

Japanese Guideline for Adult Asthma

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ABSTRACT

Adult bronchial asthma (hereinafter, asthma) is characterized by chronic airway inflammation, reversible airway narrowing, and airway hyperresponsiveness. Long-standing asthma induces airway remodeling to cause an intractable asthma. The number of patients with asthma has increased, while the number of patients who die from asthma has decreased (1.7 per 100,000 patients in 2009). The aim of asthma treatment is to enable patients with asthma to lead a healthy life without any symptoms. A partnership between physicians and patients is indispensable for appropriate treatment. Long-term management with agents and elimination of causes and risk factors are fundamental to asthma treatment. Four steps in pharmacotherapy differentiate mild to intensive treatments; each step includes an appropriate daily dose of an inhaled corticosteroid (ICS), varying from low to high doses. Long-acting β_2 agonists (LABA), leukotriene receptor antagonists, and theophylline sustained-release preparation are recommended as concomitant drugs, while anti-IgE antibody therapy is a new choice for the most severe and persistent asthma. Inhaled β_2 agonists, aminophylline, corticosteroids, adrenaline, oxygen therapy, etc., are used as needed against acute exacerbations. Allergic rhinitis, chronic obstructive pulmonary disease (COPD), aspirin induced asthma, pregnancy, and cough variant asthma are also important factors that need to be considered.

KEY WORDS

acute exacerbation, control of asthma, epidemiology of asthma, patient education, treatment step

1. AIM OF MANAGEMENT, DEFINITION, DISEASE TYPE, DIAGNOSIS AND SEVERITY OF ASTHMA

1.1. DEFINITION AND PATHOLOGY OF ASTHMA

Adult bronchial asthma (hereinafter, asthma) is characterized by repetitive cough, wheezing, dyspnea, reversible airway narrowing, and airway hyperresponsiveness. Asthma symptoms tend to be more severe in more hyperresponsive airways. Airways hyperresponsiveness is not always associated with asthma symptoms. Asthma is characterized by chronic airway inflammation accompanied by the infiltration of eosinophils, lymphocytes, mast cells, etc., and the detachment of the airway epithelial cells.^{1,2} While many patients carry IgE antibodies against environmental

allergens, airway inflammation and lymphocyte activation are noted even in patients without allergen specific IgE antibody. The clinical picture of asthma is multifactorial, thus, different clinical pictures of asthma have attracted attention. Some patients suffer from airway inflammation with predominating neutrophils. Patients with long-standing asthma suffer from airway remodeling, consisting of subepithelial fibrosis under the basement membrane, smooth muscle hypertrophy, and submucosal gland hyperplasia, which results in intractable asthma with irreversible airflow limitation and persistent airway hyperresponsiveness.³ In the elderly, clinical picture of asthma may be complicated by coexisting chronic obstructive pulmonary disease (COPD).

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Table 1 Aims of asthma treatment

1. Lead a normal and healthy life. Maintain normal growth.
2. Maintain normal respiratory function.
PEF variation is in a range of <20% of predicted value.
PEF is $\geq 80\%$ of predicted value.
3. Allow sufficient night sleep without cough or dyspnea at night or in the early morning.
4. Prevent asthma attacks.
5. Avoid death from asthma.
6. Prevent adverse effects caused by therapeutic agents.
7. Prevent the development of irreversible airway remodeling.

Table 2 Diseases that should be differentiated from asthma

1. Upper respiratory tract diseases: laryngitis, epiglottitis, vocal cord dysfunction (VCD)
2. Proximal respiratory tract diseases: endotracheal tumor, foreign body aspiration, tracheomalacia, endobronchial tuberculosis, sarcoidosis
3. Diseases from the bronchus to alveolar regions: COPD, diffuse panbronchiolitis, pulmonary fibrosis, hypersensitivity pneumonitis
4. Cardiovascular diseases: congestive heart failure, pulmonary thromboembolism
5. Cough caused by medicines, such as ACE inhibitors
6. Other causes: spontaneous pneumothorax, vagotonic effects, hyperventilation syndrome, and psychogenic cough
7. Allergic respiratory diseases: allergic bronchopulmonary aspergillosis, allergic granulomatous angitis (Churg-Strauss syndrome), eosinophilic pneumonia

Table 3 Important features for diagnosis of adult asthma

1. Paroxysmal dyspnea, wheezing, repeated cough (particularly at night and in the early morning)
2. Reversible airflow limitation: Response to treatment. Diurnal variation in the PEF rate is $\geq 20\%$. Forced expiratory volume in one second (FEV_1) is increased by $\geq 12\%$ and ≥ 200 mL in absolute volume by β_2 agonist inhalation
3. Airway hyperresponsiveness: Measurement of airway contractility to acetylcholine, histamine, and methacholine
4. Atopy: IgE antibodies against environmental allergens
5. Airway inflammation: Increased eosinophils in sputum and peripheral blood, high ECP, Creola bodies, increased fraction of exhaled nitric oxide (FeNO)
6. Differential diagnosis: Exclude diseases caused by other cardiopulmonary disorders

1.2. AIM OF THE MANAGEMENT AND TREATMENT OF ASTHMA (Table 1)

Our aim is to alleviate and ameliorate airway hyperresponsiveness and airflow limitation by eliminating the inducers of airway inflammation and airflow limitation, by suppressing inflammation by pharmacotherapy, and by dilating the constricted airway. Respiratory function is normalized as much as possible to improve patients' quality of life (QOL) and enable them to lead a normal and healthy life.

1.3. DIAGNOSIS OF ADULT ASTHMA

Diagnosing mild asthma with neither wheezing nor dyspnea is often difficult. Delayed diagnosis may cause chronic severe asthma. Generally, clinical diagnosis of asthma is based on (i) repetitive symptoms, such as paroxysmal dyspnea, wheezing, chest tightness and cough, (ii) reversible airflow limitation, and (iii) exclusion of other cardiopulmonary diseases (Ta-

ble 2). Its diagnostic criteria has not been established. Instead, "signs" suggestive of asthma are shown in Table 3.

1.3.1. Recurrence of Paroxysmal Dyspnea, Wheezing, Chest Tightness, and Cough (often develop at night and in the early morning)

Asthma is characterized in repeated exacerbation that occur amid symptom-free intervals and develop even during rest. Patients with asthma may feel dyspnea (choking) during exercise and laborious work. Asthma with such symptoms, occurring within the past 12 months, is called current asthma. The histories of (i) development and persistence of dyspnea, (ii) emergency room visits and hospitalization due to paroxysmal dyspnea, (iii) improvement of symptoms when using an anti-asthmatic drug, and (iv) dyspnea caused by exposure to certain causative substances support the diagnosis of asthma.

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	Disturb everyday life and sleep once or more a month	Disturb everyday life and sleep once or more a week	Restrict everyday life
	Symptoms at night	Less than twice a month	Twice or more a month	Once or more a week	Frequently
PEF	%FEV ₁ , %PEF	≥80%	≥80%	≥60%, <80%	<60%
FEV ₁ [‡]	Variation	<20%	20-30%	>30%	>30%

[†] Determine the severity based on the presence of any one of the symptoms.

[‡] 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. %FEV₁, (FEV₁ measured value/FEV₁ predicted value) × 100; %PEF, (PEF measured value/PEF predicted value or the best value) × 100.

1.3.2. Reversible Airflow Limitation⁴

Wheezing and dyspnea during attacks are caused by reversible airway narrowing, which develops extensively in the airway, with the peak expiratory flow (PEF) and forced expiratory volume in one second (FEV₁) altered markedly from exacerbation to stabilization periods. Asthma-specific alterations in PEF and FEV₁ have not been established, but ≥20% diurnal variation in the PEF suggests asthma. Reversible airflow limitation is regarded as significant when FEV₁ is increased by ≥12% and ≥200 mL in an absolute volume after β₂ agonist inhalation. If the increase is below that level after β₂ agonist inhalation, reversibility may be detectable after oral corticosteroid administration for 2-3 weeks. In addition, even if no significant difference is noted in respiratory function tests before and after β₂ agonist inhalation, asthma is still suspected when there is a significant difference (≥20%) between the PEF rates before using a bronchodilator in the early morning and those after inhaling a β₂ agonist between 12:00 pm and 14:00 pm.

1.3.3. Airway Hyperresponsiveness^{5,6}

The airway is contracted by stimuli to which healthy individuals show no response. A standard quantitation method of the Japanese Society of Allergology or an astograph method can be used. In the former method, a patient inhales a bronchoconstrictor (e.g., acetylcholine, methacholine, or histamine) for 2 min for the assessment of airway hyperresponsiveness us-

ing PC₂₀ (i.e., a concentration to reduce FEV₁ by 20%) and PD₂₀ (i.e., a cumulative dose during that time). In the latter method, a patient inhales methacholine of different concentrations. Airway hyperresponsiveness is assessed as D_{min}, the concentration of methacholine at which airway resistance starts increasing. Both methods are load tests that include induction of airway narrowing, thus, caution should be taken for patients with decreased respiratory function. Baseline %FEV₁ (percentage of FEV₁ against a predicted value) is desirably ≥70%.

1.3.4. Atopic State

Specific IgE antibodies against various environmental allergens indicate atopic state.

1.3.5. Exclusion of Diseases to Be Differentiated

A comprehensive diagnosis should be made if boundary regions of asthma-like symptoms, caused by other cardiopulmonary diseases, or coexisting asthma need to be considered (Table 2).

1.3.6. Airway Inflammation

Increased percentages of eosinophils, high ECP (eosinophil cationic protein) value, and Creola bodies comprised of exfoliated airway epithelial cells, detected by sputum examination, indicate allergic airway inflammation.⁷ Increased fraction of exhaled nitric oxide (FeNO) also suggests airway inflammation.^{8,9} An increased number of eosinophils in the peripheral blood and elevated serum ECP values also

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	Concomitantly use multiple agents of those below. • LABA (a compounding agent can be used) • LTRA • Theophylline sustained-release preparation If poorly controlled with all of the above agents, add either or both of the agents below. • Anti-IgE antibody [‡] • Oral corticosteroid [§]
	Additional treatment	Antiallergics other than LTRA [†]	Antiallergics other than LTRA [†]	Antiallergics other than LTRA [†]	Antiallergics 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.

[†] 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 of 30-700 IU/mL.

[§] Oral corticosteroids are intermittent administration for a short period. Keep the minimum maintenance dose if a patient cannot be controlled by enhanced treatment with other agents and short intermittent administration.

[¶] Management against mild exacerbations are shown. For other exacerbations, refer to Table 23.

suggest airway inflammation.

Of the above “signs,” (1.3.1.) respiratory symptoms, (1.3.2.) reversible airflow limitation, and (1.3.5.) asthma symptoms not caused by other cardiopulmonary diseases are diagnostically important. If the respiratory function is normal, the presence of (1.3.3.) airway hyperresponsiveness and (1.3.6.) allergic airway inflammation support a diagnosis of asthma.

1.4. CLASSIFICATION OF ASTHMA SEVERITY AND EXACERBATION INTENSITY

Assessment of asthma severity and exacerbation intensity is important for the management of asthma, and is fundamental to stepwise pharmacotherapy (Table 4). The initial treatment is selected from treatment steps 1 to 4 (Table 5) according to the severity of asthma (Table 4); i.e. step 1 for mild intermittent, step 2 for mild persistent, step 3 for moderate persistent and step 4 for severe persistent (see Table 5, “Treatment steps for asthma”). To achieve the aim of asthma treatment (Table 1), the present controlled status should be maintained (see Table 18, P17). The symptoms and the present treatment step determine a treatment strategy, such as strengthened treatment

in the same step or step-up for one or two steps (Table 6). If asthmatic symptoms are controlled for 3-6 months, step-down of treatment can be attempted. Exacerbation intensity in asthma is classified in Table 7.

1.5. INTRACTABLE ASTHMA

Intractable asthma is one of the most severe and persistent types of asthma, with daily development of symptoms, even when treatment step 4 in Table 5, except for oral corticosteroid and anti-IgE antibody, is conducted. Additional potential underlying diseases such as aspirin induced asthma, Churg-Strauss syndrome and other systemic vasculitis syndrome, and allergic bronchopulmonary aspergillosis should be considered in asthma patients requiring continuous oral corticosteroid administration.

2. EPIDEMIOLOGY OF ASTHMA

2.1. CHANGES IN ASTHMA PREVALENCE OVER TIME

Asthma prevalence has been rapidly increasing in recent years. An International Study of Asthma and Allergies in Childhood (ISAAC) survey was conducted

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

Patient's symptoms in the present treatment	Present treatment step			
	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 • Restrict everyday life • Frequently 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 compliance with treatment, and consider step-up as needed.

in Fukuoka City and Tochigi Prefecture and across Japan to examine the prevalence of asthma at specific time points (Table 8). Asthma prevalence at different areas cannot be precisely compared between years, because it markedly varies with regions. However, the mean prevalence in Japan was estimated to have increased from about 1% to 6% in children and from <1% to about 3% in adults since the 1960s. In addition, according to a survey conducted over several years, in which the same physicians used the same protocol in subjects with the same background (Table 9),^{10,11} a 1.5-2-fold increase was reported every 10 years, both in Japan and overseas (Fig. 1). In a survey of adult asthma in citizens of Fujieda City, Shizuoka Prefecture conducted in 1986 and 1999, the prevalence of asthma increased from 3.14% to 4.15%.

2.2. REGIONAL DIFFERENCES IN ASTHMA PREVALENCE

The ISAAC Steering Committee reported regional dif-

ferences in the cumulative prevalence of asthma in 13-14-year-old subjects, at 155 sites, in 56 countries in the world, ranging from 1.6% in Indonesia to 36.8% in UK (Fig. 2). The prevalence in Japan was comparable with or slightly lower than prevalence in Europe and USA (e.g. Fukuoka City, 13%, Tochigi Prefecture, 19%). A comparison of the European Community Respiratory Health Survey (ECRHS) and studies in Japan showed that the prevalence in Japan was lower (8.1%), although the surveys were conducted in different years (Table 10).¹²

2.3. MALE-FEMALE RATIO

The prevalence of asthma is more common in males at an early age in all the countries, however, after puberty, the prevalence is more common in females. At onset of asthma, the male-female ratios in Japan were 2.8 during infancy, 1.5 during childhood, and below 1.0 after 10 years of age. Among the elderly, females are more likely to have asthma, but since males ac-

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

Exacerbation severity [†]	Dyspnea	Exertion	Laboratory data [§]			
			%PEF	SpO ₂	PaO ₂	PaCO ₂
Wheezing/chest tightness	Dyspnea when in a hurry Dyspnea when moving	Almost normal	≥80%	≥96%	Normal	<45 mmHg
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
Severe (severe exacerbation)	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, use more severe one.

[‡] Perform emergency assessment against more serious symptoms, such as respiratory attenuation or arrest, anepia, impaired consciousness, and incontinence.

[§] Refer to measured values after bronchodilator administration.

Table 8 Prevalence of bronchial asthma I

	ISAAC phase I study in 1994	ISAAC phase I study in 1994	ISAAC phase III study in 2003	Study Group of the Ministry of Health, Labour and Welfare in 2005
	Fukuoka Prefecture	Tochigi Prefecture	Fukuoka Prefecture	Japan
6-7 years of age	17.3%		18.2%	13.9%
13-14 years of age	13.4%	19%	13.0%	8.8%

count for a lower percentage of the general population of the elderly, we cannot conclude that the prevalence is led in elderly males. The male-female ratios tend to be slightly higher in rural areas and slightly lower in urban areas.

2.4. NUMBER OF PATIENT VISITS AND CONSULTATION RATE

According to the statistics of the Ministry of Health, Labour, and Welfare (formerly Ministry of Health and Welfare), the number of patients with asthma, who had continued to visit a hospital until the survey date in October 1996, which calculated hospitalized patients + new outpatients + second visit outpatients × average visit interval × survey coefficient, was 1,146,000 (619,000 males and 527,000 females) (Statistical Information, Ministry of Health and Welfare,

1998). In a large-scale telephone survey, conducted in 2000, the percentage of patients who received treatment, calculated with the number of persons in the screening cooperating households (126,758) and the number of patients with asthma (1,786), was about 1.4%. Thus, the number of patients with asthma, who received treatment, was estimated to be about 1,780,000.¹¹

2.5. DEATHS FROM ASTHMA¹³

According to the Vital Statistics of the Ministry of Health, Labour and Welfare, the number of patients (of all ages) who died from asthma has gradually decreased in recent years. That stopped decreasing at a rate of 4.5-5.0 per 100,000 patients around 1975, transiently increased in 1995, decreased again after 1997, and then hit its lowest point of 1.7 per 100,000 pa-

Table 9 Prevalence of bronchial asthma II

	1960	1970	1980	1990	2000	Ages of subjects
Fukuoka City			5.7% (81-3)	7.7% (93-5)		6-12y [†]
Oslo			2.2% (81)	4.2% (93)		School children [‡]
			3.4%	8.0%		§
Western Japan			3.2% (82)	4.6% (92)	6.5% (02)	6-12y [†]
Kitakyushu		1.6% (71)	3.6% (81)	5.4% (91)		6-12y [†]
Aberdeen	10% (64)		20% (89)			7y [¶]
	4.2%		10.4%			
South Wales		17% (73) 6%	22% (88) 12%			7y [¶]
Australia			21.0% (87) 5.6% (87)	25.1% (90) 8.0% (90)		Adults [¶] #

(): Year of the survey.

[†]current asthma (ATS-DLD), [‡]current asthma (diagnosed asthma), [§]cumulated asthma (diagnosed asthma), [¶]wheezing, ^{||}cumulative asthma (diagnosed asthma), [#]current asthma.

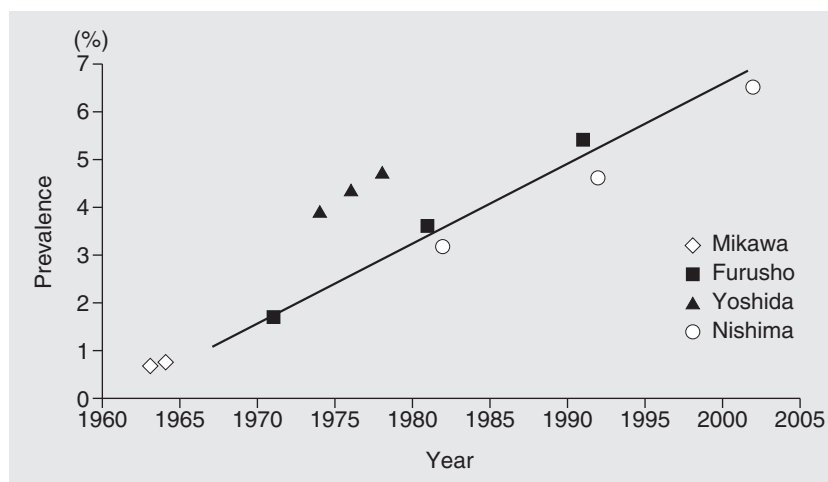


Fig. 1 Changes over years in the prevalence of bronchial asthma in Japanese elementary school students reported by four investigators.

tients (2,139 deaths) in 2009. In particular, the number of patients who died from asthma at an early age markedly decreased, thus, currently 88% of deaths occur among the elderly, aged 65 years or older.

3. PATIENTS EDUCATION AND A PARTNERSHIP BETWEEN PHYSICIANS AND PATIENTS

3.1. EDUCATIONAL NEEDS

It is required for patients to have a certain amount of knowledge in order to achieve a partnership with medical professionals and to become capable of self-management. Sufficient patient education regarding asthma reduces the prevalence and mortality of asthma, increases the patients' QOL, and is effective in reducing medical expenses.¹⁴ Patients who re-

ceived self-management training from a specialist in asthma can understand severity objectively by PEF measurements, recognize symptoms relating with asthmatic exacerbation, and take immediate and appropriate actions against attacks. Furthermore, they can appreciate agents used periodically for long-term management and those used as needed for controlling attacks. Effective education of patients includes the provision of a written self-management plan (action plan) that details issues related to severity, self-management, and self-assessment, directions for use of medications, and timing of administration.¹⁴

3.2. SUBJECTS

Education should be provided to patients, their families, neighbors, and caretakers for the elderly.

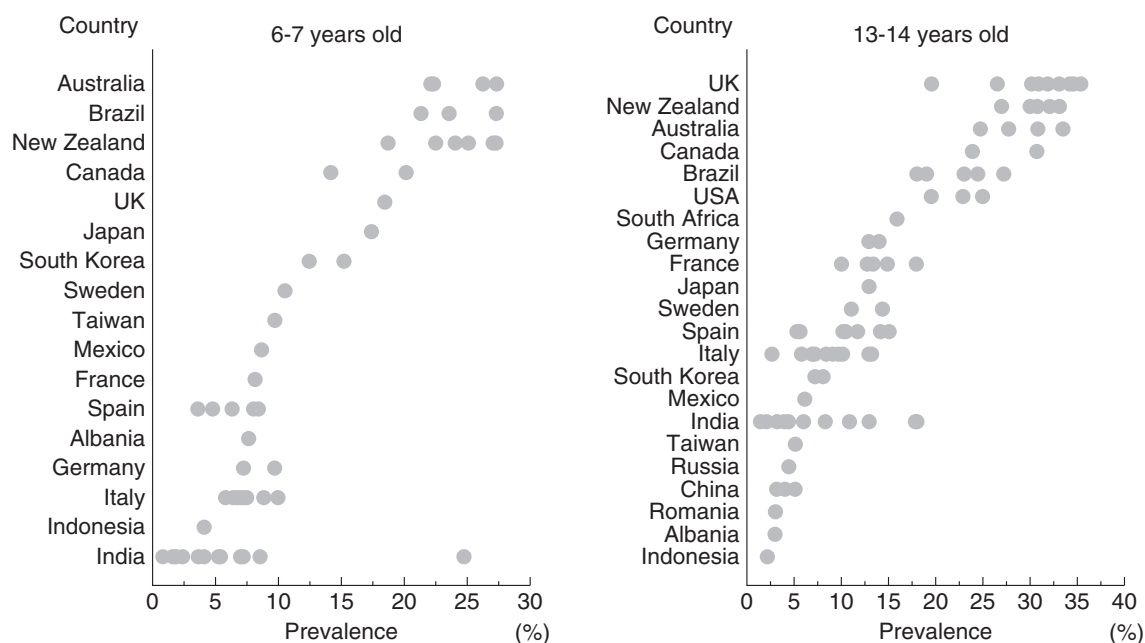


Fig. 2 Allergic asthma symptoms within 1 year based on ISAAC questionnaire (ISAAC phase I study). The survey was conducted in 1995 by ISAAC (International Study of Asthma and Allergies in Childhood) in Fukuoka, Japan. Circles show the prevalence at various survey spots. An average of 3,000 persons was included for each spot.

Table 10 Prevalence and period of asthma by ECRHS survey

Country	Year	Age	Period 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	27.0
		20-44	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

3.3. CONTENTS

Since asthma is a chronic disease, the needs of long-term management must be explained. Patients, physicians, and medical staffs should exchange information to discuss expected effects and anxiety regarding treatment. In addition, the explanation items in Table 11 should be discussed with patients. Peak expiratory flow (PEF) meters (Table 12) with measurement instructions (Fig. 3) and predicted PEF standard values

and the importance of PEF measurement (Table 13) are shown. Physicians should instruct patients on the concepts of prophylactic treatment and review the self-management plan with the patient (Fig. 4) if asthma gets worse.

3.4. EDUCATORS

Aside from specialists in asthma, non-specialists such as nurses, public health nurses, and pharmacists

should participate in education, as community-driven education is desired. In addition, patients' associations, patient support groups, etc., should be included so that they can take charge of medical education for citizens and patients.

3.5. PLACES FOR EDUCATION

Education is provided through events held by specialized institutions, health centers, patient support groups, and through distribution of various teaching materials. Ideally, personnel training for patient education should continue.

In Japan, information providing groups, such as the Independent Administrative Institution, Environmental Restoration and Conservation Agency of Japan (<http://www.erca.go.jp/asthma2/index.html>), the Japan Allergy Foundation (<http://www.jaanet.org>), and the Japan Council for Quality Health Care (<http://minds.jcqhcc.or.jp/index.aspx>) all conduct various educational activities.

Table 11 Physician's explanation to patients with asthma

- Diagnosis
- Differences between reliever agents and controller agents
- How to use an inhaler
- Instructions for prophylaxes
- Signs of asthma exacerbation
- PEF monitoring
- Methods and intervals of medical examination
- Self-management plan based on instructions

4. ASTHMA MEDICATIONS

4.1. ASTHMA MEDICATION PLAN FOR THE LONG-TERM MANAGEMENT OF ADULT ASTHMA

4.1.1. Agents

Asthma medications are divided into 2 types; long-term management agents used continuously for long-term management (controllers) and reliever agents used for a short period to treat asthma symptoms (relievers).

(1) Agents for long-term management (controllers)

Agents to alleviate and eliminate asthma symptoms, and normalize and maintain the conditions are called controllers. They are classified based on their mechanisms of action (Table 14).

a) Corticosteroids (steroids): Steroids are currently the most effective antiinflammatory agents for asthma treatment.¹⁵ Important mechanisms of action include (i) inhibiting infiltration of inflammatory cells into the lungs and airway¹⁶ and inhibiting the migration and activation of inflammatory cells, (ii) reducing vascular permeability, (iii) suppressing airway secretion, (iv) inhibiting airway hyperresponsiveness, (v) inhibiting cytokine production, (vi) promoting the effects of β_2 agonists,¹⁷ and (vii) inhibiting arachidonic acid metabolism in cells other than human mast cells and the production of leukotrienes and prostaglandins. Four forms of steroid are available, for intravenous, intramuscular, oral, and inhaled use. Those used for long-term management of asthma are usually inhaled corticosteroids. An oral corticosteroid should only be chosen when management could not be achieved

Table 12 Outline of PEF meters

Trade name	MiniLight	Assess	Personal Best	Vitalograph (Asmaplan)
Measuring range (L/min)	Children 30-400 Adults 60-800	Children 35-385 Adults 60-880	Children 50-390 Adults 60-810	Children 25-300 Adults 50-800
Weight (g)	Children 52 Adults 80	65	85	74
Photos				
Features (written in package insert)	World's first commercialized PEF meter. Most commonly used in the world including Europe.	Zone management system provided by zone clip.	Portable storage case-integrated type. Simple design for storage. Equipped with zone pointer.	Equipped with movable color zone.
Distributor	Matsuyoshi & Co., Ltd.	Polytex Chest	Polytex Chest	Takara Tsusho Co., Ltd.

(1) Measure PEF in a standing position (record posture if standing is impossible).



(5) Read the scale.



(2) Set the indicator of PEF meter to the zero or bottom of a scale.



(6) Measure similarly twice more.



(3) Inhale as deeply as possible, and put a mouthpiece into the mouth (prevent air leak).



(7) Record the highest value of the 3 measurements in an asthma and peak expiratory flow diary.



(4) Exhale as quickly as possible (no need of exhaling all the air).



Clean the PEF meter: Wash the mouthpiece at least once a day in water. When the meter become tainted (at least once a month), immerse it in a dishwashing detergent for about 30 min, rinse it in water, and wipe waterdrops, followed by air drying (at least once a month). Avoid immersion in boiling water or drying with a drier to prevent deformity. Please see a package insert for details.

Fig. 3 PEF measurement.

Table 13 Significance of PEF monitoring

1. Alteration in airway obstruction can be followed over time.
2. Detect acute exacerbation and their therapeutic effects can be evaluated.
3. Airway obstruction can be found earlier when neither subjective nor objective symptoms are noted.
4. Diurnal variation in severity can be assessed.
5. Specific antigens and inducers can be elucidated.
6. The effectiveness and appropriateness of long-term treatment can be evaluated.
7. Children with asthma voluntarily participate in treatment, thereby facilitating patient education.
8. Communication between children with asthma and physicians is facilitated.

Self-management plan				
Name:	Hospital:	Attending physician:		
Green zone: %PEF is 80-100%. Maintain in this status. Normal life can be led. No symptoms are noted at night.	<table style="width: 100%;"> <tr> <td style="width: 50%;">Daily medication</td> <td style="width: 50%;">From attending physician</td> </tr> </table>		Daily medication	From attending physician
Daily medication	From attending physician			
Yellow zone: %PEF is 50-80%. Implement this action plan. Symptoms are noted at night.	<table style="width: 100%;"> <tr> <td style="width: 50%;">Reliever agent(s)</td> <td style="width: 50%;">From attending physician</td> </tr> </table>		Reliever agent(s)	From attending physician
Reliever agent(s)	From attending physician			
Red zone: %PEF is <50% Emergency! Inform people around you about your ill condition. Immediately visit a hospital.	<table style="width: 100%;"> <tr> <td style="width: 50%;">Agents used in the course to the hospital</td> <td style="width: 50%;">From attending physician</td> </tr> </table>		Agents used in the course to the hospital	From attending physician
Agents used in the course to the hospital	From attending physician			

Fig. 4 Self-management plan.

when inhaled corticosteroids were used to the greatest extent. An aqueous suspension of triamcinolone acetonide for intramuscular injection should not be used because of its adverse effects.

Inhaled corticosteroids (i) reduce asthma symptoms, (ii) improve QOL and respiratory function, (iii) alleviate airway hyperresponsiveness,¹⁸ (iv) inhibit airway inflammation, (v) improve the frequency and intensity of acute exacerbation,¹⁹ (vi) reduce the maintenance dose of inhaled corticosteroids for a long period of time (vii) reduce the medical expenses for asthma, (viii) inhibit airway remodeling, and (ix) reduce deaths from asthma. Furthermore, after the development of asthma symptoms, early administration of an inhaled corticosteroid (early intervention) will decrease the frequency of the acute exacerbation of asthma.²⁰ However, asthma cannot be cured by the treatment and cannot be controlled if the treatment is discontinued.¹⁸ In addition, poor compliance with inhaled corticosteroid administration increases emergency room visits and frequency of hospitalization

due to exacerbation of asthma.

In treatment step 4 for severe asthma, oral corticosteroids are used as long-term management agents to complement inhaled corticosteroids, supplement adrenocortical functions, and inhibit increases in systemic inflammatory cells and inflammatory substances. However, oral corticosteroids are used for short-term intermittent administration, or are used in a minimum maintenance dose when continuous administration is inevitable.

As shown in Table 15, inhaled corticosteroids, commercially available in Japan in 2011, include fluticasone propionate (FP), budesonide (BUD), beclomethasone dipropionate (BDP), ciclesonide (CIC), and mometasone furoate (MF). FP, BUD, and MF are also available as dry power inhaler (DPI). On the other hand, pressurized metered dose inhalers (pMDI) using hydrofluoroalkane (HFA) as a base are used for FP, BDP, and CIC administration. The mean particle sizes of these agents are $6\ \mu\text{m} > \text{FP-DPI} > \text{FP-HFA} > \text{BUD-DPI} > \text{MF-DPI} > \text{CIC-HFA} = \text{BDP-HFA} >$

Table 14 Controllers (agents for long-term management)

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

Table 15 Device for inhaled corticosteroids

	pMDI (Pressurized metered dose inhaler)	DPI (Dry powder inhaler)
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)
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)

1 μ m. These agents are extensively dispersed in the airway, with smaller particles reaching further into the peripheral airway.²¹ In addition, budesonide inhalation suspension (BIS), inhaled using a nebulizer, was recently introduced as a new formulation. A jet nebulizer is recommended for BIS inhalation, but an ultrasonic nebulizer is unsuitable. To prevent adverse effects caused by BIS inhalation, agents attached to the face should be wiped off, and gargling and water intake are important.

The dosages of inhaled corticosteroids are classified into a 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 16).

Inhaled corticosteroids are effective even in relatively low doses (e.g., 200 μ g FP) in adults. But if inhalation volume is increased over the high dose, further effects proportional to the dose cannot be obtained, and risks of adverse effects are increased.²² Thus, in controlling asthma, a more favorable outcome can be achieved by adding controller(s) other than inhaled corticosteroids rather than by simply increasing inhaled corticosteroids.¹⁹ However, severe acute exacerbations can be decreased by the increasing amount of inhaled corticosteroid.¹⁹ Smoking re-

Table 16 Recommended doses of inhaled corticosteroids by treatment steps

Agent	Treatment steps 1-2 / Low dose	Treatment step 3 / Medium dose	Treatment step 4 / High dose
BDP-HFA	100-200 µg/day	200-400 µg/day	400-800 µg/day
FP-HFA	100-200 µg/day	200-400 µg/day	400-800 µg/day
CIC-HFA	100-200 µg/day	200-400 µg/day	400-800 µg/day
FP-DPI	100-200 µg/day	200-400 µg/day	400-800 µg/day
BUD-DPI	200-400 µg/day	400-800 µg/day	800-1,600 µg/day
BIS	0.5 mg/day	1.0 mg/day	2.0 mg/day
MF-DPI	100-200 µg/day	200-400 µg/day	400-800 µg/day

duces the effects of inhaled corticosteroids as well as the respiratory function in patients with asthma.²³

Aside from localized adverse effects, such as oropharyngeal candidiasis and hoarseness, systemic adverse effects of inhaled corticosteroids include effects on the eyes (cataract and glaucoma), on the skin (skin thinning and hemorrhagic), on the bone (osteoporosis), and inhibitory effects on the hypothalamic pituitary adrenal function.²⁴ After inhalation, gargling is essential for alleviating the oropharyngeal symptoms and reducing systemic absorption as much as possible.

It is difficult to make a conclusion regarding the effects on the adrenal cortex based on the previous clinical studies. While conventional doses are generally acceptable, caution should be exercised for the high dose and use in pregnant women is a concern. However, BUD-DPI, administered during early pregnancy, is reported to have caused congenital malformation no more than usual and to have had no effects on the course of pregnancy.²⁵ The US 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 inhaled corticosteroids in patients with asthma, and inhaled corticosteroids are not contraindicated for patients with active tuberculosis.

b) Long-acting β_2 agonists (LABA): β_2 agonists, used as controllers are administered via inhalation, patch, and oral route. β_2 agonists, as controllers should be used concomitantly with inhaled corticosteroids. When a LABA is combined with an inhaled corticosteroid, the steroid increases the number of β_2 receptors, and the β_2 agonist promotes the nuclear translocation of steroid receptors, thereby enhancing the steroid action. Furthermore, the combined therapy of an inhaled corticosteroid and a LABA can reduce the amount of the inhaled corticosteroid²⁶ and increase the number of well-controlled asthma patients. The combination of an inhaled corticosteroid and a LABA is more effective than an inhaled corticosteroid with a theophylline sustained-release preparation.²⁷ However, the inhalation effects of a mixed solution of BIS and a β_2 agonist

have not been demonstrated.

Salmeterol xinafoate is an inhaled LABA, which is inappropriate for treatment when used alone,²⁸ but has high synergistic effects when combined with an inhaled corticosteroid.²⁹ Conventional long-acting oral agents include procaterol hydrochloride, clenbuterol hydrochloride, and mabuterol hydrochloride. The tulobuterol patch, which was developed in Japan, is also a long-acting agent that is useful in patients, for whom inhalation and oral administration are difficult. It has a bronchodilator action, which continues for 24 h. Its clinical usefulness when used concomitantly with an inhaled corticosteroid has been reported.³⁰ LABA are highly safe in any formulation. However, adverse effects include tremor, palpitation, and tachycardia, and develop more frequently for the oral agent, the patch, and inhaled agent in this order. When adverse effects are seen, the dosage should be reduced or administration should be discontinued according to the complaint. Serious adverse effects include a decreased serum potassium level. LABA should be used more carefully in patients with ischemic heart disease, hyperthyroidism, and diabetes mellitus. In addition, the adverse effects of the tulobuterol patch include itching and/or rash at the patch area of the skin.

c) Compounding agent of inhaled corticosteroids/inhaled LABA (Table 17): In Japan, fluticasone/salmeterol and budesonide/formoterol are currently used as compounding agents of an inhaled corticosteroid and a LABA, which are more effective than when inhaled separately.³¹ Compounding agents have the following advantages: (i) number of times for inhalation can be decreased; (ii) excellent compliance can be achieved; and (iii) use of LABA alone can be avoided. Asthma treatment must be based on the control level when using these compounding agents. If the concomitant use of LABA can be omitted when asthma is well controlled, a switch to an inhaled corticosteroid alone can be made.

d) Leukotriene receptor antagonists: Leukotrienes (LT) C₄, D₄, and E₄, are called cysteinyl LT (CysLTs), whose receptors are CysLT₁, CysLT₂, and CysLT₃. A currently available leukotriene receptor antagonist

Table 17 Daily doses of combination inhaler of corticosteroids and long-acting β_2 agonists

	Low dose	Medium dose	High dose
FP/SM (DPI)	100 μ g/dose, 1 dose b.i.d. 200 μ g/100 μ g	250 μ g/dose, 1 dose b.i.d. 500 μ g/100 μ g	500 μ g/dose, 1 dose b.i.d. 1000 μ g/100 μ g
BUD/FM [†] (DPI)	One dose b.i.d. 320 μ g/9 μ g	Two doses b.i.d. 640 μ g/18 μ g	Four doses b.i.d. 1280 μ g/36 μ g
FP/SM (pMDI)	50 μ g/dose, 2 doses b.i.d. 200 μ g/100 μ g	125 μ g/dose, 2 doses b.i.d. 500 μ g/100 μ g	250 μ g/dose, 2 doses b.i.d. 1000 μ g/100 μ g

FP, fluticasone; SM, salmeterol; BUD, budesonide; FM, formoterol.
[†] Indicated in a delivered dose.

(LTRA) is a CysLT₁ receptor antagonist. Three types are available; pranlukast hydrate, zafirlukast, and montelukast. LTRAs have a bronchodilator action and inhibit airway inflammation, resulting in significant improvement of asthma symptoms, respiratory function, inhalation frequency of as-needed inhaled β_2 agonist, airway inflammation, airway hyperresponsiveness, dosage of inhaled corticosteroids, asthma exacerbations, and patients' QOL.³²⁻³⁴ LTRAs are particularly useful as agents used concomitantly with an inhaled corticosteroid in patients with asthma, which cannot be completely controlled even with a medium dose of an inhaled corticosteroid, because the additional administration of LTRAs is as effective as a double dose of an inhaled corticosteroid.³⁵ When compared with LABA, LTRAs, as concomitant agents with an inhaled corticosteroid, are less effective in improving symptoms and respiratory function and are almost equivalent in preventing exacerbation.³⁶ LTRAs are particularly useful for long-term management of patients with asthma complicated by allergic rhinitis, exercise induced asthma, and aspirin induced asthma.

In some patients, respiratory function improves early after the oral administration of a LTRA (at several hours at the earliest, on the following day at the latest), however, antiinflammatory effects develop later. Thus, efficacy is generally judged in 2-4 weeks after administration. While more reports have been published on Churg-Strauss syndrome in patients who received an LTRA than those who received other anti-asthmatic drugs, no conclusion has been reached on whether an LTRA is directly involved in the onset of Churg-Strauss syndrome.³⁷ LTRAs are generally safe drugs, but caution should be exercised for zafirlukast considering severe hepatopathy and interaction with other agents, such as warfarin, since it is metabolized by CYP2C9. LTRAs seem to be relatively safe for pregnant women.

e) Sustained-release theophylline: Theophylline sustained-release preparation is a long-acting bronchodilator with antiinflammatory effects, such as inhibition of infiltration of lymphocytes and eosinophils into the airway,³⁸ T cell proliferative response, cy-

tokine production, apoptosis induction of eosinophils,³⁹ and recovery of steroid sensitivity through histone deacetylase (HDAC) reactivation.⁴⁰ While the theophylline sustained-release preparation is clinically less effective than inhaled corticosteroids, when used concomitantly with low to medium doses of an inhaled corticosteroid, the same effects as those obtained with an increased amount of an inhaled corticosteroid can be achieved.⁴¹ However as a concomitant drug with inhaled corticosteroids, sustained-release theophylline at 300-400 mg/day improved airway obstruction less than LABA²⁷ and as good as or less than LTRAs.⁴² The effective safety range of theophylline is rather narrow, and the serum theophylline level varies with various factors (age, smoking, drug interaction, etc.), thus serum level monitoring may be useful in avoiding adverse effects. Antiinflammatory effects are obtained at 5-10 μ g/mL of serum theophylline concentration, and importantly, a bronchodilator action is achieved in a concentration-dependent manner. No serious adverse effects are noted at serum concentrations up to 20 μ g/mL. Monitoring the peak serum level of the sustained-release preparation is difficult, thus the target serum level is 5-15 μ g/mL. The adverse effects of theophylline, which are gastrointestinal symptoms such as nausea and vomiting at initial oral administration, can be prevented to some extent by gradually increasing from the low dose (200 mg) to the dose controlling asthma in each patient. Toxic symptoms caused by increased serum levels include nausea and vomiting, and can progress to tachycardia and arrhythmia, and in the most severe cases, death from convulsions. In pregnant women, no effect has been noted on the frequency of fetal disorders while appropriate serum levels are maintained.

f) Anti-IgE antibody: Omalizumab is a humanized anti-human IgE monoclonal antibody that binds to IgE to inhibit binding between IgE and the high affinity IgE receptor, thereby decreasing the expression of the high affinity IgE receptor on tissue mast cells and circulating blood basophils. Antiinflammatory effects, such as a reduced number of eosinophils, T cells, B cells, and Th2 cytokine-positive cells in the sputum and airway tissue and decreased serum IL-5

and IL-13 levels, have been reported.^{43,44}

The dose and frequency of administration are determined based on the dosage conversion table according to patient weight and serum IgE level (30-700 IU/mL serum IgE) to reduce the serum free IgE levels to ≤ 10 IU/mL. Omalizumab has the following effects in patients poorly controlled even with a high-dose inhaled corticosteroid: (i) preventing exacerbation, (ii) reducing symptom score, (iii) improving QOL, and (iv) reducing steroid dose.⁴⁵ Omalizumab should be used as a therapeutic agent in treatment step 4 for severe persistent asthma, sensitized to perennial inhalation antigens (mites, animals, fungi, etc.). Omalizumab is effective in about 60% of patients. At 16 weeks after the initiation of administration, therapeutic effects are comprehensively judged based on exacerbation frequency, QOL, respiratory function, etc., to determine whether the administration should be continued.⁴⁶ In a clinical study in Japan, the PEF rate, FEV₁, and exacerbation frequency were significantly improved in patients poorly controlled with the concomitant use of a high-dose inhaled corticosteroid and one or more controller agents. It is unknown whether patients can be withdrawn after long-term administration.

The major adverse effects are pain and swelling at the injection site. An anaphylactic reaction, reported as a serious adverse effect in 0.1-0.2% of patients overseas, could develop within 2 h after administration (about 70% of the episodes), but some reactions are reported to occur after 24 h. Symptoms may develop both at initial administration and after multiple administrations. Caution should be exercised for the development of Churg-Strauss syndrome due to the reduced amount of systemic steroids. No teratogenicity has been reported.

g) Antiallergics other than leukotriene receptor antagonists: The following antiallergics are effective in 30-40% of patients with mild to moderate atopic asthma, although 4-6 weeks or longer administration period is needed to determine their efficacy. Safety of oral antiallergics in fetuses during pregnancy has not been demonstrated.

Mediator release suppressants: The main effect of mediator antireleasers is the inhibition of the release of chemical mediators from mast cells. Long-term use of disodium cromoglycate (DSCG) inhibits airway inflammation in patients with atopic asthma.⁴⁷

Histamine H₁ antagonists: The main effect of these agents is to antagonize action of histamine through H₁ receptors and beneficial for asthma accompanied by allergic rhinitis or atopic dermatitis. Caution will be exercised for adverse effects, such as sleepiness and malaise.

Thromboxane A₂ inhibitors/antagonists: Thromboxane A₂ synthesis inhibitors and thromboxane A₂ receptor antagonists inhibit airway inflammation, improve airway hyperresponsiveness, and improve im-

paired mucociliary transport. Their adverse effects include increased bleeding tendency, thus we should be cautious about the concomitant use of other agents with platelet aggregation inhibiting activity.

Th2 cytokine inhibitor: The major effects of suplatast tosilate are inhibition of IL-4 and IL-5 production from Th2 cells, inhibition of eosinophil infiltration in the airway mucosa, and alleviation of airway hyperresponsiveness in patients with asthma.⁴⁸ They are effective in reducing the amount of an inhaled corticosteroid.⁴⁹

(2) Reliever agents

a) Short-acting inhaled β_2 agonists: Short-acting inhaled β_2 agonists are regarded as reliever agents. Inhalation therapy using a pMDI, DPI, and nebulizer shows an equivalent or higher bronchodilator action compared with oral administration. However, there are a few adverse effects, such as stimulation of the cardiovascular system, skeletal muscle tremor, and hypokalemia, which can be reduced by use of a spacer. The increased number of times of the use can be regarded as exacerbation and inhalation can be repeated as needed. If the effects are insufficient after repeated inhalation every 20 min for 1 h, a physician should be consulted. The agents are effective for the prevention of allergen- or exercise-induced asthma (EIA) and treatment of exacerbations.

b) Oral corticosteroids: For acute asthma attacks (moderate exacerbations), an oral corticosteroid together with a short-acting β_2 agonist, needs to be administered for a short period (about 1 week). Treating asthma symptoms earlier by short-term administration (usually less than 1 week) of a medium- or a high-dose oral corticosteroid (approximately 0.5 mg/kg prednisolone) prevents acute exacerbations, decreases emergency visits and hospitalization, and reduces the restrictions on daily life due to asthma attacks. In short-term administration (less than 2 weeks), adrenocortical insufficiency (steroid withdrawal syndrome) will not occur by rapid dose reduction or discontinuation.

c) Theophylline: Single use of oral aminophylline is used as a reliever agent, whose dosage is based on serum levels.

d) Inhaled anticholinergics: Inhaled anticholinergics have additive effects with β_2 agonists on acute exacerbations.

(3) Other agents and therapies

a) Chinese herbal medicines: Administration of Chinese herbal medicines is considered based on the symptoms. Selection of an agent is based on the patient's physical constitution, strength, and response to disease at the time of administration; the empirical process helps distinguishing responders and non-responders before administration.

b) Other agents: Expectorants, such as carbociste-

ine and fudosteine, may be effective in facilitating expectoration and macrolides may inhibit neutrophilic inflammation observed in some patients with asthma. However, accumulated evidence is not sufficient for recommendation of either of these agents.

c) Specific immunotherapy: Allergen specific immunotherapy is indicated for patients with symptoms caused by the inevitable relevant allergens and uncontrollable by appropriate therapy. This therapy inhibits cytokine production from Th2 cells and chemical mediator production from mast cells to improve eosinophilic airway inflammation and airway hyperresponsiveness.⁵⁰

d) Nonspecific therapy: If no sufficient effect can be achieved by general treatment, consider additional use.

4.1.2. Stepwise Administration Plan

(1) Aim of asthma treatment

The aim of asthma treatment is to achieve normal respiratory function in the absence of symptoms or adverse effects. In patients with airway remodeling, respiratory function cannot be improved to normal levels; thus, it can be assessed based on their best values. The control status is determined based on Table 18, with the aim of asthma control.

(2) Principle for treatment

A better relationship between patients and physicians largely depends on the effects of initial treatment, which focus on improvement and stability of asthma symptoms. Aside from using therapeutic agents for asthma, it is important to avoid and eliminate sensitizing allergens (mites, fungi, cockroaches, animals, pollen, etc.) and exacerbating factors, such as passive and active smoking and overfatigue. Allergen immunotherapy (hyposensitization) is considered especially for young patients with asthma complicated by allergic rhinitis. The Expert Panel Report 3 (EPR3)¹⁴ states that immunotherapy should be considered for patients with mild to moderate asthma caused by environmental allergens. Management of concomitant diseases, such as allergic rhinitis, is also important.

Asthma treatment is divided into 4 treatment steps that are outlined in the following section, based on its intensity. The aim of drug therapy is to achieve the maximum effect using the minimum dose. Symptoms at the initiation of therapy, those at consultation, and therapeutic situation are comprehensively evaluated to determine the appropriate treatment step. Treatment is stepped up when asthma symptoms deteriorate or sufficient control cannot be achieved with the pharmacotherapy being provided. Maintenance therapy is determined by referring to asthma symptoms and PEF rates. We should be cautious about step-down to prevent asthma symptoms from deterioration, and the patient should be informed of treatment against exacerbation during dose reduction.

(3) Four treatment steps of asthma (Table 5)

a) Treatment step 1: One controller agent plus reliever agent: A short-acting inhaled β_2 agonist without controllers may be administered only to patients with rare asthma symptoms (less than once a month), where no long-term management agent is needed. It should be emphasized that many patients with asthma underreport their symptoms. For patients who develop symptoms once or more a month, an inhaled corticosteroid (low dose) is recommended as a controller agent.²⁰ If inhaled corticosteroids cannot be used, or adverse effects develop after inhalation, LTRAs³² or sustained-release theophylline³⁸ can be substituted, but their antiinflammatory activities are inferior to those of inhaled corticosteroids. Short-acting inhaled β_2 agonists are administered on an as-needed basis for exacerbations.

b) Treatment step 2: Two controller agents plus reliever agent: In addition to inhaled corticosteroids (low to medium dose), a LABA,^{28,29} or an LTRA^{36,51} or sustained-release theophylline⁴¹ can be used. A compounding agent of LABA and inhaled corticosteroid can also be used.⁵² Consider LTRAs mainly for patients with coexisting allergic rhinitis, aspirin induced asthma, and sympathetic nerve stimulation caused by a LABA or theophylline. Depending on disease conditions, antiallergics other than LTRAs can be used concomitantly.

c) Treatment step 3: Three or more controller agents plus reliever agent: In addition to a continuously administered inhaled corticosteroid (medium to high dose), a LABA and an LTRA, or LABA with a sustained-release theophylline or both are used concomitantly.

d) Treatment step 4: Controller agents plus reliever agent plus additional therapy: In addition to continuous administration of an inhaled corticosteroid (high dose), concomitantly use a LABA, LTRA, or sustained-release theophylline. Anti-IgE antibody (omalizumab) is effective in poorly controlled patients sensitized to perennial allergens, whose serum total IgE value is within a therapeutic target range (30-700 IU/mL).⁴⁵ The dose of an anti-IgE antibody is determined based on the total IgE value and body weight, using a dosage conversion table. Its effects are evaluated 16 weeks after administration, and if effective, administration is continued. 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 are administered for a short period (usually less than 1 week); then a high-dose inhaled corticosteroid is subsequently used. To insufficiently controlled patients, who need prolonged administration of an oral corticosteroid, a shorter-acting oral corticosteroid (prednisolone) can be administered in the morning once daily or every other

Table 18 Assessment of control status

	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)	Within a normal range	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 [†]
[†] Determine patients with one or more exacerbations a month as being poorly controlled, even if they do not meet the other criteria.			

Table 19 Treatment steps for symptoms of untreated patients

	Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Symptoms	(Mild intermittent symptoms) - Less than once a week - Mild intermittent - Occur at night less than twice a month	(Mild persistent symptoms) - Once or more a week, not every day - Disturb everyday life and sleep once or more a month - Occur at night twice or more a month	(Moderate persistent) - Every day - Require short-acting inhaled β_2 agonist almost every day - Disturb everyday life and sleep once or more a week - Occur at night once or more a week	(Severe persistent) - Frequently exacerbated even under treatment - Every day - Restrict everyday life - Frequently occur at night

day to maintain the minimum dose (5 mg). Caution should be emphasized for adrenal insufficiency in switching from long-term administration of an oral corticosteroid to a high-dose inhaled corticosteroid.

(4) Actual treatment

a) Selection of treatment steps: In untreated patients, treatment steps are selected based on the symptoms shown in Table 19. Specifically, treatment steps are selected as follows: (i) treatment step 1 for mild intermittent symptoms, (ii) treatment step 2 for mild persistent symptoms, (iii) treatment step 3 for moderate persistent symptoms, and (iv) treatment step 4 for severe persistent symptoms. In patients under drug therapy, continue the present treatment if the asthma is controlled, or consider step-down if asthma control continues for 3-6 months, based on the assessment of the control status in Table 18. One step-up is required for insufficient control, and 2 step-ups for uncontrolled asthma.

b) Monitoring and treatment during follow-up: "Monitoring items relevant to the assessment of control status" are summarized in Table 20.

c) Management for difficult-to-treat patients: Early referral is recommended for patients with underlying diseases, such as aspirin induced asthma, Churg-

Strauss syndrome, other systemic vasculitis, and allergic bronchopulmonary aspergillosis, because, in addition to the above treatment steps, the continuous administration of a systemic steroid or immunosuppressant may be needed. Uncontrolled or partly controlled patients need adequate instruction regarding daily medication, inhalation methods, and management against acute exacerbation and are provided with an asthma diary that records the dosages and timing of inhalation and medication. Patients with worsening symptoms are instructed to follow an emergency manual immediately. In addition, dose reduction strategies are instructed. Furthermore, patients should have contact information with themselves useful when acute exacerbation occurs, addresses of emergency hospitals, and an "asthma notification card," which enables physicians, other than attending physicians, to conduct emergency treatment immediately.

(5) Guidelines for self-management

An asthma management-zone system enables a patient to self-monitor their asthma status and find signs of exacerbations to start immediate management. The zones imitate the colors of traffic lights; the green zone indicates safety, the yellow zone cau-

Table 20 Items useful for control assessment

1. Peak expiratory flow (PEF) and subjective symptoms recorded by asthma diary (or interview sheet)
2. Spirometry
3. Arterial blood gas assay and pulse oximeter
4. Airway hyperresponsiveness
5. Sputum and peripheral blood eosinophils
6. Chest radiograph and electrocardiogram
7. Specific IgE antibody and total IgE
8. Serum theophylline level
9. Plasma cortisol level
10. Fraction of exhaled nitric oxide (FeNO)
11. Routine biochemical examination, blood count, and urinalysis

Items 1 and 2 are useful for daily control assessment. Item 10 is under investigation. Items 2, 4, 5, 7, and 10 are useful for asthma diagnosis. Items 3, 6, and 11 are useful for exacerbated asthma. Items 8, 9, and 11 are recommended for monitoring of pharmacotherapy.

tion, and the red zone warning. According to the classification of symptom severity in asthma, the yellow zone corresponds to wheezing/chest tightness (mild) or moderate symptoms, and the red zone corresponds to slightly severe moderate to severe symptoms. Predicted PEF rates or % for the best value (% PEF) is indicated in the zones. Actual values enable patients to understand the zones. However, since % PEF is a rough index, physicians should create individualized plans for patients.

a) Green zone: Controlled (Table 18). %PEF is $\geq 80\%$. Patients are in a safe condition and step-down can be considered when a patient is in the green zone for 3 months or longer.

b) Yellow zone: Insufficiently controlled. %PEF is defined as 50-80%. Caution should be exercised and step-up of treatment is required under such conditions.

c) Red zone: Uncontrolled. %PEF rate is defined as $<50\%$ of the patient's best value. A short-acting β_2 agonist should be inhaled immediately and a physician should be consulted if no improvement is noted.

4.2. MANAGEMENT OF ACUTE EXACERBATION IN ADULTS

4.2.1. Therapeutic Agents

(1) Inhaled β_2 agonists

Higher therapeutic effects can be obtained by repeated administration of a small dose (1-2 puffs a time using a portable pMDI) for a fixed period than by single administration of a high dose.⁵³ Correct inhalation procedures are critical; for acute asthma symptoms, a short-acting β_2 agonist is inhaled every 20 min for the first hour and subsequently every hour until improvement is noted. Inhalation using a spacer is more effective⁵⁴ because it causes less adverse effects, however, if adverse effects, such as marked tremor and palpitation develop, the inhalation should be discontinued. A nebulizer is effective in allowing continued inhalation coupled with oxygen. Adding an inhaled anticholinergic may provide an additive bronchodilator action.⁵⁵

(2) Subcutaneous injection of 0.1% adrenaline

Catecholamine formulation (adrenaline: Bosmin[®], etc.) can be administered when no sufficient effects can be obtained with an inhaled β_2 agonist, but caution should be exercised for arrhythmia, cardiac arrest, etc. Subcutaneous injection of 0.1% adrenaline (0.1-0.3 mL) provides a bronchodilator action through the relaxation of the bronchial smooth muscles (β effect) and the removal of airway mucosal edema (α effect). The administration can be repeated every 20-30 min, while monitoring the pulse, which should be kept $\leq 130/\text{min}$. This agent is contraindicated for patients with complications, such as arteriosclerosis, hyperthyroidism, diabetes mellitus, severe arrhythmia, psychoneurosis, and glaucoma [except for open-angle (simple) glaucoma]. In addition, caution should be exercised for the following agents because of contraindication of concomitant use. i) Inhaled halogen-containing anesthetics, such as halothane carry increased risks of tachycardia and ventricular fibrillation. ii) Antipsychotics (butyrophenones, phenothiazines, iminobenzyls, zotepine, and risperidone) and α blockers have vasopressor actions, which are reversed in this combination, and may result in hypotension. iii) Catecholamine formulation, such as isoproterenol, and adrenergic agents is contraindicated for cases other than emergencies, such as resuscitation, because arrhythmia and, in some cases, cardiac arrest may develop when used concomitantly. iv) A tulobuterol patch can be concomitantly used with precaution, but is contraindicated for concomitant use with fenoterol.

(3) Theophylline

The effective serum concentration of theophylline is 8-20 $\mu\text{g}/\text{mL}$ ($<15 \mu\text{g}/\text{mL}$ in children), but adverse effects will occur when exceeding this range. Intravenous infusion of aminophylline (6 mg/kg) has a bronchodilator action, has positive effects on the respiratory drive and respiratory muscles; thus, is effective

Table 21 Factors influencing serum theophylline level

Decreased clearance (increases serum level)
- Aging (50 years or older) and extreme obesity
- Complications, such as hepatopathy, heart failure, virus infection, and fever
- Agents: allopurinol, macrolides (erythromycin, clarithromycin, and roxithromycin), cimetidine, diazepam, new quinolones (ENX, CPFX, and TFLX), thiabendazole, propranolol (contraindicated for asthma), etc.
Increased clearance (decreases serum level)
- Smoker (who smoke ≥ 15 cigarettes/day)
- Agents: barbituric acid, antiepileptics (carbamazepine and phenytoin), rifampicin, isoproterenol, etc.

Table 22 High-risk group of asthma exacerbation

High-risk group meet any one of the following criteria:
1. Receiving systemic steroid administration, or immediately after the administration was 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

in treating acute asthma attacks.⁵⁶ Aminophylline has additive effects for β_2 agonists⁵⁶ and its use decreases hospitalization rates due to asthma attacks. The level of serum theophylline should be monitored for dose adjustment when the expected effects are not obtained, or when higher serum levels are suspected. Initial administration is conducted with aminophylline (6 mg/kg, 250 mg/ampule) in 200-250 mL of isotonic fluid, assuming that theophylline was insufficiently administered before exacerbation and that theophylline clearance was normal. For safety reasons, the first half is infused over 15 min and the remaining half over 45 min. If ≥ 600 mg of sustained-release theophylline is administered daily, serum theophylline level is ≥ 8 $\mu\text{g/mL}$, or reduced clearance is suspected, the dose of aminophylline should be reduced to half or less. If toxic symptoms of theophylline (headache, nausea, vomiting, tachycardia, arrhythmia, etc.) occur during administration, the intravenous infusion must be discontinued immediately. Even if subjective symptoms are improved after intravenous infusion, patients should rest for about 30 min. Monitor serum levels of theophylline during treatment wherever possible. We should be cautious about intoxication, particularly when there are factors affecting theophylline clearance, as shown in Table 21. For continuous administration of aminophylline, 1 ampule (250 mg) of aminophylline is added to 500 mL of maintenance infusion to be used in continuous intravenous infusion for 5-7 h (about 0.6-0.8 mg/kg/h) according to the individual's physical constitution. The speed of intravenous infusion should be adjusted

to achieve 8-20 $\mu\text{g/mL}$ of serum theophylline levels. The PaO_2 may transiently fall during continuous administration of aminophylline, thus in the event that hypoxemia develops, use oxygen inhalation (1-2 L/min with nasal cannulas). An intravenous infusion kit for children, which allows easy adjustment of infusion speed, is recommended for intravenous infusion.

(4) Corticosteroids

Corticosteroids (steroids) are recommended for patients with exacerbated symptoms, whose bronchodilator action is not enough, those with moderate or severe exacerbations, and those who are already receiving a steroid.⁵⁷ The initial dose is set at 200-500 mg of hydrocortisone or 40-125 mg of methylprednisolone,⁵⁷ with subsequent intravenous infusion of 100-200 mg of hydrocortisone or 40-80 mg of methylprednisolone every 4-6 h as needed. However, considering the time and safety until clinical effects of steroid develop (approximately 4 h), intravenous infusion for about 30-60 min is recommended as initial administration. In patients with aspirin induced asthma, steroid phosphate esters should be used, because steroid succinate esters may induce worsening in 40-60% of patients.⁵⁸

Systemic steroid administration is indicated for patients with moderate or severe exacerbations, history of severe asthma attack requiring systemic steroid administration, history of advanced severe asthma attack requiring hospitalization, and high risks of exacerbations (Table 22).

Table 23 Management strategy based on the intensity of asthma attack (acute exacerbation)

Exacerbation intensity [‡]	Dyspnea	Movement	Laboratory data [†]			
			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
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
Severe (severe exacerbation)	Dyspnea, cannot move	Abasia Difficulty in speaking	<60%	≤90%	≤60 mmHg	≥45 mmHg
Serious	Respiratory attenuation Cyanosis Respiratory arrest	Anepia Akinesia Confusion Impaired consciousness Incontinence	Immeasurable	≤90%	≤60 mmHg	≥45 mmHg

Aim of treatment: Elimination of dyspnea, normal movement, normal sleep, and normal everyday life. PEF rate is ≥80% of a predicted value or the best value. Oxygen saturation >95% (values after bronchodilator administration). No exacerbation of asthma symptoms by routine medication and inhalation.

[†] Refer to values after bronchodilator administration.

[‡] Determine exacerbation grade based on the severity of dyspnea, referring to other items. If symptoms of different exacerbation intensities coexist, use more severe one.

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

¶ Repeat 1-2 puffs of β₂ agonist pMDI twice at an interval of 20 min. If ineffective or exacerbated, use 1 tablet of β₂ agonist or 200 mg choline theophylline or aminophylline.

|| Inhalation of β₂ agonist using a nebulizer: Repeat every 20-30 min. Monitor the pulse to be kept ≤130/min.

#Bosmin® (0.1% adrenaline): Bosmin® (0.1-0.3 mL) can be repeatedly administered at intervals of 20-30 min. Keep the pulse ≤130/min. This agent is contraindicated for patients with ischemic heart disease, glaucoma [except for open-angle (simple) glaucoma], and hyperthyroidism. Sphygmomanometry and electrocardiogram monitor are required for patients with hypertension.

(5) Anticholinergics

An anticholinergic, added to a β₂ agonist during acute exacerbations, may enhance the bronchodilator action to improve symptoms and respiratory function⁵⁹ and reduce hospitalization rate.

(6) Oxygen inhalation

Oxygenation can be initiated in patients with severe dyspnea or <80 mmHg PaO₂ (<95% SpO₂) with a tar-

get value of 80 mmHg PaO₂ or about 95% SpO₂. Simultaneously, prepare for endotracheal intubation and ventilator.

(7) Other therapies

- Antibiotics: Antibiotics are administered to patients with bacterial infection accompanied by fever and purulent sputum.
- Expectorants and mucolytic agents on sputum:

Treatment	Home remedy, emergency visit and hospitalization, and ICU treatment [§]
Inhaled β_2 agonist, as-needed [¶] Theophylline agent, as-needed	Home remedy
Inhaled β_2 agonist, as-needed [¶] Theophylline agent, as-needed	Home remedy
Repeated inhalation of β_2 agonist using a nebulizer [¶] Subcutaneous injection of Bosmin [®] (0.1% adrenaline) [#] Intravenous infusion of aminophylline ^{††} Intravenous infusion of steroid ^{‡‡} Oxygen ^{§§} Consider anticholinergic inhalation.	Emergency visit - If symptoms improve within 1 h, allow the patient to go home. - Insufficient response within 2-4 h - No response within 1-2 h Hospital treatment → Switch to treatment for severe asthma
Subcutaneous injection of Bosmin [®] (0.1% adrenaline) [#] Continuous infusion of aminophylline ^{¶¶} Repeated intravenous infusion of steroid ^{‡‡} Oxygen Repeated inhalation of β_2 agonist using a nebulizer [¶]	Emergency visit If no response within 1 h, hospitalization. If exacerbated, switch to treatment for serious exacerbation.
Continue the above treatment. If symptoms and respiratory function are exacerbated, conduct intubation [§] . In spite of 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, enflurane, etc.).	Immediate hospitalization and ICU treatment [§]
^{††} Intravenous infusion of aminophylline (6 mg/kg) in 200-250 mL of isotonic fluid: Administer the first half for about 15 min and the remaining half for about 45 min. If toxic symptoms (headache, nausea, palpitation, extrasystole, etc.) occur, discontinue the infusion. When a sufficient amount of theophylline was administered before exacerbation, reduce the dose of aminophylline to half or less. Routinely, measure serum theophylline levels in patients receiving it, wherever possible. ^{‡‡} Intravenous infusion of steroids: Intravenous infusion of 200-500 mg of hydrocortisone, 40-125 mg of methylprednisolone, or 4-8 mg of dexamethasone or betamethasone. Subsequently, conduct intravenous 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). ^{§§} Oxygen inhalation (1-2 L/min with nasal cannula). ^{¶¶} Continuous intravenous infusion of aminophylline: Following the first intravenous infusion (see the above ^{††}), conduct continuous intravenous infusion of 250 mg of aminophylline (1 tube) for 5-7 h (about 0.6-0.8 mg/kg/h). Monitor serum theophylline levels to be maintained at 10-20 μ g/mL (15-20 μ g/mL to achieve the maximum effects). If toxic symptoms occur, discontinue the infusion. Oxygen inhalation: Target PaO ₂ is about 80 mmHg.	

They are not essential.

- Analgesics: They are not generally used.
- Antihistamines: They have no immediate effects on acute asthma symptoms.
- Fluid replacement: Caution should be exercised for dehydration, although a large amount of fluid replacement is generally unnecessary.

4.2.2. Management at Home

Since asthma symptoms vary widely in their severity, management against acute exacerbation must be tailored to their severity, and patients must be informed

about these approaches. A self-management plan (action plan) should be provided to the patient to show specific instructions for each condition.⁶⁰ To treat wheezing/chest tightness and moderate asthma symptoms, 1-2 puffs of a short-acting inhaled β_2 agonist (see a package insert) should be administered using a pMDI. If the effects are insufficient, repeat inhalation every 20 min for 1 h and subsequently once an hour. At this time, an oral β_2 agonist or theophylline drug (choline theophylline or aminophylline) can be used concomitantly. Patients can be treated at home when these agents eliminate symptoms ($\geq 80\%$

of predicted PEF rate or the best value) and their effect continues for 3-4 h. However, if no therapeutic effect can be achieved, an oral corticosteroid (about 15-30 mg of prednisolone) should be administered and an emergency outpatient unit should be visited.

4.2.3. Treatment Procedures of Emergency Outpatients (Table 23)

Immediately upon arrival, the severity of the asthma attack should be determined. Asthma attack intensity is classified as follows: (i) mild symptoms with dyspnea but no trouble with lying down, (ii) moderate symptoms in lying down and walking difficulty, (iii) severe symptoms causing motor difficulty, abasia, and speech difficulty, and (iv) serious symptoms causing cyanosis, impaired consciousness, and respiratory arrest.

It is also important to observe the following points for quick and efficient history examination based on severity, however, caution should be exercised not to delay treatment because of the oral consultation.

- Time of onset and cause of exacerbation.
- Extent of exercise limitation and sleep disturbance.
- History of recent drug administration, agent administered last, time of the last administration, and use of steroids.
- Hospitalization and emergency visit due to asthma.
- History of respiratory insufficiency and intubation due to asthma.
- Cardiopulmonary diseases and complications.
- History of aspirin induced asthma and drug allergies.

(1) Wheezing/chest tightness, mild symptoms (mild exacerbation)

a) Assessment: "Wheezing and chest tightness" are symptoms, such as wheezing during breathing and chest tightness, but movements are almost normal. "Mild symptoms" indicates mild dyspnea during rest, which is so mild as to allow lying down, but causes difficulty with movement. These symptoms place no restraints on everyday life. Diagnosis is based on a PEF rate, which is $\geq 80\%$ of a predicted value or the best value (after bronchodilator administration). New patients should be queried about his/her history of asthma and other diseases. All patients should be questioned about treatments received after onset and undergo a physical examination, such as chest auscultation. Patients with dyspnea suspected to be due to causes other than asthma, should be examined by radiography and electrocardiogram.

b) Treatment: Inhale a β_2 agonist using pMDI, DPI, or nebulizer: If symptoms disappear and conditions are stable for 60 min without additional treatment, ensure that there is no airway obstruction ($\geq 80\%$ %PEF) and allow the patient to go home. If symptoms

are not improved and airway obstruction continues ($\leq 80\%$ %PEF), conduct moderate or higher level treatment [i.e., (2) b) (ii) as below].

(2) Moderate symptoms and duration of mild symptoms (moderate exacerbation)

a) Assessment: Moderate asthma symptoms (i.e., dyspnea and orthopnea during rest, precluding movements). Diagnosis is based on the PEF rate, which is 60-80% of a predicted value or the best value. When the patient is found to have suffered from asthma in history taking, check habitual exacerbations and treatment to be conducted for several days after the onset. Examine the entire lungs for continuous rale and check that there is no cyanosis. For differential diagnosis of other diseases, conduct various examinations, such as chest radiography, electrocardiogram, blood count, arterial blood gas analysis (see Table 2).

b) Treatment:

(i) Administer an inhaled β_2 agonist, 0.3-0.5 mL, diluted in an appropriate volume of physiological saline, using a nebulizer and repeat the inhalation every 20-30 min. The pulse should be maintained at ≤ 130 /min. pMDI also provides equivalent effects. If symptoms improve within 20-60 min and are stable for 60 min after the last administration (%PEF is $\geq 80\%$) and SpO₂ is $>95\%$, allow the patient to go home. If symptoms do not improve (%PEF is $\leq 80\%$), the following treatments should be conducted.

(ii) Intravenous infusion of aminophylline (6 mg/kg, 250 mg/ampule) in 200-250 mL of isotonic fluid. For safety reasons, administer the first half for about 15 min and the remaining half for about 45 min. If a sufficient amount of theophylline was administered before exacerbation, reduce the dose of aminophylline to half or less. If toxic symptoms of theophylline (headache, nausea, vomiting, tachycardia, arrhythmia, etc.) occur during infusion, immediately discontinue the administration. Monitor serum theophylline levels during treatment wherever possible.

(iii) Intravenous infusion of 200-500 mg of hydrocortisone, 40-125 mg of methylprednisolone, or 4-8 mg of dexamethasone or betamethasone: Systemic steroid administration should be initiated immediately to patients with moderate or worse exacerbations, who respond poorly to initial treatment with an inhaled β_2 agonist. Steroid administration should be initiated immediately, as described above, to patients who are receiving a high dose of an inhaled corticosteroid (FP ≥ 800 $\mu\text{g/day}$) or are regularly receiving an oral corticosteroid, or who belong to a high-risk group⁶¹ (Table 22). Steroid succinate esters should be avoided in patients with aspirin induced asthma. Furthermore, a 1-h intravenous infusion is recommended for patients in whom the presence or absence of aspirin induced asthma is unknown, or who receive the agent for the first time.

(iv) Subcutaneous injection of 0.1-0.3 mL of 0.1%

adrenaline: Adrenaline can be repeatedly administered at intervals of 20-30 min as needed. The pulse should be $\leq 130/\text{min}$ and caution should be exercised for dehydration and metabolic acidosis. In addition, caution should be exercised for agents, such as halothane, antipsychotic, α blocker, and catecholamine, whose concomitant use is contraindicated. This agent is contraindicated for patients with complications, such as arteriosclerosis, hyperthyroidism, glaucoma [except for open-angle (simple) glaucoma], diabetes mellitus, serious arrhythmia, and psychoneurosis. This agent is preferably avoided for pregnant women. Hypoxemic patients are at high risk for adverse effects.

(v) Oxygen inhalation: Nasally administer oxygen at 1-2 L/min to patients with severe dyspnea, ≤ 80 mmHg PaO₂, or $\leq 95\%$ SpO₂.

c) Action plan after treatment

(i) Favorable response: When wheezing and dyspnea are absent for 1 h ($\geq 80\%$ %PEF, $>95\%$ SpO₂), allow the patient to go home and step up long-term treatment. Subsequently, apply medications for long-term management to an appropriate treatment step of asthma (Table 5). In patients receiving an oral steroid, consider adding or increasing the dose of corticosteroid for 1-2 weeks.

(ii) Insufficient response: Mild wheezing and continued dyspnea ($<80\%$ %PEF, $\leq 95\%$ SpO₂). Continue the treatment but if symptoms are not improved within 2-4 h, consider hospitalization.

(iii) No response: Marked extensive wheezing and dyspnea (orthopnea) ($\leq 70\%$ %PEF) persist. Continue the treatment, but if the symptoms are not improved within 1-2 h after addition of an intravenous steroid, consider hospitalization for treatment of serious symptoms [(3) b) (ii)].

(3) Severe symptoms (severe exacerbation) or continued moderate symptoms

a) Assessment: In patients with asthma symptoms in emergency department, briefly record physical findings to determine severity and differentiate them from other diseases that cause dyspnea. Subsequently, ask short, appropriate questions about the causes of exacerbation and previous treatment.

(i) Symptoms and physical findings: Patients with serious symptoms take hunched position, and cannot move because of dyspnea. They may suffer from speech difficulty, confusion, or unconsciousness. Accessory respiratory muscles are used for breathing, with the suprasternal space depressed. Usually, marked wheezing is heard in the chest. Attenuation or elimination of breath sounds indicates respiratory arrest or its signs, but cyanosis is usually absent.

(ii) Tests: Generally, a respiratory function test cannot be performed. If possible, PEF is $<60\%$ of a predicted value or the best value. Blood gas analysis is more reliable to determine severity. Severe airway

obstruction is indicated at $\leq 90\%$ SpO₂, ≥ 45 mmHg PaCO₂, and ≤ 60 mmHg PaO₂. Dyspnea due to other causes is differentiated from asthma using blood count, chest radiography, electrocardiogram, etc.

b) Treatment

(i) Initial treatment: In patients with serious symptoms, who cannot move and have speech difficulty, establish venous access immediately, initiate treatment with an inhaled β_2 agonist using a nebulizer, and administer adrenaline, aminophylline, and steroids according to the treatment for moderate exacerbation.

- Administer 0.3-0.5 mL of an inhaled β_2 agonist, diluted in a physiological saline, using a nebulizer.
- Intravenous infusion of aminophylline (6 mg/kg, 250 mg/ampule) in 200-250 mL of isotonic fluid: Administer the first half for about 15 min and the remaining half for about 45 min. When a sufficient amount of theophylline was administered before exacerbations, reduce the dose of aminophylline to half or less.
- Intravenous infusion of 200-500 mg of hydrocortisone or 40-125 mg of methylprednisolone, or 4-8 mg of dexamethasone or betamethasone: Avoid steroid succinate esters in patients with aspirin induced asthma. In addition, 1-h intravenous infusion is recommended for patients, in whom the presence or absence of aspirin induced asthma is unknown, or who receive the agent for the first time.
- Subcutaneous injection of 0.1-0.3 mL of 0.1% adrenaline: Adrenaline can be repeatedly administered at intervals of 20-30 min as needed. Keep pulse $\leq 130/\text{min}$. Caution should be exercised for the presence of the above contraindications.
- Oxygen inhalation: Target PaO₂ in oxygenation is around 80 mmHg. Caution should be exercised for CO₂ narcosis in patients complicated by COPD. In poorly responsive patients, check normal consciousness and introduce non-invasive positive pressure ventilation (NPPV), intubation, mechanical ventilation, etc. immediately depending on the patient's status. NPPV improves the patient's breathing pattern through pressure support ventilation (PSV) and avoidance of airway collapse by end-expiration by positive end expiratory pressure (PEEP), and thus may be effective in terminating the vicious circle during acute asthma attack.⁶² However, its efficacy should be further investigated. Consider hospitalization of patients at this stage. Immediately hospitalize patients if no improvement is noted within 1 h after treatment.

(ii) Continuous treatment:

- Continuous intravenous infusion of aminophylline at 0.6-0.8 mg/kg/h: Target serum level of aminophylline is 8-20 $\mu\text{g/mL}$. If symptoms de-

Table 24 Conditions requiring tracheal intubation

- Severe ventilatory impairment or cardiac or respiratory arrest
- Marked respiratory muscle fatigue
- <50 mmHg PaO ₂ even after maximum oxygenation
- ≥5 mmHg/h elevation in PaCO ₂
- Marked elevation in PaCO ₂ and consciousness disorder

velop, for which intoxication is suspected, immediately slow down or discontinue the administration to examine excessive dosage by measuring the theophylline level. Consider various factors influencing serum theophylline level (see Table 21).

- Intravenous infusion of 100-200 mg of hydrocortisone or 40-80 mg of methylprednisolone every 4-6 h as needed: Alternatively, intravenous infusion of 4-8 mg of dexamethasone or betamethasone every 6 h as needed. Alternatively, additional intravenous infusion of prednisolone (0.5 mg/kg/day), 100-200 mg of oral 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. Since hydrocortisone causes edema when administered for 3 days or longer, switch to a different steroid. Administer an oral prednisolone (0.5 mg/kg, 20-30 mg/day) once in the morning. After remission, discontinue the administration within 7-14 days or reduce it to the usual dose used before this episode of attacks. Reportedly, there is no advantage of tapering the dose of an oral corticosteroid after remission. Instead, the administration can be discontinued abruptly.⁶³ Initiate the administration of an inhaled corticosteroid when inhalation becomes possible during the course.
- Oxygen inhalation: Continuously administer an optimal dose.

(4) Serious asthma symptoms and emergency (serious exacerbation)

a) Assessment: Conduct emergency care (e.g., endotracheal intubation and artificial respiratory management), when severe ventilatory impairment or respiratory arrest occurs, when there is no response to the above treatments, when PaO₂ is <50 mmHg even after maximum oxygenation and/or rapid increase of PaCO₂ with impaired consciousness occurs, or when PaCO₂ is rapidly increased to ≥5 mmHg an hour based on arterial blood gas analysis. If PaCO₂ exceeds 45 mmHg, prepare intubation for artificial respiratory management. Table 24 shows cases that require endotracheal intubation. Since intubation often accompanies risks, ask an experienced specialist wherever possible.

b) Treatment:

(i) Endotracheal intubation and artificial respiratory management⁶⁴: Conduct endotracheal intubation according to the routine procedures. Immediately connect the endotracheal tube to a volume-cycled ventilator. Adjust the ventilator with 100% fraction of inspired oxygen (FiO₂), 5-8 mL/kg tidal volume, and the ratio of inspiratory to expiratory phases (1 : 3 or above). Keep the airway pressure <50 cm H₂O (maximum) and <20-25 cm H₂O (average). Subsequently, set FiO₂ at about 80 mmHg PaO₂. Here, ensure the maintenance of PaO₂ and the prevention of barotrauma even if PaCO₂ values are high, until exacerbations improve. In principle, avoid using a ventilator at high PEEP. The length of intubation time under mechanical ventilation should be minimally short.

(ii) Treatment for exacerbation: Immediately after intubation, administer 0.3-1.0 mL of a β₂ agonist or adrenaline (0.1% before dilution), both diluted tenfold in physiological saline, through an endotracheal tube. Initiate and continue systemic pharmacotherapy in the same manner as for severe asthma symptoms. For symptoms refractory to pharmacotherapy, general anesthesia using a narcotic (isoflurane, sevoflurane, enflurane, etc.), which has a bronchodilator action, is effective in airway relaxation.

(Note: We should avoid using halothane, because halothane may cause ventricular arrhythmia when combined with β₂ agonists or aminophylline.)

(iii) Conditions for discontinuation: Extubate the patient when consciousness is restored and maximum airway pressure is reduced to 20 cm H₂O or below by spontaneous respiration without assisted respiration.

4.2.4. Conditions for Hospitalization

Consider hospitalizing a patient with symptoms that are not improved within several hours after the initiation of treatment (Table 25). Immediately hospitalize a patient with serious symptoms to conduct a more potent treatment.

4.2.5. Conditions for Entering ICU

Consider asthma treatment in ICU or consult to a specialist experienced in asthma treatment in the following situations (Table 26).

4.2.6. Conditions for Allowing a Patient to Go Home from an Emergency Room

Airway obstruction remits and PEF recovers to ≥80% of the predicted value or the best value. Allow a patient to go home if symptoms are stable for 60 min or longer after the last use of a bronchodilator. Attention should be paid to the following points before allowing a patient to go home (Table 27).

4.2.7. Conditions for Discharge from Hospital

It is important to educate patients who experienced severe exacerbations, which required hospitalization,

Table 25 Conditions requiring hospitalization

- Moderate symptoms (60-80% %PEF), insufficiently responsive to 2- to 4-h treatment ($\leq 70\%$ %PEF) or nonresponsive to 1- to 2-h treatment
- Severe symptoms ($< 60\%$ %PEF) 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
- Difficulties in consulting a medical institution, e.g., heavy traffic when returning home
- Mental disorders or communication difficulties
- Complications, such as pneumonia, atelectasis, and pneumothorax

Table 26 Conditions for admission to ICU

- No response to initial treatment in an emergency room
- Symptoms suggesting risks of confusion, respiratory arrest, and unconsciousness
- Imminent respiratory arrest: ≥ 45 mmHg PaCO ₂ continues (however, respiratory insufficiency may occur regardless of PaCO ₂ level)

about high risks of death from asthma and provide consistent instructions after discharge. Adequately treat a patient with repeated exacerbations considering psychological and social factors. Check that symptoms were not exacerbated for 12 or 24 h or longer after treatment before discharge from hospital. See the following conditions (Table 28).

5. CONDITIONS FOR REFERRAL TO A SPECIALIST

Asthma is a complicated disease, caused by various external and physical factors. When there is a problem with diagnosis or treatment in long-term management, refer the patient to a specialist based on hospital and clinic cooperation.

6. SPECIFIC CONSIDERATIONS

6.1. ALLERGIC RHINITIS (NASAL ALLERGY)

The lower respiratory tract is connected to bronchus and the upper respiratory tract including the nose and paranasal sinuses, thereby influencing each other. Thus, a concept of "one airway, one disease" has been proposed.

In Japan, about 50% of child patients with asthma and 44-68% of adult counterparts are complicated by allergic rhinitis. On the other hand, 15.3% of child patients with allergic rhinitis and 7.1% of adult counterparts are complicated by asthma. Allergic rhinitis, as an upper respiratory tract disease and asthma, as a lower respiratory tract disease often have a similar pathophysiological condition as airway allergy. However, they greatly differ from each other in details. Cedar pollen allergy is rarely complicated by asthma.

In patients with asthma complicated by allergic rhinitis, pharmacotherapy for rhinitis, such as topical steroid, may alleviate asthma symptoms and improve

airway hyperresponsiveness. Allergen-specific immunotherapy for allergic rhinitis may prevent the onset of asthma. In addition, an LTRA improves the clinical symptoms of patients with allergic rhinitis and asthma. Concomitant use of an LTRA is more effective in improving airway obstruction due to asthma than doubling the dose of an inhaled corticosteroid.⁶⁵

6.2. NASAL POLYPS

Asthma is frequently complicated by nasal polyps, and nasal polyps are more frequently complicated by asthma. Nasal polyps are more common among males. However, nasal polyp complicated by asthma is twice as frequent among females than among males. Nasal polyp, asthma, and aspirin sensitivity are common complications. Typically, nasal symptoms occur first, followed by nasal polyps, asthma, and aspirin sensitivity.

The effects of treating nasal polyps (intranasal steroid and surgery of the nasal cavity) on asthma symptoms and respiratory function are unclear.

6.3. SINUSITIS

The association of asthma with chronic sinusitis is known for a long time, and sinusitis has recently attracted attention in association with sinobronchial syndrome and intractable asthma. 40-60% of patients with asthma show abnormal findings in the paranasal sinuses on X-ray image. In general, chronic sinusitis often precedes asthma. However, they may occur simultaneously. It is unclear whether sinusitis causes asthma. However, several hypotheses (neural reflex, infection, β -adrenergic blockade, etc.) have been suggested. Asthma symptoms and respiratory function may be improved by surgery of sinusitis.⁶⁶ Intractable chronic sinusitis, refractory to surgery and macrolide therapy, is frequently complicated by asthma with marked eosinophilic infiltration in the paranasal sinuses.

6.4. COPD

COPD is an important coexisting disease, requiring caution in differential diagnosis in the elderly with asthma. The pathophysiological features of asthma are eosinophil predominant inflammation from the center to peripheral airway, and are characterized by

Table 27 Conditions for allowing a patient to go home from an emergency room

- Identify and avoid the causes of exacerbation.
- Consult a physician as soon as possible after going home. Inform that continuous outpatient treatment is required until PEF returns to around the best value. 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 a patient has no trouble inhaling an inhalant or using a PEF meter adequately.
- Check whether a patient or his/her family has any problem with measures against 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.

Table 28 Conditions for discharge

- No need of inhaling a bronchodilator at ≤ 4 -h intervals
- No short breath in walking
- No wake-up due to exacerbation at night or in the early morning
- (Almost) No abnormal physical findings
- PEF or FEV1 is $\geq 80\%$ of predicted values. Diurnal variation is $< 20\%$.
- Normal PaO₂ value
- No trouble handling an inhaler. No trouble handling a spacer
- Appropriate actions against exacerbation.
- Patients understand conditions for discharge and prescription.
- Creation of a treatment plan after discharge

reversible airway obstruction. On the other hand, in COPD, neutrophil predominant inflammation, and structural alterations, located at the peripheral airway and capillary vessels of the alveoli, are noted. In COPD, airway obstruction is caused by the combination of peripheral airway and emphysematous lesions. Thus, differential diagnosis based on clinical symptoms is often difficult, although their pathophysiological characteristics differ from each other. Some reports describe that as high as 24.7% (18.4-31.7%) of elderly patients aged 65 and over actually have both diseases. Particularly, elderly patients with asthma, who have a smoking history, should be diagnosed and treated considering possible COPD complication. In diagnosis, asthma is suspected if dyspnea, wheezing, and cough occur at night or in the early morning, while COPD is more likely if dyspnea occurs during physical exertion. However, it is often difficult to make a definite diagnosis based on clinical symptoms alone. Definite diagnosis of asthma can be made if respiratory function improves and normalized after β_2 agonist inhalation. If it is reversible, but not normalized, or patient response is insufficient, consider co-existing COPD. The first step of treatment is to encourage smoking cessation regardless of age. Since long-acting inhaled anticholinergics are recommended for COPD, concomitant use of inhaled tiotro-

pium is preferable in elderly patients with asthma complicated by COPD. Choose a therapeutic agent considering that a combination inhaler device of a corticosteroid (fluticasone) and a LABA (salmeterol) is also effective for COPD.⁶⁷ In Japan, a combination device containing 250 μ g of fluticasone is applied for COPD.

6.5. ASPIRIN INDUCED ASTHMA

About 10% of patients with adult asthma suffer from an asthma attack immediately or within 1 h after the oral administration, injection, or suppository administration of nonsteroidal antiinflammatory drugs (NSAIDs), having aspirin-like effects. Some patients suffer from exacerbations so severe to develop impaired consciousness or fatality. NSAID-containing patches, ointments, and eye drops also induce generally mild and delayed exacerbations. Watery rhinorrhea and nasal congestion often occur as prodromal symptoms that may be accompanied by facial flushing, conjunctival hyperemia, and digestive symptoms (abdominal pain, diarrhea, etc.). Aside from aspirin, almost all immunologically non-cross-reactive acid NSAIDs (indomethacin, ibuprofen, tolmetin, fenoprofen, naproxen, diclofenac, ketoprofen, piroxicam, mefenamic acid, sulpyrine, etc.) induce asthma.⁶⁸ Thus, an arachidonate cyclooxygenase inhibitory action (COX, especially COX-1 inhibitory action is known as prostaglandin biosynthesis inhibitory action), a common pharmacological action of these drugs, may trigger airway obstruction. This type of asthma is generally called aspirin induced asthma (aspirin-sensitive asthma, aspirin-exacerbated respiratory disease, etc.). However, it should be noted that aspirin is not the only inducer.

Although rare in children, aspirin induced asthma is more common after adolescence and most common in 30-50 year old adults. Such patients without definite diagnosis are often seen in severe intractable cases. Complications, including chronic rhinitis, chronic sinusitis, impaired sense of smell, and nasal polyps, are common, providing a clue to exact diagnosis.⁶⁹ An additional complication is eosinophilic otitis media. While serum IgE levels are generally low, high levels of serum IgE are seen in about 20% of pa-

Table 29 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. Theophylline sustained-release preparation
2. Oral β_2 agonist
3. Oral corticosteroid[¶]
4. Leukotriene receptor antagonist^{||}
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 in great detail.

[‡] There is less evidence of the safety of long-acting inhaled β_2 agonist (LABA) than those 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 administered during pregnancy.

[#] Use the subcutaneous injection of adrenaline only when inevitable. Generally avoid injection to pregnant women.

^{††} Safe as an inhalant or oral medicine. More evidences are required.

tients, complicated by predisposition to atopy. In diagnosis, it is important to obtain a detailed history after understanding the above clinical picture of NSAID-induced asthma.

Some patients may be sensitive to food and drug additives, such as Food Yellow No. 4 (tartrazine), sodium benzoate, paraben, and sulfite.⁶⁹ For long-term management, it is important to avoid the intake of these substances, including NSAIDs, which may induce exacerbation. Long-term management plan does not differ from that for general asthma. LTRAs are similarly effective for general asthma. In treating acute exacerbations, caution should be exercised for the rapid intravenous infusion of steroid succinate esters (Solu-cortef[®], Saxizon[®], water-soluble Predonine[®], Solu-Medrol[®], etc.) because they may exacerbate or induce asthma.⁵⁸ If aspirin induced asthma is suspected, intravenous infusion of steroid phosphate esters (Decadron[®], Rinderon[®], Hydrocorton[®], etc.) is recommended. Oral steroids can be safely used because of their non-ester structures. Acetaminophen is reportedly safe. However, caution should be exercised because it induces exacerbation when used in a high dose ($\geq 1,000$ mg). Celecoxib, a selective COX-2 inhibitor, can be safely administered at usual doses for aspirin induced asthma. In addition,

basic anti-inflammatory analgesics (epirizole and emorfazone), morphine, pentazocine, anticonvulsants, etc., can be safely administered.

6.6. PREGNANCY

6.6.1. Influences of Bronchial Asthma on Pregnancy and Birth

An asthma attack accompanied by airway obstruction tends to cause hypoxemia in fetuses, posing risks of miscarriage, increased prematurity, and brain disorders.⁷⁰ In fact, premature delivery, low birth weight, and malformation are more common among patients with asthma. However, appropriate management of asthma can efficiently suppress the risk of death of mother and fetus. Asthma causes no severe exacerbations when well controlled before delivery. In addition, asthma symptoms and airway hyperresponsiveness improve in late gestation, especially at 37-40 weeks. After birth, asthma status and airway hyper-sensitivity will be almost the same as those before pregnancy.⁷¹

6.6.2. Influences of Antiasthmatics on Pregnancy and Birth

There is little evidence of teratogenicity for most anti-asthmatic drugs (Table 29). There have been no re-

ports associating cleft palate and systemic high-dose steroid administration in humans. Since steroids do not readily pass through the placenta, their serum levels in fetuses are much lower than levels in mothers, thus reducing the risk of adrenal suppression. To gain control of severe asthma, which causes fetal hypoxia and harms the mother's health, do not hesitate to administer a systemic steroid, although too long administration should be avoided wherever possible. Inhaled corticosteroids are highly safe to mother and fetus. There are no reports on teratogenicity of either inhaled or oral β_2 agonists tulobuterol, and they are considered safe during pregnancy. Since a patch-type β_2 agonist is still a new drug form, put on the market only in Japan and South Korea, there is no evidence of their safety when used during pregnancy. However, patches are regarded as safe, since oral and inhaled forms (not on the market now) of tulobuterol are considered to be safe. There is no report on the teratogenicity of both oral and intravenous theophylline, suggesting its usefulness in controlling asthma during pregnancy. Since the infant's degradative rate of theophylline is slow, caution should be exercised in administering it to infants during lactation. Of allergy drugs, DSCG is safe. Since there is not enough evidence of the safety of LTRAs in humans, they should be administered during pregnancy only when the advantages outweigh the disadvantages. There seems little teratogenicity for classic antihistamines and relatively early-generational antiallergics (epinastine, emedastine, ketotifen, tazanast, pemirolast, azelastine, tranilast, etc.). However, they should be administered during pregnancy only when the advantages outweigh the disadvantages.

6.6.3. Asthma Treatment during Pregnancy

Considering the risks of asthma attack on fetuses and pregnant women, it is more beneficial to continue to treat patients with asthma during pregnancy. Appropriate actions (agents, allergen avoidance, environmental management, smoking cessation, and separation of smoking areas, rest of mind and body, etc.) should be taken against exacerbating factors to prevent symptoms and maintain respiratory function. Inhaled corticosteroids are recommended as first-line therapy for long-term management. If an inhaled corticosteroid alone is not enough effective, add a long-acting inhaled β_2 agonist, theophylline sustained-release preparation, patch-type β_2 agonist, etc. Consider LTRAs when the advantages outweigh the disadvantages.

Allergen-specific immunotherapy (hyposensitization) can be continued during pregnancy if initiated before pregnancy. However, do not initiate the therapy during pregnancy. Continue the administration of anti-IgE antibody only when the advantages outweigh the disadvantages, because of the lack of information on anti-IgE antibody during pregnancy.

To treat exacerbations, administer a short-acting inhaled β_2 agonist. If the effects are insufficient, use oral medicine or injection (steroids and intravenous infusion of aminophylline). Oxygen inhalation is recommended to prevent fetal hypoxemia. Complications, such as abortion and premature delivery, premature rupture of the membranes, albuminuria, and eclampsia, are more common among patients with asthma. Certain congenital disorders (malformation) are seen in 2-4% of normal pregnancies. These complications should be explained in detail before administration to obtain patient's trust. In addition, smoking, including passive smoking, has more serious influences than any agents clinically used for mother and fetus do. This must be emphasized to patients, their spouses, and people around the patients to understand the necessity of smoking cessation.⁷²

6.7. COUGH VARIANT ASTHMA

In Japan, chronic cough is caused by cough variant asthma (36%), atopic cough (16%), sinobronchial syndrome (16%), postinfectious cough (2%), and gastroesophageal reflux disease (2%),⁷³ with cough variant asthma, atopic cough, and sinobronchial syndrome being the three major causes. In contrast, in Europe and the United States, cough variant asthma, postnasal drip and rhinitis, and gastroesophageal reflux disease are the three major causes.⁷⁴

Cough variant asthma is distinguished from asthma by the lack of wheezing. Cough variant asthma belongs to the subgroup of asthma or intermediate asthma and is similar to asthma in the following points: (i) airway hyperresponsiveness is mildly present (intermediate between patients with mild asthma and healthy individuals)⁷⁵; (ii) cough sensitivity is within a normal range; (iii) atopic state is common; (iv) eosinophils are noted in sputum or induced sputum; (v) eosinophilic infiltration is noted in the bronchial mucosa; (vi) eosinophils are increased in bronchoalveolar lavage fluid (BALF); (vii) fraction of exhaled nitric oxide (FeNO) is increased; and (viii) inhaled or oral corticosteroids are effective. Bronchodilators, including β_2 agonists, are effective. Cough variant asthma is not usually accompanied by sputum, 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, etc. About 30% of patients with cough variant asthma develop wheezing asthma. Since cough can be prevented with an inhaled corticosteroid, long-term management with an inhaled corticosteroid is recommended.

Atopic cough is similar to "non-asthmatic eosinophilic bronchitis" in Europe and the United States.⁷⁴ Atopic cough is somewhat similar to cough variant asthma in clinical symptoms, and shows the following features: (i) there is atopic state, (ii) bronchodilators such as β_2 agonists are ineffective, (iii) there is no air-

way hyperresponsiveness, (iv) cough sensitivity is increased, (v) H₁ antagonists and steroids are effective, and (vi) asthma does not develop. Long-term management is unnecessary. In addition, unlike cough variant asthma, FeNO does not increase. Other important diseases, differentiated from chronic non-productive cough, include cough caused by postnasal drip, gastroesophageal reflux, or angiotensin converting enzyme inhibitors.

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