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Invited Review Article

Japanese guidelines for adult asthma 2020[☆]

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ABSTRACT

Bronchial asthma is characterized by chronic airway inflammation, which manifests clinically as variable airway narrowing (wheezes and dyspnea) and cough. Long-standing asthma may induce airway remodeling and become intractable. The prevalence of asthma has increased; however, the number of patients who die from it has decreased (1.3 per 100,000 patients in 2018). The goal of asthma treatment is to control symptoms and prevent future risks. A good partnership between physicians and patients is indispensable for effective treatment. Long-term management with therapeutic agents and the elimination of the triggers and risk factors of asthma are fundamental to its treatment. Asthma is managed by four steps of pharmacotherapy, ranging from mild to intensive treatments, depending on the severity of disease; each step includes an appropriate daily dose of an inhaled corticosteroid, which may vary from low to high. Long-acting β_2 -agonists, leukotriene receptor antagonists, sustained-release theophylline, and long-acting muscarinic antagonists are recommended as add-on drugs, while anti-immunoglobulin E antibodies and other biologics, and oral steroids are reserved for very severe and persistent asthma related to allergic reactions. Bronchial thermoplasty has recently been developed for severe, persistent asthma, but its long-term efficacy is not known. Inhaled β_2 -agonists, aminophylline, corticosteroids, adrenaline, oxygen therapy, and other approaches are used as needed during acute exacerbations, by selecting treatment steps for asthma based on the severity of the exacerbations. Allergic rhinitis, eosinophilic chronic rhinosinusitis, eosinophilic otitis, chronic obstructive pulmonary disease, aspirin-exacerbated respiratory disease, and pregnancy are also important conditions to be considered in asthma therapy.

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

1.1. Definition and pathophysiology of asthma

Bronchial asthma (hereinafter, asthma) is characterized by chronic airway inflammation, which clinically manifests as variable airway narrowing (wheezes and dyspnea) and cough. Airway narrowing is reversible and derives from airway inflammation and hyperresponsiveness. Pathological analyses of asthma demonstrate chronic airway inflammation accompanied by the infiltration of

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pro-inflammatory cells such as eosinophils and the detachment of the airway epithelial cells.^{1,2} While many patients are atopic, i.e. they are positive for immunoglobulin E (IgE) antibodies against environmental allergens, the infiltration of eosinophils, Th2 cells, type 2 innate lymphoid cells (ILC2), CD8⁺ T cells, B cells, and dendritic cells is present even in patients without allergen-specific IgE antibodies.³ The etiology of asthma is multifactorial, and its clinical picture varies among patients. Some asthmatic patients demonstrate airway inflammation that predominantly involves neutrophils. Long-standing asthma induces airway remodeling, which entails subepithelial fibrosis under the basement membrane, smooth muscle hypertrophy, and goblet cell hyperplasia. This results in intractable asthma characterized by irreversible airflow limitation and persistent airway hyperresponsiveness.⁴

1.2. Aim of the management and treatment of asthma

The aim of asthma management and treatment is symptom control and the prevention of future risks (Table 1). Thus, it is important to alleviate airway inflammation and fully dilate the constricted airway by eliminating the inducers of airway inflammation and adopting pharmacotherapy. In this way, respiratory function can be normalized to improve patients' quality of life (QoL) and enable normal and healthy living.

1.3. Phenotype/endotype

Asthma patients are characterized by widely variable clinical pictures; asthma is thus often recognized as a syndrome and classified into several phenotypes. Recent progress in genetics and molecular biology has led to the pathogenetic classification into endotypes. The eosinophils and type 2 cytokines dominant subset of adult-onset asthma is widely observed in global assessments, and it should be considered in the management of severe asthma.

1.4. Diagnosis of adult asthma

Generally, clinical diagnosis of asthma is based on the following features (Table 2): (1) repetitive symptoms, such as paroxysmal dyspnea, wheezing, chest tightness, and cough; (2) reversible airflow limitation; (3) airway hyperresponsiveness; (4) airway inflammation; (5) an atopic state; (6) exclusion of other cardiopulmonary diseases (Table 3). The clinical course of asthma varies with patients, and it may lack typical symptoms and signs. The diagnosis of asthma is often difficult in patients with COPD or heart failure.

1.4.1. Typical asthma symptoms

Typical asthma symptoms include the recurrence of paroxysmal dyspnea, wheezing, and cough. Exacerbations may be induced by a viral infection, exercise, allergen exposure, climate change, cold air, or cigarette smoking. Asthma symptoms often vary with seasons and even with the time of the day; they may occur at night or early in the morning.

Table 1
Aims of asthma treatment.

I. Symptom control
1. To regulate airway inflammation.
2. To maintain normal respiratory function: Peak expiratory flow (PEF), $\geq 80\%$ of the predicted value PEF variation, $< 10\%$
II. Avoidance of future risk
1. To prevent decline of respiratory function.
2. To prevent death due to asthma.
3. To prevent adverse effects caused by therapeutic agents.

Table 2
Diagnosis of asthma: key features.

1. Recurrence of paroxysmal dyspnea, wheezing, chest tightness, and cough
2. Reversible airflow limitation
3. Airway hyperresponsiveness
4. Airway inflammation
5. Atopy
6. Differential diagnosis

Items 1, 2, 3, and 6 are important for diagnosis.

Item 4, if eosinophilic, is indicative of asthma.

Item 5 supports the diagnosis of asthma.

Table 3
Differential diagnosis of asthma.

1. Upper airway diseases: laryngitis, epiglottitis, and vocal cord dysfunction
2. Proximal respiratory tract diseases: endotracheal tumor and foreign body aspiration, tracheomalacia, endobronchial tuberculosis, sarcoidosis, and re-lapsing polychondritis
3. Diseases of the bronchus to bronchioles regions: COPD, diffuse pan-bronchiolitis, pulmonary fibrosis, and hypersensitivity pneumonitis
4. Cardiovascular diseases: congestive heart failure and pulmonary thromboembolism
5. Drugs: cough induced by angiotensin-converting enzyme inhibitors
6. Other causes: spontaneous pneumothorax, vagal nerve stimulation, hyper-ventilation syndrome, psychogenic cough

1.4.2. Reversible airflow limitation

Wheezing and dyspnea during attacks are induced by reversible airway narrowing, which occurs diffusely throughout the airways and ranges from mild to severe. The peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV₁) often differ markedly between exacerbations and controlled periods in each patient (Table 4). The reversible airflow limitation is regarded as significant when FEV₁ increases by $\geq 12\%$ and ≥ 200 ml of the absolute volume after β_2 -agonist inhalation or if a PEF diurnal variation of $\geq 20\%$ is present. Long-standing asthma often presents with stable low PEF and FEV₁, without significant fluctuations due to airway remodeling.

1.4.3. Airway hyperresponsiveness

Weak stimuli, even those healthy individuals show no response to, cause airway contraction. A standard quantitative method for assessing changes in FEV₁ recommended by the Japanese Society of Allergology or a method using an Astograph, which monitors respiratory system impedance, is recommended.^{5,6} However, both methods involve load tests that induce airway narrowing, and patients with severely decreased respiratory function should not be tested with them.

1.4.4. Airway inflammation

Increased percentages of eosinophils and Creola bodies detected by sputum analysis indicate allergic airway inflammation.⁷ Sputum eosinophil percentage of $\geq 3\%$ is regarded as a significant elevation. Blood eosinophilia is useful, but its sensitivity and specificity are lower than those of sputum eosinophilia. The fractional exhaled nitric oxide (FeNO) level is related to eosinophilic airway inflammation, and its upper limit among normal volunteers is 37 ppb in domestic studies (Table 4).^{8,9}

1.4.5. Atopy

An elevated concentration of total IgE and/or specific IgE antibodies against various environmental allergens indicate an atopic state. A history or family history of allergic diseases suggests atopy. Atopic asthma is considered when immediate skin reaction or specific IgE is positive against airborne inhalant allergens.

Table 4

Useful tests for asthma management.

Test	Summary	Interpretation	Appendix
Spirometry	To measure the following: FVC FEV ₁ FEV ₁ (= FEV ₁ /FVC × 100) %FEV ₁	Good: FEV ₁ % ≥ 70% and %FEV ₁ ≥ 80% (or ≥ 80% of personal best value). Airway reversibility is positive when FEV ₁ increases to ≥12% AND ≥200 ml following treatment.	This test is useful for the diagnosis and monitoring of asthma. It is recommended for the assessment of the extent of airflow limitation or airway reversibility.
Peak expiratory flow (PEF)	Patients can easily assess airflow limitation by using a PEF meter and detect and manage worsening of asthma promptly. Daily or weekly variations of PEF can be assessed by daily PEF measurements in the morning and at night.	Normal: PEF ≥80% of predicted value. When PEF <80% of predicted value and PEF variation ≥20%, worsening of bronchial hyperresponsiveness is suspected, and a step-up of long-term therapy may be necessary.	This test is useful for the diagnosis and monitoring of asthma. The extent and variability of airflow limitation can be assessed at home. Daily measurement is recommended for unstable asthma and patients lacking obvious dyspnea during attack. Low values may be due to insufficient expiratory effort.
Asthma Control Test (ACT)	Questionnaire focusing on symptoms (3 items), rescue drug use (1 item), and general condition (1 item).	Good: 25 points Fair: 20–24 points Poor: ≤ 19 points	Child ACT can be used for children who are 4 years or older.
Asthma Control Questionnaire (ACQ)	Questionnaire focusing on symptoms (5 items), rescue drug use (1 item), and FEV ₁ (1 item).	Good: mean ≤ 0.75 Insufficient: mean ≥ 1.5	Useful for adults and children who are ≥5 years old. ACQ5 for evaluating only symptoms is also useful.
Japan Asthma Control Survey (JACS)	Includes 15 questions. Total score and scores of 4 categories (symptoms, psychological, therapy, and physical activity) can be used.	Good: > 8 points Insufficient: > 4.8 and ≤ 8.0 points Poor: ≤ 4.8 points	This questionnaire includes VAS.
Sputum eosinophil count	Spontaneously expectorated or induced sputa are used.	Eosinophilic inflammation is thought to be present when the percentage of eosinophils is ≥ 2–3%.	Useful for both diagnosis and monitoring of asthma. Sputum eosinophil percentage may be useful as a clue of ongoing exacerbation that can be suppressed by modification of drugs.
Bronchial hyperresponsiveness	Assess airway narrowing following inhalation of irritant substances. Physicians should stand by since asthma attacks may be induced.	Specificity is not high since patients with COPD may show positive results. Sensitivity is high; thus asthma can be ruled out if this test is negative.	Useful for the diagnosis of asthma. Not recommended for patients with low FEV ₁ (≤1 L) or low %FEV ₁ (≤50%), since excess airway narrowing may occur due to irritant inhalation.
FeNO	Easy, rapid, reproducible, non-invasive test. Flow rate and lung volume affect the data. NIOX MINO®, NIOX VERO®, and NObreath are registered in the domestic health care system.	Normal: ≤ 37 ppb. Trend of data is useful since a decline is associated with improvements in airflow limitation and bronchial hyperresponsiveness, whereas FeNO increase may indicate worsening of asthma control and/or therapeutic adherence.	Useful as an additional test for the diagnosis of asthma. Although FeNO is not a useful single test for showing the need for the modification of drugs, it is useful for successful ICS tapering if FeNO and symptoms are assessed. ICS and tobacco smoking will decrease the levels of FeNO.
Blood eosinophil count	Easy and inexpensive test. Evidence is accumulated on blood eosinophil number, rather than percentage of eosinophils.	Elevated eosinophil count suggests eosinophilic airway inflammation. An eosinophil count of ≥300–400 μL is related to an increased risk of symptomatic asthma and poor control of asthma.	Useful for the diagnosis and monitoring of asthma. It may also increase in other allergic diseases and may be predictive of the clinical efficacy of biological agents.

Table 5

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

Severity [†]		Mild and intermittent	Mild and persistent	Moderate and persistent	Severe and persistent
Features of asthma symptoms	Frequency	Less than once a week	Once or more a week but not every day	Every day	Every day
	Intensity	Mild and transient	Disturbs daily life or sleep at least once a month	Disturbs daily life or sleep at least once a week	Restricts daily life
	Symptoms at night	Less than twice a month	Twice or more a month	Once or more a week	Frequently
PEF FEV ₁ [‡]	%FEV ₁ , %PEF	≥80%	≥80%	≥60%, <80%	<60%
	Diurnal variation of PEF	<20%	20–30%	>30%	>30%

[†] Determine the severity based on the presence of any one of the features or measured percentages.[‡] In patients with severe or long-standing symptoms, severity may be underestimated when it is 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.

Table 6
Treatment steps for asthma.

	Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Long-term management agents	Inhaled corticosteroid (low dose)	Inhaled corticosteroid (low to medium doses)	Inhaled corticosteroid (medium to high doses)	Inhaled corticosteroid (high dose)
Basic treatment	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) • LAMA [†] • LTRA • Theophylline sustained-release preparation	Concomitantly use one or more of the agents below. • LABA (a compounding agent can be used) • LAMA [†] • LTRA • Theophylline sustained-release preparation • Anti-IL-4R α antibody ^{††,‡,§§}	Concomitantly use two or more of the agents below. • LABA (a compounding agent can be used) • LAMA [†] • LTRA • Theophylline sustained-release preparation • Anti-IL-4R α antibody ^{††} • Anti-IgE antibody ^{††} • Anti-IL-5 antibody ^{††} • Anti-IL-5R α antibody ^{††} • Oral corticosteroid ^{††} • Bronchial thermoplasty ^{††,§§}
Additional treatment	Anti-allergics other than LTRA [†]	Anti-allergics other than LTRA [†]	Anti-allergics other than LTRA [†]	Anti-allergics other than LTRA [†]
Exacerbation treatment [¶]	Inhaled SABA	Inhaled SABA	Inhaled SABA	Inhaled SABA

LTRA, leukotriene receptor antagonists; LABA, long-acting β_2 agonist; SABA, short-acting β_2 agonist; LAMA, long-acting muscarinic antagonist.

[†] Antiallergics refer to mediator antireleasers, histamine H1 antagonists, thromboxane A2 inhibitors, and Th2 cytokine inhibitors.

[‡] Anti-IgE antibody is indicated for patients who are positive for perennial inhaled allergen with serum total IgE value within 30–1500 IU/ml.

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

[¶] Management against mild exacerbations is shown. For other exacerbations, refer to Table 20.

^{||} In patients treated with a combination of budesonide/formoterol as a controller, the agent should not be used beyond the recommended maximum per time and per day if it is used as a rescue; the recommended maximum is generally up to 8 inhalations/day. However, it can be used for up to 12 inhalations/day (for 3 days: budesonide, 1920 mg/day; formoterol 54 mg/day) temporarily. When more than 8 inhalations/day of budesonide/formoterol are needed, a physician should be consulted.

[#] Soft mist inhaler of tiotropium.

^{††} When asthma control cannot be achieved with inhaled corticosteroid plus LABA and LTRA, etc.

^{‡‡} Suitable for adults and children over 12 years.

^{§§} Indications for patients are selected by a specialist in the Japanese Respiratory Society or a specialist in the Japanese Society of Allergy. The procedure is performed during hospitalization under the guidance of a Japanese Society of Respiratory Endoscopy Bronchoscope Specialist.

^{¶¶} Indicated only in patients in whom high-dose ICS use is not applicable due to side effects.

1.4.6. Differential diagnosis

Differential diagnoses include heart failure, bronchial tuberculosis, and COPD. A comprehensive diagnosis should be made, especially in smokers and elderly. Asthma COPD overlap (ACO) should be considered when a patient demonstrates features of both asthma and COPD.

1.5. Classification of the severity of asthma and asthma exacerbation

The assessment of the severity of asthma is important in management and stepwise pharmacotherapy. Untreated asthma has four categories based on severity (Table 5). These categories correspond to the recommendations for treatment steps 1 to 4, respectively (Table 6). For patients undergoing treatment, the symptoms and the present treatment step determine the severity (Table 7). The classification of exacerbation severity is shown in Table 8.

1.6. Markers and clues for diagnosis and management of asthma

Spirometry, PEF, Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT), sputum eosinophils, airway hyper-responsiveness, FeNO, and blood eosinophils are important for the diagnosis and management of asthma (Table 4).

1.7. Intractable asthma

Intractable asthma is the most severe and persistent type of asthma, regardless of whether it is or is not controlled well by the administration of step 4 treatment, which involves high-dose inhaled corticosteroids (ICSs), long-acting β_2 -agonists (LABAs), long-acting muscarinic antagonists (LAMAs), leukotriene receptor antagonists (LTRAs), sustained-release theophylline (SRT), anti-IgE, anti-IL-5, anti-IL-5R α or anti-IL-4R α antibody, oral corticosteroids, and bronchial thermoplasty (BT) (Table 6, 7). Intractable asthma is often called severe asthma. Additional underlying diseases, such as aspirin-exacerbated respiratory disease (AERD; also known as aspirin-intolerant asthma and aspirin-induced asthma), eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome) and other systemic vasculitis syndromes, and allergic bronchopulmonary mycosis (ABPM), should be considered in patients requiring continuous administration of oral corticosteroids.

2. Epidemiology of asthma

2.1. Changes in asthma prevalence over time

The mean prevalence of asthma in Japan has increased from 1% to 10% or higher in children and to 6%–10% in adults since the 1960s. A 2-fold increase in the prevalence of asthma in children

Table 7

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

Patient 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 transient • Less than twice a month at night	Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Mild persistent [§] • Once or more a week but not everyday • Once or more a month and disturbs everyday life activities and sleep • Twice or more a month at night	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Moderate persistent [§] • Everyday • Requires a short-acting inhaled β_2 agonist almost every day • Once or more a week and disturbs everyday life activities 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 • Everyday • Restricts everyday life activities • Frequently occurs at night	Severe persistent	Severe persistent	Severe persistent	Most severe persistent

[†] Consider a step-down after continued treatment for 3–6 months.[‡] Enhance treatment at each step.[§] Check treatment compliance and consider step-up as needed.

between 1982 and 2002 was reported by a survey conducted by physicians who used the same protocol in subjects with the same background (Table 9).^{10,11} Surveys conducted among the citizens of Fujieda City in Shizuoka Prefecture in 1985, 1999, and 2006 showed that the prevalence of adult asthma increased by 1.5-fold per decade. However, the latest study on children in western Japan has indicated a decrease in the prevalence of asthma (Table 9).¹²

2.2. Regional differences in asthma prevalence

An International Study of Asthma and Allergies in Childhood survey has been conducted across Japan to assess the prevalence of asthma at specific time points. The International Study of Asthma and Allergies in Childhood Steering Committee has reported clear regional differences in the prevalence of asthma: 3.5% in Indonesia, 34.8% in Costa Rica for 6- to 7-year-old subjects, 3.0% in Albania, and 32.3% in the Isle of Man for 13- to 14-year-old

subjects. The prevalence of asthma in Japan (Fukuoka City, 13%) assessed in 1994 and 2003 was slightly lower than that in Europe and the USA. Asthma prevalence is generally higher in developed than developing countries; it is also higher in warm climate areas than cold areas.

2.3. Male-to-female ratio

Globally, asthma is more common in men than women before puberty; after puberty, the prevalence is higher in women (Fig. 1). According to a survey conducted in 2003, the male-to-female ratios were 1.4 during infancy (0–5 years of age) and 0.8 during adulthood (18 years of age and older).

2.4. Number of patients

According to the 2014 Statistical Information from the Japanese Ministry of Health, Labour, and Welfare, the number of patients with asthma who continued to visit the hospital as determined by a

Table 8

Classification of asthma symptoms and exacerbation severity (adults).

Exacerbation severity [†]	Dyspnea	Exertion	Measured values [§]			
			%PEF	SpO ₂	PaO ₂	PaCO ₂
Wheezing/chest tightness	Dyspnea on exertion	Almost normal	≥80%	≥96%	Normal	<45 mmHg
Mild (mild attack)	Dyspnea but no trouble with lying down	Slight dyspnea				
Moderate (moderate attack)	Dyspnea with trouble with lying down	Difficulty in moving and walking	60–80%	91–95%	>60 mmHg	<45 mmHg
Severe (severe attack)	Dyspnea, cannot move	Abasia, difficulty in speaking	<60%	≤90%	≤60 mmHg	≥45 mmHg
Serious [‡]	Respiratory insufficiency, Cyanosis, respiratory arrest	Anepia, Akinesia, Confusion, Impaired consciousness, and incontinence	immeasurable	≤90%	≤60 mmHg	≥45 mmHg

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

Table 9
Prevalence of asthma.

	Age (yr)	Region	Year analyzed	Methods	n	Prevalence (%)
Children	6–12	11 Prefectures in Western Japan	1982	ATS-DLD	55,388	3.2
			1992		45,674	4.6
			2002		35,582	6.5
			2012		33,902	4.7
	6–7	All districts of Japan	2005	ISAAC	47,050	13.9
			2008		43,813	13.5
			2015		43,493	10.1
	13–14	All districts of Japan	2005	ISAAC	47,050	8.8
			2008		43,813	9.6
			2015		43,493	8.3
Adults	≥15	Fujieda, Shizuoka	1985	Original questionnaire	12,152	3.14
	≥15		1999	Original questionnaire + ATS-DLD	3,829	4.15
	20–79		2006	ECRHS	2,710	7.2
	20–44	9 Big cities of Japan	2010	ECRHS (Web-based)	7,596	8.7
			2012		16,329	9.1
			2017		14,351	10.4

ATS-DLD, American Thoracic Society–Division of Lung Disease; ISAAC, The International Study of Asthma and Allergies in Childhood; ECRHS, European Community Respiratory Health Survey.

survey conducted in October 2014 was 1,177,000 (515,000 men and 662,000 women). The medical treatment rate for asthma per 100,000 population was 103 in 2014, which was slightly lower than that in 2000 (Table 10). The rate may change with asthma therapy improvements, which will lower the frequency of hospital visits of asthma patients.

2.5. Deaths from asthma

According to the Vital Statistics of the Japanese Ministry of Health, Labour, and Welfare, the number of patients who die of asthma has decreased in recent years¹³; it was approximately 6,000 during the 1980s and early 1990s and 1,454 in 2016. The rate of

asthma deaths per 100,000 population was 1.0 in males and 1.6 in females in 2018; the rate of deaths in females has been higher than that in males since 2006, probably because the proportion of the aged population is increasing especially for females (Fig. 2, 3). The number of patients who die of asthma at an early age has markedly decreased; approximately 90% of asthma deaths occur among adults who are 65 years or older (Fig. 4). The rate of asthma deaths among 5–34-year-olds is often used for comparison among nations since the diagnosis of asthma at this age is reliable, and the rate is minimally affected by the variations in average lifespan. The rate in Japan has been very low; 0.1 in males and 0.0 in females since 2012. These rates are among the lowest globally.

3. Patient education and physician–patient partnership

3.1. Aim

Adequate management of asthma is based on patient education and physician–patient partnership. Patients may be educated on what asthma is, the continuing long-term management for good asthma control, and prompt awareness and self-management of signs of asthma exacerbations.

3.2. Subjects

Patients and their families, neighbors, and caretakers of older adults should be educated sufficiently.

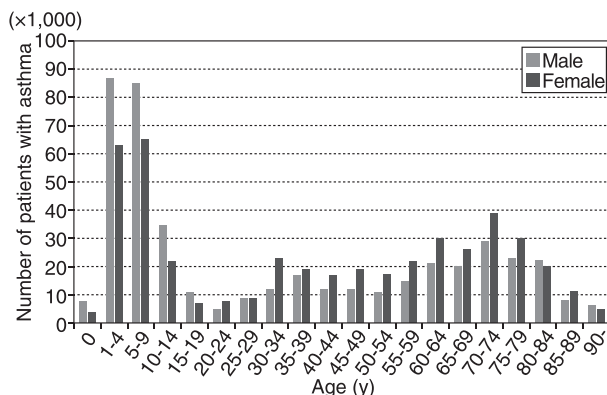


Fig. 1. Number of patients with asthma in Japan stratified by age and sex.

Table 10
Medical treatment rates for asthma in Japan.

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

Per 100,000 population.

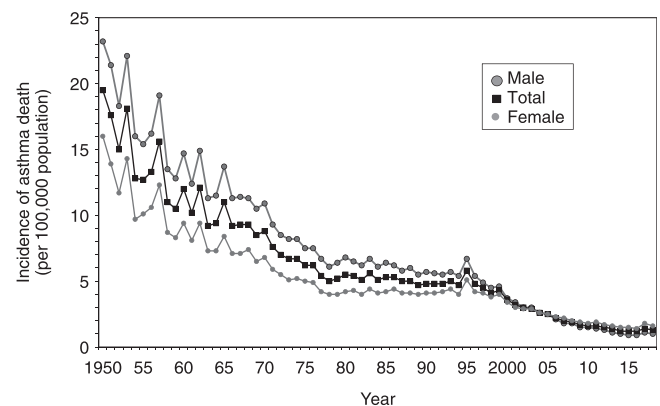


Fig. 2. Asthma mortality rates in Japan (1950–2018).

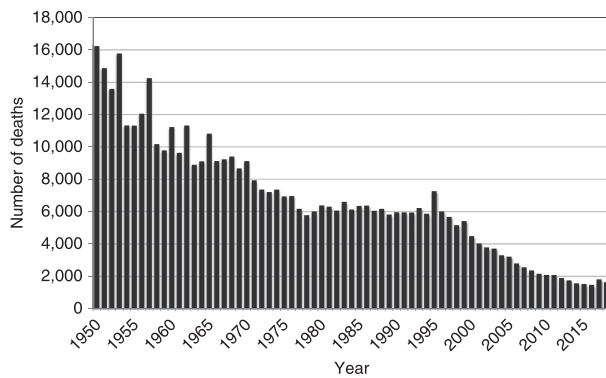


Fig. 3. Number of deaths due to asthma in Japan (1950–2018).

3.3. Contents

Patients need to be educated on the diagnosis, pathogenesis, risk factors, long-term therapy, and management of the exacerbations of asthma. The outcomes of patient education include the improvement in asthma control and patients' behaviors (Table 11). Education should be repeated if patient understanding is insufficient.¹⁴ Patient education is effective when an interdisciplinary approach is used; various tools such as inhalation instruction and evaluation forms will be useful for the satisfactory cooperation of physicians and medical staff. In Japan, information on asthma and related educational activities are provided by various associations; they include the Japanese Society of Allergology, Japanese Society of Pediatric Allergy and Clinical Immunology, Japan Allergy Foundation, Independent Administrative Institution, Environmental Restoration and Conservation Agency of Japan, and the Japanese Ministry of Health, Labour and Welfare.

3.4. QoL

QoL assessment is important for good asthma management. QoL cannot be substituted by physiological measurements since these tests give unidentical results. Asthma-specific QoL assessment tests are often used, which include the Asthma Quality of Life Questionnaire (AQLQ) and Asthma Health Questionnaire-33, Japan. The AQLQ is widely used for epidemiological surveys and the evaluation of the clinical efficacy of new drugs. The Asthma Health Questionnaire-33 was prepared by the Japanese Society of Allergology, and it is reproducible, reliable, and useful for the assessment of asthma symptoms, emotion, risk factors, limitations of daily and social activities, financial implications, and face scale.

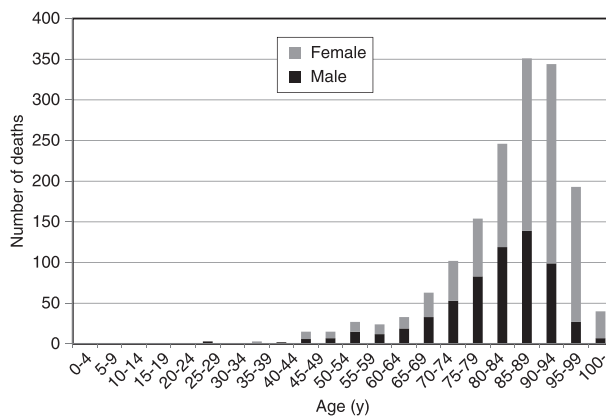


Fig. 4. Number of deaths due to asthma in Japan stratified by age (2018).

Table 11

Requirements for improving asthma therapy adherence of patients.

- Patients know that they need to use medicines daily, as asthma is a chronic disease.
- Patients know that prescribed medicines are safe when properly used.
- Patients realize that their symptoms due to asthma improve with therapy.
- Physicians and medical staff develop good partnership with patients.
- Patients evaluate the effectiveness of their managing actions at reducing asthma symptoms, and are sure of their good self-management.

Table 12

Controllers (agents for long-term management).

1. Corticosteroids
 - a) Inhaled corticosteroids
 - i) Beclomethasone dipropionate
 - ii) Fluticasone propionate
 - iii) Budesonide
 - iv) Ciclesonide
 - v) Mometasone furoate
 - vi) Fluticasone furoate
 - b) Oral corticosteroids
2. Long-acting β_2 agonists
 - a) Inhalants
 - Salmeterol xinafoate
 - b) Patch
 - Tulobuterol
 - c) Oral medicines
 - i) Procaterol hydrochloride
 - ii) Clenbuterol hydrochloride
 - iii) Formoterol fumarate
 - iv) Tulobuterol hydrochloride
 - v) Mabuterol hydrochloride
3. Combination inhaler of corticosteroid/long-acting β_2 agonist
 - a) Combination inhaler of fluticasone propionate/salmeterol xinafoate
 - b) Combination inhaler of budesonide/formoterol fumarate
 - c) Combination inhaler of fluticasone propionate/formoterol fumarate
 - d) Combination inhaler of fluticasone furoate/vilanterol trifenate
4. Leukotriene receptor antagonists
 - a) Pranlukast hydrate
 - b) Montelukast sodium
5. Theophylline sustained-release preparation
6. Long-acting muscarinic receptor antagonist
 - Tiotropium bromide hydrate
7. Biologic agent
 - a) Anti-IgE antibody
 - Omalizumab
 - b) Anti-IL-5 antibody
 - Mepolizumab
 - c) Anti-IL-5 receptor α chain antibody
 - Benralizumab
 - d) Anti-IL-4 receptor α -chain antibody
 - Dupilumab
8. Anti-allergics other than leukotriene receptor antagonists
 - a) Mediator antireleasers
 - i) Sodium cromoglicate
 - ii) Tranilast
 - iii) Amlexanox
 - iv) Repirinast
 - v) Ibudilast
 - vi) Tazanolast
 - vii) Pemirolast Potassium
 - b) Histamine H1 receptor antagonists
 - i) Ketotifen fumarate
 - ii) Azelastine hydrochloride
 - iii) Oxatomide
 - iv) Mequitazine
 - v) Epinastine hydrochloride
 - c) Thromboxane inhibitors
 - i) Thromboxane-A2 synthesis inhibitor - Ozagrel hydrochloride
 - ii) Thromboxane-A2 receptor antagonist - Seratrodast
 - d) Th2 cytokine inhibitor
 - Suplatast tosilate
9. Other agents and therapies
 - a) Chinese medicines
 - b) Specific immunotherapy
 - c) Non-specific immunotherapy

Table 13
Device for inhaled corticosteroids.

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

4. Asthma medications

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

4.1.1. Agents

Asthma agents can be classified into two types; long-term controller agents are used for long-term management (controllers) and reliever agents are used in the short-term to treat asthma symptoms (relievers). Controllers are defined as “regular-use agents aimed at achieving good control” and relievers are defined as “rescue-use agents aimed at treating asthma exacerbations.” It is important to understand the role of each agent for appropriate treatment (Table 12).

(1) Corticosteroids (steroids)

Corticosteroids are currently the most important and effective anti-inflammatory agents among asthma treatments. The main mechanisms of action include (i) inhibition of inflammatory-cell infiltration into the lungs and airways and inhibition of migration and activation of inflammatory cells; (ii) reduction of vascular permeability; (iii) suppression of airway secretion; (iv) inhibition of airway hyperresponsiveness; (v) inhibition of cytokine production; (vi) promotion of the effects of β_2 -agonists; (vii) inhibition of arachidonic acid metabolism in cells other than human mast cells and production of leukotrienes and prostaglandins. Currently, four forms of steroids are available: intravenous, intramuscular, oral, and inhaled. Steroids used for long-term management of asthma are usually ICSs because they have a lower risk of side-effects. When

Table 14
Recommended doses of inhaled corticosteroids by treatment steps.

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

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

asthma cannot be controlled with ICSs and ICSs plus other asthma drugs, such as bronchodilators, or there are complications, an oral corticosteroid should be used. An aqueous suspension of triamcinolone acetonide should not be injected intramuscularly because of its adverse effects. ICSs have been reported to (i) improve asthma symptoms; (ii) improve QoL and respiratory function¹⁵; (iii) alleviate airway hyperresponsiveness¹⁶; (iv) suppress airway inflammation¹⁷; (v) reduce the frequency and severity of exacerbations¹⁸; (vi) reduce the maintenance dose of ICSs for a long period¹⁹; (vii) reduce the medical expenses associated with asthma²⁰; (viii) suppress airway remodeling²¹; (ix) reduce the mortality rate due to asthma.²² Once asthma symptoms have developed, the early administration of an ICS (early intervention) will decrease the frequency of acute exacerbations.²³ However, asthma cannot be cured by ICS treatment. If the treatment is discontinued, asthmatic symptoms cannot be controlled. Furthermore, poor compliance during ICS use causes an increase in the frequency of emergency room visits and hospitalization due to asthma exacerbations. Oral corticosteroids are used as long-term management agents to complement ICSs, supplement adrenocortical function, and reduce the levels of systemic inflammatory cells and inflammatory substances in step 4 of treatment. As shown in Table 13, the ICSs commercially available in Japan in 2020 include fluticasone propionate (FP), budesonide (BUD), beclomethasone dipropionate, ciclesonide, mometasone furoate (MF), and fluticasone furoate (FF). FP, BUD, MF, and FF are also available as a dry powder inhaler (DPI), whereas FP, beclomethasone dipropionate, and ciclesonide are available as pressurized metered-dose inhaler (pMDI), using hydrofluoroalkane as a propellant. In addition, the effects of FF ester/LABA (vilanterol) are sustained for 24 h, and a single FF agent can also be used. BUD inhalation suspension, inhaled using a nebulizer, has been introduced, and a jet nebulizer, not an ultrasonic nebulizer, is recommended for BUD inhalation suspension. In general, BUD inhalation suspension at a dose of 0.5 mg twice daily or 1 mg once-daily (maximum 2 mg/day) is used in adults. ICS escalates doses according to severity. The dosage of ICSs is classified into high (the highest dose covered by health insurance), medium (half of the high dose), and low (half of the medium dose) (Table 14). Severe acute exacerbations can be alleviated by increasing the ICS dose. On the other hand, if the dosage exceeds the high dose, further effects proportional to the dose cannot be achieved, and the risk of adverse effects increases.²⁴ Thus, in controlling asthma, adding one or more agents other than ICSs, rather than simply increasing the dose of an ICS, is recommended. Smoking does not only reduce the effects of ICSs²⁵; it also impairs respiratory function in asthmatic patients. Although ICSs have fewer systemic adverse effects than other steroid formulations, localized adverse effects such as oropharyngeal candidiasis and hoarseness can sometimes become problematic. After inhalation, gargling or drinking water is essential. While the

inhibitory effects on adrenal glands in conventional doses are generally acceptable.^{26,27} careful monitoring of adrenal gland function is necessary when high doses are used. BUD-DPI, which can be administered even during early pregnancy, has not been reported to cause congenital malformation or have any effects on the course of pregnancy.²⁸ The US Food and Drug Administration (FDA) has certified the safety of BUD-DPI in pregnant women as Category B. There is no evidence of the increased risk of respiratory tract infection, including tuberculosis, with the use of ICSs in patients with asthma, and ICSs are not contraindicated in patients with active tuberculosis.

(2) LABAs

β_2 agonists bind to β_2 receptors in the smooth muscles in the airway and cause their relaxation. They are potent bronchodilators that enhance airway mucus removal by activating epithelial cilia, and they are administered via inhalation, patches, and the oral route. β_2 -Agonists should be used concomitantly with ICSs as controllers. When a LABA is combined with an ICS, the steroid increases the number of β_2 receptors, and the β_2 agonist amplifies the nuclear translocation of steroid receptors and further enhances the effects of the steroid. Furthermore, ICS/LABA allows the reduction of the ICS dose, and it improves the control of asthma.²⁹ The combination of an ICS and a LABA is more effective than that of an ICS and an SRT.³⁰ Salmeterol xinafoate (SM) is an inhaled LABA that cannot be used as monotherapy for the treatment of asthma because of the risk of exacerbations possibly induced by LABA without ICS, and it is often used as a compounding agent with FP. Conventional oral LABAs include procaterol hydrochloride, clenbuterol hydrochloride, and mabuterol hydrochloride. A tulobuterol patch, which was developed in Japan, is a long-acting agent with a bronchodilatory action that lasts for 24 h. Its clinical usefulness when combined with an ICS has been reported.³¹ Although LABAs have a high safety profile in any formulation, they sometimes have adverse effects, including tremors, palpitations, and tachycardia, which occur most frequently for oral agents, followed by patches, and inhaled agents. When adverse effects are observed, the dose should be reduced or the administration should be discontinued. Serious adverse effects include a decreased serum potassium level. LABAs

should be used more carefully in asthmatic patients with ischemic heart disease, hyperthyroidism, and diabetes mellitus. The adverse effects of the tulobuterol patch are skin itching or rashes (or both) around the patch area. LABA patches of generic products can be used, however, caution is required because the transdermal absorption rate may differ from that of the original products depending on the skin condition due to the difference in drug storage systems between them.

(3) Combination agents comprising ICS and inhaled LABA (ICS/LABA) (Table 15)

The combined inhalation of ICS and LABA are more effective than their separate inhalation.³² In Japan, FP/salmeterol (SM), BUD/formoterol (FM), FF/FM, and FF/vilanterol (VI) are used as combination ICS/LABA agents. The formulations of FP/SM, BUD/FM, FF/VI are available as DPI, while FP/SM and FF/FM are available as pMDI. The advantages of the ICS/LABA combination are (i) the number of inhalations can be reduced; (ii) excellent adherence can be achieved; (iii) the use of LABAs alone can be avoided. Furthermore, the use of the FM formulation as rescue, instead of a short-acting β_2 -agonist (SABA), can improve asthma symptoms and reduce the rate of asthma exacerbations (single maintenance and reliever therapy: SMART).³³ On the other hand, SMART carries the risk of promoting poor adherence to regular therapy as well as excessive use, as the patients can determine their treatment. Therefore, it is important to select patients for SMART carefully and educate them. Higher compliance is expected for FF/VI use because the dose is once-daily; in clinical trials, symptom improvements superior to those following the usual asthma treatment, including other ICS and ICS/LABA, were observed.³⁴ A warning based on the 2010 U.S. FDA recommendation about the use of LABA and ICS in combination for pediatric and adult asthma was given³⁵; however, the safety of using LABA and ICS together was confirmed and the warning was removed. Viral infection is a major cause of asthma exacerbations. The combination of ICS and LABA agents are reported to be superior to ICS monotherapy for reducing exacerbations due to viral infection.³⁵

(4) LTRAs

Leukotrienes (LT) C4, D4, and E4 are termed cysteinyl LTs (CysLTs), and they bind to the CysLT1, CysLT2, and CysLT3 receptors, respectively. Currently available LTRAs are CysLT1 receptor antagonists, which include pranlukast hydrate and montelukast in Japan. LTRAs facilitate bronchodilation and inhibit airway inflammation, which results in significant improvement of asthma symptoms and respiratory function, asthma exacerbations, and patient QoL.^{36,37} Because the effect of a single agent is inferior to that of low-dose ICS, LTRAs are mainly used in concomitance with ICSs, but they can be used in isolation for their anti-inflammatory effects. Compared with LABAs, LTRAs used in combination with ICSs are less effective.³⁸ LTRAs are useful for long-term management of patients with asthma complicated by allergic rhinitis, exercise-induced asthma (EIA), and AERD.³⁹ LTRAs are generally safe drugs, but they interact with other agents, such as warfarin, since they are also metabolized by CYP2C9. LTRAs seem to be relatively safe for pregnant women.

(5) SRT

Theophylline has bronchodilator and anti-inflammatory effects, and promotes mucociliary transport.⁴⁰ Currently, it is mostly administered as sustained-release preparations. Its use is recommended if other treatments are inadequate. The bronchodilator effect is stronger with β_2 stimulants than SRT, and SRT is more valuable when added to LABA than when used alone. The anti-

Table 15

Suggested daily doses of a corticosteroid and long-acting β_2 agonist combination.

	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/FM (pMDI)	50 μ g/dose, 2 doses b.i.d. 200 μ g/20 μ g	125 μ g/dose, 2 doses b.i.d. 500 μ g/20 μ g	125 μ g/day, 4 doses b.i.d. 1000 μ g/40 μ g
FF/VI (DPI)	100 μ g/dose, 1 dose s.i.d. 100 μ g/25 μ g	100 μ g/dose, 1 dose s.i.d. 100 μ g/25 μ g or 200 μ g/dose 1 dose s.i.d. 200 μ g/25 μ g	200 μ g/dose, 1 dose s.i.d. 200 μ g/25 μ g

FP, fluticasone propionate; SM, salmeterol xinafoate; BUD, budesonide; FM, formoterol fumarate.

FF, fluticasone furoate; VI, vilanterol trifenate.

[†] Indication in a delivered dose.

inflammatory effects after increasing ICS usage and those when using SRT with low to medium-dose ICS are similar. However, when it is used concomitantly with ICS, its effect is slightly inferior to when it is used with LABA and comparable to or slightly lower than when it is used with LTRA. The adverse effects of theophylline include gastrointestinal symptoms such as nausea and vomiting, palpitations, and tachycardia, among others. Convulsions occur when blood levels rise further. Therefore, blood concentration monitoring is important for preventing side-effects; a target of 5–15 µg/ml is recommended. Caution should be exercised when theophylline is used in combination with histamine H₂ receptor antagonists, macrolide antibacterial agents, and new quinolone antibacterial agents because blood levels can increase.

(6) LAMAs

Tiotropium bromide is available as a LAMA controller in Japan. It is frequently used in patients with COPD, and its use in a soft mist inhaler (Respimat®) is allowed for asthma treatment. It should be used in combination with ICSs for long-term management. Tiotropium acts on muscarinic M₃ receptors in the airway smooth muscle. The bronchodilatory effects of tiotropium are sustained for 24 h, and it improves pulmonary function in asthmatic patients with once-daily use. It has been reported that tiotropium improved pulmonary function in asthmatic patients who remained symptomatic after treatment with mild to moderate doses of ICSs.⁴¹ It improves pulmonary function and reduces exacerbations in severe asthmatic patients who continue to have asthma symptoms even when treated with high doses of ICSs plus LABAs.⁴² Dry mouth is sometimes observed as a side-effect of tiotropium. Careful administration is required for patients with severe heart disease. It is contraindicated in patients with angle-closure glaucoma and benign prostatic hyperplasia with dysuria.

(7) Anti-IgE antibody

Omalizumab is a humanized anti-human IgE monoclonal antibody. It controls IgE-mediated reactions and suppresses asthma symptoms. In Japan, omalizumab is available for the following asthmatic patients: (i) those who have unstable asthmatic symptoms, even when treated with high doses of ICSs plus more than one controller agent; (ii) those who are positive for perennial inhaled antigens, such as house dust; (iii) those whose weight and serum IgE level are within the dosage conversion table (IgE level should be among 30–1500 IU/ml serum IgE). The dose and frequency of administration (subcutaneous injection every 2–4 weeks) are determined based on those data. Omalizumab has effects in patients with poor asthma control, even with high-dose ICS treatment; it (i) prevents exacerbation, (ii) reduces the frequency of asthmatic symptoms, (iii) improves QoL, (iv) improves pulmonary function, (v) reduces the frequency of emergency room visits and hospital admissions, and (vi) reduces steroid dose.⁴³ Omalizumab improves the reduced antiviral immunity in asthmatics, and it is especially effective in preventing asthma exacerbations triggered by viral infections in the respiratory tract.⁴⁴ At 16 weeks after administration, the therapeutic effects can be comprehensively judged. It is effective in about 60% of patients. The factors predictive of effectiveness are higher serum eosinophil counts, higher serum periostin level, and higher levels of FeNO.⁴⁵ The major adverse effects of omalizumab are pain and swelling at the injection site. No teratogenicity has been reported, but its safety has not been established in pregnant women.

(8) Anti-IL-5 antibody and anti-IL-5 receptor α chain antibody

Mepolizumab, an anti-IL-5 antibody, is a humanized monoclonal antibody against IL-5 that blocks the binding of IL-5 to the IL-

5 receptor α -chain expressed on the surface of eosinophils. Mepolizumab suppresses the proliferation, differentiation, invasion, activation, survival of eosinophils, and, ultimately, the development of asthma symptoms. Mepolizumab is injected subcutaneously every 4 weeks in patients who develop exacerbations requiring systemic steroids despite high-dose ICS with multiple treatments. A greater number of blood eosinophils before administration results in more effective suppression of asthma exacerbations. The prevention of exacerbation, reduction of symptom score, improvement of QoL, improvement of respiratory function, reduction of hospitalization/emergency consultation, and reduction of steroids are observed in patients with eosinophilic asthma that are not sufficiently controlled even with high-dose ICS.^{46,47} It is highly effective when the peripheral blood eosinophil count at the start of administration is 150/µL or more.⁴⁸ The use of omalizumab before mepolizumab administration does not affect mepolizumab efficacy.⁴⁹ The timing of the effect evaluation and the administration period are not clear. The main side-effects include injection site reactions, headaches, and irritability. Its safety in pregnant women has not been established. Attention should be paid to helminthic infection, as eosinophils are involved in the immune response to some parasitic (helminth) infections. Benralizumab, an anti-IL-5 receptor α -chain antibody, reduces eosinophils by antibody-dependent cell-mediated cytotoxic activity in addition to its action on IL-5, and its mechanism of action is different from that of mepolizumab. Benralizumab is associated with the prevention of exacerbation, improvement of respiratory function and QoL, and steroid-sparing effect in severe asthma patients with peripheral blood eosinophilia.^{50,51}

(9) Anti-IL-4 receptor α -chain antibody

Dupilumab, an anti-IL-4 receptor α -chain antibody, is a humanized monoclonal antibody against the IL-4 receptor α -chain, which blocks the binding of IL-4/IL-13 to the IL-4 receptor α -chain and suppresses IL-4/IL-13-mediated asthma symptoms. Dupilumab is injected subcutaneously every two weeks in asthmatics who develop asthma that requires the administration of systemic steroids or other medications in combination with medium or high-dose ICS and other long-term management drugs. The efficacy of additional administrations (suppression of exacerbation/improvement of respiratory function) has been confirmed in asthma patients whose control is insufficient even when other long-term management drugs are used in combination with middle-dose ICS.⁵² However, the concomitant use with medium-dose ICS is necessitated when a physician determines that it is difficult to increase the ICS dosing because of adverse effects. The effect on prevention of exacerbation, improvement of respiratory function, reduction in symptom score, improvement of QoL, reduction in hospitalizations and emergency consultations, and reduction of steroids is observed in asthmatics with insufficient control even with medium or high-dose ICS.^{52,53} Compared with placebo, significant efficacy was observed in populations without baseline biomarkers, and higher concentrations of biomarkers related to type 2 inflammation (peripheral blood eosinophil count, FeNO, IgE, etc.) are considered to be more effective.^{52,53} However, at this time, there is no standard biomarker value for selecting patients with indications for this drug, and there are no certain conclusions about the timing of effect evaluation and the administration. The main side-effects were injection local pain and swelling, and serious side-effects such as eosinophilic pneumonia and EGPA were observed. At the time of administration of this drug, attention should be paid to changes in eosinophil count, vasculitic eruption, worsening pulmonary symptoms, cardiac complications, and

Table 16

Assessment of asthma control.

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

[†] Upper limit of normal diurnal variability from the baseline values of PEF, measured twice daily, is 8%.[‡] Define patients with one or more exacerbations a month as being poorly controlled, even if they do not meet the other criteria.

neuropathy, among others. Although teratogenicity has not been reported, its safety in pregnant women has not been established.

(10) Anti-allergics other than LTRAs

They are categorized as (i) mediator-release suppressants, (ii) histamine H1-antagonists, (iii) thromboxane A2 inhibitors/antagonists, and (iv) Th2 cytokine inhibitors. Th2 cytokine inhibitors have good potential as ICS alternatives and concomitant drugs.⁵⁴ Histamine H1 receptor antagonists may improve asthma symptoms by improving allergic rhinitis in patients.

(11) Other agents

A selection of Chinese herbal medicines is used, based on the patient's physical constitution, strength, and response to the disease at the time of administration; the empirical process helps distinguish responders from non-responders before administration. Expectorants, such as carbocysteine and fudosteine, may facilitate expectoration. However, the accumulated evidence is not sufficient to allow the recommendation of any of these agents. Macrolide antibiotics are expected to improve neutrophilic inflammation because they suppress neutrophil infiltration into the respiratory tract of asthmatics,⁵⁵ and improvements in airway hyperresponsiveness and asthma symptoms and exacerbations have also been reported.⁵⁶ Although macrolide antibiotics are not indicated for asthma, clarithromycin can be administered for neutrophilic inflammatory airway disease.

(12) Drugs expected in the future

Therapeutic effects of tezepelumab, an antibody against thymic stromal lymphopoietin (TSLP) involved in Th2 differentiation derived from airway epithelium, on severe asthma is observed regardless of peripheral blood eosinophils, FeNO, and serum total IgE levels. Tezepelumab is expected to be a therapeutic drug for non-eosinophilic refractory asthma.⁵⁷ An oral inhibitor of CRTH2, a PGD2 receptor, is under development as a low-molecular-weight compound. It is reported that fevipiprant reduces sputum eosinophils and improves respiratory function and QoL in patients with moderate to severe eosinophilic asthma.⁵⁸

4.1.2. Stepwise treatment plan

(1) Goal of asthma treatment

The goal of asthma treatment is to achieve normal respiratory function and eliminate symptoms, exacerbations, or adverse effects. Because normal respiratory function cannot be restored in patients with airway remodeling, it can be assessed based on their personal best respiratory function after 3–6 months controller

treatment. The control status is determined as shown in Table 16; the aim is to achieve good asthma control.

(2) Principle for treatment

Physicians have noted that a better relationship with their patients largely depends on the effects of the initial treatment, which focuses on the improvement of asthma symptoms. It is important to avoid and eliminate sensitizing allergens and exacerbating factors, such as passive and active smoking and excessive fatigue. The management of the inhalation technique, adherence to the drugs, and management of concomitant diseases, such as allergic rhinitis, obesity, gastroesophageal reflux disease (GERD), and COPD, are also important.

Asthma treatment is divided into four steps based on asthma severity. The steps are stated in the following section. It is useful to select and combine the drugs with consideration of the therapeutic spectrum of each drug.

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

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

a) Step 1 treatment: One (or no) controller agent plus a reliever agent. A SABA may only be administered to patients with the rare occurrence of asthma symptoms (less than once a month) without controllers, and no long-term management agent is needed. For patients who develop symptoms once or more a month, a low dose of an ICS is recommended as a controller agent.²³ If ICSs cannot be used or adverse effects develop after inhalation, they can be substituted by LTRAs⁵⁹ or SRT.⁶⁰ Anti-allergics other than LTRAs, such as a histamine H1 blocker, thromboxane A2 inhibitors, and Th2 cytokine inhibitors can be used, according to the pathophysiology of asthma.

b) Step 2 treatment: One or two controller agents plus a reliever agent. In addition to ICSs (low dose), a LABA is recommended.^{61,62} The effects of ICS/LABA combinations are superior to those of ICSs plus LABAs. ICS (medium dose) alone may be used instead of low-dose ICS/LABA. LAMAs,^{63,64} LTRAs,^{65,66} or SRT⁶⁷ can be used if patients cannot use LABAs. Early treatment with ICS/LABA can rapidly improve asthmatic symptoms and pulmonary function compared to ICS monotherapy.^{68,69} LTRAs are useful mainly in patients with coexisting allergic rhinitis and exercise- or non-steroidal antiinflammatory drugs (NSAIDs)-induced asthma.

c) Step 3 treatment: Two or more controller agents plus a reliever agent. Medium to high-dose ICS/LABA combination is recommended. If the effects of an ICS/LABA are insufficient, an LTRA, an SRT, or LAMA should be used.

Table 17

Management of difficult-to-treat asthma; items to be evaluated when good control cannot be obtained by treatment.

Differential diagnosis (Is the diagnosis of asthma correct?)	Are diseases that are easily misdiagnosed for asthma identified? Vocal cord dysfunction (VCD), airway narrowing due to bronchial tuberculosis and lung cancer, tracheomalacia, bronchiectasis, COPD, heart failure, aspiration, coughing with drugs such as angiotensin converting enzyme inhibitors
Confirmation of drug therapy (Treatment compliance and inhalation techniques)	- Are there any mistakes in usage such as inhalation techniques and number of doses? - Is the need for long-term management understood, and is there good compliance with treatment? - Is the drug selected at a dose appropriate for its severity and control status?
Management of comorbidities	Are the appropriate diagnosis and treatment of comorbidities associated with severe asthma? Rhinitis, sinusitis, COPD, gastroesophageal reflux disease, eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary mycosis, sleep apnea syndrome, obesity, depression, anxiety, etc.
Confirmation and elimination of exacerbation factors	- Are there any medications that could worsen asthma? - Are exacerbation factors at work, school, and home properly avoided or eliminated? NSAIDs, β blockers, etc. Smoking, sensitizing allergens such as mites, fungi, pets, etc.

d) Step 4 treatment: Controller agents plus additional therapy plus reliever agent. In addition to the continuous administration of an ICS (high dose) plus LABA, LAMAs, LTRAs, or SRT can be used. In difficult-to-treat cases, even after administering these drugs as much as possible, the administration of an anti-IgE antibody, anti-IL-5 antibody, anti-IL-5R antibody, anti-IL-4 receptor α -chain antibody, or BT may be considered. In some patients, an anti-IgE

antibody (omalizumab) is effective, particularly in poorly controlled patients sensitized to perennial allergens whose serum total IgE is within a therapeutic target range (30–1500 IU/ml).⁷⁰ The dose of the anti-IgE antibody is determined using a dosage conversion table. Its effects are evaluated 16 weeks after administration, and if it is effective, its administration is continued. If it is not effective, this treatment should be discontinued. Anti-IL-5 antibodies, including anti-IL-5 monoclonal antibody (mepolizumab), which acts as a neutralizing antibody, and anti-IL-5 receptor α -chain antibody (benralizumab), which is a receptor inhibitor having antibody-dependent cell-mediated cytotoxic activity, were shown to be effective for poorly controlled severe eosinophilic asthma. The higher the number of peripheral blood eosinophils before the administration of both antibodies, the higher the exacerbation inhibitory effect and the improvement effect on FEV1.^{71–75} Anti-IL-4 receptor α -chain antibody (dupilumab) suppresses type 2 inflammatory responses involved in asthma pathology by inhibiting IL-4 and IL-13 signaling.^{52,53} BT, an intervention that differs from conventional drug therapy, is indicated in patients with severe asthma who are 18 years of age or older. Indications for patients are set by a specialist in the Japanese Respiratory Society or a specialist in the Japanese Society of Allergy. The procedure is performed under the guidance of a Japanese Society of Respiratory Endoscopy Bronchoscope specialist. Although BT requires three hospitalizations, it reduces severe exacerbations and improves AQLQ, and these effects last for five years.^{76,77} Oral corticosteroids should be intermittently administered for a short period to avoid prolonged administration as much as possible. Specifically, about 0.5 mg/kg or the equivalent amount of prednisolone is administered for a short period (usually less than 1 week), and a high-dose ICS is subsequently used. In patients with insufficient asthma control who need prolonged administration of an oral corticosteroid, a shorter-acting oral corticosteroid (prednisolone) can be administered every day or every other day in the morning to maintain the minimum dose (5 mg). Caution should be taken when switching from long-term

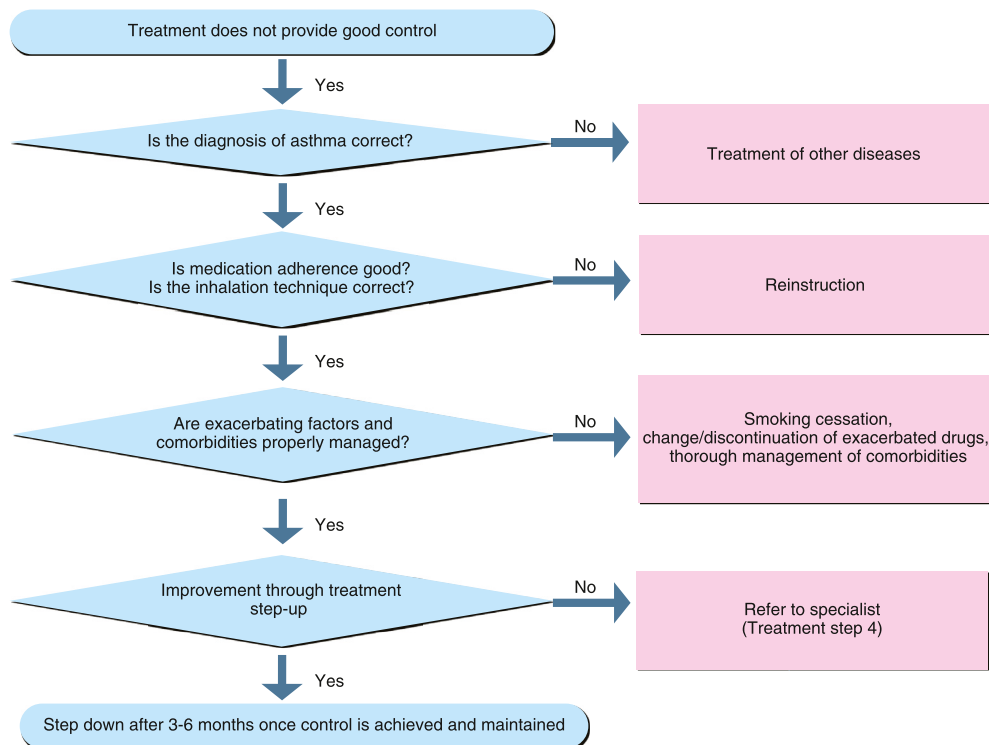


Fig. 5. Proceeding with long-term management of asthma. In the case of poor control despite treatment of treatment step 3 or higher, referral to a specialist is recommended.

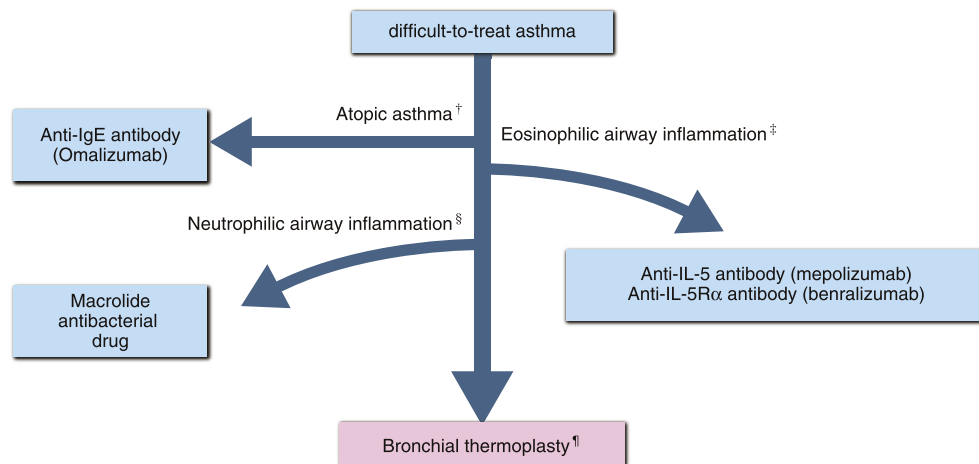


Fig. 6. Flow chart for difficult-to-treat asthma. [†]A case in which a specific IgE antibody is detected and the serum total IgE level is within 30–1500 IU/ml. [‡]Patients with blood eosinophil count ≥ 150 –300/ μ l or sputum eosinophil ratio $\geq 3\%$ regardless of atopic predisposition. [§]Sputum eosinophil ratio $< 3\%$ and high neutrophil count. [¶]The indication is judged by a specialist in the Japanese Respiratory Society or a specialist in the Japanese Society of Allergy, and patient is admitted to a hospital under the guidance of a specialist in fiberoptic bronchoscopy.

administration of an oral corticosteroid to a high-dose ICS because of possible adrenal insufficiency.

(4) Practical application (selection of treatment)

In untreated patients, the appropriate treatment step is determined based on the asthma symptoms shown in Table 4. Specifically, treatment steps are selected as follows: (i) step 1 treatment for mild intermittent symptoms, (ii) step 2 treatment for mild persistent symptoms, (iii) step 2–3 treatment for moderate persistent symptoms; and (iv) step 3–4 treatment for severe persistent symptoms. Asthma severity is essentially determined based on the symptoms; however, assessments of pulmonary function, using parameters such as PEF and FEV₁, are important for evaluating the disease condition and determining the treatment step. In patients who have already received drug therapy, such as controllers, which is often the case, the treatment step should be determined according to Table 6. When symptoms cannot be controlled in patients treated with step 3 treatment, they should consult a specialist. It is important to maintain a well-controlled status in asthma patients (Table 16). In general, control status should be evaluated within 1 month of starting treatment with the drugs, based on symptoms, frequency of reliever use, limitations on daily life, pulmonary function, and asthma exacerbations (Table 16). The inhalation technique, drug adherence, side-effects, degree of understanding of the treatment plan, and the satisfaction with the treatment are also evaluated. If asthma symptoms are not controlled, treatment may be intensified. When symptoms occur less than once a week, intensification of treatment within the same treatment step should be considered. When asthma symptoms occur every week or every day, one step-up or two steps-up are required to achieve good control. In patients receiving drug therapy, a step-down should be considered if the asthma control status remains good for 3–6 months, based on the assessment presented in Table 16. The goal of treatment is to maintain good asthma control using a minimum number of drugs. Evaluation of control status and adjustment of treatment every 1–3 months are necessary.

(5) Management of difficult-to-treat patients

In uncontrolled or partly controlled patients, asthma diagnosis, adequate instructions regarding daily medication, management of complications, and avoidance of exacerbating factors should be

monitored (Table 17, Fig. 5). If asthmatic patients remain uncontrolled with treatment step 3, they should consult a specialist. Management of acute exacerbation needs to be provided with an asthma diary, in which the doses and timing of asthma medication are recorded. If it is confirmed that a case of difficult-to-treat asthma is poorly controlled even after treatment in step 4 at a specialized facility, an anti-IgE antibody, anti-IL-5 antibody, anti-IL-5 receptor α -chain antibody, or BT should be considered. The selection of each treatment should be based on the condition of each patient. In the flowchart (Fig. 6), in patients with atopic asthma who have specific IgE antibody and total IgE level of 30–1500 IU/ml (therapeutic range) (predominant in Th2), an anti-IgE antibody is useful.^{70,78} For blood eosinophil count $> 150/\mu$ l with or without atopic asthma, an anti-IL-5 antibody or an anti-IL-5 receptor α -chain antibody is recommended, especially blood eosinophil count $> 300/\mu$ l or sputum eosinophil ratio in sputum $> 3\%$.^{71–75} In such a case of steroid-insensitive neutrophilic airway inflammation, or bacterial infection due to coexisting bronchiectasis, it is useful to use a macrolide in combination.⁵⁵ In addition, BT can be performed at specialized facilities, and BT has been shown to suppress severe asthma and improve QoL.^{76,77} However, the use of biologics and macrolide antibiotics is prioritized, as at this time there are no known biomarkers for BT effectiveness. Patients with worsening symptoms are instructed to follow an emergency manual immediately. In addition, patients

Table 18

Indications for visit to the emergency outpatient unit.

- Moderate dyspnea (e.g., with trouble with lying down) or more severe symptoms
- Requirement of SABA inhalation every 1–2 h
- Worsening symptoms after treatment

Table 19

Points for history taking in an emergency outpatient unit.

- Time of onset and cause of exacerbations
- Recent drug use and time of last administration, as well as use of steroids
- History of hospitalization and emergency visit because of asthma
- History of respiratory failure and intubation because of asthma
- Cardiopulmonary diseases and complications (e.g., heart failure, pneumothorax, pulmonary embolism)
- History of AERD and drug allergies

Table 20

Treatment steps for asthma exacerbation.

	Treatment	Standard action
Treatment step 1	Inhaled SABA [†] Additional inhalation of budesonide/formoterol, as needed (if SMART is introduced)	Treatment at home if instructions are provided by the physician
Treatment step 2	Repeated inhalation of SABA using a nebulizer [‡] Oxygen (target SpO ₂ of 95%) Systemic administration of steroid [§] Consider intravenous drip infusion of aminophylline. [¶] Consider subcutaneous injection of adrenaline, 0.1% (Bosmin®).	Emergency visit If insufficient response within 2–4 h or no response within 1–2 h, advise hospitalization. On admission, switch to treatment step 3, similar to that for severe exacerbation.
Treatment step 3	Repeated inhalation of SABA using a nebulizer [‡] Oxygen (target SpO ₂ of 95%) Systemic administration of steroid [§] Intravenous drip infusion of aminophylline (continuous) [¶] Consider subcutaneous injection of adrenaline, 0.1% (Bosmin®). Consider inhaled anticholinergics.	Emergency visit If no response within 1 h, advise hospitalization. If exacerbated, switch to treatment for serious exacerbation.
Treatment step 4	Continue the above treatment. If symptoms and respiratory function are exacerbated, intubate. ^{††} If PaO ₂ ≤50 mmHg and/or there is rapid elevation of PaCO ₂ with impaired consciousness despite oxygenation, initiate mechanical ventilation ^{††} Consider bronchial lavage Consider general anesthesia using isoflurane, sevoflurane, etc.	Immediate hospitalization and ICU treatment ^{††}

Aims of treatment: Relief of dyspnea and normal daily life; PEF rate of ≥80% of the predicted value or personal best value; oxygen saturation of >95%; no exacerbation of asthma symptoms with routine medication and inhalation.

Consider treatment step-up when the aims of treatment cannot be achieved within 1 h.

PEF, peak expiratory flow; pMDI, pressurized metered dose inhaler; SABA, short-acting β₂-agonist; SMART, budesonide/formoterol (Symbicort®) maintenance and reliever therapy.

[†] Repeat 1–2 puffs of SABA pMDI twice at an interval of 20 min.

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

[§] Intravenous drip infusion of steroids: 4–8 mg of betamethasone or 6.6–9.9 mg of dexamethasone every 6 h as needed. When aspirin-exacerbated respiratory disease is ruled out, intravenous drip infusion of 200–500 mg of hydrocortisone or 40–125 mg of methylprednisolone is possible. Subsequently, administer intravenous drip infusion of 100–200 mg of hydrocortisone or 40–80 mg of methylprednisolone every 4–6 h, as needed, or administer oral prednisolone (0.5 mg/kg/day).

[¶] Refer to the main text. Administer intravenous drip infusion of aminophylline in 200–250 ml of isotonic fluid for about 1 h. If adverse reactions, such as headache, nausea, palpitation, or arrhythmia occur, discontinue the infusion. If theophylline has been administered before the exacerbation, reduce the dose of aminophylline to half or less. Measure serum theophylline levels, whenever possible.

^{||} Adrenaline, 0.1% (Bosmin®, 0.1–0.3 ml) can be repeatedly administered at intervals of 20–30 min. Monitor the pulse and maintain at ≤ 130 beats/minute. This agent is contraindicated in patients with ischemic heart disease, glaucoma (except for open-angle or simple glaucoma), and hyperthyroidism. Sphygmomanometry and electrocardiography are required for patients with hypertension.

[¶] Continuous intravenous infusion of aminophylline: following the first intravenous infusion (see^{||} above), administer continuous intravenous infusion of 125–250 mg of aminophylline for 5–7 h. Monitor serum theophylline levels to maintain within 8–20 µg/ml. If adverse reactions occur, discontinue the infusion.

^{††} ICU or hospital rooms where intubation, assisted ventilation, etc., can be performed and continuous sphygmomanometer, electrocardiogram, and pulse oximeter monitoring can be conducted. Intubation and mechanical ventilation should be performed by experienced specialists, except in highly emergent situations.

should be acquainted with dose-reduction strategies. Furthermore, in cases of acute exacerbation, they should have contact information and addresses of emergency hospitals, and an “asthmatic patient card” should be handy to enable treating physicians and other physicians to administer emergency treatment.

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

Table 21

Checklist upon discharge from the emergency room.

- Confirm the causes of exacerbation and instruct patients to avoid them; recommend smoking cessation to smokers.
- Check whether a patient or his/her family has any problem in coping with the exacerbation (e.g., recognition of the signs of exacerbation, initial action, and access to hospital, etc.), and provide advice for improvement in action, as needed.
- Reassess whether the use of drugs for long-term treatment was adequate (adherence and inhalation technique) and explain the importance of continuous treatment.
- Prescribe agents for the treatment of exacerbation for 3–5 days (bronchodilators, oral steroids, etc.).
- Instruct patients to consult a primary care physician or asthma specialist early and continue outpatient treatment.

4.2. Management of acute exacerbations in adults

4.2.1. Management at home

Because the severity of the symptoms of exacerbation varies widely, management should be tailored to severity and approached individually. For this purpose, it is desirable to provide an action plan for each condition.⁷⁹ In case of wheezing or chest tightness and moderate symptoms, 1–2 puffs of a SABA in pMDI should be inhaled. If the effect is insufficient, inhalation can be repeated every 20 min for 1 h and once every hour subsequently. Patients placed on SMART therapy with BUD/FM can take one inhalation for exacerbation, followed by one more inhalation if symptoms do not improve within a few minutes.⁸⁰

Patients can be treated at home continuously when the symptoms disappear with the above-mentioned treatments and the treatment effect persists for 3–4 h. However, if the therapeutic effect is insufficient and the symptoms shown in Table 18 are present, the patient should be instructed to visit an emergency outpatient unit immediately after taking oral steroids (prednisolone equivalent 15–30 mg).

4.2.2. Assessment of acute exacerbation

Upon arrival at the emergency outpatient clinic, the severity of exacerbation should be immediately determined based on the symptoms (Table 19). To assess the cause of exacerbation, the

important points to take note of during history taking are listed in Table 20.

When a respiratory infection is suspected, chest radiography and sputum culture are recommended. In older adult patients, in whom wheezes can be caused by cardiac diseases or aspiration, electrocardiogram and chest radiography should be performed. If possible, PEF may be compared with the personal best value and blood tests, including eosinophil and neutrophil counts and C reactive protein, should be performed.

4.2.3. Treatment procedures in emergency outpatients (Table 21)

Treatment for exacerbations is classified into four steps, which are determined by the corresponding severity (Table 19).

(1) Oxygen

Usually, oxygenation should be initiated for patients with SpO₂ of <95%. Even if the SpO₂ is maintained at ≥ 95%, the respiratory rate should also be monitored, because tachypnea may compensate for the oxygenation. If the SpO₂ is judged to be compensated by tachypnea, 1 L/min of oxygen should be initiated, and arterial blood gas analysis is recommended. When the SpO₂ is <90%, the flow rate of oxygen should be gradually increased to maintain a SpO₂ of ≥90%.

(2) Inhaled short-acting β₂-agonists (SABA)

During acute exacerbations, in which effective delivery of SABA may be impaired because of shortened inhalation time and inhomogeneous bronchoconstriction, a nebulized administration is recommended. The inhalation should be discontinued if adverse effects, such as marked tremor or palpitation, develop. If SABA is observed to be efficacious and there are no obvious adverse effects, repeated administration is possible.

(3) Corticosteroids

Corticosteroids (steroids) are administered as anti-inflammatory drugs. The safety of steroid phosphate esters, including betamethasone and dexamethasone, has been estimated as high. The recommended dose of betamethasone and dexamethasone is 4–8 mg and 6.6–9.9 mg, respectively. In patients with AERD, the use of steroid succinate esters should be avoided because they were reported to worsen asthma in 40%–60% of patients.^{81,82}

(4) Theophylline

Although systemic steroids have anti-inflammatory effects, and they improve bronchoconstriction and airway edema, the onset of action was reported to be around 4 h. In Japan, aminophylline has been widely administered as an additional treatment, and it was recommended as a treatment option in the 2018 Japanese Guideline.⁸³ Although aminophylline was not proven to add to the efficacy of β₂-agonists in a meta-analysis,⁸⁴ its additional effect of bronchodilation was shown in a Japanese study that monitored its serum concentration.⁸⁵

An intravenous drip infusion of 250 mg of aminophylline for one hour (equivalent to approximately 200 mg of theophylline)

Table 23

Indications for ICU admission.

- Serious exacerbation or need for step-up to exacerbation treatment step 4
- No response to the initial treatment in the emergency room
- Symptoms of confusion or narcosis, suggesting risk for respiratory arrest or loss of consciousness
- Severe respiratory failure that can cause respiratory arrest

was reported to increase the serum concentration to approximately 8 µg/ml.⁸⁶ Because the average concentration of serum theophylline in patients taking 400 mg/day of oral SRT is approximately 10 µg/ml, the concentration may reach approximately 18 µg/ml after intravenous drip infusion. Before the administration of aminophylline, the daily use of oral theophylline should be checked; patients who are not taking oral theophylline can be safely treated. However, for patients who are already being treated with oral theophylline, the initial dose of aminophylline infusion is suggested to be approximately 125 mg, and side-effects should be closely monitored. If adverse reactions occur during administration, the drip infusion must be immediately discontinued, even if the level of theophylline does not reach toxic concentrations.

(5) Fluid replacement

Caution should be exercised for dehydration secondary to tachypnea or difficulty in oral ingestion, and fluid replacement is recommended as needed.

4.2.4. Checklist upon discharge from the emergency room

If symptoms are stable for 60 min or longer after the last treatment, the patient may be discharged. PEF should recover to ≥80% of the predicted or best value. The checklist upon discharge from the emergency room is shown in Table 22.

Because treatment with systemic steroids may decrease following exacerbations or hospitalization,⁸⁷ 0.5 mg/kg of oral prednisolone for five days may be prescribed if the treatment step during the exacerbation was ≥2. Even when symptom relief is achieved, patients should be informed about the risk of repeat exacerbation and the importance of continuous treatment and rest. Exacerbation is an important opportunity for the reassessment of long-term management and the instructions for the self-management of asthma. The patient referral document, which indicates the need to step-up long-term therapy, should be written to the primary care doctor or specialist, if necessary.

4.2.5. Indications for hospitalization or intensive care unit admission

Hospitalization should be considered when symptoms do not improve within several hours after the initiation of treatment or in patients who fulfill the conditions shown in Table 22. A patient who had serious symptoms should be immediately hospitalized (Table 8). Intensive care should be considered in situations shown in Table 23. In such cases, the patient should be immediately

Table 22

Indications for hospitalization.

- Moderate symptoms (treatment step 2 for exacerbation), insufficiently responsive to 2–4 h of treatment or nonresponsive to 1–2 h of treatment
- Severe symptoms (treatment step 3), non-responsive to treatment within 1 h
- History of severe asthma attack requiring hospitalization
- Symptoms of exacerbation for a long duration (several days to 1 week)
- Complications, such as pneumonia, atelectasis, and pneumothorax
- Mental disorders or communication difficulties
- Difficulties in visiting a medical institution because of insufficient transportation

Table 24

Required conditions for discharge.

- Normal PaO₂ value
- (Almost) no abnormal physical findings
- No shortness of breath on walking
- No waking up at night or in the early morning due to exacerbation
- No requirement for SABA inhalation within 4-h intervals
- Patients can adequately utilize the prescriptions, including inhalers, upon discharge
- Appropriate self-assessment and self-control based on action plan
- PEF is ≥ 80% of the predicted values and diurnal variation is <20%, if possible

transferred to the intensive care unit and administered with initial oxygen treatment, SABA inhalation, and subcutaneous injection of catecholamine (adrenaline, 0.1%).

4.2.6. Indications for discharge from the hospital

Before discharging a patient from the hospital, it should be confirmed that the symptoms have not exacerbated for ≥ 12 h of the treatment regimen during discharge (Table 24). It is important to inform the patients about the high risk of death from asthma, particularly those who have experienced severe exacerbations, and consistent instructions should be provided after discharge. Patients who have repeated exacerbations should be adequately treated in cooperation with a specialist, taking psychological and social factors into account.

5. Specific considerations

5.1. Steroid-resistant asthma

5.1.1. Definition

The definition of steroid-resistant asthma is that FEV₁% is less than 70% and bronchodilators have airway reversibility of 15% or more, and even if PSL (0.5 mg/kg; 20–40 mg) is taken for 10–14 days, improvement is less than 15%.⁸⁸ It may be clinically consistent with cases in which asthma control is insufficient, even with medium to high doses of ICS (FP 500 μ g or more or BUD 800 μ g or more) and LABA/LTRA/theophylline. Typical cases suffer severe exacerbations requiring systemic steroids for at least 3 days twice a year or hospitalization more than once a year.⁴²

5.1.2. Diagnosis and treatment

In clinical practice, it is important to note the following points to confirm steroid resistance when steroid treatment (including treatment with inhaled drugs) does not show a therapeutic effect.

- (1) Are the dosage of inhaled drugs used and device selection appropriate for the patient?
- (2) Is the operation of inhalation correct?
- (3) Is the compliance to medication maintained?
- (4) Have environmental factors related to asthma (food, alcohol, exercise, NSAIDs, β -blockers, air pollutants, airborne fungi, weather changes, mite, pets, fungi, tobacco smoke, exacerbating factors in the workplace, etc.) been avoided or eliminated?
- (5) Are comorbidities and complications such as rhinitis, sinusitis, ABPA, EGPA, obesity, GERD, sleep apnea syndrome, depression, anxiety not overlooked? If they exist, are they managed?
- (6) Is the diagnosis of asthma correct? It is necessary to differentiate it from other diseases and conditions such as endotracheal tuberculosis, presence of tumor or foreign body, vocal cord dysfunction, tracheomalacia, bronchiectasia, COPD, congestive heart failure, cough due to drugs such as angiotensin converting enzyme (ACE) inhibitors, and psychogenic cough.

If true steroid resistance is considered, the next treatment step including biologics should be performed.⁸⁹

5.2. AERD

5.2.1. Definition

AERD is a non-allergic hypersensitivity (intolerance), and it shows severe airway symptoms induced by aspirin and NSAIDs in general, particularly arachidonate cyclooxygenase (COX)-1 inhibitors. The pathogenesis of this disease is arachidonate COX-1 inhibitor hypersensitivity; hypersensitivity symptoms are exhibited more easily and selective arachidonate COX-2 inhibitors can be used safely.⁹⁰

5.2.2. Epidemiology, clinical aspect, and symptoms

Five to ten percent of adult asthma patients have AERD, which is rare in children who are 10 years or younger, and the ratio of men to women is 1:2. AERD usually develops in 20- to 40-year-olds, and it is characterized by weak or no atopy.⁹¹ Half of the patients with AERD are severe asthmatics, and they often have fixed airflow obstruction. When the attack in AERD patients is caused by the administration of COX inhibitors, severe watery rhinorrhea and nasal congestion often develop as prodromal symptoms, which can be accompanied by facial flushing and conjunctival hyperemia, and one-third of patients have digestive symptoms, including abdominal pain, diarrhea, and others. Sometimes, chest pain, skin itching, and urticaria may occur simultaneously. Patients with AERD often have eosinophilic rhinitis with a nasal polyp and a distorted sense of smell. Similarly, more than half of asthmatic patients with a nasal polyp have AERD and nasal symptoms, particularly the distorted sense of smell. More than 50% of patients with nasal polyps have eosinophilic otitis media, approximately 30% have symptoms of eosinophilic colitis, and approximately 10%–20% have variant angina pectoris.

5.2.3. Pathogenesis

AERD is characterized by an overproduction of CysLTs,⁹² and the mechanism is thought to be a decrease in COX-2 and EP2 receptor function in the airways.⁹³ Interestingly, smoking may suppress the onset of AERD by inducing COX-2.⁹⁴ Specific activation of platelets and their enhanced adhesion to granulocytes, sustained activation of mast cells, and involvement of ILC2 cells in nasal polyps have also been reported.^{95,96}

5.2.4. Diagnosis

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

5.2.5. Management of fever and pain in patients with AERD

Because of the relatively low threshold for causing an AERD attack, it appears that taking NSAIDs is dangerous in patients with AERD, even if NSAIDs are taken under the supervision of a doctor. The severity of an AERD attack is depicted in the order injection > suppository > oral NSAIDs. Adhesive skin patches, ointment, and ophthalmic drugs should be prohibited in patients with AERD. Oral administration of acetaminophen is considered to be safer than regular NSAIDs. However, it has been reported that in 34% of asthmatic patients with AERD, pulmonary function worsens at a dose of 1000–1500 mg of acetaminophen; therefore, it is safe to administer less than 500 mg of acetaminophen (or preferably even less than 300 mg) in patients with AERD.⁹⁷ A selective COX-2 inhibitor, celecoxib, has a high safety profile, but may rarely induce an attack in unstable and severe asthmatic patients with AERD.

5.2.6. Management of aspirin-induced attack of asthma

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

- (1) Acute and high-dose infusions of succinic esters of steroids often induce severe asthma attacks that are sometimes fatal.

Phosphate esters of steroids are thought to be safe for patients with AERD, but acute intravenous infusion often induces severe asthma attacks because some additives could cause worsening of exacerbations. Therefore, a rapid intravenous administration of these agents is not safe, even intramuscularly. NSAIDs should be administered slowly in drip intravenous infusion for over a period of more than 1–2 h.

- (2) Because of some additives, the inhalation of bromhexine hydrochloride salt sometimes induces an AERD attack. On the other hand, oral administration is known to be safe.
- (3) Adrenaline (0.1%) is effective for the treatment of AERD attacks. Standard treatment for acute asthma exacerbation should be carried out. A low dose of adrenaline (0.1–0.2 ml) can be used for AERD attacks, and repeated administration is possible.

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

Long-term management of AERD is essentially the same as that of asthma without AERD. ICS is the first choice and key drug in patients with AERD. Omalizumab improves upper and lower respiratory tract symptoms in severe AERD patients and suppresses CysLT overproduction and mast cell activation.⁹⁸ LTRAs in combination with ICSs are better for long-term management, because CysLTs may be associated with the pathogenesis of AERD. LTRAs improve asthmatic symptoms and sinusitis in patients with AERD, and they may partially inhibit AERD attacks. Treatment for chronic sinusitis and nasal polyps is important, and a severe nasal polyp should be removed by endoscopic surgery to stabilize symptoms of AERD.

5.3. Exercise-induced asthma

5.3.1. Concept of EIA

Asthma attack or transient bronchoconstriction several minutes after exercise is EIA or exercise-induced bronchospasm (EIB).⁹⁹ Problems associated with exercise-related asthma include: (i) the diagnosis, treatment, and prevention of EIA and (ii) relationship between treatment and doping for athlete's asthma. Most pediatric asthmatics and more than half of adult asthmatics experience deterioration during exercise.

It is known that EIB rarely occurs during swimming, and it is likely to occur during running, especially repetitive short-distance or medium-distance running. The presumed mechanism of EIB is that a rapid change in airway temperature and an increase in osmotic pressure due to airway water loss stimulate the release of various inflammatory mediators that cause contraction.¹⁰⁰

5.3.2. Diagnosis of EIA

EIA is diagnosed by a decrease in FEV1 of 10% or more by 3–8 min of exercise that increase maximal oxygen uptake to 70–80% or a maximum heart rate of 85% or more. However, in clinical practice, EIA is diagnosed by the presence of cough, dyspnea, and wheezing, among others, after exercise.¹⁰¹

5.3.3. Prevention of EIA

SABA, disodium cromoglicate (DSCG), and LTRA are used for the prevention of EIA.^{100,102} Since SABA has a strong inhibitory effect on bronchoconstriction, it is used 5–20 min before exercise, and the effect continues for 2–4 h. A single inhalation of DSCG before exercise also showed a significant inhibitory effect for 1–2 h. LTRA has both airway contraction suppression and anti-inflammatory effects.

Although its effect is inferior to SABA, it does not produce tolerance due to continuous use. Usually, the effect lasts 24 h when taken 2 h before exercise.

5.4. Asthma in athletes

5.4.1. Concept of asthma in athletes

The prevalence of asthma is known to be higher in athletes than in non-athletes.¹⁰³ It has been reported that the prevalence of asthma in Japan's Olympic team is 11.2–12.9%, which is significantly higher than that of ordinary adults, as in the United States and other countries. Therefore, accurate diagnosis and optimal treatment of asthma are crucial. The asthma drugs allowed or prohibited, as well as the route of administration in athletes, are determined by the World Anti-Doping Agency (WADA). For use of prohibited asthma drugs, asthmatic athletes should apply for a Therapeutic Use Exemption (TUE).

5.4.2. Pathogenesis of asthma in athletes

In this group of asthmatics, the pathogenesis is thought to be associated not only with the general mechanisms of cooling of the airways or changes in osmotic pressure, but also with some specific mechanisms. During intense exercise, excessive ventilation induces the stretching of the airway epithelial cells and causes tissue damage and repair in the airways, resulting in airway hyper-responsiveness and remodeling.¹⁰⁴

5.4.3. Diagnosis of asthma in athletes

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

5.4.4. Treatment of asthma in athletes

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

(1) Long-term management

Inhalation of ICS, oral LTRAs, and theophylline are approved for preventing EIB in asthmatic athletes. SM and FM are approved; however, the patch formulation of tulobuterol and oral β_2 stimulants are prohibited, even with a TUE application.

(2) β_2 stimulants

Inhalation of salbutamol up to 1600 $\mu\text{g/day}$ is approved for use without TUE; however, TUE requires inhaled procaterol. In SMART treatment, a maximum of 12 puffs/day of the combination of BUD/FM can be used in acute exacerbations.

5.4.5. Prevention of EIB in asthma in athletes

To prevent EIB in asthma, athletes need to be treated with SABAs 10–15 min before exercise or warming-up before exercise.

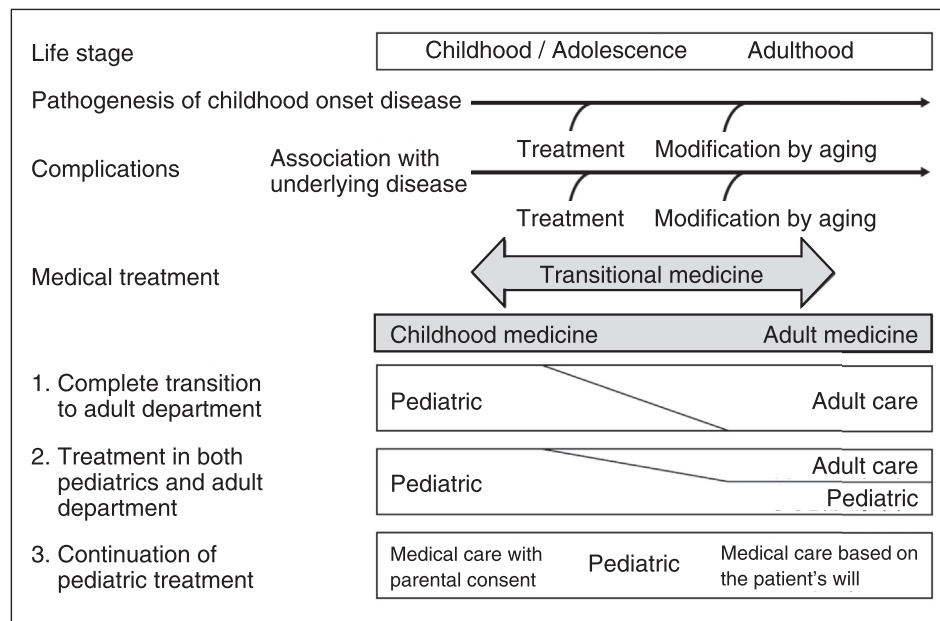


Fig. 7. Concept of transitional medicine.

Adequate controllers should be considered to prevent EIB in asthmatic athletes. Asthmatic athletes need to avoid exercise in cold and/or dry air conditions.

5.4.6. TUE

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

5.5. Adolescent asthma and transitional medicine

5.5.1. Adolescent asthma

Adolescence is the period from the onset of the development of secondary sexual characteristics to its completion. The male:female ratio is around 1.5 before adolescence, but it reverses between 15 and 25 years, falling below 1.0. A survey of 7–15-year-olds in Japan reported that asthma was significantly more prevalent in obese girls. Adolescent asthma is characterized by secondary sexual characteristics, mental sensitivity and instability due to independence from parents, and social peculiarities such as school advancements, employment, and change from maternal to paternal care. Uncontrolled asthma during adolescence tends to carry over into adulthood. Adolescent asthma may be associated with poor compliance and reduced therapeutic effects; it has a higher risk of being fatal or near-fatal than childhood asthma.

5.5.2. Transitional medicine

The transition from protective medicine by childhood parents and pediatricians to voluntary medicine by adult patients themselves must be carried out smoothly (Fig. 7). The basic concept of transitional medical care is 1) self-determination, 2) treatment against pathological conditions and complications that change with age, and 3) appropriate care based on age and personal maturity. Many children with asthma transition from pediatrics to adult health care facilities. However, some children with asthma have difficulties transitioning to internal medicine because of intellectual disability, autism spectrum disorders, attention-deficit/hyperactivity disorder, localized learning, severe handicap, and psychological factors, which

necessitates internal and pediatric treatment or ongoing pediatric treatment.

In transitional medicine, the requirements of the medical practitioner and the patient are as follows.

(1) Medical staff

• Re-evaluation of medical conditions

Obstacles to adherence, symptoms using asthma control assessing tools, presence of EIA, daily PEF value, flow-volume curve, FeNO, airway hyperreactivity, presence of allergic rhinitis and sinusitis as complications, psychological problems, pathological severity, and developmental disabilities should all be re-evaluated.

• Re-consideration of management strategy

Since ICS dosages and drugs differ during childhood and adolescence, it is necessary to consult a physician and treat according to guidelines.

• Re-education for patients

Etiology, worsening factors, treatment strategy, and prognosis should be explained according to the patient's level of understanding. Asthma can be fatal and regular visits are required.

• Establishment of trust and partnership with patients and families

Medical staff need to support the process of parent and child adaptation to physical, mental, and social changes in adolescence.

(2) Patient

• Re-evaluation of medical conditions

An understanding of asthma treatment, regular consultation, what is necessary for an emergency, and independent participation in medical treatment are desirable.

5.6. Asthma in older adults

5.6.1. Characteristics of asthma in older adults

Because the World Health Organization defines individuals older than 65 years as older persons, asthmatic patients older than 65 years are considered as older patients in Japan. In 2016, while the total population of Japan decreased by 210,000, the number of older adults increased by 570,000, and the ratio of older adults to the total population was 27.7%, the highest worldwide. In addition

to the aging of society, the prevalence of allergic conditions is increasing, and the prevalence of asthma in older adults is also increasing. Because senescent changes related to aging in older adults vary considerably and comorbid conditions are present, the pathophysiology of asthma in this group is more complex and it is often difficult to diagnose asthma in these individuals because of the senescent changes. In recent years, older adults accounted for close to 90% of total asthma death. In 2016, this rate was extremely high at 89.4%, and patients aged 75 years or older accounted for approximately 80% of the total deaths. To reduce mortality from asthma in Japan, it is important to prevent death and diagnose and manage asthma in older patients appropriately.

5.6.2. Classification of older adult asthma

Asthma in older adults is classified into early-onset (child-adolescent onset) and late-onset (adult-onset) based on the onset period. The former can be classified into 2: childhood-onset that is long-lasting and adult recurrent type after one remittance.¹⁰⁵ More than 60% of asthma in older adults develop after age 50; the later the onset age, the more severe it is.

5.6.3. Diagnosis of older adult asthma

Asthma symptoms in older patients are similar to those in younger asthmatic patients; however, symptoms of patients in a stable condition and pulmonary function are not fully reversible. In older asthmatics, the severity of asthma is often evaluated as mild because of the poor sensation of dyspnea during bronchoconstriction. The diagnosis of asthma is often difficult when asthma is mild, or if it occurs in the presence of senescence-related comorbidities. Sometimes, it may be difficult to recognize the clinical history of asthma because older adult patients often have COPD, heart failure, and reflux esophagitis. A careful physical examination in combination with an electrocardiogram and chest X-ray, is necessary for the diagnosis.¹⁰⁶

5.6.4. Pharmacological treatment of older adult asthma

Since older adults are often excluded from large-scale clinical trials because of comorbid conditions, there is currently limited evidence regarding the effects of asthma treatments. Even in older-adult asthma, the basic condition is a chronic inflammation of the respiratory tract, and ICS is the first-line drug in long-term management. Inhalation therapy is the standard treatment is the same as in other age groups during the stable period and attacks, and it is important to confirm the availability of inhalation procedures, understanding of operating procedures, and inspiratory flow rate in each case; it is also important to select a device that matches the characteristics. Also, if it is difficult to synchronize the inhalation and the nebulization when using pMDI, spacers, and nebulizers with BUD inhalation suspensions are suitable alternatives. At the time of therapeutic intervention, whether or not to administer the drug and the dose should be determined after considering comorbidities and physiological deterioration of organ function. If asthma control is poor, the current status of inhalation therapy (whether the operating procedure is accurate, whether it is inhaled properly, or adherence is good) and a change in device or the addition of drugs should be considered.

(1) Corticosteroids

ICSs are the first choice for treatment of older patients with asthma. Oral corticosteroids may cause neurological symptoms, including excitation or confusion, in this group. ICSs do not cause systemic adverse effects and are safe even in older patients. On the other hand, older asthmatics tend to show poorer adherence to ICSs than younger asthmatics; therefore, older patients need to assess

their technique of inhalation repeatedly and receive instruction on how to use inhaled drugs, given the various types of devices for inhaled drugs available. When older patients are unable to use a dry-powder inhaler because of insufficient inspiratory flow, it is sometimes useful to change to a pMDI with a spacer or a suspension of corticosteroids delivered by a jet nebulizer. Before stepping up treatment, the inhalation technique should be checked in this group. In this group of patients, long-term treatment with high doses of ICSs (equivalent dose of 800 µg of FP per day) may cause systemic adverse effects, including progression of osteoporosis, changes in glucose metabolism and estrogen levels, hypertension, peptic ulcer, or immunosuppression. It should be noted that female older patients are particularly susceptible to progression to osteoporosis and bone fracture.

(2) Bronchodilators

SABAs and LABAs are the first choices of bronchodilators in older asthmatics, but their effectiveness is lower than that in younger patients. When older patients cannot breathe in the pMDI drugs, the use of a spacer or jet nebulizer should be considered. A tulobuterol patch is effective in terms of adherence and efficacy. The side-effects of these drugs should be carefully evaluated in older patients because adverse events, particularly cardiovascular events, including arrhythmia, angina, and tremor are increased in this group. Short-acting muscarinic antagonist or LAMAs are relatively useful in patients with ACO or in those who are less responsive to β₂-stimulants. A LAMA needs to be administered carefully in patients with anuresis (difficulty in urination) due to benign prostatic hypertrophy. Its use is prohibited in patients with angle-closure glaucoma.

(3) Combination agents comprising ICS and inhaled LABA (ICS/LABA)

The ICS/LABA combination is more effective than inhaling ICS and LABA individually.³² Four combinations can be used in Japan: FP/SM, BUD/FM, FP/FM, and FF/VI (Tables 12–14). The devices are DPI and pMDI for FP/SM, DPI for BUD/FM and FF/VI, and pMDI for FP/FM. The advantages of the combination are that the number of inhalation operations is reduced, compliance is improved, and LABA alone can be prevented. Since the bronchodilator effect of formoterol is immediate, the additional inhalation of the BUD/FM combination instead of SABA during exacerbations stabilizes the symptoms and reduces the frequency of exacerbations (SMART therapy). However, such treatments tend to be patient-driven, and therefore care must be taken to prevent reduced compliance and abuse of the drug. It is important to select patients for which SMART therapy is effective and educate them. Because the FF/VI combination is inhaled once a day, high compliance can be expected, and it is more effective than other ICS and ICS/LABA-based asthma treatments based on reports from clinical trials conducted in real-world settings.

(4) Leukotriene receptor antagonists

LTRAs are effective and safe for use in older patients.

(5) Theophylline

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

(6) LAMAs

Among LAMAs, only tiotropium bromide hydrate can be used for long-term management of asthma. Tiotropium is widely used in the treatment of COPD, and can be administered in two ways: Handy Heller and Soft Mist In Heller (Respimat®). For asthma, only the usage with a soft mist inhaler is approved. When LAMA is used for long-term management, ICS combination is essential. Tiotropium

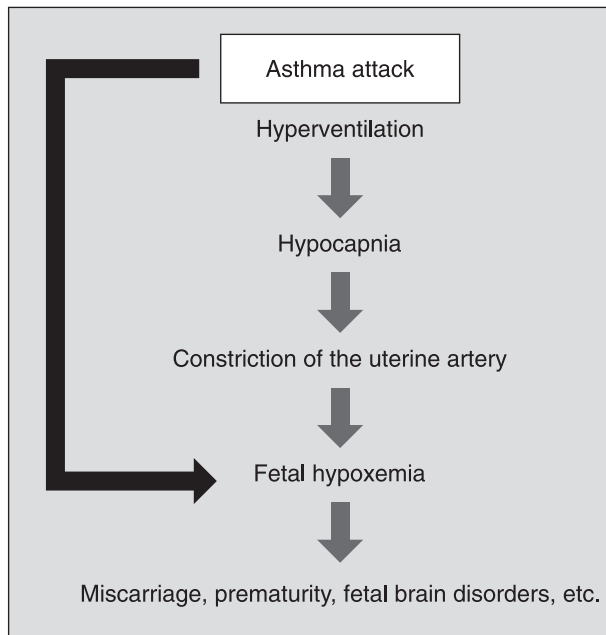


Fig. 8. Asthma exacerbations in pregnancy.

acts on the muscarinic M3 receptor in the airway smooth muscle, and it significantly improves respiratory function by inhalation once-daily. The addition of tiotropium in patients with asthma symptoms placed on low to moderate doses of ICS is comparable to LABA; even for patients with severe persistent asthma, it improves respiratory function and prevents asthma exacerbation. Dry mouth is the most common side-effect of LAMAs. Careful administration is required for patients with severe heart disease. LAMA is contraindicated in angle-closure glaucoma and benign prostatic hyperplasia with dysuria.

(7) Anti-allergic drugs

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

5.7. Asthma and pregnancy

5.7.1. Influence of bronchial asthma on pregnancy and birth

The prevalence of asthma tends to increase among women during adolescence and early adulthood. Asthma is the most common respiratory disease that complicates pregnancy¹⁰⁷ and respiratory function changes in non-asthmatic women with normal

Table 26

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 cromoglicate (DSCG)
4.	Inhaled anticholinergic [§]
Oral medicine	
1.	Oral corticosteroid [†]
2.	Leukotriene receptor antagonist
3.	Theophylline sustained-release preparation
4.	Oral β_2 agonist
5.	Antihistamine
Injections	
1.	Steroid [†]
2.	Aminophylline
3.	Adrenaline (0.1%) [#]
Others	
	Patch-type β_2 agonist: Tulobuterol ^{††}

[†] Safety of budesonide in humans has been demonstrated clearly.

[‡] There is less evidence of the safety of long-acting inhaled β_2 agonist (LABA) than that of short-acting inhaled β_2 agonist (SABA). However, these agents are almost comparable in their safety during pregnancy.

[§] There is no evidence of safety as a long-term management agent used during pregnancy. Safety as a reliever agent has been demonstrated.

[#] Prednisolone and methylprednisolone do not appreciably pass through the placenta.

^{||} Can be administered during pregnancy only when the advantages outweigh the disadvantages. Have few risks even if unknowingly administered during pregnancy.

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

^{††} Safe as an inhalant or oral medicine. More evidence is needed.

pregnancies. Among these changes, uterine enlargement elevates the diaphragm, reducing functional residual capacity; likewise, increased concentrations of serum progesterone result in increased tidal volumes that may lead to respiratory alkalosis. Consequently, pregnant women may experience a gradual increase in respiratory discomfort during pregnancy. Respiratory issues in pregnant women should be carefully evaluated to differentiate those associated with a normal pregnancy from those associated with underlying diseases.

The management of asthma in pregnant women has unique challenges (Fig. 8). Asthma exacerbations may result in fetal hypoxemia that can increase the risk of miscarriage, prematurity, and fetal central nervous system disorders.¹⁰⁸ A recent study reported that premature delivery, low birth weight, and fetal malformations are more common among pregnant women with asthma than

Table 25

Long-term management of pregnant women with asthma.

Severity	Symptoms	PEF or FEV ₁	Recommended medications
Mild intermittent	≤2 days/week or ≤2 nights/month	≥80%	No daily medications are necessary; SABA as needed
Mild persistent	3–6 days/week or ≥3 nights/month	≥80%	Low-dose ICS; LTRA, controlled-release theophylline, and/or DSCG as needed
Moderate persistent	Almost every day or ≥1 night/week	61%–79%	Low-dose ICS and LABA or moderate-dose ICS and LABA in combination with LTRA or controlled-release theophylline as needed
Severe persistent	Persistent attacks or frequent attacks during night	≤60%	High-dose ICS and LABA; oral steroids as needed (≤60 mg/day)

ICS, inhaled corticosteroid; SABA, short-acting inhaled β_2 -agonist; LABA, long-acting inhaled β_2 -agonist; DSCG, disodium cromoglicate; LTRA, leukotriene receptor antagonist; PEF, peak expiratory flow.

Table 27

Treatment for asthma exacerbations during pregnancy.

1. Monitor the pregnant patient and her fetus.
2. Administer a short-acting inhaled β_2 -agonist: 2–4 puffs every 20 min for 1 h via a pressurized metered dose inhaler (for salbutamol) or nebulizer.
3. Maintain oxygen saturation (SpO_2) of $\geq 95\%$.
4. Consider the management of fluid intake and intravenous infusion to maintain adequate cardiac output.
5. Use subcutaneous injection of 0.1% adrenaline (Bosmin®), which induces constriction of the uterine artery in case of anaphylaxis or other reactions.
6. Administer steroids intravenously, depending on the severity of the exacerbations. Succinate preparations should not be used in patients with a history of aspirin-exacerbated respiratory disease (or non-steroidal anti-inflammatory drug-sensitive asthma).
7. Consider endotracheal intubation and mechanical ventilation if the patient poorly responds to the treatment described above. Consider intubation if $\text{pH} < 7.35$, a carbon dioxide partial pressure (PCO_2) ≥ 28 –32 mmHg (the normal range for women with normal pregnancy), or an oxygen partial pressure (PO_2) < 70 mmHg.

women with normal respiratory function, although the study primarily included women with poorly controlled disease.¹⁰⁹ Careful management of asthma, regardless of severity, can reduce the risk of poor outcomes in the mother and the fetus.¹¹⁰

5.7.2. Treatment during pregnancy

Pregnant women are generally quite concerned about the impact of pharmacotherapy on fetal development and delivery, and they prefer to avoid drugs and medications during pregnancy. Unfortunately, pregnancy may present additional risks for those with asthma; even women with well-controlled asthma have increased vulnerability to exacerbations. Given these observations, women should be advised to continue treatment, as this is beneficial for both the mother and the fetus.¹¹¹ However, it is critical to recognize that complications, including miscarriage, premature delivery, premature rupture of membranes, proteinuria, and eclampsia, are reported more frequently in asthmatic women than in women without respiratory dysfunction. Likewise, abstaining from medications cannot protect against congenital anomalies, which are observed even in 2%–4% of pregnancies in women who received no medications. Clear explanations are critical to avoid creating an unnecessary sense of distrust among patients. In addition to pharmacological treatment, practical measures to manage the environment should be implemented; these include avoidance of known respiratory allergens and irritants, avoidance of cigarette smoke, and sufficient mental and physical rest. These strategies will aid in preventing asthma attacks and maintaining healthy respiratory function.

The findings presented in Table 25 focus on long-term management of pregnant women with asthma,¹¹² and they include frequently-used medications with their appropriate safety profiles (Table 26). ICSs are recommended as first-line treatment. If an ICS monotherapy is not sufficient to control symptoms, LABAs, controlled-release theophylline preparations, and/or β_2 -agonist patches can be administered; LTRAs can be considered if the benefits exceed the risk. Treatment with biologicals, including monoclonal anti-IgE¹¹³ or allergen-specific immunotherapy, can be continued if initiated before pregnancy, although the initiation of these modalities during pregnancy should be avoided if at all possible. There is currently only limited data available on the administration of anti-interleukin-5 (IL-5)¹¹⁴ or anti-IL-5 receptor- α antibodies, and as such, they should be avoided. Table 27 includes recommendations for the treatment of asthma exacerbations in pregnant women managed with long-term maintenance therapy.¹¹⁵

5.8. Comorbidity

5.8.1. ACO

COPD is the most important disease in the differential diagnosis and identification of comorbidities in older patients with asthma. In COPD, neutrophilic inflammation is observed in the peripheral airways, and airway obstruction results from a combination of peripheral airway obstruction and pulmonary emphysema. Thus, although the diseases differ in their pathophysiological characteristics, the differential diagnosis of asthma vs. COPD based on clinical symptoms is often difficult in older patients. Interestingly, recent reports indicate that 18.4%–31.7% of asthma patients aged 65 years or more have both diseases; a previous epidemiological study reported that more than half of older patients with COPD could be diagnosed with ACO.¹¹⁶ Patients with ACO have relatively poor prognoses as they experience frequent asthma exacerbations, a rapid decline in pulmonary function, and a lower QoL. A means to differentiate among the diagnoses of asthma, COPD, and ACO was proposed in a joint statement from the Global Initiative for Asthma and the Global Initiative for Chronic Obstructive Lung Disease; the statement also included recommendations for treatment with ICS, LABAs, and, occasionally, LAMAs.

5.8.2. Allergic rhinitis

Allergic rhinitis is common among the Japanese people, with ~40% of the population having this diagnosis. The prevalence of seasonal allergic rhinitis has also increased in recent years. Allergic rhinitis is characterized by three symptoms: episodic and repeated sneezing, watery nasal discharge, and nasal congestion. Asthma is commonly associated with allergic rhinitis; the “one airway, one disease” concept addresses the close relationships frequently observed among disorders of the upper and lower respiratory tracts. Notably, approximately 80% of asthmatic patients also experience allergic rhinitis, and 10%–20% of patients with allergic rhinitis have also been diagnosed with bronchial asthma. As an example, patients with seasonal allergic rhinitis experience asthma exacerbations during pollen allergy seasons, although pollen grains are relatively large and do not ordinarily reach the lower airways.¹¹⁷ Likewise, the exposure to house dust mites is associated with both perennial allergic rhinitis and likewise induces symptoms characteristic of asthma. Nasal corticosteroids used to treat allergic rhinitis may also have a positive impact on asthma symptoms, and LTRAs can promote improvement in patients with asthma as well as those with allergic rhinitis. Hyposensitization therapy has been reported to be effective for allergic rhinitis, and it also promotes the control of asthma; very low rates of asthma exacerbations have been observed (1/1000–1/2000 injections). Nonetheless, this modality should be avoided in patients with severe asthma.¹¹⁸ Sublingual allergen immunotherapy has recently received considerable attention because of its marked efficacy and reduced invasiveness.

5.8.3. Chronic sinusitis

Chronic sinusitis is a frequent comorbidity in patients with severe asthma. Nasal polyps are also often identified in patients with severe asthma. Furthermore, more than half of patients diagnosed with asthma have abnormal findings in the paranasal sinuses on radiography; the asthma exacerbation rate correlates directly with the sinusitis score as assessed on computed tomography (CT) scans. Chronic sinusitis has recently been identified as a factor promoting resistance to asthma therapy. Macrolides are effective for neutrophilic sinusitis, and reducing post-nasal drip often improves asthma symptoms as well.

5.8.4. Eosinophilic sinusitis

Eosinophilic sinusitis is characterized by dramatic eosinophil infiltration of the nasal mucosa and polyps. Eosinophilic sinusitis is

also associated with severe asthma, particularly in patients with AERD. The diagnosis is based on symptoms and CT findings, and treatment is largely conservative as patients respond to oral steroids. Although surgery can be effective for eosinophilic sinusitis, approximately half of the patients who undergo surgical intervention experience relapses.

5.8.5. Eosinophilic otitis media

Eosinophilic sinusitis may progress into eosinophilic otitis media. Both diseases result in diminished QoL due to the impairment of smell and hearing. Local treatment with steroids promotes the resolution of this condition.

5.8.6. EGPA and AGA

(1) Definition

EGPA is an important comorbidity of asthma, and it may be life-threatening. EGPA is characterized by a history of asthma, increased eosinophils in the blood and tissues, and multiple organ mononeuropathy and polyangiitis. The pathogenesis of EGPA includes systemic angiitis secondary to antineutrophil cytoplasmic antibodies (ANCA) as well as granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis. Microvessels within the lungs and kidneys are often impaired.

(2) Epidemiology

EGPA is generally diagnosed in individuals older than 45 years. In Japan, the prevalence of this disease in the asthmatic population is approximately 0.2% among males and 0.5% among females.

(3) Typical disease progression

The progression of EGPA can be divided into three clinical stages. In the first stage, patients develop eosinophilic sinusitis with asthma and nasal polyps. This is followed by an increase in peripheral blood eosinophil counts and loss of asthma control; the second stage of this disease may also include eosinophilic pneumonia. Systemic polyangiitis develops in the third stage of the disease. Signs and symptoms of EGPA include fever, muscle pain, and weight loss; multiple mononeuropathies and peripheral eosinophilia are observed in more than 90% of EGPA patients. Furthermore, two-thirds of the patients have increased serum IgE concentrations, and they become rheumatoid factor positive; half of the patients with this diagnosis develop skin symptoms, cardiac disturbances, and ischemic bowel disease. The ratio of anti-myeloperoxidase to total ANCA is typically 0.3–0.4 in these patients.

(4) Characteristic manifestations in asthma with EGPA

Asthma that precedes EGPA usually develops during adulthood, and most of the patients with EGPA have severe disease with profound eosinophilia; approximately 70%–80% of the patients with EGPA present with eosinophilic sinusitis, and, occasionally, eosinophilic otitis media; peripheral blood eosinophilia and eosinophils in the sputum may predict relapse.¹¹⁹ Fewer than half of the patients are atopic prior to the onset of EGPA, and they typically develop fixed airflow limitation after remission.

(5) Diagnosis and treatment

In Japan, EGPA is diagnosed based on criteria set by the American College of Rheumatology and the Ministry of Health, Labour, and Welfare of Japan. Physicians should be aware of the clinical course of patients with severe asthma, particularly those who develop atopic eosinophilia, eosinophilic pneumonia, or eosinophilic sinusitis. It is also critical to recognize that a diagnosis of EGPA cannot be excluded based on a single negative perinuclear ANCA test. Early diagnosis and treatment, typically with systemic steroids, are important so that polyangiitis does not progress rapidly. In patients with severe disease and/or those with complicated cardiac and/or digestive disorders, cyclophosphamide can be

added to the therapeutic regimen. Intravenous administration of high-dose immunoglobulin should be considered for treatment-resistant patients who develop EGPA-related neural or cardiac dysfunction.

5.8.7. ABPA

(1) Definition

ABPA is an ABPM that develops in asthmatic patients typically in response to inhalation of microorganisms from the genus *Aspergillus*. The fungi *Aspergillus niger*, *A. oryzae*, *Penicillium*, *Cladosporium*, and *Candida* species can also induce ABPM in susceptible individuals. Antigen-specific IgE and IgG are detected in sensitized asthmatic patients and central bronchiectasis and thickening of the airway walls are observed at a relatively early stage of the disease. Type I and type III allergic reactions have been associated with these pathological changes, resulting in tissue destruction in the airways.

(2) Pathogenesis

ABPA results in injury to the airway epithelial cells in asthmatic patients. Genetic diversity, notably HLA-DRB1 alleles, have been associated with a predisposition to developing ABPA, as pronounced Th2 responses to *Aspergillus* antigens have been identified in patients with this genetic background.¹²⁰ After exposure to *Aspergillus*, the fungus generates a persistent infection in the walls of the lower airway. The strong Th2 response to *Aspergillus* contributes to disease pathogenesis and tissue destruction. Furthermore, *Aspergillus* secretes several proteases that can also contribute to airway destruction. These features ultimately promote mucoid impaction followed by atelectasis and further infiltration with immune cells.

(3) Diagnosis

Early diagnosis is critical for effective intervention in this disease; the morbidities associated with chronic airway infection, airway wall destruction, and mortality associated with respiratory failure contribute to the overall prognosis. There are seven diagnostic criteria for ABPA which include: (i) pre-existing asthma, (ii) peripheral blood eosinophilia, (iii) an immediate hypersensitivity response to *Aspergillus* antigens, (iv) precipitating antibodies targeting *Aspergillus* antigens, (v) increased serum IgE concentrations, (vi) a history of lung infiltration, and (vii) central bronchiectasis. A confirmed diagnosis of ABPA includes all seven criteria, although the fulfillment of six of the seven criteria may be considered as nearly, or almost confirmed.¹²¹ The diagnostic parameters introduced by Greenberger *et al.* have been modified to address early and/or atypical cases of ABPA that may present with signs and symptoms that are not fully consistent with all the aforementioned criteria.

(4) Morbidity

The morbidity associated with ABPA has been reported to be 1%–2% in patients with asthma. In those with severe asthma, the morbidity has been reported to be higher.

(5) Treatment

Systemic steroids (prednisolone, at > 0.5 mg/kg for several weeks) should be administered to asthma patients with ABPA to limit immune cell infiltration of the lungs and prevent irreversible airway destruction. Some individuals respond to oral steroids administered at low doses. The concomitant use of itraconazole may prevent relapse and lung infiltration and has been associated with promoting a reduction in serum IgE concentrations and sputum eosinophil counts.

5.8.8. Heart failure

Acute left ventricular failure may present as “cardiac asthma.” The signs and symptoms of this condition are similar to those

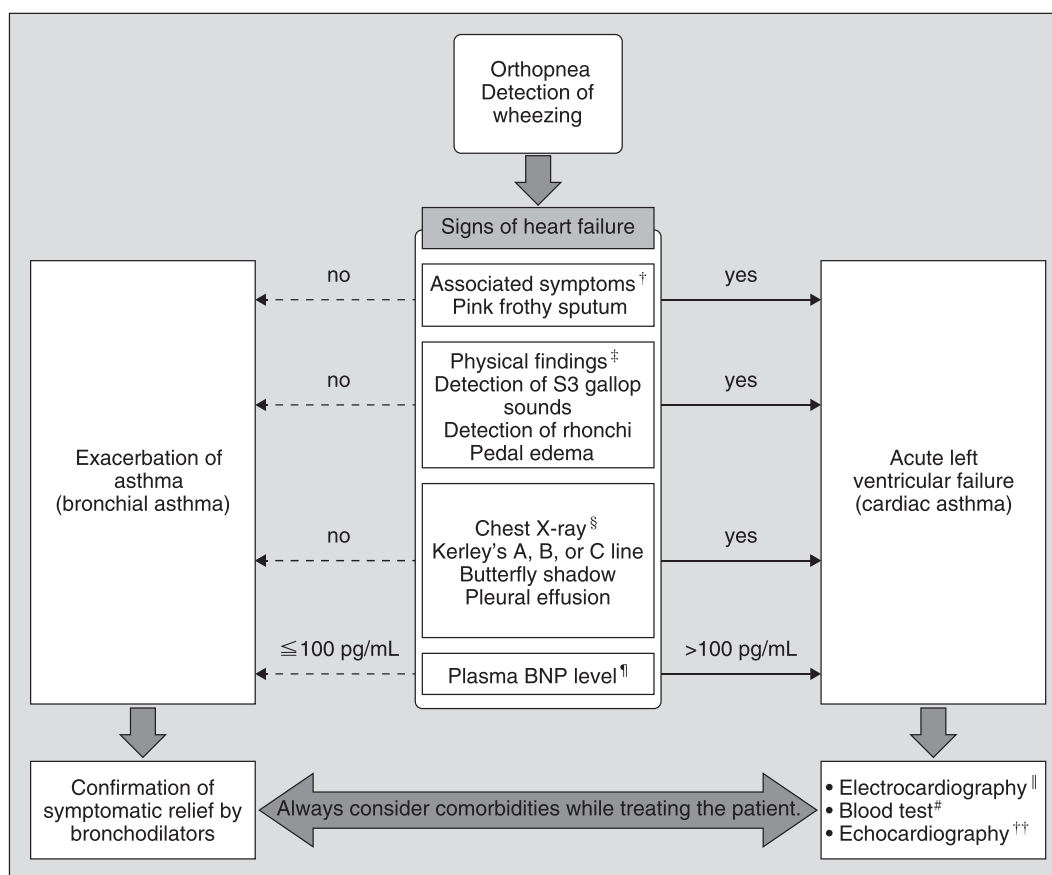


Fig. 9. Differential diagnosis of asthma exacerbation and acute left ventricular failure. Administer oxygen while monitoring vital signs. Treat acute exacerbation of asthma (attack) ^{#, ††} and heart failure according to the respective guidelines. ^{122,125} Even if patients have no signs or symptoms of heart failure, the presence of concomitant heart failure cannot completely be ruled out. [†] Although the prevalence of frothy sputum is unknown, patients who exhibit it are likely to have acute heart failure. [‡] The prevalence of S3 gallop sounds, rhonchi, and pedal edema is 40%, 78%, and 65%, respectively. [§] Cardiomegaly is difficult to evaluate with a portable X-ray device. However, Kerley's lines and butterfly shadow are detected when pulmonary venous pressure is 20–30 mmHg and ≥ 30 mmHg, respectively. [¶] Besides brain natriuretic peptide (BNP), a serum N-terminal pro-B-type natriuretic peptide (NT-pro BNP) level of >400 pg/ml is suggestive of heart failure. [‖] It is useful for searching the causes of heart failure, such as myocardial ischemia and arrhythmia. [#] Measurement of cardiac enzymes (e.g., creatine kinase and troponin T) is useful in case of ischemic heart disease. ^{††} Echocardiography, including Doppler echocardiography, is useful for searching the causes of heart failure.

associated with an acute asthma exacerbation, which include orthopnea, coughing, sputum expectoration, and wheezing. These findings result from elevated pulmonary venous pressure characteristic of heart failure that results in pulmonary edema, stenosis, mucus hypersecretion, and reactive constriction of the airway. ^{122–124} It may be difficult to differentiate between an asthma exacerbation and symptoms secondary to heart failure in an emergency setting, and the two conditions can coexist in a single patient (Fig. 9). ^{122–125} A definitive diagnosis can be reached once the patient has been stabilized. Toward this end, it is critical to recognize that patients with chronic heart failure often have a decreased FEV₁ and high levels of FeNO and/or airway hyperreactivity may be detected in this patient cohort. ¹²⁶

There are important challenges involved in treating patients with coexisting conditions. While heart failures should certainly be addressed and treated as per the current published guidelines, ^{122–125} the use of β -blockers poses a significant problem in the treatment of patients with coexisting asthma. If the benefits of β -blockers are determined to exceed the risk, the selection of a cardio-selective agent may be preferable. ^{127,128} Non-selective β -blockers are not safe for use even in those patients with adequately controlled asthma. ¹²⁹ Anticholinergics can be used to improve dyspnea and respiratory function in patients with heart failure. ¹³⁰

Aminophylline and controlled-release theophylline preparations have been approved for insurance reimbursement for the treatment of cardiac asthma and congestive heart failure, and they are effective at suppressing myocardial stress and reducing pulmonary edema. ¹³¹ Systemic steroids and β_2 -agonists may cause or exacerbate heart failure. Caution should be exercised so that theophylline toxicity is avoided in patients with heart failure as clearance is decreased in this condition.

5.8.9. Gastroesophageal reflux disease (GERD)

Although there are differences in patient populations and survey methods, the prevalence of GERD among the Japanese is reported to be approximately 8%–14%; a significant increase in this diagnosis has been observed in recent years. ^{132,133} The widespread use of agents that eradicate *Helicobacter pylori* is reported to promote the increase in disease prevalence. ¹³⁴ The results of a cross-sectional study indicate that the prevalence of asthma is high in patients with symptoms of GERD; conversely, the prevalence of GERD is high among asthma patients. ¹³⁵ The mechanisms linking these two disorders to one another are unknown. Asthma is also more difficult to control in patients with GERD than in those without GERD. ¹³⁶ While acid-suppressive therapy may relieve asthmatic symptoms and improve respiratory function, ¹³⁷ this

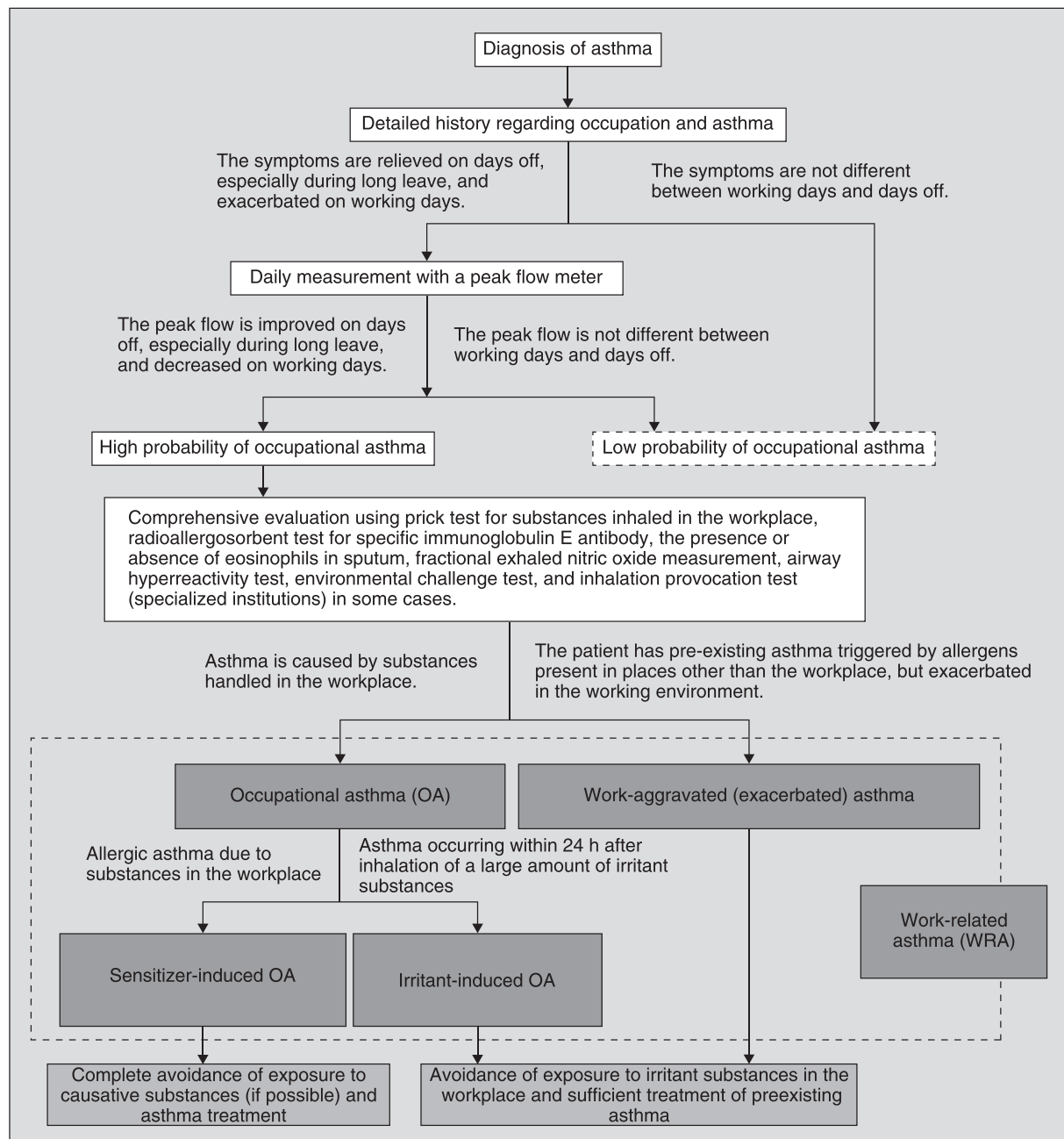


Fig. 10. Diagnostic algorithm for occupational asthma.

mode of therapy is useful only in patients diagnosed with GERD.^{138,139} Clearly, a definitive diagnosis of GERD is critical for determining optimal therapeutic strategies.¹³²

5.9. Occupational asthma

(1) Definition

Occupational asthma is defined as asthma induced by exposure to a specific occupation-related substance at work. Pre-existing asthma exacerbated by work-related factors is termed as “work-aggravated asthma.” Both conditions are within the diagnosis of work-related asthma.

Occupational asthma can be subdivided into “sensitizer-induced occupational asthma,” which is asthma induced by antigens and sensitizing substances in the workplace and “irritant-induced

occupational asthma,” which is asthma induced by irritants (Fig. 10).^{140,141} Reactive airways dysfunction syndrome is a condition in which asthmatic symptoms occur within a few hours after the inhalation of high concentrations of irritant substances and persist for a few months; it is a subcategory of irritant-induced occupational asthma.¹⁴⁰

(2) Prevalence

Patients with occupational asthma account for approximately 15% of adult asthma patients.¹⁴² Occupations associated with a high prevalence of occupational asthma include coating manufacturing (e.g., isocyanates from paints and varnishes), bread and noodle manufacturing, nursing, jobs that include handling of chemical substances, care of animals or plants, welding, and/or food and wood processing. Although the major sensitizing agents were

formerly high-molecular-weight substances derived from animals and plants, low-molecular-weight substances have been identified in an increasing number of recent cases.¹⁴³ The risk factors in these settings include frequent exposure, high concentrations of causative substances, atopic tendencies, and smoking.

(3) Diagnosis

A thorough history in person or by questionnaire is essential for establishing the diagnosis of occupational asthma. Importantly, occupational asthma is often preceded by allergic rhinitis and conjunctivitis in the work setting. For the definitive diagnosis, PEF measurements are quite useful; these should be taken 4 times per day on consecutive days for 4 weeks, including work and non-work days.¹⁴⁴ Similarly, tests for airway hyperreactivity are performed on the last working day and the first day after a leave of absence of 10–14 days. Occupational asthma is diagnosed if any of these measures document an improvement of 20% or more after periods of leave; this can also be established comprehensively with measurements of eosinophils in induced sputum and FeNO tests, among others.^{145,146} If sensitizer-induced occupational asthma is suspected, a prick test and tests to evaluate antigen-specific IgE should be attempted (Fig. 10).¹⁴⁰ These tests may not be fully diagnostic as (except in the cases of isocyanate and a few others) specific IgE responses to low-molecular-weight antigens are not always detectable. An environmental challenge test and/or antigen inhalation provocation (at specialized centers) may be considered.

(4) Treatment and management

Patients diagnosed with sensitizer-induced occupational asthma should be counseled to avoid all causative antigens and substances (Fig. 10); therapeutic ICSs may be introduced at the early stages of this disorder. For those with severe asthma, anti-IgE (omalizumab) may also be effective. If an individual is unable to avoid exposure to causative agents, allergen immunotherapy (hyposensitization), if available, may be effective in patients who test positive for immediate cutaneous reactions to antigens or increased concentrations of antigen-specific IgE.¹⁴⁰ For all forms of asthma that are aggravated by the work environment, exposure to causative substances should be reduced through environmental interventions and/or providing workers with protective devices. Adequate pharmacological treatment of asthma is also critical (Fig. 10). Even if complete antigen or substance avoidance can be achieved, non-specific airway hyperreactivity may remain and symptoms secondary to respiratory dysfunction may persist for several years thereafter. The remission of occupational asthma can be achieved in only one-third of patients.¹⁴⁷ Respiratory function at diagnosis, duration of exposure to causative substances, and age of diagnosis are all prognostic factors.¹⁴⁸ Early diagnosis and treatment may limit the extent and duration of persistent respiratory dysfunction.

(5) Prevention

The complete elimination of inhaled toxins and allergens should be a priority in the work environment; efforts can be made to reduce exposure by replacing causative substances with neutral alternatives. Other interventions can include the installation of complete sealing around working equipment, improvements to the ventilation system, and the relocation of workers.¹⁴⁹ Exposure to causative agents may also be reduced by proper use of respiratory protective devices; these should be replaced frequently for maximum effectiveness. Screening and surveillance for occupational asthma can be performed by questionnaires, followed by respiratory function tests, prick tests, and measurements of antigen-specific IgE. Consultation with environmental specialists is recommended in the case of any uncertainty regarding the

identification of causative substances, improvements to be made in the workplace, and the initiation of pharmacological treatments.

5.10. Surgery

Perioperative bronchoconstriction is observed in 1.7% of asthmatic patients who undergo surgery.¹⁵⁰ This condition may be life-threatening; as such, caution should be exercised in the preoperative consideration of patients with severe asthma; this applies as well to those with poorly controlled symptoms, recent asthma exacerbations, and irreversible airflow obstruction.¹⁵¹ Patients with low FEV₁ are at increased risk of postoperative respiratory complications, and they should be managed similar to patients with COPD.¹⁵²

The incidence of respiratory complications is influenced by many factors, including the severity of asthma at the time of surgery, the type of surgery (e.g., surgeries of the chest and upper abdomen carry a higher risk), and the method of anesthesia (e.g., intubation and sympathetic nerve block carry a higher risk). The severity of asthma should be evaluated prior to surgery by clinical history, clinical symptoms, physical findings, and respiratory function tests. This information will guide the selection of anesthetic agents and methodologies. Smoking cessation is necessary. Second-hand smoke is an important risk factor, especially for pediatric patients¹⁵³; as such, all individuals in the household should be questioned regarding smoking and advised accordingly.

5.10.1. Management before surgery

(1) Evaluation of asthma severity

During a preoperative examination, the severity of asthma and the status of asthma control should be evaluated, and this should include clinical history, a list of symptoms, physical examination, pulmonary function, PEF values, and an arterial blood gas analysis. The nature and extent of previous and current medications, surgical history, and history of latex allergy should also be determined prior to surgery. Furthermore, patients should be questioned regarding aspirin and NSAID use and any association with asthma symptoms (i.e., AERD); this information will guide in the appropriate selection of postoperative analgesia.

(2) Timing of surgery

Surgery should be performed during a long period without exacerbations; both FEV₁ and PEF should be at or near the individual predicted or personal best. In pediatric patients with a history of asthma, surgery should be postponed for 4–6 weeks after any upper respiratory tract infection.¹⁵³

(3) Pharmacological treatment before surgery

If asthma is adequately controlled by conventional treatments, these should be continued until immediately prior to surgery. If there is sufficient time, ICSs can be initiated prior to surgery, at a prednisolone-equivalent dose of 0.5 mg/kg/day for ≤ 1 week.¹¹² In cases of emergency surgery, steroids should be administered intravenously both before and during surgery. For patients managed on systemic steroids (including routine use of oral steroids) within 6 months before surgery for 2 weeks or longer, they should be administered intravenously before and during surgery to avoid the risk of adrenal insufficiency.¹⁵⁴ Hydrocortisone (100 mg) may be administered before and every 8 h during surgery; the dose should be reduced within 24 h after surgery.¹¹² In patients who are taking high-dose ICSs regularly and are unable to inhale ICSs during the perioperative period, intravenous steroids should be administered; intravenous infusions should be tapered and discontinued once the patient can resume inhalation therapy.

5.10.2. Anesthesia

(1) Local and spinal anesthesia

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

(2) General anesthesia

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

(3) Anesthetic agents

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

5.10.3. Treatment of asthma attack during surgery

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

5.10.4. Postoperative management

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

5.11. Cough-variant asthma

Cough-variant asthma (CVA) is a type of asthma that is characterized only by chronic dry cough without wheezing and an attack of dyspnea. Bronchodilators are effective in this group. CVA is the major cause of chronic cough continuing for more than 8 weeks. The features of CVA are the following: (i) increased cough reflex against the constriction of the airway smooth muscle; (ii) cough sensitivity that is within the normal range; (iii) frequent atopy; (iv) eosinophils present in the sputum, bronchial mucosa, and bronchoalveolar lavage fluid; (v) increased FeNO; (vi) inhaled or oral corticosteroids are effective. CVA is more severe at bedtime, during the night, and early morning, and it is induced by cold and warm air, passive smoking, conversation, exercise, alcohol, mental stress, and other factors.

5.12. Immunization

Allergen-specific immunotherapy includes subcutaneous and sublingual immunotherapy, but the only formulation that has insurance coverage for asthma is the subcutaneous mite antigen formulation. Allergen-specific immunotherapy is indicated for patients with an apparent allergen who want to reduce the dose of their current medication or have adverse effects from treatment with the usual medicines. The mite subcutaneous immunotherapy is indicated for patients aged 5 years or older, ranging in severity from mild to severe (but not requiring systemic steroids) with % FEV1 of 70% or more.

5.13. Aspects of psychosomatic medicine

Psychosomatic factors have long been reported to be associated with asthma, since the time of Hippocrates. Because asthma control

is strongly affected by psychosomatic factors, psychosomatic medicine may become more important in the management of asthma.

5.13.1. Mind-body connection

(1) Influence of psychosomatic social factors on asthma

Social stress affects the development, exacerbation, and management of asthma. Associations between panic disorder and emergency room visits have been reported.¹⁵⁵

(2) Influence of asthma on psychosomatic conditions

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

5.13.2. Diagnosis of asthma in psychosomatic medicine

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

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

(2) Social adaptation problems associated with asthma

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

(3) Non-adherence to asthma treatment

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

5.13.3. Psychophysiological treatment

In this group of patients, counseling is the principal method for psychophysiological treatment. If asthmatic patients with anxiety or mood disorders often suffer from exacerbated asthma, anti-anxiety or antidepressant agents may be effective in the management of attacks, in addition to the regular asthma drugs. Besides the regular treatment of asthma, pharmacotherapy, autogenic training, cognitive behavioral therapy, family therapy, and fasting therapy have been attempted. Diary writing alone has been reported to improve the symptoms of asthma in psychosomatic patients.¹⁵⁶

5.14. Asthma treatment in disaster

Many natural disasters occur frequently in Japan such as floods caused by heavy rains or typhoons, volcanic eruptions, and earthquakes. Major earthquakes include the Great Hanshin-Awaji Earthquake on January 17, 1995 (M7.3), the Great East Japan Earthquake on March 11, 2011 (M9.0), and the Kumamoto Earthquake on April 14, 2016 (M6.5, 7.3). Chronic diseases such as asthma, diabetes, and ischemic heart disease may worsen in such natural disasters. Causes of exacerbation of asthma during natural disasters include the disruption of the supply of anti-asthmatic drugs to patients, the spread of infectious diseases, cold exposure, air pollution, and mental stress. Since there are few specialists in allergies and respiratory diseases among emergency medical staff who rush to the site in the early stage of the earthquake, the Japanese Society of Allergology has developed a manual for allergic

diseases for emergency medical staff in cooperation with the Japan Allergy Foundation.

5.15. Asthma treatment for severely handicapped people

It is described on the website of the Japanese Society of Pediatric Allergy and Clinical Immunology (https://www.jspaci.jp/assets/documents/jpgl2017_00_web.pdf).

Conflict of interest

Honoraria: YN, GlaxoSmithKline; JT, Boehringer Ingelheim, AstraZeneca, Astellas, MSD; HN, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi; MY, AstraZeneca; TH, Nippon Boehringer Ingelheim, AstraZeneca, Taiho Pharma; SH, GlaxoSmithKline, AstraZeneca, Novartis, Astellas, Kyorin Pharmaceutical, Sanofi; MI, AstraZeneca, Nippon Boehringer Ingelheim; TI, Kyorin Pharmaceutical; MN, AstraZeneca, GlaxoSmithKline, Sanofi, Novartis, Kyorin Pharmaceutical, Torii Pharmaceutical; AY, AstraZeneca, Novartis, GlaxoSmithKline, Sanofi, Boehringer Ingelheim; YT, Kyorin Pharmaceutical. **Research funding:** TI, Kyorin Pharmaceutical, Meiji Seika Pharma, Boehringer Ingelheim, Teijin Pharma, Daiichi-Sankyo, Astellas, Pearl Therapeutics; AY, Astellas; YT, Kyorin Pharmaceutical, Meiji Seika Pharma, Boehringer Ingelheim, Teijin Pharma, Daiichi-Sankyo, Astellas, Pearl Therapeutics. **Employment:** JT, GlaxoSmithKline. **Stock ownership:** JT, Novartis, AbbVie. RK has no conflict of interest.

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