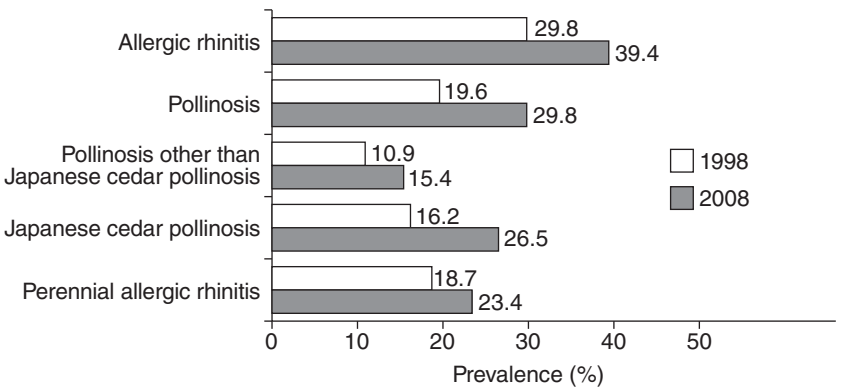


Fig. 1 Prevalence in 1998 and 2008. Adapted from reference 1.

with eosinophilia syndrome is characterized by nasal discharge eosinophilia, and other negative allergy tests.[3]

Noninfectious, nonallergic rhinitis also includes rhinorrhea, congestive, and dry types. Rhinorrhea types include gustatory rhinitis. Congestive types include medicament rhinitis and psychogenic rhinitis, pregnant rhinopathy, hormonal rhinitis, and cold rhinitis. Medicament rhinitis is caused by the long-term administration of sympathomimetics, vasodilatory antihypertensives, β-stimulatory antihypertensives, bronchodilators, antidepressants, or contraceptive pills. However, the most common cause is the overuse and overdose of sympathomimetic nose drops prescribed for nasal blockage.[4]

3. EPIDEMIOLOGY OF ALLERGIC RHINITIS

The number of patients with allergic rhinitis, particularly common sinusitis, has decreased since the 1960s. In contrast, the number of patients with allergic rhinitis has increased. Recently, the number of patients with pollinosis, particularly with Japanese cedar pollinosis, has markedly increased. An epidemiological study revealed a marked increase in the prevalence of allergic rhinitis between 1998 and 2008 (Fig. 1).[5] In particular, the number of patients with Japanese cedar pollinosis has increased. Data on prevalence by age shows that perennial allergic rhinitis is common among young people and that Japanese cedar pollinosis is common among middle-aged people (Fig. 2). According to the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence in Japan is at a medium level in the world (Fig. 3).[6]

4. PATHOGENIC MECHANISMS OF ALLERGIC RHINITIS (Fig. 4)

There are various diatheses for allergic rhinitis sensi-

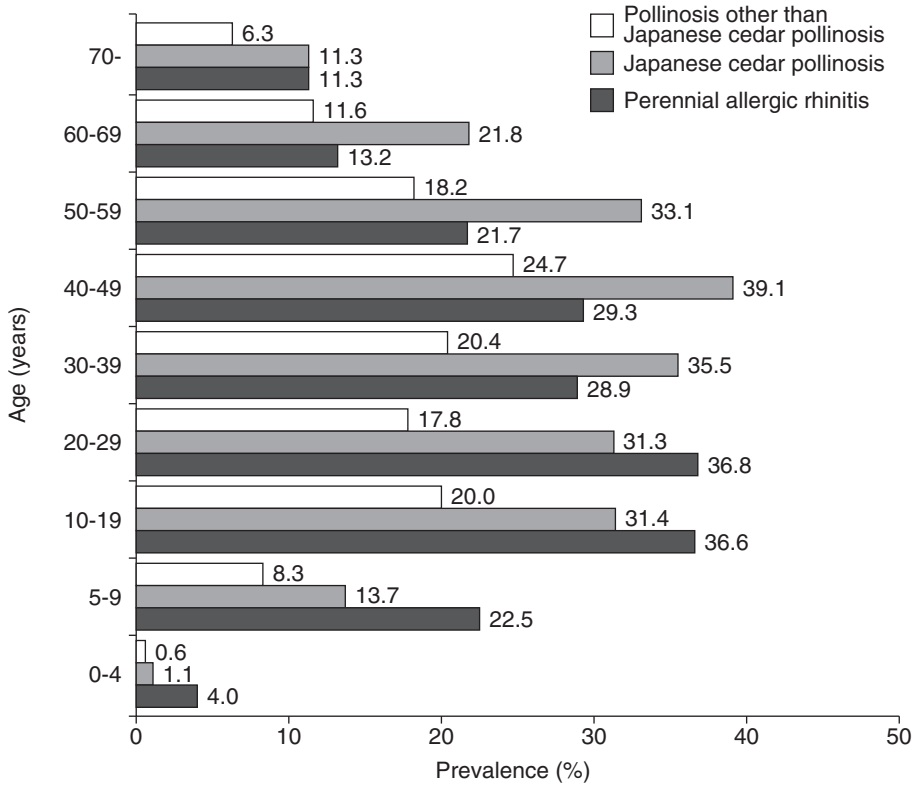


Fig. 2 Prevalence by age. Adapted from reference 1.

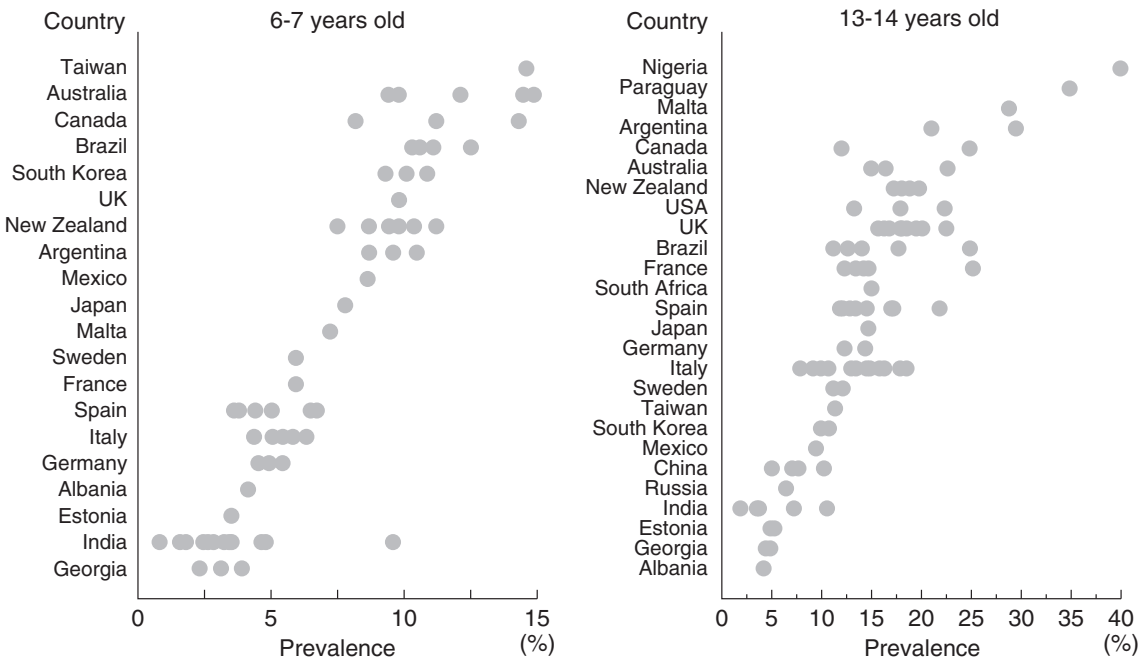


Fig. 3 Allergic rhino conjunctivitis symptoms within one year by ISAAC questionnaire (ISAAC phase I test). Survey in 1995 by ISAAC (The International Study of Asthma and Allergies in Childhood). The survey point in Japan is Fukuoka. Circles indicate the prevalence for each survey point (average 3,000 subjects/point).

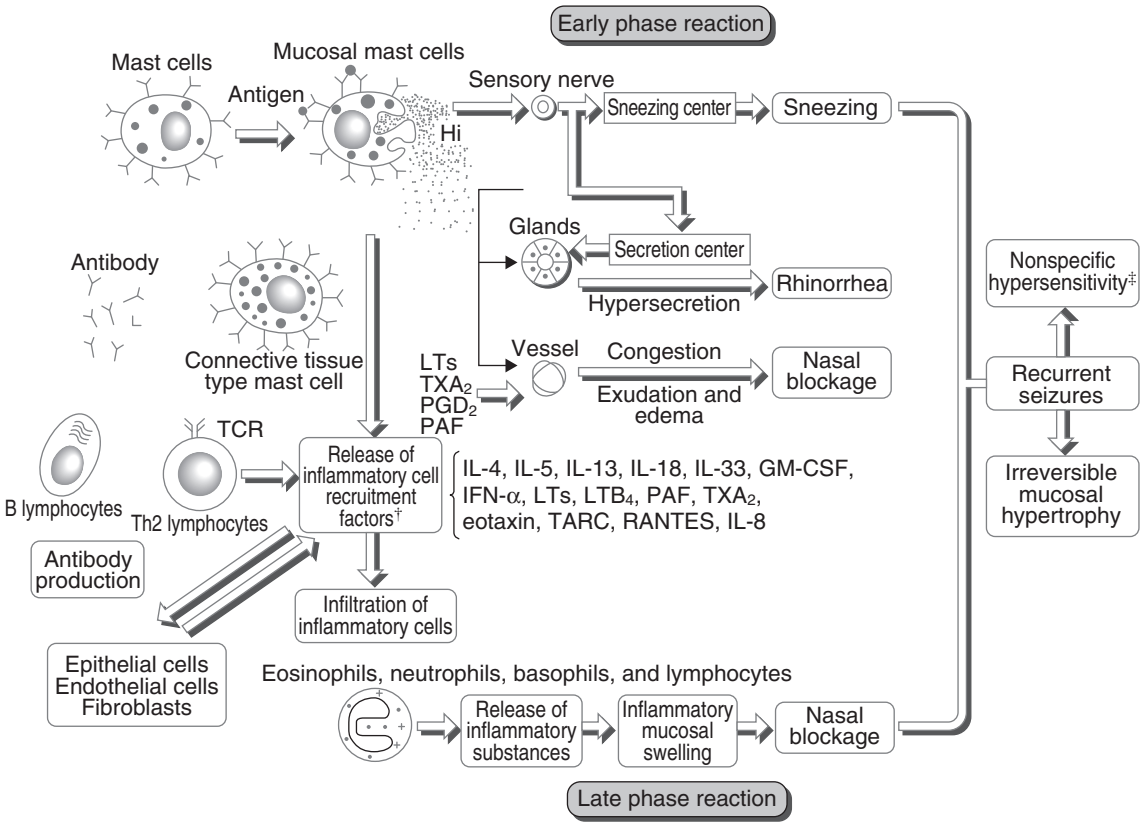


Fig. 4 Mechanism of allergic rhinitis. Hi, histamine; LT, leukotriene; TXA_2, thromboxane A_2; PGD_2, prostaglandin D_2; PAF, platelet activating factor; IL, interleukin; GM-CSF, granulocyte/macrophage colony stimulating factor; IFN-γ, Interferon-γ; TARC, thymus and activation-regulated chemokine; RANTES, regulated upon activation normal T expressed, and presumably secreted; TCR, T cell receptor.

†Only possible migration factors are listed because no theory has been established.

‡Presumed to be caused by allergic reaction.

Adapted from reference 1.

tization, but their mechanisms remain largely unknown. Genetic factors and diatheses for IgE antibody production are the most important. In response to antigen entry into the mucous membrane, IgE antibodies are produced in the nasal mucosa and regional lymphatic tissues. Most causative antigens are inhalation antigens, such as *Dermatophagoides* (a major antigen in house dust), pollens (trees, herbs, and weeds), fungi, and pets. Of these, *Dermatophagoides* and pollens are most common.

In sensitized individuals, antigens inhaled through the nasal mucosa pass through the nasal mucosal epithelial cells to bind to IgE antibodies on mast cells distributed over the nasal mucosa. In response to an antigen-antibody reaction, chemical mediators, such as histamine and peptide leukotrienes (LTs), are released from mast cells. These irritate the sensory nerve endings and blood vessels of the nasal mucosa to cause sneezing, watery rhinorrhea, and nasal mucosal swelling (nasal blockage). This is an early phase reaction. Various inflammatory cells, such as activated eosinophils, infiltrate into the nasal mucosa exposed to antigens in response to cytokines, chemical mediators, and chemokines. Leukotrienes, produced by these inflammatory cells, cause nasal mucosal swelling. This is a late phase reaction, seen at 6-10 hours after antigen exposure.[7]

4.1. SNEEZING

Sneezing is caused by histamine irritation of the sensory nerve (trigeminal nerve) in the nasal mucosa, transmitted to the sneezing center of the medulla oblongata. The irritant effects of histamine on the sensory nerve are enhanced by allergies to cause sneezing.

4.2. WATERY RHINORRHEA

The sensory nerve irritation in the nasal mucosa causes parasympathetic nerve excitement, resulting in sneezing reflex. Acetylcholine is released from the parasympathetic nerves. Histamine acts directly on the nasal mucosal vessels to cause plasma leakage.

Table 2A Classification of the severity of allergic rhinitis symptoms I

Severity		Paroxysmal sneezing or rhinorrhea†				
		++++	+++	++	+	-
Nasal blockage	++++	Most severe	Most severe	Most severe	Most severe	Most severe
	+++	Most severe	Severe	Severe	Severe	Severe
	++	Most severe	Severe	Moderate	Moderate	Moderate
	+	Most severe	Severe	Moderate	Mild	Mild
	-	Most severe	Severe	Moderate	Mild	No symptoms

Sneezing and rhinorrhea type, ▭; Nasal blockage type, ▭; Combined type, ▭.

† Select more severe one, sneezing or rhinorrhea.

Severe, moderate, and mild symptoms are determined according to conventional classification. Uncontrollable severe symptoms are classified into the most severe symptoms, because they may occur during a heavy pollen dispersal period. Adapted from reference 1.

Table 2B Classification of the severity of allergic rhinitis symptoms II: severity of the symptoms

Types \ Severity	++++	+++	++	+	-
Paroxysmal sneezing (Average number of episodes of paroxysmal sneezing in a day)	≥21 times	20-11 times	10-6 times	5-1 times	Below +
Rhinorrhea (Average number of episodes of nose blowing a day)	≥21 times	20-11 times	10-6 times	5-1 times	Below +
Nasal blockage	Completely obstructed all day	Severe nasal blockage causing prolonged oral breathing in a day	Severe nasal blockage causing occasional oral breathing in a day	Nasal blockage without oral breathing	Below +
Troubles with daily life†	Impossible	Painful and complicating daily life	Intermediate between (+++) and (+)	Few troubles	Below +

† Troubles with daily life: Troubles with work, study, household work, sleep, going out, etc.

Adapted from reference 1.

However, it accounts for only 10% of rhinorrhea. Most rhinorrhea is secreted from the nasal glands.[8]

4.3. NASAL MUCOSAL SWELLING

Nasal mucosal swelling is caused by interstitial edema in the nasal mucosa, due to plasma leakage, and congestion of the nasal mucosal vessels. The direct actions of chemical mediators, such as histamine, PAF, prostaglandin D2, kinin, and particularly leukotriene, are essential. Leukotrienes released from infiltrating inflammatory cells, particularly eosinophils, play a major role in nasal mucosal swelling, observed in a late phase.[7-9]

Thus, the early phase reaction of allergic rhinitis is caused by an IgE antibody-mediated type I antigen-antibody reaction. Then, infiltrating inflammatory cells induce a late phase reaction. Continuous antigen irritation cause chronic lesions.

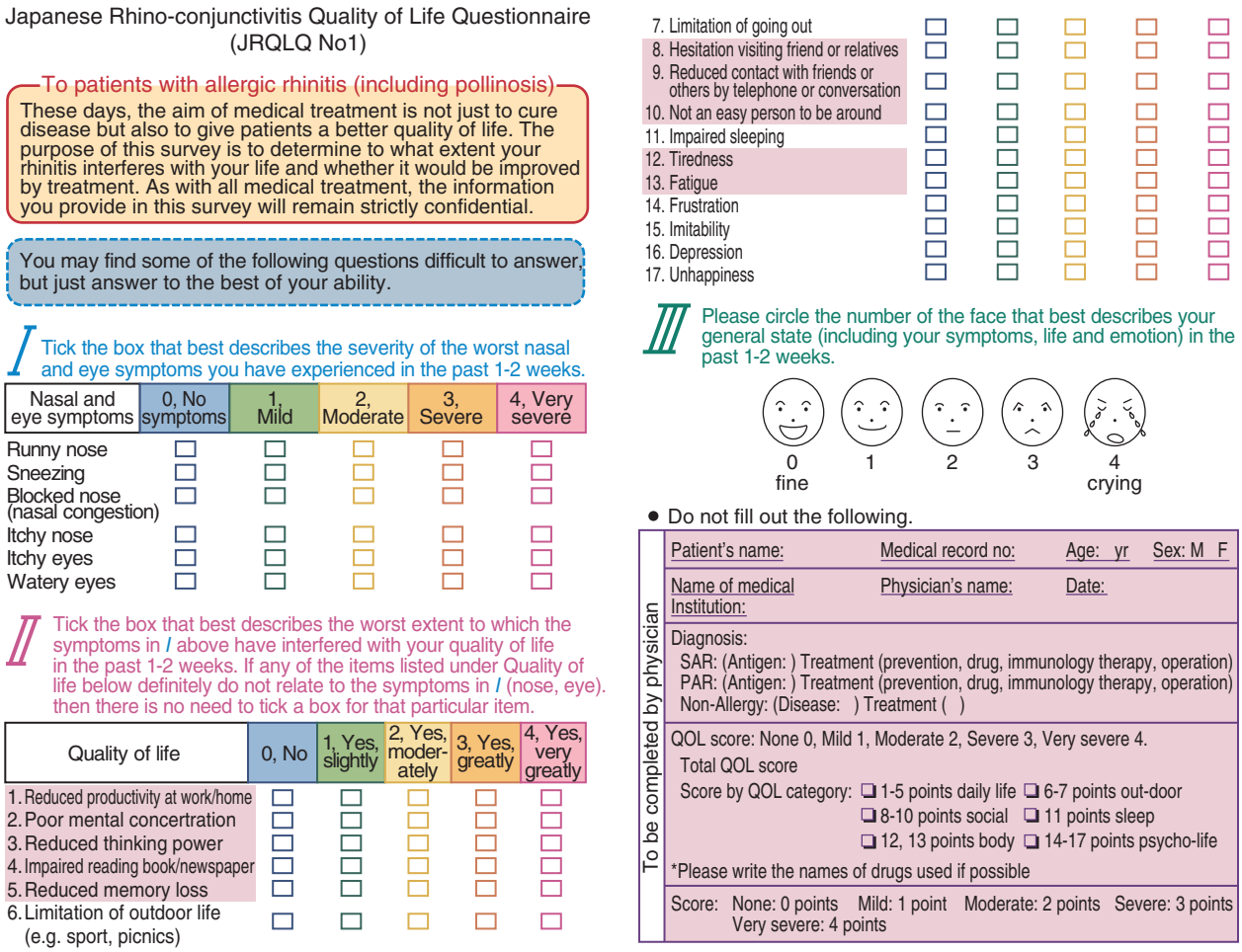
5. TESTS AND DIAGNOSIS OF ALLERGIC RHINITIS

5.1. TESTS

Nasal eosinophil staining in the nasal secretion and serum IgE antibody measurement are useful for diagnosis. Potential causative allergens should be identified based on skin reactions or serum allergen-specific IgE antibody measurements. A nasal mucosa provocation test can be conducted for house dust and ragweed, but their assessments may be difficult. Rhinoscopy and x-ray examinations (Caldwell and Waters methods) are performed for differential diagnosis.

5.2. DIAGNOSIS

A definite diagnosis is made based on three symptoms (sneezing and nasal itch, watery rhinorrhea, and nasal blockade), together with positive nasal eosinophil tests, and identified causative allergens, based on skin reactions or serum allergen-specific IgE antibody measurements.


Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ No1)

To patients with allergic rhinitis (including pollinosis)

These days, the aim of medical treatment is not just to cure disease but also to give patients a better quality of life. The purpose of this survey is to determine to what extent your rhinitis interferes with your life and whether it would be improved by treatment. As with all medical treatment, the information you provide in this survey will remain strictly confidential.

You may find some of the following questions difficult to answer, but just answer to the best of your ability.

I Tick the box that best describes the severity of the worst nasal and eye symptoms you have experienced in the past 1-2 weeks.

Nasal and eye symptoms	0, No symptoms	1, Mild	2, Moderate	3, Severe	4, Very severe
Runny nose	☐	☐	☐	☐	☐
Sneezing	☐	☐	☐	☐	☐
Blocked nose (nasal congestion)	☐	☐	☐	☐	☐
Itchy nose	☐	☐	☐	☐	☐
Itchy eyes	☐	☐	☐	☐	☐
Watery eyes	☐	☐	☐	☐	☐

II Tick the box that best describes the worst extent to which the symptoms in I above have interfered with your quality of life in the past 1-2 weeks. If any of the items listed under Quality of life below definitely do not relate to the symptoms in I (nose, eye). then there is no need to tick a box for that particular item.

Quality of life	0, No	1, Yes, slightly	2, Yes, moder-ately	3, Yes, greatly	4, Yes, very greatly
1. Reduced productivity at work/home	☐	☐	☐	☐	☐
2. Poor mental concertration	☐	☐	☐	☐	☐
3. Reduced thinking power	☐	☐	☐	☐	☐
4. Impaired reading book/newspaper	☐	☐	☐	☐	☐
5. Reduced memory loss	☐	☐	☐	☐	☐
6. Limitation of outdoor life (e.g. sport, picnics)	☐	☐	☐	☐	☐
7. Limitation of going out	☐	☐	☐	☐	☐
8. Hesitation visiting friend or relatives	☐	☐	☐	☐	☐
9. Reduced contact with friends or others by telephone or conversation	☐	☐	☐	☐	☐
10. Not an easy person to be around	☐	☐	☐	☐	☐
11. Impaired sleeping	☐	☐	☐	☐	☐
12. Tiredness	☐	☐	☐	☐	☐
13. Fatigue	☐	☐	☐	☐	☐
14. Frustration	☐	☐	☐	☐	☐
15. Imitability	☐	☐	☐	☐	☐
16. Depression	☐	☐	☐	☐	☐
17. Unhappiness	☐	☐	☐	☐	☐

III Please circle the number of the face that best describes your general state (including your symptoms, life and emotion) in the past 1-2 weeks.

0 fine 1 2 3 4 crying

● Do not fill out the following.

To be completed by physician

Patient's name: Medical record no: Age: yr Sex: M F

Name of medical Institution: Physician's name: Date:

Diagnosis:
SAR: (Antigen:) Treatment (prevention, drug, immunology therapy, operation)
PAR: (Antigen:) Treatment (prevention, drug, immunology therapy, operation)
Non-Allergy: (Disease:) Treatment ( )

QOL score: None 0, Mild 1, Moderate 2, Severe 3, Very severe 4.
Total QOL score
Score by QOL category: ❑ 1-5 points daily life ❑ 6-7 points out-door ❑ 8-10 points social ❑ 11 points sleep ❑ 12, 13 points body ❑ 14-17 points psycho-life
*Please write the names of drugs used if possible

Score: None: 0 points Mild: 1 point Moderate: 2 points Severe: 3 points Very severe: 4 points

Fig. 5 Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ No. 1). Adapted from reference 12.

6. CLASSIFICATION OF ALLERGIC RHINITIS

Allergic rhinitis is roughly classified based on causative antigens, predilection time, disease types, and severity of symptoms.

6.1. PREDILECTION TIME

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

6.2. DISEASE TYPES

"Sneezing and rhinorrhea type" is collectively used because of a strong correlation between sneezing and rhinorrhea. "Nasal blockage type" is used for symptoms with more severe nasal blockage. Symptoms between these types are "combined type."

6.3. SEVERITY

Determine severity based on symptoms, test results, and inspection for nasal mucosa. In general, the determined level of severity based on symptoms is important (Table 2).[10]

7. ASSESSMENT BASED ON QOL

Allergic rhinitis is manageable when treated, but resists cure. Thus, treatment is aimed at improvement in quality of life (QOL). A QOL questionnaire for Japanese with allergic rhinitis was developed in 2002 (Fig. 5).[11]

8. TREATMENT OF ALLERGIC RHINITIS

8.1. AIM OF TREATMENT

The aim of treatment is to alleviate symptoms and remove difficulties with everyday life. Choose a treatment based on severity, disease type, and lifestyle.

8.2. TREATMENT (Table 3)

8.2.1. Natural Courses and Communication with Patients

Combinations of pharmacotherapies based on sever-

Table 3 Therapy

1. Communication with patients
2. Elimination and avoidance of antigens
- Mites: cleaning, dehumidification, mite control blanket cover, etc.
- Pollen: mask, glasses, etc.
3. Pharmacotherapy
- Chemical mediator receptor antagonists (antihistamine, leukotriene receptor antagonists, anti-prostaglandin D_2/thromboxane A_2 agents) (nasal spray, oral medication)
- Mast cell stabilizer (nasal spray, oral medication)
- Steroids (nasal spray, oral medication)
- Autonomic drugs (α-sympathomimetics)
- Others
4. Specific immunotherapy (conventional or rapid procedures)
5. Operative treatment
- Coagulation necrosis (radiofrequency electrocoagulation, laser surgery, trichloroacetic acid chemo-surgery, etc.)
- Resection (corrective surgery of nasal cavity, extensive turbinectomy, nasal polypotomy, etc.)
- Vidian neurotomy and posterior nasal neurotomy

Adapted from reference 1.

ity and disease types and communication with patients improve patients' satisfaction and QOL. Japanese cedar pollinosis, which developed during childhood or early or late middle ages, should be treated in view of a prolonged course.

8.2.2. Elimination and Avoidance of Antigens (Table 4)

In addition to the cleaning, lowering humidity with dehumidifier is effective in reducing mites. For Japanese cedar pollinosis, refer to pollen dispersal information to consider measures to prevent pollen inhalation. For pet allergy, avoid contact with causative pets and keep dogs and cats clean.

8.2.3. Pharmacotherapy

Therapeutic agents for allergic rhinitis, with different mechanisms of action, are classified as shown in Table 5. Alpha-sympathomimetics (vasoconstrictor nose drops), which temporarily alleviate nasal blockage, are also used.

(1) Mast cell stabilizer: Since the development of disodium cromoglicate (DSCG), local agents (eye drops and nasal spray) and oral agents, such as tranilast, amlexanox, and pemirolast potassium, have been on the market. They have mild effects. To achieve sufficient clinical effects, 2-week prolonged administration is required. Amelioration rates are increased by continuous administration. Adverse effects, such as sleepiness and dry mouth, do not occur.

(2) Chemical mediator receptor antagonists

a) Histamine H1 receptor antagonists (antihistamine)

(i) First-generation antihistamine: First-generation antihistamine often cause adverse effects, such as sleepiness, impaired performance, and dry mouth, but have immediate effects on sneezing and watery rhinorrhea. First-generation antihistamine are contraindicated for patients with glaucoma, prostatic hyperplasia, and asthma because of their potent anticholinergic effects. They have less central nervous system depressant actions in children than in adults. Caution should be exercised for excitatory effects, such as convulsions. Most of first-generation antihistamine are marketed as OTC.

(ii) Second-generation antihistamine (Table 6): Second-generation antihistamine, such as ketotifen fumarate, oxatomide, azelastine hydrochloride, emedastine difumarate, and mequitazine, are effective to some extent for nasal blockage aside from sneezing and watery rhinorrhea. However, they may cause adverse effects, such as sleepiness and impaired performance, in early versions. Thus, caution should be exercised in administering them. The adverse effects of late versions, such as epinastine hydrochloride, ebastine, bepotastine besilate, fexofenadine, loratadine, olopatadine hydrochloride, and levocetirizine, have been reduced.[12] Priority indications are mild to moderate sneezing and rhinorrhea type. Combine them with topical steroids depending on severity.

b) Leukotriene receptor antagonists (antileukotrienes) (Table 7): Peptide leukotrienes, produced and released by mast cells, eosinophils, and macrophages, have potent relaxing effects on the vascular smooth muscles of the nasal mucosa, enhancing effects on vascular permeability, and stimulating effects on eosinophil migration. Pranlukast and montelukast are available. They are effective for nasal blockage. Their effects are increased by prolonged administration. Comparable effects with those of antihistamines can be achieved for sneezing and rhinorrhea within 4 weeks.[13] Primary indications are treatment of symptoms of the moderate or milder nasal blockage type

Table 4 Elimination and avoidance of antigens

<Elimination of house dust mites>
1. For indoor cleaning, use an exhaust circulation-type cleaner.
   Clean room for 20 s/m^2 twice a week.
2. Avoid using textile sofa, carpet, and tatami wherever possible.
3. Put antimite covers over mattresses, beds, and pillows.
4. Keep humidity at 50% and room temperature at 20-25°C.

<Avoidance of cedar pollen>
1. Collect pollen information.
2. Stay at home during a heavy pollen dispersal period.
3. Shut windows and doors during a heavy pollen dispersal period.
4. When going out during a heavy pollen dispersal period, wear a mask and glasses.
5. When going out, avoid wearing woolen coats.
6. When going home, shake dust off from suit and hair before entering. Wash the face, gargle, and blow your nose.
7. Clean rooms frequently.

<Reduce pet (especially cat) antigens>
1. Stop keeping pets if possible.
2. Keeps pets outdoors and keep them away from bedroom.
3. Clean pets and their environments.
4. Change carpet to flooring.
5. Improve ventilation, and clean rooms.

Adapted from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

Table 5 Therapeutic agents for allergic rhinitis

1. Mast cell stabilizer
   Disodium cromoglycate (Intal®), tranilast (Rizaben®), amlexanox (Solfa®), pemirolast potassium (Alegysal®, Pemilaston®)
2. Chemical mediator receptor antagonists
   a. Histamine H_1 receptor antagonists (antihistamine)
      <First-generation>
      d-chlorpheniramine maleate (Polaramin®), clemastine fumarate (Tavegyl®), etc.
      <Second-generation>
      Ketotifen fumarate (Zaditen®), azelastine hydrochloride (Azeptin®), oxatomide (Celtect®), mequitazine (Zesulan®, Nipolazin®), emedastine difumarate (Daren®, Remicut®), epinastine hydrochloride (Alesion®), ebastine (Ebastel®), cetirizine hydrochloride (Zyrtec®), levocabastine hydrochloride (Livostin®), bepotastine besilate (Talion®), fexofenadine hydrochloride (Allegra®), olopatadine hydrochloride (Allelock®), loratadine (Claritin®)
   b. Leukotriene receptor antagonists
      Pranlukast hydrate (Onon®), montelukast sodium (Singulair®, Kipres®)
   c. Prostaglandin D_2/thromboxane A_2 receptor antagonists (anti-prostaglandin D_2/thromboxane A_2 agents)
      Ramatroban (Baynas®)
3. Th2 cytokine inhibitor
   Suplatast tosilate (IPD®)
4. Steroids
   a. Nasal spray
      Beclomethasone propionate (Aldecin® AQ Nasal, Rhinocort®), fluticasone propionate (Flunase®), mometasone furoate hydrate (Nasonex®), dexamethasone cipecilate capsule for external use (Erizas®)
   b. Oral medication
      Compounding agent of betamethasone/d-chlorpheniramine maleate (Celestamine®)
5. Others
   Nonspecific allassotherapy agents, biological preparations, and herbal medicines

Modified from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

Table 6 Characteristics of second-generation antihistamine (compared with first-generation antihistamine)

1. Few adverse effects, such as central sedation and anticholinergic effects
2. Slightly favorable general improvement
3. Slightly effective for nasal blockage
4. Mild, delayed, and prolonged effects
5. Improvement rate is increased by prolonged administration.

Relatively effective; however, it takes about 2 weeks to achieve sufficient effects in a clinical test on perennial allergic rhinitis. This is the time required to suppress hypersensitivity with a single treatment.

Modified from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

Table 7 Characteristics of leukotriene receptor antagonists

1. Suppress the vascular dilation and permeability of the nasal mucosa, and improve nasal blockage.
2. More effective for nasal blockage than second-generation antihistamine.
3. Suppress eosinophilic infiltration and nasal secretion, and improve sneezing and rhinorrhea by ≥2-week prolonged administration.
4. Effects are noted at 1 week after start of oral administration, reaching a peak at 4 weeks.

Modified from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

Table 8 Characteristics of prostaglandin D_2/thromboxane A_2 receptor antagonists

1. Suppress the vascular permeability of the nasal mucosa, and improve nasal blockage.
2. More effective for nasal blockage than second-generation antihistamine.
3. Inhibit eosinophil migration caused by PGD_2, and improve sneezing and rhinorrhea by ≥2-week prolonged administration.
4. Effects are relatively slow, reaching a peak at 4 weeks.

Modified from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

Table 9 Characteristics of nasal spray steroids

1. Potent effects
2. Relatively rapid effects
3. Few adverse effects
4. Effective equally to the 3 symptoms of nasal allergy
5. Effective only at administration site

Modified from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

and those of intermediate type with nasal blockage as the chief complaint. No adverse effects of sleepiness, occur.

c) Prostaglandin D2 and thromboxane A2 receptor antagonists (Table 8): Ramatroban enhances vascular permeability in the nasal mucosa and suppresses eosinophil migration by blocking thromboxane receptors, and suppresses eosinophil migration by blocking CRTh2 (chemoattractant receptor-homologous receptor expressed on Th2 cell), a part of the prostaglandin D2 receptor. They have strong delayed effects on nasal blockage.[14] Primary indications are treatment of symptoms of nasal blockage type and those of combined type with nasal blockage as a chief complaint. The agents interact with some other medicines, but cause no adverse effects of sleepiness.

(3) Th2 cytokine inhibitors: IPD inhibits the production of Th2 cytokines, such as IL-4 and IL-5, in T lymphocytes to alleviate allergic inflammation. No adverse effects of sleepiness, occur.

(4) Steroids

a) Nasal spray steroids (Table 9): Beclomethasone propionate, fluticasone propionate, mometasone furoate, fluticasone furoate, and dexamethasone cipecilate are available. All agents have strong local effects in small amounts, and are poorly absorbed and readily degraded. Thus, they have few systemic adverse effects. They are highly effective for sneezing, watery rhinorrhea, and nasal mucosal swelling, and exert their effects within 1-3 days. A slight feeling of nasal irritation, feeling of dryness, and epistaxis may occur.[15]

b) Steroids for internal use: Only for intractable cases with severe nasal blockage and laryngopharynx symptoms, uncontrollable with nasal spray steroids, prednisolone (20-40 mg/day) can be administered for 4-7 days at the start of treatment. Caution should be exercised for adverse effects.

(5) Alpha-sympathomimetics (vasoconstrictor nose drops): Alpha-sympathomimetics act on the α-receptors of vascular smooth muscles to cause vasoconstriction and temporarily alleviate nasal mucosal swelling. Long-term continuous administration

Table 10 Characteristics of nonspecific allassotherapy agents, biological preparations, and herbal medicines

Nonspecific allassotherapy agents	
	Histamine added gamma globulin, bacterial vaccine, and gold preparations are available. They are rarely used alone. Their mechanisms of action are unclear.
Biological preparations	
	Neurotropin is commercially available. Its mechanism of action is unclear. They have no instantaneous effect.
Herbal medicines	
	Syoseiryuto, Kakkonto, Syosaikoto, etc., are used. A placebo-controlled test was conducted only for Syoseiryuto to demonstrate its efficacy.

Modified from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

Table 11 Adverse effects of therapeutic agents for allergic rhinitis

Medicines	Adverse effects
First-generation antihistamine	Sleepiness, systemic malaise, dry mouth, etc. (asthma, dysuria, glaucoma, and contraindication to driving)
Second-generation antihistamine	Hepatic and gastrointestinal disorders, sleepiness, and myocardiopathy for some agents
Oral mast cell stabilizer	Hepatic and gastrointestinal disorders, rash, and cystitis for some agents
Leukotriene receptor antagonists	Leukopenia, thrombocytopenia, hepatic disorders, rash, diarrhea, abdominal pain, etc.
Prostaglandin D_2/thromboxane A_2 receptor antagonists	Bleeding tendency, hepatic disorders, rash, abdominal pain, headache, etc.
Th2 cytokine inhibitors	Hepatic disorders, jaundice, nephrosis, etc.
Oral corticosteroids	Infection, adrenocortical insufficiency, diabetes, peptic ulcer, moon face, glaucoma, etc. (contraindicated for treatment of infection, peptic ulcer, hypertension, diabetes, glaucoma, etc.)
Nasal spray steroids	Nasal irritation, feeling of dryness, epistaxis, etc.
Mast cell stabilizer and antihistamine for nasal spray	Nasal irritation and sleepiness (for some agents)
Vasoconstrictor nose spray	Habituation, rebound phenomena, hyporesponsiveness, etc.

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causes medicament rhinitis. For the most severe pollinosis, they can be administered 2-3 times a day for 1-2 weeks.

(6) Other pharmacotherapy (Table 10): Nonspecific allassotherapy agents, biological preparation, and herbal medicines can be used.

(7) Adverse effects and drug interactions of therapeutic agents for allergic rhinitis (Table 11, 12): Therapeutic agents for allergic rhinitis are those for symptomatic treatment, used to alleviate symptoms. Caution should be exercised for harmful adverse effects and drug interactions during treatment. If they occur, take immediate measures and switch to a different treatment.

8.2.4. Specific Immunotherapy

Specific immunotherapy has been used over the past century. Its demonstrated effects may be exerted via immunological mechanisms. Of note, local mast cells are decreased, the Th1/Th2 balance is altered, and regulatory T cells are increased. It takes several months to develop effects, requiring routine injection for $\geq$3 years. Furthermore, a systemic anaphylaxis response may develop in a small number of cases.[16] The characteristics of this method are shown in Table 13.

(1) Indications: This therapy is indicated for the treatment of patients aged $\geq$6 years, without severe systemic symptoms, to whom emergency adrenaline may be administered. Exclude patients on β-blocker therapy or with severe asthma. While this therapy has no harmful effects on pregnant women, it should not be started during pregnancy.

(2) Implementation

a) Specialists should prescribe antigen extracts and take measures against systemic reactions, such as anaphylactic shock.

b) In patients with asthma complications, avoid this therapy during a paroxysmal period. In patients with pollinosis, avoid starting this therapy during dispersal of causative pollen.

c) For initial injection, reduce the threshold con-

Table 12 Drug interactions of therapeutic agents for allergic rhinitis and measures

Therapeutic agents	Concomitant agents	Effects	Measures
Second-generation antihistamine	Alcohol Sedatives, hypnotics, psychotropics Cold medicines	Enhanced central inhibition → Hypnosis, vertigo, weakness, malaise	Caution should be exercised for combined use. → Reduce dose if adverse effects are noted.
Ketotifen fumarate	Tolbutamide	Thrombocytopenia → Bleeding tendency	
Oxatomide	Antipsychotics Tricyclic antidepressants Digestive function activators Antiarrhythmics	Exacerbation of extrapyramidal disturbances → Tremor and difficulty in walking	Caution should be exercised for combined use. → Discontinue the combined use if adverse effects are noted.
	Tricyclic antidepressants Anticholinergics	Enhanced anticholinergic effects → Dry mouth and exacerbation of glaucoma	
	β2 stimulants Theophylline	Exacerbation of tremor	
Ebastine	Erythromycin	Inhibition of liver drug-metabolizing enzymes → Increased serum carebastine level	Caution should be exercised for combined use. → Reduce dose if adverse effects are noted.
Fexofenadine hydrochloride	Antacids	Decreased absorption → Reduced effects	Caution should be exercised for combined use. → Discontinue the combined use if adverse effects are noted.
	Erythromycin	Increased absorption and decreased clearance → Increased serum level	Caution should be exercised for combined use. → Reduce dose if adverse effects are noted.
Loratadine	Erythromycin Cimetidine	Inhibition of liver drug-metabolizing enzymes → Increased serum levels	Caution should be exercised for combined use. → Reduce dose if adverse effects are noted.
Mast cell stabilizer Tranilast	Warfarin potassium	Inhibition of liver drug-metabolizing enzymes → Bleeding tendency	Caution should be exercised for combined use. → Discontinue the combined use if adverse effects are noted.
Leukotriene receptor antagonists Pranlukast hydrate	Itraconazole Erythromycin	Inhibition of liver drug-metabolizing enzymes → Increased serum levels	Caution should be exercised for combined use. → Reduce the dose if adverse effects are noted.
Montelukast	Phenobarbital	Induction of liver drug-metabolizing enzymes → Decreased serum levels	Caution should be exercised for combined use. → Increase dose if adverse effects are noted.
Prostaglandin D_2/thromboxane A_2 receptor antagonist Ramatroban	Antithrombotics	Enhanced inhibitory effects on platelet aggregation → Bleeding tendency	Caution should be exercised for combined use. → Discontinue the combined use if adverse effects are noted.
	Aspirin	Decline in plasma protein binding → Increased serum level of free aspirin	
	Theophylline	Competition of liver drug-metabolizing enzymes → Increased serum levels	

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Table 13 Characteristics of specific immunotherapy in WHO views report

1. Perform specific immunotherapy alone or in combination with a different therapy to treat allergic rhinitis.
2. Effective also for allergic conjunctivitis and allergic asthma.
3. Should be performed by a physician specialized in allergy.
4. Avoid using allergen mixtures for treatment. Use standardized allergen vaccines.
5. Gradually increase allergen to reach maintenance dose.
6. Optimal maintenance dose contains 5-20 μg of a major allergen for each injection.
7. Because of the risks of anaphylaxis, respond appropriately in an emergency.
8. Optimal duration is unknown, generally 3-5 years.

Adapted from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

Table 14 Operative treatment for allergic rhinitis

1. Surgery to contract and modulate nasal mucosa	
	Electrocoagulation, cryosurgery, laser surgery, 80% trichloroacetic acid chemo-surgery. Laser surgery is characterized by various procedures, instruments, and objectives, such as cauterizing the surface with a laser beam (CO_2, semiconductor), evaporating to a deep layer (semiconductor, potassium-titanyl phosphate [KTP]), and widely excising the mucous membrane (KTP).
2. Corrective surgery of nasal cavity to improve nasal ventilation	
	Submucosal turbinectomy, inferior turbinectomy, septoplasty, Takahashi operation method, extensive turbinectomy, and nasal polypotomy.
3. Surgery to improve rhinorrhea	
	Vidian neurectomy and posterior nasal neurectomy.

Adapted from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

centration for intradermal reaction to 1/10. Before injection, ask more than one physicians or health care professionals about concentration and dosage.

d) Before increasing an aqueous solution concentration or changing lots, conduct an intradermal test. For patients with erythema of ≥50 mm diameter, carefully conduct the test and follow-up the patients for 20-30 minutes after injection.

e) Perform therapy for at least 3 years. Therapeutic effects often continue for several years after discontinuation of administration.

f) Instruct patients to continue the therapy.

8.2.5. Surgical Treatment

Nasal blockage in allergic rhinitis is often caused by nasal deformities, such as deviated septum, hypertrophic rhinitis, and nasal polyps. In this case, perform corrective surgery of nasal cavity to improve nasal ventilation. Before pollen season, laser surgery is also performed for Japanese cedar pollinosis, but the effects of this surgery do not continue in the following year.[17] The main purpose is to alleviate nasal blockage. Various techniques shown in Table 14 are used. For intractable rhinorrhea, perform posterior nasal neurectomy.

8.3. CHOICE OF THERAPY

8.3.1. Perennial Allergic Rhinitis

Select a therapy based on severity and disease type. Selection criteria are shown in Table 15. For mild symptoms, second-generation antihistamine or mast cell stabilizer are first-line agents. For moderate symptoms of sneezing and rhinorrhea type, choose one of the following: (i) second-generation antihistamine, (ii) mast cell stabilizer, and (iii) nasal spray steroids. Add (i) or (ii) with (iii) as needed. For symptoms of nasal blockage or combined type, choose an agent from (i) leukotriene receptor antagonists, (ii) prostaglandin D2/thromboxane A2 receptor antagonists, and (iii) nasal spray steroids. Combine (i) or (ii) with (iii) as needed.

For severe cases with severe sneezing and rhinorrhea, combine second-generation antihistamine with nasal spray steroids. For symptoms of nasal blockage or combined type, add nasal spray steroids with leukotriene receptor antagonists or prostaglandin D2/thromboxane A2 receptor antagonists. 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.

8.3.2. 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 (Table 16).

(1) Primal therapy (primary care) (Fig. 6): The aim

Table 15 Treatment of perennial allergic rhinitis

Severity	Mild	Moderate		Severe	
Disease types		Sneezing and rhinorrhea type	Nasal blockage type or combined type with nasal blockage as a chief complaint	Sneezing and rhinorrhea type	Nasal blockage type or combined type with nasal blockage as a chief complaint
Treatments	a. Second-generation antihistamine b. (Mast cell) stabilizer	a. Second-generation antihistamine b. (Mast cell) stabilizer c. Th2 cytokine inhibitors d. Nasal spray steroids	a. Anti-LTs agents b. Anti-PGD_2/TXA_2 agents c. Nasal spray steroids	Nasal spray steroids + Second-generation antihistamine	Nasal spray steroids + Anti-LTs agents or anti-PGD_2/TXA_2 agents
	Choose one of (a), (b).	Choose one of (a), (b), (c), and (d). Combine (a), (b), or (c), with (d), as needed.	Choose one of (a), (b), and (c). Combine (a) or (b) with (c) as needed.		Use vasoconstrictor nose spray for only 5-7 days at the start of treatment as needed.
				Perform surgery for cases with nasal deformities of a nasal blockage type.	
	Specific immunotherapy				
	Elimination and avoidance of antigens				

Note 1) Second-generation antihistamine are often used. First-generation antihistamine are inexpensive, rapidly effective, and short-acting agents, and are used as such. However, avoid their use for those with severe sleepiness, urination disorder, glaucoma, or asthma.

Note 2)Stabilizer = Mast cell stabilizer, Anti-LTs agents = Leukotriene receptor antagonists, Anti-PGD_2/TXA_2 agents = Prostaglandin D_2/Thromboxane A_2 receptor antagonists.

Note 3) For severe nasal blockage, use vasoconstrictor nose drops for ≤1 week.

Note 4) Use one or more agents depending on symptoms.

Note 5) Even if symptoms are alleviated, do not discontinue the agent immediately, but confirm stability for several months to reduce dose gradually.

Note 6) For severe cases unresponsive to the above agents, oral corticosteroids may have to be used for a short period (1-2 weeks).

Adapted from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

of primary care 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 second-generation antihistamine for symptoms of sneezing and rhinorrhea type. Administer leukotriene receptor antagonists for symptoms of nasal blockage type and those of combined type with nasal blockage as a chief complaint.[18] If symptoms are exacerbated as pollen dispersal increases, use the combination of nasal spray steroids early.

(2) Mild symptoms: For mild symptoms, administer second-generation antihistamine or leukotriene receptor antagonists. If symptoms are exacerbated, concomitantly use nasal spray steroids early.

(3) Moderate symptoms: For symptoms of sneezing and rhinorrhea type, start treatment by the combination of second-generation antihistamine and nasal spray steroids. For symptoms of nasal blockage type, use a combination of nasal spray steroids and leukotriene receptor antagonists. For symptoms of combined type, add second-generation antihistamine.

(4) Severe and the most severe cases: For symptoms of sneezing and rhinorrhea type, use a combination of nasal spray steroids and second-generation antihistamine. For symptoms of the nasal blockage type and those of combined type, add leukotriene receptor antagonists. For cases with severe nasal blockade, concomitantly administer vasoconstrictor nose spray to start treatment. For cases with severe nasal mucosal swelling and severe pharyngeal and laryngeal symptoms at hospital visit, administer oral corticosteroids for up to 4-7 days. Start treatment by the combination of nasal spray steroids, second-generation antihistamine, and leukotriene receptor antagonists.

9. POINTS TO REMEMBER IN TREATING COMPLICATIONS

9.1. ACUTE AND CHRONIC SINUSITIS

In patients with allergic rhinitis, imaging tests may show opacities in the paranasal sinuses. Diagnose them as sinusitis complications. It is controversial whether sinusitis occurs in patients with type I allergy. Among children, particularly infants, infectious sinusitis, including an acute one, is common, which requires composite treatment. Allergic inflammation is characterized by transparent and watery or viscous

Table 16 Choice of therapy for pollinosis based on severity

Severity	Primal therapy	Mild	Moderate		Severe	
Disease types			Sneezing and rhinorrhea type	Nasal blockage type or combined type with nasal blockage as a chief complaint	Sneezing and rhinorrhea type	Nasal blockage type or combined type with nasal blockage as a chief complaint
Treatments	a. Second-generation antihistamine b. Stabilizer c. Th2 cytokine inhibitors d. Anti-LTs agents e. Anti-PGD_2/TXA_2 agents	a. Second-generation antihistamine b. Nasal spray steroids	Second-generation antihistamine + Nasal spray steroids	Anti-LTs agents + Nasal spray steroids + Second-generation antihistamine	Nasal spray steroids + Second-generation antihistamine	Nasal spray steroids + Anti-LTs agents + Second-generation antihistamine
	Choose one of (a), (b), (c), (d), and (e).	Start treatment with (a) and eye drops, and add (b) as needed.				Use vasoconstrictor nose spray for only 7-10 days at the start of treatment as needed. For cases with severe nasal blockage, treatment may be started with oral corticosteroid administration for 4-7 days.
		Antihistamine for eye drops or stabilizer			Antihistamine for eye drops, stabilizer, or steroids	
					Perform surgery for cases with nasal deformities of a nasal blockage type.	
	Specific immunotherapy					
	Elimination and avoidance of antigens					

Note) Stabilizer = mast cell stabilizer, Anti-LTs agents = Leukotriene receptor antagonists, Anti-PGD_2/TXA_2 agents = Prostaglandin D_2/Thromboxane A_2 receptor antagonists.

Adapted from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

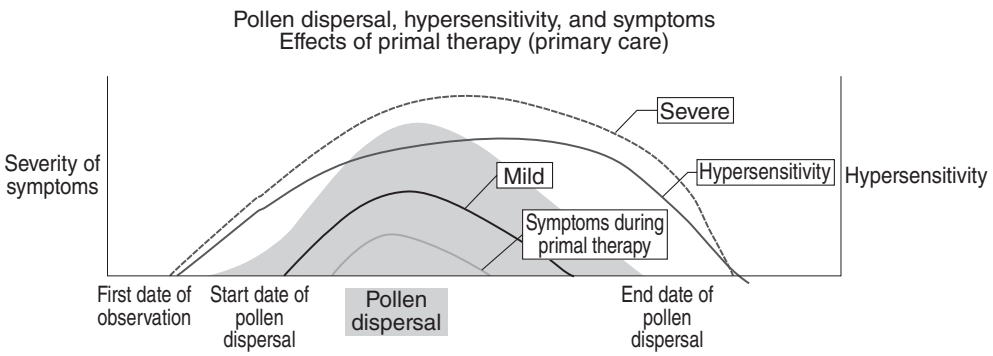

Fig. 6 Primal therapy for Japanese cedar pollinosis. Adapted from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

rhinorrhea. Differential diagnosis of early infection is difficult because of serous and watery rhinorrhea. Mucin and neutrophils increase as prophylaxis reactions progress, resulting in viscosity increase of rhinorrhea. Epithelial detachment causes the accumulation of neutrophils and bacteria, resulting in purulent or yellow-green rhinorrhea. For cases with nasal discharge eosinophilia, consider allergic rhinitis. However, in most cases with neutrophils coexisting or predominating, symptoms cannot be improved by allergy therapy alone. Thus, sinusitis should be diagnosed and treated. Conduct X-ray examination (Caldwell and Waters methods) to check opacities in the paranasal sinuses. In some cases, causative bacteria should be identified from the bacterial cultures of rhinorrhea or upper pharynx. For acute bacterial sinusitis, administer an oral antimicrobial, amoxicillin, as a first-line agent. For chronic sinusitis, 14-membered ring macrolides are effective when long-term administered in small amounts. Caution should be exercised for the combination of theophylline and 14-membered ring macrolides because serum theophylline levels may rise and cause poisoning symptoms.

9.2. EOSINOPHILIC SINUSITIS

Some patients with chronic sinusitis present with massive submucosal eosinophilic infiltration. Eosinophilic sinusitis is characterized by multiple nasal polyps, viscous rhinorrhea, and olfactory disorder, and is often complicated by asthma. Eosinophilic sinusitis is extremely intractable and resistant to surgery, resulting in repeated relapses. Oral corticosteroid therapy often results in a complete response. Eosinophilic otitis media is a frequent complication. Eosinophilic otitis media is characterized by an accumulation of sticky viscous liquid in the middle ear. Eosinophilic otitis media is an intractable disease characterized by eosinophilic infiltration in the accumulated liquid. Hearing loss is often exacerbated. Tinnitus and aural fullness cause severe discomfort. The symptoms of asthma complications, particularly asthma attack, are often exacerbated. Systemic or intratympanic steroid administration is effective.[19]

9.3. CORRELATION BETWEEN ASTHMA AND ALLERGIC RHINITIS OR EOSINOPHILIC SINUSITIS IN VIEW OF ONE AIRWAY ONE DISEASE

Approximately 30% of patients with allergic rhinitis are complicated by asthma. Reportedly, 28%-85% of patients with asthma are complicated by allergic rhinitis. Additionally, 75% of patients with atopic asthma and 40% of patients with nonatopic asthma are complicated by allergic rhinitis. Most patients with allergic rhinitis present with bronchial hyperreactivity. This also suggests that allergic rhinitis is a risk factor for asthma. The contribution rate of eosinophilic sinusitis to the severity of asthma is 34.5%. Eosinophilic sinusitis is fundamental to considering the pathology and treatment of asthma. Antigens, induced in the nasal mucosa, increase intercellular adhesion molecules and eosinophils in the lower respiratory tract, and exacerbate airway hyperresponsiveness.[20] In contrast, among patients with asthma, complicated by allergic rhinitis, those who underwent treatment for allergic rhinitis showed significantly reduced emergency visits and hospitalization as compared with those who were not treated. Surgical treatment (endoscopic sinus surgery) or medication for eosinophilic sinusitis or nasal polyp improves pulmonary functions. Thus, to diagnose patients with asthma complicated by allergic rhinitis or eosinophilic sinusitis, examine both upper and lower respiratory tracts. Examine the pathology in view of "one airway and one disease" to understand their correlation. Take an approach based on the correlation.[21]

9.4. TREATMENT OF SINUSITIS IN PATIENTS WITH ASPIRIN INTOLERANCE

In treating eosinophilic sinusitis in patients with aspirin intolerance, avoid using analgesics, antipyretics and antiinflammatory drugs (nonsteroidal antiinflammatory drugs [NSAIDs]) because they may cause an asthmatic attack. Basic antiinflammatory drugs cause no, or mild if any, asthmatic attacks. If pain occurs after surgery for sinusitis, pentazocine can be injected intramuscularly. Intravenous injection of hydrocortisone may exacerbate asthma. This may be caused by succinic acid ester contained in the injection. If corticosteroids are used, choose betamethasone sodium phosphate.

9.5. ALLERGIC CONJUNCTIVITIS

Allergic conjunctivitis includes hyperemic conjunctivitis and vernal keratoconjunctivitis (proliferative conjunctivitis). Atopic keratoconjunctivitis, complicated by atopic dermatitis, has also become common as the number of patients with atopic dermatitis increases. Hyperemic conjunctivitis is a common complication. Complications are common among patients with pollinosis. Most patients with pollinosis suffer from ocular itching, lacrimation, hyperemia, eye discharge, etc. Severe symptoms cause eyelid swelling. When children rub their eyes with their hands, they cause dark circles to form under their eyes. Eye discharge shows eosinophilia. Eosinophilia can be detected only by scratching the conjunctiva.

For pollinosis, wear glasses and avoid wearing contact lens if possible. For prolonged administration of steroid eye drops, caution should be exercised for adverse effects, such as glaucoma and corneal ulcer. Eye irrigation is effective in eliminating pollen.[22]

10. PRECAUTIONS

10.1. PRECAUTIONS FOR PREGNANT WOMEN (Table 17)

During pregnancy, congestive and allergic rhinitis

Table 17 Risks of medication in pregnant women with allergic rhinitis

Generic name	Trade name	Australian standards	FDA standards
Antiallergics (for internal use)			
d-chlorpheniramine maleate	Polaramin®	A	B
d-chlorpheniramine maleate	Allergin®	A	B
Diphenhydramine hydrochloride	Vena®, Restamin®	A	B
Cyproheptadine hydrochloride	Periactine®	A	B
Promethazine hydrochloride	Pyrethia®, Hiberna®		C
Clemastine fumarate	Tavegyl®	A	B
Diphenylpyraline teoclate	Agiell®, Plokon®	B2	
Loratadine	Claritin®	B1	B
Cetirizine hydrochloride	Zyrtec®	B2	B
Fexofenadine hydrochloride	Allegra®	B2	C
Amlexanox	Solfa®		B
Epinastine hydrochloride	Alesion®		C
Azelastine hydrochloride	Azeptin®		C
Ketotifen fumarate	Zaditen®		C
Nasal sprays			
Beclomethasone propionate	Aldecin® AQ Nasal, Rhinocort®	B3	C
Fluticasone propionate	Flunase®	B3	C
Disodium cromoglycate	Intal®		B
Amlexanox	Solfa®		B
Ketotifen fumarate	Zaditen®		C

Adapted from Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, digest version.

often occurs, and symptoms are exacerbated. Consider the impact of medication to pregnant and breast-feeding women on their fetuses and infants. For the 4.5 months between early pregnancy and organogenesis in particular, perform treatment only when benefits outweigh risks. For nasal blockage, hyperthermia, bathing, steamed towel, and masks are effective. If medication is required after the fourth month of pregnancy, minimize the use of local agents, such as DSCG, nasal spraymast cell stabilizer, nasal spray antihistamine, and nasal spray steroids.

10.2. PRECAUTIONS FOR CHILDREN

Allergic rhinitis is common among male infants, often complicated by atopic dermatitis and asthma. Although it is less common than atopic dermatitis and asthma, allergic rhinitis may heal spontaneously. Severe nasal itching and nasal blockade often cause nasal rubbing and facial movements and alterations (dark circle under the eyes [allergic shiner] and horizontal lining on the tip of the nose). Since children have large adenoids, palates, and tonsils, caution should be exercised for various infections. Childhood allergic rhinitis is generally intractable and requires long-term treatment. Thus, avoid irresponsible treatment and frequent hospital visits. Allergic rhinitis may be exacerbated by cold syndromes. Mite allergy is common among children. Eliminate and avoid mites, and instruct children to stay away from pets.

Pharmacotherapy for adults is also indicated for children. However, few therapeutic agents are indicated for the treatment of childhood allergic rhinitis. For elementary and junior high school students, give half the adult dose. Perform specific immunotherapy for patients aged $\geq$6 years. For asthma complications, carefully adjust the antigen dose. Perform surgery to improve nasal ventilation only for senior elementary students.

10.3. ORAL ALLERGY SYNDROME

Oral allergy syndrome (OAS) is an IgE antibody-dependent immediate food allergy, which causes hypersensitivity in the oropharyngeal mucosa and local and systemic type I allergic reactions after ingestion of food. OAS is often complicated by pollinosis or latex allergy. Potential allergens include cross reacting molecules, which is common between pollen antigens or latex allergens of fruits, vegetables, and cereals and causative food allergens of OAS. In patients with allergies to the pollens of *Betula platyphyla*, Rosaceae fruits (e.g., apples and peaches) cause frequently OAS. Reportedly, the common causative foods of OAS are tomato, melon, watermelon, and orange in patients with grass pollinosis. In patients with mugwort and ragweed pollinosis, the common causative foods are melon, watermelon, and celery. Melon, watermelon, and kiwi fruit are relatively common causative foods. In patients with latex allergy, avo-

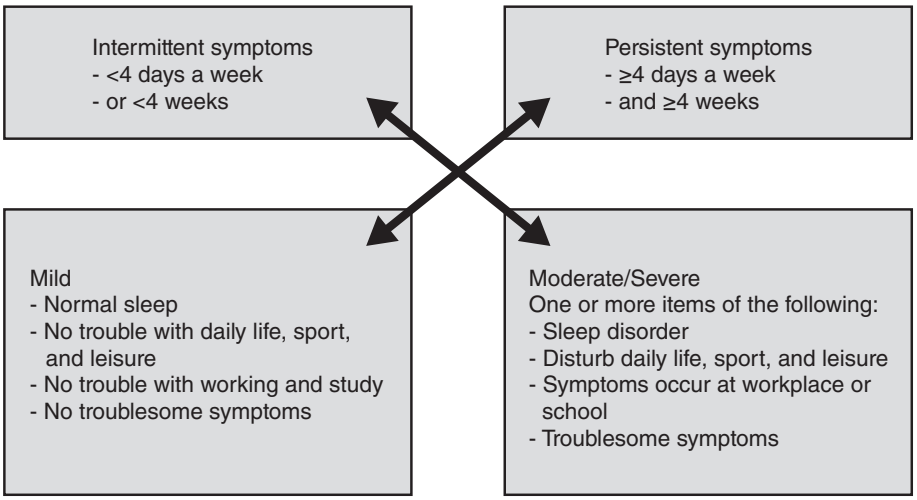

Fig. 7 Classification of allergic rhinitis by ARIA. Modified from ARIA 2008, Japanese version.

cado, chestnut, banana, and kiwi fruit are the common causative foods of OAS. In patients with Japanese cedar pollinosis, OAS caused by tomato has been reported. In most patients with OAS, local symptoms, such as itching, tingling, and edematous swelling on the oropharyngeal mucosa and lips, occur within 15 minutes after food ingestion. Digestive symptoms, such as diarrhea and abdominal pain, laryngeal edema, watery rhinorrhea, and conjunctival hyperemia also occur. Systemic symptoms include urticaria, eczema-like cutaneous symptoms, asthmatic symptoms, and sometimes anaphylactic shock. Avoiding causative food intake is the only the reliable treatment.

10.4. RELATIONSHIP WITH ARIA (ALLERGIC RHINITIS AND ITS IMPACT ON ASTHMA)

In 2001, allergy researchers from many countries published a consensus report, "Allergic Rhinitis and its Impact on Asthma (ARIA)" with WHO's recommendation.[21] This is sometimes considered as a standard international guideline for allergic rhinitis. As the title indicates, allergic rhinitis is examined regarding the effects on asthma. Hereinafter, major differences from the Practical Guideline for the Management of Allergic Rhinitis in Japan are described.

10.4.1. Classification of Rhinitis

In the Japanese guideline, rhinitis is classified based on pathology. In the ARIA2008, rhinitis is classified based on causes, with some diseases overlapping (Fig. 7).

10.4.2. Classification of Pathology

In the Japanese guideline, rhinitis is roughly divided into perennial and seasonal rhinitis based on the causative antigens of allergic diseases. In the ARIA 2008, rhinitis is divided into persistent symptoms, which continue $\geq$4 days a week for $\geq$4 weeks a year, and intermittent symptoms, which continue <4 days a week for <4 weeks a year. Behind this background, there are multiple sensitizations and a confusing classification of perennial and seasonal rhinitis symptoms. However, Japanese cedar pollinosis and perennial mite allergic rhinitis, affecting most Japanese patients with rhinitis, are similarly classified as persistent rhinitis.

10.4.3. Classification of Severity

In the ARIA2008, rhinitis is simply classified into "mild symptoms" and "moderate/severe symptoms." This classification is based on patients' assessments regarding influences on sleep, everyday life, work, etc. Behind this background, QOL assessment is emphasized. In the Japanese guideline, most patients who visit medical institutions are classified as having moderate or more severe symptoms. Thus, ARIA2008 classification is unsuitable for actual treatment.

10.4.4. Treatments (Fig. 8)

Treatments are simply described because of the simple classification of allergic rhinitis. For example, for persistent moderate/severe symptoms, the main therapeutic targets in this classification, first administer nasal spray steroids, and if the symptoms are not improved within 2-4 weeks, increase the dosage or use different agents. Most patients with Japanese cedar pollinosis are classified into severe diseases according to the Japanese guideline. Because of exposure to large amounts of pollen, treating these patients with a single agent is often difficult. Thus, descriptions that are more detailed are needed.

The ARIA2008 provides sufficient descriptions to allow the understanding of pathology, evidence of the

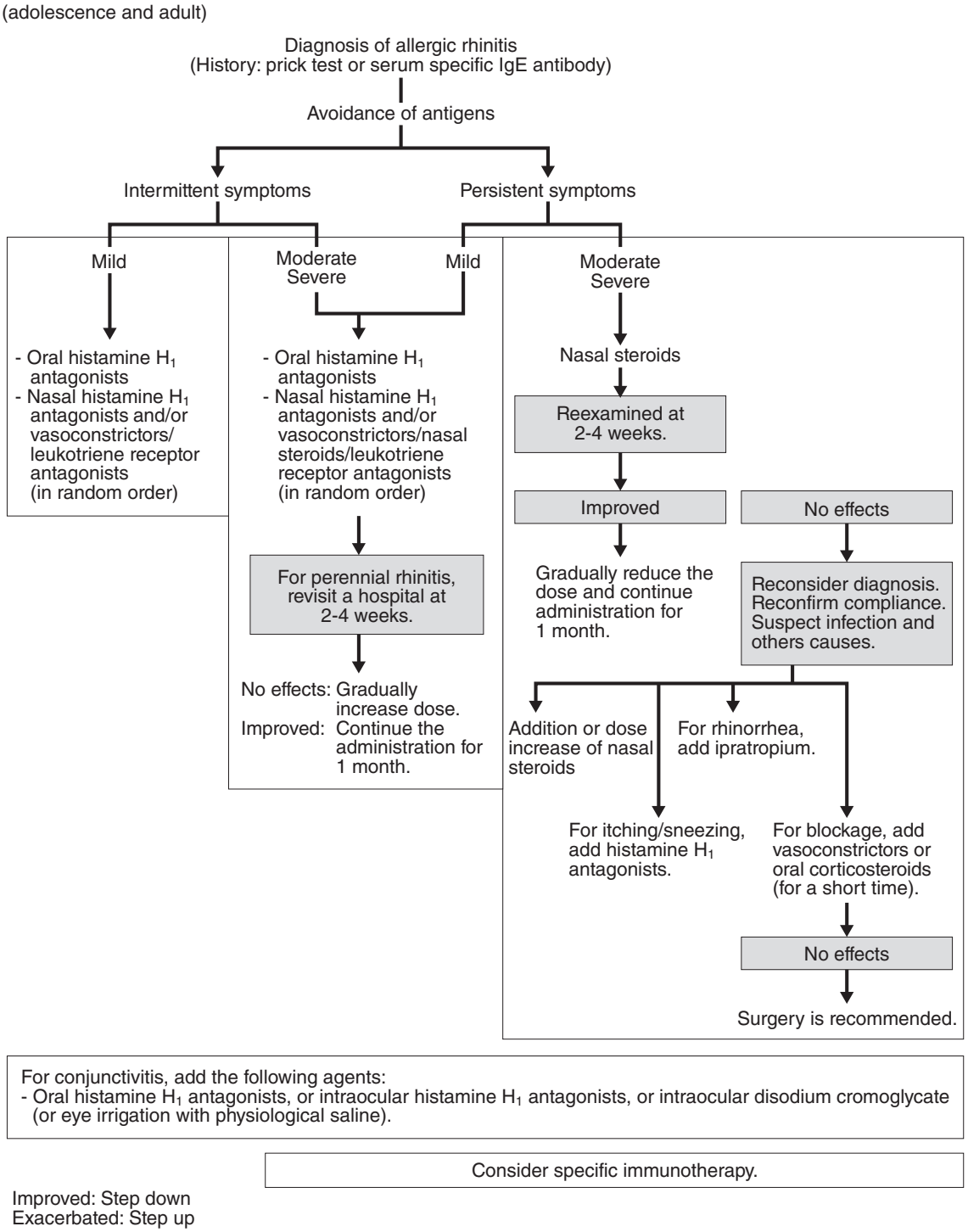

Fig. 8 Step-by-step approach for treatment by ARIA. Modified from ARIA 2008, Japanese version.

therapy, etc. However, important issues in the ARIA 2008, such as cost-benefit and the establishing evidence for inapplicable therapies to Japanese circumstances, where characteristic pollinosis like Japanese cedar pollinosis exists, should be examined in Japan.

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