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REVIEW ARTICLE

Japanese Guideline for Childhood Asthma 2014

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ABSTRACT

The Japanese Guideline for the Diagnosis and Treatment of Allergic Diseases 2013 (JAGL 2013) describes childhood asthma after the Japanese Pediatric Guideline for the Treatment and Management of Asthma 2012 (JPGL 2012) by the Japanese Society of Pediatric Allergy and Clinical Immunology. JAGL 2013 provides information on diagnosis by age group from infancy to puberty (0-15 years of age), treatment for acute exacerbations, long-term management by anti-inflammatory drugs, daily life guidance, and patient education to allow non-specialist physicians to refer to this guideline for routine medical treatment. JAGL differs from the Global Initiative for Asthma Guideline (GINA) in that JAGL emphasizes early diagnosis and intervention at <2 years and 2-5 years of age. A management method, including step-up or step-down of long-term management drugs based on the status of asthma control levels, as in JAGL, is easy to understand, and thus the Guideline is suitable as a frame of reference for routine medical treatment. JAGL has also introduced treatment and management using a control test on children, recommending that the physician aim at complete control by avoiding exacerbation factors and by appropriate use of anti-inflammatory drugs.

KEY WORDS

acute exacerbation, anti-inflammatory drugs, childhood asthma, guideline, long-term management

1. Definition and Pathophysiology of Childhood Asthma (Fig. 1)

Childhood asthma (0-15 years old) 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]

Chronic airway inflammation is caused by the activation of eosinophils, mast cells and lymphocytes, and by airway mucosal damage. The view that asthma is a condition of chronic inflammation has important implications for asthma treatment and management; it is fundamental to the understanding of the need for anti-inflammatory drugs for basic treatment of persistent asthma. Remodeling, which may influence the prognosis of asthma, is still unknown in many aspects, such as its causes, onset time, and effects of anti-inflammatory treatment. Airway hyperresponsiveness, which is characteristic of asthma, is intensified by airway epithelial damage caused, in turn, by airway inflammation. Airway hyperresponsiveness can be assessed by patient's reactions to inhaled histamine, acetylcholine, etc. Exercise-induced asthma (EIA) is also considered to be a phenomenon associated with airway hyper-responsiveness.

2. Diagnosis and Differential Diagnosis of Childhood Asthma

The typical symptom of asthma exacerbation is dyspnea accompanied by whistling/wheezing. Expiratory

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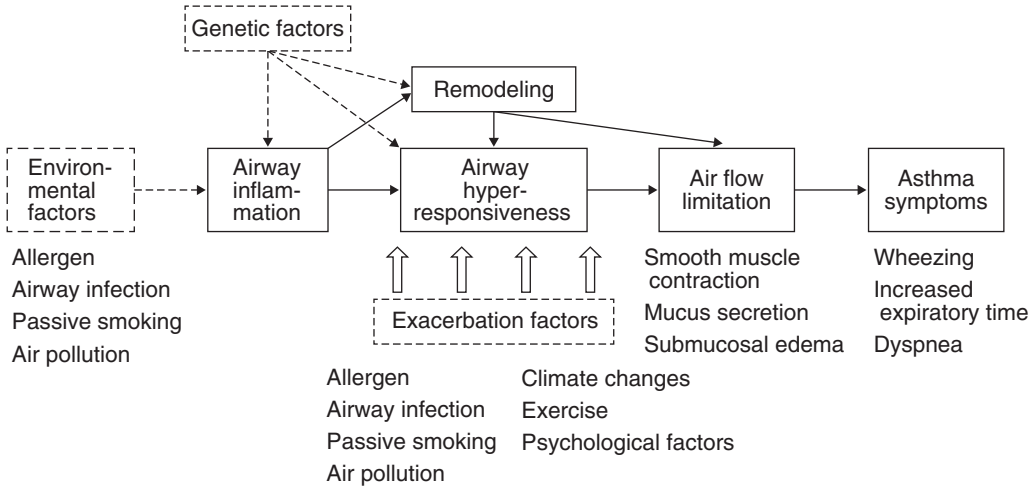

Fig. 1 Pathophysiology of bronchial asthma.

Table 1 References for asthma diagnosis

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

Table 2 Differential diagnosis

Anomalies	Others
Chest vascular malformation	Hypersensitive pneumonitis
Congenital heart diseases	Bronchial foreign bodies
Anomalies of airway	Psychogenic cough
Laryngomalacia	Vocal cord dysfunction
Bronchomalacia	Compression of airway
Tracheomalacia	Pulmonary edema
Immotile cilia syndrome	Allergic bronchopulmonary aspergillosis
Infection	Cystic fibrosis
Nasopharyngitis, sinusitis	Sarcoidosis
Croop (acute laryngitis)	Pulmonary embolism
Bronchitis	
Bronchiolitis	
Pneumonia	
Bronchiectasis	
Pulmonary tuberculosis	

dyspnea occurs mainly during an asthma exacerbation. As symptoms progress, however, inspiratory dyspnea may coexist. If such symptoms are repeated, it is reasonable to diagnose symptomatic asthma. But some patients present with misleading symptoms. Table 1 summarizes the physiological and immunological examinations and allergy tests, which may aid in enhancing the accuracy of diagnosis.

2.1. Differential Diagnosis

Table 2 shows diseases that figure in differential diagnosis of wheezing in children. Children with wheezing symptoms, particularly those with acute wheezing must be differentially diagnosed. In infants, an accumulation of secretion in the lower respiratory tract, resulting from bronchitis, pneumonia, and others may cause repeated wheezing; a differential diagnosis is thus called for. Recurrent wheezing is easily diagnosed in older children with underlying diseases, such as history of respiratory disorder and congenital heart disease during infancy. However, caution should be taken in the case of airway stenosis caused by a vascular ring, for instance, and of wheezing resulting from gastro-esophageal reflux disease.

2.2. Atopic Asthma and Non-Atopic Asthma

There are two types of childhood asthma: atopic asthma and non-atopic asthma. Most of childhood asthma cases are atopic, in which many patients exhibit elevated specific IgE levels for house dust mites.

2.3. Asthma Phenotype

Recently, different asthma phenotypes in infantile period came to be discussed. Martinez *et al.* classified wheezing infants into three subtypes: transient early wheezers, non-atopic wheezers and IgE-associated wheezers[8] (Fig. 2). Brand *et al.*, in contrast, classified wheezes among infants into two subtypes: multi-

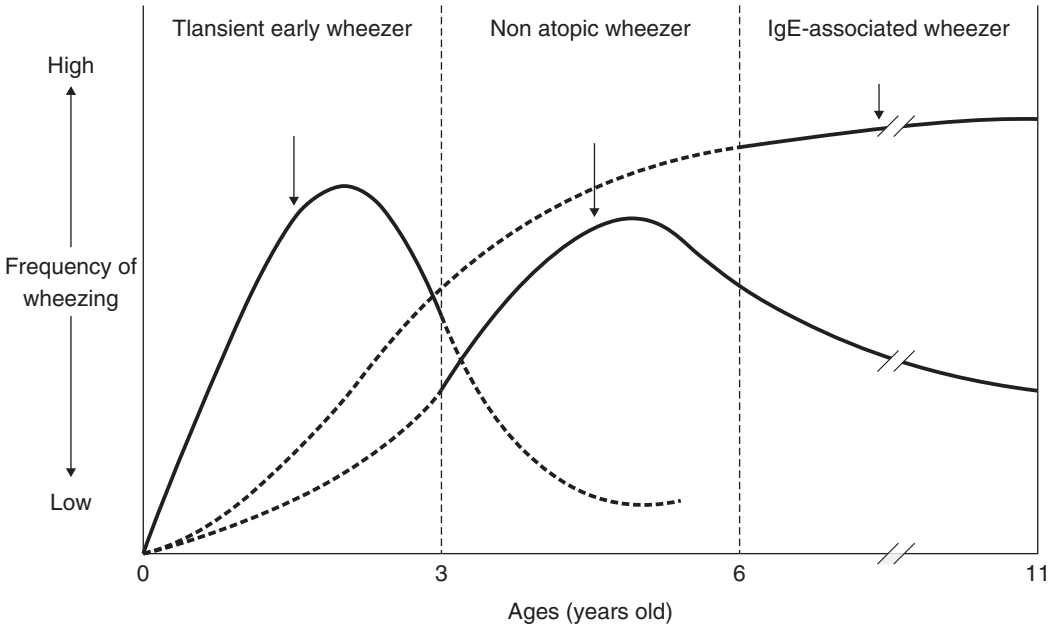

Fig. 2 Asthma phenotypes in infancy.

Table 3 Asthma prevalence rate in Japan

Surveillance area	Age (years old)	Surveillance method	Surveillance year							
			1982	1992	1994	2002	2003	2005	2008	2012
Western area of Japan	6-12	ATS-DLD	3.20%	4.60%		6.50%				4.70%
Fukuoka Prefecture of Japan	6-7	ISAAC			17.3%		18.2%			
	13-14				13.4%		13.0%			
All Japan	0-4	Prevalence rate trend-surveillance					13.6%			
	5-9						12.7%			
	10-14						9.0%			
	15-19						5.4%			
All Japan	3-5	ISAAC							19.9%	
	6-7							13.9%	13.5%	
	13-14							8.8%	9.6%	
	16-17								8.3%	
All Japan	Elementary school	School health surveillance						6.8%		
	Junior high school							5.1%		
	High school							3.6%		

trigger wheeze and episodic (viral-induced) wheeze.[9] It is important that asthma phenotypes should be reflected on the differential diagnosis and therapeutic strategies.

3. Epidemiology of Childhood Asthma

3.1. Prevalence

Reported prevalence differs depending on the survey method. Two survey methods, the International Study of Asthma and Allergies in Childhood (ISAAC) and the American Thoracic Society-Division of Lung Diseases (ATS-DLD) with modification are utilized in Japan.[10,11] The prevalence of asthma in Japan as determined by ATS-DLD shows 3.2-6.5%. Asthma prevalence in school children has been increasing in these two decades according to the survey targeting at children of the same elementary schools in the same given area. However, very recent survey data indicates the prevalence tends to be declining (Table 3) with the following characteristics: (1) it is more com-

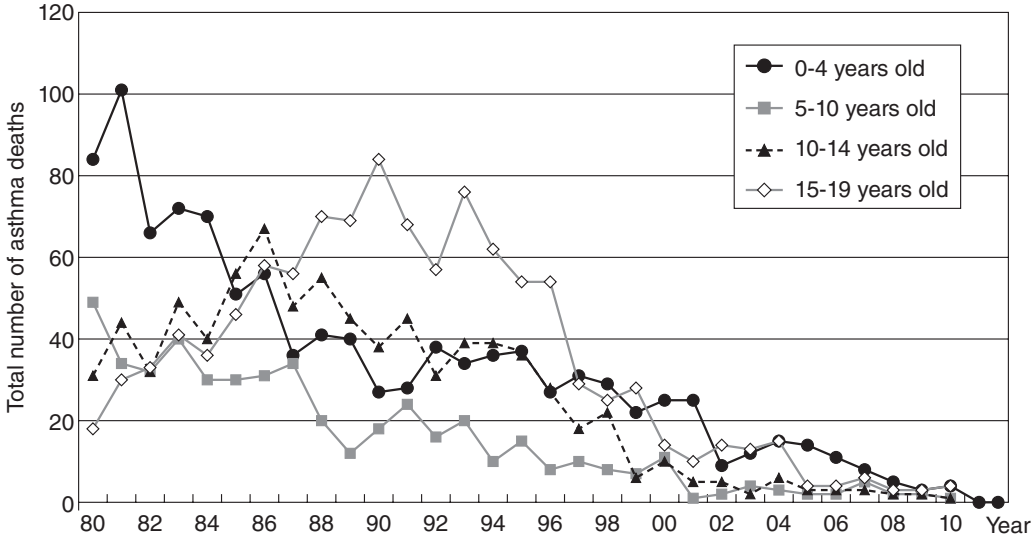

Fig. 3 Mortality from asthma in children from 1980 to 2009.

mon among juveniles, particularly male children, more specifically male infants; (2) it varies twofold or more among regions; (3) it shows higher prevalence in children with family history of allergic diseases. Children with higher BMI (>90th percentiles) indicate higher prevalence of asthma from infancy to adolescence.[12]

Prevalence of childhood asthma in Japan is ranked at the middle of various countries in the world.

3.2. Complications

Allergic rhinitis, allergic conjunctivitis, and atopic dermatitis are common as coexisting allergic diseases caused by the same mechanism as asthma. Of note, the complication rates of these allergic diseases are ≥30%.[13]

3.3. Prognosis

The remission rate is lower in patients with more severe asthma. Remission is defined as an asymptomatic status 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 hyper-responsiveness recover to normal levels, the status is determined as a functional cure.

Sixty percent of children who have had wheezing before age 6 experience no more wheezing at the age of 6 years old. On the other hand, 52-72% of children diagnosed as asthmatic at the age of 6, turn out to present with asthma symptoms at the age of 22 years old.[14,15]

3.4. Death from Asthma (Fig. 3)

The number of deaths from asthma during childhood has markedly decreased. The following characteristics can be noted:

(1) Mortality in patients with asthma, aged 5-34 years, has decreased to ≤0.1 per 100,000 population;

(2) Mortality in infants and children aged 0-4 years is higher than that in older children;

(3) Mortality in patients aged 15-19 years decreases and is higher among males and unstable;

(4) Suffocation is the leading cause of death;

(5) Most deaths result in patients with severe persistent asthma, but some patients with moderate or mild persistent asthma may also die from asthma[16];

(6) Sudden and unexpected exacerbation and delayed appropriate consultation are common as causes of death from asthma; and

(7) Misjudgment of the severity of exacerbation and excessive dependence on pressurized metered dose inhalers (pMDI) of short-acting β_2 stimulants are other causes of death.

To reduce the number of deaths from asthma, early and accurate diagnosis and treatment, and patient education should be thoroughly conducted. Instructions about the appropriate use of pMDI of short-acting β_2 stimulant against acute exacerbation, thorough anti-inflammatory therapy with inhaled corticosteroids, and good compliance to asthma management, are particularly important.

4. Management of Acute Asthma Exacerbation

4.1. Intensity of Asthma Exacerbation

The intensity of asthma exacerbation is classified into 4 stages: mild, moderate, severe exacerbations, and respiratory failure. It is based on the degree of impairment of respiratory status and the conditions of daily life such as eating, speaking, sleeping and exercising (Table 4). Since infants cannot complain of dyspnea themselves, the intensity of exacerbation in them is determined on the basis of objective findings.

Table 4 Intensity of asthma exacerbation

Component		Mild exacerbation	Moderate exacerbation	Severe exacerbation	Respiratory failure
Respiratory status	Wheezing	Mild	Apparent	Marked	Reduced or eliminated
	Retractive breathing	None - mild	Apparent	Marked	Marked
	Prolonged expiration	(-)	(+)	Apparent†	Marked
	Orthopnea	Can lie down	Prefers sitting position	Bends forward	
	Cyanosis	(-)	(-)	Possibly (+)	(+)
	Respiratory rate	Slightly increased	Increased	Increased	Undetermined
Normal respiratory rate		<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	Can not walk
Daily life	Speech	Pause after one sentence	Pause after phrases	Pause after one word	Impossible
	Feeding	Almost normal	Slightly difficult	Difficult	Impossible
	Sleep	Can sleep	Occasionally wake up	Disturbed	Disturbed
Disturbed consciousness	Agitation	(-)	Slightly excited	Excited	Confused
	Lowered level of consciousness	(-)	(-)	Slightly lowered	(+)
PEF	(before β_2 inhalation)	>60%	30-60%	<30%	Unmeasurable
	(after β_2 inhalation)	>80%	50-80%	<50%	Unmeasurable
SpO_2 (room air)		≥96%	92-95%	≤91%	<91%
$PaCO_2$		<41 mmHg	<41 mmHg	<41-60 mmHg	>60 mmHg

† Difficult to determine during tachypnea. During severe exacerbation, 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 intensity of exacerbation increases, infants present with see-saw 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 5 Symptoms during severe exacerbation in infantile asthma

1. Severe cough (with occasional vomiting)	8. Inability to 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-temper
6. Seesaw breathing	13. Scream
7. Comfort when held upright (orthopnea)	14. Lowered level of consciousness

Ill-temper, vomiting, screaming, and difficulty sleeping unless held by mother are important interview items for severe exacerbation (Table 5).

The criteria of intensity are determined by oxygen saturation (SpO_2) measured by pulse oximeter and peak expiratory flow (PEF) by spirometer. However, since SpO_2 widely varies among infants compared with school children, caution should be taken in evaluating the intensity of exacerbation in infants.

4.2. History Taking at Outpatient Department

At the outpatient department, the intensity, duration and cause of exacerbation must be assessed. The patient's previous history of exacerbation and medical

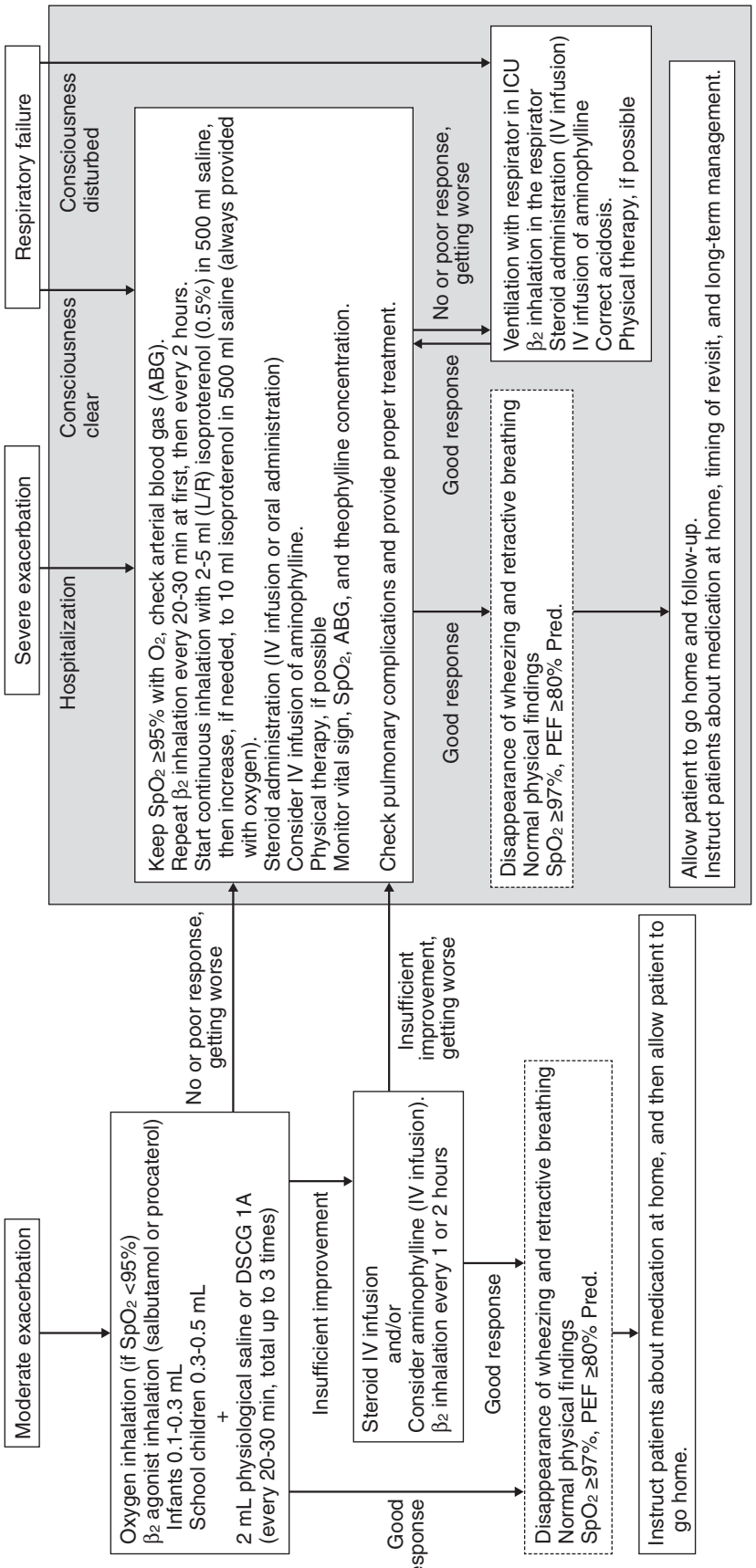

Fig. 4 Treatment for acute exacerbation in hospital (2-15 years old). Weak exacerbation usually responds to β_2 inhalation at home.

Table 6 Formulas for glucocorticosteroids

	Intravenous injection			
	Initial doses		Maintenance doses	
	2-15 y.o.	<2 y.o.	2-15 y.o.	<2 y.o.
Hydrocortisone	5-7 mg/kg	5 mg/kg	5-7 mg/kg every 6 hours	5 mg/kg every 6-8 hours
Prednisolone	1-1.5 mg/kg	0.5-1.0 mg/kg	0.5 mg/kg every 6 hours	0.5-1 mg/kg every 6-12 hours (max: 2 mg/kg/day)
Methyl-prednisolone	1-1.5 mg/kg	0.5-1.0 mg/kg	1-1.5 mg/kg every 6 hours	0.5-1.0 mg/kg every 6-12 hours
	Per oral administration			
Prednisolone	0.5-1.0 mg/kg/day (divided in three doses)			
Alternative:	Betamethasone or dexamethasone syrup 0.5 ml (0.05 mg)/kg/day (divided in two doses)			

Intravenous injection: infuse for 10-30 min. Pay attention to allergic reaction.

Hydrocortisone: discontinue within 3-4 days.

Systemic administration of glucocorticosteroids should be limited to less than three occasions per month. Patient should be referred to an expert in cases requiring more than these.

treatment on such occasions, if any, is also evaluated before a treatment plan is determined.

4.3. Treatment of Acute Exacerbation in Outpatient Departments (Fig. 4)

Treatment of mild exacerbation: Administer an inhaled β_2 stimulant (salbutamol or procaterol) using a nebulizer. Either give 0.1-0.3 mL to infants and 0.3-0.5 mL to school children or older adolescents, diluted in physiological saline (2 ml) or DSCG inhalant solution (1 ampule = 2 mL). After β_2 stimulant inhalation for 15-30 min, when cough and wheezing disappear, and SpO_2 becomes ≥97% and the PEF rates become ≥80% of predicted values and/or personal best, the patient can go home. If mild cough and wheezing remain even after the β_2 stimulant inhalation, administer an inhaled β_2 stimulant again 20-30 min later. If the β_2 stimulant induces no response or exacerbates symptoms, conduct an additional treatment equivalent to that for moderate exacerbation.

Treatment of moderate exacerbation: Administer an inhaled β_2 stimulant using a nebulizer. Administer oxygen inhalation on patients with <95% SpO_2. For patients with insufficient response, do the inhalation again 20-30 min later. Inhalation can be repeated three times. If ineffective, consider additional treatment. (See below.) When a favorable response is obtained after the initial treatment, the patient should be observed for an additional hour. If asymptomatic then, give instructions about future treatment and allow the patient to go home. If no remission is achieved after 2 or more β_2 stimulant inhalations, conduct an additional treatment. In the case of an infant, treat him/her after hospitalization.

Additional treatment for moderate exacerbation: Administer a steroid and/or aminophylline. However, caution should be taken for adverse effects when using aminophylline. If additional treatment results in unfavorable response or exacerbates symptoms, treat the patient after hospitalization.

a) Steroids: Administer a steroid via an intravenous or oral route. See Table 6 for initial and maintenance doses. Even on patients with moderate exacerbation, consider using an intravenous steroid for early medical treatment if they are patients (1) under treatment step 3 or above for long-term management; (2) with a history of hospitalization due to asthma exacerbation in the past year; or (3) with a history receiving endotracheal intubation for the treatment of asthma exacerbation induced by impaired consciousness.

b) Aminophylline: Indication of aminophylline is difficult to be secure unequivocally; aminophylline is not recommended for the patients shown in Table 7.

4.4. Treatment and Procedures in Wards

Indications for in-hospital treatment are shown in Table 8. Patients with respiratory failure require intensive care with the assistance of emergency specialists and anesthesiologists.

Treatment of severe exacerbation: Administer an inhaled β_2 stimulant with a nebulizer along with oxygen inhalation. Start initial transfusion along with intravenous steroid administration (Table 6). Aminophylline can be administered concomitantly. However, caution should be taken for patients aged 0-2 years (Table 9). If symptoms are markedly improved, follow up the patient every 4-6 hours while he/she is undergoing β_2 stimulant inhalation and maintenance

Table 7 Patients with moderate exacerbation for whom aminophylline administration is not advisable (2-15 years old)

1. Patients with a history of convulsions or with complications of CNS disease.
2. Caution should be taken in treatment of the following patients whose serum theophylline levels cannot be quickly measured.
(a) Patients with a history of adverse effects caused by aminophylline or theophylline.
(b) Patients periodically receiving sustained release theophylline, with serum theophylline level maintained at >15 microgram/mL.
(c) Patients for whom it is difficult to determine the safety of intravenous aminophylline infusion, because of above, or the use status of theophylline is unclear.

Table 8 Indications for hospital admission

1. Severe exacerbation and respiratory failure
2. Moderate exacerbation
- Past history of severe exacerbation
- Not improved by ambulatory treatment for about 2 hours
- Moderate exacerbation, continuing from the previous day and accompanied by sleep disturbance
(Hospitalize patients who are younger than 2 years old)
3. Complications
- Pneumonia, atelectasis, mediastinal emphysema, subcutaneous emphysema, pneumothorax, etc.

transfusion. If needed, concomitantly conduct repeated glucocorticosteroid administration and continuous intravenous aminophylline infusion. If exacerbation shows no improvement at 30 min after the start of treatment, proceed with an additional treatment. Consider continuous isoproterenol (e.g. Asthpul) inhalation.[17-19] During this treatment, monitor blood pressure, heart rate, respiratory rate, SpO_2, etc. The continuous inhalation is usually very effective, whose effects can be noted within 30 min. Periodically conduct intravenous glucocorticoidsteroid administration (Table 6), which may be discontinued within several days after remission. (Table 10)

4.5. Treatment of Respiratory Failure

Respiratory failure results in the alleviation and disappearance of wheezing and causes instead 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, and the like). Although there is no definite indication for artificial respiratory management, when one or more of the following signs are apparent, consider it indicated:

(1) Reduced respiratory sounds and wheezing in the presence of cyanosis;

Table 9 Cautions against aminophylline administration for patients younger than 2 years old

1. If β_2 stimulants or steroids are not effective for severe exacerbation or respiratory failure, theophylline should be prescribed by a specialist.
2. Do not prescribe theophylline for the patients with convulsive disorders, such as febrile convulsions and epilepsy.
3. If there is fever, carefully refer to indications.
4. Determine dosage based on 10 microgram/mL of serum level. Monitor serum level as needed. Adjust dosage as needed, with an upper limit of 15 maicrogram/mL.
5. Theophylline clearance is reduced by fever, viral infection, foods, concomitant drugs, etc. In some cases, serum levels are elevated.

(2) Impaired consciousness resulting in somnolence or coma;

(3) <60 mmHg PaO_2 (<90% SpO_2) even after sufficient oxygen inhalation;

(4) Elevated $PaCO_2$ (≥65 mmHg or ≥5 mmHg/h).

Usefulness of noninvasive positive ventilation is still under investigation for childhood asthma.

4.6. Complications with Acute Asthma Exacerbation

Air leak syndrome: Mediastinal emphysema, subcutaneous emphysema and pneumothorax are major forms of air leak syndrome. In pneumothorax, patients complain of chest pain which exacerbates with exertion and deep respiration. Cough and dyspnea is often observed. Leaked air is usually absorbed spontaneously.

Atelectasis: In acute asthma exacerbation, airway obstruction often occurs with airway constriction, mucus hypersecretion and submucosal edema, resulting in pulmonary atelectasis after air absorption in bronchi and alveoli of the lung. Atelectasis is most often observed in the middle lobe of right lung as a silhouette sign on Chest X-ray. CT-scan is more helpful for diagnosis. Treatment of asthma exacerbation is the highest priority, and postural drainage, physical therapy and administration of expectants may be helpful.

5. Basics of Long-Term Management of Childhood Asthma

5.1. Severity Determination

Asthma severity is classified into 4 levels: intermittent, mild persistent, moderate persistent and severe persistent, and the level of severe persistent includes most severe persistent as a sub-group.

The severity of disease in patients not taking long-term management drugs is shown in Table 11. If long-term management drugs are already administered, determine the "true" severity considering the present treatment step (Table 12). For example, if the "apparent" severity of a patient at treatment step 2 is mild persistent, determine the "true" severity as their

Table 10 Continuous inhalation therapy with β_2 agonist

Nebulizer
Inspiron nebulizer & face mask (or O_2 tent)
Inhalation liquid
R/L-isoproterenol (0.5%) 2-5 ml (or L-isoproterenol 10-25 ml) + 0.9%NaCl 500 ml
(double dose of R/L-isoproterenol (0.5%) can be used according to symptoms)
Methods
1. Start with 50%O_2 at 10 L/min.
2. Adjust O_2 concentration and flow in order to maintain SpO_2 over 95%.
3. If patient's status is not improved after 30 min, step up the inhalation condition, or consider management with respirator.
4. When patient's status is improved, step down the inhalation condition and stop continuous inhalation therapy; then change to intermittent inhalation with β_2 stimulant.
Monitoring
1. SpO_2 with pulse oximeter, ECG, blood pressure, respiratory rate
2. Electrolytes, CPK, LDH, GOT, blood gas
Cautions
1. Keep in mind the timing to change to management with respirator.
2. Regular sputum cough-up, body position change and body movement are encouraged.
3. Watch out for obstruction in tubes and failure of inhalation devices (give special attention to clogging of Inspiron nebulizer).
4. Watch out for signs of myocardial infarction: abnormal ECG findings and chest pain Check cardiac enzymes (CPK GOT and LDH), and consider changing to therapy with management with respirator.

Table 11 Definition of asthma severity in Japanese Pediatric Guideline

Asthma severity	Symptoms
Intermittent	• Seasonal cough and/or wheeze (2-3 times/year) • Sometimes dyspnea also, but recovers soon with SABA
Mild persistent	• Cough and/or mild wheezing; more than 1/month, less than 1/week • Sometimes dyspnea also, but it does not continue for long enough to disturb daily life
Moderate persistent	• Cough and/or mild wheezing; more than 1/week, but not everyday • Sometimes progresses to moderate to severe exacerbation, and disturbs daily life
Severe persistent	• Cough and/or mild wheezing occurs everyday • Moderate to severe exacerbation occurs 1-2/week, disturbing daily life and sleep
Most severe persistent (sub-group of severe persistent)	• Asthma symptoms continue despite the treatment for severe persistent asthma. • Frequent asthma exacerbation requiring treatment at ER and hospitalization. Daily life is disturbed to a large extent.

intersection point, i.e. moderate persistent asthma. In patients with symptoms not controlled by treatment step 4, whose "apparent" severity is moderate or severe persistent, the "true" severity is determined as the most severe persistent asthma.

Comparison of asthma severities between children and adults demonstrates one-level differences: intermittent, mild persistent, and moderate persistent in adults correspond, respectively, to mild persistent, moderate persistent, and severe persistent in children.

5.2. Treatment Goal of Childhood Asthma

Treatment goal of childhood asthma is shown in Table 13. Although the ultimate goal of childhood asthma treatment is complete remission or cure, practical targets in daily life are (1) controlling symptoms, (2) restoring and/or maintaining normal respiratory functions, and (3) keeping good quality of life (QOL).

5.3. Control Level

Control levels are determined by symptoms, interference with daily activities and frequency of inhalation of short-acting β_2 stimulants (Table 14).

5.4. Control of Asthma

The level of complete control is the status which JPGL 2012 intends to help non-specialist physicians to aim at in asthma treatment and management. Important factors in attempts to attain this goal are: (1) appropriate use of anti-inflammatory drugs, (2) elimi-

Table 12 How to determine true asthma severity in patients under treatment with anti-asthma drugs

Asthma severity decided from patient's symptoms without considering current treatment step	Current treatment step			
	Step 1	Step 2	Step 3	Step 4
Intermittent asthma	Intermittent asthma	Mild persistent	Moderate persistent	Severe persistent
Mild persistent asthma	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Moderate persistent asthma	Moderate persistent	Severe persistent	Severe persistent	Most severe persistent
Severe persistent asthma	Severe persistent	Severe persistent	Severe persistent	Most severe persistent

Table 13 Treatment goal of childhood bronchial asthma

Although final goal is remission or cure, the aims of daily control are:

1. Complete control of asthma symptoms
   - Reduced or no need for β_2 stimulants in exacerbation.
   - No symptoms day and night.
2. Normal respiratory functions
   - Stable PEF rate. Stable pulmonary function tests.
   - Improved airway hyper-responsiveness (no symptom aggravation after exercise, cold air inhalation, etc.).
3. Improved QOL
   - Normal daily life, including sports. No absence from school.
   - No side effects associated with drug therapies.

nation of environmental risk factors, and (3) educational and enlightening activities for patients and caregivers regarding adequate asthma management in daily life. The first factor, i.e., appropriate use of anti-inflammatory drugs, becomes the most efficient and effective strategy along with the recent development of anti-inflammatory drugs for chronic airway inflammation. Favorable control can be achieved by selecting an appropriate treatment step based on asthma severity. However, insufficient treatment, inappropriate medication, and unavoidable exacerbation factors result in poor control. The asthma control test was devised for the evaluation of control levels, the result of which would help adjust the treatment and management towards favorable control.

5.5. Evaluation Methods of Asthma Control Levels

(1) Asthma dairy: A diary kept by a patient would be useful for doctors to gain access to the information pointing to asthma control through the patient's own description of respiratory symptoms, and conditions of sleeping, feeding, and exercising in daily life. The information about drug use and the values of peak flow meter monitoring would also be important for the evaluation of control. In addition, assessment of the respiratory functions by spirometer is important.

(2) Childhood Asthma Control Test (C-ACT)[20]: C-ACT is a childhood asthma control test used in many countries for children aged 4-11 years. The test consists of 7 questions, of which diseased children answer the first 4 and their parents answer the remaining 3. The first 4 questions are of a face scale type to allow children to answer them easily. Scoring is as follows: 27 points is complete control; ≥20 is favorable control; and <20 is poor control. Long-term management is conducted with a goal of 27 points in the minds of medical staff. For children aged ≥12, the Asthma Control Test (ACT) for adults can be used.

(3) Japanese Pediatric Asthma Control Program (JPAC)[21]: Severity and control status can be assessed by the JPAC system. It allows the selection of treatment step according to the guideline. Step-up and step-down may also be determined. Scoring is as follows: 15 points is complete control; 12-14 is favorable (but still insufficient) control; and ≤11 is poor control. Conduct treatment and management with a goal of 15 points in mind. Full scores in both C-ACT and JPAC correspond to well-controlled state in JAGL 2013.

5.6. Avoidance of Exacerbation Factors

Most patients with childhood asthma have atopic diathesis and produce specific IgE antibodies to mites in house dust. Tests are needed to determine the specific IgE antibodies to house dust mites and other possible allergens, and the elimination of these allergens from patients' living environment is necessary.

5.7. Allergy Tests and Assessment

Mean total IgE values vary with age. High values are those that exceed the mean + ≥2 SD. The first step of investigating the allergens of childhood asthma is to presume environmental antigens by history taking. Routine examinations include skin tests and measurement of serum specific IgE antibodies in the blood. However, even if the results prove positive for specific IgE antibodies, they are not all causes of asthma.

5.8. Instructions for Environmental Improvement (Table 15)

Cleaning rooms with a vacuum cleaner is an important measure against mite antigens. Using a wood or cushioned floor as flooring material is effective. Measures for bedclothes are also important; bedclothes should preferably be vacuumed at least once a week. Sensitization to pets (e.g. cats, dogs, and rodents) may induce exacerbation, so contact with

Table 14 Asthma control levels

Component of control	Classification of asthma control		
	Well-controlled	Partially controlled	Poorly controlled
Mild symptoms	none	≥1/month ≤1/week	≥1/week
Apparent symptoms	none	none	≥1/month
Interference with normal activity	none	none	≥1/month
SABA use for symptom control	none	≥1/month ≤1/week	≥1/week

Control levels are evaluated by conditions during the recent 4 weeks.

Mild symptoms indicate transient cough and/or wheezing induced by exercise, laughing and crying. Also included are short periods of coughing at the time of awakening and during sleep.

Apparent symptoms indicate continuous coughing and wheezing with dyspnea and chest tightness.

>80% of predicted/personal best in PEF and/or FEV1.0%, <20% of circadian changes in PEF, and <12% of FEV increase by β_2 stimulant inhalation are preferable as well-controlled conditions.

At the time of assessment, hospital admission due to severe exacerbation, use of oral glucocorticosteroid for symptom control, and seasonal exacerbation in recent 12 months should be considered.

Table 15 Points for improvement in environmental conditions

Bedding	Use anti-mite sheets and covers; wash bedding frequently and hang it outdoors to dry in the sun
Mattress	Do not use mattresses; wooden floors are preferable
Sofa	Use sofas made of leather or artificial leather; no fabric-made sofas
Stuffed toys	Do not use stuffed toys; use washable ones if necessary
Furniture	Use easily cleanable furniture only
Drapes	Use window shades instead of curtains; washable curtains if necessary
Pet animals	Do not keep mammals and/or birds inside rooms
Vacuum cleaner	Use one equipped with 2-layered dust bag
Potted plants	Do not grow plants inside rooms
Laundry	Do not hang the laundry inside rooms
Heating appliances	Exhaust gas must be ducted outdoors if kerosene or gas heater is used
Materials for building houses	Eliminate architectural materials containing volatile chemicals such as aldehyde and phenol
Tobacco-smoking	Persuade family members to discontinue smoking inside rooms

these animals should be avoided.

5.9. Instructions for Smoking Cessation

Smoking, active or passive, is an exacerbation factor of asthma. Smoking by 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 children themselves are smokers, instruct them about the adverse influences on treatment and have them undergo smoking cessation therapy.

6. Long-Term Management by Medication

6.1. Formulations and Characteristics of Long-Term Management Drugs (Controllers)

Long-term management drugs (controllers) are those drugs that are continuously used to reduce and eliminate patients' asthma symptoms, improve their QOL, and normalize and maintain their respiratory function. Controller drugs should have anti-inflammatory effects. Drugs with anti-inflammatory effects include inhaled corticosteroids (ICSs), leukotriene receptor antagonists (LTRAs), and theophylline. Per-oral steroid administration for long-term management is limited to the most severe cases because of adverse effects. ICSs are routinely used for patients at the level of severity that is higher than moderate persistent, because ICSs have strong anti-inflammatory action with relatively low systemic adverse effects. Long-acting β_2 agonists (LABAs) are concomitantly used with an ICS for long-term management; LABAs should not be used alone.[23]

(1) Inhaled corticosteroids (ICSs): ICSs potently suppress airway inflammation and play an important role in long-term asthma control. As airway inflammation is ameliorated, there occurs an improvement in subjective symptoms, respiratory function, and air-

Table 16 Asthma management in children under 2 years of age

	Step 1	Step 2	Step 3	Step 4
Basal therapy	SABA As needed	LTRA and/or DSCG	ICS (medium dose)	ICS (high dose) possibly add LTRA
Additional therapy	LTRA and/or DSCG	ICS (low dose)	LTRA LABA (p.o. or adhesive skin patch)	LABA (p.o. or adhesive skin patch) Theophylline (maintain at 5-10 mg/mL in blood conc.) can be considered

LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; DSCG, disodium cromoglycate; LABA, long acting beta agonist.

LABA is discontinued when good control level is achieved. LABA (p.o.) is defined as the β_2 stimulants prescribed as twice a day.

Theophylline is not used for patients under 6 months of age. Theophylline is not recommended for patients with history of convulsion. Prescription of theophylline for patients with fever should be with caution.

Strongly recommend that uncontrollable patients with step 3 or step 4 management strategy be referred to experts in treating severe childhood asthma.

way hyper-responsiveness, and also hospitalization due to exacerbation and deaths from asthma decrease in number.[24-26] However, no evidence has been obtained regarding improved natural outgrowth of symptoms by persistent use of ICSs for long periods.[27,28] Combination drugs of ICS and LABA can be used for children aged ≥5 years. Select an adequate drug formulary depending on the patient's age and/or inhalation techniques to maximize the efficiency of inhalation.

(2) Leukotriene receptor antagonists (LTRAs): LTRAs inhibit bronchoconstriction and airway inflammation,[29] and are effective for long-term management. In many cases, LTRAs improve respiratory function and reduce the frequency of exacerbations within 1-2 weeks after administration. In patients with mild persistent asthma, LTRAs are as effective as ICSs.[30,31] Efficacy of LTRAs as additional drugs to ICSs has also been demonstrated.[32-34]

(3) Sustained release theophylline (SRT): SRT, which has a bronchodilator action and an anti-inflammatory effect, is used as a controller. The dosage of theophylline is determined with factors that influence metabolisms, such as individual differences, infections, meal contents, and concomitant drugs. Caution should be taken for an elevated serum theophylline level resulting from decreased clearance caused by fever during viral infection. In infants, an intractable convulsion associated with theophylline administration causes a problem.[35]

(4) Long-acting β_2 agonists (LABAs): Since β_2 stimulants have no inhibitory effect on airway inflammation, LABAs may be used concomitantly with ICSs or other anti-inflammatory drugs. Besides inhaled LABAs, transdermal patches[36,37] and per-oral medicines are available as LABAs in Japan. The serum tulobuterol level is maintained for 24 hours after pasting of transdermal tulobuterol patch.

6.2. Long-Term Management Plan

Selection of treatment step based on asthma severity: In a pharmacotherapy plan for long-term control of asthma, determine its severity on the basis of symptoms and their frequency during the most recent one month (see Table 11) and select a long-term management drug combination for the treatment step determined by the severity (Table 12). The pharmacotherapy plan for long-term management is divided into three age groups: <2, 2-5, and 6-15 years old (Table 16-18). Table 19 indicates doses of different products of ICS in treatment steps 1 to 4.

During treatment, the control status can be evaluated by monitoring subtle asthma symptoms, apparent asthma exacerbation, daily life restrictions such as in sleeping, feeding and speaking, and frequency of unexpected inhalations of β_2 stimulant (Table 14). Favorable control is indicated by ≤20% diurnal variation in PEF rate or ≥80% of the patient's personal best rate. Using a control questionnaire, C-ACT and/or JPAC and asthma diary is also useful for the evaluation. Table 20 lists criteria that indicate the status of favorable asthma control.

If control is insufficient or poor, try to achieve complete control through additional treatment or step-up. It is also important to re-examine the appropriateness of medication, allergen avoidance and the effects of psychosocial factors. If there are no positive effects even at treatment step 4, consider hospitalization for further treatment[38] or per-oral corticosteroid administration as in the case of most severe persistent asthma.

If complete control has been achieved for 3 months or longer, consider a step-down depending on the severity, history of disease, respiratory function, and medication. Provided a step-down is applicable, reduce the dosage to the lowest recommended dose to maintain the control level. When management works out well and asthma symptoms are controlled below the intermittent level, and, at the same time, respira-

Table 17 Asthma management in children 2-5 years of age

	Step 1	Step 2	Step 3	Step 4
Basal therapy	SABA as needed	LTRA and/or DSCG and/or ICS (low dose)	ICS (medium dose)	ICS (high dose) + (possibly add one or more of the following drugs) LTRA Theophylline LABA or SFC
Additional therapy	LTRA and/or DSCG		LTRA LABA or SFC Theophylline (consider)	Consider the following: Increase ICS/SFC to higher doses or p.o. steroid

LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; DSCG, disodium cromoglycate; LABA, long-acting beta agonist; SFC, salmeterol/fluticazone combined drug.

LABA is discontinued when good control level is achieved. When SFC is started, oral and percutaneous LABA should be discontinued.

Addition of SFC to ICS is acceptable; however, total dose of steroid is limited within the dose of basal therapy. SFC should be used for patients 5 years or more of age.

Uncontrollable patients with step 3-management strategy are recommended to be referred to experts in treating severe childhood asthma.

As an additional therapy at step 4, an increase of ICS/SFC to higher doses or p.o. steroid therapy or long-term admission management is considered. Patients should be controlled under experts in treating severe childhood asthma.

Table 18 Asthma management in children 6-15 years of age

	Step 1	Step 2	Step 3	Step 4
Basal therapy	SABA as needed	ICS (low dose) and/or LTRA and/or DSCG	ICS (medium dose)	ICS (high dose) + (possibly add one or more of the following drugs) LTRA Theophylline LABA or SFC
Additional therapy	LTRA and/or DSCG	Theophylline (consider)	LTRA Theophylline LABA or SFC	Consider the following: Increase ICS/SFC to higher doses or p.o. steroid

LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; DSCG, disodium cromoglycate; LABA, long-acting beta agonist; SFC, salmeterol/fluticazone combined drug.

LABA is discontinued when good control level is achieved. When SFC is started, oral and percutaneous LABA should be discontinued. Addition of SFC to ICS is acceptable; however, total steroid dose is limited within the dose of basal therapy.

It is recommended that uncontrollable patients with step 3 management strategy be referred to experts in treating severe childhood asthma.

As an additional therapy at step 4, an increase of ICS/SFC to higher doses or p.o. steroid therapy or long-term admission management is considered. Patients should be controlled under experts in treating severe childhood asthma.

tory function is favorable after reduction to the lowest recommended dosage, treatment can be discontinued (Fig. 5). At present, there are no explicit criteria for discontinuation of drugs. Even if symptoms are not apparent any longer (i.e. a status without treatment or symptoms), the patient should be followed up. That is because remission does not mean cure.

7. Diagnosis and Treatment of Persistent Cough

7.1. Persistent Cough and Asthma

No definite criteria exist for persistent cough in children. In adults, The Japanese Respiratory Society defines three types of coughs: chronic cough, prolonged cough and acute cough. Symptoms continue, respectively, for ≥8 weeks, <8 weeks ≥3 weeks, and <3 weeks. Patients with underlying diseases which cause persistent cough for over 8 weeks are diag-

Table 19 Dose comparison of ICS

Manufacture of drug	Low dose (mcg)/day	Medium dose (mcg)/day	High dose† (mcg)/day
Fluticasone (FP)	-100	-200	-400
Beclomethasone (BDP)	-100	-200	-400
Ciclesonide (CIC)	-100	-200	-400
Budesonide (BDP-DPI)	-200	-400	-800
Budesonide inhalation solution (BIS)	-250	-500	-1,000

†High doses of ICS should preferably be administered under the control of a physician with enough experience in childhood asthma management.

Table 20 Conditions for well-controlled status

1. No wheeze or exacerbation; no limitation in daily life (e.g. sleeping, exercising).
2. No subtle respiratory symptoms indicative of airway hyper-responsiveness (i.e. transient wheeze and cough associated with exercise, laughing and/or URI).
3. No needs for β_2 stimulant. No improvement of FEV1 by β_2 stimulant inhalation.
4. Full scores of JPAC and/or C-ACT.
5. Daily variation of PEF <20%. Keeping of FEV1 >80% of self best.
6. FEV1 is kept >80% of expected value; rise in FEV1 by β_2 stimulant inhalation <12%.

Caution: *No overmedication!* Always remind yourself.

nosed as having chronic cough in a broad sense. In this broad sense, asthma is the leading cause of chronic cough. Other causes are postnasal drainage, diseases associated with other atopic illness, and gastro-esophageal reflux.

Cough-variant asthma is a unique condition demonstrating persistent cough which has airway hyperresponsiveness but no history of wheezing. Inhalation of β_2 stimulant is effective as its treatment. Some of the patients with cough-variant asthma end up by having bronchial asthma.

Underlying mechanisms of persistent cough are (1) airway inflammation by infection and allergy, (2) direct and/or indirect stimulation by sputum, nasal discharge and gastric juice, and (3) stimulation by airway smooth muscle constriction and mucosal edema in various pathological conditions.

7.2. Treatment of Persistent Cough

Fundamental strategy for the treatment of persistent cough is first to determine the underlying mechanisms, and then deal with them. In the cases of poor asthma control, step up the treatment level, eliminate exacerbation factors from the patient's immediate environment and educate him/her about asthma control.

8. Inhalers and Spacer

Inhalation therapy is critical and effective for the daily management and treatment of asthma exacerbation in children including infants. Have a good understanding of the characteristics (i.e. merits and demerits) of inhalers for the selection of an adequate type based on the child's status.

8.1. 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). In Table 21, combinations of nebulizers and aiding tools (i.e. mask and spacer) and drugs for different age groups are demonstrated. It can be selected by assessing various conditions such as efficiency of inhalation, compliance, patients' preference, financial matters, and so forth.

(1) Nebulizer: Since respiratory control is not required during inhalation, a nebulizer can be used regardless 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 vaporizing capacity. Ordinary ultrasonic nebulizers are unsuitable for inhaling anti-asthma drugs because of thermal denaturation and concentration changes of drugs in the reserve-tank. A defect of ultrasonic nebulizer is that they do not nebulize suspensions of budesonide inhalation solution very well.[39]

(2) Use of nebulizers: Children should inhale at a resting respiratory rate in a sitting position. Those old enough to breathe orally inhale with a mouthpiece, attached to the nozzle of nebulizer, put in the mouth. With infants, use a nebulizer with a mask attached to the nozzle, to cover the mouth and nose. Adhesion of mask to patient's face greatly influences inhalation efficiency, which gets reduced by nasal inhalation or

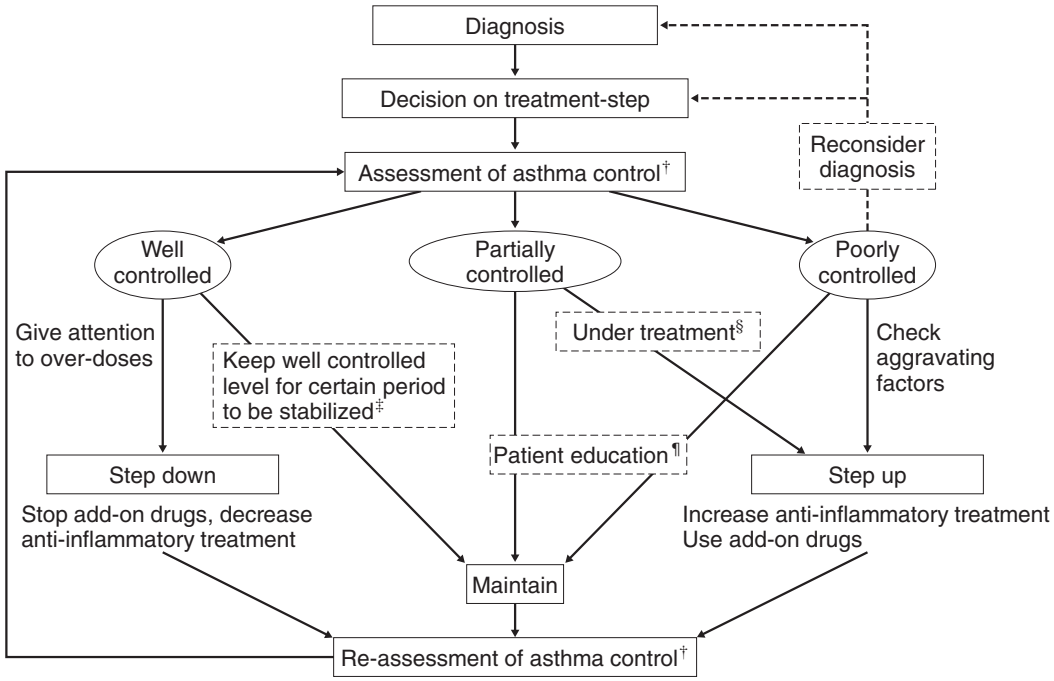

Fig. 5 Strategy of long-term management of asthma.
† At the assessment of patient asthma control, it is important to check drug-adherence, inhalation techniques, and environmental controls for eliminating aggravating factors.
‡ Keep treatment regimen at least 3 months till patient's control levels are well maintained.
§ It is preferable to step up treatment regimen when patient's control levels stay at the partially controlled level for 3 months.
¶ In cases where patient's control level is expected to improve through education (†), treatment regimen can be maintained at the same step.

Table 21 Combination of inhalation device and aiding tools

Age	Drug	Inhalation devices and aiding tools
Baby	Solution	nebulizer + mask
	pMDI	spacer with mask
Infant	Solution	nebulizer + mask or mouth piece
	pMDI	spacer with mask or mouth piece
School children	Solution	nebulizer + mouth piece
	pMDI	spacer with mouth piece
	DPI	(-)

crying.[40,41]

(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 and inhalation cannot be synchronized, pMDI can be employed by using a spacer and a mask. Using DPI, a patient inhales a drug through self-respiration. 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 applied.

8.2. Spacer

A spacer is an indispensable aiding instrument (tool) for pMDI in infants who cannot accurately perform the procedures for the synchronization of spray and inhalation. Concomitant use of a spacer allows inhalation at a normal respiratory rhythm even without synchronizing spray and inhalation; it thus results in increased inhalation efficiency. In addition, a spacer is useful in adsorbing large particles (≥5 μm) 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, cover the nose and mouth with a mask to maintain inhalation efficiency.

Many types of spacers are available. Select a spacer with data assuring aerodynamic properties, clinical usefulness and safety. The effectiveness of a spacer is greatly influenced by concomitant agents, procedures as well as its shape, structure, and physical properties. To maximize the benefit from a spacer, mask the face closely without leakage and prevent static electricity.

Technical mastery in the adequate use of inhalation devices and aiding accessories is essential to obtain maximal efficacy of inhalation drugs (Table 22).

Table 22 Check list of inhalation therapy

- Nebulizer
  - ☐ bite mouth-piece firmly
  - ☐ expectorate salivary fluid without reversing from time to time
  - ☐ can ventilate through mouth
  - ☐ adhere mask tightly on the face
  - ☐ can ventilate without crying
  - ☐ wipe away solution on the face after inhalation
- pMDI
  - ☐ can synchronize actuation and inhalation
  - ☐ can ventilate through mouth
  - ☐ can ventilate slow and deep
  - ☐ can hold breath for certain periods of time
- pMDI + spacer
  - ☐ when using mouth-piece, can bite mouth-piece firmly
  - ☐ when using mask, can adhere mask tightly on the face
  - ☐ inhale at every actuation
  - ☐ can ventilate without crying
  - ☐ can hold breath for certain periods of time
- DPI
  - ☐ keep device in appropriate position
  - ☐ do not blow away drug-powder before inhalation
  - ☐ can ventilate with strong inspiration
  - ☐ can ventilate deep
  - ☐ can hold breath for certain periods of time
- Other points
  - ☐ gargle or drink water after inhalation (in the case of using ICS)

9. Patient Education

To perform asthma treatment effectively, educate patients and their caregivers to be actively involved in the treatment.[42,43]

(1) Infants (2-4 years old): Do not discomfort patients during treatment. Get them interested in the treatment and kept motivated. Encourage and compliment them on their good performance in inhalation and habituate them to the treatment gradually.

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

(3) Pre-puberty children (upper graders of elementary school): Instruct patients about the need for continuing treatment without interruption. According to their level of understanding, educate them about the pathophysiology of asthma and its treatment. Since it is difficult to make such young patients take charge of the part of treatment and management that their parents have taken care of, compliment them on their efforts to achieve self-fulfillment and eventual self-management.

(4) Children in puberty (junior high school students or older): More patients likely disobey their parents because of parent-child conflicts during puberty. Treatment and management will be interrupted by insufficient education and instruction. This results in poor control and increased risks of death from asthma. Directly instruct patients at consultation. It is often the case that not enough time may be taken in outpatient departments, so it is far more effective to hospitalize patients with severe persistent asthma for education and instruction during a summer vacation, or when they can take time off from schoolwork without difficulty.

9.1. Improvement in Adherence

Sharing a treatment goal and establishing a partnership are important to both patient and doctor. Repeatedly check the patient's basic knowledge and skills at consultation to help him/her take a positive attitude toward treatment and high adherence.[44]

9.2. Pubertal to Adolescent Asthma

Problems increase during puberty, e.g., low compliance, remodeling, and death from asthma.[45] Understanding the characteristics and problems of pubertal asthma on the patient's part is important for treatment and management (Fig. 6). Points of management and treatment for pubertal asthma are demonstrated in Table 23.

10. Exercise-Induced Asthma (EIA)

(1) EIA: EIA is a phenomenon in which wheezing and dyspnea occur temporarily during exercise. Its pathology is yet to be clarified. Cooling in the airway, caused by hyperventilation during exercise,[46] and elevated osmolarity in the airway epithelium, caused by water loss, are potential underlying pathophysiology.[47,48] Increased airway temperature after exercise may also be involved.[49]

(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.[50,51] If maximal percent falls of FEV1 and PEF are, respectively, larger than 15% and 20%, a diagnosis of EIA is confirmed.

(3) Severity: The maximum decreasing rate of FEV1 after exercise is higher in patients with more severe asthma. This serves as a parameter in the determination of the severity of asthma.[52] Since EIA is also associated with airway hyperresponsiveness, history taking about EIA serves as a clue to whether or not the current treatment step is appropriate.

(4) Prevention: To prevent EIA, select the appropriate treatment step based on the severity. If in fact EIA has occurred, prevent its repetition by resorting to

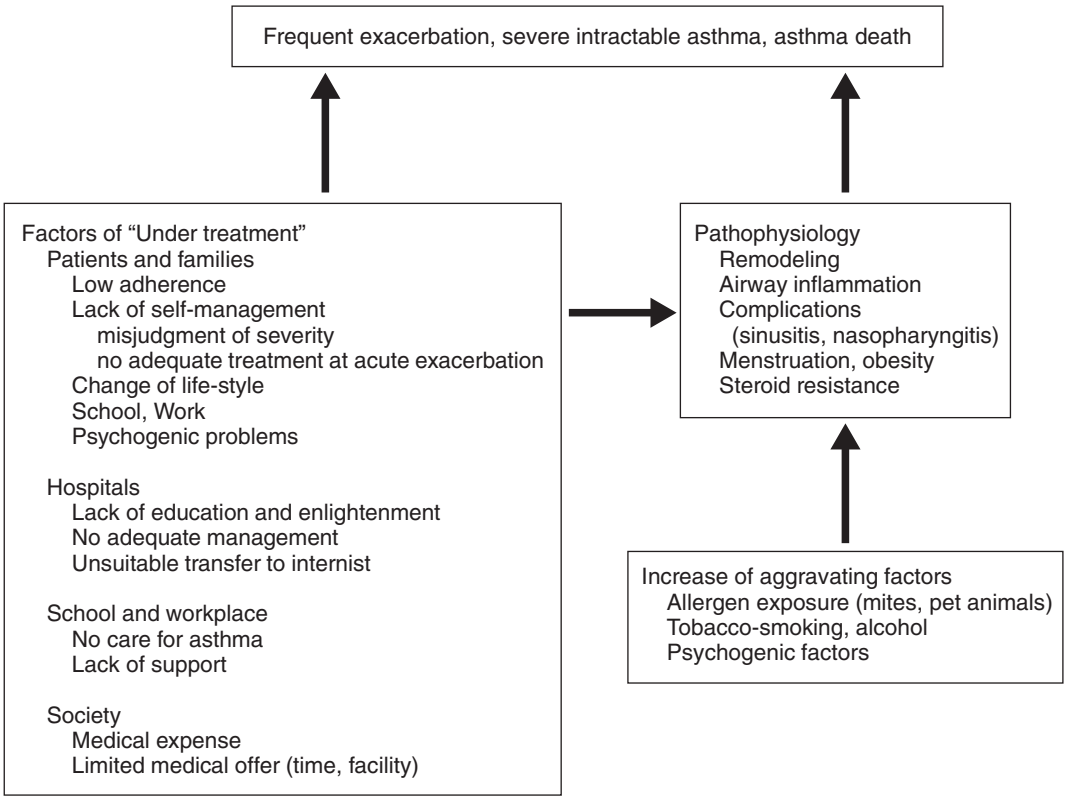

Fig. 6 Problems of adolescent asthma.

the procedures shown in Table 24.

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

11. Participation in Events at Preschools and Schools

Parents of children with asthma and their attending physicians should help to make supportive plans for their extracurricular studies and club activities, such as school trips, school camps, and excursions in cooperation with preschools and schools so that those children can participate in those events whenever possible. Instruct children with asthma and their parents beforehand about cautions they should keep in mind when taking part in such events and measures against acute exacerbation.

(1) If children with asthma develop acute exacerbation while participating in an event, make them inhale a bronchodilator (β_2 stimulant) earlier than in a regular treatment schedule because of the special situation. Likewise, depending on the status of daily symptoms, consider an increase of daily dose of ICS and/or short-term per-oral administration of a corticosteroid.

(2) Hand a disease referral form to a physician in emergency so that the patient can receive appropriate treatment at a nearby medical institution in acute exacerbation that occurs during travel.

(3) If patients have histories of allergic symptoms after contact with animals, caution should be taken for contact with animals at zoos and similar facilities.

(4) Stand on the windward side to avoid wafts of smoke from fireworks or a campfire.

(5) Instruct roommates, if applicable, to refrain from wrestling and pillow fights on beds to keep the room free from allergens and stimulants.

11.1. 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 slowly.

(2) If allergies occur upon a child's contact with an animal, then keep the child from taking care of animals at school.

(3) Have class teachers explain about EIA to patient's classmates.

(4) Take care so as for a child with asthma to avoid allergens and airway stimulators during clean up duties at school.

Table 23 Countermeasures for adolescent asthma

1. Recognition of features and pathophysiology in adolescent asthma
2. Evaluation
Adherence
Disincentive factors
Motivation to adherence
Ease of access to medical facilities
Control levels
Asthma diary
PEF (peak expiratory flow) monitoring
EIA
JPAC (Japanese Pediatric Asthma Control Program)
C-ACT (Childhood Asthma Control Test)
Remodeling, small airway obstruction and airway inflammation
Circadian variation of PEF
Flow volume curve
3. Support for increasing self management ability
Establishment of good relationships between medical staff and patients and family members
Easy and sufficient explanation for asthma pathophysiology
Provision of education programs
Sufficient advice for cessation of smoking, school activities, work, marriage, child birth, etc.
Raise awareness of asthma-death
Provision of specific action plan for asthma management
Reconfirmation of own management and treatment goal
4. Establishment of medical support in various places
Local community
Preparation of instruction forms in acute exacerbation
Provision of medical information about patients
School
Use of instruction table for school life management in school
Preparation of referral forms in school trips, extra curricular activities and travels
Workplace
Support to enhance understanding in workplace
5. Assessment of complications
Allergic rhinitis, sinusitis,
Pneumothorax, subcutaneous emphysema, mediastinal emphysema
Psychosomatic diseases
6. Reevaluation of treatment and management
Evaluation of current medical plan
Step up therapeutic plan if necessary

11.2. Instruction Table for School Life Management

An instruction table (http://www.gakkohoken.jp./book/bo0002.html, in Japanese) for school life management was made for allergic diseases, which include asthma, atopic dermatitis, allergic conjunctivitis, anaphylaxis and food allergies, and allergic rhinitis. In Japan, children with these 5 allergic diseases are asked to submit this table to preschool and school administrations; the table gives the information about the treatment for the child patients' allergic diseases, including asthma, with precautionary measures to take on the part of the administration. The table also gives emergency contact telephone numbers, and names of consulting medical institutions and physicians in emergency for patients' safety.

Table 24 Prophylaxis of exercise-induced asthma (EIA)

1. Warm-ups before exercise †
2. Drugs
β_2 stimulant ‡
DSCG §
LTRA ¶
Other medications ‖
3. Others
Mask #
Training regularly ††

† Light exercise causing mild EIA reduces EIA that is induced subsequent to hard exercise because of the refractory period.

‡ Inhalation or intake of β_2 stimulant 15 min or 60 min before exercise inhibits EIA. However, use of β_2 stimulant should be limited, because β_2 stimulant may induce airway hyper-responsiveness. Reduction of EIA by training regularly is preferable.

§ Inhalation of DSCG 15 min before exercise prevents reduction of FEV1 and PEF.

¶ LTRA inhibits EIA.

‖ EIA indicates poor control of asthma. Adequate treatment with controller drugs including ICS and LTRA prevents EIA.

Wearing mask prevents EIA because it helps inhalation of air with adequate moisture and temperature.

†† Regular training reduces severity of EIA.

11.3. Precautions for Vaccination

Conditions such as bronchial asthma, atopic dermatitis, allergic rhinitis, urticaria, or allergic predisposition alone do not preclude vaccination. However, caution should be taken as to whether patients are potentially allergic to vaccine components. Conduct a preliminary diagnosis considering previous allergic symptoms and vaccine additives. ICS and topical use of glucocorticosteroid does not exclude vaccination.

11.4. Vaccine Additives and Inoculum Components for Allergy

Reportedly, gelatin (stabilizer), thimerosal (antiseptics), egg ingredients (culture components), and antimicrobials can cause allergy. The physician should carefully refer to the attached document before giving an injection because constituents may differ in formulation produced in different pharmaceutical companies.

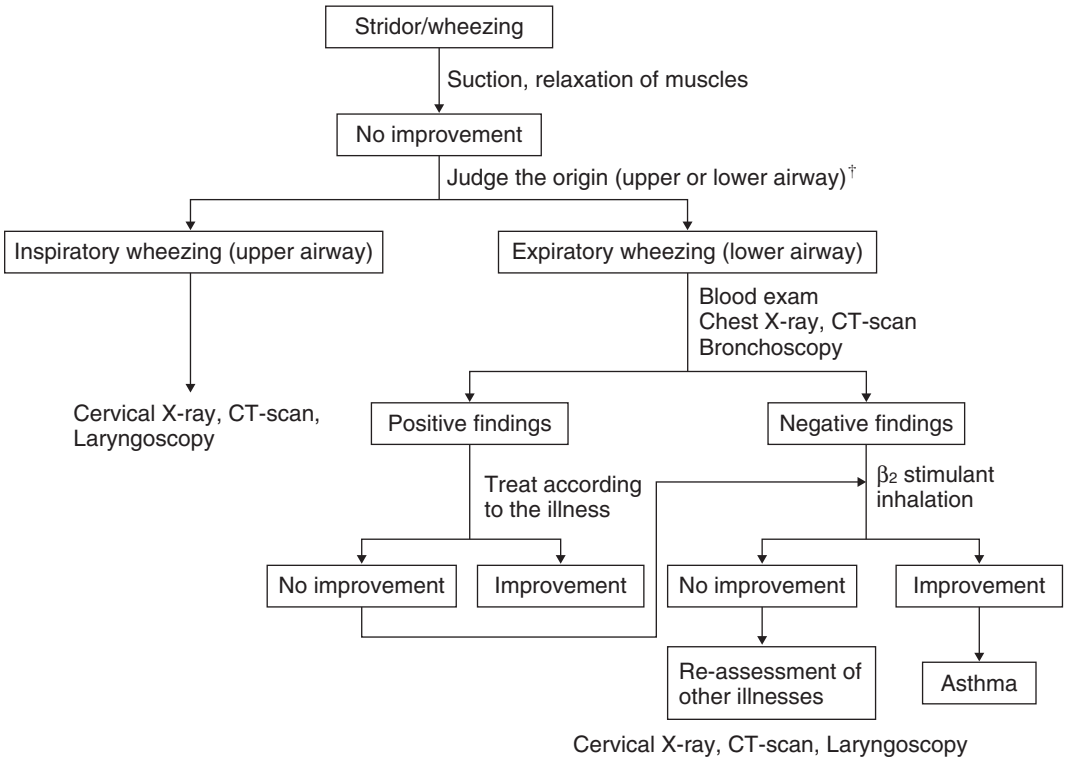

Fig. 7 Diagnostic approach for severely retarded children with bronchial asthma.
† If the origin of wheezing cannot be determined, start work-up from upper airway.

11.5. Major Vaccines for Children with Asthma

(1) Influenza vaccine: Influenza vaccines can be safely used to inoculate children, who eat egg-processed products without serious adverse effects.

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

11.6. Considerations for Surgical Operation

Since asthma is a risk factor in putting the patient under general anesthesia, especially inhalation anesthesia, caution should be taken in the management of physical conditions before and during surgical operation and also for respiratory management after operation.

For non-emergency surgery, a period exceeding at least 2 weeks of no paroxysmal symptoms is required after exacerbation even in patients with mild persistent asthma. If asthma exacerbation occurs within 2 weeks of the previous exacerbation, surgical operation should be postponed. In the cases of non-emergency operation, no-exacerbation periods of 2 or 3 months before operation is recommended, because it takes several months before airway hyperresponsiveness becomes sufficiently reduced.

Complications and allergic reactions to drugs, medical materials, latex, foods, and the like must be investigated prior to surgery. Caution is demanded for patients under systemic steroid administration for 6 months or longer and also for those with adrenocortical insufficiency. Systemic steroid administration should be applied after surgical operation as well.

12. Cautions for Severely Retarded Children with Bronchial Asthma

12.1. Diagnosis

Making a diagnosis of bronchial asthma in child patients with severe retardation is not easy, because these patients often have stridor and/or wheezing due to underlying pathophysiological conditions other than bronchial asthma. Difficulty of conducting respiratory function tests in severely retarded children makes it more difficult to make a definite diagnosis.

12.2. Differential Diagnosis

Basic treatment for stridor and/or wheezing (i.e. suction of secretion, airway management, postural change, relaxation of body muscles) is the first step in making a diagnosis of bronchial asthma. If wheezing does not change by these procedures, further as-

sessment of diagnosis is advanced through the chart shown in Figure 7. Chest X-ray, CT-scan, laryngoscopy and bronchoscopy may be useful. Improvement of stridor and/or wheezing by inhalation of β_2 stimulants may indicate a higher possibility of bronchial asthma. However, unequivocal diagnosis cannot be made by this procedure, because the expectant effect by hydration may improve wheezing.

12.3. Treatment and Management

Basic strategy in the treatment and management for severely retarded children with bronchial asthma is the same as asthma children without severe retardation. However, specific consideration is needed for the treatment and management for the severely retarded when they are in acute exacerbation as well as for a long-term management of them with controller drugs.

12.4. Caution in Acute Exacerbation

Intensity of exacerbation is assessed based on objective signs and symptoms (i.e. wheezing, cough, retractive respiration, etc.), which should be compared with those of the patient under usual conditions. Special devices must be applied to the patient with airway management for inhalation therapy. Application of per-oral theophylline and intravenous injection of aminophylline has to be careful. That is because many severely retarded children are associated with convulsive illnesses. As children with severe retardation easily fall into respiratory failure, early and intensive treatment is necessary.

12.5. Long-Term Management

As shown previously, asthma diagnosis is difficult to make in severely retarded children. Long-term management with anti-asthma drugs should not continue without regular evaluation of drug efficacy. Differential diagnosis is necessary in the cases without improvement by treatment based on asthma severity ranks. When ICS is applied, adequate combinations of inhalation devises, accessories and drugs (i.e. jet nebulizer + mask + budesonide inhalation solution) must be selected. Frequent use of β_2 stimulant must be considered with a combined use of anti-inflammatory drugs such as ICS.

Regular clearance of airways by suction, postural change and other kinds of physical therapy are important in the long-term management of asthma in severely retarded children with bronchial asthma.

13. Conclusion

A new edition of JAGL has been introduced, which reflects recent progresses of strategy in asthma treatment and management for children. A long-term management with anti-inflammatory controller drugs, elimination of airborne antigens from the patient's living environment, and enlightenment and education about bronchial asthma including pathophysiology are the three fundamental factors for the treatment and management of childhood asthma. It is important to maintain "a well-controlled state" for long enough a period, which in turn affords good quality of life and may ultimately result in remission and cure. "Well-controlled state" is defined as completely controlled status without subtle symptoms such as even a short period of wheezing. Essential information is summarized in this review.

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