Japanese Guideline for Allergic Rhinitis

Kimihiro Okubo¹, Yuichi Kurono², Shigeharu Fujieda³, Satoshi Ogino⁴, Eiichi Uchio⁵, Hiroshi Odajima⁶, Hiroshi Takenaka⁷ and Kohtaro Baba⁸

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.

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.
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 rhinopathy, 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.](image-url)

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 sens-

---

Okubo K et al.
**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).
Okubo K et al.

Fig. 4  Mechanism of allergic rhinitis. Hi, histamine; LT, leukotriene; TXA₂, thromboxane A₂; PGD₂, prostaglandin D₂; 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.

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

2 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

<table>
<thead>
<tr>
<th>Severity</th>
<th>Paroxysmal sneezing or rhinorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++++</td>
<td>Most severe</td>
</tr>
<tr>
<td>+++</td>
<td>Most severe</td>
</tr>
<tr>
<td>++</td>
<td>Most severe</td>
</tr>
<tr>
<td>+</td>
<td>Most severe</td>
</tr>
<tr>
<td>-</td>
<td>Most severe</td>
</tr>
</tbody>
</table>

Nasal blockage

<table>
<thead>
<tr>
<th>Severity</th>
<th>Paroxysmal sneezing or rhinorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++++</td>
<td>Most severe</td>
</tr>
<tr>
<td>+++</td>
<td>Severe</td>
</tr>
<tr>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>+</td>
<td>Moderate</td>
</tr>
<tr>
<td>-</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Nasal blockage

<table>
<thead>
<tr>
<th>Severity</th>
<th>Paroxysmal sneezing or rhinorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++++</td>
<td>Most severe</td>
</tr>
<tr>
<td>+++</td>
<td>Severe</td>
</tr>
<tr>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>+</td>
<td>Mild</td>
</tr>
<tr>
<td>-</td>
<td>Mild</td>
</tr>
</tbody>
</table>

Nasal blockage

<table>
<thead>
<tr>
<th>Severity</th>
<th>Paroxysmal sneezing or rhinorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++++</td>
<td>Most severe</td>
</tr>
<tr>
<td>+++</td>
<td>Severe</td>
</tr>
<tr>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>+</td>
<td>Mild</td>
</tr>
<tr>
<td>-</td>
<td>Mild</td>
</tr>
</tbody>
</table>

Nasal blockage

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

<table>
<thead>
<tr>
<th>Types</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal sneezing (Average number of episodes of paroxysmal sneezing in a day)</td>
<td>≥21 times</td>
</tr>
<tr>
<td>Rhinorrhea (Average number of episodes of nose blowing a day)</td>
<td>20-11 times</td>
</tr>
<tr>
<td>Nasal blockage</td>
<td>10-6 times</td>
</tr>
<tr>
<td>Troubles with daily life †</td>
<td>5-1 times</td>
</tr>
<tr>
<td></td>
<td>Below +</td>
</tr>
</tbody>
</table>

† 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.

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.

Nasal and eye symptoms
0, No symptoms 1, Mild 2, Moderate 3, Severe 4, Very severe

Quality of life
0, No 1, Yes, slight 2, Yes, moderately 3, Yes, greatly 4, Yes, very greatly

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

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.

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.

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 D2/thromboxane A2 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 polinosis, 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 polinosis, 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

<table>
<thead>
<tr>
<th>Elimination of house dust mites</th>
<th>Avoidance of cedar pollen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For indoor cleaning, use an exhaust circulation-type cleaner. Clean room for 20 s/m² twice a week.</td>
<td>1. Collect pollen information.</td>
</tr>
<tr>
<td>2. Avoid using textile sofa, carpet, and tatami wherever possible.</td>
<td>2. Stay at home during a heavy pollen dispersal period.</td>
</tr>
<tr>
<td>3. Put antmite covers over mattresses, beds, and pillows.</td>
<td>3. Shut windows and doors during a heavy pollen dispersal period.</td>
</tr>
<tr>
<td>4. Keep humidity at 50% and room temperature at 20-25°C.</td>
<td>4. When going out during a heavy pollen dispersal period, wear a mask and glasses.</td>
</tr>
</tbody>
</table>

### Table 5 Therapeutic agents for allergic rhinitis

1. **Mast cell stabilizer**
   - Disodium cromoglycate (Intal®), tranilast (Rizaben®), amlexanox (Sofla®), pemilostat potassium (Alegysal®, Pemilast®)

2. **Chemical mediator receptor antagonists**
   - **Histamine H1 receptor antagonists (antihistamine)**
     - **First-generation**
       - d-chlorpheniramine maleate (Polaramin®), clemastine fumarate (Tavegyl®), etc.
     - **Second-generation**
       - Ketotifen fumarate (Zaditen®), azelastine hydrochloride (Azeptin®), oxatomide (Celtec®), mequitazine (Zesulan®, Nipolazin®), emedastine difumarate (Daren®, Remicured®), epinastine hydrochloride (Alesion®, Bepotastine besilate (Talion®), fexofenadine hydrochloride (Allegra®), olopatadine hydrochloride (Allelock®), loratadine (Claritin®)
   - **Leukotriene receptor antagonists**
     - Pranlukast hydrate (Onon®), montelukast sodium (Singular®, Kipes®)
   - **Prostaglandin D2/thromboxane A2 receptor antagonists (anti-prostaglandin D2/thromboxane A2 agents)**
     - Ramatroban (Baynas®)

3. **Th2 cytokine inhibitor**
   - Suplatast tosilate (IPD®)

4. **Steroids**
   - **Nasal spray**
     - Beclomethasone propionate (Aldecin® AQ Nasal, Rhinocort®), fluticasone propionate (Flunase®), mometasone furoate hydrate (Nasonex®), dexamethasone cipiclate capsule for external use (Erizas®)
   - **Oral medication**
     - Compounding agent of betamethasone/d-chlorpheniramine maleate (Celestamine®)

5. **Others**
   - Non-specific allergy therapy agents, biological preparations, and herbal medicines

Adapted 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.


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.


Table 8 Characteristics of prostaglandin D2/thromboxane A2 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 PGD2, and improve sneezing and rhinorrhea by ≥2-week prolonged administration.
4. Effects are relatively slow, reaching a peak at 4 weeks.


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


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. 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 cipocinate 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.14

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 alllassotherapy agents, biological preparations, and herbal medicines

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


Table 11  Adverse effects of therapeutic agents for allergic rhinitis

<table>
<thead>
<tr>
<th>Medicines</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation antihistamine</td>
<td>Sleepiness, systemic malaise, dry mouth, etc. (asthma, dysuria, glaucoma, and contraindication to driving)</td>
</tr>
<tr>
<td>Second-generation antihistamine</td>
<td>Hepatic and gastrointestinal disorders, sleepiness, and myocardopathy for some agents</td>
</tr>
<tr>
<td>Oral mast cell stabilizer</td>
<td>Hepatic and gastrointestinal disorders, rash, and cystitis for some agents</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists</td>
<td>Leukopenia, thrombocytopenia, hepatic disorders, rash, diarrhea, abdominal pain, etc.</td>
</tr>
<tr>
<td>Prostaglandin D2/thromboxane A2 receptor antagonists</td>
<td>Bleeding tendency, hepatic disorders, rash, abdominal pain, headache, etc.</td>
</tr>
<tr>
<td>Th2 cytokine inhibitors</td>
<td>Hepatic disorders, jaundice, nephrosis, etc.</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>Infection, adrenocortical insufficiency, diabetes, peptic ulcer, moon face, glaucoma, etc. (contraindicated for treatment of infection, peptic ulcer, hypertension, diabetes, glaucoma, etc.)</td>
</tr>
<tr>
<td>Nasal spray steroids</td>
<td>Nasal irritation, feeling of dryness, epistaxis, etc.</td>
</tr>
<tr>
<td>Mast cell stabilizer and antihistamine for nasal spray</td>
<td>Nasal irritation and sleepiness (for some agents)</td>
</tr>
<tr>
<td>Vasoconstrictor nose spray</td>
<td>Habitation, rebound phenomena, hyporesponsiveness, etc.</td>
</tr>
</tbody>
</table>

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

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 alllassotherapy 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. 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 $\beta$-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>
<thead>
<tr>
<th>Therapeutic agents</th>
<th>Concomitant agents</th>
<th>Effects</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation antihistamine</td>
<td>Alcohol, Sedatives, hypnotics, psychotropics, Cold medicines</td>
<td>Enhanced central inhibition → Hypnosis, vertigo, weakness, malaise</td>
<td>Caution should be exercised for combined use. → Reduce dose if adverse effects are noted.</td>
</tr>
<tr>
<td></td>
<td>Tolbutamide</td>
<td>Thrombocytopenia → Bleeding tendency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Exacerbation of extrapyramidal disturbances → Tremor and difficulty in walking</td>
<td>Caution should be exercised for combined use. → Discontinue the combined use if adverse effects are noted.</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants</td>
<td>Enhance anticholinergic effects → Dry mouth and exacerbation of glaucoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticholinergics</td>
<td>Exacerbation of tremor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β2 stimulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Inhibition of liver drug-metabolizing enzymes → Increased serum carebastine level</td>
<td>Caution should be exercised for combined use. → Reduce dose if adverse effects are noted.</td>
</tr>
<tr>
<td></td>
<td>Antacids</td>
<td>Decreased absorption → Reduced effects</td>
<td>Caution should be exercised for combined use. → Discontinue the combined use if adverse effects are noted.</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Increased absorption and decreased clearance → Increased serum level</td>
<td>Caution should be exercised for combined use. → Reduce dose if adverse effects are noted.</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Inhibition of liver drug-metabolizing enzymes → Increased serum levels</td>
<td>Caution should be exercised for combined use. → Reduce dose if adverse effects are noted.</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin potassium</td>
<td>Inhibition of liver drug-metabolizing enzymes → Bleeding tendency</td>
<td>Caution should be exercised for combined use. → Discontinue the combined use if adverse effects are noted.</td>
</tr>
<tr>
<td>Mast cell stabilizer</td>
<td>Itraconazole</td>
<td>Inhibition of liver drug-metabolizing enzymes → Increased serum levels</td>
<td>Caution should be exercised for combined use. → Reduce the dose if adverse effects are noted.</td>
</tr>
<tr>
<td>Tranilast</td>
<td>Erythromycin</td>
<td>Induction of liver drug-metabolizing enzymes → Decreased serum levels</td>
<td>Caution should be exercised for combined use. → Increase dose if adverse effects are noted.</td>
</tr>
<tr>
<td>Leukotriene receptor</td>
<td>Montelukast</td>
<td>Enhanced inhibitory effects on platelet aggregation → Bleeding tendency</td>
<td>Caution should be exercised for combined use. → Discontinue the combined use if adverse effects are noted.</td>
</tr>
<tr>
<td>antagonists</td>
<td>Phenoobarbital</td>
<td>Decline in plasma protein binding → Increased serum level of free aspirin</td>
<td></td>
</tr>
<tr>
<td>Pranlukast hydrate</td>
<td>Antithrombotics</td>
<td>Competition of liver drug-metabolizing enzymes → Increased serum levels</td>
<td></td>
</tr>
</tbody>
</table>

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 cautering the surface with a laser beam (CO2, 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. 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
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. If symptoms are exacerbated as pollen dispersal increases, use the combination of nasal spray steroids and second-generation antihistamine. 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 15  Treatment of perennial allergic rhinitis**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease types</td>
<td>Sneezing and rhinorrhea type</td>
<td>Nasal blockage type or combined type with nasal blockage as a chief complaint</td>
<td>Sneezing and rhinorrhea type</td>
</tr>
<tr>
<td></td>
<td>Choose one of (a), (b).</td>
<td>Choose one of (a), (b), (c), and (d). Combine (a), (b), or (c), with (d), as needed.</td>
<td>Use vasoconstrictor nose spray for only 5-7 days at the start of treatment as needed.</td>
</tr>
</tbody>
</table>

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-PGD2/TXA2 agents = Prostaglandin D2 Thromboxane A2 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 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.
Table 16  Choice of therapy for pollinosis based on severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primal therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sneezeing and rhinorrhea type</td>
<td>Nasal blockage type or combined type with nasal blockage as a chief complaint</td>
<td>Sneezeing and rhinorrhea type</td>
<td>Nasal blockage type or combined type with nasal blockage as a chief complaint</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease types</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b. Nasal spray steroids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatments</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Choose one of (a), (b), (c), (d), and (e).</td>
<td>Start treatment with (a) and eye drops, and add (b) as needed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antibiotic for eye drops or stabilizer</td>
<td>Antibiotic for eye drops, stabilizer, or steroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perform surgery for cases with nasal deformities of a nasal blockage type.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specific immunotherapy

Elimination and avoidance of antigens

Note) Stabilizer = mast cell stabilizer, Anti-LTs agents = Leukotriene receptor antagonists, Anti-PGD2/TXA2 agents = Prostaglandin D2/Thromboxane A2 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. 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 irritation 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

<table>
<thead>
<tr>
<th>Antiallergics (for internal use)</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Australian standards</th>
<th>FDA standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-chlorpheniramine maleate</td>
<td>Polaramin®</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>d-chlorpheniramine maleate</td>
<td>Allergin®</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine hydrochloride</td>
<td>Vena®, Restamin®</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine hydrochloride</td>
<td>Periactin®</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Promethazine hydrochloride</td>
<td>Pyrethia®, Hiberna®</td>
<td>A</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Clemastine fumarate</td>
<td>Tavegyl®</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Diphenylpyraline tooclate</td>
<td>Agiell®, Plonon®</td>
<td>B2</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Loratadine</td>
<td>Claritin®</td>
<td>B1</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Cetirizine hydrochloride</td>
<td>Zyrtec®</td>
<td>B2</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Fexofenadine hydrochloride</td>
<td>Allegra®</td>
<td>B2</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Amlexanox</td>
<td>Solfa®</td>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Epinastine hydrochloride</td>
<td>Alesion®</td>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Azelastine hydrochloride</td>
<td>Azeptin®</td>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Ketotifen fumarate</td>
<td>Zaditen®</td>
<td></td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

| 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 sprays mast 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 ≥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 platyphylla, 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-
Intermittent symptoms
- <4 days a week
- or <4 weeks

Persistent symptoms
- ≥4 days a week
- and ≥4 weeks

Mild
- Normal sleep
- No trouble with daily life, sport, and leisure
- No trouble with working and study
- No troublesome symptoms

Moderate/Severe
One or more items of the following:
- Sleep disorder
- Disturb daily life, sport, and leisure
- Symptoms occur at workplace or school
- Troublesome symptoms

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 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. 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 ARIA2008, rhinitis is divided into persistent symptoms, which continue ≥4 days a week for ≥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.

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

**REFERENCES**


