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Inhaled Corticosteroids in the Management of Adult Asthma

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Abstract: The basic condition underlying bronchial asthma is a chronic airway inflammation that involves inflammatory cells and cells constituting the respiratory tract. Repeated inflammation elicits airway remodeling, leading to severer and more intractable asthma. Airway inflammation causes airway hyperresponsiveness, which results in air flow limitation. There is no marked difference in the status of airway inflammation according to whether the condition is atopic or non-atopic or whether the patient is an adult or a child. The goal of treatment of asthma is to control and resolve airway inflammation. Inhaled corticosteroids represent safe, effective anti-inflammatory therapy and occupy a central role in the long-term management of asthma. The main elements in the application of inhaled corticosteroids include an understanding of the importance of choosing a dose commensurate with the severity of the condition, use of the step-down technique, and early intervention of therapy. Because it is not possible to control all cases of asthma with inhaled corticosteroids alone, it is important to appropriately combine long-acting β_2 agonists, slow sustained theophylline, and leukotriene antagonists.

Key words: Inhaled corticosteroids; Airway inflammation; Anti-inflammatory drugs; Airway remodeling; Early intervention

Introduction

Bronchial asthma is basically a disease of the airways, regardless of whether it is atopic or non-atopic and whether the patient is an adult or a child. The central picture of bronchial asthma is that of a chronic airway inflammation that involves inflammatory cells such as eosinophils, mast cells, T cells (Th2), basophils, and neutrophils, and airway component cells such as airway epithelial cells and fibroblasts. This airway inflammation is worsened and prolonged by the production and release of various mediators and cytokines.

In addition, repeated airway inflammation induces airway remodeling that includes thick-

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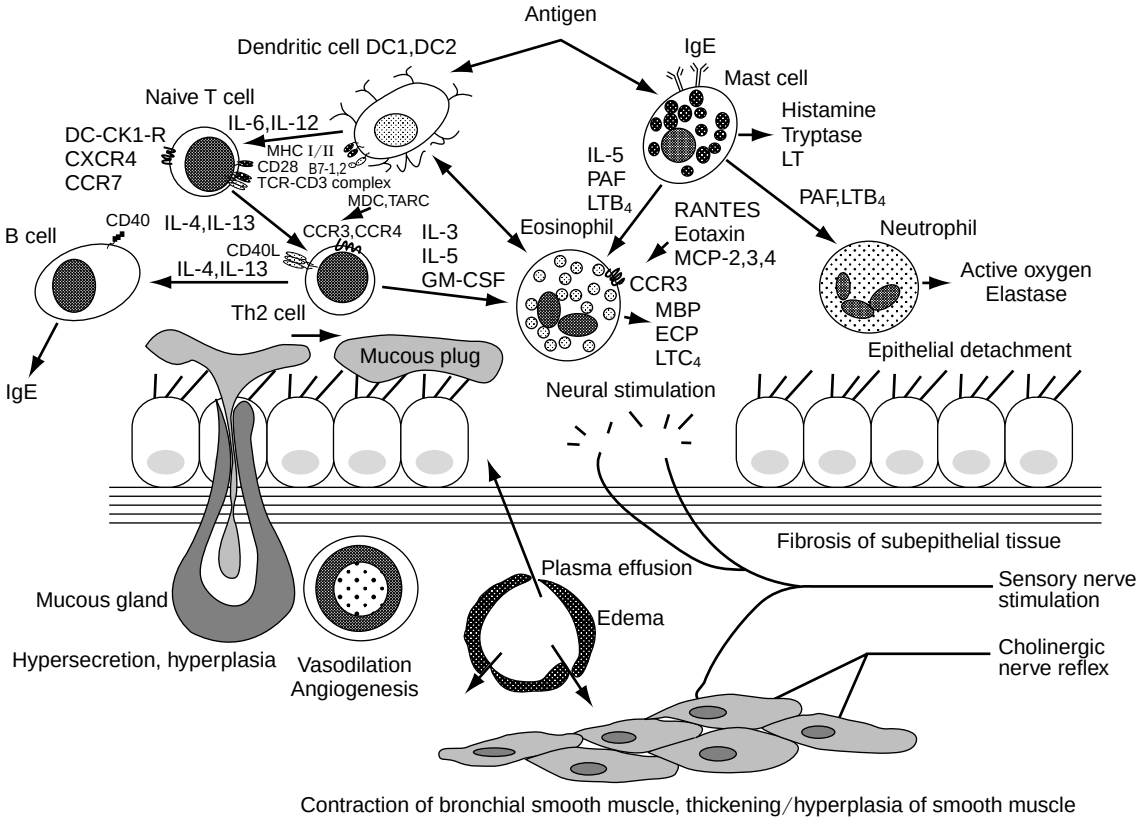

Fig. 1 Pathological condition of the asthmatic airway

ening of the reticular layer under the basement membrane, epithelial metaplasia, proliferation of the submucosal glands, and thickening of the smooth muscle, leading to severer and more intractable asthma. Airway inflammation causes increased airway responsiveness, which easily brings about contraction of the bronchial smooth muscle, increased vascular permeability, and hypersecretion of the airways, resulting in air flow limitation (Fig. 1). Therefore, the inhalation of anti-asthmatic drugs for direct application to the airway seems to be more effective at lower doses and to have fewer systemic effects.

Current anti-asthmatic drugs available for this route include sodium cromoglycate (DSCG), β_2 agonists, corticosteroids, and anticholinergic drugs. Inhaled β_2 agonists and inhaled corticosteroids occupy central roles as bronchodilators and anti-inflammatory drugs, respectively.[1)] This paper describes the use of inhaled anti-asthmatic drugs, particularly inhaled corticosteroids, in the treatment of asthma, and outlines their place in guidelines for the treatment of asthma.

Remedies for Asthma Attack (Relievers)

Asthma attacks vary in degree, ranging from mild wheezing that is barely perceivable by the patient him- or herself to severe attacks that render the patient unable to walk or talk. At any degree of severity, inhaled β_2 agonists play a central role in the treatment of asthma attacks through their potent bronchodilator action. In addition to β_2 agonists, inhaled anticholinergic drugs are used for the treatment of

Table 1 Anti-asthma Actions of Steroids[2)]

General effects related to asthma
- (A) Increase in β-receptors
  - Effects on adenylate cyclase and cyclic AMP
- (B) Effects on leukocytic migration
  1. Decreased number of lymphocytes in blood
  2. Suppression of aggregation of monocytes and macrophages to the site of inflammation
  3. Inhibition of increase in number of neutrophils and their aggregation to the site of inflammation
  4. Decreased number of eosinophils in blood
  5. Inhibition of expression of adhesion molecules
- (C) Effects on cytokines
  - Inhibition of the production of IL-1, TNFα, GM-CSF, IL-3, IL-2, IL-4, IL-5, IL-6, IL-8, IL-11, IL-12, IL-13, INF-γ, RANTES, MIP-1α, and SCF
  - Inhibition of expression of GM-CSF in airway epithelial cells
- (D) Enhancement of neutral endopeptidase
- (E) Activation of endonuclease
- (F) Increase in lipocortin-1 production

Specific effects related to asthma
- (A) Inhibition of IgE production
- (B) Effects on mediators
  1. Inhibition of histamine production
  2. Inhibition of eicosanoid release
- (C) Effects on the pathological condition of asthma
  1. Vasoconstriction
  2. Suppression of vascular permeability
  3. Inhibition of late asthmatic response
  4. Inhibition of mucous secretion

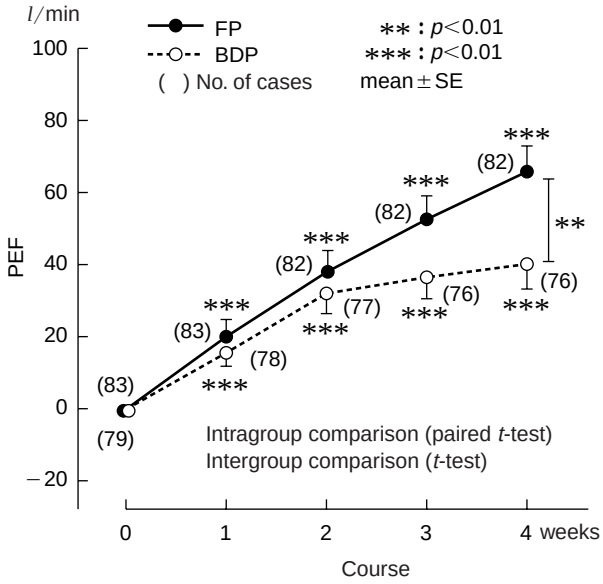

Fig. 2 Changes in morning PEF on inhaled DBP (400μg/day) or FP (200μg/day) therapy[3)]

asthma attacks.

For the treatment of mild symptoms of wheezing or chest tightness to those of moderate asthma, one or two puffs of a β_2 agonist should be administered using a pressurized metered-dose inhaler (pMDI), followed by additional doses at 20-min intervals for one hour and then at one-hour intervals thereafter. At the same time, oral therapy including a β_2 agonist and theophylline should be given. If symptoms are eliminated [as indicated by 70% or greater of predicted peak expiratory flow (PEF)] or if the medication has been successful for 3–4 hours, the patient can remain at home. If symptoms fail to respond to the medication and repeated inhaled β_2 agonist therapy is necessary, the patient will need to make an emergency visit.

The bronchodilator effect of inhaled anticholinergic drugs is weaker and slower than that of inhaled β_2 agonists. However, inhaled anticholinergic drugs exert a greater bronchodilator action than inhaled β_2 agonists in patients with emphysema and therefore are useful in the treatment of patients with asthma complicated by emphysema.

Drugs for Long-term Management of Asthma (Controllers)

Drugs used for improving and eliminating the symptoms of asthma, normalizing respiratory function, and maintaining normalized respiratory function are called controllers. They are divided into anti-inflammatory drugs and long-acting bronchodilators.

1. Anti-inflammatory drugs

Anti-inflammatory drugs used as inhaled anti-asthma drugs include disodium cromoglycate (DSCG) and corticosteroids. Corticosteroids have the most potent anti-inflammatory activity and a wide spectrum of anti-asthma actions (Table 1).[2)]

Inhaled corticosteroids are extremely effec-

tive for relieving the symptoms of asthma, reducing the frequency of acute exacerbation, and improving pulmonary function and suppressing its circadian variation. Since they are inhaled, they act directly at the site of the lesion and are thus effective at a lower dose than that used for systemic administration. In addition, more than 90% of the drug that is swallowed will be metabolized and inactivated by first-pass metabolism in the liver, providing a high level of safety. Therefore, inhaled corticosteroids occupy a central position in long-term drug treatment.

Unlike other drugs, the use of inhaled corticosteroids permits a great deal of flexibility in dose depending on the severity of the disease. In Japan, fluticasone propionate (FP) as well as the conventional beclomethasone dipropionate (BDP) are available as dry powder inhalation. FP, which is equivalent to a half dose of BDP (Fig. 2),[3] seems likely to acquire a central role in anti-inflammatory therapy in the future.

Although the inhalation of DSCG is commonly used in children and is effective in them, its efficacy is limited in adults. However, it has been reported that combination therapy with an inhaled β_2 agonist and inhaled DSCG liquid is effective for severe adult cases.

2. Long-acting bronchodilators

All bronchodilators currently used in Japan are of the short-acting type. Since they are superior in immediate action and effectiveness, they are often used on an as-needed. Although some reports suggest that they have anti-inflammatory action, not much can be expected from them in this regard in the actual clinical setting. Although long-acting inhaled β_2 agonists such as formoterol and salmeterol are not yet available in Japan, these drugs combined with low-dose inhaled corticosteroid therapy have shown to be superior to high-dose inhaled corticosteroid therapy in improving respiratory function.[4]

Inhaled Anti-asthma Drugs Recommended for Long-term Management in Guidelines for the Prevention and Management of Asthma

In severity-matched stepwise drug treatment prescribed for the long-term management of asthma in the Guidelines for the Prevention and Management of Asthma (Ministry of Health and Welfare Immunity/Allergy Study Group) (see appendix, page 368),[5] inhalation of DSCG is considered suitable for mild intermittent type (Step 1) and moderate persistent type (Step 3), while serial usage is recommended for mild persistent type (Step 2) (DSCG is categorized as a mediator antireleaser in the aforementioned table). Single use before exercise or exposure to the allergen is considered particularly effective in Step 1.

Combined use of inhaled anticholinergic drugs is considered useful for Step 3. This class of drugs is relatively safe for elderly patients and is expected to be useful for patients who have concomitant chronic obstructive pulmonary disease (COPD) or severe shortness of breath. Serial use of inhaled β_2 agonists for Step 2 cases is prescribed in the Guidelines. However, due caution is necessary with the serial use of these drugs because there is a risk of aggravating the symptoms of asthma if serial treatment is prolonged.

Inhaled corticosteroids play a central role in the long-term management of asthma. The use of BDP 200μg/day or FP 100μg/day is considered useful for Step 1; BDP 200–400μg/day or FP 100–200μg/day is prescribed for Step 2; BDP 400–800 (up to 1,200) μg/day or FP 200–400μg/day is recommended for Step 3; and BDP 800–1,200 (up to 1,600) μg/day or FP 400–800μg/day is suggested for Step 4. Most important techniques are the accurate assessment of the severity of disease on the basis of clinical signs, symptoms and PEF values and the use of the necessary and sufficient dose of inhaled corticosteroids.

Practical Aspects of Drug Treatment in the Long-term Management of Asthma

1. Initial dose setting for inhaled corticosteroid therapy: the step-down technique

The former guidelines direct that, in principle, the dose should be increased if response to the current dose is insufficient. However, asthma is a paroxysmal disease, and it is important in the actual clinical setting to provide rapid relief of symptoms and improve the quality of the patient's life. Currently, it is more common to adopt a step-down technique to achieve an adequate anti-asthma effect within a short period of time. In this technique, inhaled corticosteroid therapy is begun with a high dose, followed by dose reduction as clinical symptoms improve.

The initial dose of BDP is 600–800μg/day for Step 2 cases and 1,200–1,600μg/day for Step 3 cases, while the initial doses of FP are half the respective BDP doses. It is desirable that these doses be reduced to appropriate maintenance doses after a certain period of time. In the introductory phase of inhaled corticosteroid therapy or under the condition of sustained asthma attack, oral corticosteroid therapy with prednisolone 0.5 mg/kg given for 4–7 days in parallel with the initiation of inhaled corticosteroid therapy provides rapid elimination of symptoms and smooth introduction of inhaled corticosteroid therapy. This method is also a kind of step-down corticosteroid therapy.

2. Early intervention with inhaled corticosteroids and its clinical efficacy[6)]

Asthma is associated with varying degrees of airway remodeling depending on the severity and duration of illness. The possibility that this remodeling is involved in the aggravation and intractability of asthma has begun to draw more attention.

Inhaled corticosteroids are considered effective in preventing and improving airway remodeling by inhibiting the production of inflammatory cytokines in the airway. In actuality, however, it has become apparent that there is a significant difference in the degree of improvement in respiratory function and airway hyperresponsiveness in terms of PEF and $FEV_{1.0}$ according to when inhaled corticosteroid therapy is introduced (Fig. 3).[7)]

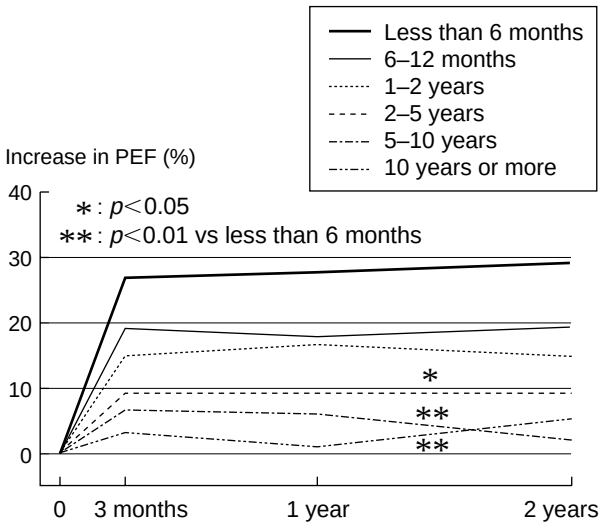

Fig. 3 Changes in PEF after inhaled steroid therapy in 105 asthma patients in relation to the timing of initiation of therapy[7)]

The longer the time until inhaled steroid therapy is introduced, the worse the improvement in PEF.

More specifically, the anti-asthma activity of delayed inhaled corticosteroid therapy is less than that of early therapy, and improvement in respiratory function and airway hyperresponsiveness are delayed in comparison with those after early therapy over the course of illness. This may be explained as follows: Airway remodeling progresses to cause irreversible organic change in the airway when the introduction of inhaled corticosteroid therapy is delayed, and this organic change results in reduced responsiveness to inhaled corticosteroids. If symptoms persist in mild (Step 2) or severer cases, inhaled corticosteroids play the central role in treatment. However, no definite consensus has been reached as to the propriety or timing of their introduction in milder cases.

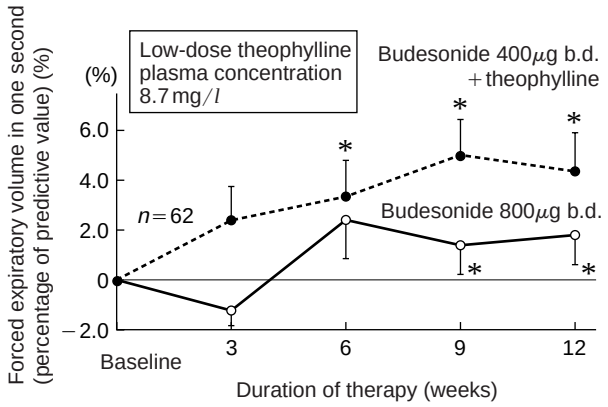

Fig. 4 Additive effect of low-dose theophylline[8]

If there are relatively constant symptoms even in mild cases or airway inflammation is apparent from eosinophilia in sputum, early intervention with inhaled corticosteroid therapy is considered to prevent future aggravation and intractability of the disease. Cough variant asthma (CVA), which proceeds to bronchial asthma in some cases, is considered to be a precursor to asthma. Introduction of inhaled corticosteroid therapy lasting for a certain period may prevent the onset of asthma in such cases. This issue deserves further consideration.

3. Drugs combined with inhaled steroids

If low- or moderate-dose inhaled corticosteroid therapy does not achieve sufficient control in patients with Step-2 or Step-3 disease, two treatment options are available. One is to increase the dose of corticosteroid to high-dose inhaled corticosteroid therapy, and the other is to keep using the same dose of corticosteroid and combine a long-acting inhaled β_2 agonist, slow sustained theophylline, or leukotriene antagonist. The combined effect of inhaled corticosteroids and long-acting inhaled β_2 agonists[4] has already been discussed. Combined use of sustained-release theophylline is also more effective than increased doses of inhaled corticosteroid therapy alone (Fig. 4),[8] and the usefulness of combined leukotriene antagonists has been reported.

Future Prospects of Inhaled Drug Therapy in the Treatment of Asthma

Inhaled β_2 agonists and inhaled corticosteroids represent two main axes in the treatment of asthma. Inhaled β_2 agonists are the most potent bronchodilators, and no effective anti-inflammatory agents are superior to inhaled corticosteroids. Although long-acting inhaled β_2 agonists are not yet available in Japan, the introduction of a compound drug consisting of an inhaled corticosteroid and β_2 agonist is currently under consideration, leading to expectations of high efficacy (as of February 2001).

BDP is administered in the form of a pressurized metered-dose inhaler (pMDI), with fluorocarbon gas acting as the propellant. However, the industrial use of regulated chlorofluorocarbons (CFC) has been prohibited because of the issue of ozone depletion, and suspension of the ban on their medical use soon may be terminated. Since there are also concerns about the influence on the environment of the CFC substitute HFA, medication via a dry power inhaler (DPI), as in the case of FP, seems likely to become more common in the future.

Budesonide, available in the form of a dry powder, is expected to be introduced in Japan. A highly efficient dry power inhaler (Turbuhaler) is used for the inhalation of this product. Improvement in the quality of life of asthma patients is likely to be attempted through the development of safer, more effective corticosteroids and better inhalers.

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APPENDIX

Severity-matched Stepwise Drug Treatment in the Long-term Management of Asthma

Severity of symptoms	Step 1: mild intermittent disease	Step 2: mild sustained disease	Step 3: moderate sustained disease	Step 4: severe sustained disease
Distinctive features of symptoms	■ Stridor, cough*, dyspnea; once or twice a week. ■ Short-term intermittent symptoms. ■ Nocturnal symptoms occurring at most one or two times a month.	■ Symptoms occurring 2 or more times a week. ■ Activities of daily living or sleep disturbed 2 or more times a month. ■ Nocturnal symptoms occurring at least twice a month.	■ Chronic symptoms present. ■ Inhaled β_2 agonist therapy required almost every day. ■ Activities of daily living or sleep disturbed at least once a week. ■ Nocturnal symptoms occurring at least once a week.	■ Frequent aggravation (even on therapy). ■ Persistent symptoms. ■ Activities of daily living limited. ■ Frequent nocturnal symptoms. (■ Serial use of oral steroids.)
PEF, $FEV_{1.0}$	■ 80% of< the patient's best value/predicted value. ■ 20%> variation.	■ 70–80% of the patient's best value/predicted value. ■ 20–30% variation.	■ 60–70% of the patient's best value/predicted value. ■ 30%< variation.	■ 60%> of the patient's best value/predicted value. ■ 30%< variation.
Treatment	● Single use of inhaled/oral β_2 agonist and theophylline. ● Inhaled β_2 agonist or inhaled DSCG; single use before exercise or exposure to the allergen. (Anti-allergic drugs) • Serial use of leukotriene antagonist/thromboxane A_2 inhibitor-antagonist should be considered. • Serial use of mediator release inhibitor/histamine H_1-antagonist/Th2 cytokine inhibitor should be considered. • (Inhaled steroids)[#] Serial use of BDP 200μg/day or FP 100μg/day should be considered.	● Inhaled steroids[#]: serial low-dose therapy with BDP 200–400μg/day or FP 100–200μg/day. ● Serial use of sustained-release theophylline. (Anti-allergic drugs) ● Serial use of leukotriene antagonist/thromboxane A_2 inhibitor-antagonist. ● Serial use of mediator release inhibitor/histamine H_1 antagonist/Th2 cytokine inhibitor. ● Serial use of transdermal/oral/inhaled β_2 agonist.	● Inhaled steroids[#]: serial moderate-dose therapy with BDP 400–800μg/day or FP 200–400μg/day. ● Serial use of sustained-release theophylline. ● Serial use of transdermal/oral/inhaled β_2 agonist. (Anti-allergic drugs) ● Serial use of leukotriene antagonist/thromboxane A_2 inhibitor-antagonist. • Mediator release inhibitor/histamine H_1 antagonist/Th2 cytokine inhibitor should be considered. • Combined use of inhaled anticholinergic drug should be considered.	● Inhaled steroids[#]: serial high-dose therapy with BDP 800–1,500μg/day or FP 400-800μg/day. ● Oral steroids: short-term moderate- to high-dose therapy. Maintenance dose should be as low as possible and given once a day or every other day. ● Serial use of sustained-relapse theophylline. ● Serial use of transdermal/oral/inhaled β_2 agonist. (Anti-allergic drugs) • Serial use of leukotriene antagonist/thromboxane A_2 inhibitor-antagonist should be considered.
		● Additional single use of inhaled β_2 agonist (up to 3–4 times per day)	● Additional single use of inhaled β_2 agonist (up to 3–4 times per day)	● Additional single use of inhaled β_2 agonist (up to 3–4 times per day)

[#]: A spacer generally is used when using BDP. The doses prescribed in the present guidelines are set after consideration of approved doses and their safety, and they do not represent potency ratios.

■: If one of the given items is met, the patient is categorized in that step. If there is overlap with another step, the severer step is adopted. The specified symptoms and respiratory function test results provide an outline of each step. They may vary or overlap with adjoining steps.

*: If the patient has stridor and cough alone, he or she is categorized as having mild intermittent disease (step 1) even if the symptoms appear 3 times a week.

Step-up:	Proceed to the next step if the current treatment fails to control the condition. (In cases of <PEF60%, short-term moderate- or high-dose oral steroid therapy should be given.)
Step-down:	The intensity of treatment may be decreased if the patient's condition has been stable for at least 3 months since the treatment goal was achieved. Continue with the level of treatment needed to maintain control of the condition.

(From the Ministry of Health and Welfare Immunity/Allergy Study Group: *Guidelines for Prevention and Management of Asthma (1998 edition)* (ed. Makino, S. *et al.*) Kyowa Kikaku, Tokyo, 2000.)

Self-Management with Peak Expiratory Flow Monitoring

—Treatment for Bronchial Asthma—

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Abstract: Peak expiratory flow (PEF) monitoring should be considered in patients with moderate to severe asthma, who are older than 5 years of age, have measurable PEF values, and receive medication on a daily basis. In the practical treatment and management of asthma, the PEF monitoring is most effective in cases where step-wise therapy according to asthma severity is applied in long-term management. The guidelines recommend to determine asthma severity on the basis of symptoms and PEF, and subsequently to select a controller medication for each patient consistent with the severity of the disease. The following two basic strategies are useful for increasing or decreasing the medication dosage: One is the step-up therapy in which treatment is moved to the next step if the disease is not controlled by the current treatment, and the other is the step-down therapy in which the dosage can be reduced if the target of each treatment is achieved and the disease is controlled and confirmed to be stable for at least 3 months. In these strategies, PEF monitoring serves as an important indicator. The guidelines also recommend the ZONE SYSTEM to detect the earliest possible signs of asthma exacerbation and start the use of a reliever medication as early as possible.

Key words: Peak expiratory flow; Controller; Reliever; Step up; Step down; Zone system

Introduction

The international standardization and unification of the treatment for bronchial asthma have been roughly attained by the guidelines issued in Western countries from the second half of the 1980's to the first half of the 1990's, followed by the International Consensus Report (ICR)[1] in 1992 by the National Institute of Health in the U.S.A., and the subsequently

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issued Global Strategy for Asthma Management and Prevention (GINA)[2] summarized as the NHLBI/WHO Workshop report in 1995, and "Guidelines for Prevention and Management of Asthma, 1998 revised edition (JGL'98)[3]" in Japan.

Although traditionally bronchial asthma had been considered to be a functional disease due to the reversible contraction of bronchial smooth muscles, the concept that bronchial asthma is a chronic inflammatory disease of the airways caused by inflammatory cells such as lymphocytes and eosinophilic leukocytes is currently well established, and it has been demonstrated that inhaled adrenocortical steroids, which are the most potent anti-inflammatory drugs, are the initial drugs of choice to treat the inflammation of the airways in bronchial asthma.

Medications for bronchial asthma can be subdivided broadly into long-term control medications for prevention (controller medications) and medications used on demand in attacks (reliever medications).

Bronchial asthma is a chronic disease that requires the patient's self-management, the same as high blood pressure and diabetes. Patient education is essential for appropriate self-management.

Patient Education in the Guidelines

Although the Japanese guidelines specify patient education and self-management methods in accordance with the GINA and with the addition of original Japan-oriented recommendations, the GINA presents more precise and concrete guidelines on patient education and self-management methods, which are emphasized in this guideline.

Firstly, it is emphasized that education and instructions to patients should be given not only verbally but also in writing. It is worthy of note that this point is emphasized repeatedly even in Western countries where physicians can afford to take enough time when examining a patient, and sufficient communication with the patient is possible. This must be emphasized even more strongly in Japan where physicians have to examine a patient with the least expenditure of time. As is often the case, what the physician considers common sense may not appear as such to patients, and conversely, what a patient considers to be common sense may not appear as such to the physician. In addition to written instructions to each patient prepared by each hospital, booklets distributed by the Japan Allergy Foundation or pharmaceutical companies may be useful.

Secondly, the GINA emphasizes the thorough conduct of self-management with peak expiratory flow (PEF) monitoring. In Japan, a unique asthma diary has been employed as a tool for communication between a patient and a physician and it has been considered very useful. However, the description of symptoms based only on the patient's subjective perceptions differs occasionally from the objective evaluation in the determination of asthma severity, because a patient gets used to asthma symptoms and the response to low concentrations of oxygen decreases gradually. In the GINA and JGL '98, it is recommended that a patient should measure PEF several times a day using a PEF meter to evaluate asthma condition objectively. The zone system is set up as an asthma management tool using this PEF monitoring. In this system, PEF monitoring is likened to a traffic signal light in a patient's self-management plan, and measured PEF values are separated into the green zone (safe zone), yellow zone (caution zone), and red zone (medical warning zone). For each zone, a written instruction about how to use drugs and manage symptoms is given to the individual patient. This is an unequivocal method and easy for patients to understand. In the practical applications of PEF monitoring, however, PEF does not necessarily decrease before the development of subjective symptoms, and there is the problem of how to deal with "patients with consistent low PEF values", that is, those who have asymptomatic asthma without an increase in PEF.

Thirdly, the guidelines provide detailed instructions about home treatment method for managing exacerbation of asthma. Probably due to the differences in medical care systems and medical insurance systems between Western countries and Japan, physicians in Japan, at least the author, for one, direct patients to take an inhaled β_2-agonist using a metered dose inhaler (MDI) and an oral β_2-agonist immediately after an attack occurs, and to come to the hospital as soon as possible, if a few inhalations of β_2-agonist with MDI did not improve the symptoms; the patients are also instructed to simply come to the hospital whenever they are worried.

In contrast, the instructions in the ICR and GINA place higher priority on the guidance to minimize the number of visits to the hospital. It is also to be noted that these guidelines are in a position to make patients aware of the importance of self-management, probably in relation to their medical care systems. For example, the GINA says that it is important for the successful management of asthma exacerbation to start asthma therapy when a slight sign of a reduction in asthma control is observed, and that the initiation of therapy at home by patients may avoid the delay of treatment and make the patients aware that they can manage their own asthma exacerbation. Furthermore, the straightforward contents of the instructions to patients, including dosing frequencies and dosages stated in figures, is thought to facilitate the understanding by patients.

Peak Expiratory Flow Monitoring[4)]

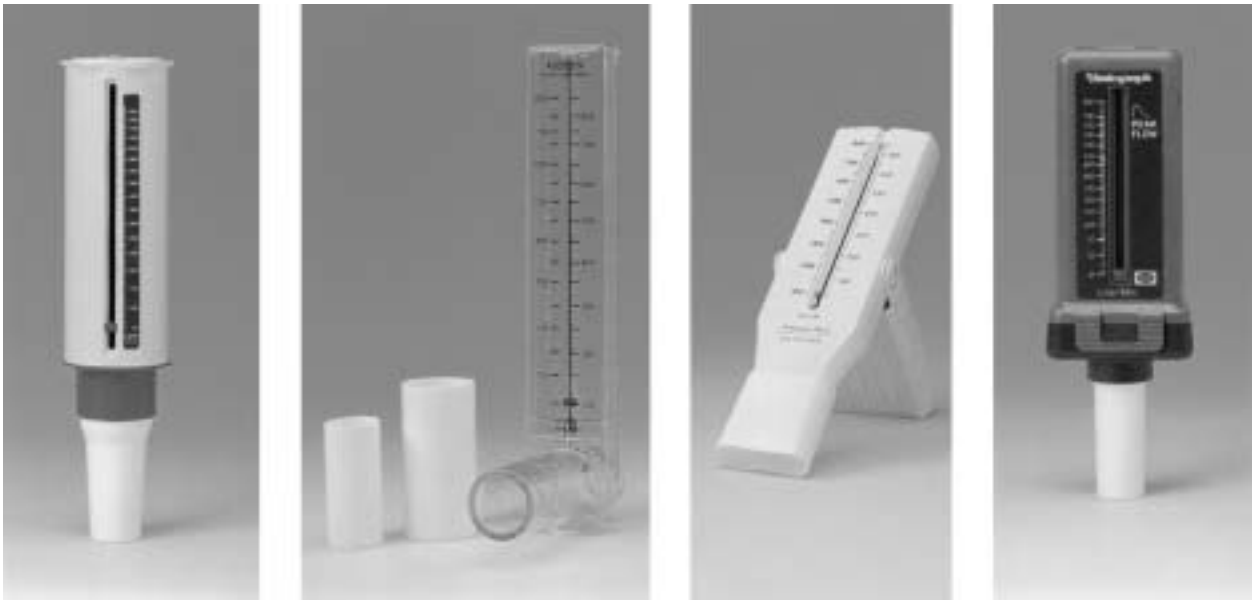
Also, the Japanese guidelines (JGL '98) recommend self-management methods appropriate to the medical circumstances in Japan, while incorporating the points to be learned from the ICR and GINA. This article mentions several matters related to self-management in the treatment for bronchial asthma that require attention, particularly self-management with peak expiratory flow monitoring.

1. Matters that require attention when performing peak expiratory flow monitoring

Peak expiratory flow monitoring should be considered in patients with moderate to severe asthma, who are older than 5 years of age, have precisely measurable PEF values, and receive medication on a daily basis. Currently, various peak flow meters are available commercially, such as Mini-Wright®, Assess®, Personal Best®, and Vitarograph®. Although there are differences in measurement values among these devices, any device can be used without problems, as long as the same device is used continuously. A patient may select a device easy to use (Fig. 1). Measurement is performed preferably while sitting up or sitting on a chair, and must be carried out in the same position every time.

Peak expiratory flow is, so to speak, the marker of the maximum instantaneous wind speed, which is proportional to the degree of airway occlusion, and is supposed to be correlated with forced expiratory volume in one second. However, quite a few patients who have normal peak expiratory flow values complain of breathlessness as a subjective symptom, since peak expiratory flow indicates only the flow rate in the central airway. In the flow volume curves of such patients, V_{50} and V_{25} are lower, and the constriction and occlusion of peripheral airways are observed occasionally. Thus, it must be understood that peak expiratory flow is not always an all-purpose marker to indicate the state of the airways. As the extent of diurnal variation in peak expiratory flow would serve as a measure of the state of asthma control, measurement twice a day (morning and evening), and before inhalation or oral administration of antiasthmatic drugs is necessary.

To find the personal best value of peak expiratory flow for each patient, it is useful to add two measurements around 11 a.m. and 2 p.m. during the early stage of peak expiratory flow monitoring, when ventilatory function works best in many patients. By making a comparison between peak expiratory flow values before



Mini-Wright
Clement Clarke (England)
product imported by
Matsuyoshi & Co., Ltd.

Assess
HealthScan (U.S.A.)
product imported by
Chest MI

Personal Best
HealthScan (U.S.A.)
product imported by
Polytechs, Ltd.

Vitarograph
Vitarograph (U.S.A.)
product imported by
Suzume Medical

Fig. 1 Commercially available peak flow meters[4)]

and after the use of bronchodilators such as β_2-agonists, its reversibility can be known. If peak expiratory flow remains at low values without showing reversibility, this indicates that the current therapy is insufficient and another therapy should be selected. If peak expiratory flow increases significantly, this indicates that the bronchodilator currently used is effective and the long-term management method to maintain the peak expiratory flow value after the use of the bronchodilator should be reconsidered.

2. Significance in long-term management

In cases where step-wise therapy according to asthma severity (see appendix, page 368) is applied in long-term management, the effect of peak expiratory flow monitoring works effectively in the practical treatment and management of asthma. The guidelines recommend to determine asthma severity on the basis of symptoms and PEF, and subsequently to select a long-term management medication (controller medication) depending on the severity.

When PEF is not less than 80% of the personal best value or the predicted value and the daily variability is less than 20%, asthma severity is classified as "Mild Intermittent in STEP 1"; when PEF is 70–80% of the personal best value or the predicted value and the daily variability is 20–30%, it is classified as "Mild Persistent in STEP 2"; when PEF is 60–70% of the personal best value or the predicted value and the daily variability is not less than 30%, it is classified as "Moderate Persistent in STEP 3; and when PEF is not more than 60% of the personal best value or the predicted value and the daily variability is not less than 30%, it is classified as "Severe Persistent in STEP 4", and the type and dosage of the drug consistent with the degree of severity are specified. The purpose is to allow a patient to perform self-management without visiting on each occasion, by giving to the patient the physician's instructions on what actions to take at each step.

Table 1 Home Management for Asthma Exacerbation (Attack)[3)]

Therapy is performed according to the zone system. When the response to an inhaled β_2-agonist used at the initiation of asthma control is insufficient, medical examination by a physician is necessary even if the symptoms or the reduction in peak expiratory flow is minor.

- Green Zone (peak expiratory flow value: 80–100% of the personal best value)
  Asthma is under control. The symptoms of asthma, if any, include wheezing.
  If any symptom is observed, an inhaled β_2-agonist should be taken.
- Yellow Zone (peak expiratory flow value: 50–80% of the personal best value)
  Some symptoms of asthma (nighttime symptoms, disturbance in daily activity, cough, wheezing, feeling chest pressure at rest and on exercise) are observed. An inhaled β_2-agonist should be taken up to 3 times per hour, and, if the response to the inhaled β_2-agonist is insufficient, an oral steroid should be taken at a dosage designated by the physician, and see the physician. If peak expiratory flow returns to and stays in the green zone, progress may be observed without seeing the physician.
- Red Zone (peak expiratory flow value: less than 50% of the personal best value)
  The symptoms of asthma are observed at rest and affect daily life. An inhaled β_2-agonist should be taken right away, followed by early administration of an oral steroid. If a rapid improvement of peak expiratory flow cannot be obtained, the patient must see the physician immediately. Administration of oxygen should be initiated, if it is in readiness.

To increase or decrease the medication dosage, the following two basic strategies are useful: one is the step-up therapy in which treatment is moved to the next step if the disease is not controlled by the current treatment; the other is the step-down therapy in which the dosage is reduced if the target of each treatment can be achieved and the disease is controlled, and confirmed to be stable for at least 3 months. For these strategies, PEF monitoring serves as an important indicator.

3. Zone system (Table 1)

Asthma is a highly variable disease. As has been mentioned, the purpose of the asthma management zone system is to prevent the exacerbation of asthma by having the patient monitor his own asthma state, in order to detect the earliest possible signs of exacerbation and take prompt actions at home.

The Green Zone with a peak expiratory flow value of 80–100% of the personal best value indicates that asthma is controlled well. If this state continues for at least 3 months, a step down in long-term management will be warranted.

The Yellow Zone with a peak expiratory flow value of 50 to 80% of the personal best value signals the presence of an episode of asthma. In this case, it is advisable that an inhaled β_2-agonist be taken to relieve the attack quickly and, if the response to the medication is insufficient, an oral steroid previously designated by the physician should be taken before seeing the physician.

The Red Zone with a peak expiratory flow value of less than 50% of the personal best value signals a state in which the symptom of asthma is observed even at resting and affect daily life. In this case, the patient must take an inhaled β_2-agonist right away and an oral steroid early, and must see the physician immediately if the peak expiratory flow value is not improved.

Conclusion

The results of the studies by the Japanese Society of Allergology and the Japanese Respiratory Society have demonstrated that the majority of the causes of deaths due to asthma attacks, numbering 6,000 yearly, are attributed to the delay of appropriate treatment. It is hoped that the widespread use of the zone system, utilizing peak expiratory flow monitoring, would result in prompt and appropriate treatment and reduce deaths due to asthma attacks. The recent significant advances in controller medications and reliever medications have facilitated the control of bronchial asthma markedly.

We, as clinical physicians, want to achieve a better control of bronchial asthma and to improve patient QOL in the clinical setting by providing appropriate treatment and management utilizing various available tools.

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How to Use Anti-Allergy Drugs

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Abstract: Currently, anti-allergy drugs are classified, on the basis of their action mechanism, into 5 types including mediator-release inhibitors, histamine H_1 antagonists, thromboxane A_2 inhibitors, leukotriene antagonists, and Th2 cytokine inhibitors. The asthma treatment guideline released in Japan stipulates treatment with one of these types of anti-allergy drugs, regardless of the severity of disease. There are no definite grounds for the choice of anti-allergy drugs. When the patient has complications involving other allergic diseases, the physician chooses, in order of preference, histamine H_1 antagonists, mediator-release inhibitors, and Th2 cytokine inhibitors, depending on the indications with the concomitant allergic disease. When symptoms are severe, leukotriene antagonists and thromboxane A_2 inhibitors are chosen. The physician may also consider increased doses of steroid inhalants and sustained release theophylline. At present, the use of two or more anti-allergy drugs together is not acknowledged, but this will be the subject of research in the future, because anti-allergy drugs with different mechanisms of action used at the same time will theoretically increase their effects.

Key words: Mediator-release inhibitors; Histamine H_1 antagonists; Thromboxane A_2 inhibitors; Leukotriene antagonists; Th2 cytokine inhibitors

Introduction

Bronchial asthma is an obstructive respiratory disease characterized by reversible occlusion, hypersensitivity, and chronic inflammation of the airway. Allergic reactions play an important role as a factor in inducing airway inflammation. When asthma patients are tested for allergies, using a skin reaction test, about 70% exhibit the presence of IgE antibodies by showing positive reactions to house dust and its major component, the house dust mite (dermatophagoides). About 70% of these patients had diseases involving atopic conditions. The test results revealed that allergic reactions can be considered an important target of asthma treatment.

What Are Anti-allergy Drugs?

"Anti-allergy drug" is the general term for drugs that regulate the release and action of

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Table 1 Biological Activity of Inflammatory Mediators Considered to Be Involved in Asthma[1)]

Action	Histamine	PGD_2	$PGF_2\alpha$	TXA_2	LTB_4	LTC_4, D_4, E_4	PAF
Bronchial smooth muscle contraction	+	++	++	++	−	++	++
Airway hyperresponsiveness	−	+	+	+	?	+	++?
Capillary permeation enhancement	+	+	−	−	?	++	++
Airway mucus secretion enhancement	+	+	+	?	−	++	+
Leukocyte migration activity	+	+	?	?	++	?	++

"+", "++", "−" and "?" in the table refer to "action", "strong action", "no action" and "unknown or not definite," respectively.

Table 2 Types and Names of Drugs for Long Term Asthma Control[2)]

1. Steroids
   1) Steroid inhalants
      i) Beclometasone propionate
      ii) Fluticasone propionate
   2) Oral steroids
2. Sustained release theophylline
3. Long-acting β_2 stimulants
4. Anti-allergy drugs
   1) Mediator-release inhibitors
      i) Sodium cromoglicate
      ii) Tranilast
      iii) Amlexanox
      iv) Repirinast
      v) Ibudilast
      vi) Tazanolast
      vii) Pemirolast potassium
   2) Histamine H_1 antagonists
      i) Ketotifen fumarate
      ii) Azelastin hydrochloride
      iii) Oxatomide*
      iv) Mequitazine
      v) Terfenadine
      vi) Epinastine hydrochloride
      vii) Astemizole
   3) Thromboxane A_2 inhibitors
      (1) Thromboxane A_2 synthetase inhibitors
         i) Ozagrel hydrochloride
      (2) Thromboxane A_2 antagonists
         i) Seratrodast
   4) Leukotriene antagonists
      i) Pranlukast hydrate
   5) Th2 cytokine inhibitors
      i) Suplatast tosilate

* Contraindicated in pediatric asthma, not adult asthma.

chemical mediators involved in allergic reaction, mediated by IgE (immediate or type I allergic reaction), or inflammatory mediators (Table 1).[1)] The many anti-allergy drugs currently on the market are classified, on the basis of their action mechanism, into 5 types including mediator-release inhibitors, histamine H_1 antagonists, thromboxane A_2 inhibitors, leukotriene antagonists, and Th2 cytokine inhibitors.

Types of Anti-allergy Drugs (Table 2)[2)]

1. Mediator-release inhibitors

Mediator-release inhibitors include DSCG (sodium cromoglicate), which was the first anti-allergy drug developed. These drugs are expected to be effective in 30 to 40% of mild to moderate cases with atopic asthma, but it takes them 4 to 6 weeks to manifest any effect. As these drugs do not have anti-histamin action, they do not induce drowsiness in patients.

2. Histamine H_1 antagonists

Histamine H_1 antagonists more or less induce drowsiness, which generally remits or disappears within several days after the start of treatment. Histamine H_1 antagonists also inhibit mediator release and are effective in 20 to 30% of mild to moderate cases with atopic asthma, but it takes them 4 to 6 weeks to manifest

any effect.

3. Thromboxane A_2 inhibitors and antagonists

Thromboxane A_2 inhibitors consist of 2 types of agents, i.e., thromboxane A_2 synthetase inhibitors and thromboxane A_2 antagonists (receptor antagonists).

These drugs are effective in 40% of mild to moderate atopic and mixed-type asthma. Since their effects can be observed in only 2 to 4 weeks of treatment, it is possible to assess results at an earlier stage than with mediator-release inhibitors and histamine H_1 antagonists, which must be administered for 4 to 6 weeks before any effect can be observed.[3,4]

These drugs are also reported to be effective against infectious asthma. However, due to a case of severe hepatic disorder reported after marketing, physicians are recommended to administer the thromboxane A_2 antagonist, seratrodast, and conduct monthly hepatic function tests.

4. Leukotriene antagonists

LTC_4, D_4 and E_4 receptor antagonists are available for use as leukotriene antagonists. Much attention has been focused on these drugs in Europe and the U.S., where two drugs were developed, but Japan took the lead and developed pranlukast hydrate, which has been valuated highly since it went on the market.

These drugs are effective in 50 to 60% of mild to moderate atopic and mixed-type asthma. Since the effects of the drug appear in only several days to 1 week, or 2 to 4 weeks at the latest, results can be assessed much sooner than with mediator-release inhibitors and histamine H_1 antagonists, which must be administered for 4 to 6 weeks before any effects can be observed.[5] Another report[6] found that these drugs not only inhibited airway inflammation but also inhibited airway hypersensitivity in asthma patients. Moreover, aspirin- and exercise-induced asthma is expected to be inhibited with these drugs since they showed inhibitory effects in both a sulpyrine inhalation and an exercise-induced asthma tests.

Zafirlucast and Montelukast, developed in the West, have recently been put on the market in Japan.

Table 3 Cytokines Produced by Th1 and Th2 Cells

Cytokines	Th1 cells	Th2 cells
IL-2	+	−
IFN-γ	+	−
TNF-β	+	−
GM-CSF	+	+
TNF-α	+	+
IL-3	+	+
IL-4	−	+
IL-5	−	+
IL-6	−	+
IL-10*	−	+
IL-13	−	+

* IL-10 is produced by both Th1 and Th2 cells in humans.

5. Th2 cytokine inhibitors

Th2 cytokine inhibitors inhibit the production of excessive production of Th2 cytokines that induce the IgE antibodies and allergic inflammation. Among Th2 cytokines (Table 3), IL-4, which is involved in the production of the IgE antibody, and IL-5, which is involved in the activation of eosinophil, have been attracting particular attention. Reports have also found that IL-5 production is enhanced in asthma patients, regardless of any allergic conditions, suggesting that Th2 cells are generally predominant in asthma.

Currently, the only drug available in this category is suplatast tosilate, which was developed in Japan. This drug inhibits the production of IL-4 and IL-5 and is reported to inhibit both eosinophil infiltration in the airway mucosa and airway hypersensitivity.[7] However, the drug has to be administered for 6 to 8 weeks

before any effect can be observed, and its effects are manifested slowly. In view of the pathology of asthma, more attention should be paid to the development of Th2 cytokine inhibitors.

Positioning Anti-allergy Drugs in Asthma Treatment Guidelines

This section describes how the above-mentioned anti-allergy drugs are positioned in asthma treatment guidelines, according to the "Asthma Prevention and Control Guidelines" (prepared in 1998 by the Immunity & Allergy Research Group of Ministry of Health & Welfare in Japan; revised in 2000).[2] Anti-asthma drugs are classified into those that act against asthma attacks, or relievers which remove asthma symptoms, and those for long-term control, or controllers which alleviate inflammation and stabilize the patient's condition. Obviously, anti-allergy drugs are classified as the controllers (Table 2).

According to the guidelines, asthma is classified into 4 steps of severity, i.e., mild intermittent, mild persistent, moderate persistent, and severe persistent. The guidelines recommend the continuous or persistent use of anti-allergy drugs in treating each of these steps (refer to appendix, page 368).

1. Step 1

Step 1 severity consists of the onset of asthmatic symptoms such as cough and respiratory difficulty once or twice a week. At this stage, physicians may consider using any of the anti-allergy drugs, excluding DSCG (sodium cromoglicate), and the positioning of anti-allergy drugs is similar to that of low-dose inhalant steroids. Use of β_2 stimulants and theophylline for controlling the symptoms as well as DSCG inhalation before exercise and exposure to allergens is recommended at this step.

2. Step 2

Step 2 severity consists of the onset of the above symptoms two or more times a week. At this step, the guidelines recommend the continuous use of any of the anti-allergy drugs, in addition to the continuous use of low-dose inhalant steroids (beclomethasone dipropionate; BDP 200–400μg/day, fluticasone propionate; FP 100–200μg/day) and sustained-release theophylline.

3. Step 3

Step 3 severity consists of the presence of chronic symptoms. At this step, the guidelines recommend the continuous use of leukotriene antagonists/thromboxane A_2 inhibitors in addition to the continuous use of middle-dose inhalant steroids (BDP 400–800μg/day, FP 200–400μg/day), sustained-release theophylline, and patch/oral/inhalant β_2 stimulants.

4. Step 4

Step 4 severity consists of not only very severe and persistent but also aggravated symptoms. At this step, the guidelines suggest the intermittent use of oral steroids and the continuous use of leukotriene antagonists/thromboxane A_2 inhibitors in addition to the continuous use of high dose inhalant steroids (BDP 800–1,600μg/day, FP 400–800μg/day), sustained-release theophylline, and patch/oral/inhalant β_2 stimulants.

The continuous use of anti-allergy drugs is suggested rather than recommended in Step 1 and Step 4 because their usefulness has not yet been fully proven. However, it has already been reported that these drugs could reduce the use of high-dose inhalant steroids.[8]

Personal Views on the Administration of Anti-allergy Drugs

As described above, anti-allergy drugs are positioned for long-term control of asthma and are selected according to the severity of the patient's condition. This leads to various questions about the administration methods of these drugs.

The usefulness of anti-allergy drugs at Step 1 has yet to be established. In other words, the guidelines will recommend aggressive treatments with these drugs if they are proven to be effective as a part of an early intervention against asthma. At this moment the author generally starts administering anti-allergy drugs to patients at Step 2 or higher.

I will prescribe anti-allergy drugs with antihistamin action if the patient has complications involving other allergic diseases such as allergic rhinitis and atopic dermatitis, even if the asthma itself is mild. Since leukotriene antagonists have recently been demonstrated to be effective on nasal occlusion attributable to allergic rhinitis, treatment with this type of drug should be taken into consideration, depending on the patient's symptoms. Based on their pharmacological action and therapeutic effects, it is all together conceivable that we will include leukotriene antagonists among the first drugs of choice used at Step 1.

For the treatment of the patient at Step 2 I start with a low-dose inhalant steroid and sustained-release theophylline.[9] Additional anti-allergy drugs will be administered if the patient's symptoms are not controlled with satisfaction. There are no definite criteria for selection. When the patient has additional allergic diseases, drugs are chosen according to the presence or absence of contraindications against that disease. In such cases, physicians may choose from mediator-release inhibitors, histamine H_1 antagonists or Th2 cytokine inhibitors.

Caution must be exercised and it is not always possible to administer histamine H_1 antagonists, as they may induce drowsiness in some patients. Since the efficacy rate of mediator-release inhibitors is rather low, treatment with Th2 cytokine inhibitors should be attempted if no effect is observed in 4 to 6 weeks with mediator-release inhibitors. If both types of drugs are ineffective, I will consider administration of leukotriene antagonists as well as increase of doses of inhalant steroids and sustained release theophylline.

When the condition of a patient corresponds to Step 3 or 4, I administer a leukotriene antagonist first. If ineffective, I will administer thromboxane A_2 inhibitors. What is especially important in the treatment of patients at Steps 3 and 4 is adding a concomitant drug while prescribing each drug at a satisfactory dose, within the safe range. This is expected to enhance the actions of leukotriene antagonists and thromboxane A_2 inhibitors.

Though leukotriene antagonists and thromboxane A_2 inhibitors are similarly classified as anti-allergy drugs, mechanisms of their action are distinct. Concomitant administration of these drugs is not allowed at present, but concomitant use of anti-allergy drugs with different mechanisms of action is theoretically expected to increase their effectiveness. In this regard, we should investigate if the concomitant administration of these drugs is beneficial.

Future Prospects for Anti-allergy Drugs

Due to their slow action and rather low efficacy rate, the development of anti-allergy drugs was criticized at the initial stage. Thanks to earnest support and efforts, researchers in Japan were able to develop the first leukotriene antagonist and the first thromboxane A_2 inhibitor and antagonist. I strongly hope that a highly specific anti-allergy drug will be developed to improve asthma treatment in the future. When it becomes possible to predict the efficacy of a drug at the genetic level,[10] it will become possible to perform so-called "tailor-made medicine."

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Managing Exacerbation of Asthma: Pharmacologic Therapy

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Abstract: The deterioration of asthmatic conditions is divided into "symptom" and acute exacerbation. "Symptom" is a pathological state in which the contraction of bronchial smooth muscles is observed predominantly, and acute exacerbation is considered to be a more serious condition in which a severe inflammation of the airways is observed. The basic drugs used for treatment of these pathological states include bronchodilators, corticosteroids, and oxygen. For mild symptoms, bronchodilators such as inhaled β_2-agonists are used as a quick reliever. When the symptoms are relieved, treatment is considered successful. When the symptoms cannot be relieved or deteriorate rapidly, the condition is judged as acute exacerbation, and bronchodilators and systemic corticosteroids are used together, as well as oxygen if necessary. It is essential to make the patients understand the difference between these two pathological states and the difference between the treatments for each state, and the importance of a prompt judgment of the pathological state. The short-term use of oral corticosteroids in acute exacerbation is possible under patient self-management and is highly useful.

Key words: Acute exacerbation; Symptom; Bronchodilators; Systemic corticosteroid; Oxygen therapy; Patient education

Definition of Terms

Asthma is both a chronic inflammatory disease of the airway and a disease with acute exacerbation. To treat asthma, either long-term control or quick relief medication is selected according to the pathological state. Prompt judgment and treatment are needed when there is deterioration of the disease.

The term "acute attack" is used conventionally; lately, "acute exacerbation" has also come into use. The two terms are nearly synonymous.

The international guidelines recommend that distinction should be made between the acute exacerbation of asthma and the "symptom" of asthma. This means that the nature of the symptoms of asthma should be broadly classified and should be managed accordingly.

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Table 1 Classification of Severity of Acute Exacerbation

	Breathlessness/symptoms	Activity	Laboratory test values	Treatment
Mild	Breathless, but can lie down	Slightly difficult	PEF>70–80% Pao_2; normal Spo_2>95%	Home treatment Emergency treatment
Moderate	Cannot lie down due to breathlessness	Considerably difficult	PEF: 50–80% Pao_2>60 torr Spo_2; 91–95%	Emergency or hospital treatment
Severe	Cannot move due to breathlessness Agitation Cyanosis	Difficult to walk and talk	PEF<50% Pao_2<60 torr $Paco_2$>45 torr Spo_2<91%	Emergency or hospital treatment
Serious	Mental confusion and somnolence Disturbed consciousness Incontinence Respiratory arrest	Impossible to talk and move the body		Hospital treatment ICU

(*Guidelines for the Prevention and Management of Asthma*, 1998 revised edition, excerpts from Table 4 in page 88)

"Symptom", as used here, refers to mild conditions which can be relieved by an inhaled β_2-agonist within several hours, and therefore transient. The peak expiratory flow value (PEF) is not less than 60% of the personal best one.

On the other hand, acute exacerbation refers to conditions that cannot be relieved easily by an inhaled β_2-agonist and continue for more than a day, and in which PEF is less than 60% of the personal best one. The severity of acute exacerbation is classified as indicated below and the treatment is proposed in accordance with the severity of asthma.

Classification of Severity of Acute Exacerbation (Table 1)

In the Japanese guideline, the severity of an acute exacerbation is classified into four levels according to clinical symptoms (mild, moderate, severe, serious). For example, when the patient experiences difficulty in lying down due to breathlessness, the severity is regarded as "moderate"; a state milder than "moderate" is regarded as "mild". In a narrow sense, the above-mentioned "symptom" is included in the "mild" classification. When the patient experiences difficulty in talking or shows agitation and cyanosis, the state is referred to as "severe"; if there is mental confusion, somnolence, disturbed consciousness, incontinence, and respiratory arrest, the state is evaluated as "serious".

For a mild acute exacerbation, home treatment by self-management is possible. For moderate, severe and serious acute exacerbation, appropriate management such as treatment in an emergency room or hospitalization is necessary.

Pharmacologic Therapy

Pharmacologic therapy for asthma is basically the combination of a corticosteroid and a bronchodilator, and administration of oxygen (Table 2).

The following methods for corticosteroids treatment are used: (1) Administration of an inhaled corticosteroid at a dose 2 or 3 times higher than the usual dose, (2) intensive use of

Table 2 Pharmacologic Therapy for Acute Exacerbation of Asthma

Severity	Inhaled β_2-agonist	Subcutaneous administration of Bosmin®	Intravenous administration of aminophylline	Steroids	Oxygen
Mild	◎	×	△	△○	△
Moderate	◎	○	○	◎	○
Severe	◎	○	◎	◎	◎
Serious	◎	○	◎	◎	◎

◎ Definitively indicated, ○ Indicated, △ Not definitively indicated, but can be used, × Not indicated

an oral corticosteroid, and (3) intravenous administration. For mild severity, method (1), and for moderate or more severe severity, methods (2) and (3) are selected, respectively.

Treatment method with bronchodilators includes β_2-agonists, inhalation, subcutaneous injection of β_2-agonists, intravenous administration of aminophylline and subcutaneous injection of epinephrine. Epinephrine has both pharmacological activity of a β-action inducing bronchodilation and an α-action suppressing bronchoedema.

Oxygen is administered using a nasal cannula, face mask and respirator. Recently, it was reported that the noninvasive BiPAP method is also effective. Oxygen is administered while monitoring with a pulse oximeter to keep Spo_2 at not less than 90% or Pao_2 at not less than 80 torr.

These drugs are combined, and the dosages and administration frequency are determined in accordance with the severity of symptoms.

The practical applications of pharmacologic therapy are described below.

1. Initial treatment

(1) For mild symptoms

The use of an inhaled β_2-agonist is the first choice. This method can relieve symptoms rapidly and act quickly. A metered dose inhaler (MDI) is sprayed 2 to 4 times into a spacer which a patient is supposed to inhale. When a sufficient response cannot be obtained, inhalation is repeated every 20 minutes for 1 hour.

A patient is allowed to go home when PEF reached at more than 60% of the personal best value. In this case, short-term treatment with an oral corticosteroid is instructed, and if this medication does not relieve symptoms, prompt visiting outpatient clinic should be recommended.

An oral corticosteroid should be continued once a day or twice a day in a daily dose equivalent to 20–30 mg of prednisolone until the peak expiratory flow value returns to the personal best value.

(2) For moderate or more severe symptoms

1) Inhalation of β_2-agonist using a nebulizer: When inhalation of β_2-agonist with the aid of a spacer is possible, it may be done in the same manner described in the previous section, but when it is difficult due to severe conditions, the use of a nebulizer is effective.

Dose: salbutamol 5 mg (ex. 1.0 m*l* of 0.5% Venetlin® solution) + 10–15 m*l* of physiological saline with ultrasonic nebulizer. When the response to a dose of inhaled β_2-agonist is insufficient, the same treatment is repeated every 20 minutes for 1 hour followed by repetition every 60 minutes (Table 3). If any side effect due to an excessive dose is observed, treatment is interrupted temporarily. The frequent use of inhaled β_2-agonists for chronic asthma generally causes fewer side effects.

2) The switch to intravenous administration of aminophylline may be effective. Although there is a tendency to avoid the use of aminophylline because of the narrow range of effective concentrations (10–20 μg/d*l*) and the possible occur-

Table 3 How to Use β_2-agonists and Epinephrine in the Acute Exacerbation of Asthma (From the Guideline 1988 by the Japanese Society of Allergology)

	β_2-agonists	Treatment mode
Mild	β_2 MDI[a)]	Home treatment is possible
Moderate	β_2 nebulizer[b)] Epinephrine s.c.[c)]	Emergency/outpatient treatment Hospital treatment
Severe	Epinephrine s.c. β_2 nebulizer	Emergency/outpatient treatment Hospital treatment
Serious	Epinephrine s.c. β_2 nebulizer	Hospital treatment ICU

a) 2 puffs/each dose, every 20 minutes for 1 hour
b) Every 20–30 minutes, repeated administration is possible with condition of HR≤130/minute
c) 0.1–0.3 m*l*, every 20–30 minutes, repeated subcutaneous administration is possible

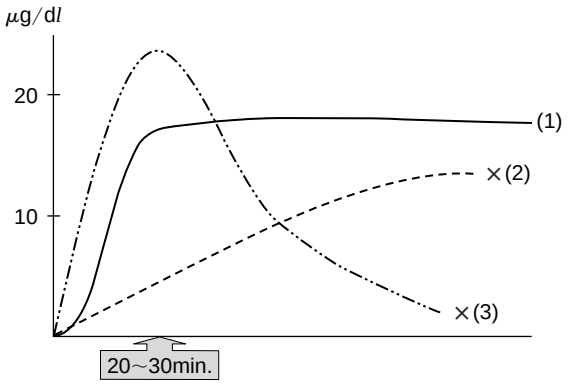

Fig. 1 Drip infusion method of aminophylline (indicated in moderate or more severe symptoms)
(1) The method described in the text.
(2) An insufficient dose is administered over a long time via drip infusion.
(3) An excessive dose is administered rapidly via drip infusion.
Both cases of (2) and (3) lack the efficacy of aminophylline or cause side effects, respectively.

rence of serious side effects in high concentrations, treatment with aminophylline is less difficult and useful method once it is learned how to use it safely. For safe administration, it is given over 20 to 30 minutes to obtain and then maintain the effective concentration of the drug (Fig. 1). A relatively easy method is described below.

The loading dose (LD) is 6 mg/kg, and the drip infusion rate (DIR) is 0.6 to 0.8 mg/kg/hr, respectively (the average values derived statistically from a multitude of examples). If possible, the blood concentration is monitored at a few points in time after administration, and the DIR is adjusted to gain the optimal concentration of aminophylline. Again to ensure safe treatment, it is necessary to take 20 to 30 minutes for the intravenous administration of LD.

With regard to theophylline, various factors affecting the blood concentration have been reported. For example, the blood concentration rises in heart failure, liver diseases, and viral infection, as well as in the concomitant use with macrolides. It decreases in smokers. Since theophylline is metabolized by the drug-metabolizing enzyme P450 in the liver, it is influenced by concomitant used-drugs and the pathological state of patient. For more detailed information, see the established literature.

3) Subcutaneous administration of epinephrine is used for moderate or more severe asthma exacerbation. This drug is injected subcutaneously at a dosage of 0.2 to 0.3 m*l*. As far as pulse rate is less than 130/minute, repeated administration every 20–30 minutes is possible. For serious or life-threatening conditions, it is administered at a dosage of 0.3 to 0.5 m*l*. This drug,

Table 4 Indications, Timing and Cautions for the Use of Oral Steroids in the Acute Exacerbation of Asthma —Home Treatment and Hospital Treatment—

■ *BMJ* 1993 S3: Rescue use of Cs tablets
1. When symptoms or PEF deteriorates on a daily basis
2. When PEF is 60% of the personal best value or lower
3. Somnipathy
4. When morning symptoms continue during daytime
5. When the response to bronchodilators becomes weaker

Adult: equivalent to 30–60 mg/day of PSL, for 2 days after the symptoms are controlled, then, administration is interrupted or the dosage is reduced

Children: equivalent to 1–2 mg/kg of body weight of PSL, for 1–5 days, then, administration is interrupted

■ Japanese guidelines 1998 (by the Japanese Society of Allergology)

Equivalent to approximately 0.5 mg/kg of body weight/day of PSL, for 1–2 weeks, then, administration is interrupted or the dosage is reduced

* Cautions in diabetes—an increase in blood sugar level or ketosis is caused.

with both α-action and β-action, acts quickly. Its α-action reduces bronchoedema and its β-action induces bronchodilation. Epinephrine is contraindicated in the presence of hyperthyroidism, ischemic heart disease, or glaucoma. The use of this drug is also contraindicated in dehydration and should be avoided during pregnancy.

4) Corticosteroid therapy: When corticosteroids are used to treat acute exacerbation of asthma, these drugs tend to be administered at insufficient doses due to fear of the general side effects of steroids, or at excessive doses in order to intend to improve the symptoms quickly. The standard method including appropriate dosage is recommended in the guidelines. Generally, the side effects of corticosteroids occur when they are administered systemically and for a long term. The period during which steroids are used for acute exacerbation would be relatively short.

It is important in acute exacerbation to use the appropriate amounts of corticosteroids without concern about their side effects, but with several cautions. That is because acute exacerbation of asthma is a state in which the inflammation has progressed markedly, and because corticosteroids are the most potent drugs in inflammation of asthma.

The guidelines recommend short term treatment with oral corticosteroids (Table 4). In Japan, corticosteroids are administered at a dose of 0.5 mg per kg of body weight in the form of prednisolone (PSL) for about 1–2 weeks, until PEF returns to the personal best value. Subsequently, the basic treatment for the patient, that is, the use of a regular dose of an inhaled corticosteroid or a regular dose of an oral corticosteroid, is substituted without tapering process.

The necessary corticosteroid amount should be prescribed in advance, and the patients should be educated to take oral corticosteroid by their decision when they experience such states as listed in Table 4. In this way, the patient will feel secure, will learn how to prevent serious acute exacerbation, and will acquire self-management skills.

With regard to intravenous administration method: Administration of hydrocortisone or methylprednisolone starting from 200–500 mg or 40–125 mg as a loading dose, respectively, followed by 200 mg or 40–80 mg, respectively, is added every 4–5 hours for moderate or more severe acute exacerbation.

With regard to the side effects of corticosteroids to be kept in mind as mentioned below:

First, patients with diabetes complicated with asthma are in danger of increasing their blood sugar level, occasionally resulting in ketosis. For these patients, hospital treatment

using insulin should be determined, since treatment under self-management or on an outpatient basis is difficult. Luckily, treatment with inhaled corticosteroids never increases blood sugar level.

Second, bolus intravenous administration of large doses of corticosteroids in patients with aspirin-induced asthma requires another caution. Aspirin-induced asthma is a disease that involves acute exacerbation occurring immediately after administration of aspirin, pilin derivatives or acidic nonsteroidal anti-inflammatory drugs, and it is said to account for approximately 5% of adult asthma cases. Bolus intravenous administration of large amounts of succinate corticosteroids (for example, hydrocortisone, methylprednisolone, and prednisolone) or steroids containing paraben preservatives is considered to induce asthma exacerbation.

When the presented case is aspirin-induced asthma or when the presented ease is not certain about complicity with aspirin-induced asthma, the use of such steroids should be avoided. To be enough safer from serious side effects, phosphate corticosteroids (ex. betamethasone, dexamethasone) should be used instead, or succinate corticosteroids, if used, should be given slowly (taking 1–2 hours) via drip infusion, not via bolus intravenous injection to prevent side effects.

5) Hospital treatment: When hospitalization is required because initial treatment did not result in satisfactory improvement, the same initial treatment should be continued also in the hospital in principle. In serious conditions such as near death, management with a respirator or systemic management should be performed with adequate pharmacologic therapy. If the symptoms are still not improved and expectoration is caught extensively in the lumen of bronchi, the use of inhalation anesthetics such as isoflurane and enflurane followed by washing of the bronchi may be effective. In such cases, it is necessary to treat the patient in cooperation with anesthesiologists.

Treatment During Recovery Phase from Acute Exacerbation

The transition from acute phase to recovery phase is evaluated on the basis of peak expiratory flow value returned to at least 75% of the personal best value, or a daily variability in peak expiratory flow value of 25% or less. Reaching these values, therapy is switched from drip infusion treatment to oral treatment at reduced dosages, and finally returned to the regular treatment.

An example is given here: for steroids, drip infusion is switched to oral administration at a dosage equivalent to 20–30 mg/day of prednisolone, and then to inhalation of corticosteroids; for theophyllines, drip infusion is switched to oral administration; inhaled β_2-agonists are given on an on-demand basis; administration of oxygen is interrupted when Spo_2 reaches 95% or Pao_2 reaches 80 torr.

Various Questions Concerning Treatment Methods

1. Inhalation of β_2-agonists or drip infusion of Aminophylline

As discussed, there are several treatment methods aiming at bronchodilation. No conclusion has been determined yet as to which one of these is best. Treatment with inhaled β_2-agonists is easy to use and works quickly. To gain the efficacy of drip infusion of aminophylline, theoretical calculations for optimal serum concentration must be learned. The pharmacological efficacy of aminophylline for asthma are not only bronchodilating but also stimulus on respiratory muscles and respiratory center. Some reports have indicated that there is no difference in efficacy between treatment with inhaled β_2-agonists, treatment with aminophylline, and a combination of both treatments, if each treatment is carried out correctly.

It should be said at this point that a physician may apply the treatment which is the physician's own forte after he or she has understood

the advantages and disadvantages of each treatment.

2. Other treatments

The use of antibiotics should be limited to bacterial infection and is not necessary for viral infection. Bacterial infection is differentiated from viral infection by leukocytosis, an increase in CRP, pneumonic shadow in chest x-ray, and the detection of bacteria in sputum. Generally, expectorants are not used because there is no expectorant that is more effective than corticosteroids. The use of sedatives in general is limited to use only in ICU. Large amounts of fluid should not be supplemented, which is hazardous. Supplementation of normal amounts of fluid is appropriate.

3. Laboratory examinations

Laboratory examinations are generally performed when hospitalization is needed. For such examinations, blood sampling, chest x-ray study, and expectoration test are carried out, giving particular attention to the bacterial infection of the airways, cardiopulmonary complications and blood sugar level.

Asthma Prevention

Once asthma exacerbation has developed, it is important to improve it quickly with appropriate treatment. Prevention of the development of asthma exacerbation is also important. Patient education under long-term management is essential for this purpose. Patient education includes learning about long-term management and therapies, how to recognize the early signs of asthma exacerbation using peak expiratory flow monitoring, and how to step up in pharmacologic therapy on the basis of objective indices under self-management. Detailed instruction on the use of oral corticosteroids is a critical point for successful self-management.

In addition, the factors contributing to asthma exacerbation should be pointed out and the removal or avoidance of these risk factors is advised to individual patient. It is recommended, for example, to avoid indoor pets, smoking, and drinking alcohol. It is very important to prevent acute exacerbation in this way and to avoid the development of severe exacerbation.

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Current Treatment of Childhood Bronchial Asthma Based on the Guidelines

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Abstract: According to "Guidelines for Treatment and Control of Childhood Bronchial Asthma 2000," guidance on daily living combined with pharmacotherapy is important in the treatment of bronchial asthma. Since atopic asthma is common in childhood, environmental control may be effective if the antigens responsible are identified. In the event of acute attacks, therapeutic drugs should be selected according to the severity of the attack. For symptomatic relief, inhaled bronchodilators should be administered repeatedly for mild attacks, followed by intravenous injection of aminophylline for moderate attacks. In the case of severe attacks, intravenous injection of steroids should be added to the above-described treatment. For long-term control (controllers), anti-inflammatory drugs, such as oral anti-allergic drugs and inhaled steroids, as well as drugs providing symptomatic relief (relievers), such as long-acting bronchodilators, should be administered according to the severity of the disease. Patient education should aim at promotion of self care. The patients should be encouraged to objectively monitor their condition by maintaining diaries and regularly monitoring their peak expiratory flows. It is also important to promote patients' understanding of the content of the treatment, and to gain their cooperation. Group therapy by admission to camps or facilities may also be effective. At school, where asthmatic children spend a large part of their daily lives, cooperation between the medical staff and educational staff is important.

Key words: Children; Bronchial asthma; Guidelines; Controllers; Relievers

Introduction

In this article, I shall discuss, in brief, the treatment of childhood bronchial asthma (hereinafter referred to as asthma), mainly based on "Guidelines for Treatment and Control of Childhood Bronchial Asthma 2000,"[1] published by the Japanese Society of Pediatric Allergy &

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The Japanese text is a transcript of a lecture originally aired on February 16, 2001, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

Table 1 Criteria for Evaluation of the Severity of Attacks[1)]

	Pulmonary function status	Activities of daily life				Matters for reference	
		Play	Sleep	Mood & Speech	Appetite	Spo_2	PEF[NOTE2)]
Mild attack	Mild stridor or wheeze is present, associated with mild intercostal retraction.	Normal	Normal	Talk normally	Normal	96% or more	60% or more
Moderate attack	Obvious stridor, intercostal retraction and dyspnea are noted.	Rather difficult	Occasionally wake up	Rather bad Can reply when talked to	Rather bad	92–95%	30–60%
Severe attack	Marked stridor, dyspnea and orthopnea are noted. Cyanosis is occasionally observed.	Impossible or almost impossible	Impossible or almost impossible	Bad Cannot reply when talked to	Bad or almost bad	91% or less	30% or less

Note) Signs of respiratory failure (marked dyspnea, cyanosis, diminished breath sounds, and neurological disorder, including diminished reaction to pain, irritability or consciousness disturbance) should be watched for.

Note 2) PEF is expressed as a percentage of the predicted value before inhalation of β_2-agonist, or against the self-best value.

Additional note) The severity of attacks is determined based on the above-described clinical symptoms. In children, the pulmonary function status does not always corroborate the severity of the clinical symptoms. Nonetheless, pulmonary functions are also determined to help in guiding the treatment in the "Guidelines". At present, standard values for the pulmonary functions are not specified. Therefore, the values presented here are just for the sake of reference. Re-examination of this subject is necessary in the near future. It goes without saying that priority should be accorded to clinical symptoms when judging the severity of the attacks for the purpose of treatment.

Clinical Immunology in April 2000.

Characteristics of Childhood Asthma

Since atopic asthma, in which past and family history reveal a history of allergy, is common in childhood, the antigens responsible can be identified, based on information collected from detailed history taking as well as the results of specific IgE antibody testing and skin tests. Elimination of the environmental antigens thus identified often leads to symptomatic improvement. In this respect, childhood asthma differs significantly from adult asthma, which is of the non-atopic type in most cases.

The severity of asthmatic attacks is evaluated by the degree of disturbance of daily living and the pulmonary function status, and is classified as mild, moderate or severe (Table 1). When the severity of childhood asthma is compared with that of adult asthma based on the degree of disturbance of daily living, mild attacks in adults are equated to moderate attacks in children.

In childhood asthma, reversibility of airway obstruction is preserved relatively well, and pulmonary functions are almost normal during the intervals between attacks. In contrast, in adults, pulmonary functions are often impaired even in between the attacks, the airway obstruction is less reversible, and bronchodilators tend to be relatively less effective.

Measures against Acute Asthmatic Attacks

It is necessary to explain the measures taken to handle acute asthmatic attacks, as described below, to children who have the ability to understand, as well as to guardians, such as parents, under whose direct care they are placed.

Table 2 Treatment of Acute Attacks of Childhood Asthma at Medical Institutions[1)]

	Symptoms	Spo_2	PEF (School children or older)	Treatment
Mild attack	Mild stridor or wheeze, sometimes associated with mild intercostal retraction.	96% or more	Often 60% or more	(Step 1) • Inhaled β_2-agonists
Moderate attack	Obvious stridor, with intercostal retraction and dyspnea.	92–95%	Often between 30% and 60%	(Step 1) • Repeated β_2-agonist inhalation (Step 2) • Intravenous infusion or bolus injection of aminophylline
Severe attack	Marked stridor, with dyspnea and orthopnea. Cyanosis is occasionally observed.	91% or less	Often 30% or less	(Step 1) • β_2-agonist inhalation with supplemental oxygen (Step 2) • Intravenous infusion of aminophylline and fluid replacement • Correction of acidosis (Step 3) • Intravenous injection of steroids
Respiratory failure	Marked dyspnea, cyanosis, diminished breath sounds and neurological disorder (irritability, disturbed consciousness, or diminished reaction to pain)	90% or less (With supplemental O_2)	Impossible to determine	Continuation of above-described treatment (Step 3) Reference • Continuous isoproterenol inhalation (Step 4) • Endotracheal intubation • Artificial ventilation

Note) PEF is expressed as a percentage of the predicted value before inhalation of β_2-agonists, or against the self-best value.

1. Measures at home

When mild attacks occur at home, the patient should be advised to relax and practice abdominal breathing, and simple physical therapy, such as encouraging water intake to facilitate expectoration of sputum, should be instituted, before pharmacotherapy is started. Such a calm approach to assess the severity of attacks can help avoid overuse of β_2-agonists by metered dose inhalers (MDI). However, it should be ensured that there is no delay in the start of appropriate treatment. If oral bronchodilators and inhaled β_2-agonists as prescribed by the physician do not work, local medical facilities must be consulted.

2. Measures at medical institutions

When mild attacks occurring at home do not respond to the usual treatment, or progress to moderately severe attacks, treatment should be sought at a medical institution. If the condition does not respond to the treatment instituted according to the severity of the attack, treatment recommended for the next higher grade of severity should be commenced. If adequate response is observed, the treatment may be downgraded again.

3. Drugs for treating acute attacks (drugs providing symptomatic relief: relievers) (Table 2)

Bronchodilators that help in remitting or eliminating the symptoms of acute attacks are called relievers. Differences in the measures adopted to treat acute attacks in children and adults are summarized by Hosoi as follows.[2)]

1) The severity of attacks in children is equated to the next higher grade of severity in adults.

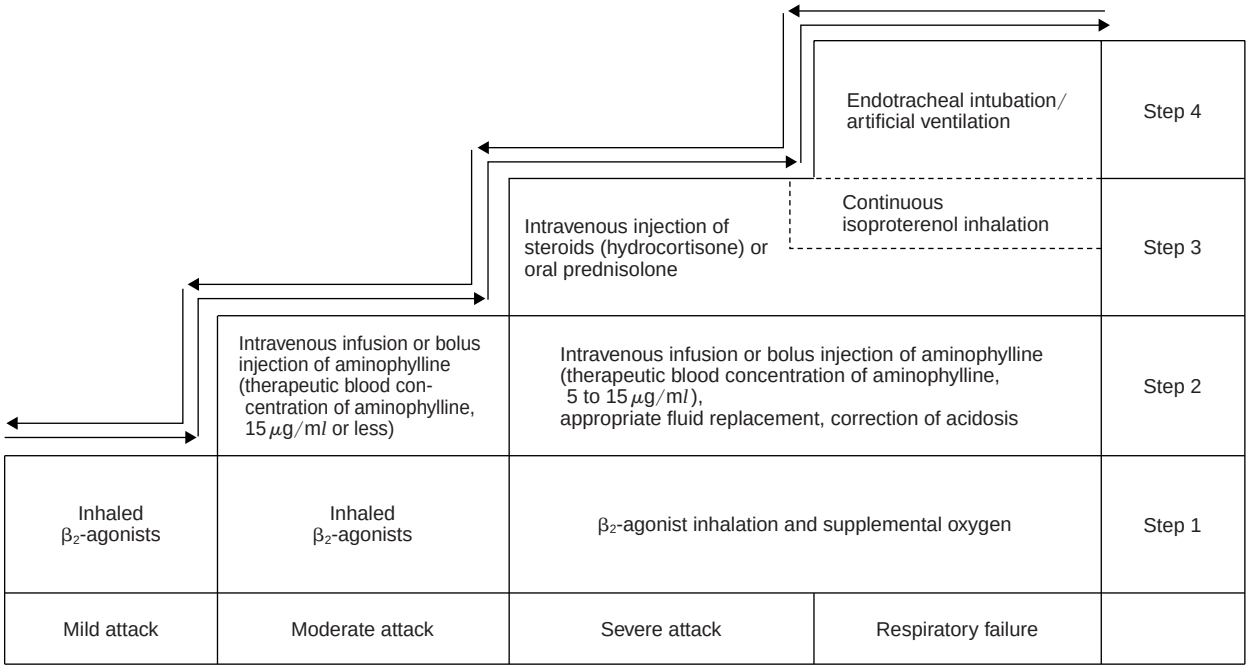

Fig. 1 Plan of pharmacotherapy for acute attacks of childhood asthma at medical institutions[1)]

2) Oral β_2-agonists play a greater role in mild cases of childhood asthma (mild intermittent and mild persistent cases), while MDIs are indicated carefully.
3) Oral steroids are used with prudence.
4) Aminophylline infusion and fluid replacement are commonly adopted for the treatment of moderate to severe attacks (Step 2).
5) Subcutaneous injection of Bosmin® (epinephrine) is not adopted as standard therapy.
6) Continuous inhalation of isoproterenol is used in the treatment of very severe attacks.

In the treatment of acute attacks in children, β_2-agonists are administered orally or by inhalation, and epinephrine is injected subcutaneously in emergent situations. Theophylline is administered orally or aminophylline by intravenous injection, and in some rare cases, inhaled anticholinergic drugs are used.

4. Treatment of acute attacks (Fig. 1)

(1) Treatment of mild attacks

β_2-agonists are administered by inhalation, and after monitoring the clinical course for 15 minutes, the severity of the attack is evaluated again. If there is some improvement, but the response is still inadequate, the inhalation should be repeated. If the response is not satisfactory, the treatment should be upgraded to that recommended for moderate attacks.

(2) Treatment of moderate attacks

β_2-agonists are administered first by inhalation. A venous line is secured, and an intravenous injection or drip infusion of 4 to 6 mg/kg body weight of aminophylline, added to maintenance fluid or 20% glucose solution, is administered over 20 minutes or longer. If the response observed is not satisfactory, the β_2-agonist inhalation should be repeated, and continuous aminophylline infusion must be started. If the latter becomes necessary, the patient should be hospitalized first.

(3) Treatment of severe attacks

In children, great individual differences are noted in the response to treatment, and effective treatment often varies among individuals.

β_2-agonists are administered by inhalation while supplemental oxygen is started, and amino-

phylline is administered by continuous intravenous infusion. Hydrocortisone at the dose of 5 to 7 mg/kg body weight is administered by slow intravenous injection at intervals of 4 to 6 hours, or prednisolone injection is started at the dose of 1 to 1.5 mg/kg body weight. If no adequate response is noted, continuous isoproterenol inhalation in an oxygen tent is employed. The heart rate, respiratory rate, and oxygen saturation should be closely monitored.

(4) Treatment of respiratory failure

If the pulmonary functions do not improve despite the above measures, endotracheal intubation, assisted ventilation, and artificial ventilation may become necessary.

(5) Indications for hospitalization

Children with acute asthma are hospitalized more frequently than adult patients with acute asthma, so as to ensure that they are treated as quickly and as safely as possible. The indications for hospitalization can be summarized as follows.

1) Severe attacks
2) Moderate attacks that do not respond even after 2 hours of appropriate treatment at the outpatient clinic
3) Moderate attacks lasting more than 24 hours
4) Acute asthma in infants
5) Complications, such as pneumonia, atelectasis, and pneumothorax
6) Inadequate response despite upgradation of long-term control

Measures for Long-term Control of Asthma

1. Drugs used for long-term control (controllers)

The drugs used for long-term control of bronchial asthma are called controllers, because they stabilize respiratory functions and improve the quality of life (QOL) of the subjects. The pharmacotherapy for long-term control of childhood asthma differs from that for adult-onset asthma in the following ways.[2)]

1) Even if the same terms are used for classification of the severity of symptoms, the same clinical condition is assigned a higher level of severity in children.
2) The intermittent type of adult asthma encompasses the mild intermittent type, mild persistent type, and moderate persistent type of childhood asthma.
3) Basically, the timing of initiation of inhaled steroids is the same in both groups.
4) Treatment from Step 1 to Step 3 is carried out before starting inhaled steroids.
5) Specialist guidance is required for long-term administration of oral steroids.
6) In the treatment of the severe persistent type of asthma, psychosocial factors and long-term hospitalization (institutionalization) should be considered.

(1) Anti-inflammatory drugs

1) Inhaled steroids

Beclomethasone dipropionate is available in two formulations, which deliver 50μg and 100μg per inhaled dose. Fluticasone propionate, which is commonly used in adults, has begun to be used in some older children, but the drug should be administered with caution in children.

2) Sodium cromoglycate (DSCG)

DSCG is available in capsule, liquid, and aerosol formulations. Inhaled DSCG in combination with β_2-agonists has been reported to be effective in the treatment of moderate or severe asthma in children.

3) Oral anti-allergic drugs

Oral anti-allergic drugs include inhibitors of the release of chemical mediators, histamine H_1-receptor antagonists, and leukotriene antagonists. When administered systemically, they are known to exert effects against allergic diseases in general.

(2) Long-acting bronchodilators

1) Long-acting β_2-agonists

In Japan, only short-acting β_2-agonists are commercially available, and sufficient information regarding long-acting β_2-agonists is lacking.

2) Sustained-release theophylline

The rate of metabolism of theophylline in the liver differs among different individuals,

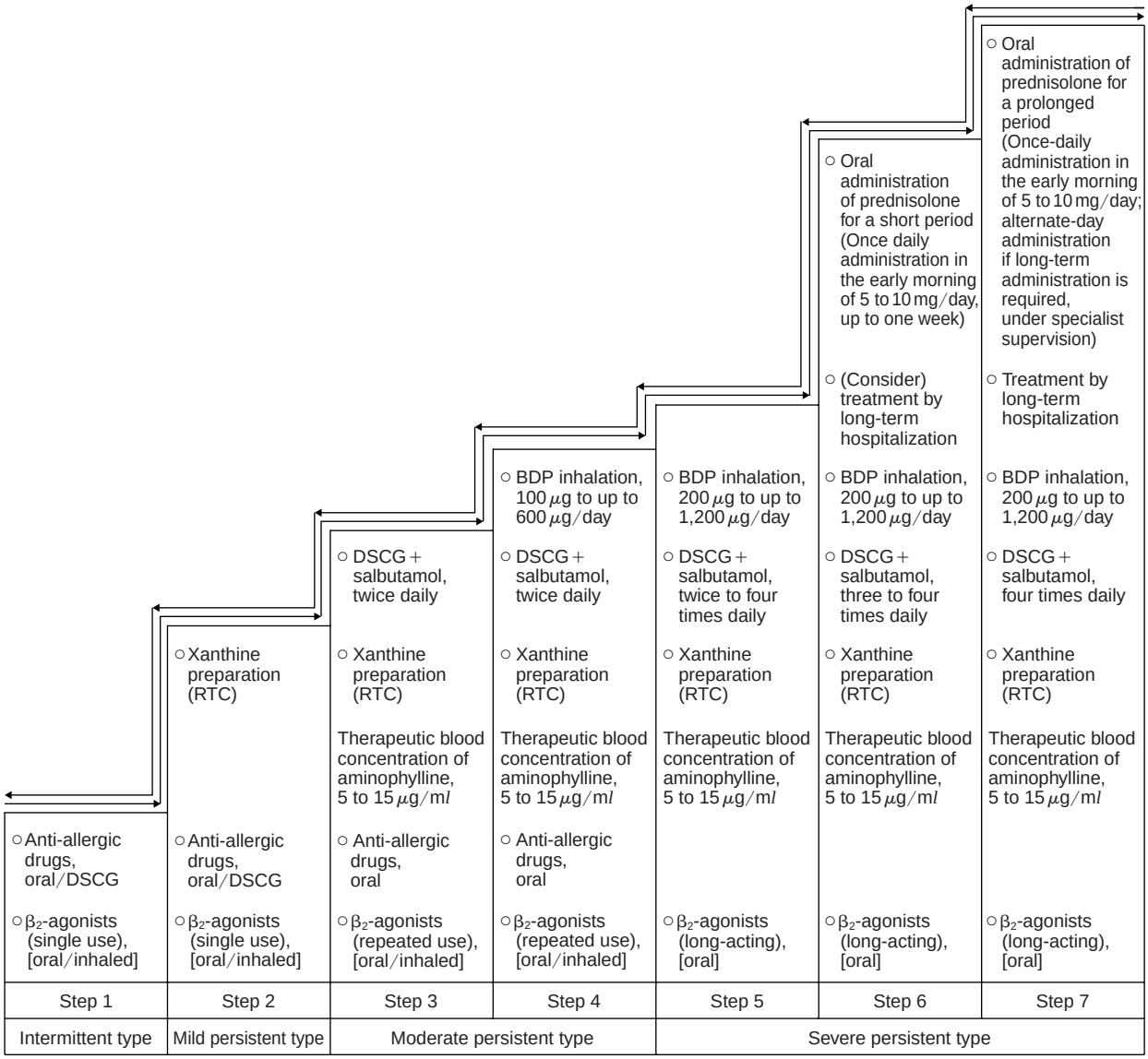

Fig. 2 Pharmacotherapy plan for long-term control of childhood asthma[1)]

Note 1) BDP: beclomethasone dipropionate RTC: round the clock DSCG: disodium cromoglycate

Note 2) When multiple drugs are used concomitantly, it is important to ensure that ineffective drugs are eliminated in each patient, and that more than the required number of drugs are not administered.

Note 3) The efficacy of oral anti-allergic drugs in combination with leukotriene antagonists in severe persistent asthma is still unknown.

and is also dependent on the age of the subject. Moreover, the influences of complications, such as infection, contents of meals, and concomitantly administered drugs should also be taken into consideration. When adequate effects are not obtained after administration of the usual dose, or adverse drug reactions are suspected, the blood concentration of the drug should be determined. Since the drug is known to induce convulsions even at low concentrations in patients with a past history of central nervous system disorder, caution must be exercised during administration of the drug.

2. Pharmacotherapy for long-term control (Fig. 2)

(1) Intermittent asthma

Drugs are administered according to the severity of the attacks. Administration of anti-allergic drugs should be started immediately, depending on the symptoms.

Inhaled DSCG or β_2-agonists should be used for the prevention of exercise-induced asthma.

(2) Mild persistent asthma

Round-the-clock (RTC) administration of theophylline is required. In addition, single use of oral or inhaled β_2-agonists is recommended.

(3) Moderate persistent asthma

Inhaled DSCG in combination with β_2-agonists is administered regularly. When oral or adhesive β_2-agonists are used regularly, they should be discontinued as the symptoms improve. If satisfactory response is obtained, combined inhalation of DSCG and β_2-agonists and RTC theophylline should be continued. When the treatment is ineffective, or only partially effective, inhaled beclomethasone should be used concomitantly. As to the standard dose, 100 to 150μg per dose should be administered two to four times a day using a spacer, and the patients should be advised to gargle after the inhalation.

(4) Severe persistent asthma

Beclomethasone dipropionate is administered at the dose of 100 to 300μg per dose two to four times a day, and the maximum daily dose should not exceed 1,200μg. Regular combined inhalation of a mixture of DSCG and β_2-agonists, oral β_2-agonists, and RTC theophylline is recommended.

When the condition does not respond to the above-described treatment and the patient's daily life is disturbed, the patient is referred to a specialist, or on the basis of consultation with a specialist, the dose of inhaled beclomethasone is increased, or 5 to 10 mg of prednisolone are administered once daily in the morning for up to one week.

If the condition still does not respond to these treatments, the patient should be admitted to a specialized medical institution for long-term hospitalization, while arranging for the children to receive education, possibly at a school for children with the disease.

Patient Education

Patient education regarding childhood asthma should be provided to both patients and their guardians, depending on the degree of understanding. In the case of infants, in particular, guardian education is essential. On the other hand, in the case of adolescents, the patients gradually come to play the main role in treatment, but often they are not sure at this age whether they should still be dependent on their parents or can act independently, and may become somewhat confused about their treatment. Since patients in their adolescence do not visit the hospital very often, the physicians should actively engage themselves in the task of educating this group of patients.

1. Promotion of self care

We have established the following goals to promote objective understanding by the patients of their condition.

1) Maintenance of an asthmatic diary.
2) Monitoring of peak flow rate.
3) Acquire knowledge and skills regarding how to use the drugs, the effects of the drugs, and adverse drug reactions.

2. Training

During the growing stage, physical training, while ensuring precautions to prevent exercise-induced asthma, is useful in improving the children's QOL. Instructions are given so that children will be able to enjoy swimming, which is considered relatively less likely to induce attacks, as well as various other types of sports.

3. Group therapy

Group therapy plays an educational role by providing opportunities for developing interpersonal skills, and asthmatic children can learn to help each other through such activities as

summer camps.

4. Liaison between school and medical institution

The communication between the medical staff and educational staff to exchange information is expected to assume increasing importance, so that the children can play active roles in school, where they lead a large part of their daily lives.

Conclusion

Thus, as is evident from the above, "Guidelines for Treatment and Control of Childhood Bronchial Asthma 2000" comprehensively covers not only pharmacotherapy for the control of asthma, but also provides guidance on daily living. I would be greatly pleased if physicians found the "Guidelines" useful in their daily medical practice.

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A Preliminary Study of the Impact of Managed Care on Psychotherapy in Massachusetts

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Abstract:
Objectives: We conducted a questionnaire survey to assess the impact of managed care on psychotherapy in Massachusetts.
Methods: The subjects of the study were 198 psychotherapists and psychiatrists affiliated with McLean Hospital and Massachusetts General Hospital, Massachusetts, USA. We asked all 772 professionals affiliated with those institutions to complete a questionnaire on the impact of managed care and socio-demographic characteristics between February 25 and April 25, 1999.
Results: Of the 772 subjects targeted, 198 (25.6%) responded. Three fourths of the respondents reported that managed care increased administrative time for paperwork, and 41.9% said that managed care decreased the average number of sessions for patients/clients. The respondents sometimes (66.2%) or often (10.6%) had to terminate treatment because managed care did not pay for continued care. They sometimes (45.5%) or often (32.3%) terminated contracts or refused to sign contracts with "managed care" organizations or turned down referrals from "managed care." Psychotherapists fell into two groups: those who spent much of their time with managed care patients and those who did not, whereas there was no such difference between psychiatrists.
Conclusions: Managed care has reduced the number of psychotherapy sessions in Massachusetts and increased administrative work.

Key words: Managed care; Psychotherapy

Introduction

In this article "managed care" refers any form of external utilization review. Managed care has recently provided a model for a future health care system, and many articles on managed care have been published.[1)] In Japan, for example, managed care as practiced in the

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United States has been introduced on various health plans, because Japan is facing a turning point in its health care system and is searching for new models for the system of the future. Feasibility studies on a prospective payment system based on diagnostic related groups (DRG/PPS) represents a new trend in Japan, and managed care is one of the subjects of the new models.

Based on a recent survey, Simon *et al.* concluded that negative views of managed care were widespread among medical students, residents, faculty members, and medical school deans.[2] State and local governments are also moving rapidly to contract with managed care companies for mental health and substance-abuse services covered by Medicaid, one of the major public programs funding services of this type.[3] Massachusetts was the first state to introduce a statewide managed-care plan for mental health services within its Medicaid program.[4]

Psychiatry, especially psychotherapy, will be deeply impacted by the introduction of managed care. Because psychiatry requires a certain period of time for treatment to be effective, limitations on mental health care resources by managed care changes the dynamic flow of treatment for psychiatric patients. Managed care has had a major impact on psychotherapy in the United States. Since managed care companies cover only medical necessities,[5–7] the number of sessions is restricted. Bennet has noted that long-term psychotherapy is difficult in the managed care era.[5]

In contrast to the United States, it is difficult for psychotherapists to open private offices in Japan for financial reasons. Although the universal insurance program has included psychotherapy since 1964, the fee is 3,700 yen (about US$31) in 2001. If the introduction of managed care into the Japanese health care system reduces the utilization of psychotherapy, the development of psychotherapy will fall even further behind.

In this study, we examined the differences in the impact of managed care on psychotherapists and psychiatrists in Massachusetts, which has the longest history of statewide managed care. We hypothesized that (1) managed care has impacted paperwork, average number of sessions, and the number of patients with severe mental illness who are treated, (2) and that psychotherapists and psychiatrists have had to terminate treatment earlier.

Subjects and Method

We asked all 772 professionals affiliated with McLean Hospital and Massachusetts General Hospital in Massachusetts, to complete a questionnaire between February 25 and April 25, 1999. Of them, 198 (25.6%) returned the questionnaire. Since 2 were excluded because of incompleteness of the "profession" item, ultimately the 196 professionals (86 psychotherapists and 110 psychiatrists) were subjects of the study. Of the 86 psychotherapists, 73 (84.9%) had a Ph.D. degree.

The questionnaire inquired about the impact of managed care and about socio-demographic characteristics such as gender, age, profession, years in practice, hours of direct patient care a week, and percentage of managed care patients/clients. The questions regarding the impact of managed care were: (Q1) Do you think that administrative time for managed care paperwork has changed?; (Q2) Has the average number of your sessions for managed care patients/clients changed?; (Q3) Must you terminate treatment because managed care does not pay for continued care?; (Q4) Do you think that the number of your patients/clients with severe mental illness has changed due to managed care?; and (Q5) Are you terminating contracts or refusing to sign contracts with "managed care" organizations or turning down referrals from "managed care"? Participants answered each question on a 3 point-scale.

We performed the statistical analysis by using the chi-square test and analysis of variance with a SPSS software package. Hours of man-

aged care a week were calculated based on the hours in direct care practice and percentages of managed care patients.

Results

1. Characteristics of respondents

The characteristics of the respondents are shown in Table 1. Mean age was 48.5 years old, with a mean of 17.8 years in practice. The per-

Table 1 Demographic Characteristics of Respondents

		Total	Psychiatrist	Psychotherapist	Test
Mean age in years (SD)	$n=196$	48.5 (10.5)	49.4 (11.4)	47.2 (9.1)	ns
Gender	Male Female	118 (59.6) 79 (39.9)	77 (70.0) 33 (30.0)	41 (47.7) 45 (52.3)	χ^2 (df = 1) = 10.0**
Length of practice in years (SD)	$n=193$	17.8 (10.5)	18.5 (11.5)	16.8 (9.1)	ns
Length of direct care a week in hours (SD)	$n=192$	26.7 (11.9)	28.2 (13.0)	24.7 (9.9)	t (df = 190) = 2.0*
Percentage of managed care patients (SD)	$n=188$	49.6 (30.6)	51.9 (30.9)	46.8 (30.2)	ns
Hours of managed care patients a week	≦4 5–20 21≦	45 (24.1) 95 (50.8) 47 (25.1)	24 (22.9) 46 (43.8) 35 (33.3)	21 (25.6) 49 (59.8) 12 (14.6)	χ^2 (df = 2) = 8.86*

*$p<0.05$ **$p<0.001$
ns: not significant

Table 2 Results for Each Question (%)

		Psychiatrist	Psychotherapist	Total
Q1. Do you think that a dministrative time for managed care paperwork has changed? ($n=189$)	Increased	86 (80.4)	61 (74.4)	147 (77.8)
	Unchanged	15 (14.0)	17 (20.7)	32 (16.9)
	Decreased	6 (5.6)	4 (4.9)	10 (5.3)
Q2. Has the average number of your sessions for managed care patients/clients changed? ($n=188$)	Increased	11 (10.4)	7 (8.5)	18 (9.6)
	Unchanged	48 (45.3)	39 (47.6)	87 (46.3)
	Decreased	47 (44.3)	36 (43.9)	83 (44.1)
Q3. Must you terminate your treatment because managed care does not pay for continued care? ($n=188$)	Never	26 (24.3)	11 (13.6)	37 (19.7)
	Sometimes	71 (66.4)	59 (72.8)	130 (69.1)
	Often	10 (9.3)	11 (13.6)	21 (11.2)
Q4. Do you think that the number of your patients/clients with severe mental illness has changed due to managed care? ($n=183$)	Increased	25 (23.8)	18 (23.1)	43 (23.5)
	Unchanged	71 (67.6)	55 (70.5)	126 (68.9)
	Decreased	9 (8.6)	5 (6.4)	14 (7.7)
Q5. Are you terminating contracts or refusing to sign contracts with "managed care" organizations or turning down referrals from "managed care"? ($n=186$)	Never	20 (18.7)	13 (16.5)	33 (17.7)
	Sometimes	49 (45.8)	41 (51.9)	90 (48.5)
	Often	38 (35.5)	25 (31.6)	63 (33.9)

There are no significant differences in items between psychotherapist and psychiatrists.
Total numbers differ because of missing values.

centage of female psychotherapists was significantly higher than the percentage of female psychiatrists.

The average number of hours spent in direct patient care was 26.7, and 49.6% of the time was spent with managed care patients. The proportions of respondents who spent less than half day, between half day and 2.5 days, and more than 2.5 days were 23%, 49%, and 24%, respectively. The time spent on managed care patients by psychotherapists was significantly shorter than the time spent by psychiatrists.

2. Responses to each question

As shown in Table 2, 77.8% of the respondents thought that managed care had increased administrative time for paperwork, and 44.1% thought that managed care had decreased the average number of sessions for patients/clients. The respondents sometimes (69.1%) or often (11.2%) had to terminate treatment because managed care did not pay for continued care. They thought that the number of patients/clients with severe mental illness had increased (23.5%) or was unchanged (68.9%) as a result of managed care. They sometimes (48.5%) or often (33.9%) terminated contracts or refused to sign contracts with "managed care" organizations or turned down referrals from "managed care."

There were no significant differences between psychotherapists and psychiatrists in any of the item.

There were no significant relationships between replies to individual items except (Q3) "terminating their treatment because of managed care." The relationships between replies to Q3 and other items are shown in Table 3. The more psychiatrists and psychotherapists terminated treatment because of managed care, the

Table 3 Termination of Treatment and Other Responses

		Must you terminate treatment because managed care does not pay for continued care? (Q3)							
		Psychiatrists			χ^2 (4)	Psychotherapists			χ^2 (4)
		Never	Sometimes	Often		Never	Sometimes	Often	
Do you think that administrative time for managed care paperwork has changed? (Q1)	Increased	18 (72.0)	59 (83.1)	8 (80.0)	ns	5 (45.5)	45 (77.6)	10 (90.9)	ns
	Unchanged	4 (16.0)	10 (14.1)	1 (10.0)		5 (45.5)	10 (17.2)	1 (9.1)	
	Decreased	3 (12.0)	2 (2.8)	1 (10.0)		1 (9.1)	3 (5.2)	0 (0)	
Has the average number of your sessions for managed care patients/clients changed? (Q2)	Increased	3 (11.5)	8 (11.4)	0 (0)	13.7**	0 (0)	5 (8.6)	2 (18.2)	11.2*
	Unchanged	17 (65.4)	30 (42.9)	1 (10.0)		10 (90.9)	23 (39.7)	5 (45.5)	
	Decreased	6 (23.1)	32 (45.7)	9 (90.0)		1 (9.1)	30 (51.7)	4 (36.4)	
Do you think that the number of your patients/clients with severe mental illness has changed due to managed care? (Q4)	Increased	3 (12.0)	18 (26.1)	4 (40.0)	ns	0 (0)	14 (25.5)	4 (36.4)	ns
	Unchanged	22 (88.0)	44 (63.8)	4 (40.0)		10 (100)	36 (65.5)	7 (63.6)	
	Decreased	0 (0)	7 (10.1)	2 (20.0)		0 (0)	5 (9.1)	0 (0)	
Are you terminating contracts or refusing to sign contracts with "managed care" organizations or turning down referrals from "managed care"? (Q5)	Never	6 (24.0)	14 (19.7)	0 (0)	ns	4 (40.0)	9 (15.8)	0 (0)	10.6*
	Sometimes	11 (44.0)	34 (47.9)	3 (30.0)		1 (10.0)	33 (57.9)	6 (60.0)	
	Often	8 (32.0)	23 (32.4)	7 (70.0)		5 (50.0)	15 (26.3)	4 (40.0)	
Total		37	131	21		37	131	21	

*$p<0.05$ **$p<0.001$

ns: not significant

more the average number of sessions decreased. Psychotherapists who had never terminated treatment were divided into two groups: those who had never terminated contracts or refused to sign contracts with managed care and those who had often terminated or refused such contracts.

As shown in Table 4, the responses of psychotherapists differed according to the length of time spent with managed care patients a week. Psychotherapists who spent more time with managed care patients reported there was an increase in time for managed care paperwork significantly greater than those who spent less than 4 hours a week. Psychotherapists who spent more time with managed care patients terminated treatment more frequently than those who spent less than 4 hours a week. However, they less frequently terminated or refused to sign contracts with "managed care" organizations or turned down referrals from "managed care" than those who spent less than 4 hours a week.

There were no significant correlations between any of the items and time spent with managed care patients.

Discussion

1. Methodological issues and characteristics of respondents

The response rate for mailed questionnaire surveys is usually said to be much lower than with other methods in the United States, even

Table 4 Each Item and Hours of Managed Care Patients a Week by Professional

		Psychiatrists				Psychotherapist			
		Hours spent with managed care patients per week				Hours spent with managed care patients per week			
		≦4	5–20	21≦	χ^2 (4)	≦4	5–20	21≦	χ^2 (4)
Q1. Do you think that administrative time for managed care paperwork has changed?	Increased	16 (72.7)	35 (76.1)	32 (91.4)		9 (45.0)	42 (85.7)	8 (72.7)	
	Unchanged	6 (27.3)	7 (15.2)	1 (2.9)	ns	10 (50.0)	6 (12.2)	1 (9.1)	18.3**
	Decreased	0 (0)	4 (8.7)	2 (5.7)		1 (5.0)	1 (2.0)	2 (18.2)	
Q2. Has the average number of your sessions for managed care patients/clients changed?	Increased	2 (9.5)	4 (8.9)	5 (14.3)		0 (0)	6 (12.2)	1 (8.3)	
	Unchanged	13 (61.9)	20 (44.4)	12 (34.3)	ns	14 (73.7)	19 (38.8)	6 (50.0)	ns
	Decreased	6 (28.6)	21 (46.7)	18 (51.4)		5 (26.3)	24 (49.0)	5 (41.7)	
Q3. Must you terminate your treatment because managed care does not pay for continued care?	Never	7 (33.3)	12 (26.1)	6 (17.1)		6 (31.6)	2 (4.2)	2 (16.7)	
	Sometimes	13 (61.9)	31 (67.4)	24 (68.6)	ns	12 (63.2)	37 (77.1)	9 (75.0)	10.7*
	Often	1 (4.8)	3 (6.5)	5 (14.3)		1 (5.3)	9 (18.8)	1 (8.3)	
Q4. Do you think that the number of your patients/clients with severe mental illness has changed due to managed care?	Increased	5 (23.8)	6 (13.6)	12 (34.3)		1 (5.3)	14 (29.8)	3 (27.3)	
	Unchanged	15 (71.4)	33 (75.0)	20 (57.1)	ns	16 (84.2)	31 (66.0)	7 (63.6)	ns
	Decreased	1 (4.8)	5 (11.4)	3 (8.6)		2 (10.5)	2 (4.3)	1 (9.1)	
Q5. Are you terminating contracts or refusing to sign contracts with "managed care" organizations or turning down referrals from "managed care"?	Never	4 (18.2)	8 (17.4)	7 (20.6)		1 (5.3)	8 (17.0)	3 (25.0)	
	Sometimes	7 (31.8)	21 (45.7)	18 (52.9)	ns	7 (36.8)	26 (55.3)	8 (66.7)	9.8*
	Often	11 (50.0)	17 (37.0)	9 (26.5)		11 (57.9)	13 (27.7)	1 (8.3)	

*$p<0.05$ **$p<0.001$

ns: not significant

when the surveyor pays a fee to respondents for their cooperation.[8] In this study, more than one fourth of the psychotherapists and psychiatrists returned the questionnaire, and there was no fee for their cooperation. The shortness of the questionnaire may have contributed to the higher response rate than expected, although the response rate was not high and not very satisfactory.

The mean age of the respondents was 48 years old and they had an average of 18 years of clinical experience. They spent an average of 27 hours on direct patient care, which meant that the respondents spent more than half of their working hours on direct care of the patients. These results suggest that the respondents were clinical professionals spending most of their time on clinical services.

2. Impact of managed care

Respondents generally recognized the three changes in direct patient care: administrative time for managed care had increased the administrative time for paperwork; termination of treatment by professionals because of managed care had increased; and termination of contracts or refusal to sign contracts with "managed care" organizations or turning down referrals from "managed care" had increased.

Managed care organizations always require that direct care professionals precisely document their practice for review. Direct care professionals need to explain why and how they provide treatment, and the increases in administrative time reflect these requirements by managed care. In addition, increases in termination of treatment because of managed care's refusal to pay for continued care represents a serious problem for direct care. Managed care generally limits the number of sessions per year or per lifetime. From a clinical standpoint, however, such limitations seem inappropriate because long-term psychotherapy can not be provided when needed (Bennett, 1996).

The increases in termination or refusal of contracts with "managed care" organizations show another trend among direct care professionals. The psychotherapists who responded could be divided into two groups: those who spent a great deal of time with managed care patients but frequently terminated their treatment, and those who did not see any managed care patients at all. These results suggest that psychotherapists decide whether or not to see managed care patients in their practice. This psychotherapists' response suggests that direct care professionals themselves decide to contract with managed care organizations. Psychotherapists seem to select clients with or without managed care.

By contrast, there was no such difference among psychiatrists, although they spent longer time in direct care to see managed care patients than psychotherapists. It seems difficult for psychiatrists to decide not to spend time with managed care patients. This is partly because medical treatment by psychiatrists is more closely related to the managed care payment system in reimbursement than psychotherapy by psychotherapists. This means that managed care has a greater impact on psychotherapy by psychiatrists than by psychotherapists.

Conclusion

Managed care has had a great impact on psychotherapy in Massachusetts. It has reduced the number of sessions, and increased administrative work. Some psychiatrists and psychotherapists terminate their contract with managed care to maintain their clinical practice under their own control. Policy makers should carefully review the impact of payment system changes on clinical services before hastening to introduce a new system.

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Treatment of Age-related Macular Degeneration

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Key words: Age-related macular degeneration (ARD); Photodynamic therapy; Radiation therapy; Thermal therapy

Introduction

Age-related macular degeneration (ARD) is a disease of the macula in the retina, the incidence of which increases with age. Since the macula is affected, patients with ARD acknowledge visual impairment from the onset of the disease. ARD is the leading cause of blindness among adults in the U.S. and Europe, and its incidence in Japan is also gradually increasing.

Epidemiological data from a study conducted in Rotterdam reported an incidence of ARD of 1.1% of the residents aged 55 and older. In a similar study conducted in Hisayama-machi, Fukuoka Pref., Japan, the incidence of ARD in residents aged 50 and older was 0.67%.

The International Classification of Diseases defines two types of maculopathy: early age-related maculopathy (drusen and retinal pigment epithelium abnormalities) and late age-related maculopathy (hemorrhage due to choroidal and subretinal neovascularization; wet and dry forms). ARD generally refers to late age-related maculopathy, and risk factors associated with it include genetic predisposition, hypertension, smoking, and exposure to sunlight. Included in the genetic factors are ATP-binding cassette transporter retina and A2E proteins.

Diagnosis

Funduscopy reveals subretinal neovascularization in the macular area, exudation from the newly formed blood vessels, retinal edema, and hemorrhage in patients with ARD. Fluorescein fundus angiography with indocyanine green is now available to identify choroidal neovascularization, in addition to conventional angiography with sodium fluorescein. Optical coherence tomography makes possible the cross-sectional examination of the retina, and plays a critical role in investigating the presence of subretinal neovascularization, the extent of retinal detachment, and in providing improved images after treatment.

These new techniques have allowed visualization of the detailed state of spread of subretinal neovascularization, which was previously impossible with conventional funduscopic examination or fluorescein fundus angiography using sodium fluorescein.

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Treatment

This section describes the pharmacotherapy, non-invasive and invasive treatments that are currently available for ARD.

1. Pharmacotherapy

Although there is no well established pharmacotherapy for ARD, therapeutics including peripheral vasodilating drugs, vitamin B_{12}, or α and β- interferon have been used. In animal experiments, tranilast, kinase inhibitors, and peroxisome proliferator activated receptor-γ ligands have been found effective in suppressing neovascularization. Studies have also been conducted on antagonists for vascular endothelial growth factors and their receptors.

2. Non-invasive treatment

Laser photocoagulation is performed when the distance between the neovascular membrane and the center of the macula is over 200μm, as measured by fluorescein fundus angiography with sodium fluorescein or indocyanine green. The entire neovascular membrane should be thoroughly photocoagulated, or recurrence may occur in areas not coagulated. However, photocoagulation cannot be performed on bleeding areas. In addition, caution should be exercised when performing photocoagulation, as neurons within the photocoagulated areas die. Subsequently, the area of coagulation may enlarge in the healing process and reach the central portion of the macula, resulting in an unexpected deterioration of visual acuity.

Low dose radiation therapy is used to occlude newly formed vessels by irradiation of the posterior pole of the fundus with about 20 Gy. The therapy is highly effective in some cases, particularly when the hemorrhage has already reached the macula, as photocoagulation therapy is not applicable in such cases.

Photodynamic therapy (PDT) is a treatment method that has recently attracted attention. PDT is designed to selectively destroy only neovascular membranes by intravenously injecting a photosensitive agent, followed by irradiation with a laser at a specific wavelength that does not harm normal neurons. This methodology makes possible the coagulation of newly formed blood vessels in the fovea centralis of the macula, which should not be photocoagulated. Verteporfin (Visudyne) has been used as a photosensitive agent. Results of one- and two-year clinical studies have demonstrated the effectiveness of PDT with verteporfin in the wet form of ARD. Other photosensitive agents have also been studied and PDT is likely to become an important treatment option in the future.

Transpupillary thermal therapy is designed to occlude newly formed blood vessels by heating choroidal neovascular membranes with a near-infrared diode laser. Its effectiveness, however, has not been established.

3. Invasive treatment

Evacuation of subretinal hematoma is a surgical technique designed to remove hematoma, before accumulation of blood in the inferior portion of the retinal macula results in irreversible damage to retinal neurons. In this procedure, an incision is made in the retina close to the hematoma, and tissue plasminogen activator is injected via the incision into the hematoma which is dissolved and is removed. Although this technique has yielded favorable results, it must be performed before the presence of a hematoma results in retinal neuron disorders.

Surgical removal of subretinal neovascular membranes is designed to resect submacular neovascular membranes by insertion of a forceps via a retinal incision near the macula. However, the surgery results in inevitable damage to retinal pigment cells or their extraction together with resected neovascular membranes during surgery. As a result, the retinal neurons of the macula cease to function and the prognosis is by no means favorable.

Recently, a surgical procedure has been per-

formed in which pigment cells from the patient's iris have been cultured and then transplanted to the area where retinal pigment cells were lost after surgical removal of vascular membranes. This procedure was shown to be successful and is likely to provide a promising treatment option in the future.

Macular translocation surgery is performed to preserve the function of photoreceptor cells of the macula. In the procedure, the entire retina is cut around the periphery, and it is rotated around the optic nerve papilla and repositioned to an area where the retinal pigment cells are healthier. Although the rotation of the retina leads to anomalous retinal correspondence, resulting in a distorted image (the extent of distortion corresponds to the degree of rotation), the patients eventually become accustomed to this new image.

Conclusion

The incidence of ARD is expected to increase in Japan. Although there are no well established treatments for ARD at present, a number of promising pharmacotherapy, non-invasive and invasive treatment options are being investigated.

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