

Japanese Guideline for Childhood Asthma

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ABSTRACT

The Japanese Guideline for the Diagnosis and Treatment of Allergic Diseases 2010 (JAGL 2010) describes childhood asthma based on the Japanese Pediatric Guideline for the Treatment and Management of Asthma 2008 (JPGL 2008) published by the Japanese Society of Pediatric Allergy and Clinical Immunology. JAGL 2010 provides information on diagnosis by age groups from infancy to puberty, treatment for acute exacerbations, long-term management by medication, daily life guidance, and patient education to allow physicians, not specialized in childhood asthma, to refer to this guideline for routine medical treatment.

JAGL differs from the Global Initiative for Asthma Guideline (GINA) in that the former emphasizes long-term management of childhood asthma based on asthma severity and early diagnosis and intervention at <2 years and 2-5 years of age. However, a management method, including step-up or step-down of long-term management agents based on the status of asthma symptoms, is easy to understand and thus JAGL is suitable for routine medical treatment. JAGL also introduced treatment and management using a control test for children, recommending treatment and management aimed at complete control through avoiding exacerbation factors and appropriate use of antiinflammatory agents.

KEY WORDS

acute attack, childhood asthma, guideline, long-term management, prevention

1. DEFINITION AND PATHOPHYSIOLOGY OF CHILDHOOD ASTHMA

Childhood asthma causes repeated dyspnea accompanied by paroxysmal whistling/wheezing. The dyspnea is spontaneously or therapeutically remitted or cured and rarely lethal. Like adult asthma, childhood asthma is characterized by chronic airway inflammation^{1,2} and airway remodeling.³⁻⁷

Asthma is chronic airway inflammation caused by the activation of eosinophils, mast cells, lymphocytes, etc., and airway mucosal damage. The view that asthma is a condition of chronic inflammation has important implications for asthma treatment and management, being fundamental to understanding the need for antiinflammatory agents for basic treatment of persistent asthma. Remodeling, which may influence the prognosis of asthma, is unknown in many aspects, such as causes, onset time, and effects of antiinflammatory treatment.

Airway hyperresponsiveness, which is characteristic of asthma, is promoted by airway epithelial damage caused by airway inflammation. It can be assessed based on reactions to inhaled histamine, acetylcholine, etc. Exercise induced asthma is also considered a phenomenon associated with airway hyperresponsiveness.

2. DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF CHILDHOOD ASTHMA

The typical symptom of asthma attack is dyspnea accompanied by whistling/wheezing. Expiratory dyspnea occurs mainly during an asthma attack. However, as symptoms progress, inspiratory dyspnea may co-exist. If such symptoms are repeated, it is relatively easy to diagnose symptomatic asthma. However, some patients present with misleading symptoms. Table 1 summarizes the physiological and immunological examinations and allergy tests, which may aid in increasing the accuracy of diagnosis.

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Table 1 Reference criteria for asthma diagnosis

1. Respiratory functions: spirogram, flow volume curve, peak expiratory flow (PEF) rate, and reactivity and reversibility for β_2 stimulants
2. Airway hyperresponsiveness test: acetylcholine, methacholine, and histamine thresholds and exercise stress test
3. Data indicating airway inflammation: eosinophils in rhinorrhea and sputum, mast cells (basophils), and fraction of exhaled nitric oxide (FeNO)
4. IgE: total serum IgE level, specific IgE antibody, immediate skin response, and antigen inhalation test
5. Family and past histories of allergic diseases

Table 2 Findings for infantile asthma diagnosis

- At least one of parents is diagnosed with bronchial asthma by a physician (including past history).
- Specific IgE antibody for inhalation antigen is detected in at least one of parents.
- Diseased child is diagnosed with atopic dermatitis by a physician (including past history).
- Specific IgE antibody for inhalation antigen is detected in diseased child.
- High serum IgE level in diseased child or his/her family (serum IgE level should be determined by considering age).
- Eosinophils and creola bodies found in sputum (examine nasal discharge eosinophilia and peripheral blood eosinophilia).
- Expiratory wheezing occurs when there is no airway infection.
- Expiratory wheezing and labored respiration or oxygen saturation are improved after β_2 stimulant inhalation.

2.1. DIAGNOSIS OF INFANTILE ASTHMA

In this textbook, infantile asthma is defined as asthma affecting infants aged <2 years. It is difficult to define the criteria of infantile asthma. However, for early intervention, a diagnosis of infantile asthma can be made if there are 3 or more episodes of marked expiratory wheezing, regardless of the presence of respiratory tract infection. These criteria may include wheezing caused by viral infection, etc. Table 2 lists findings for infantile asthma for more accurate diagnosis.

2.2. DIFFERENTIAL DIAGNOSIS

Table 3 shows differential diagnosis of wheezing in children. If wheezing occurs first, differential diagnosis should be made for children with wheezing symptoms, particularly with acute wheezing. In infants, even the accumulation of secretion in the lower respiratory tract, resulting from bronchitis, pneumonia, etc., may cause repeated wheezing, thus requiring a differential diagnosis. Recurrent wheezing is easily diagnosed in children with underlying diseases, such as history of respiratory disorder and congenital heart disease during infancy. However, caution should be exercised for airway stenosis caused by a vascular ring, etc., and wheezing caused by gastroesophageal reflux disease.

2.3. COUGH VARIANT ASTHMA AND TYPICAL ASTHMA

Cough variant asthma (CVA)⁸⁻¹⁰ differs from typical asthma in that the former presents with prolonged cough and exacerbation of airway hyperresponsive-

ness, but lacks wheezing. Inhaled β_2 stimulants are effective for cough in CVA. CVA presents with airway inflammation; however, CVA is milder than asthma and has a higher threshold for wheezing than for airway constriction and a lower rate of airway constriction to stimuli. The underlying mechanism of prolonged cough is unknown. Reportedly, half of patients with CVA develop asthma during the course.

3. EPIDEMIOLOGY OF CHILDHOOD ASTHMA

3.1. PREVALENCE

Three nationwide surveys have been conducted in Japan, i.e., American Thoracic Society Division of Lung Diseases (ATS-DLD),^{11,12} International Study of Asthma and Allergies in Childhood (ISAAC),^{13,14} and a school health survey. The prevalence of asthma is characterized by (i) being more common among juveniles, particularly male children, more particularly male infants; (ii) varying 2-fold or more among regions; and (iii) having increased 2-fold in Japan in the past 20 years.

3.2. COMPLICATIONS (Table 4)

Allergic rhinitis, allergic conjunctivitis, and atopic dermatitis are common as coexisting allergic diseases caused by the same mechanism as asthma. Of note, the complication rate of allergic rhinitis is $\geq 50\%$.

3.3. PROGNOSIS

The remission rate is lower in cases that are more serious. Remission is defined as an asymptomatic status

Table 3 Differential diagnosis of wheezing in children

	Acute wheezing	Recurrent wheezing
Infants (<2 years old)	Acute bronchiolitis Bronchitis and pneumonia Anaphylaxis caused by food allergy, etc. Croup Foreign body in airway	Infantile asthma Laryngomalacia and tracheomalacia Chronic lung disease (after respiratory disorder during the newborn period) Airway stenosis caused by congenital disorder (vascular ring, etc.) Gastroesophageal reflux disease Aspiration Bronchiolitis obliterans Heart failure
Infants (2-5 years old)	Foreign body in airway Anaphylaxis caused by food allergy, etc. Croup Airway compressed by tumor (mediastinal tumor, etc.)	Asthma Chronic lung disease (after respiratory disorder during the newborn period) Bronchiectasis Gastroesophageal reflux disease Bronchiolitis obliterans Congenital immunodeficiency disease (recurrent respiratory tract infection)
School age or older	Bronchitis Pneumonia Pulmonary tuberculosis Pulmonary embolism and pulmonary edema Airway compressed by tumor (mediastinal tumor, etc.) Foreign body in airway	Asthma Vocal cord dysfunction Psychogenic cough Rhinitis and sinusitis Hypersensitivity pneumonitis Allergic broncho pulmonary aspergillosis Sarcoidosis

Table 4 Frequency of allergy complications in children with bronchial asthma

Allergy complications	Names of allergic diseases				
	Bronchial asthma	Atopic dermatitis	Allergic rhinitis	Allergic conjunctivitis	Pollinosis
Bronchial asthma (%)	—	14.6	16.9	16.3	14.2
Atopic dermatitis (%)	30.9	—	26.2	27.6	27.3
Allergic rhinitis (%)	52.8	38.8	—	64.1	87.8
Allergic conjunctivitis (%)	24.4	19.5	30.6	—	72.2
Pollinosis (%)	12.5	11.3	24.6	42.3	—

Survey in elementary school students in western Japan in 2002.

without any treatment, and is thus differentiated from cure. A remission status that continues for 5 years or longer is considered a clinical cure. Furthermore, if respiratory function and airway hyperresponsiveness recover to normal levels, the status is determined as a functional cure.

3.4. DEATH FROM ASTHMA (Fig. 1)

The number of deaths from asthma during childhood has markedly decreased. Some characteristics can be noted: (i) mortality in patients with asthma, aged 5-34 years, has decreased to ≤ 0.1 per 100,000 population; (ii) mortality in those aged 0-4 years is higher than that in older children; (iii) mortality in those aged 15-

19 years decreases and is more common among males and unstable; (iv) suffocation is the leading cause of death; (v) most deaths result from severe symptoms, but some moderate or mild symptoms may also result in death¹⁵; (vi) unexpected sudden exacerbation and delayed appropriate consultation are common as causes of death from asthma; and (vii) misjudgment of seizure severity and excessive dependence on pressurized metered dose inhalers (pMDI) of short-acting β_2 agonists are other causes of death.¹⁶

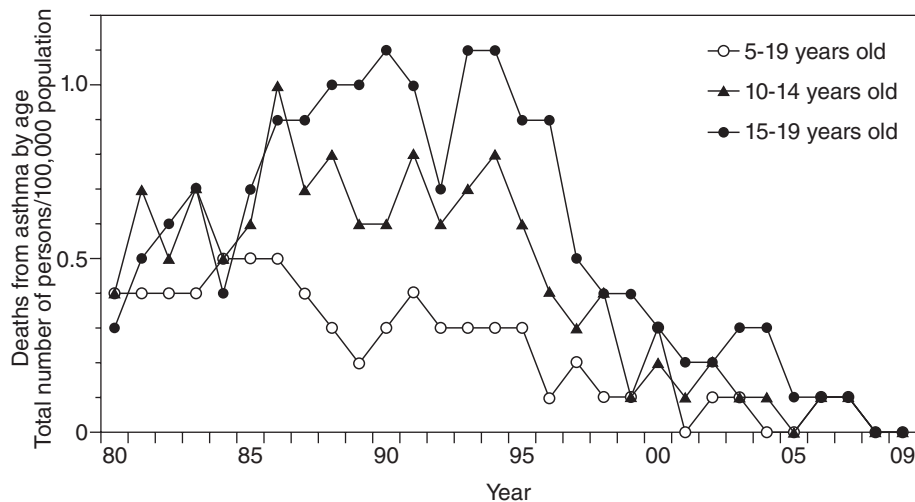


Fig. 1 Mortality from asthma in children of 5-19 years old from 1980 to 2009.

3.5. PREVENTION OF AND MEASURES AGAINST DEATH FROM ASTHMA

To reduce deaths from asthma, early diagnosis and treatment and patient education should be thoroughly conducted. Instructions for appropriate use of short-acting β_2 agonist pMDI, measures against acute seizures, thorough antiinflammatory therapy with inhaled corticosteroids, compliance, etc., are particularly important.

4. MEASURES AGAINST ACUTE SEIZURES IN CHILDHOOD ASTHMA

4.1. ASSESSMENT OF SEIZURE INTENSITY

Seizure intensity is classified into 4 stages, i.e., minor, moderate, and major seizures and respiratory insufficiency, based on the degree of impairment of respiratory status and living conditions (Table 5). Since infants cannot recognize dyspnea, seizure intensity is determined based on objective findings. Ill-temper, vomiting, screaming, and difficulty sleeping unless held by mother are important interview items for severe seizure (Table 6).

The criteria of seizure intensity are determined by measuring oxygen saturation (SpO_2) using a pulse oximeter and peak expiratory flow (PEF) using a PEF meter. However, since SpO_2 widely varies among infants compared with schoolchildren, caution should be exercised in evaluating seizure intensity in infants.

4.2. TREATMENT AND PROCEDURES IN OUTPATIENT DEPARTMENTS (Fig. 2)

4.2.1. Initial Treatment

(1) Treatment of minor seizure: Administer an inhaled β_2 stimulant (salbutamol or procaterol) using a nebulizer. Use 0.1-0.3 mL for infants and 0.2-0.4 mL for school children or older adolescents, diluted in physiological saline (2 mL) or DSCG inhalant solution (1 ampule = 2 mL).

(2) Treatment of moderate seizures: Administer an inhaled β_2 stimulant using a nebulizer. Consider oxygen inhalation for patients with $<95\%$ SpO_2 . For patients with insufficient response, perform inhalation again 20-30 min later. Inhalation can be repeated three times. If ineffective, consider additional treatment.

(3) Treatment of major seizures and respiratory insufficiency: Administer an inhaled β_2 stimulant with a nebulizer, while performing oxygenation. After securing vascular access, start initial transfusion and intravenous steroid administration. Intravenous infusion of aminophylline can also be added for children aged ≥ 2 years. Consider its indications before use (Table 7). It is recommended that specialists use this treatment for children aged <2 years.

4.2.2. Determination of Efficacy and Measures (Fig. 2)

The efficacy of initial treatment is determined based on changes in seizure intensity. Classify the efficacy into favorable response, insufficient response, no response, and exacerbation based on the changes.

(1) Minor seizure

(i) Favorable response: After β_2 stimulant inhalation for 15-30 min, cough and wheezing almost disappear and SpO_2 becomes $\geq 97\%$. The peak expiratory flow rates among school children or older adolescents are predicted values or $\geq 80\%$ of the best value. If in this status, the patient can go home. (ii) Insufficient response: Mild cough and wheezing remain even after β_2 stimulant inhalation. Administer an inhaled β_2 stimulant again 20-30 min later. (iii) No response or exacerbation: If β_2 stimulant inhalation causes no response or exacerbates symptoms, conduct an additional treatment equivalent to that for moderate seizure.

(2) Moderate seizure

Table 5 Criteria for seizure intensity

		Minor seizures	Moderate seizures	Major seizures	Respiratory insufficiency
Respiration status	Wheezing	Mild	Apparent	Marked	Reduced or eliminated
	Retractive breathing	None - mild	Apparent	Marked	Marked
	Prolonged expiration	-	+	Apparent [†]	Marked
	Orthopnea	Can lie down	Like sitting position	Bend forward	
	Cyanosis	-	-	Possible	+
	Respiratory rate	Slightly increased	Increased	Increased	Undetermined
Normal respiratory rate in children when awaking			<2 months	<60/min	
			2-12 months	<50/min	
			1-5 years old	<40/min	
			6-8 years old	<30/min	
Feeling of dyspnea	During rest	-	+	Marked	Marked
	During walking	(+) when in a hurry	Marked during walking	Difficulty in walking	Abasia
Daily life	Speech	Pause after one sentence	Pause after phrases	Pause after one word	Impossible
	Diet	Almost normal	Slightly difficult	Difficult	Impossible
	Sleep	Can sleep	Occasionally wake up	Disturbed	Disturbed
Impaired consciousness	Excitation	Normal	Slightly excited	Excited	Confused
	Lowering of consciousness	-	-	Slightly lowered	+
PEF	(before inhalation)	>60%	30-60%	<30%	Unmeasurable
	(after inhalation)	>80%	50-80%	<50%	Unmeasurable
SpO ₂ (atmosphere)		≥96%	92-95%	≤91%	<91
PaCO ₂		<41 mmHg	<41 mmHg	<41-60 mmHg	>60 mmHg

[†] Difficult to determine during polypnea. During major seizures, the expiratory phase is at least twice longer than the inspiratory phase.

There are several criteria. It is not required that all criteria be met.

As seizure intensity increases, infants present with seesaw breathing, not shoulder breathing. During expiration and inspiration, distention and depression of the chest and abdomen repeat like a seesaw. Exclude intentional abdominal breathing.

Table 6 Symptoms during severe seizures in infantile asthma

1. Severe cough (occasionally vomiting)	8. Do not sleep (or cannot sleep)
2. Marked wheezing (occasionally reduced)	9. Cyanosis
3. Depression of suprasternal space and supraclavicular fossa and between ribs	10. Moaning
4. Tachypnea	11. Tachycardia
5. Nasal alar breathing	12. Ill-tempered
6. Seesaw breathing	13. Scream (excited)
7. Comfort when held (orthopnea)	14. Lowering level of consciousness

(i) Favorable response: If a favorable response is obtained after the initial treatment, the patient should be observed for an additional hour. If asymptomatic, give instructions for future treatment and allow the patient to go home. (ii) Insufficient response: If no remission is achieved after 2 or more β_2 stimulant inhalations, conduct an additional treatment. Treat infants

after hospitalization. (iii) No response or exacerbation: If initial treatment results in unfavorable response or exacerbates symptoms, treat the patient after hospitalization.

(3) Additional treatment for moderate seizure: Administer a steroid and/or aminophylline. However, caution should be exercised for adverse effects when

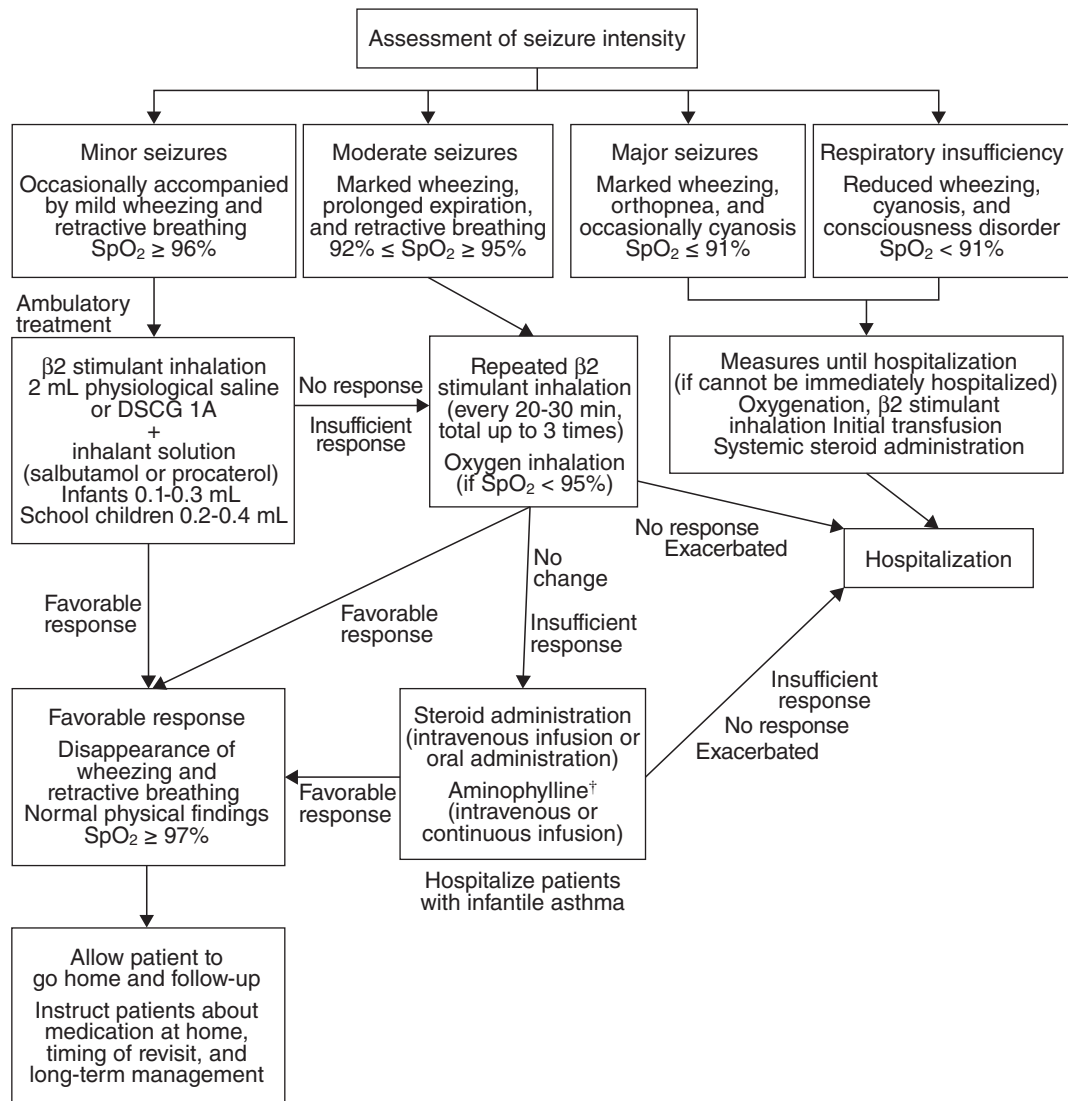


Fig. 2 Measures against acute seizures at outpatient departments.

†(i) Children aged ≤5: Desirably performed by a specialist in childhood asthma. (ii) Infantile asthma: Avoid overdose. Avoid administration to infants with convulsive disorders. (iii) Caution should be exercised for patients with fever because of increased intermediate concentration.

Table 7 Patients with moderate seizures who are discouraged from aminophylline administration (2-15 years old)

1. Patients with history of convulsions or those complicated by CNS diseases
2. Treatment for the following patients whose serum theophylline levels cannot be quickly measured
 - (i) Patients with a history of adverse effects caused by aminophylline or theophylline.
 - (ii) Patients periodically receiving sustained release theophylline, with serum theophylline level maintained at $\geq 15 \mu\text{g/mL}$.
 - (iii) Patients for whom it is difficult to determine the safety of intravenous aminophylline infusion, because the above 1) and the use status of theophylline are often unclear.

using aminophylline in infants.

a) Steroids: Administer a steroid via an intravenous or oral route. See Table 8 for initial doses. Even for patients with moderate seizures, consider combined use with an intravenous steroid for early medical

treatment of patients: (i) receiving treatment step 3 or above for long-term management; (ii) having a history of hospitalization due to asthma attack in the past year; and (iii) receiving endotracheal intubation for the treatment of asthma attack accompanied by im-

Table 8 Initial dosage of therapeutic agent for acute seizures

	<2 years old	2-5 years old	6-15 years old
β ₂ stimulant Nebulizer inhalation With oxygen if SpO ₂ < 95%	0.1-0.3 mL of salbutamol or procaterol + 2 mL of physiological saline or DSCG		0.2-0.4 mL of salbutamol or procaterol + 2 mL of physiological saline or DSCG
Aminophylline Intravenous infusion for ≥30 min Intravenous injection	<Hospitalize patients with major or more severe seizures> No history of oral theophylline administration: 3-4 mg/kg History of oral theophylline administration: Reduce the dose of 3-4 mg/kg if needed	<Additional treatment for moderate or more severe seizures> No history of oral theophylline administration: 4-5 mg/kg History of oral theophylline administration: 3-4 mg/kg	
Intravenous steroid injection Slow intravenous injection for about 10 min or intravenous infusion for about 30 min	Hydrocortisone: 5 mg/kg Prednisolone: 0.5-1 mg/kg Methylprednisolone: 0.5-1 mg/kg	Hydrocortisone: 5-7 mg/kg Prednisolone: 1-1.5 mg/kg Methylprednisolone: 1-1.5 mg/kg	
Oral corticosteroid	Prednisolone: 0.5-1 mg/kg/day 3 divided doses <If oral prednisolone administration is impossible> Betamethasone syrup or dexamethasone elixir: 0.05 mg (0.5 mL) /kg/day 2 divided doses		
Rapid initial transfusion	Infants: 100-150 mL/h, ≥10 kg body weight: 200 mL/h Until urination occurs		

Table 9 Indications for hospital treatment

1. Major seizures and respiratory insufficiency
2. Moderate seizures
- Past history of severe seizures
- Not improved by ambulatory treatment for about 2 h
- Moderate seizures, continuing from the previous day and accompanied by sleep disturbance (Hospitalize patients with infantile asthma.)
3. Complications
- Pneumonia, atelectasis, mediastinal emphysema, subcutaneous emphysema, pneumothorax, etc.

paired consciousness or seizures.

b) Aminophylline: Conduct intravenous infusion of an initial dose for 30 min or longer, followed by continuous infusion. The dosage is determined based on the presence of oral administration of sustained release theophylline and the infant's age. Desirably, aminophylline is administered to children aged ≤5 years by a specialist in childhood asthma, and to children aged <2 years after hospitalization. Aminophylline is not recommended for the patients shown in Table 7.

4.3. TREATMENT AND PROCEDURES IN WARDS

Indications for hospital treatment are shown in Table 9. Patients with respiratory insufficiency require intensive care with the assistance of emergency specialists and anesthesiologists.

4.3.1. Initial Treatment (Table 8)

Administer an inhaled β₂ stimulant with a nebulizer

along with oxygen inhalation. Start initial transfusion along with intravenous steroid administration (Table 10). Aminophylline can be administered concomitantly. However, caution should be exercised for patients aged 0-2 years (Table 11).

(1) Favorable response: If symptoms are markedly improved, follow-up the patient while performing β₂ stimulant inhalation every 4-6 h and maintenance transfusion. If needed, concomitantly conduct repeated steroid administration and continuous intravenous aminophylline infusion.

(2) Insufficient or no response: If seizures are not improved at 30 min after the start of treatment, proceed with an additional treatment.

4.3.2. Additional Treatment

Consider continuous isoproterenol (e.g., Asthpul®) inhalation.¹⁷⁻¹⁹ During this treatment, monitor blood pressure, heart rate, respiratory rate, SpO₂, etc. Inhalation is very effective, whose effects can usually be noted within 30 min. Periodically conduct intravenous

Table 10 Systemic steroid administration

	Intravenous			
	Initial dose		Routine dose	
	2-15 years old	<2 years old	2-15 years old	<2 years old
Hydrocortisone	5-7 mg/kg	5 mg/kg	5-7 mg/kg Every 6 h	5 mg/kg Every 6-8 h
Prednisolone	1-1.5 mg/kg	0.5-1 mg/kg	0.5 mg/kg Every 6 h	0.5-1 mg/kg Every 6-12 h (max: 2 mg/kg/day)
Methylprednisolone	1-1.5 mg/kg	0.5-1 mg/kg	1-1.5 mg/kg Every 4-6 h	0.5-1 mg/kg Every 6-12 h
Oral				
Prednisolone	0.5-1 mg/kg/day (3 divided doses)			

If oral prednisolone administration is difficult, administer 0.5 mL (0.05 mg) /kg/day of betamethasone syrup or dexamethasone elixir (2 divided doses).

Intravenous administration: Intravenous injection for about 10 min or intravenous infusion for about 30 min.

Precautions: (i) Hydrocortisone: Limit the use to several days because of mineralocorticoid effects. (ii) Intravenous administration may cause immediate allergic reaction. (iii) Limit the use to 3 days a month or several times a year. If these limits are exceeded, refer to a specialist in childhood allergy.

Table 11 Precautions for aminophylline injection for seizures caused by infantile asthma

- If β_2 stimulants or steroids are not effective for major seizures or respiratory insufficiency, theophylline should be prescribed by a specialist.
- Do not prescribe theophylline for convulsive disorders, such as febrile convulsions and epilepsy.
- If there is fever, carefully refer to indications.
- Determine dosage based on 10 $\mu\text{g/mL}$ of serum level. Monitor serum level as needed. Adjust dosage as needed, with an upper limit of 15 $\mu\text{g/mL}$.
- Theophylline clearance is reduced by fever, viral infection, diet, concomitant drugs, etc. In some cases, serum levels are elevated.

steroid administration (see Table 10). Routinely, steroid administration can be discontinued within several days after remission.

4.3.3. Treatment of Respiratory Insufficiency

Respiratory insufficiency results in the alleviation and disappearance of wheezing and causes severe cyanosis, and may be accompanied by urinary and fecal incontinence and unconsciousness. Analyze arterial blood gases to assess respiration and examine the presence of complications that preclude treatment (subcutaneous emphysema, mediastinal emphysema, atelectasis, pneumonia, pneumothorax, etc.). There is no definite indication for artificial respiratory management. Check the following signs:

- reduced respiratory sounds and wheezing;
- impaired consciousness resulting in somnolence or coma;
- <60 mmHg PaO₂ (<90% SpO₂) even after sufficient oxygen inhalation;
- elevated PaCO₂ (≥ 65 mmHg or ≥ 5 mmHg/h).

5. BASICS OF LONG-TERM MANAGEMENT OF CHILDHOOD ASTHMA

5.1. SEVERITY DETERMINATION AND CONTROL ASSESSMENT OF CHILDHOOD ASTHMA

5.1.1. Severity Determination

The severity of disease in patients not on long-term management agent is shown in Table 12. If a long-term management agent is already administered, determine the “true severity” considering the present treatment step (Table 13). For example, if the “apparent severity” of a patient in treatment step 2 is mild persistent, determine the “true severity” as their intersection point, i.e., moderate persistent. Patients with symptoms not controlled in treatment step 4, whose apparent severity is moderate/severe persistent is determined as the most severe persistent.

A comparison of severity determination between children and adults demonstrate one-stage differences: mild and intermittent, mild persistent, and moderate persistent in adults correspond to mild persistent, moderate persistent, and severe persistent in

Table 12 Severity classification of childhood bronchial asthma based on clinical symptoms before treatment

Severity	Severity and frequency of symptoms
Intermittent	- Cough and mild wheezing seasonally occur several times a year. - Although occasionally accompanied by dyspnea, the symptom is improved in a short time with a β_2 stimulant of single use.
Mild persistent	- Cough and mild wheezing occur once or more a month or less than once a week. - Although occasionally accompanied by dyspnea, the symptoms continue for a short time and rarely disturb daily life.
Moderate persistent	- Cough and mild wheezing occur once or more a week. The symptoms do not continue every day. - The symptoms may become moderate or major seizures and disturb everyday life.
Severe persistent	- Cough and mild wheezing continue every day. - The symptom may become moderate or major seizures once or twice a week and disturb everyday life and sleep.
Most severe persistent	- Even if treatment for severe and persistent symptoms is performed, the symptom continues. - Moderate or major seizures at night cause frequent consultation after surgery hours and repeated hospitalization, and restrict daily life.

Table 13 Severity of childhood bronchial asthma, determined based on present treatment step

Severity based on symptoms alone (apparent severity)		Severity based on present treatment step (true severity)			
		Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Intermittent	- Cough and mild wheezing seasonally occur several times a year. - Although occasionally accompanied by dyspnea, the symptoms are improved in a short time with a β_2 stimulant of single use.	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Mild persistent	- Cough and mild wheezing occur once or more a month or less than once a week. - Although occasionally accompanied by dyspnea, the symptoms continue for a short time and rarely disturb daily life.	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Moderate persistent	- Cough and mild wheezing occur once or more a week. The symptoms do not continue every day. - The symptoms may become moderate or major seizures and disturb everyday life and sleep.	Moderate persistent	Severe persistent	Severe persistent	Most severe persistent
Severe persistent	- Cough and wheezing continue every day. - The symptoms may become moderate or major seizures once or twice a week and disturb everyday life and sleep.	Severe persistent	Severe persistent	Severe persistent	Most severe persistent

children, respectively.

5.1.2. Treatment Goal of Childhood Asthma

To the pre-existing treatment goals 1 to 6, JPGL2008 added a seventh goal: improvement of airway hyperresponsiveness, aiming at final remission and cure (Table 14). It is difficult to conduct an airway hyperre-

sponsiveness test in non-specialized medical institutions. Thus, conduct treatment and management, aiming at statuses indicating improvement of airway hyperresponsiveness. For example, no exercise induced asthma is induced during routine medical treatment and no symptoms are induced by stimuli, such as cold air and smoke.

Table 14 Treatment goal of childhood bronchial asthma

Besides final remission and cure, the aims of daily control are:

1. Reduced or no need for β_2 stimulants of single use.
2. No symptom day and night.
3. No absence from school.
4. Normal daily life, including sports.
5. Stable PEF rate.
6. Almost normal pulmonary function.
7. Improved airway hyperresponsiveness (no symptom provocation after exercise, cold air inhalation, etc.).

For children aged 4-11 years

Childhood Asthma Control Test

▼ Children answer the following questions.

(1) How are you feeling? Score

Very bad 0	Bad 1	Good 2	Very good 3	
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(2) How is asthma troubling you during running, exercise, or sports?

So troubled that I cannot do what I want to do 0	Troubled and hateful 1	Slightly troubled but OK 2	No trouble 3	
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(3) Do you cough because of asthma?

Yes, always 0	Yes, almost always 1	Yes, occasionally 2	No, not at all 3	
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(4) Do you awake at night because of asthma?

Yes, always 0	Yes, almost always 1	Yes, occasionally 2	No, not at all 3	
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▼ Guardians answer the following questions.

(5) How many days did asthma symptoms occur in the daytime in these four weeks? Score

0 days 5	1-3 days 4	4-10 days 3	11-18 days 2	19-24 days 1	Every day 0	
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(6) How many days did wheezing occur because of asthma in the daytime in these four weeks?

0 days 5	1-3 days 4	4-10 days 3	11-18 days 2	19-24 days 1	Every day 0	
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(7) How many days did your child awake because of asthma in the nighttime in these four weeks?

0 days 5	1-3 days 4	4-10 days 3	11-18 days 2	19-24 days 1	Every day 0	
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Show the results to physician!

See the back to check childhood asthma control status based on total score.

Total score

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Fig. 3 C-ACT questionnaire. Adapted from the web page of Japanese Society of Pediatric Allergy and Clinical Immunology, <http://zensoku.jp/check/check2.html#info>.

5.1.3. Control of Asthma

Complete control is a status in which the aim of asthma treatment is achieved. Favorable control can be achieved by selecting an appropriate treatment step based on severity. However, insufficient treatment, inappropriate medication, and inevitable exac-

erbation factors result in poor control. The asthma control test was developed for treatment and management aimed at favorable control.

(1) Childhood Asthma Control Test (C-ACT)²⁰: C-ACT is a childhood asthma control test for children aged 4-11 years (Fig. 3). The test consists of 7 ques-

Severity Determination of Childhood Asthma and Asthma Control Test

Answer the following questions 1-5 about asthma symptoms and troubles in daily life in the last month. Check the appropriate boxes about frequency and severity.

- How many days did wheezing occur in the last month?

Not at all (3)	Once or more a month, less than once a week (2)	Once or more a week, not every day (1)	Continued every day (0)
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- How often did seizures accompanied by dyspnea (choking) occur in the last month?

Not at all (3)	Occasionally occurred and not maintained (2)	Frequently occurred and maintained (1)	Continued almost every day (0)
----------------	--	--	--------------------------------
- How many days did you awake because of asthma at night in the last month?

Not at all (3)	Occasionally, less than once a week (2)	Once or more a week, not every day (1)	Every day (0)
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- Are you troubled with wheezing during exercise or romping about?

Not at all (3)	Slightly, but not troubled (2)	Frequently, and troubled (1)	Always, and troubled (0)
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- How many days did you use an inhalant, oral medicine, or patch for seizures in the last one month? (The term "medicines" of this questionnaire means medicines used not for prevention, but for the treatment of seizures, including cough and wheezing.)

Not at all (3)	Less than once a week (2)	Several times a week, not every day (1)	Used daily (0)
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- Show the name of a long-term management agent (prophylactic agent) for asthma, being used now (Circle to the agents). If using an inhaled corticosteroid, show inhalation frequency a day.

Inhaled corticosteroid

(i) Flutide Diskus (50 µg), (100 µg), (200 µg)	[inhalation frequency a day: Twice]
(ii) Flutide Rotadisk (50 µg), (100 µg), (200 µg)	[inhalation frequency a day: times]
(iii) Flutide Aerosol (50 µg), (100 µg)	[inhalation frequency a day: times]
(iv) Qvar (50 µg), (100 µg)	[inhalation frequency a day: times]
(v) Pulmicort inhalant solution (0.25 mg), (0.5 mg)	[inhalation frequency a day: times]
(vi) Adair (50/100 mg)	[inhalation frequency a day: times]

Leukotriene receptor antagonists: (i) Onon, (ii) Singulair, (iii) Kipres

Long-acting β₂ agonists: (i) Serevent Diskus, (ii) Serevent Rotadisk

Sustained release theophylline: (i) Theodur, (ii) Slo-bid, (iii) Theolong, (iv) Uniphyll

Intal inhalation: (i) inhalant solution, (ii) Intal capsule (E-haler), (iii) Aerosol

- Severity: Moderate and persistent (mild and persistent symptoms at the treatment step 2)
 - Control status: JPAC 12 points (favorable insufficient control)
 - Measure: Treatment step 3, ICS 100 µg × 2

Fig. 4 JPAC questionnaire. Modified from the web page of Japanese Society of Pediatric Allergy and Clinical Immunology, <http://zensoku.jp/check/check2.html#info>.

tions, of which diseased children answer the first 4 and their parents answer the remaining 3. The first 4 questions are face scale to allow children to answer them easily. Scoring is as follows: 27 points is perfect control; ≥ 20 is favorable control; and < 20 is poor control. Long-term management is conducted with a goal of 27 points. For children aged ≥ 12 , the Asthma Control Test (ACT) for adults can be used.

(2) Japanese Pediatric Asthma Control Program (JPAC)²¹: Severity and control statuses can be assessed by JPAC. The former allows the selection of

treatment step according to the guidelines. Step-up and step-down are determined using the latter. Scoring is as follows: 15 points is complete control; 12-14 is favorable (insufficient) control; and ≤ 11 is poor control. Conduct treatment and management with a goal of 15 points.

Figure 4 shows an example of JPAC. In this example, treatment step 2 is conducted with question 6. "Mild persistent" is circled for the questions 1-3. True severity is determined as "moderate persistent" based on Table 13. JPAC score, a total score of ques-

Table 15 Major inhalation antigens and food antigens

1. Inhalation antigens
- House dust (HD)
- Mites (DP or DF)
- Cedar pollen
- Cat (dander)
- Dog (dander)
- Fungi (<i>Alternaria</i> , <i>Aspergillus</i> , <i>Cladosporium</i> , <i>Penicillium</i>)
- Other pollens (cypress, orchard grass, ragweed, mugwort, etc.)
- Other pets (hamster, guinea pig, and rabbit)
- Others (cockroach, chironomid midge)
2. Food antigens
- Egg white, egg yolk, ovomucoid
- Cow's milk, casein, α -lactalbumin, β -lactoglobulin
- Wheat
- Cereals, such as soybean, rice, and buckwheat
- Fish and shellfishes
- Fruits

tions 1-5, is 12. Thus, this case is determined as insufficient control. Since the true severity is moderate persistent, step up to treatment step 3.

(3) Objective assessment of control status: Appropriate assessment of the statuses of diseased children is important for long-term management. For this purpose, asthma diary and measurement of peak expiratory flow are utilized. In addition, assessment of the peripheral airway using a flow volume curve is important.

5.2. AVOIDANCE OF EXACERBATION FACTORS

Most patients with childhood asthma have an atopic diathesis and produce specific IgE antibodies to mites in house dust. Tests are needed to examine specific IgE antibodies to other allergens and changes in specific IgE antibody titers during treatment and management.

5.2.1. Allergy Tests and Assessment

Mean total IgE values vary with age. High values are those that exceed the mean + ≥ 2 SD. Typical antigens are shown in Table 15. To investigate the allergens of childhood asthma, begin by presuming environmental antigens by history taking to select inspection items. Routine inspection methods include skin tests and measurement of serum specific IgE antibodies in the blood, however even if positive for specific IgE antibodies, not all cause asthma.

5.2.2. Instructions for Environmental Improvement

Cleaning rooms with a vacuum cleaner is an important measure against mite antigens. Using a wood or cushioned floor as flooring material is more effective. Measures for bedclothes are also important; bed-

clothes are preferably vacuumed at least once a week. Sensitization to pets (e.g., cats, dogs, and rodents) may induce seizures, so contact with these animals should be avoided.

5.2.3. Instructions for Smoking Cessation

Smoking, both active and passive smoking, is an exacerbation factor of asthma. Smoking of pregnant mothers affects the respiratory function of their children after birth.²² Parents with smoking habits must be instructed about the need for smoking cessation as a vital component of childhood asthma treatment. If the children themselves are smoking, instruct them about the adverse influences on treatment and conduct smoking cessation therapy.

5.3. LONG-TERM MANAGEMENT BY MEDICATION

5.3.1. Formulations and Characteristics of Long-Term Management Agents (Controllers)

Agents continuously used to reduce and eliminate asthma symptoms, improve QOL, and normalize and maintain respiratory function are called long-term management agents (controllers). Long-term management agents should have antiinflammatory effects. Agents with antiinflammatory effects include steroids, leukotriene receptor antagonists (LTRAs), and theophylline. Systemic steroid administration for long-term management is limited to the most severe cases because of adverse effects. Inhaled corticosteroids are routinely used. Long-acting β_2 agonists (LABAs) are concomitantly used with an inhaled corticosteroid for long-term management, and are not used alone.²³

(1) Inhaled corticosteroid (ICSs): ICSs potently suppress airway inflammation and play an important role for long-term management. As airway inflammation is ameliorated, subjective symptoms, respiratory function, and airway hyperresponsiveness improve,^{24,25} and hospitalization due to seizures and deaths from asthma decrease.²⁶ However, no evidence has been obtained regarding increased natural outgrowth of symptoms. ICSs indicated for children are shown in Table 16. A compounding agent of ICS and LABA can be used for children aged ≥ 5 years. Select agents depending on ages or inhalation methods to achieve efficient inhalation.

(2) Leukotriene receptor antagonists (LTRAs): LTRAs inhibit bronchoconstriction and airway inflammation,²⁷ and are effective for long-term management. LTRAs indicated for childhood asthma are shown in Table 17. In many cases, LTRAs improve respiratory function and reduce seizures within 1-2 weeks after administration. In patients with mild symptoms, LTRAs are as effective as ICSs.^{28,29} Efficacy of LTRAs as additional agents for ICSs has been demonstrated.³⁰⁻³²

(3) Sustained release theophylline (SRT): SRT,

Table 16 Inhaled corticosteroids indicated for children

Formulation	Generic name	Trade name	Contents	Remarks
pMDI	Fluticasone	Flutide® Aerosol	50,100 µg	Maximum 200 µg/day
	Beclomethasone	Qvar®	50,100 µg	Maximum 200 µg/day
DPI	Fluticasone	Flutide® Diskus	50,100 µg	Maximum 200 µg/day
		Flutide® Rotadisk	50,100 µg	Maximum 200 µg/day
	Budesonide	Pulmicort® Turbuhaler	100,200 µg	Maximum 800 µg/day
Suspension	Budesonide	Pulmicort® inhalant solution	0.25,0.5 mg	Maximum 1.0 mg/day ≥0.5 to <5 years old
Compound with a long-acting β2 agonist				
pMDI	Fluticasone	Adoair® 50 Aerosol	50 µg	Maximum 200 µg/day
	Salmeterol		25 µg	Maximum 100 µg/day
DPI	Fluticasone	Adoair® 100 Diskus	100 µg	Maximum 200 µg/day
	Salmeterol		50 µg	Maximum 100 µg/day
800 µg of BUD is equivalent in titer to 400 µg of FP and BDP.				

Table 17 Leukotriene receptor antagonists indicated for children and their dosages

Generic name	Trade name	Formulation	Dose
Pranlukast	Onon®	Dry syrup Capsule	7 mg/kg/day (<450 mg a day) 2 divided doses
Montelukast	Singulair®	Chewable tablet 5	Routinely administer 5 mg once a day to children aged ≥6 years before bedtime.
		Fine granule 4 mg	Routinely administer 4 mg once a day to children aged 1-6 years before bedtime.
	Kipres®	Chewable tablet 5	Routinely administer 5 mg once a day to children aged ≥6 years before bedtime.
		Fine granule 4 mg	Routinely administer 4 mg once a day to children aged 1-6 years before bedtime.

Table 18 Precautions for long-term management with a sustained release theophylline for infantile asthma

- Consider the use of a sustained release theophylline as an additional treatment for patients at treatment step 3 or above. - Do not perform long-term management with a sustained release theophylline in children aged <6 months. - Avoid the use of a sustained release theophylline even for patients aged ≥6 months if they have epilepsy or febrile convulsion. - Desirably, instruct patients to reduce dosage or discontinue administration if fever occurs. - During the administration of a sustained release theophylline, caution should be exercised for the combined use of other agents (e.g., erythromycin, and clarithromycin), which reduces theophylline clearance and raises its serum level. - Caution should be exercised for the combined use of antiallergics for infantile asthma. Reportedly, antiallergics with histamine H₁ antagonist action actively migrate to the CNS to lower convulsant threshold. - Avoid the use of an aminophylline suppository.
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which has a bronchodilator action and an antiinflammatory effect, is used as a controller. The dosage of theophylline is determined considering factors that influence metabolisms, such as individual differences, infection, meal contents, and concomitant drugs. Caution should be exercised for elevated serum theophylline level resulting from decreased clearance caused by fever during viral infection. In infants, a convulsive status epilepticus associated with theophylline administration causes a problem.³³ Precautions for use

are shown in Table 18.

(4) Long-acting β₂ agonists (LABAs): Since β₂ stimulants have no inhibitory effect on airway inflammation, use LABAs concomitantly with ICSs. Besides inhaled LABAs, transdermal patches^{34,35} and oral medicines are available as LABAs. After pasting of transdermal tulobuterol patch, serum tulobuterol level is maintained for 24 h. Use them concomitantly with ICSs for long-term management.

Table 19 Pharmacotherapy plan for long-term management of childhood bronchial asthma (<2 years old)

	Treatment step 1	Treatment step 2	Treatment step 3 [#]	Treatment step 4 [#]
Basic treatment	None (pharmacotherapy according to seizure intensity)	- Leukotriene receptor antagonist [†] and/or - DSCG inhalation (2-4 times/day) ^{‡,}	- Inhaled corticosteroid [§] (100 µg/day FP or BDP, 0.25-0.5 mg/day BIS)	- Inhaled corticosteroid [§] (150-200 µg/day FP or BDP, 0.5-1.0 mg/day BIS) One of the followings or both - Leukotriene receptor antagonist [†] - DSCG inhalation ^{‡,} (2-4 times/day)
Additional treatment	- Leukotriene receptor antagonist [†] and/or - DSCG inhalation (2-4 times/day) ^{‡,}	- Inhaled corticosteroid [§] (50 µg/day FP or BDP, 0.25 mg/day BIS)	Either or both of the followings: - Leukotriene receptor antagonist [†] - DSCG inhalation (2-4 times/day) ^{‡,} - β2 stimulant (2 times/day, patch or p.o. before bedtime) Sustained release theophylline [¶] (in mind) (serum level: 5-10 µg/mL)	- β2 stimulant (2 times/day, patch or p.o. before bedtime) - Sustained release theophylline [¶] (in mind) (serum level: 5-10 µg/mL)

[†] Antiallergics indicated for other childhood asthma symptoms: chemical mediator release suppressants, some histamine H1 antagonists, and Th2 cytokine inhibitors.

[‡] To inhale a DSCG inhalant solution using a nebulizer, inhale it with a small amount (0.05-0.1 mL) of β2 stimulant as needed.

[§] FP: fluticasone propionate, BDP: beclomethasone dipropionate, BIS: budesonide inhalation suspension.

Inhale FP and BDP using a spacer with a mask. Inhale BIS with a nebulizer.

[¶] Do not use this agent for children aged <6 months. Caution should be exercised for indications. Do not use this agent for convulsive disorders. Desirably, instruct patients to reduce dosage or discontinue administration if fever occurs.

^{||} Once symptom is controlled, discontinue the administration of a β2 stimulant.

[#] Desirably, perform treatment step 3 or above according to the instructions and management of a specialist in childhood allergy. A specialist treats a patient with asthma, insufficiently controlled by treatment step 4.

5.3.2. Long-Term Management Plan

(1) Selection of treatment step based on severity: In a pharmacotherapy plan for long-term management, determine severity based on symptoms and their frequency for last 1-2 months (see Table 12) and select a long-term management agent for the treatment step selected based on the severity. The pharmacotherapy plan for long-term management is divided into age groups: <2, 2-5, and 6-15 years old (Table 19-21).

Select a long-term management agent for a step determined based on true severity (Table 13). During treatment, examine the control status using a control questionnaire, etc., to maintain complete control. If control is insufficient or poor, achieve complete control through an additional treatment or step-up. If complete control is achieved for 3 months or longer, reduce the dosage to the lowest recommended one to maintain control.

(2) Therapeutic agents according to control statuses: Determine control statuses referring to asthma symptoms written in an asthma diary, difficulties in daily life, and usage of short-acting β2 agonists, PEF

monitoring,^{36,37} etc. Favorable control is indicated by ≤20% diurnal variation in PEF rate or ≥80% of the best value. C-ACT and JPAC, described above, are also appropriate for the assessment of control status. If control is insufficient or poor, examine the appropriateness of medication and allergen avoidance or the effects of psychosocial factors. If no effects are obtained in treatment step 4, consider hospitalization for treatment³⁸ or oral corticosteroid administration for the most severe persistent cases.

If symptoms are controlled for 3 months or longer, consider step-down for a period based on severity, history of disease, respiratory function, and medication. If asthma symptoms are controlled below intermittent type and respiratory function is favorable after reduction to the lowest recommended dosage, treatment can be discontinued. At present, there are no criteria for discontinuation. If symptoms remit (i.e., a status with neither treatment nor symptoms), the patient should be followed-up. Here, the remission does not mean cure.

Table 20 Pharmacotherapy plan for long-term management of childhood bronchial asthma (2-5 years old)

	Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Basic treatment	Pharmacotherapy according to seizure intensity	- Leukotriene receptor antagonist [†] and/or - DSCG ^{†, , #} or Inhaled corticosteroid [‡] (in mind) (50-100 µg/day FP or BDP, 0.25 mg/day BIS)	Inhaled corticosteroid [‡] (100-150 µg/day FP or BDP, 0.5 mg/day BIS)	Inhaled corticosteroid ^{‡, ¶} (150-300 µg/day FP or BDP, 1 mg/day BIS) Either or both of the followings: - Leukotriene receptor antagonist - DSCG ^{, #} - Sustained release theophylline [§] - Long-acting β2 agonist [#] (patch/oral/inhalation ^{††})
Additional treatment	- Leukotriene receptor antagonist [†] and/or - DSCG [†]	- Sustained release theophylline [§]	Either or both of the followings: - Leukotriene receptor antagonist - DSCG ^{, #} - Sustained release theophylline [§] - Long-acting β2 agonist [#] (patch/oral/inhalation ^{††})	

[†] Antiallergics indicated for other childhood asthma symptoms: chemical mediator release suppressants, histamine H1 antagonists, and Th2 cytokine inhibitors.

[‡] FP: fluticasone propionate, BDP: beclomethasone dipropionate, BIS: budesonide inhalation suspension.

[§] Caution should be exercised for the adverse effects of a sustained release theophylline, accompanying elevated serum level due to fever.

[¶] For patients with symptoms that cannot be controlled by treatment step 4, perform treatment, including oral corticosteroid administration, under the management of a specialist.

^{||} To inhale a DSCG inhalant solution using a nebulizer, inhale it with a small amount (0.05-0.1 mL) of β2 stimulant as needed.

[#] Once symptom is controlled, discontinue the administration of a β2 stimulant.

^{††} Children who can inhale with a dry powder inhaler (DPI).

(Notes) A compounding agent of salmeterol xinafoate and fluticasone propionate (SFC) is indicated for children aged ≥5. Thus, in children aged 5, the compounding agent can be used from treatment step 3 (additional treatment). However, it is not shown in this table because of insufficient evidence.

6. INHALERS AND SPACER

Inhalation therapy is critical and effective for daily management and seizure treatment of childhood asthma. Understand the characteristics (i.e., merits and demerits) of inhalers for their selection based on the child's status.

6.1. INHALERS

Inhalers are classified into nebulizers and metered dose inhalers. Three types of nebulizers, based on their drive systems, are available: jet, ultrasonic, and mesh. Metered dose inhalers include the pressurized metered dose inhaler (pMDI) and the dry powder inhaler (DPI). Table 22 shows their merits and demerits. Select an inhaler considering agents, spacer, child's age, severity, compliance, economic conditions, etc.

(1) Nebulizer: Since respiratory control is not required during inhalation, a nebulizer can be used re-

gardless of age, if a mask is used. Jet nebulizers are most widely used for inhalation therapy of asthma. Mesh nebulizers are a subtype of ultrasonic nebulizers. Mesh nebulizers are lightweight, power saving, and have high spray capacity. Ultrasonic nebulizers are unsuitable for inhaling an anti-asthmatic drug because of heat effects on agents, concentration changes in a drug tank, etc.

(2) Use of nebulizers: The child should inhale at a resting respiratory rate in a sitting position. Children, old enough to oral breathing, inhale with a mouthpiece, attached to the nozzle of nebulizer, put in the mouth. For infants, use spray with a mask, attached to the nozzle, to cover the mouth and nose. Airtightness greatly influences inhalation efficiency. Inhalation efficiency is reduced by nasal inhalation or crying.^{39,40}

(3) Metered dose inhalers: pMDI and DPI are available. If no spacer is used for pMDI, synchronize spray and inhalation. Even in infants, for whom spray

Table 21 Pharmacotherapy plan for long-term management of childhood bronchial asthma (6-15 years old)

	Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Basic treatment	Pharmacotherapy according to seizure intensity	Inhaled corticosteroid [‡] (100 µg/day FP or BDP, 100-200 µg/day BUD) or - Leukotriene receptor antagonist [†] and/or - DSCG [†]	Inhaled corticosteroid [‡] (100-200 µg/day FP or BDP, 200-400 µg/day BUD)	Inhaled corticosteroid ^{‡,§} (200-400 µg/day FP or BDP, 400-800 µg/day BUD) Either or both of the followings: - Leukotriene receptor antagonist - Sustained release theophylline - DSCG - Long-acting β ₂ agonist [¶] (inhalation/patch/oral) or SFC (100/200 µg/day)
Additional treatment	- Leukotriene receptor antagonist [†] and/or - DSCG [†]	Sustained release theophylline	Either or both of the followings: - Leukotriene receptor antagonist - Sustained release theophylline - DSCG - Long-acting β ₂ agonist [¶] (inhalation/patch/oral) or switch to - SFC (50/100-100/200 µg/day)	- Oral corticosteroid [§] (short term and intermittent in mind) - Hospitalization (in mind)

[†] Antiallergics indicated for other childhood asthma symptoms: chemical mediator release suppressants, histamine H1 antagonists, and Th2 cytokine inhibitors.

[‡] Inhaled corticosteroids: FP (fluticasone propionate), BDP (beclomethasone dipropionate), or BUD (budesonide). BUD dose, converted at a ratio of FP/BUD: BUD = 1: 2, is indicated. If symptom can be well controlled by treatment step 2, BUD dose can be reduced to 100 µg/day once a day.

[§] For patients with symptoms that cannot be controlled by treatment step 4, perform treatment, including oral corticosteroid administration, under the management of a specialist.

[¶] Once symptom is controlled, discontinue the administration of a β₂ stimulant.

^{||} SFC: a compounding agent of salmeterol xinafoate and fluticasone propionate. Salmeterol/fluticasone dose is indicated. To use a compounding agent, switch from FP or BDP. Avoid combined use with a long-acting β₂ agonist. Leukotriene receptor antagonist, DSCG, or theophylline can be used concomitantly.

and inhalation cannot be synchronized, pMDI can be employed by using a spacer and a mask. Using DPI, a patient inhales an agent by self inspiration. School children or older adolescents can use DPI, because a certain amount of inspiratory force is required and a spacer and a mask cannot be used concomitantly. Agents for metered dose inhalers, which can be used for childhood asthma, are shown in Table 23.

6.2. SPACER

A spacer is an indispensable instrument for pMDI in infants who cannot accurately perform the procedures for synchronizing spray and inhalation. Concomitant use of a spacer allows inhalation at a normal respiratory rhythm even without synchronizing spray of an agent, thus increasing inhalation efficiency. In

addition, a spacer is useful in adsorbing large particles ($\geq 5 \mu\text{m}$) onto the inner wall of the spacer to prevent deposition of excess agent in the oral cavity and reduce adverse effects. In infants who cannot breathe through the mouth, mask the nose and mouth to maintain inhalation efficiency.

Many types of spacers are available. Select a spacer with data assuring aerodynamic properties and clinical usefulness and safety. The effectiveness of a spacer is greatly influenced by concomitant agents and procedures as well as the shape, structure, and physical properties of the spacer. Thus, assessment under various conditions according to certain criteria should be established in the future.⁴¹⁻⁴³

Precautions for using a spacer are shown in Table 24. To benefit from a spacer, mask the face closely

Table 22 Inhalers and their characteristics

Type	Merits	Demerits	System	Merits	Demerits
Nebulizer	Inhalable by normal respiration; Usable for infants; Inhalable without fail; Easy adjustment of liquid medicine.	Large and expensive inhalator; Time-consuming; Limited use of medicines; Need for power supply; Noisy.	Jet	High durability	Noisy; Relatively large size; Need for alternating current source.
			Ultrasonic	Massive spray; Quiet.	Denaturation of medicine; Excessive water inhalation; Unsuitable for spraying a small amount; Large size; Cannot inhale a steroid suspension.
			Mesh	Quiet; Lightweight and small size; Run on batteries.	Durability unknown; Few instruments available.
Metered dose inhaler (MDI)	Lightweight and small size; Portable; No need for special device; No noise; No need for power supply; Quick inhalation.	Complicated inhalation procedures; Unstable inhalation; Difficult usage for juveniles; Minor volume adjustment impossible; Tendency of repeated excessive use; Risks of overdose.	Pressurized metered dose inhaler (pMDI)	Synchronization can be omitted by using a spacer; Portable.	Need for synchronization of inhalation and spray; Need for sufficient shaking and mixing before use; Need for spray solvent.
			Dry powder inhaler (DPI)	No need for synchronization of inhalation and spray; Easy handling and management; No need for spray solvent.	Need for inhalation power; Unusable for juveniles; Limited types of agent.

Table 23 Metered dose inhalers

Pressurized metered dose inhaler (pMDI)	β 2 stimulants	Salbutamol; Sultanol® Inhaler, Airomir® Aerosol, Procaterol; Meptin® Air, Meptin® Kid air
	Inhaled corticosteroids	Beclometasone; Qvar® Fluticasone; Flutide® Aerosol
	Anticholinergics	Ipratropium; Atrovent® Aerosol
	Compounding agent of inhaled corticosteroid/ β 2 stimulant	Fluticasone/salmeterol; Adoair® Aerosol
	Antiallergics	DSCG; Intal® Aerosol
Dry powder inhaler (DPI)	Inhaled corticosteroids	Fluticasone; Flutide® Rotadisk, Flutide® Diskus Pulmicort® Turbuhaler
	β 2 stimulants	Salmeterol; Serevent® Rotadisk, Serevent® Diskus, Procaterol; Meptin® Clickhaler
	Compounding agent of inhaled corticosteroid/ β 2 stimulant	Fluticasone/salmeterol; Adoair® Diskus
	Antiallergic	DSCG capsule; Intal® + E-haler®

without leakage and prevent static electricity.

7. PROBLEMS IN DAILY LIFE AND THEIR MANAGEMENT

7.1. EXERCISE INDUCED ASTHMA (EIA)

(1) EIA: EIA is a phenomenon in which wheezing and dyspnea occur temporarily during exercise. Its pathology is unclear. Cooling in the airway, caused by hyperventilation during exercise⁴⁴, and elevated

osmolarity in the airway epithelium, caused by water loss, are potential causes.^{45,46} Increased airway temperature after exercise may also be involved.⁴⁷

(2) Diagnosis: If coughing, wheezing, and dyspnea occur during or after exercise, a diagnosis of EIA may be made. Conduct an exercise stress test to quantitate EIA.^{48,49}

(3) Severity: The maximum decreasing rate of forced expiratory volume in one second (FEV₁) after

Table 24 Precautions for using a spacer

1. After spraying, inhaled as immediately as possible.
2. Do not rub a plastic spacer (to prevent static electricity).
3. Water washing and natural drying are desirable.
4. Avoid spraying one inhalation dose multiple times.

exercise is higher in patients with more severe asthma. This serves as a parameter to determine the severity.⁵⁰ Since EIA is also correlated with airway hyperresponsiveness, history taking of EIA is important to determine the appropriateness of treatment step.

(4) Prevention: To prevent EIA, select the treatment step based on severity. Once it has occurred, prevent EIA using the procedures in Table 25.

(5) Exercise instructions: Do not restrict exercise because it benefits the child's growth in various ways. Parents, kindergarten teachers, school officials, school physicians, and attending physicians should collaborate to take measures so that children with asthma can safely participate in exercise at kindergartens and schools. Specific procedures are shown in Table 26.

7.2. PARTICIPATION IN EVENTS AT KINDERGARTEN AND SCHOOLS

Make supportive plans for extracurricular studies and club activities, such as school trips, school camps, and excursions in cooperation with kindergartens and schools so that children with asthma can participate whenever possible. Instruct children with asthma and their parents beforehand about cautions for participating in events and measures against seizures.

(1) If children with asthma develop seizures when participating in events, make them inhale a bronchodilator early because of the special situation. Depending on the statuses of daily seizures and medication, consider a dose increase of an ICS and short-term administration of an oral corticosteroid when participating in events.

(2) Hand disease records to attending physicians so that patients can receive appropriate treatments at nearby medical institutions, when seizures occur during travel.

(3) If allergies occur after contact with an animal, caution should be exercised for contact with animals at zoos, etc.

(4) Stand on the windward side to avoid the smoke from fireworks or campfires.

(5) Instruct roommates to refrain from wrestling and pillow fights on the beds.

7.3. PRECAUTIONS FOR SCHOOL ACTIVITIES

(1) Since EIA is most likely to occur during a dead run or a long-distance race, instruct patients to start

Table 25 Effective measures for EIA prevention

1. Warming up
2. Prevention by medication
 - (i) β 2 stimulants
 - (ii) DSCG
 - (iii) Leukotriene receptor antagonists
 - (iv) Others
3. Other prophylaxes
 - (i) Mask
 - (ii) Routine training

slowly.

(2) If allergies occur after contact with domestic animals, do not allow the children take care of animals.

(3) Make class teachers explain to patient's classmates about EIA, which slows the pace and may interrupt exercise.

(4) Consider avoiding allergens and airway stimulators during clean-up duty.

7.4. INSTRUCTION TABLE FOR SCHOOL LIFE MANAGEMENT

In 2008, an instruction table for school life management was created for allergic diseases. The allergic diseases include asthma, atopic dermatitis, allergic conjunctivitis, anaphylaxis and food allergies, and allergic rhinitis. Disease types and treatments, precautions for school life, emergency contact numbers, and names of medical institutions and physicians should be submitted to the schools (<http://www.gakkohoken.jp./book/bo0002.html>).

8. PATIENT EDUCATION

To perform asthma treatment effectively, educate patients and their parents to be actively involved in asthma treatment.^{51,52}

(1) Infants (2-4 years old): Do not discomfort patients during treatment. Make them have interest in the treatment, to be motivated. Encourage and compliment inhalation to habituate them gradually.

(2) School age (from 5 years old to lower grades of elementary school): Explain the pathology of asthma to patients, using simple terms and metaphors, to make them understand the need for treatment. Instruct patients about abdominal breathing, PEF measurement, etc., cheerfully as if they were playing some kind of game.

(3) Prepuberty (upper grades of elementary school): Instruct patients about the need for continuing treatment without interruption. According to their understanding, educate them about pathophysiology and treatment. Since it is difficult to make patients take charge of treatment and management that their parents have taken care of, compliment them to achieve self-fulfillment and lead to self-management.

Table 26 Specific measures for exercise instructions

1. Prior information gathering
(i) Relationship between the amount and contents of exercise and the degree and frequency of EIA
(ii) Precautions for exercise by patients and people around them
(iii) Presence and contents of prophylactic agent before starting exercise
(iv) Measures for EIA, conducted by patients and people around them
2. Precautions for exercise
(i) Consider pleasures for inexperienced participants who are not good at exercise.
(ii) Check seizures and PEF rate on the day.
(iii) Check the contents and intensity of exercise.
- Adjust exercise intensity to allow for pleasant participation.
- If seizures occurred at previous night or on the day, adjust amount of exercise.
- If participation in exercise is difficult
Change clothes into gym suit, and consider participation as a recorder, measurer, referee, etc.
(iv) Check medication before starting exercise.
(v) Check EIA measures by patients and people around them.
3. Precautions after starting exercise
(i) Use of prophylactic agent
(ii) Sufficient warming up
(Causing and alleviating mild EIA before exercise may reduce the risks of EIA during exercise)
(iii) Perform interval training and repetition training.
(Repeat slow down and rest during exercise.)
4. Measures for EIA
(i) For children with asthma, who are prone to EIA, carefully observe them during exercise. If the signs of dyspnea appear, temporarily discontinue the exercise for abdominal breathing to recover from dyspnea.
Note) Explain EIA to other children beforehand to prevent them from misunderstanding.
(ii) Patients with severe dyspnea incurable by abdominal breathing
(e.g., (i) intensive retractive breathing, (ii) fragmentary speech, and (iii) cyanosis)
Use a preliminarily-prepared agent (e.g., inhaled β_2 stimulant), or deliver to a medical institution.
5. If exercise is performed more intensively than routine exercise at school
Reportedly, some athletes, who participate in national athletic meetings, suffer from severe asthma during intensive training or die from asthma if insufficiently controlled.
Thus, to perform exercise more intensively than usual, examine amount of exercise, training methods, and medications with attending physicians.

Food dependent exercise-induced anaphylaxis (FDEIA):

Anaphylaxis, caused by both food intake and exercise, is called food dependent exercise-induced anaphylaxis (FDEIA). Typically, following eruption of about 10-15 mm urticaria, FDEIA causes respiratory symptoms, such as wheezing, laryngeal edema, and dyspnea and gastrointestinal symptom, such as nausea and vomiting, and may progress to the collapse accompanied by unconsciousness.

Symptoms are generally induced by exercise ≤ 4 h after food intake. No anaphylaxis is induced by exercise >4 h after food intake. Common causative foods include wheat, squid, octopus, shellfish, shrimp, and crab. Others include fruits and nuts.

FDEIA may be caused by increased histamine level due to mast cell degranulation. If cutaneous symptoms are noted during exercise, immediately discontinue the exercise, prescribe an antihistaminics, and consult a medical institution. Instruct patients to avoid causative foods of FDEIA. For emergency use, instruct them to carry antihistaminics and adrenaline for self-injection at any time (Epipen®).

(4) Puberty (junior high school students or older children): More patients disobey their parents because of parent-child conflicts during puberty. Treatment and management will be interrupted by delayed education and instruction. This results in poor control and increased risks of death from asthma. Directly instruct patients at consultation. Since enough time cannot be taken in outpatient departments, it is effective to hospitalize patients with a severe persistent asthma for education and instruction during summer vacation, etc.

9. IMPROVEMENT IN COMPLIANCE

Sharing a treatment goal and establishing a partnership are important. Repeatedly check basic knowledge and skills at consultation to achieve a positive attitude toward treatment and high compliance.⁵³ Points to improve compliance are shown in Table 27.

10. PRECAUTIONS FOR VACCINATION

Conditions such as bronchial asthma, atopic dermatitis, allergic rhinitis, urticaria, or allergic predisposi-

Table 27 Points to improve compliance

- Recognize seriousness and urgency of asthma and death from it.
Asthma may cause death. Overuse of β_2 stimulants, omission of long-term management agents, and emergency department visits only when seizures occur increase the risks of death from asthma.
- Patients should have prospects of cure through proper management.
Asthma remits if managed properly. Indicate a proper treatment method for patients to have prospects of asthma treatment.
- Develop self-efficacy, "I can."
Confidence in asthma management, "I can do this," results in continued treatment. For that purpose, practical, specific, and less stressful instructions are required depending on their lives.
At every visit, praise the efforts and results of self-monitoring using asthma diary, prepared by patients or their families, to increase their confidence in treatment.

Table 28 Precautions for examining pubertal and adolescent asthma

1. Caution should be exercised for progress (regarding disease conditions).
 - Reduced relations of respiratory function and airway hyperresponsiveness with symptoms
 - Reduced involvement of atopy
 - More common among women (seizures during the second half of menstrual period).
 2. Complications (chest pain, dyspnea, headache, vomiting, etc.).
 - Mediastinal and subcutaneous emphysema, pneumothorax, etc.
 - Psychosomatic complications (hyperventilation syndrome, etc.)
 - Intentional overdose, underdose, etc.
 3. Management shift (patients' acceptance of change from maternal to paternal management)
 - Partnerships between hospitals and clinics, pediatric and internal departments, and hospitals and workplaces/schools.
 4. Death from suffocation.
 - Take cautions for patients living alone.
 - Instructions for inhalation and medication
 - Establishment of emergency system and staffing of personnel who takes charge of respiratory management on ambulances
 5. Prevention of suffocation during puberty
 - Appropriate early intervention
 - Knowledge about environmental management (pet, tobacco, etc.)
 - Partnership among hospitals, schools, and families
 - Career and academic advices
 6. Others
 - Partnership with asthma (get along with asthma).
- If poorly-controlled, reexamine the followings:
- (i) Compliance
 - (ii) Periodic consultation
 - (iii) Overuse of β_2 blocker
 - (iv) Indication of inhaled corticosteroids
- Discuss these with patients.

tion alone do not preclude vaccination; however, caution should be exercised for patients potentially allergic to vaccine components. Conduct a preliminary diagnosis considering previous allergic symptoms and vaccine additives.

10.1. VACCINE ADDITIVES AND INOCULUM COMPONENTS FOR ALLERGY

Reportedly, gelatin (stabilizer), thimerosal (antiseptics), egg ingredients (culture components), and antimicrobials can cause allergy. Of domestically-produced vaccines, only the polio vaccine contains gelatin (≤ 0.00375 mg/dose). In inactivated vaccines,

thimerosal is removed or reduced to about $\leq 1/10$ or a substitute is used.

10.2. MAJOR VACCINES FOR CHILDREN WITH ASTHMA

(1) Influenza vaccine: Influenza vaccines can be safely used to inoculate children with ≥ 3.5 UA/mL egg white-specific IgE antibody titer (RAST score ≥ 3), who eat egg processed products, etc., without serious adverse effects. Refer to a specialist for inoculation of children (i) on an egg-free diet who are known to have an egg allergy, (ii) with serious anaphylaxis after egg consumption, and (iii) with poorly

controlled severe asthma.

(2) Mixed vaccine for measles and rubella: If immediate hypersensitivity reaction (urticaria, etc.) occurs immediately after the first inoculation with a measles vaccine, measure measles antibody titer (neutralizing or EIA-IgG antibody), and avoid a second inoculation if antibody is found, or perform an intradermal reaction test before the second inoculation is given. Avoid reinoculation into patients with an immediate anaphylactic reaction after the last inoculation of a measles vaccine.

11. CONSIDERATIONS FOR SURGERY

Since asthma is a risk factor in performing general anesthesia, especially inhalation anesthesia, caution should be exercised for management of physical conditions before and during surgery and for respiratory management after surgery. For nonemergent surgery in patients with aggressively introduced ICS, a period exceeding 2 weeks of non-paroxysmal symptoms is recommended. Even for nonemergent surgery, relatively short-term asthma control is often demanded. However, it takes several months to reduce airway hyperresponsiveness sufficiently. Postpone surgery until sufficient control is achieved. If asthma attack occurs within 2 weeks, surgery should be postponed. Complications and allergic reactions to medications, medical materials, latex, foods, etc. must be investigated prior to administration.

For patients receiving systemic steroid administration for severe asthma for ≥ 6 months and those with adrenocortical insufficiency, 2 mg/kg prednisolone should be started on the day before surgery, and continued even during surgery if possible. Systemic steroid administration should be applied after surgery as well.

12. PUBERTAL TO ADOLESCENT ASTHMA

Problems increase during puberty, e.g., low compliance, remodeling, and death from asthma.⁵⁴ Understanding the characteristics and problems of pubertal asthma is important for treatment and management. Precautions for patients, whose consultation is irregular and compliance with medication is low, are shown in Table 28.

13. PATIENTS TO BE REFERRED TO A SPECIALIST

If there is any problem with diagnosis or treatment, determined by control status, or if complications are found, refer the patient to a specialist for consultation. Even if a patient is well-controlled, a non-specialist and specialist should cooperate to assess the patient's condition objectively. Refer the following patients to a specialist:

- (1) Patients <2 years old
- (i) Patients who require systemic steroid treatment for ≥ 3 days a month or several times yearly. (ii) Pa-

tients who require treatment step 3 or above.

- (2) Patients ≥ 2 years old

(i) Patients who require systemic steroid treatment frequently or continuously because of repeated seizures. (ii) Patients who cannot be controlled by treatment step 4.

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