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Invited review article

Japanese guidelines for adult asthma 2017☆

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ABSTRACT

Adult bronchial asthma is characterized by chronic airway inflammation, and presents clinically with variable airway narrowing (wheezes and dyspnea) and cough. Long-standing asthma induces airway remodeling, leading to intractable asthma. The number of patients with asthma has increased; however, the number of patients who die of asthma has decreased (1.2 per 100,000 patients in 2015). The goal of asthma treatment is to enable patients with asthma to attain normal pulmonary function and lead a normal life, without any symptoms. A good relationship between physicians and patients is indispensable for appropriate treatment. Long-term management by therapeutic agents and elimination of the causes and risk factors of asthma are fundamental to its treatment. Four steps in pharmacotherapy differentiate between mild and intensive treatments; each step includes an appropriate daily dose of an inhaled corticosteroid, varying from low to high levels. Long-acting β_2-agonists, leukotriene receptor antagonists, sustained-release theophylline, and long-acting muscarinic antagonist are recommended as add-on drugs, while anti-immunoglobulin E antibody and oral steroids are considered for the most severe and persistent asthma related to allergic reactions. Bronchial thermoplasty has recently been developed for severe, persistent asthma, but its long-term efficacy is not known. Inhaled β_2-agonists, aminophylline, corticosteroids, adrenaline, oxygen therapy, and other approaches are used as needed during acute exacerbations, by choosing treatment steps for asthma in accordance with the severity of exacerbations. Allergic rhinitis, eosinophilic chronic rhinosinusitis, eosinophilic otitis, chronic obstructive pulmonary disease, aspirin-induced asthma, and pregnancy are also important issues that need to be considered in asthma therapy.

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1. Aim of the management, definition, type, diagnosis, and severity of asthma

1.1. Definition and pathophysiology of asthma

Adult bronchial asthma (hereinafter, asthma) is characterized by chronic airway inflammation, clinically presenting variable airway narrowing (wheezes and dyspnea) and cough. Airway narrowing is reversible, and derives from airway inflammation and hyperresponsiveness. Pathological analyses in asthma demonstrate chronic airway inflammation accompanied by the infiltration of proinflammatory cells such as eosinophils, lymphocytes, mast cells, and others, and by the detachment of the airway epithelial cells.[1,2]

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While many patients are atopic, i.e., positive for immunoglobulin E (IgE) antibodies against environmental allergens, airway inflammation and lymphocyte activation are present even in patients without allergen-specific IgE antibodies. The etiology of asthma is multifactorial, and its clinical picture varies greatly among patients. Some asthmatic patients demonstrate airway inflammation, predominantly involving neutrophils. Long-standing inflammation will damage airways, and induces airway remodeling, entailing subepithelial fibrosis under the basement membrane, smooth muscle hypertrophy, and submucosal gland hyperplasia. This results in intractable asthma, presenting irreversible airflow limitation and persistent airway hyperresponsiveness.[3]

1.2. Aim of the management and treatment of asthma

The aim of asthma management and treatment is to improve airway hyperresponsiveness and airflow limitation by eliminating inducers of airway inflammation, by adopting pharmacotherapy to alleviate inflammation, and by dilating the constricted airway (Table 1). In this way, respiratory function can hopefully be normalized to improve the patients' quality of life (QOL) and enable them to lead a normal and healthy life without exacerbations or asthma-related death.

1.3. Phenotype/endotype

Asthma patients are characterized by widely variable clinical pictures; asthma is thus often recognized as a syndrome, and is classified into several phenotypes. Recent progress in genetics and molecular biology has led to the etiological and/or pathogenetic classification of the condition into endotypes.

1.4. Diagnosis of adult asthma

Generally, clinical diagnosis of asthma is based on the following factors (Table 2): (1) repetitive symptoms, such as paroxysmal dyspnea, wheezing, chest tightness, and cough; (2) reversible airflow limitation; (3) airway hyperresponsiveness; and (6) exclusion of other cardiopulmonary diseases (Table 3). (4) An atopic state and (5) airway inflammation, which is usually indicative of eosinophilia, support a diagnosis of asthma. Diagnosing mild asthma in the absence of either wheezes or dyspnea can be difficult.

1.4.1. Recurrence of paroxysmal dyspnea, wheezing, chest tightness, and cough

Asthma symptoms often occur at night and in the early morning. Repeated exacerbations occur amid symptom-free intervals and develop even at rest. Patients with asthma may experience dyspnea (choking) during exercise and while performing laborious work.

1.4.2. Reversible airflow limitation

Wheezing and dyspnea during attacks are induced by reversible airway narrowing, which occurs diffusely throughout the airways and ranges from mild to severe. In its mild form, it can be detected only by respiratory function tests, while in its severe form, it could induce near-fatal exacerbations. The peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV_1) often differ markedly between exacerbations and controlled periods, in each patient. Reversible airflow limitation is regarded as significant when FEV_1 is increased by 12% or more, and 200 mL or more of the absolute volume, after β_2-agonist inhalation.[4] In addition, even if no significant difference is noted in respiratory function tests before and after β_2-agonist inhalation, reversible airflow limitation is still suspected when a diurnal variation in PEF of 20% and higher if present. Long-standing asthma often shows stably low PEF and FEV_1, without significant fluctuation due to airway remodeling; in such cases, chronic obstructive pulmonary disease (COPD) cannot be ruled out.

Table 1
Aims of asthma treatment.

1. To lead a normal and healthy life.
2. To prevent the development of irreversible airway remodeling and maintain normal respiratory function:
   Peak expiratory flow (PEF), ≥80% of the predicted value;
   PEF variation, <20% of the predicted value.
3. To prevent asthma attacks all day long.
4. To prevent death due to asthma.
5. To prevent adverse effects caused by therapeutic agents.

Table 2
Diagnosis of adult asthma: key features.

1. Recurrence of paroxysmal dyspnea, wheezing, chest tightness, and cough (particularly at night and in the early morning)
2. Reversible airflow limitation
3. Airway hyperresponsiveness
4. Atopy
5. Airway inflammation
6. Differential diagnosis

Items 1, 2, 3, and 6 are important for diagnosis.
Items 4 and 5, in combination with symptoms, support the diagnosis of asthma.
Item 5 is usually indicative of eosinophilia.

Table 3
Differential diagnosis of asthma.

1. Upper respiratory tract diseases: laryngitis, epiglottitis, vocal cord dysfunction
2. Proximal respiratory tract diseases: endotracheal tumor, foreign body aspiration, tracheomalacia, endobronchial tuberculosis
3. Diseases of the bronchus and alveolar regions: chronic obstructive pulmonary disease
4. Cardiovascular diseases: congestive heart failure, pulmonary thromboembolism
5. Cough induced by medicines, such as angiotensin-converting enzyme inhibitors
6. Other causes: spontaneous pneumothorax, hyperventilation syndrome, and psychogenic cough

1.4.3. Airway hyperresponsiveness

Weak stimuli cause the airway to contract, even stimuli to which healthy individuals show no response. A standard quantitation method of the Japanese Society of Allergology for assessing changes in FEV_1, or a method using an Astograph, which monitors respiratory system impedance, are recommended.[5,6] In the former method, a patient inhales a bronchoconstrictor (e.g., serially diluted acetylcholine, methacholine, or histamine) for 2 min before assessment of FEV_1. PC_{20} (i.e., the concentration that can reduce FEV_1 by 20%) and PD_{20} (i.e., the cumulative dose at that time-point) represent airway responsiveness. In the latter method, the patient automatically inhales serially diluted methacholine. Airway responsiveness is assessed as Dmin, the concentration of methacholine at which airway resistance starts to increase. Both methods involve load tests that induce airway narrowing; thus, patients with severely decreased respiratory function should not be tested in this way. A desirable baseline percentage of FEV_1 against a predicted value (%FEV_1) is 70% or higher.

1.4.4. Atopy

Specific IgE antibodies against various environmental allergens indicate an atopic state.

1.4.5. Airway inflammation

Increased percentages of eosinophils, high eosinophil cationic protein values, and Creola bodies, consisting of detached airway

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epithelial cells, detected by sputum analysis, indicate allergic airway inflammation.[7] An increased fraction of exhaled nitric oxide (FeNO) also suggests eosinophilic airway inflammation, and is often observed in untreated asthma.[8,9] FeNO levels decrease with the use of inhaled corticosteroids; thus, it is useful for monitoring airway inflammation. An increased eosinophil count in the peripheral blood and elevated serum levels of eosinophil cationic protein also suggest airway inflammation, although they are nonspecific.

1.4.6. Differential diagnosis

A comprehensive diagnosis should be made if asthma-like symptoms are borderline, which maybe caused by other cardiopulmonary diseases, are considered (Table 3). Differential diagnosis of COPD should be made carefully, as this disease may overlap with asthma.

1.5. Classification of the severity of asthma and asthma exacerbation

Assessment of the severity of asthma and its exacerbation is important in the management of asthma and stepwise pharmacotherapy (Table 4). Untreated asthma is classified into 4 categories based on severity, i.e., mild intermittent, mild persistent, moderate persistent, or severe persistent (Table 4). These categories correspond to the recommendations for treatment steps 1–4, respectively (Table 5). For patients under treatment, the symptoms and the present treatment step determine the severity (Table 6). The classification of exacerbation severity is shown in Table 7.

1.6. Intractable asthma

Intractable asthma is the most severe and persistent type of asthma, whether controlled by, or uncontrolled despite administration of, step 4 treatment, involving high-dose inhaled corticosteroids (ICSs), long-acting β_2-agonists (LABAs), leukotriene receptor antagonists (LTRAs), theophylline, anti-IgE antibody, and oral corticosteroid (Table 5, 6). Intractable asthma is often called severe asthma. Additional underlying diseases, such as aspirin-exacerbated respiratory disease (AERD; also known as aspirin-intolerant asthma and aspirin-induced asthma, AIA), eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–-Strauss syndrome, CSS) and other systemic vasculitis syndromes, and allergic bronchopulmonary mycosis (ABPM), should be considered in patients requiring continuous administration of oral corticosteroid.

2. Epidemiology of asthma

2.1. Changes in asthma prevalence over time

Asthma prevalence has rapidly increased in recent years. An International Study of Asthma and Allergies in Childhood (ISAAC) survey has been conducted across Japan to assess the prevalence of asthma at specific time points. The mean prevalence of asthma in Japan has increased from about 1% to 10% or higher in children and to about 6–10% in adults since the 1960s. In addition, according to a survey in which the same physicians used the same protocol in subjects with the same background (Table 8),[10,11] a 1.5-fold increase per decade was noted in the prevalence of asthma. Surveys conducted among the citizens of Fujieda City in Shizuoka Prefecture in 1985, 1999, and 2006, showed that the prevalence of adult asthma has been increasing, while the latest study of children in western Japan has indicated a decrease in the prevalence of asthma (Table 8).

2.2. Regional differences in asthma prevalence

The ISAAC Steering Committee has reported clear regional differences in the prevalence of asthma: 3.5% in Indonesia, 34.8% in Costa Rica in 6- to 7-year-old subjects, 3.0% in Albania, and 32.3% in the Isle of Man in 13- to 14-year-old subjects. The prevalence of asthma in Japan (Fukuoka City, 13%) was slightly lower than that in Europe and the USA. The European Community Respiratory Health Survey showed that the prevalence of asthma in Japan was lower (8.1%); however, these surveys were conducted in different years (Table 9).[12]

2.3. Male-to-female ratio

Globally, asthma is more common in men than in women, at an early age; however, after puberty, the prevalence is higher in women (Fig. 1). In terms of age of onset of asthma according to gender in Japan, the male-to-female ratios were 1.4 during infancy (0–5 years of age), 1.0 during childhood (6–17 years of age), and 0.8 in adulthood (18 years of age and older).

2.4. Number of patients

According to the 2014 Statistical Information from the Japanese Ministry of Health, Labour, and Welfare, the number of patients with asthma who continued to visit the hospital in a survey conducted in October 2014, was 1,177,000 (515,000 men and 662,000 women). These were calculated as the number of hospitalized patients + new outpatients + second-visit outpatients × average visit interval × survey coefficient. Medical treatment rates in the hospital and outpatient settings are shown in Table 10. In a telephone survey conducted in 2011 (Asthma Insight and Reality in Japan, AIRJ2011), the percentage of patients who reported

Table 4
Classification of asthma severity based on clinical findings before treatment (adults).

Severity[†]		Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Features of asthma symptoms	Frequency	Less than once a week	Once or more a week, not every day	Every day	Every day
	Intensity	Mild and brief	Disturbs daily life or sleep at least once a month	Disturbs daily life or sleep at least once a week	Restricts daily life
				Worsens frequently	Worsens frequently
	Symptoms at night	Less than twice a month	Twice or more a month	Once or more a week	Frequently
PEF FEV_1[‡]	%FEV_1, %PEF	≥80%	≥80%	≥60%, <80%	<60%
	Diurnal variation of PEF	<20%	20–30%	>30%	>30%

[†] Determine the severity based on the presence of any one of the features or measured percentages.
[‡] In patients with severe or long-standing symptoms, severity may be underestimated when determined based on symptoms. Respiratory function indicates the objective severity of airway obstruction. Its variation is associated with airway hyperresponsiveness. %FEV_1, (FEV_1 measured value/FEV_1 predicted value) × 100; %PEF, (PEF measured value/PEF predicted value or the best value) × 100.

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Table 5
Treatment steps for asthma.

		Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Long-term management agents	Basic treatment	Inhaled corticosteroid (low dose)	Inhaled corticosteroid (low to medium doses)	Inhaled corticosteroid (medium to high doses)	Inhaled corticosteroid (high dose)
		If the above agent cannot be used, use one of the following agents. • LTRA • Theophylline sustained-release preparation (unnecessary for rare symptoms)	If the above agent is ineffective, concomitantly use one of the following agents. • LABA (a compounding agent can be used)‖ • LTRA • Theophylline sustained-release preparation	Concomitantly use one or more of the agents below. • LABA (a compounding agent can be used)‖ • LTRA • Theophylline sustained-release preparation • LAMA #	Concomitantly use multiple agents of those below. • LABA (a compounding agent can be used) • LTRA • Theophylline sustained-release preparation • LAMA# • Anti-IgE antibody‡,†† • Oral corticosteroid§,††
	Additional treatment	Anti-allergics other than LTRA†	Anti-allergics other than LTRA†	Anti-allergics other than LTRA†	Anti-allergics other than LTRA†
Exacerbation treatment¶		Inhaled SABA	Inhaled SABA	Inhaled SABA	Inhaled SABA

LTRA, leukotriene receptor antagonists; LABA, long-acting β_2 agonist; SABA, short-acting β_2 agonist; LAMA, long-acting muscarinic antagonist.
† Antiallergics refer to mediator antireleasers, histamine H1 antagonists, thromboxane A2 inhibitors, and Th2 cytokine inhibitors.
‡ Anti-IgE antibody is indicated for patients who are positive for perennial inhaled allergen with serum total IgE value within 30–1500 IU/ml.
§ Oral corticosteroids are intermittently administered for a short period. Maintain the minimum maintenance dose if a patient cannot be controlled by enhanced treatment with other agents and short intermittent administration.
¶ Management against mild exacerbations is shown. For other exacerbations, refer to Table 19, 21.
‖ In patients treated with a combination of budesonide/formoterol as a controller, if used as a rescue, the agent should not be used beyond the maximum number of uses per time and per day. The maximum number of uses is generally up to 8 inhalations/day; however, temporarily, it can be used up to 12 inhalations/day (for 3 days: budesonide, 1920 μg/day; formoterol 54 μg/day). When more than 8 inhalations/day of budesonide/formoterol are needed, a physician should be consulted.
Soft mist inhaler of tiotropium.
†† Anti-IgE antibody and oral corticosteroid are considered when asthma control cannot be achieved with inhaled corticosteroid plus LABA and LTRA, etc.

symptoms within a month was 62% (adults) and 60% (children). ICSs were used by 34% and 20% of adults and children, respectively, and these percentages may increase in future.

2.5. Deaths from asthma

According to the Vital Statistics of the Japanese Ministry of Health, Labour, and Welfare, the number of patients who died of asthma has decreased in recent years.[13] This number was high, reaching a rate of 4.5–5.0 per 100,000 population between 1975 and 1994, then transiently increased in 1995, and decreased again after 1997, reaching its lowest point of 1.2 per 100,000 population (1510 deaths) in 2015 (Fig. 2, 3). In particular, the number of patients who died of asthma at an early age has markedly decreased; about 90% of asthma deaths occur among the elderly, aged 65 years or older (Fig. 4).

3. Patient education and physician–patient relationship

3.1. Educational needs

It is necessary for patients to have a certain amount of knowledge in order to create a good relationship with medical professionals and to ensure self-management. Sufficient patient education regarding asthma reduces the prevalence and mortality of asthma, improves the patients' QOL, and reduces medical costs.[14] Effective education includes the preparation of a written self-management plan (action plan) that outlines severity assessment and self-management of asthma, and instructions on the use of long-term and add-on medications.[14]

3.2. Subjects

Education should be provided to patients, as well as to their families, neighbors, and caretakers of the elderly. It is important not only for specialists but also for general physicians and medical staff to update their knowledge of asthma.

3.3. Contents

Since asthma is a chronic disease, the importance of long-term management should be explained to patients. Patients, physicians, and medical staff should discuss the expected outcomes and any concerns regarding treatment. In addition, the crux of asthma management, listed in Table 11, should be conveyed to patients. Self-monitoring of PEF is important to avoid and manage exacerbations; it is important for patients to understand how and why PEF is measured and monitored. Physicians should provide patients with the concept of prophylactic treatment and review the self-management plan, including its application when, for example, PEF remains low even after the use of add-on medications.

3.4. Educators

Specialists in asthma cannot devote all their time to patient education. Therefore, general physicians, together with nurses, public health nurses, and pharmacists can participate in education, while community-driven education is also desirable. Recently, expert pharmacists, who excel at educating inhalation techniques, have been generated in several regions.

3.5. Places of education

Education is a continuous task and is provided by specialized institutions, health centers, patient support groups, as well as through distribution of various teaching materials. Ideally, medical personnel are trained in patient education at health centers, schools, and other facilities. In Japan, information on asthma and

Table 6
Classification of asthma severity based on the present treatment (adults).

	Present treatment step			
Patient's symptoms in the present treatment	Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Controlled† • No symptoms • No symptoms at night	Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Mild intermittent‡ • Less than once a week • Mild and brief • Less than twice a month at night	Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Mild persistent§ • Once or more a week, not every day • Once or more a month, disturbs everyday life and sleep • Twice or more a month at night	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Moderate persistent§ • Every day • Requires short-acting inhaled β_2 agonist almost every day • Once or more a week, disturbs everyday life and sleep • Once or more a week at night	Moderate persistent	Severe persistent	Severe persistent	Most severe persistent
Severe persistent§ • Frequently exacerbated even under treatment • Every day • Restricts everyday life • Frequently occurs at night	Severe persistent	Severe persistent	Severe persistent	Most severe persistent

† Consider step-down after continued treatment for 3–6 months.
‡ Enhance treatment at each step.
§ Check adherence to treatment, and consider step-up as needed.

related educational activities are provided by various associations. Examples are the Japanese Society of Allergology (http://www.jsaweb.jp), Japanese Society of Pediatric Allergy and Clinical Immunology (http://www.jspaci.jp), Japan Allergy Foundation (http://www.jaanet.org), Independent Administrative Institution, Environmental Restoration and Conservation Agency of Japan (http://www.erca.go.jp/asthma2/index.html), and the Japanese Council for Quality Health Care (http://minds.jcqhc.or.jp/n).

3.6. QOL

QOL assessment is important for good asthma management, as in other chronic diseases. QOL refers to general well-being, according to the Global Initiative for Asthma (GINA), and is useful for morbidity analysis. In addition to the Nottingham Health Profile and SF-36 Health Status Questionnaire, asthma-specific assessment tests are often used, including the Asthma Quality of Life Questionnaire (AQLQ) and Asthma Health

Table 7
Classification of asthma symptoms and exacerbation severity (adults).

Exacerbation severity†	Dyspnea	Exertion	Measured values§			
			%PEF	SpO_2	PaO_2	$PaCO_2$
Wheezing/chest tightness	Dyspnea on exertion	Almost normal				
Mild (mild attack)	Dyspnea, but no trouble with lying down	Slight dyspnea	≥80%	≥96%	Normal	<45 mmHg
Moderate (moderate attack)	Dyspnea, with trouble with lying down	Difficulty in moving Difficulty in walking	60–80%	91–95%	>60 mmHg	<45 mmHg
Severe (severe attack)	Dyspnea, cannot move	Abasia difficulty in speaking	<60%	≤90%	≤60 mmHg	≥45 mmHg
Serious‡	Respiratory insufficiency Cyanosis respiratory arrest	Anepia, Akinesia Confusion, Impaired consciousness, Incontinence	Immeasurable	≤90%	≤60 mmHg	≥45 mmHg

† Determine exacerbation severity based on the extent of dyspnea, referring to other items. If symptoms of different exacerbation intensities coexist, choose the most severe one.
‡ Serious conditions, such as respiratory attenuation or arrest, anepia, impaired consciousness, and incontinence are regarded as emergency.
§ Refer to measured values after bronchodilator administration.

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Table 8
Prevalence of asthma.

	Age (yr)	Region	Year analyzed	Methods	n	Prevalence (%)
Children	6–12	11 Prefectures in Western Japan	1982	ATS-DLD	55,388	3.2
			1992		45,674	4.6
			2002		35,582	6.5
			2012		33,902	4.7
Adults	≥15	Fujieda, Shizuoka	1985	Original questionnaire	12,152	3.14
	≥15		1999	Original questionnaire + ATS-DLD	3829	4.15
	20–79		2006	ECRHS	2710	7.2

ATS-DLD, American Thoracic Society-Division of Lung Diseases; ECRHS, European Community Respiratory Health Survey.

Table 9
Prevalence of asthma by country, year, and age group according to the European Community Respiratory Health Survey.

Country	Year	Age	Prevalence (%)
Japan	05	20–44	8.1
Australia	92–93	20–44	28.1
Australia Aborigine	90–91	20–84	11.1
UK	92–93	20–44 20–44	27.0 30.3
Germany	92–93	20–44	17.0
Spain	92–93	20–44	22.0
France	92–93	20–44	14.4
USA	92–93	20–44	25.7
Italy	92–93	20–44	9.5
Iceland	92–93	20–44	18.0
Greece	92–93	20–44	16.0

Questionnaire-33-Japan (AHQ-33J). AHQ-33J was prepared by the Japanese Society of Allergology, and is reproducible, reliable, and useful for assessment from a social, familial, and emotional point of view.

4. Asthma medications

4.1. Asthma medication plan for the long-term management of adult asthma

4.1.1. Agents

Asthma agents consist of two types of drugs; long-term controller agents are used continuously for long-term management (controllers) and reliever agents are used in the short term to treat asthma symptoms (relievers). Controllers are defined as "regular-use agents aimed at achieving good control" and relievers are defined as "rescue-use agents aimed at treating asthma exacerbations". They are administered orally, via inhalation, injection (drip infusion, subcutaneous, or intramuscular), or skin patches. Inhaled agents can directly access the inflammatory sites, with increased local concentration; therefore, the agents are remarkably effective and allow the systemic concentration of the drugs to be

Table 10
Medical treatment rates for asthma in Japan.

	Total	In-hospital	Outpatient
1999	132	12	120
2002	120	9	111
2005	122	7	115
2008	93	4	88
2011	107	3	103
2014	103	3	100

Per 100,000 population.

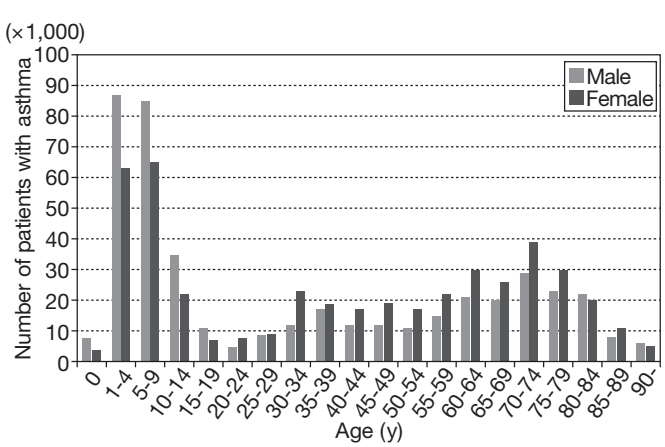

Fig. 1. Number of patients with asthma in Japan, by age and sex.

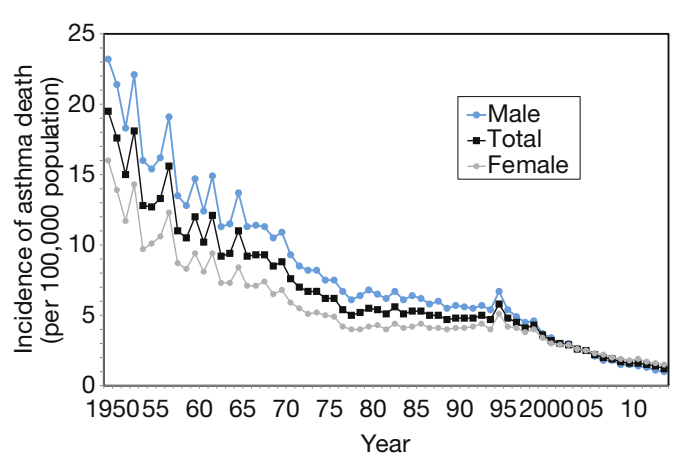

Fig. 2. Asthma mortality rates in Japan (1950–2014).

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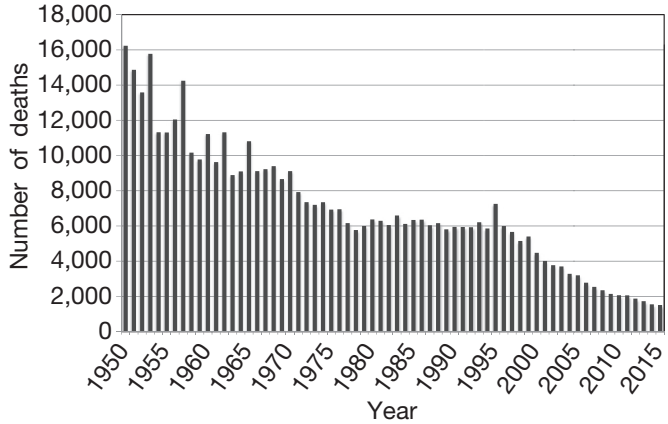

Fig. 3. Number of deaths due to asthma in Japan (1950–2015).

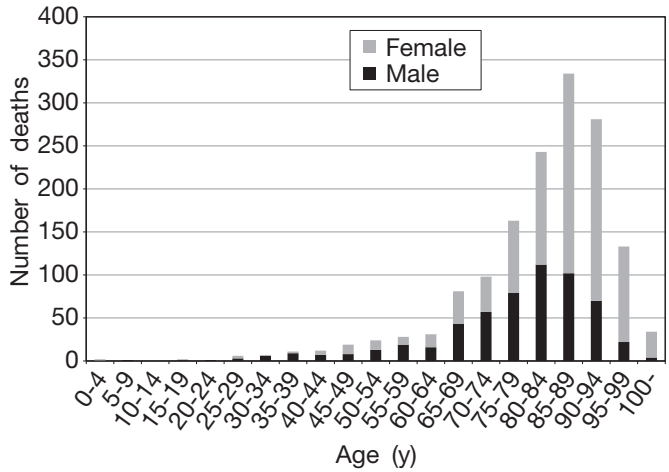

Fig. 4. Number of deaths due to asthma by age in Japan (2015).

maintained at lower levels, so that systemic side effects can be lower frequencies. However, it is necessary to gargle after inhalation because the higher concentration of the drugs in the oral cavity, pharynx, larynx, and esophagus could induce side effects. Inhalation using a pressurized metered-dose inhaler (pMDI) requires synchronization of drug inhalation with its release and breath-holding to ensure drug deposition in the airways. A dry powder inhaler (DPI) always requires sufficient inspiratory flow. A soft mist inhaler allows easy synchronization of inhalation, because the period of drug release as a mist is longer than that in a pMDI. Further research should be performed on inhaled drugs, in terms of the devices and drugs used. Nebulizer inhalation is often used in patients with asthma attacks, children, or aged patients who cannot properly use a pMDI or a DPI.

Table 11
Physician's instructions for patients with asthma.

- Diagnosis
- Differences between reliever agents and controller agents
- How to use an inhaler
- Instructions for prophylaxis
- Signs of asthma exacerbation
- PEF monitoring
- How and when to visit clinics
- Self-management plan based on instructions

(1) **Agents for long-term management (Controllers)**

Controllers are considered as agents for alleviating and eliminating asthma symptoms, and normalizing and maintaining respiratory functions. They have anti-inflammatory effects and/or long-term bronchodilatory effects, and are classified based on their mechanisms of action (Table 12).

a) Corticosteroids (steroids): corticosteroids are currently the most important and effective anti-inflammatory agents among asthma treatments.[15] The main mechanisms of action include (i) inhibition of inflammatory cell infiltration into the lungs and airways,[16] and inhibition of migration and activation of inflammatory cells; (ii) reduction of vascular permeability; (iii) suppression of airway secretion; (iv) inhibition of airway hyperresponsiveness; (v) inhibition of cytokine production; (vi) promotion of the effects of β_2-agonists[17]; and (vii) inhibition of arachidonic acid metabolism in cells other than human mast cells and the production of leukotrienes and prostaglandins. Currently, 4 forms of steroids are available: intravenous, intramuscular, oral, and inhaled. Steroids used for long-term management of asthma are usually ICSs, because these have a lower risk of side effects. When control of asthma cannot be achieved with ICSs and ICSs plus other asthma drugs, such as bronchodilators, or in patients with complications, an oral corticosteroid only should be used. An aqueous suspension of triamcinolone acetonide in an intramuscular injection should not be used, because of its adverse effects. ICSs have been reported to (i) improve asthma symptoms; (ii) improve QOL and respiratory function; (iii) alleviate airway hyperresponsiveness[18]; (iv) suppress airway inflammation; (v) reduce the frequency and severity of exacerbations[19]; (vi) reduce the maintenance dose of ICSs for a long period of time; (vii) reduce the medical expenses associated with asthma; (viii) suppress airway remodeling; and (ix) reduce the mortality rate due to asthma. Once asthma symptoms have developed, early administration of an ICS (early intervention) will decrease the frequency of acute exacerbations.[20] However, asthma cannot be cured by ICS treatment. If the treatment is discontinued, asthmatic symptoms cannot be controlled.[18] Furthermore, poor compliance with ICS use causes an increase in the frequency of emergency room visits and hospitalization due to asthma exacerbations. Oral corticosteroids are used as long-term management agents to complement ICSs, supplement adrenocortical function, and reduce the levels of systemic inflammatory cells and inflammatory substances in step 4 of treatment. As shown in Table 13, the ICSs commercially available in Japan in 2016 include fluticasone propionate (FP), budesonide (BUD), beclomethasone dipropionate (BDP), ciclesonide (CIC), mometasone furoate (MF), and fluticasone furoate. FP, BUD, and MF are also available as a DPI, whereas FP, BDP, and CIC are pMDI, using hydrofluoroalkane (HFA) as propellant. The mean particle sizes of these agents are 6 μm > FP-DPI > FP-HFA > BUD-DPI > MF-DPI > CIC-HFA = BDP-HFA > 1 μm. These agents are extensively dispersed in the airway, generally, with smaller particles reaching further into the peripheral airway.[21] In addition, the effects of fluticasone furoate ester (FF)/LABA (vilanterol), a new ICS (FF)/LABA combination, are sustained for 24 h. BUD inhalation suspension, inhaled using a nebulizer, has been introduced, and a jet nebulizer, not an ultrasonic nebulizer, is recommended for BUD inhalation suspension. In general, BUD inhalation

Table 12
Controllers (agents for long-term management).

1. Corticosteroids
   1) Inhaled corticosteroids
      i) Beclomethasone dipropionate
      ii) Fluticasone propionate
      iii) Budesonide
      iv) Ciclesonide
      v) Mometasone furoate
   2) Oral corticosteroids
2. Long-acting β_2 agonists
   1) Inhalants
      Salmeterol xinafoate
   2) Patch
      Tulobuterol
   3) Oral medicines
      Procaterol hydrochloride
      Clenbuterol hydrochloride
      Formoterol fumarate
      Tulobuterol hydrochloride
      Mabuterol hydrochloride
3. Combination inhaler of corticosteroid/long-acting β_2 agonist
   1) Combination inhaler of fluticasone propionate/salmeterol xinafoate
   2) Combination inhaler of budesonide/formoterol fumarate
   3) Combination inhaler of fluticasone propionate/formoterol fumarate
   4) Combination inhaler of fluticazone furate/vilanterol trifenatate
4. Leukotriene receptor antagonists
   1) Pranlukast hydrate
   2) Montelukast sodium
5. Theophylline sustained-release preparation
6. Long-acting muscarinic receptor antagonist
   Tiotropium bromide hydrate
7. Anti-IgE
   Antibody
   Omalizumab
8. Anti-allergics other than leukotriene receptor antagonists
   1) Mediator antireleasers
      Sodium cromoglicate, tranilast, amlexanox, repirinast, ibudilast, tazanolast, and pemirolast potassium
   2) Histamine H_1 receptor antagonists
      Ketotifen fumarate, azelastine hydrochloride, oxatomide, mequitazine, and epinastine hydrochloride
   3) Thromboxane inhibitors
      i) Thromboxane-A_2 synthesis inhibitor
         Ozagrel hydrochloride
      ii) Thromboxane-A_2 receptor antagonist
         Seratrodast
   4) Th2 cytokine inhibitor
      Suplatast tosilate
9. Other agents and therapies (Chinese medicines, specilic immunotherapy, and non-specific immunotherapy)

suspension at a dose of 0.5 mg twice daily or 1 mg once daily (maximum 2 mg/day) is used for adults. ICSs are considered to be the first choice agents for asthma treatment. The dosage of ICSs is classified into high dose (the highest dose covered by health insurance), medium dose (half of the high dose), and low dose (half of the medium dose) (Table 14). In adult asthmatic patients, ICSs are effective even at relatively low doses (e.g., 200 μg/day FP). On the other hand, if the dosage exceeds the high dose, further effects proportional to the dose cannot be achieved, and the risk of adverse effects increases.[22] Thus, in controlling asthma, adding 1 or more controller other than ICSs, rather than simply increasing the dose of an ICS, should be recommended.[19] However, severe acute exacerbations can be alleviated by increasing the ICS dose.[19] Smoking not only reduces the effects of ICSs, but also impairs the respiratory function in asthmatic patients.[23] Localized adverse effects, such as oropharyngeal candidiasis and hoarseness can sometimes become problematic, although ICSs have a few systemic adverse effects compared with other steroid formulations. After inhalation, gargling or drinking water is essential to alleviate oropharyngeal symptoms and to reduce systemic absorption. While the inhibitory effects on adrenal glands in conventional doses are generally acceptable, a careful follow-up of adrenal gland function is necessary when high doses are used. BUD-DPI, which can be administered even during early pregnancy, has not been reported to cause congenital malformation or to have any effects on the course of pregnancy.[24] The US Food and Drug Administration (FDA) has certified the safety of BUD-DPI in pregnant women as Category B. There is no evidence of the increased risk of respiratory tract infection, including tuberculosis, caused by ICSs in patients with asthma, and ICSs are not contraindicated in patients with active tuberculosis.

Table 13
Device for inhaled corticosteroids.

	Pressurized metered dose inhaler (pMDI)	Dry powder inhaler (DPI)
BDP (beclomethasone dipropionate)	BDP-HFA (Qvar®)	None
FP (fluticasone propionate)	FP-HFA (Flutide® Air)	FP-DPI (Flutide® Diskus, Flutide® Diskhaler)
Combination inhaler with SM (salmeterol xinafoate)	FP/SM HFA (Adoair® aerosol)	FP/SM DPI (Adoair® Diskus)
Combination inhaler with FM (formoterol fumarate hydrate)	FP/FM (Flutiform®)	None
BUD (budesonide)	None	BUD-DPI (Pulmicort® Turbuhaler)
Combination inhaler with FM (formoterol fumarate hydrate)	None	BUD/FM (Symbicort® Turbuhaler)
CIC (ciclesonide)	CIC-HFA (Alvesco®)	None
MF (mometasone furoate)	None	MF-DPI (Asmanex® Twisthaler)
FF (fluticazone furate) Combination inhaler with VI (vilanterol trifenatate)	None	FF/VI-DPI (Relvar® Ellipta)

Table 14
Recommended doses of inhaled corticosteroids by treatment steps.

Agent	Treatment steps 1–2/low dose	Treatment steps 2–3/medium dose	Treatment steps 4/high dose
BDP-HFA	100–200 μg/day	400 μg/day	800 μg/day
FP-HFA	100–200 μg/day	400 μg/day	800 μg/day
CIC-HFA	100–200 μg/day	400 μg/day	800 μg/day
FP-DPI	100–200 μg/day	400 μg/day	800 μg/day
MF-DPI	100–200 μg/day	400 μg/day	800 μg/day
BUD-DPI	200–400 μg/day	800 μg/day	1600 μg/day
BIS	0.5 mg/day	1.0 mg/day	2.0 mg/day

BDP-HFA, beclometasone dipropionate hydrofluoroalkane; FP-HFA, fluticasone hydrofluoroalkane; CIC-HFA, ciclesonide hydrofluoroalkane; FP-DPI, fluticasone propionate dry powder inhaler; MF-DPI, mometasone furoate dry powder inhaler; BUD-DPI, budesonide dry powder inhaler; BIS, budesonide inhalation suspension.

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b) Long-acting β_2 agonists (LABAs): β_2-agonists bind to β_2 receptors in airway smooth muscle, relaxing the airway smooth muscle. These are potent bronchodilators that enhance airway mucus removal by activating epithelial cilia, and are administered via inhalation, patches, and the oral route. β_2-Agonists should be used concomitantly with ICSs as controllers. When a LABA is combined with an ICS, the steroid increases the number of β_2-receptors, and the β_2-agonist amplifies the nuclear translocation of steroid receptors and further enhances the effects of the steroid. Furthermore, ICS/LABA allows reduction of the ICS dose,[25] and improves the control of asthma. Combination of an ICS and LABA is more effective than an ICS with sustained-release theophylline.[26]

Salmeterol xinafoate (SM) is an inhaled LABA that cannot be used as monotherapy for the treatment of asthma[27]; however, it has strong synergistic effects when combined with an ICS.[28] Conventional oral LABAs include procaterol hydrochloride, clenbuterol hydrochloride, and mabuterol hydrochloride. A tulobuterol patch, which was developed in Japan, is a long-acting agent with a bronchodilatory action that lasts for 24 h. It is useful for patients in whom inhalation and oral administration are difficult. Its clinical usefulness when combined with an ICS has been reported.[29] Although LABAs have a high safety profile in any formulation, they sometimes have adverse effects, including tremor, palpitations, and tachycardia, which occur most frequently for oral agents, followed by patches, and inhaled agents. When adverse effects are observed, the dose should be reduced or administration should be discontinued. Serious adverse effects include a decreased serum potassium level. LABAs should be used more carefully in asthmatic patients with ischemic heart disease, hyperthyroidism, and diabetes mellitus. The adverse effects of the tulobuterol patch are skin itching or rash (or both) around the patch area.

c) Combination agents comprised of ICS and inhaled LABA (ICS/LABA) (Table 15): combined inhalation of ICS and LABA are more effective than their separate inhalation.[30] In Japan, FP/salmeterol (SM), BUD/formoterol (FM), fluticasone furoate ester (FF)/FM, and FF/vilanterol (VI) are used as combination ICS/LABA agents. The formulations of FP/SM, BUD/FM, FF/VI are available as DPI and FF/FM as pMDI. The advantages of the ICS/LABA combination are (i) the number of inhalations can be reduced; (ii) excellent adherence can be achieved; and (iii) the use of LABAs alone can be avoided. Furthermore, the rescue use of the FM formulation instead of a short-acting β_2-agonist (SABA) can improve asthma symptoms and reduce the rate of asthma exacerbations (single maintenance and reliever therapy: SMART).[31] SMART treatment has been approved in Japan since 2012. On the other hand, SMART carries the risk of promoting poor adherence to regular therapy as well as excessive use, as the patients can determine their own treatment. Therefore, it is important to select patients for SMART carefully and educate them. FF/VI is expected to achieve higher adherence, because it requires once-daily use. According to the 2010 FDA recommendations, asthma treatment should be based on an assessment of the level of control when using these combination agents.[32] If the simultaneous use of LABA can be discontinued when asthma is well controlled, a switch to ICS monotherapy can be made. However, it remains controversial whether combination agents should be continued after good control of asthma is achieved, because they can reduce the rate of severe exacerbations as compared to ICSs monotherapy.[33,34] Viral infection is a major cause of asthma exacerbations. Combination ICS/LABA agents are reported to be superior to ICS monotherapy for reducing exacerbations due to viral infection.[35,36]

d) Leukotriene receptor antagonists (LTRAs): leukotrienes (LT) C4, D4, and E4, are termed cysteinyl LTs (CysLTs), and bind to the CysLT1, CysLT2, and CysLT3 receptors, respectively. A currently available LTRA is a CysLT1 receptor antagonist, which includes pranlukast hydrate and montelukast in Japan. LTRAs have a bronchodilator action and inhibit airway inflammation, resulting in significant improvement of asthma symptoms and respiratory function; allow as-needed inhalation of a β_2-agonist, reduce airway inflammation, airway hyperresponsiveness, the dosage of ICSs, and asthma exacerbations; and improve patients' QOL[37–39] LTRAs are used concomitantly with an ICS in patients with asthma that cannot be completely controlled even with a medium dose of an ICS, because the additional administration of LTRAs is as effective as a double-dose of an ICS.[40] Compared with LABAs, LTRAs used in combination with an ICS are less effective in improving asthma symptoms and respiratory function and in preventing exacerbation; the equivalent effects in oral LTRAs compared to LABAs may be due to excellent adherence.[41] LTRAs are useful for long-term management of patients with asthma complicated by allergic rhinitis, exercise-induced asthma (EIA), and aspirin-exacerbated respiratory disease (AERD). Generally, LTRA monotherapy is less effective than that with low-dose ICSs in mild asthmatic patients.[42,43] The oral administration of an LTRA improves pulmonary function in some patients (at several hours at the earliest, on the following day at the latest); however, their anti-inflammatory effects develop later. Thus, efficacy is generally judged only after 2–4 weeks of administration. Nevertheless, the effects of LTRAs have not been established in acute asthma exacerbations.[44] While more reports have been published on EGPA in patients who have

Table 15
Suggested daily doses of a combination inhaler containing corticosteroids and long-acting β_2 agonists.

	Low dose	Medium dose	High dose
FP/SM (DPI)	100 μg/dose, 1 dose b.i.d. 200 μg/100 μg	250 μg/dose, 1 dose b.i.d. 500 μg/100 μg	500 μg/dose, 1 dose b.i.d. 1000 μg/100 μg
BUD/FM† (DPI)	One dose b.i.d. 320 μg/9 μg	Two doses b.i.d. 640 μg/18 μg	Four doses b.i.d. 1280 μg/36 μg
FP/SM (pMDI)	50 μg/dose, 2 doses b.i.d. 200 μg/100 μg	125 μg/dose, 2 doses b.i.d. 500 μg/100 μg	250 μg/dose, 2 doses b.i.d. 1000 μg/100 μg
FP/FM (pMDI)	50 μg/dose, 2 doses b.i.d. 200 μg/20 μg	125 μg/dose, 2 doses b.i.d. 500 μg/20 μg	125 μg/dose, 4 doses b.i.d. 1000 μg/40 μg
FF/VI (DPI)	100 μg/dose, 1 dose s.i.d. 100 μg/25 μg	100 μg/dose, 1 dose s.i.d. 100 μg/25 μg or 200 μg/dose, 1 dose s.i.d. 200 μg/25 μg	200 μg/dose, 1 dose s.i.d. 200 μg/25 μg

FP, fluticasone propionate; SM, salmeterol xinafoate; BUD, budesonide; FM, formoterol fumarate; FF, fluticazone furate; VI, vilanterol trifenatate.
† Indication in a delivered dose.

received an LTRA than in those who have received other anti-asthmatic drugs, it is not yet clear whether an LTRA is directly involved in the onset of EGPA.[45] LTRAs are generally safe drugs, but interact with other agents, such as warfarin, since they are also metabolized by CYP2C9. LTRAs seem to be relatively safe for pregnant women.

e) Sustained-release theophylline: sustained-release theophylline is a long-acting bronchodilator with anti-inflammatory effects. It exerts bronchodilatory actions via nonselective inhibition of phosphodiesterases. It inhibits airway infiltration of lymphocytes and eosinophils,[46] a proliferative T cell response, cytokine production, induction of apoptosis in eosinophils,[47] and recovery of steroid sensitivity through histone deacetylase (HDAC) reactivation.[48] To avoid the adverse effects of theophylline, sustained-release theophylline is used in clinical practice. While sustained-release theophylline is clinically less effective than ICSs, when used in combination with low-to-medium doses of an ICS, the same effects as those obtained with an increased ICS dose can be achieved.[49] Therefore, sustained-release theophylline is recommended for use when asthma control cannot be achieved by using other bronchodilators. However, in patients treated with ICSs, sustained-release theophylline, at a dose of 300–400 mg/day, improved airway obstruction to a lesser extent than LABAs[26] and to a comparable (the same or slightly lesser) extent as LTRAs.[50] Monitoring of the serum level is useful for avoiding adverse effects. Anti-inflammatory effects are obtained at a serum theophylline level of 5–10 μg/mL, although bronchodilatory action is achieved in a concentration-dependent manner. No serious adverse effects have been noted at serum theophylline concentrations of up to 20 μg/mL. Monitoring the peak serum theophylline level is difficult; thus, the target level ranges from 5 to 15 μg/mL. The adverse effects of theophylline include gastrointestinal symptoms such as nausea and vomiting at initial oral administration. In addition, toxic symptoms may progress to tachycardia and arrhythmia. In the most severe cases, convulsions may occur that can lead to death.

f) Long-acting anti-muscarinic receptor antagonist (LAMA): tiotropium bromide is available as a LAMA controller in Japan. It is frequently used in patients with COPD, and a soft mist inhaler (Respimat®) is allowed for use as asthma treatment. It should be used in combination with ICSs for long-term management. The bronchodilatory effects of tiotropium are sustained for 24 h[51,52] and it improves pulmonary function of asthmatic patients with once daily use. It improves pulmonary function and reduces exacerbations in severe asthmatic patients who continue to have asthma symptoms even when treated with high doses of ICSs plus LABAs.[53] It has been reported that tiotropium improved pulmonary function in asthmatic patients who remained symptomatic after treatment with mild to moderate doses of ICSs.[54,55] It also improved pulmonary function in patients carrying the 16Arg/Arg SNP in the ADRB region, to the same extent as Serevent (salmeterol). Dry mouth is sometimes observed as a side-effect of tiotropium. Because systemic absorption of tiotropium is much lower, systemic side-effects can be ignored. It should not be used in cases with closed-angle glaucoma. Dysuria may rarely occur in patients with benign prostatic hypertrophy, but withdrawal of tiotropium improves the dysuria.

g) Anti-IgE antibody: omalizumab is a humanized anti-human IgE monoclonal antibody. In Japan, omalizumab is available for the following asthmatic patients: (i) those who have unstable asthmatic symptoms, even when treated with high doses of ICSs plus more than 1 controller agent; (ii) those who are positive for perennial inhaled antigens, such as house dust; (iii) the dose and frequency of administration are determined based on the dosage conversion table, according to the patient's weight and serum IgE level (30–1500 IU/mL serum IgE). Omalizumab has the following effects in patients with poor asthma control, even despite treatment with a high dose of ICS: (i) it prevents exacerbation; (ii) reduces the frequency of asthmatic symptoms; (iii) improves QOL; (iv) reduces the frequency of emergency room visit and hospital admission; and (v) reduces the steroid dose.[56] Omalizumab modestly improves FEV_1 and PEF values. It has only been confirmed to be effective in poorly controlled patients treated with ICS/LABA. Omalizumab should be used as a therapeutic agent in step 4 treatment for severe persistent asthma. At 16 weeks after administration, the therapeutic effects can be comprehensively judged and it should then be determined whether the treatment needs to be continued.[57] It is effective in about 60% of patients. Factors predicting effectiveness are higher serum eosinophil counts and higher levels of FeNO.[58] The major adverse effects of omalizumab are pain and swelling at the injection site. An anaphylactic reaction, reported as a serious adverse effect in 0.1–0.2% of the non-Japanese patients, could develop within 2 h after administration (about 70% of the episodes), but some reactions have been reported to occur after 24 h. There is no evidence that omalizumab causes development of malignancy, but care should be taken with its use, as EGPA may develop due to the reduced amount of systemic steroids. No teratogenicity has been reported, but its safety has not been established in pregnant women.

h) Anti-allergics other than LTRAs: anti-allergic agents include either mediator release suppressants or mediator inhibitors. They are categorized as (i) mediator-release suppressants, (ii) histamine H_1-antagonists, (iii) thromboxane A_2 inhibitors/antagonists, (iv) Th2 cytokine inhibitors. A few papers have shown the utility of Th2 cytokine inhibitors with or without ICSs,[59,60] but the utility of the other anti-allergics is limited. The safety of oral anti-allergic agents in fetuses during pregnancy has not been demonstrated.

i) Other agents and therapies.
   (i) Bronchial thermoplasty (BT): Bronchial thermoplasty is a novel intervention for severe asthma that delivers controlled thermal energy to the airway wall during a series of bronchoscopy procedures, resulting in a prolonged reduction in ASM mass.[61] BT therapy has been approved in Japan since 2015. Only 1 report has stated that BT in patients with severe persistent asthma improves asthma-specific QOL, with a reduction in severe exacerbations and healthcare use in the 5 years post-treatment.[61] However, the long-term efficacy and safety of this therapy remain unknown and should be studied in future.
   (ii) Allergen immunotherapy: Allergen immunotherapy is a therapeutic strategy that induces immune tolerance by administration of specific antigens to allergic asthmatics. It simultaneously cures allergic rhinitis and allergic keratoconjunctivitis in addition to

treating asthma.[62] It has been reported that allergen immunotherapy prevents asthmatic patients from acquiring new antigens and improves the severity of asthma over the long-term,[63] based on intracutaneous injection, rather than sublingual administration. The administration methods are the following: (i) the conventional method, in which the antigen is administered once or twice weekly and the doses of the antigen is increased over several months; (ii) the cluster method, in which the antigen is administered several times on 1 or 2 days per week, (iii) the acute immune method, in which the antigen is administered several times in 1 day and the doses are increased over 3–14 days. Allergen immunotherapy is effective for 3 years, even after withdrawal of treatment.[64]

(iii) Other agents: A selection of Chinese herbal medicines is used, based on the patient's physical constitution, strength, and response to disease at the time of administration; the empirical process helps distinguish responders from non-responders before administration. Expectorants, such as carbocisteine and fudosteine, may facilitate expectoration. However, the accumulated evidence is not sufficient to allow recommendation of any of these agents.

j) New therapeutic strategies: Antibodies against IL-5 and IL-13 have been developed for severely asthmatic patients.[65–67] The anti-IL-5 antibody reduces asthmatic exacerbations, improves respiratory symptoms and pulmonary function, and can reduce the doses of oral steroids in patients with higher blood eosinophil counts.[68–70] The anti-IL-13 antibody and anti-IL-4 receptor α-chain antibody improves pulmonary function in moderately to severely asthmatic patients and also reduces the frequency of exacerbations with a reduction of ICSs. The anti-IL-13 antibody is particularly effective in patients with higher levels of serum periostin or blood eosinophil counts.[67,71] The anti-TSLP antibody and anti-IL-17 antibody are still under development. Furthermore, a PGD2 receptor CRTH2 has been developed and has been reported to be effective in moderately affected asthmatics.[72]

(2) **Reliever agents**

a) Short acting β agonists (SABAs): SABAs are regarded as reliever agents. Inhalation therapy using a pMDI, DPI, and nebulizer shows a comparable or even higher bronchodilator action than with oral administration. There are a few adverse effects, such as stimulation of the cardiovascular system, skeletal muscle tremor, and hypokalemia. The increasing need for the use of a SABA can be regarded as loss of asthma control. The use of a SABA as a reliever 5 or more times daily indicates controller agents need to be increased. When an asthma attack occurs, 1 or 2 puffs of SABAs are administered. If the effects are not satisfactory after repeated inhalation every 20 min for 1 h, medical consultation is needed.

b) Oral corticosteroids: an oral corticosteroid together with a SABA needs to be administered for about 1 week in moderate exacerbations. Prior short-term treatment of asthma symptoms (usually less than 1 week) with a dose of an oral corticosteroid (approximately 0.5 mg/kg of prednisolone) prevents acute exacerbations, reduces emergency visits and hospital admissions, and improves daily life. Adherence to the asthma drugs and inhalation technique should be checked and changes of controllers and addition of other agents should be considered when the asthmatic patient has frequent exacerbations requiring short-term oral corticosteroids. In general, viral infection is more often involved in asthma exacerbations than bacterial infection, and short-term treatment is not likely to cause serious infection. In short-term treatment, a sudden dose reduction or discontinuation of treatment will not result in adrenocortical insufficiency (i.e., steroid withdrawal syndrome).

c) Theophylline: aminophylline is usually used as a drip in vessels or continuous drip in vessels in case of a reliever. Because of its narrow therapeutic range, aminophylline should be used by monitoring the serum levels. In Europe and the United States, administration of aminophylline is not recommended for exacerbations, considering its effectiveness and side effects.[73]

d) Short-acting muscarinic receptor antagonists (SAMAs): SAMAs have additive effects with β_2-agonists and reduce the rate of hospital admissions and improve pulmonary function for moderate to severe exacerbations.[74] Although the onset of bronchodilatory effects of SAMAs is slower than that of SABAs, SABAs are available for acute exacerbations when SABAs are unavailable.

4.1.2. *Stepwise treatment plan*

(1) **Goal of asthma treatment**

The goal of asthma treatment is to achieve normal respiratory function, with an absence of symptoms, exacerbations, or adverse effects. Because normal respiratory function cannot be restored in patients with airway remodeling, it can be assessed based on their best values. The control status is determined as shown in Table 16, with the aim being to achieve good asthma control.

(2) **Principle for treatment**

Physicians have noted that a better relationship between patients and physicians largely depends on the effects of the initial treatment, which focuses on the improvement of their asthma symptoms. It is important to avoid and eliminate sensitizing

Table 16
Assessment of asthma control.

	Well-controlled (meet all the criteria)	Insufficiently-controlled (meet 1 or 2 criteria)	Poorly-controlled
Asthma symptoms (in the daytime or at night)	None	Once or more a week	Meet 3 or more criteria of insufficient control
Use of reliever	None	Once or more a week	
Limitation of activities, including exercise	None	Restricted	
Lung function (FEV_1 and PEF)	Predicted value or ≥80% of the best value	Predicted value or <80% of the best value	
Diurnal (weekly) variation in PEF	<20%†	≥20%	
Exacerbation	None	Once or more a year	Once or more a month‡

† Upper limit of normal diurnal variability from the baseline values in measurement of PEF, twice daily, is 8%.

‡ Define patients with one or more exacerbations a month as being poorly controlled, even if they do not meet the other criteria.

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allergens and exacerbating factors, such as passive and active smoking and excessive fatigue. Management of inhalation technique, adherence to the drugs, and management of concomitant diseases, such as allergic rhinitis, obesity, gastroesophageal reflux disease (GERD), and COPD, are also important.

Asthma treatment is divided into 4 treatment steps based on asthma severity. The steps are stated in the following section. The aim of drug therapy is to achieve the maximum effect using the minimum number or dosage of drugs. Symptoms at the initiation of therapy, those at consultation, and in a therapeutic situation are comprehensively evaluated to determine the appropriate treatment step.

(3) **Four treatment steps for asthma (Table 5)**

When an asthma attack occurs during long-term management, a SABA should generally be used as a reliever. In steps 2 and 3 of asthma treatment, if patients are treated with combination of BUD and formoterol as a controller (SMART), its use as a reliever should not exceed the maximum number of inhalations (generally 8 puffs/day) for each use and per day, as shown in the legend of Table 5.

a) Step 1 treatment: One (or no) controller agent plus reliever agent. A SABA may be administered only to patients with rare occurrence of asthma symptoms (less than once a month) without controllers, and no long-term management agent is needed. For patients who develop symptoms once or more a month, a low dose of an ICS is recommended as a controller agent.[20] If ICSs cannot be used, or adverse effects develop after inhalation, LTRAs[37] or sustained-release theophylline[46] can be substituted. Anti-allergics other than LTRAs, such as a histamine H1 blocker, thromboxane A2 inhibitors, and Th2 cytokine inhibitors can be used, according to the pathophysiology of the asthma.
b) Step 2 treatment: Two controller agents plus a reliever agent. In addition to ICSs (low to medium dose), use of a LABA is recommended.[27,28] When ICSs plus LABAs are used, the effects of ICS/LABA combination preparation are superior to those of ICSs plus LABAs, respectively. ICSs plus LABAs are considered to be more effective than moderate doses of ICS monotherapy.[75] If the patients cannot use LABAs, LTRA,[41,76] or sustained-release theophylline[49] can be used instead. Early treatment with ICS/LABA can rapidly improve asthmatic symptoms and pulmonary function, as compared with ICS monotherapy.[75,77] LTRAs are useful mainly in patients with coexisting allergic rhinitis, exercise- or aspirin-induced asthma.
c) Step 3 treatment: Two or more controller agents plus reliever agent. Combination with a LABA is recommended, in addition to the current treatment. If the effects of an ICS/LABA are insufficient, either an LTRA, a sustained-release theophylline, or LAMA should be used.
d) Step 4 treatment: Controller agents plus additional therapy plus reliever agent. In addition to continuous administration of an ICS (high dose) plus LABA, an LTRA, sustained-release theophylline, and/or LAMA are used. In some patients, anti-IgE antibody (omalizumab) is effective, particularly in poorly controlled patients sensitized to perennial allergens, whose serum total IgE is within a therapeutic target range (30–1500 IU/mL).[56] The dose of the anti-IgE antibody is determined using a dosage conversion table. Its effects are evaluated 16 weeks after administration, and if effective, administration is continued. If it is not effective, this treatment should be withdrawn. Oral corticosteroids should be intermittently administered for a short period to avoid prolonged administration wherever possible. Specifically, about 0.5 mg/kg or the equivalent amount of prednisolone is administered for a short period (usually less than 1 week), and a high-dose ICS is subsequently used. In patients with insufficient asthma control, who need prolonged administration of an oral corticosteroid, a shorter-acting oral corticosteroid (prednisolone) can be administered every day or every other day in the morning to maintain the minimum dose (5 mg). Caution should be taken when switching from long-term administration of an oral corticosteroid to a high-dose ICS because of possible adrenal insufficiency.

Bronchial thermoplasty (BT) is an intervention for severe asthma resulting in a prolonged reduction in ASM mass.[61] BT therapy has been approved in Japan since 2015. It has been reported that use of BT in patients with severe persistent asthma improves asthma-specific QOL with a reduction in severe exacerbations and healthcare use in the 5 years post-treatment.[61] However, the long term efficacy and safety remains unknown and should be considered in future.

(4) **Practical application**

a) Selection of treatment steps: In untreated patients, the appropriate treatment step is determined on the basis of the asthma symptoms shown in Table 4. Specifically, treatment steps are selected as follows: (i) step 1 treatment for mild intermittent symptoms, (ii) step 2 treatment for mild persistent symptoms, (iii) step 3 treatment for moderate persistent symptoms; and (iv) step 4 treatment for severe persistent symptoms. When the asthma severity is determined from the symptoms, (i) symptoms that do not occur every week, are mild intermittent, (ii) symptoms that occur every week, but not every day, are mild persistent, (iii) symptoms that occur every day, but do not disturb daily life, are moderate persistent, (iv) symptoms that occur every day and disturb daily life, are severe persistent. Asthma severity is essentially determined on the basis of the symptoms; however, measurement of pulmonary function, including such parameters as PEF and FEV_1, is important for evaluating the disease condition and determining treatment step. In patients who have already received drug therapy, such as controllers, which is often the case, the treatment step should be determined according to Table 6. When symptoms cannot be controlled in patients treated with step 3 treatment, they should consult a specialist. It is important to maintain a well-controlled status in asthma patients (Table 16). In general, control status should be evaluated within 1 month of starting treatment with the drugs, in terms of the symptoms, frequency of reliever use, limitations on daily life, pulmonary function, and asthma exacerbations (Table 16). The inhalation technique, drug adherence, side-effects, degree of understanding of the treatment plant, and satisfaction with the treatment are also evaluated. If asthma symptoms are not controlled, intensification of treatment should be considered. When symptoms occur less than once a week, intensification of treatment within the same treatment step should be considered. When asthma symptoms occur every week or every day, 1 step-up or 2 steps-up are required to achieve good control. In patients receiving drug therapy, a step-down should be considered if the asthma control status remains good for 3–6 months, based on the assessment of the control status presented in Table 16. The goal of treatment is to

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maintain good asthma control using the minimum of drugs. Evaluation of control status and adjustment of treatment every 1–3 months are necessary.

b) Useful considerations for monitoring asthma management.
   i) Spirometry: The measurement of pulmonary function (airflow limitation) is quite important for determining the severity of asthma and evaluating the effectiveness of treatment.[78] The degree of airflow limitation is determined by a reduction in FEV_1, $FEV_1\%$ ($FEV_1\% = FEV_1/FVC \times 100$), and PEF. Decreased values of V50 and V25 and increased values of the V50/V25 ratio are useful for early detection of peripheral airway diseases. Spirometry should be measured at the first visit and within 1–3 months after treatment, and once a year thereafter.
   ii) PEF: To evaluate the degree of airflow limitation objectively every day in asthmatic patients, monitoring of PEF is recommended. It is particularly beneficial in asymptomatic patients or in those with frequent exacerbations. It can also be useful for identification of allergens or exacerbation factors. Diurnal variation of PEF is correlated with the degree of airway hyperresponsiveness. Because large daily variation of PEF indicates increased airway hyperresponsiveness, it is a good marker for evaluating asthma control.[79]
   iii) Asthma diary and questionnaire: An asthma dairy, the Asthma Control Questionnaire (ACQ), and the Asthma Control Test (ACT) are useful for evaluating asthma control.[80]
   iv) Percentage of sputum eosinophils: Sputum induction by inhalation of hypertonic saline is recommended if spontaneous sputum cannot be obtained. When sputum is induced, SABA should be inhaled to avoid hypertonic saline-induced bronchoconstriction. The management of eosinophil-oriented asthma is reported to be superior to that of symptom-oriented asthma in reducing asthma exacerbations.[81]
   v) Airway hyperresponsiveness: Using the threshold values of airway hyperresponsiveness can achieve better management than that achieved by using conventional symptoms and pulmonary function.[82]
   vi) Measurement of fractional exhaled nitric oxide (FeNO): Exhaled nitric oxide (NO) is derived from the inducible type of NO synthase (iNOS) in airway epithelial cells. It reflects the degree of airway eosinophilic inflammation. Because measurement of FeNO is easy and non-invasive, it is useful for diagnosis of asthma and monitoring of airway inflammation. Moreover, high levels of FeNO are indicative of good responsiveness to steroid treatment.[83,84] However, there is little evidence indicating whether monitoring of FeNO can be used for management of asthma in clinical practice.
   vii) Other parameters: Eosinophil counts in the peripheral blood and specific IgE antibodies are sometimes useful for the diagnosis of asthma. Blood theophylline concentration or corticosteroid levels are important for monitoring patients receiving asthma pharmacotherapy. In asthma exacerbations, respiratory failure should be evaluated by pulse oximeter and arterial blood gas analysis. In such cases, blood examination, chest radiography, and electrocardiography should be used for differential diagnosis and diagnosis of complicating diseases.

(5) **Management of difficult-to-treat patients**

In uncontrolled or partly controlled patients, asthma diagnosis, adequate instructions regarding daily medication, management of complications, and avoidance of exacerbating factors should be monitored. If asthmatic patients remain uncontrolled with treatment step 3, they should consult a specialist. Management of acute exacerbation needs to be provided with an asthma diary, in which the doses and timing of asthma medication are recorded. Patients with worsening symptoms are instructed to follow an emergency manual immediately. In addition, patients should be acquainted with dose-reduction strategies. Furthermore, in cases of acute exacerbation, they should have contact information handy, addresses of emergency hospitals, and an "asthmatic patient card," which enables treating physicians and other physicians to administer emergency treatment.

Early referral to a specialist is recommended for patients with underlying diseases, such as aspirin exacerbated respiratory disease (AERD), eosinophilic granulomatosis with polyangitis (EPGA), other systemic vasculitis, and allergic bronchopulmonary aspergillosis (ABPA), because continuous administration of a systemic steroid or immunosuppressant may be needed in addition to the above treatment step.

a) AERD (AIA): About 50% of aspirin-induced asthma occurs in refractory asthmatic patients. They often have nasal polyps and eosinophilic sinusitis. Not only aspirin, but also acidic NSAIDs induce severe asthma attacks; therefore, a physician should instruct patients not to use NSAID-containing oral medicines, suppositories, patches, and ointments. A physician should consider treatment of the complicating nasal polyps and eosinophilic sinusitis. Management of AERD is similar to that of adult asthma. ICSs should be used for long-term management of AERD, and LTRAs have been reported to be effective in AERD. In treating acute exacerbations, caution should be exercised for induction of asthma attack by prompt intravenous infusion of some types of steroids. When administration of systemic steroids is needed in an asthma attack, oral steroids or intravenous infusion of steroid phosphate esters are recommended.
b) EPGA: EPGA is also known as CSS, and is characterized by asthma, increase of eosinophil levels in the blood and tissues, and polyangiitis of many organs.[85] The treatment of EPGA involves systemic steroids. Poor-prognosis factors (a 5-factor score) has been proposed.[86] In patients with severe asthma and cardiac disease or in steroid-resistant patients, cyclophosphamide is used in combination with systemic steroids. Sometimes, an intravenous infusion of immunoglobulin is administered in treatment-resistant patients with nervous system or cardiac disorders.
c) ABPM and ABPA: ABPM and ABPA are diseases characterized by asthma and lung infiltration induced by abnormal immunoreactivity against fungi and *Aspergillus*, resulting in irreversible destruction of the airway architecture (bronchiectasis) and lung fibrosis. To avoid progression of lung tissue destruction, early diagnosis is important; however, some cases do not fulfill the diagnostic criteria. In addition to asthma treatment, systemic steroids are required.[87] When the dose of systemic steroids cannot be reduced, administration of antifungal drugs should be considered.
d) GERD: GERD is a complicating disease in asthmatic patients, and the symptoms of GERD are frequently observed in uncontrolled asthmatic patients. Administration of theophylline,

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β_2-agonists, or oral steroids sometimes exacerbates GERD, which is treated with proton-pump inhibitors. Treatment with proton-pump inhibitors does not necessarily improve asthma control in uncontrolled asthmatic patients with asymptomatic GERD.

e) Asthma with allergic rhinitis: Asthma is significantly complicated by allergic rhinitis. Active complicating allergic rhinitis in patients with asthma should be simultaneously treated.[88] Pharmacotherapy for allergic rhinitis may alleviate asthma symptoms, inflammation of the lower airways, and improve airway hyperresponsiveness.[89] Concomitant use of an LTRA is more effective in improving airway obstruction due to asthma than doubling the dose of an ICS.[90]

f) Asthma-COPD overlap syndrome (ACOS): COPD is an important coexisting disease in asthma, requiring caution in differential diagnosis in the elderly with asthma. COPD is also an important disease as a comorbidity. Particularly, elderly patients with asthma, who have a smoking history, should be diagnosed appropriately. ACOS is considered as a condition involving both asthma and COPD. Because patients with ACOS often have severe symptoms and experience frequent exacerbations, it causes refractoriness of asthma. Patients with ACOS should essentially be treated with ICSs, and LAMA or LABA is added to ICS as needed.

4.2. Management of acute exacerbations in adults

4.2.1. Therapeutic agents

(1) **Inhaled short-acting β_2-agonists (SABA)**

Inhaled short-acting β_2-agonists (SABA) are the first-line drug for the treatment of acute exacerbations. Repeated administration of a small dose (1–2 puffs at a time, using a portable pMDI) exerts better therapeutic effects than a single administration of a high dose.[91] For acute exacerbation, a SABA can be inhaled every 20 min for the first hour and subsequently every hour until symptom relief is obtained. Inhalation with a spacer causes fewer adverse effects and is more efficacious.[92] If adverse effects, such as marked tremor or palpitation, develop, the inhalation should be discontinued. A nebulizer coupled with oxygen is effective for continued inhalation. Adding an inhaled anticholinergic may have an additive bronchodilatory action.[93] Patients treated with a combination of budesonide/formoterol (BUD/FM) as both the controller and the reliever medication (SMART), should be instructed to inhale once for exacerbations. If the symptoms do not improve within a few minutes, 1 more inhalation can be added.[94] At maximum, reliever use is limited to 6 inhalations per exacerbation (8 inhalations per day for the total of controller and reliever use). If symptom persists, the patient should visit an outpatient clinic immediately.

(2) **Corticosteroids**

Corticosteroids (steroids) are recommended for patients experiencing insufficient bronchodilator action, moderate or severe exacerbations, or who are already treated with steroids.[95] The initial dose is 200–500 mg of hydrocortisone or 40–125 mg of methylprednisolone,[95] followed by subsequent intravenous drip infusion of 100–200 mg of hydrocortisone or 40–80 mg of methylprednisolone every 4–6 h as needed. Prednisolone, at a dose of 0.5 mg/kg, can also be administered orally or by intravenous drip infusion. Because of the relatively long duration until the clinical effects of the steroids emerge (ca. 4 h) and safety, slow intravenous drip infusion for 30–60 min is recommended at initial administration.

When symptoms deteriorate after the initial infusion of steroid succinate esters, including hydrocortisone or methylprednisolone, it should be considered due to steroid-induced exacerbation, and another steroid should be substituted. In patients with AERD, as steroid succinate esters may induce worsening in 40–60% of patients,[96] steroid phosphate esters (i.e., dexamethasone, betamethasone, or another hydrocortisone) should be used.

Table 17
High-risk asthma exacerbation group.

The high-risk group meets any one of the following criteria:
1. Receiving systemic steroid administration, or systemic steroid administration has recently been discontinued
2. History of hospitalization due to asthma attack in the past 1 year
3. Emergency visit due to asthma attack in the past 1 year
4. Tracheal intubation due to asthma attack in the past
5. Coexisting mental disorder
6. Noncompliance with asthma treatment plan
7. Not using an inhaled corticosteroid
8. Excessive use of short-acting β_2 agonist

Systemic steroid administration is indicated for patients with: (a) moderate-to-severe exacerbations, (b) history of a severe exacerbation requiring systemic steroid, (c) history of a serious exacerbation requiring hospitalization, (d) significant risk factors of exacerbations (Table 17).

(3) **Oxygen**

Usually oxygenation should be initiated for patients with SpO_2 less than 95% ($PaO_2 < 80$ mmHg) or with symptoms suggesting the existence of hypoxemia (cyanosis, dyspnea, or tachypnea). Maintaining SpO_2 at almost 100% is not required and, in turn, can be a risk for delaying the detection of worsening of respiratory failure.[97] In case of serious exacerbation, arrangements for endotracheal intubation and ventilator use should be made simultaneously.

(4) **Theophylline**

The effective serum concentration of theophylline for bronchodilation (8–20 μg/mL in adults) is close to the concentration that causes adverse reactions. Intravenous infusion of aminophylline (6 mg/kg) has a bronchodilatory action and is effective in treating acute asthma attacks.[98] Aminophylline has additive effects for β_2-agonists,[98] and its use decreases hospitalization rates due to asthma attacks. Aminophylline also has positive effects on respiratory drive and respiratory muscles. As there are individual differences in the onset of action and pharmacokinetics, monitoring the level of serum theophylline is recommended. Measurement of serum theophylline concentration is covered by medical insurance in Japan as a management charge for therapeutic drug monitoring. Caution should be exercised against intoxication in the presence of factors affecting theophylline clearance, as shown in Table 18.

For initial administration, 6 mg/kg of aminophylline in 200–250 mL of isotonic fluid is infused for about 1 h. If 600 mg or more of sustained-release theophylline per day is already administered, the serum theophylline concentration is above 8 μg/mL, or reduced theophylline clearance is suspected, the aminophylline

Table 18
Factors influencing serum theophylline levels.

Decreased clearance (increases serum level)
- Aging, obesity
- Hepatopathy, heart failure, viral infection, and fever
- Agents: allopurinol, macrolides, cimetidine, diazepam, new quinolones, etc.
Increased clearance (decreases serum level)
- Smoker (≥15 cigarettes/day)
- Agents: barbiturates, antiepileptics, rifampicin, isoproterenol, etc.

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dose should be reduced to half or less. If toxic symptoms, including headache, nausea, vomiting, tachycardia, or arrhythmia occur, infusion must be stopped immediately.

For continuous administration of aminophylline, aminophylline (250 mg) in 500 mL of maintenance infusion fluid is intravenously dripped for 5–7 h (about 0.6–0.8 mg/kg/h). The infusion speed should be adjusted to achieve 8–20 μg/mL of serum theophylline levels. If toxic symptoms occur during administration, the drip infusion must be slowed down or discontinued, and the level of theophylline should be measured to rule out overdose.

(5) **Inhaled anticholinergics**

If the effect of SABA is insufficient, adding anticholinergics can be considered. Anticholinergics (ipratropium or oxitropium) added to SABA may enhance the bronchodilator effect, improve symptoms and respiratory function,[99] and reduce hospitalization.

(6) **Subcutaneous injection of adrenaline**

Catecholamine (adrenaline, 0.1%) may be administered when the effects of an inhaled β_2-agonist is insufficient. Care should be taken for cardiac arrest, arrhythmia, and other adverse effects. Subcutaneous injection of adrenaline (0.1%, 0.1–0.3 mL) shows a bronchodilator effect through the bronchial smooth muscles relaxation (β effect) and the improvement in mucosal edema (α effect). Although adrenaline can be administered repeatedly every 20–30 min, pulse rate should be monitored and kept below 130/min. Adrenaline is preferably avoided in pregnant women and is contraindicated in patients with arteriosclerosis, diabetes mellitus, glaucoma (except for open-angle glaucoma), hyperthyroidism, psychoneurosis, and severe arrhythmia. Hypoxemic patients are at high risk for adverse effects. The following agents are contraindicated for concomitant use with adrenaline. (i) Inhaled halogen-containing anesthetics, such as halothane, because of an increased risk of tachycardia and ventricular fibrillation. (ii) Antipsychotics (butyrophenones, iminodibenzyls, phenothiazines, risperidone, and zotepine) and α-blockers may result in hypotension due to epinephrine reversal. (iii) Catecholamine formulation, such as isoproterenol, and adrenergic agents are principally contraindicated, except in emergency cases, such as resuscitation, because concomitant use may develop arrhythmia and cardiac arrest. (iv) A tulobuterol patch may be concomitantly used with caution, but fenoterol is contraindicated.

(7) **Antibiotics**

Administered to patients when bacterial infection is suspected by fever and purulent sputum.

(8) **Fluid replacement**

Although substantial fluid replacement is generally unnecessary, caution should be exercised for dehydration.

(9) **Analgesics**

Use of analgesics for severe exacerbation is not recommended because of the possibility of worsening of respiratory conditions.

4.2.2. Management at home

As the severity of asthma symptoms vary widely, management of exacerbations should be tailored according to their severity, and the approach for managing exacerbations must be relayed to patients individually. For this purpose, an action plan with specific instructions for each condition should be provided.[100] In case of wheezing/chest tightness and moderate asthma symptoms, 1–2 puffs of a SABA in pMDI should be administered. If insufficient, inhalation can be repeated every 20 min for 1 h and subsequently once an hour. Patients under SMART treatment using BUD/FM can inhale once for exacerbation. If the symptoms do not improve within a few minutes, 1 more inhalation can be added.[94]

Patients can be treated at home continuously when symptoms disappear with the use of these agents and their effects persist for 3–4 h. However, if sufficient therapeutic effect cannot be obtained, oral prednisolone at 15–30 mg should be administered, and the patient should be referred to an emergency outpatient unit immediately.

4.2.3. Treatment procedures in emergency outpatients (Table 19)

On arrival at the emergency outpatient clinic, the severity of exacerbation should be immediately determined based on symptoms. Exacerbation is classified based on the symptoms as follows: (i) mild: dyspnea without difficulty in lying down; (ii) moderate: difficulty in lying down and walking; (iii) severe: abasia, difficulty in moving and speaking; and (iv) serious symptoms: cyanosis, impaired consciousness, and respiratory arrest. Treatment for exacerbations is classified into 4 steps (Table 19). It is also important to take the history quickly and to initiate treatment without delay. Important points for history taking are: the extent and duration of exacerbation, recent treatment and steroid use, history of hospitalization and intubation due to asthma, history of AERD or other complications, including drug allergy, cardiac diseases, pneumothorax, and pulmonary embolism (Table 20).

After assessment of the severity of exacerbation, the treatment step is selected (Table 21).

(1) **Wheezing/chest tightness, mild symptoms (mild exacerbations)**
   a) Assessment: Although wheezing and chest tightness is present, normal movements are maintained. The term "mild symptoms" indicates mild dyspnea at rest, without difficulty in lying down, but slightly hampered movement. Daily activities are not impaired by these symptoms. The value of PEF is 80% or more of the predicted value, or the best value after using a bronchodilator. For new patients, a history of asthma and already administered treatments should be obtained. Radiography and an electrocardiogram is helpful for excluding dyspnea unrelated to asthma.
   b) Treatment: Administer step 1 treatment. Inhale SABA in pMDI, DPI, or nebulizer format. If symptoms disappear and are stable for 60 min without additional treatment, confirm that there is no airway obstruction (%PEF $\geq$ 80%) and discharge the patient. If symptom improvement is insufficient and airway obstruction persists (%PEF < 80%), proceed to step 2 treatment.

(2) **Moderate symptoms and continuous mild symptoms (moderate exacerbation)**
   a) Assessment: Moderate asthma symptoms include dyspnea and orthopnea at rest, with difficulty in movements. The PEF is 60–80% of the predicted or the best value. When the patient has already been diagnosed with asthma, examination for exacerbation can be performed as usual. For new patients, a differential diagnosis of other diseases by arterial blood gas analysis, blood count, chest radiography, and electrocardiogram should be considered. When SpO_2 is less than 92%, arterial blood gas analysis should be performed to rule out hypercapnia.
   b) Treatment: Administer step 2 treatment for asthma exacerbations.

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Table 19
Treatment steps for asthma exacerbation.

	Treatment	Home remedy, emergency visit and hospitalization, and ICU treatment†
Treatment step 1	Inhaled short-acting β_2-agonist (SABA) Additional inhalation of budesonide/formoterol, as needed‡	Home remedy
Treatment step 2	Repeated inhalation of SABA using a nebulizer§ Intravenous drip infusion of aminophylline¶ Oxygen (target SpO_2 at 95%) Systemic administration of steroid‖ Inhaled anticholinergics Subcutaneous injection of Bosmin® (adrenaline, 0.1%)#	Emergency visit - If symptoms improve within 1 h, the patient may be discharged. - Insufficient response within 2–4 h - No response within 1–2 h Hospital admission: Switch to treatment step 3 as for severe exacerbation.
Treatment step 3	Repeated inhalation of SABA using a nebulizer§ Repeated administration of systemic steroid‖ Oxygen (target SpO_2 at 95%) Intravenous drip infusion of aminophylline (continuous)†† Inhaled anticholinergics Subcutaneous injection of Bosmin® (adrenaline, 0.1%)#	Emergency visit If no response within 1 h, hospitalization. If exacerbated, switch to treatment for serious exacerbation.
Treatment step 4	Continue the above treatment. If symptoms and respiratory function are exacerbated, conduct intubation.† Despite oxygen inhalation, ≤50 mmHg PaO_2 and/or rapidly elevated $PaCO_2$ with impaired consciousness. Mechanical ventilation,† Bronchial lavage Consider general anesthesia (using isoflurane, sevoflurane, etc.).	Immediate hospitalization and ICU treatment†

Aim of treatment: Elimination of dyspnea, normal movement, normal sleep, and normal everyday life. PEF rate is ≥80% of the predicted value or the best value. Oxygen saturation >95% (values after bronchodilator administration). No exacerbation of asthma symptoms by routine medication and inhalation.
Consider treatment step-up when the aim of treatment cannot be achieved within 1 h.

† ICU or hospital rooms where tracheal intubation, assisted ventilation, bronchial lavage, etc., can be performed and continuous monitoring can be conducted using a sphygmomanometer, electrocardiogram, and pulse oximeter. Since intubation and mechanical ventilation during severe respiratory insufficiency are often life-threatening, they should be used by experienced specialists when inevitable in emergency.

‡ Repeat 1–2 puffs of SABA pMDI twice at an interval of 20 min.

§ Inhalation of SABA using a nebulizer: repeat every 20–30 min. Monitor the pulse, which should be maintained at ≤130/min.

¶ Intravenous drip infusion of aminophylline (6 mg/kg) in 200–250 mL of isotonic fluid: Administer for about 1 h. If adverse reactions occur, discontinue the infusion. When a sufficient amount of theophylline had been administered before exacerbation, reduce the dose of aminophylline to half or less. Routinely, measure serum theophylline levels in patients receiving this drug, wherever possible.

‖ Intravenous drip infusion of steroids: intravenous drip infusion of 200–500 mg of hydrocortisone, 40–125 mg of methylprednisolone, or 4–8 mg of dexamethasone or betamethasone. Subsequently, conduct intravenous drip infusion of 100–200 mg of hydrocortisone, or 40–80 mg of methylprednisolone every 4–6 h as needed, or 4–8 mg of dexamethasone or betamethasone every 6 h as needed, or oral prednisolone (0.5 mg/kg/day). Steroid succinate esters (i.e., methyl prednisolone, prednisolone sodium succinate) should be avoided in patients who have or are suspected of having aspirin-induced asthma.

Bosmin® (adrenaline, 0.1%): Bosmin® (0.1–0.3 mL) can be repeatedly administered at intervals of 20–30 min. Monitor the pulse to be maintained at ≤30/min. This agent is contraindicated in patients with ischemic heart disease, glaucoma (except for open-angle [simple] glaucoma), and hyperthyroidism. Sphygmomanometry and electrocardiography are required for patients with hypertension.

†† Continuous intravenous infusion of aminophylline: following the first intravenous infusion (see ¶ above), conduct continuous intravenous infusion of 250 mg of aminophylline for 5–7 h (about 0.6–0.8 mg/kg/h). Monitor serum theophylline levels which shoud be maintained at 10–20 μg/mL (15–20 μg/mL to achieve the maximum effects). If adverse reactions occur, discontinue the infusion.

(i) Administer 0.3–0.5 mL of SABA diluted in physiological saline, via a nebulizer, and repeat every 20–30 min until symptoms improve. A SABA in a pMDI with a spacer has the same efficacy. The pulse rate should be maintained below 130/min. If symptoms improve within 60 min and are stable for 60 min after the last administration (%PEF ≥ 80%) and SpO_2 is 95% or higher, the patient can be discharged. If improvement is insufficient (%PEF < 80%), the following treatments should be initiated.

Table 20
Important points for history-taking in an emergency outpatient unit.

- Time of onset and cause of exacerbations
- Extent of exercise limitation and sleep disturbance
- History of recent drug administration, names of drugs and time of their last administration, and use of steroids
- Hospitalization and emergency visit due to asthma
- History of respiratory failure and intubation due to asthma
- Cardiopulmonary diseases and complications (heart failure, pneumothorax, pulmonary embolism)
- History of AERD and drug allergies

AERD, aspirin-exacerbated respiratory disease.

(ii) Intravenous drip infusion of 200–500 mg of hydrocortisone, 40–125 mg of methylprednisolone, or 4–8 mg of dexamethasone or betamethasone: systemic steroid should be administered immediately in cases of moderate or more severe exacerbations, poor response to the initial SABA inhalation, current treatment with a high dose ICS (equivalent to FP ≥ 800 μg/day) or an oral corticosteroid on regular basis, or high-risk group (Table 18).[101] Patients with or suspected of AERD should be treated using steroid phosphate esters. Slow intravenous infusion for about an hour is recommended for patients with unconfirmed AERD, or patients who are receiving the agent for the first time.

(iii) Oxygen: Oxygenation should be initiated nasally at a dose of 1–2 L/min to patients with SpO_2 less than 95% (PaO_2 < 80 mmHg), or with symptoms suggesting hypoxemia (cyanosis, dyspnea, or tachypnea).

(iv) Intravenous infusion of 6 mg/kg of aminophylline in 200–250 mL of isotonic fluid: administer for about 1 h. If sufficient theophylline had already been administered, reduce the aminophylline dose to half of this dose or less. If adverse reactions to theophylline (arrhythmia,

Table 21
Severity of an asthma attack and the corresponding treatment step.

Exacerbation intensity	Dyspnea	Movement	Measured values†				Treatment steps in exacerbation
			PEF	SpO_2	PaO_2	$PaCO_2$	
Wheezing/chest tightness	Dyspnea when in a hurry Dyspnea when in moving	Almost normal	≥80%	≥96%	Normal	<45 mmHg	Treatment step 1
Mild (mild exacerbation)	Dyspnea, but no trouble with lying down	Slight dyspnea					
Moderate (moderate exacerbation)	Dyspnea, with trouble with lying down	Difficulty in moving Difficulty in walking	60–80%	91–95%	>60 mmHg	<45 mmHg	Treatment step 2
Severe (severe exacerbation)	Dyspnea, cannot move	Abasia Difficulty in speaking	<60%	≤90%	≤60 mmHg	≥45 mmHg	Treatment step 3
Serious	Respiratory attenuation cyanosis Respiratory arrest	Anepia, Akinesia Confusion Impaired consciousness Incontinence	Immeasurable	≤90%	≤60 mmHg	≥45 mmHg	Treatment step 4

† Refer to values after bronchodilator administration.

headache, nausea, tachycardia, vomiting, and others) occur, immediately reduce or discontinue the administration. Monitoring serum theophylline levels during treatment is recommended wherever possible.

(v) Inhaled anticholinergics: Anticholinergics can be administered additionally if the treatment effect described above is insufficient.

(vi) Subcutaneous injection of 0.1–0.3 mL of adrenaline (0.1%): Adrenaline can be injected repeatedly at intervals of 20–30 min, but the pulse rate should be monitored and kept below 130/min.

c) Action plan after treatment.

(i) Favorable response: When wheezing and dyspnea are absent for 1 h (%PEF ≥ 80%; SpO_2 > 95%), discharge the patient. At discharge, step up the long-term treatment, and, in patients receiving an oral steroid, consider increasing the steroid dose for 1–2 weeks.

(ii) Insufficient response: Mild wheezing and dyspnea persists (%PEF < 80%; $SpO_2 \leq 95\%$). Proceed to step 3 treatment. When symptoms do not improve within 2–4 h, hospitalization should be considered.

(iii) No response: Marked wheezing and dyspnea or orthopnea persists (%PEF < 70%). Proceed to step 3 treatment. When improvement is not observed within 1–2 h after administration of intravenous steroids, consider hospitalization.

(iv) After hospitalization: Continue step 3 treatment.

(3) **Severe symptoms (severe exacerbations) or continued moderate symptoms**

a) Assessment: On arrival, briefly check the physical findings, differentially diagnose other diseases that cause dyspnea, and ask short questions about previous treatments and the causes of exacerbation.

(i) Symptoms and physical findings: Patients adopt a hunched position and cannot move. Accessory respiratory muscles are used, with depression of the suprasternal space. Speech difficulty, confusion, or unconsciousness may be observed. Cyanosis is a symptom of serious exacerbation. Attenuation or elimination of breath sounds suggests respiratory arrest or its signs.

(ii) Tests: Spirometry cannot be performed, or if it possible, the %PEF is less than 60%. Arterial blood gas analysis should be performed and if $PaCO_2 \geq 45$ mmHg, or $PaO_2 \leq 60$ mmHg, or $SpO_2 \leq 90\%$ is found, it suggests severe airway obstruction. Blood count, chest radiography, and electrocardiography are useful for differentiating other causes of dyspnea.

b) Treatment: Establish venous access immediately and initiate step 2 treatment, followed by step 3 for continuous treatment.

(i) Initial treatment: Step 2 treatment.

- Administer SABA using a nebulizer.
- Intravenous drip infusion of corticosteroids.
- Oxygen. Target PaO_2 is approximately 80 mmHg (SpO_2 95%). Attention should be paid for CO_2 narcosis in patients with COPD complications. In case of a poor response, assess consciousness and consider the introduction of noninvasive positive-pressure ventilation (NPPV), endotracheal intubation, and mechanical ventilation. NPPV improves respiratory function through pressure support ventilation, avoids airway collapse by positive end-expiratory pressure (PEEP), and shortens hospitalization. NPPV can be initiated if treatment by experienced specialists and medical staff is available. Note that initiation of intubation or mechanical ventilation should not be delayed, particularly in cases with disturbed consciousness or hypersecretion. Caution should be exercised for worsening symptoms after introduction of a sedative.
- Intravenous drip infusion of aminophylline.
- Subcutaneous injection of adrenaline.

If symptoms do not improve within 1 h, consider immediate hospitalization.

(ii) Continuous treatment: Continue step 3 treatment.

- Repeated administration of systemic corticosteroids. Intravenous drip infusion of 100–200 mg of hydrocortisone or 40–80 mg of methylprednisolone every 4–6 h, or alternatively, 4–8 mg of dexamethasone or betamethasone every 6 h as needed. Administration of hydrocortisone for longer than 3 days can cause edema; switch to a different steroid if this occurs. An oral prednisolone (approximately 0.5 mg/kg/day) once in the morning can also be used and can be discontinued or reduced to the usual dose by 7–14 days after remission. There is no benefit of tapering the dose of an oral corticosteroid, and the administration can be abruptly discontinued.[102] Initiate ICS when inhalation becomes possible during treatment.

- Oxygen. Maintain the targeted oxygenation (SpO_2 95%, PaO_2 80 mmHg).
- Continuous intravenous drip infusion of aminophylline at a dose of 0.6–0.8 mg/kg/h. Adjust the serum level of aminophylline at 8–20 μg/mL. If adverse reactions develop, immediately reduce or discontinue the administration and measure the serum theophylline levels. Consider factors affecting theophylline clearance (Table 18).

(4) **Serious asthma symptoms and emergency (serious exacerbations)**

a) Assessment: Emergency care including endotracheal intubation and mechanical ventilation is indicated, when severe ventilatory impairment or respiratory arrest occurs, no response to the above treatments are observed, PaO_2 is below 50 mmHg even after maximum oxygenation, or there is a rapid increase of $PaCO_2$ to ≥5 mmHg per hour with impaired consciousness. Preparations should be made for intubation when $PaCO_2$ exceeds 45 mmHg. The indications for endotracheal intubation are listed in Table 22. Since intubation for serious exacerbation is associated with a considerable risk, an experienced specialist should perform intubation wherever possible. Although NPPV may improve the patient's respiratory status and prevent airway collapse, treatment by an experienced specialist is desirable. Initiation of intubation or mechanical ventilation should not be delayed, especially in cases with hypersecretion or impaired consciousness.

b) Treatment: Administer step 4 treatment.

(i) Endotracheal intubation and mechanical ventilation[103]: After intubation, adjust the ventilator to 100% fraction of inspired oxygen (FiO_2), 5–8 mL/kg tidal volume, but maintain the maximum airway pressure below 50 cmH_2O and the average pressure at 20–25 cmH_2O. Set the ratio of inspiratory-to-expiratory phases at 1:3 or above to equalize the duration of each phase. Subsequently, set FiO_2 to achieve 80 mmHg PaO_2. Permit $PaCO_2$ values to be as high as 50–80 mmHg, to prevent barotrauma, until exacerbations improve. In serious exacerbations, the airway is under the auto-PEEP condition caused by the elevation of airway pressure at the end of expiration, due to central airway obstruction. Although it is reported that PEEP may be effective for rescinding the auto-PEEP, avoid using a ventilator at high PEEP as a rule, given the risk of barotrauma.

(ii) Treatment for exacerbation: Using an endotracheal tube, 0.3–1.0 mL of SABA or adrenaline (0.1% before dilution), both diluted 10-fold in physiological saline, can be administered. Initiate and continue pharmacotherapy as for severe asthma symptoms. When symptoms are refractory to treatment, consider general anesthesia using a narcotic agent (isoflurane, sevoflurane, and others), as these agents have bronchodilatory action that is effective in airway relaxation. The use of halothane should be avoided because it may cause ventricular arrhythmia when used concomitantly with β_2-agonists or aminophylline.

(iii) Conditions for extubation: Restored consciousness and maximum airway pressure reduced to 20 cmH_2O or less at spontaneous respiration.

Table 22
Indications for endotracheal intubation.

- Severe ventilatory impairment or cardiac or respiratory arrest
- Marked respiratory muscle fatigue
- PaO_2 < 50 mmHg even after maximum oxygenation
- Elevation in $PaCO_2$ ≥ 5 mmHg/h
- Marked elevation in $PaCO_2$ and consciousness disorder

4.2.4. Indications for hospitalization or intensive care unit admission

Consider hospitalization when symptoms are not improved within several hours after the initiation of treatment (Table 23). Immediately hospitalize a patient with serious symptoms. Consider an intensive care or consult an experienced specialist in the situations shown in Table 24.

4.2.5. Check points at discharge from an emergency room

If symptoms are stable for 60 min or longer after the last treatment, the patient may be discharged. PEF should be recovered to 80% or higher of the predicted or best value. Conditions for discharge from an emergency room are listed in Table 25.

4.2.6. Indications for discharge from the hospital

Check that symptoms have not exacerbated for 12 h or longer after treatment, before discharging the patient from hospital (Table 26). It is important to inform the patients about the high risk

Table 23
Indications for hospitalization.

- Moderate symptoms (%PEF 60–80%), insufficiently responsive to 2 to 4 h treatment (%PEF ≤ 70%) or nonresponsive to 1–2 h treatment
- Severe symptoms (%PEF < 60%) nonresponsive to treatment within 1 h
- History of severe asthma attack requiring hospitalization
- Chronic symptoms that had continued for a long period (several days to 1 week) until emergency visit
- Complications, such as pneumonia, atelectasis, and pneumothorax
- Mental disorders or communication difficulties
- Difficulties in consulting a medical institution, e.g., heavy traffic when returning home

Table 24
Indications for ICU admission.

- No response to initial treatment in an emergency room
- Symptoms suggesting risks of confusion, respiratory arrest, and unconsciousness
- Imminent respiratory arrest: $PaCO_2$ ≥ 45 mmHg continues (however, respiratory insufficiency may occur regardless of $PaCO_2$ level)

Table 25
Check points at discharge from an emergency room.

- Identify and avoid the causes of exacerbation
- Consult a physician as soon as possible after going home. Emphasize sufficiently that continuous outpatient treatment is required. In addition, examine the appropriateness of daily long-term treatment
- Prescribe agents for 3–5 days when the patient goes home. Optionally, oral corticosteroids, as well as bronchodilators, are often needed
- Check whether the patient experiences difficulty with the inhalation technique or with measuring PEF
- Check whether a patient or his/her family has any problem in coping with exacerbation. It is particularly important to explain medicines and self-management in detail, to recognize the signs of exacerbation, immediately initiate treatment, and visit a medical institution

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Table 26
Conditions for discharge.

- No requirement for bronchodilator inhalation at ≤4 h intervals
- No shortness of breath in walking
- No waking up at night or in the early morning due to exacerbation
- (Almost) no abnormal physical findings
- PEF or FEV_1 is ≥80% of predicted values. Diurnal variation is <20%
- Normal PaO_2 value
- No trouble handling an inhaler and a spacer
- Appropriate actions against exacerbation
- Patients understand the prescription at discharge
- Presentation of a treatment plan after discharge

of death from asthma, particularly to those who have experienced severe exacerbations, and to provide consistent instructions after discharge. Patients with repeated exacerbations should be adequately treated by a specialist, taking psychological and social factors into account.

5. Indications for a referral to a specialist

The pathophysiology of asthma is complex and the specific considerations shown below should be taken into account for long-term management. When the diagnosis or long-term treatment is difficult, the patient should be referred to an asthma specialist based on a cooperative system between hospitals and clinics.

6. Specific considerations

6.1. AERD

6.1.1. Definition

AERD is not an allergic reaction against aspirin. NSAIDs, particularly arachidonate cyclooxygenase-1 (COX-1) inhibitors, induce symptoms in the airways, including nasal congestion, nasal discharge, and severe asthma attacks. Because selective COX-2 inhibitors, such as celecoxib, can be used safely in patients with AERD, this reaction is due to hypersensitivity to COX-1 inhibitors. AERD is also known as “aspirin-intolerant asthma”; however, recently, it has been termed “aspirin-exacerbated respiratory disease (AERD)” because it induces symptoms in the upper respiratory tract, as well as asthma.[104]

6.1.2. Epidemiology, clinical aspect, and symptoms

Five to 10 percent of adult asthma patients have AERD, and the ratio of men to women is 1:2. AERD usually develops in 20- to 40-year-old individuals, and is characterized by weak or no atopy.[105] Half of the patients with AERD are severe asthmatics and often have fixed airflow obstruction. When the attack in AERD patients is caused by the administration of COX inhibitors, strong watery rhinorrhea and nasal congestion often develop as prodromal symptoms, which can be accompanied by facial flushing, conjunctival hyperemia, and one-third of patients have digestive symptoms, including abdominal pain, diarrhea, and others. Sometimes, chest pain, skin itching, and urticaria may occur simultaneously. Patients with AERD often have eosinophilic rhinitis with a nasal polyp and a distorted sense of smell. Similarly, more than half of asthmatic patients with a nasal polyp have AERD and nasal symptoms, particularly the distorted sense of smell. More than 50% of patients with nasal polyps have eosinophilic otitis media, about 30% have symptoms of eosinophilic colitis, and about 10–20% have variant angina pectoris.

6.1.3. Pathogenesis

AERD is thought to result from the overproduction of CysLTs.[106] Urinary LTE4 concentrations are several times higher in stable patients with AERD than in those without AERD, and in AERD attack, urinary LTE4 levels are more than several to several dozen times higher than in the stable condition.

6.1.4. Diagnosis

AERD cannot be diagnosed using tests for allergies, because AERD is characterized by nonallergic mechanisms. A medical interview is therefore quite important. Challenge test are sometimes required to diagnose AERD. In a medical interview, a physician should ask about the adverse effects of NSAIDs, disturbances in the sense of smell, the presence of a nasal polyp, and eosinophilic sinusitis. To confirm the diagnosis, it is recommended to perform a challenge test for NSAIDs, preferably in a specialist center with experienced experts.

6.1.5. Management of fever and pain in patients with AERD

Because of the relatively low threshold for causing an AERD attack, it appears that taking NSAIDs is dangerous in patients with AERD, even if NSAIDs are taken under the supervision of doctor. The severity of an AERD attack becomes stronger in the order injection > suppository > oral NSAIDs. Adhesive skin patches, ointment, and ophthalmic drugs should be prohibited in patients with AERD. Oral administration of acetaminophen is considered to be safer than regular NSAIDs. However, it has been reported that in 34% of asthmatic patients with AERD, the pulmonary function worsens at a dose of 1000–1500 mg of acetaminophen; therefore, it is safe to administer less than 500 mg of acetaminophen (or preferably even less than 300 mg) in patients with AERD.[107] A selective COX-2 inhibitor, celecoxib, has a high safety profile, but it rarely induces an attack in unstable and severe asthmatic patients with AERD.

6.1.6. Management of aspirin-induced attack of asthma

In the management of an asthma attack induced by NSAIDs, it is essentially the same as the standard treatment for exacerbations of asthmatic patients without AERD, but the following 3 issues should also be taken into consideration.

(1) Acute and high dose infusions of succinic esters of steroids often induce a severe asthma attack, and are sometimes fatal. Phosphate esters of steroids are thought to be safe for patients with AERD, but acute intravenous infusion often induces severe asthma attack because some additives could cause worsening of exacerbations. Therefore, a rapid intravenous administration of these agents is not safe, even intramuscularly. NSAIDs should be administered slowly in drip intravenous infusion over a period of more than 1–2 h.
(2) Because of some additives, inhalation of bromhexine hydrochloride salt sometimes induces an AERD attack. On the other hand, oral administration is known to be safe.
(3) Adrenaline (0.1%) is effective for the treatment of AERD attacks. Standard treatment for acute asthma exacerbation should be carried out. A low dose of adrenaline (0.1–0.2 mL) can be used for AERD attack and repeated administration is possible.

6.1.7. Long-term management of aspirin-induced asthma and prevention of NSAID use

Long-term management of AERD is essentially the same as that of asthma without AERD. ICS is the first choice and key drug in patients with AERD. LTRAs in combination with ICSs are a better choice for long-term management, because CysLTs could be associated with the pathogenesis of AERD. LTRAs improves asthmatic symptoms and sinusitis in patients with AERD and could partially inhibit AERD attacks. Treatment for chronic sinusitis and nasal polyps is important and a severe nasal polyp should be removed by endoscopic surgery to stabilize symptoms of AERD.

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6.2. Exercise-induced asthma (EIA)

6.2.1. Concept of (EIA)

Asthma attack or transient bronchoconstriction several minutes after exercise is called "exercise-induced asthma (EIA)" or "exercise-induced bronchospasm (EIB)".

6.2.2. Prevention of EIA

According to the guidelines of the American Thoracic Society (ATS), inhalation of SABAs before exercise is effective and is the first choice for patients with EIA. In frequent inhalation of SABAs or ineffective cases, controller drugs, such as ICS and LTRAs, are used for patients with EIA.

6.3. Asthma in athletes

6.3.1. Concept of asthma in athletes

The prevalence of asthma is known to be higher in athletes than in non-athletes. The asthma drugs allowed, or prohibited, as well as the route of administration, in athletes are determined by the World Anti-Doping Agency (WADA). For use of prohibited asthma drugs, asthmatic athletes should apply for a Therapeutic Use Exemption (TUE). For application for TUE, asthmatic athletes should be diagnosed as having asthma by a physician. The pathogenesis of asthma in athletes could differ from that of asthma in the general population.

6.3.2. Pathogenesis of asthma in athletes

In this group of asthmatics, the pathogenesis is thought to be associated not only with the general mechanisms of cooling of the airways or changes in osmotic pressure, but also with some specific mechanisms. During hard exercise, excessive ventilation reaches 200 L/min, and it induces stretching of the airway epithelial cells and causes tissue damage and repair in the airways, resulting in airway hyperresponsiveness and remodeling.[108] In the airways of asthmatic athletes, infiltration of neutrophils and lymphocytes are observed.

6.3.3. Prevalence of asthma in athletes

About 10–12% of Olympic athletes in Japan have asthma. This prevalence is markedly higher than that of the general populations (3–6%).

6.3.4. Diagnosis of asthma in athletes

When athletes apply for a TUE, they should be objectively diagnosed as having asthma. If they have asthmatic symptoms, including wheezing, chest tightness, dyspnea on exertion and cough, spirometry should be performed. If they have airflow limitations ($FEV_1\% < 85\%$), airway reversibility should be examined. If the test is positive, a physician can diagnose them as an athlete with asthma. If they have no airflow limitation ($FEV_1\% \geq 85\%$) or negative for airway reversibility in individuals with positive airflow limitation ($FEV_1\% < 85\%$), an airway hyperresponsiveness test or exercise-induced bronchoconstriction test should be considered. If either of these tests are positive, the athletes can be diagnosed with asthma.

6.3.5. Treatment of asthma in athletes

Inhalation of SABA before exercise and treatment with controllers are important for long-term management in athletes for prevention of exercise-induced bronchoconstriction. Although actual long-term management during a stable condition and management of exacerbations are similar to those for the general management of asthma, physicians should be careful about using asthma drugs in athletes, given that a number of asthma drugs are prohibited by the WADA.

(1) Long-term management: Inhalation of ICS, oral LTRAs and theophylline are approved for avoiding EIB in asthmatic athletes. Both SM and FM are approved; however, the patch formulation of tulobuterol and oral β_2 stimulants are prohibited, even with a TUE application.
(2) β_2 stimulants: Inhalation of salbutamol up to 1600 μg/day are approved for use without TUE; however, TUE requires inhaled procaterol. In SMART treatment, they can use maximum 12 puffs/day of a combination of BUD/FM in acute exacerbations.

6.3.6. Prevention of EIB in asthma in athletes

To prevent EIB of asthma, athletes need to be treated with SABAs 10–15 min prior to exercise or warming-up before exercise. Adequate controllers should be considered to prevent EIB in asthmatic athletes. Asthmatic athletes need to avoid exercise in cold and/or dry air conditions.

6.3.7. TUE

Application for TUE is regulated by the WADA. The rules and prohibited drugs are often changed, and athletes with asthma should take note of such changes.

6.4. Elderly patients with asthma

Because the World Health Organization (WHO) defines individuals older than 65 years as elderly persons, asthmatic patients older than 65 years are often defined as elderly patients in Japan. Because elderly adults vary considerably in senescent changes related to aging and comorbid conditions are present, the pathophysiology of asthma in this group is more complex and it is often difficult to diagnose asthma in these individuals because of their senescent changes. In 2013, 1728 patients were reported to have died of asthma, of whom 90% were older than 65 years. To reduce mortality from asthma in Japan, it is important to prevent death as well as to diagnose and manage asthma in elderly patients appropriately.

6.4.1. Diagnosis

Asthma symptoms in elderly patients are similar to those in younger asthmatic patients; however, symptoms of patients in a stable condition and of pulmonary function are not fully reversible. In elderly asthmatics, the severity of asthma is often evaluated as mild because of their poor sensation of dyspnea during bronchoconstriction. The diagnosis of asthma is often difficult when asthma is mild or occurs in the presence of senescence-related comorbidities. It may at times be difficult to recognize the clinical history of asthma because elderly patients often have COPD, heart failure, and reflux esophagitis. Yet, differential diagnosis between asthma and COPD is particularly important in this group. In asthma, eosinophilic inflammation is predominant in the central to peripheral airways, whereas neutrophilic inflammation is generally observed in the airways of patients with COPD. In COPD, stenosis and peribronchial fibrosis in peripheral airways and pulmonary emphysema are observed, these pathological alterations cause airflow obstruction in COPD. The brain natriuretic peptide levels, chest radiographs, and echocardiography are useful to distinguish asthma from heart failure.

6.4.2. Complications

(1) **COPD**

COPD is a significant coexisting disease in patients with asthma. In 2014, asthmatic patients with COPD were termed ACOS by the GINA and Global Initiative for Chronic Obstructive Pulmonary

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Diseases (GOLD) committees. Diagnosis and treatment for ACOS are presented in their statement.

(2) **Dementia, cranial nerve disease and disease of motor organs**

In patients with dementia or cranial nerve disease and disease of motor organs, health care personnel may be required to support and instruct patients in the use of asthma drugs, including inhaled agents.

6.4.3. Pharmacological treatment

(1) **Corticosteroids**

ICSs are the first choice for treatment of elderly patients with asthma. Oral corticosteroids may cause neurological symptoms, including excitation or confusion, in this group. ICSs do not cause systemic adverse effects and are safe even in elderly patients. On the other hand, elderly asthmatics tend to show poorer adherence to ICSs than younger asthmatics; therefore, it is important for elderly patients to assess their technique of inhalation repeatedly and to receive instruction on how to use inhaled drugs, given the various types of devices for inhaled drugs available. When elderly patients are unable to use a dry-powder inhaler because of insufficient inspiratory flow, it is sometimes useful to change to a pMDI with a spacer or to change to a suspension of corticosteroids delivered by jet nebulizer. Before stepping up treatment, the inhalation technique should be checked in this group. In this group of patients, long-term treatment with high-doses of ICSs (equivalent dose of 800 μg of FP per day) may cause systemic adverse effects, including progression of osteoporosis, changes in glucose metabolism and estrogen levels, hypertension, peptic ulcer, or immunosuppression. It should be noted that female elderly patients are particularly susceptible to progression of osteoporosis and bone fracture.

(2) **Bronchodilators**

SABAs and LABAs are the first choice for bronchodilators in elderly asthmatics, but their effectiveness is weaker than that in younger patients. When the elderly patients cannot breathe in the pMDI drugs, use of a spacer or jet nebulizer should be considered. A tulobuterol patch is effective in terms of adherence and efficacy. The side effects of these drugs should be carefully evaluated in elderly patients because adverse events, particularly cardiovascular events, including arrhythmia, angina, and tremor are increased in this group. SAMAs or LAMAs are relatively useful in patients with ACOS or in those who are less responsive to β_2-stimulants. A LAMA needs to be administered by paying thorough attention in patients with anuresis (difficulty in urination) due to benign prostatic hypertrophy. Its use is prohibited in patients with angle closure glaucoma.

(3) **Theophylline**

Serum theophylline levels should be checked and maintained at 5–10 μg/mL, and concomitant use with other asthma drugs is recommended because of the low clearance capacity in elderly patients. The adverse effects caused by overdose may be severe and even fatal in elderly patients.

(4) **Leukotriene receptor antagonist**

LTRAs are effective and safe for use in elderly patients.

(5) **Anti-allergic drugs**

Anti-allergic drugs are not effective in elderly patients, because these patients frequently have non-atopic asthmatic mechanisms.

6.5. Asthma and pregnancy

6.5.1. Influence of bronchial asthma on pregnancy and birth

The prevalence of asthma tends to increase during the ages of pregnancy. Because the levels of functional residual capacity in pregnancy decreases, an asthma attack accompanied by airway obstruction could cause hypoxemia in the fetus, posing risks of miscarriage, increased prematurity, and brain disorders.[109] Premature delivery, low birth weight, and malformation are reported to be more common among pregnant women with asthma. However, careful management of asthma can reduce the risk of death of the mother and fetus. No severe exacerbations are observed if good control is achieved in pregnant women with asthma before delivery.

6.5.2. Influence of anti-asthmatic drugs on pregnancy and birth

There is little evidence of teratogenicity for most anti-asthmatic drugs, as shown in Table 27. The influence of the drugs is as follows.

(1) Steroids: Most of anti-asthmatic drug seems to be non-teratogenic and are thought to be safe for use during pregnancy. Since steroids do not readily pass through the placenta, the serum levels of steroids in fetuses are markedly lower than those in their mothers. In fetuses, the risk of adrenal suppression is thought to be lower than in adults. To gain control of severe asthma, which causes fetal hypoxia and harms the mother's health, systemic steroids should be administered without hesitation. However, overlong administration of steroids in pregnant patients should be avoided wherever possible. ICSs are considered very safe for the pregnant patient and fetus. According to the FDA, all asthma drugs are categorized into 5 classes based on safety. Among asthma drugs, BUD (dry powder) is considered safer and is categorized in class B. Other ICSs are categorized as class C. According to the National Asthma Education Prevention Program, all ICSs are not classified, and they are all

Table 27
Agents that can be used for asthma during pregnancy and precautions for their use.

Inhalants
1. Inhaled corticosteroid†
2. Inhaled β_2 agonist (including a combination inhaler with an inhaled corticosteroid)‡
3. Disodium cromoglycate (DSCG)
4. Inhaled anticholinergic§
Oral medicine
1. Oral corticosteroid¶
2. Leukotriene receptor antagonist‖
3. Theophylline sustained-release preparation
4. Oral β_2 agonist
5. Antihistamine‖
Injections
1. Steroid¶
2. Aminophylline
3. Adrenaline (0.1%)#
Others
Patch-type β_2 agonist: Tulobuterol††

† Safety of budesonide in humans has been demonstrated clearly.
‡ There is less evidence of the safety of long-acting inhaled β_2 agonist (LABA) than that of short-acting inhaled β_2 agonist (SABA). However, these agents are almost comparable in their safety during pregnancy.
§ There is no evidence of safety as a long-term management agent used during pregnancy. Safety as a reliever agent has been demonstrated.
¶ Prednisolone and methylprednisolone do not appreciably pass through the placenta.
‖ Can be administered during pregnancy only when the advantages outweigh the disadvantages. Have few risks even if unknowingly ad- ministered during pregnancy.
Use the subcutaneous injection of adrenaline only when unavoidable. Generally avoid injection in pregnant women.
†† Safe as an inhalant or oral medicine. More evidence is needed.

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recommended as the first-choice drugs in patient requiring step 2 treatment, even during pregnancy and breast feeding.

(2) Other drugs: There have been no reports of teratogenicity for either inhaled or oral β_2-agonists. A patch formulation of tulobuterol is also considered safe during pregnancy. Anticholinergic agents are better avoided during pregnancy and breast feeding. Although there have been no reports on teratogenicity for either oral or intravenous theophylline, caution should be exercised in administering it to infants during breast feeding, because of the low rate of digestion of theophylline in infants. Since the LTRAs are not considered safe enough, they should be administered during pregnancy only when the advantages outweigh the disadvantages.

6.5.3. Treatment during pregnancy

It is worth continuing treatment of patients with asthma during pregnancy in order to avoid the risk of asthma attack, although pregnant women are generally nervous about the administration of drugs. Allergen avoidance, environmental management, and smoking cessation should be implemented to avoid exacerbating factors, with a view to preventing asthmatic symptoms and exacerbations. ICSs are recommended as first-line therapy for long-term management, as well as regular treatment of adult asthma. If ICS monotherapy is not sufficient to control the symptoms, other controllers should be considered. Allergen-specific immunotherapy (hyposensitization) can be continued during pregnancy if it had been initiated before pregnancy; however, it should not be initiated during pregnancy. Because of the lack of data, anti-IgE antibody should not be used during pregnancy. When asthma attacks occur, SABA inhalation should be administered. Similar to the general management of exacerbations in non-pregnant asthmatic patients, not only systemic steroids, but also infusion of aminophylline should be used. Oxygen inhalation is recommended to prevent fetal hypoxemia. In general, complications, such as abortion and premature delivery, premature rupture of the membranes, albuminuria, and eclampsia, are more common among patients with asthma. On the other hand, certain congenital disorders are seen in 2–4% of normal pregnancies. Therefore, these complications should be explained in detail before administration, and the patient's consent should be obtained. As mentioned above, it is important to avoid exacerbation factors, such as allergens, stress, and smoking. Smoking, including passive smoking, has serious consequences for the mother and fetus.[110]

6.6. Comorbidity

6.6.1. Asthma-COPD overlap syndrome (ACOS)

COPD is the most important disease in differential diagnosis and comorbidity in elderly patients with asthma. In COPD, neutrophilic inflammation is observed in the peripheral airways and airway obstruction is caused by a combination of peripheral airway obstruction and pulmonary emphysema. Thus, a differential diagnosis between asthma and COPD based on clinical symptoms is often difficult in elderly patients, although the diseases differ in their pathophysiological characteristics. According to previous reports, 18.4–31.7% of elderly patients aged 65 years and over actually have both diseases. A previous epidemiological report has shown that more than half of elderly patients with obstructive pulmonary disease had ACOS.[111] Because patients with ACOS are reported to have frequent exacerbations, lower levels of QOL, and a rapidly decline in pulmonary function, their prognosis are speculated to be worse. Methods of differential diagnosis of asthma, COPD, and ACOS were proposed in the joint statement made by GINA and GOLD. According to this statement, it is recommended that these patients are treated with ICS and LABA, and occasionally with LAMA.

6.6.2. Allergic rhinitis

About 40% of people in Japan have allergic rhinitis, and the number of patients with seasonal allergic rhinitis has increased. Allergic rhinitis is characterized by 3 main symptoms, including episodic and repeated sneezing, watery nasal discharge, and nasal congestion. Asthma is commonly associated with allergic rhinitis. The concept of “one airway, one disease” has been proposed because the lower respiratory tract is connected to the upper respiratory tract; these regions therefore influence each other. About 80% of asthmatic patients have allergic rhinitis, and 10–20% of patients with allergic rhinitis also have bronchial asthma. Pollen does not affect the development of asthma because pollen cannot act on the lower airways because of its size. Perennial allergic rhinitis caused by house dust mite is thought to be involved in the symptoms of asthma. Moreover, patients with seasonal allergic rhinitis experience asthma exacerbations during pollen allergy season.[112] When asthmatic patients with allergic rhinitis are treated with nasal corticosteroids, asthmatic symptoms are often improved. LTRA is beneficial for asthmatic patients with allergic rhinitis. Hyposensitization therapy is reportedly effective not only for allergic rhinitis, but also for asthma control; however, this therapy is prohibited in severe asthma.[113] Nevertheless, it rarely causes an asthma attack (1/1000–2000 injections). Sublingual allergen immunotherapy has recently received attention because of its efficacy reduced invasiveness.

6.6.3. Chronic sinusitis

Chronic sinusitis in asthmatic patients has recently been focused on as a factor causing refractoriness in asthma. The relationship between asthma and chronic sinusitis is well-established. More than half of asthmatic patients have abnormal findings in the paranasal sinuses on radiography. Chronic sinusitis is significantly frequently found in patients with severe asthma. The rate of exacerbations is positively correlated with the sinusitis score as assessed by computed tomography in asthmatic patients. Nasal polyps are often observed in patients with severe asthma. Low-dose macrolide therapy is effective for neutrophilic sinusitis, and improving post-nasal drip often improves asthma symptoms.

6.6.4. Eosinophilic sinusitis

Severe infiltration of eosinophils into the nasal mucosa and polyps is observed in eosinophilic sinusitis. Eosinophilic sinusitis is associated with severe asthma, particularly in patients with AERD. It can be diagnosed based on symptoms and CT findings. Conservative treatment involves only oral steroids. Although surgery is effective for eosinophilic sinusitis, half of the patients suffer relapse.

6.6.5. Eosinophilic otitis media

Eosinophilic sinusitis sometimes induces otitis media, termed eosinophilic otitis media. Both diseases worsen the QOL by impairing the sense of smell and hearing. Local treatment with steroids is effective for eosinophilic otitis media.

6.6.6. EGPA and CSS/allergic granulomatous angiitis (AGA)

(1) **Definition**

EGPA is an important comorbidity in asthma and is often life-threatening. EGPA is characterized by a history of asthma, increased eosinophil count in the blood and tissues, and multiple organ mononeuropathy and polyangiitis. CSS is now usually referred to as “eosinophilic granulomatosis with polyangiitis” or EGPA. EGPA is an antineutrophil cytoplasmic antibody (ANCA)-related systemic polyangiitis as well as granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis. Microvessels of the lungs and kidneys are often impaired.

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(2) **Epidemiology**

The age of onset of EGPA is generally older than 45 years. In Japan, the prevalence of CSS is about 0.2% in male and 0.5% in female patients with asthma.

(3) **Typical disease progression**

Disease progression in EGPA is divided into 3 clinical stages. In the first stage, patients develop eosinophilic sinusitis with asthma and nasal polyps. Next, increased blood eosinophil counts, worsening of asthma control, and occasionally, eosinophilic pneumonia are observed. In the third stage, systemic polyangiitis develops. Symptoms of EGPA are fever, muscle pain, and body weight loss. Multiple mononeuropathy and blood eosinophilia are observed in more than 90% of the patients. Half of the patients have skin symptoms, cardiac disturbances, and ischemic bowel disease. Two-thirds of the patients have elevated serum IgE levels, and are positive for conversion of rheumatoid factor. The positive ratio of myeloperoxidase (MPO) to ANCAs is about 30–40% in patients with EGPA.

(4) **Characteristic manifestations in asthma with EGPA**

Asthma that precedes EGPA usually develops in adulthood, and most of the patients with EGPA have severe disease with marked eosinophilia. Less than a half of the patients are atopic before the onset of EGPA. The patients often have fixed airflow limitation after remission. It has been reported that eosinophil count both in the peripheral blood and sputum may predict relapse in EGPA.[114] About 70–80% of the patients with EGPA show eosinophilic sinusitis and, occasionally, eosinophilic otitis media.

(5) **Diagnosis and treatment**

In Japan, EGPA is diagnosed based on the diagnostic criteria of the American College of Rheumatology (ACA) or Health, Labor, and Welfare Ministry of Japan. A physician should carefully observe the clinical course of severe asthma, especially in patients with weak atopic eosinophilia, frequent eosinophilic pneumonia, or eosinophilic sinusitis. The positivity rate for perinuclear antineutrophil cytoplasmic antibody (P-ANCA) needs to be about 30–40% for a diagnosis of EGPA; therefore, EGPA cannot be excluded on the basis of negative P-ANCA test results. Early diagnosis and treatment are important, because polyangiitis may progress rapidly. Patients with EGPA should be treated with systemic steroids. In patients with severe disease, cardiac disease, or digestive disorders, cyclophosphamide is concomitantly used with systemic steroids. Intravenous administration of high-dose immunoglobulin should be considered for treatment-resistant patients who have nervous system or cardiac disorders.

6.6.7. ABPA

(1) **Definition**

ABPA is an ABPM and develops after inhalation of *Aspergillus* spp. in asthmatic patients. *A. niger*, *A. oryzae*, *Penicillium*, *Cladosporium*, or *Candida* spp. can induce ABPM. Specific IgE and IgG are produced in sensitized asthmatic patients repeatedly infected by the fungus. Both types I and III allergic reactions are associated with pathological changes and destruction of the airways. Central bronchiectasis and thickening of the airway walls are observed in a relatively early stage of the disease.

(2) **Pathogenesis**

ABPA occurs in the injured airway epithelial cells, such as are found in asthmatic patients. HLA-DRB1 genes reportedly predispose to ABPM, because the Th2 reaction against *Aspergillus* easily occurs in patients with this genetic background.[115] After exposure to *Aspergillus*, the fungus persistently infects the lower airway walls. After Th2 cells are activated, a strong Th2 allergic reaction against *Aspergillus* occurs. *Aspergillus* secretes various types of proteases that cause airway destruction. Tissue destruction in ABPA is considered not to be due to infiltration of *Aspergillus* into the airway walls, but due to tissue immunological reactions. A mucoid impaction is formed and, subsequently, atelectasis and lung infiltration develops.

(3) **Diagnosis**

It is important to diagnose the condition in the early stage of the disease, because any delay in diagnosis will result in chronic airway infection, airway wall destruction, and respiratory failure. The diagnostic criteria for ABPA include (i) asthma, (ii) eosinophilia of the peripheral blood, (iii) positive results for an immediate allergic reaction test against *Aspergillus*, (iv) positivity for precipitation antibodies against *Aspergillus*, (v) elevated serum IgE levels, (vi) a history of lung infiltration, and (vii) central bronchiectasis. If all criteria are fulfilled, the diagnosis is considered as "confirmed"; if 6 of the 7 criteria are fulfilled, the diagnosis is considered as "almost confirmed".[116] However, early in the condition or in atypical cases of ABPA, the criteria are not fully matched, and the criteria by Greenberger et al. have been modified.

(4) **Morbidity**

Overseas, the morbidity of ABPA has been reported to be about 1–2% in patients with asthma. In severe asthma, the morbidity has been reported to be higher.

(5) **Treatment**

Systemic steroids should be administered to improve lung infiltration and prevent irreversible airway destruction in acute exacerbations. Doses of steroid higher than medium (prednisolone, 0.5 mg/kg) should be administered and be reduced over several weeks. In some cases, low doses of oral steroid are needed. Concomitant use of itraconazole is used to prevent relapse and lung infiltration, and cause a reduction in serum IgE levels and sputum eosinophil count.

6.6.8. Heart failure

Because symptoms of heart failure mimic those of asthma, a differential diagnosis is often difficult. A differential diagnosis is made on the basis of symptoms and clinical signs. In heart failure, pulmonary vasodilation and heart enlargement are observed on a chest radiograph, in addition to other common signs, such as Kerley lines, ground-glass opacity, a butterfly pattern, or a bat's wing pattern. The measurement of brain natriuretic peptide levels and serum N-terminal pro-B-type natriuretic peptide levels, echocardiograms, and Swan-Ganz catheter are useful for diagnosis of heart failure. Patients with heart failure may show obstructive lesions on spirometry as well as airway hyperresponsiveness. Physicians should be cautious, because systemic steroids and β_2-stimulants may worsen heart failure. Theophylline and aminophylline improve cardiac stress and pulmonary edema and are approved for use and are covered by insurance in Japan. β-Blockers are effective for the treatment of heart failure. Highly selective β1-blockers should be used for asthmatic patients. There is no reason to withdraw β-blockers in asthmatic patients with heart failure when these are effective for their heart failure.

6.6.9. GERD

GERD is caused by reflux of the gastric contents from the stomach into the esophagus, and induces various clinical symptoms and complications. It often causes chronic cough, throat pain, and sometimes induces asthma. About 45–70% of asthmatic patients have GERD. Asthmatic patients with GERD are more symptomatic than those without GERD. Proton-pump inhibitors only improve morning PEF in asthmatic patients with GERD. Surgery for GERD is sometimes effective as a non-pharmacological treatment.

6.7. Occupational asthma

Occupational asthma is defined as "asthma induced by exposure to a specific occupation-related substance in the office". In these

patients, asthmatic symptoms are often exacerbated in the office. Recently, asthma exacerbated by work-related factors has been termed "work-related asthma". The prevalence of occupational asthma in Japan is unknown, but in other countries, about 9–15% of asthmatic patients have occupational asthma.

6.7.1. Causative substance

Occupational asthma is induced by various types of substances, in general, they are classified into 2 types: irritant substances and sensitizing substances. Sensitizing substances are further classified into high molecular weight substances, such as proteins, and low molecular weight substances, such as chemicals. Most of the high molecular weight substances and some of the low molecular weight substances induce sensitized occupational asthma. Specific IgE against the causative substance is sometimes detected in this group; therefore, it is thought that IgE may be involved in the development of asthma. Genetic factors, frequent exposure to causative substances, atopy, and smoking are risk factors for sensitized occupational asthma.

6.7.2. Diagnosis

The diagnosis is mainly based on a medical history. It is necessary to evaluate (i) whether patients are exposed to the causative substances in the office within 24 h, (ii) whether asthma symptoms are improved during holidays or when the individual is out of the office, or (iii) whether allergic rhinitis or allergic conjunctivitis is exacerbated in the office. On the other hand, it is difficult to diagnose sensitized occupational asthma only via a medical interview. In these cases, monitoring of PEF 4 times daily (at least for 2 weeks in the office and 2 weeks out of office) is often useful, as is measurement of airway hyperresponsiveness and sputum eosinophil count in and out of the office. A challenge test is also a useful diagnostic tool. In some cases, detection of specific IgE may be useful. To diagnose irritant-induced occupational asthma, a medical interview is the most important, as it can reveal that asthma symptoms are induced within 24 h after exposure to an occupation-related irritant.

6.7.3. Precaution

First, environmental measures, including clearance or reduction of the causative substances at the office, are important. Next, medical surveillance is required to avoid exacerbations when sensitized occupational asthma occurs at the office.

6.7.4. Treatment

It is most important to avoid and reduce the causative substances in the office. Pharmacological treatment is similar to that used in the general treatment of asthma. If a causative antigen has been identified, allergen immunotherapy may be effective. A recent report has shown that monoclonal anti-IgE antibody was effective in a patient with severe occupational asthma who worked at a bakery.[117]

6.8. Surgery

About 2% of asthmatic patients who underwent surgery had bronchoconstriction during the perioperative period.[118] In addition, there were no asthmatic patients with pneumothorax, pneumonia, or death due to asthma attack during this period. However, caution should be exercised in surgery on asthmatic patients, despite the low rate of respiratory complications. In particular, postoperative respiratory complications could be higher in patients with lower pulmonary function. The incidence of respiratory complications is associated with the severity of asthma, the type of surgery (surgeries of the chest and upper abdomen carry a higher risk), or the method of anesthesia (intubation and sympathetic nerve block carry a higher risk). The severity of asthma should be evaluated before surgery.

6.8.1. Management before surgery

(1) **Evaluation of the severity of asthma**

The severity of asthma should be accurately evaluated in terms of the clinical history, symptoms, physical examination, pulmonary function, PEF values, and arterial blood gas analysis. AERD and latex allergy should also be evaluated before surgery.

(2) **Timing of surgery**

Additional treatment should be considered until good control and normal pulmonary function are achieved before surgery. In the case of emergency operations, systemic steroid should be administered to unstable patients during the perioperative period.

(3) **Pharmacological treatment before surgery**

If the asthma condition is unstable, additional treatment should be considered. In steroid-naïve asthmatic patients, ICSs should be given. If the condition is unstable, treatment with oral corticosteroids should be considered. If there is not enough time before the surgery or oral steroids cannot be administered, intravenous administration of corticosteroids should be considered. Steroid cover should be considered during the perioperative period if the patients have taken more than 2 weeks within 6 months. In patients taking high-dose ICSs, intravenous administration of a systemic steroid should be also considered if they will not be able to inhale ICSs during the perioperative period. A systemic steroid should then be switched to an ICS as soon as possible.

6.8.2. Anesthesia

(1) **Local and spinal anesthesia**

Local or spinal anesthesia can be performed without any effect on the respiratory system.

(2) **General anesthesia**

Intubation may induce bronchoconstriction in asthmatic patients. Anesthetic agents with bronchodilatory action should be used in anesthesia.

(3) **Anesthetic agents**

Sevoflurane is the first-choice drug for asthmatic patients. Thiopental, thiamylal, ketamine, propofol, midazolam, remifentanil, and fentanyl are used in intravenous anesthesia. On the other hand, the use of thiopental and thiamylal is contraindicated in asthmatic patients. Although propofol has bronchodilatory action and is used for inducing anesthesia, it should be administered with caution because of the possibility of bronchial spasm.

6.8.3. Treatment of asthma attack during surgery

Similar to exacerbations, when asthma attacks occur during surgery, inhaled β_2-stimulant, intravenous drip infusion of corticosteroid (hydrocortisone, methylprednisolone) and aminophylline, subcutaneous injection of adrenaline (0.1%), and inhalation of oxygen are recommended.

6.8.4. Postoperative management

When wheezing continues after the surgery, a β_2-stimulant should be inhaled before extubation and a sufficient dose of a systemic steroid should be administered. Morphine hydrochloride is contraindicated because of its bronchoconstrictive action.

6.9. Cough variant asthma (CVA)

Cough-variant asthma (CVA) is a type of asthma that is characterized only by chronic dry cough without wheezing and an attack of dyspnea. Bronchodilators are effective in this group. CVA is the major cause of chronic cough continuing for more than 8 weeks. The features of CVA are the following: (i) increased cough

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reflex against constriction of airway smooth muscle; (ii) cough sensitivity that is within the normal range; (iii) frequent atopy; (iv) eosinophils present in the sputum, bronchial mucosa, and bronchoalveolar lavage fluid; (v) increased FeNO; and (vi) inhaled or oral corticosteroids are effective. CVA is more severe at bedtime, during the night and early morning, and is induced by cold and warm air, passive smoking, conversation, exercise, alcohol, mental stress, and other factors.

6.10. Aspects of psychosomatic medicine

Psychosomatic factors have long been reported to be associated with asthma, since the time of Hippocrates. Because asthma control is strongly affected by psychosomatic factors, psychosomatic medicine may become more important in the management of asthma.

6.10.1. Mind-body connection

(1) **Influence of psychosomatic social factors on asthma**

Psychosomatic social stress affects the development, exacerbation, and management of asthma. Associations between panic disorder and emergency room visits have been reported.[119]

(2) **Influence of asthma on psychosomatic conditions**

In asthmatic patients, the rate of psychosomatic disorders tends to increase, especially in patients treated with oral corticosteroids.

6.10.2. Diagnosis of asthma in psychosomatic medicine

(1) **Development, relapse, exacerbation, and persistence of asthma due to psychosomatic stress**

Changes in lifestyle and various events (childbirth, marriage, divorce, moving house, losing a job, job change, hospital admission, death of a close relative) or the stresses of daily life (at home, work, school, etc.) are often observed prior to the development or relapse of asthma.

(2) **Social adaptation problems associated with asthma**

Asthma carries a considerable physiological, psychological, temporal, and economic burden. It is associated with sleep disorders, problems in personal relations, social isolation, worse performance at school or work, depression, and anxiety.

(3) **Non-adherence to asthma treatment**

Psychosomatic factors may lead to poor adherence to asthma treatment. Moreover, they cause irrational anxiety, fear, inadequate self-management of asthma, a pessimistic view on the prognosis of asthma, and a sense of helplessness in controlling the disease, as a result of which, patients often develop distrust in physicians or medical care. This leads to treatment failure or considerable delays. Questionnaires for evaluating psychosomatic and social background of asthma may be useful.

6.10.3. Psychophysiological treatment

In this group of patients, counseling is the principal method for psychophysiological treatment. If asthmatic patients with anxiety disorder or mood disorders often suffer from exacerbated asthma, anti-anxiety or antidepressant agents may be effective in the management of an asthma attack, in addition to the regular asthma drugs. Besides the regular treatment of asthma, pharmacotherapy, autogenic training, cognitive behavioral therapy, family therapy, and fasting therapy have been attempted. Diary writing alone has been reported to improve the symptoms of asthma in psychosomatic patients.[120]

6.11. Immunization

The Japanese guidelines on immunization were revised in 2014; they present the perspective of the Japanese Society of Pediatric Allergy and Clinical Immunology. Constituents of vaccine that are related to allergy include egg-related antigen, antiseptic agents, or additive substances, medium or antimicrobial agents, and vaccine antigens. Latex allergy may sometimes also be problematic (e.g., yellow fever vaccine).

In the USA, immunization is recommended for asthmatic patients, except for specific cases, since asthmatic patients tend to exaggerate serious symptoms and attack with respiratory infection. In general, immunization with live viral vaccine can be used in asthmatic patients taking low-to-intermediate doses of systemic steroids (lower than 20 mg/day). However, live viral vaccine should be discontinued a month later in patients receiving 2 mg/kg/day, or more than 20 mg/day of prednisolone over a 2-week period.

Conflict of interest

MI received honoraria from AstraZeneca, Nippon Boehringer Ingelheim, Novartis Pharma. HSu received lecture fees from AstraZeneca. HN received honoraria from Astellas Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Kyorin Pharmaceutical, Novartis Pharma, and research funding from Kyorin Pharmaceutical. HI received lecture fees from AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceutical, GlaxoSmithKline, and research grant from Boehringer Ingelheim, Ono Pharmaceutical.

HSa received honoraria from Astellas Pharma, Nippon Boehringer Ingelheim, AstraZeneca, Novartis Pharma, Kyorin Pharmaceutical, GlaxoSmithKline. JT received honoraria from AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MSD, Taisho Toyama Pharmaceutical, and research funding from AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MSD, Taisho Toyama Pharmaceutical. YT received AstraZeneca, Astellas Pharma, GlaxoSmithKline, Kyorin Pharmaceutical, Teijin Pharma, Ono Pharmaceutical, and research funding from Boehringer Ingelheim, Novartis Pharma. MM received honoraria from Boehringer Ingelheim. KY received honoraria from Nippon Boehringer Ingelheim, AstraZeneca, Kyorin Pharmaceutical. KO received honoraria from Kyorin Pharmaceutical, Astellas Pharma, Boehringer Ingelheim. MY has no conflict of interest.

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