*Allergology International. 2009;58:217-224*
*DOI: 10.2332/allergolint.08-OA-0012*

ORIGINAL ARTICLE

# Adherence with Long-Term Asthma Management in Patients Who Experienced Hospitalized Asthma Exacerbation

Kenji Baba[1], Tsutomu Hattori[1], Takeo Yagi[1], Kazuyuki Onoe[1], Seiko Kawai[1], Kazuhito Yoshida[1] and Etsuro Yamaguchi[1]

## ABSTRACT

**Background:** In Japan, the number of asthma deaths has been gradually decreasing. However, in the management of asthma, there are still some problems originating from patient-related factors and iatrogenic factors, both of which should be further analyzed.

**Methods:** We investigated clinical and background characteristics of 164 patients with asthma who were admitted to our hospital with acute exacerbations, by reviewing their clinical records.

**Results:** Fifty-two patients had received long-term management (LTM) based on the guidelines (the LTM group), while 112 had not (the non-LTM group). In patients whose asthma severity had been intermittent (step 1), the proportion of severe and near fatal exacerbations was significantly higher in the non-LTM group than in the LTM group. However, even in the LTM-group, 23% of mild persistent (step 2) and 38% of moderately and severely persistent (step 3 & 4) patients had severe or near fatal exacerbations. In these patients, the peak expiratory flow rate significantly improved after discharge, and poor adherence was also significantly higher in the non-LTM group than in the LTM group. A multivariate analysis revealed that the factors associated with poor adherence were: 1) no history of previous admission due to asthma exacerbation; 2) the patient was male; and 3) the patient was young (<60 years).

**Conclusions:** In the LTM group, re-evaluation of the actual severity of asthma and prompt treatment corresponding to the severity of disease should still be encouraged. In the non-LTM group, establishing countermeasures against factors causing poor adherence would be the next step in ensuring strong adherence with LTM.

## KEY WORDS

adherence, asthma, exacerbation, long-term management, near fatal asthma

## *INTRODUCTION*

According to annual reports of the Japan Ministry of Health, Labour and Welfare, there were 7253 asthma deaths in 1995. However, this number has been gradually decreasing, and in 2006, there were a total of 2770 asthma deaths.[1] There is no doubt that distribution of the guidelines for management of asthma that advocated corticosteroid inhalation therapy has greatly contributed to the decrease in asthma mortality. However, some patients with asthma who have little understanding of the disease can result in poor adherence with asthma management. It can be considered iatrogenic if the physician underestimates the severity of asthma and fails to sufficiently educate the patient about the importance of long-term management. Poor adherence has been considered to be one reason for poor asthma control, with resultant exacerbation possibly leading to death.[2] However, asthma exacerbation may occur even in patients with good

[1]Division of Respiratory Medicine and Allergology, Department of Internal Medicine, Aichi Medical University School of Medicine, Aichi, Japan.
Correspondence: Kenji Baba, MD, Division of Respiratory Medicine and Allergology, Department of Internal Medicine, Aichi Medical University School of Medicine, 21 Karimata, Yazako, Nagakute, Aichi 480–1195, Japan.
Email: baken@aichi-med-u.ac.jp
Received 29 May 2008. Accepted for publication 26 September 2008.

adherence. Thus in the management of asthma, there are still problems related to from patients' factors and iatrogenic factors, both of which should be further clarified.

Our hospital is a central regional hospital serving a community of 50,000. A substantial number of patients with asthma exacerbation are treated at our hospital due to the availability of highly advanced medical services. In the present study, we retrospectively assessed clinical characteristics of the asthma patients who required hospitalization due to asthma exacerbation and the state of long-term management of asthma before the exacerbation. We set out to clarify causative factors of acute exacerbation in patients with good or poor adherence, respectively. By comparing the degree of adherence, the background associated with poor adherence with asthma management is also highlighted, describing the difficulties in providing long-term management.

## *METHODS*

### SUBJECTS

We studied 164 asthma patients admitted to our hospital with acute exacerbation of asthma from January 1, 1998 to December 31, 2004. The indications for admission are listed in the *Appendix*. The patients' clinical records were reviewed to determine the treatment for the exacerbation, in addition to their outpatient records. The background characteristics that were assessed included: age, gender, type of asthma, occupation, long-term management status, asthma control level before hospitalization (i.e., asthma severity), cause of the exacerbation, and severity of the exacerbation. Furthermore, questionnaires were sent out to patients who had stopped receiving medical care after discharge, and their backgrounds and reasons for the discontinuation of long-term management were examined.

### BACKGROUND FACTOR DEFINITIONS

#### 1) Long-Term Management

Long-term management (LTM) was defined as conditions under which the patients were managed based on the guidelines of asthma management[3]; i.e., 1) regular stepwise management according to asthma symptoms, regardless of daily monitoring of the peak expiratory flow (PEF) rate and 2) education about on-demand inhalation of short acting β2-stimulant for mild exacerbation. The patients who satisfied the conditions for LTM constituted the LTM group, while patients who did not satisfy these conditions constituted the non-LTM group. Patients in whom an asthma attack was the initial presentation of the disease were assigned to the non-LTM group.

#### 2) Severity of Asthma

For determination of the severity of asthma before admission, the "Asthma Prevention and Management Guideline 2003, Japan" (JGL2003) was used.[3] In this study, asthma severity was determined based on the step corresponding to the worst symptoms and/or lung function, including daily PEF values and daily variability, during the month before admission. Patients whose asthma attack was the initial symptom of the disease were assigned to the unknown severity group.

#### 3) Severity of Asthma Exacerbation

The severity of asthma exacerbation was also determined based on the JGL2003 criteria[2]: mild, moderate, severe, or near fatal asthma, requiring mechanical ventilation or had a $PaCO_2$ of 45 mmHg or more.

### STATISTICAL ANALYSIS

The data are expressed as median values (range). Differences in the parameters were evaluated using the Mann-Whitney U test or the Wilcoxon signed-rank test for comparing the 2 groups. Differences in the proportions between the 2 groups were evaluated using $\chi$-square analysis. For factor analysis, univariate and multivariate logistic regression analyses were used. Differences with a $p$ value of less than 0.05 were considered to indicate a statistically significant difference.

## *RESULTS*

Table 1 shows patient background characteristics. Before admission, 52 patients had received LTM (the LTM group) and 112 patients had not (the non-LTM group). The proportion of males was significantly higher in the non-LTM group than in the LTM group. There were significantly more younger patients in the non-LTM group than in the LTM group. Asthma severity before admission was step 1 (intermittent) in 52 patients (31.7%), ≧step 2 (i.e., mild persistent, moderate persistent, and severe persistent) in 71 patients (43.3%), and unknown in the others. The distribution of severity was similar in the non-LTM group and the LTM group. An asthma attack was the initial presentation of their asthma in 33 patients (29.5%) in the non-LTM group. Although there were a greater number of smokers in the LTM group than in the non-LTM group; no significant difference could be found in the incidence of chronic obstructive pulmonary disease (COPD) between the 2 groups. In both the non-LTM and the LTM groups, this was the first hospitalization for most patients and there was no significant difference between the 2 groups in the frequency of past admissions.

Figure 1 shows the age distribution of the patients by gender in the non-LTM and the LTM groups, respectively. In the non-LTM group, the patients were distributed in a wide range, 20–70 age group, however the number of male patients in the 20–40 age group was more than any other age groups. In the LTM group, the 60–70 age group predominated in

**Table 1** Characteristics of the patient

| Status of long-term management (LTM) | Total | | |
|---|---|---|---|
| | Non-LTM | LTM | |
| Gender (Male/Female) | 63/101 | | |
| | 53/59 | 10/42 | * |
| Age (y): Median (Range) | 52 (16－98) | | |
| | 45 (16－83) | 66 (23－98) | * |
| Type of asthma (Allergic/Non-allergic/Unknown) | 111/31/22 | | |
| | 86/18/8 | 25/13/14 | * |
| Severity of asthma before admission (Step1/2/3/4/1st onset/Unknown) | 52/42/27/2/41 | | |
| | 30/29/19/1/33 | 22/13/8/1/8 | N.S. |
| Smoking habits (Y/N/Unknown) | 74/76/14 | | |
| | 59/45/8 | 15/31/6 | * |
| COPD (Y/N) | 25/139 | | |
| | 20/92 | 5/47 | N.S. |
| Living with pets (Y/N/Unknown) | 36/37/91 | | |
| | 27/28/57 | 9/9/34 | N.S. |
| Frequency of previous hospitalizations (0/1/2/3/4/ >4 times) | 122/24/8/3/7 | | |
| | 91/12/4/2/3 | 31/12/4/1/4 | N.S. |

* $P < 0.05$

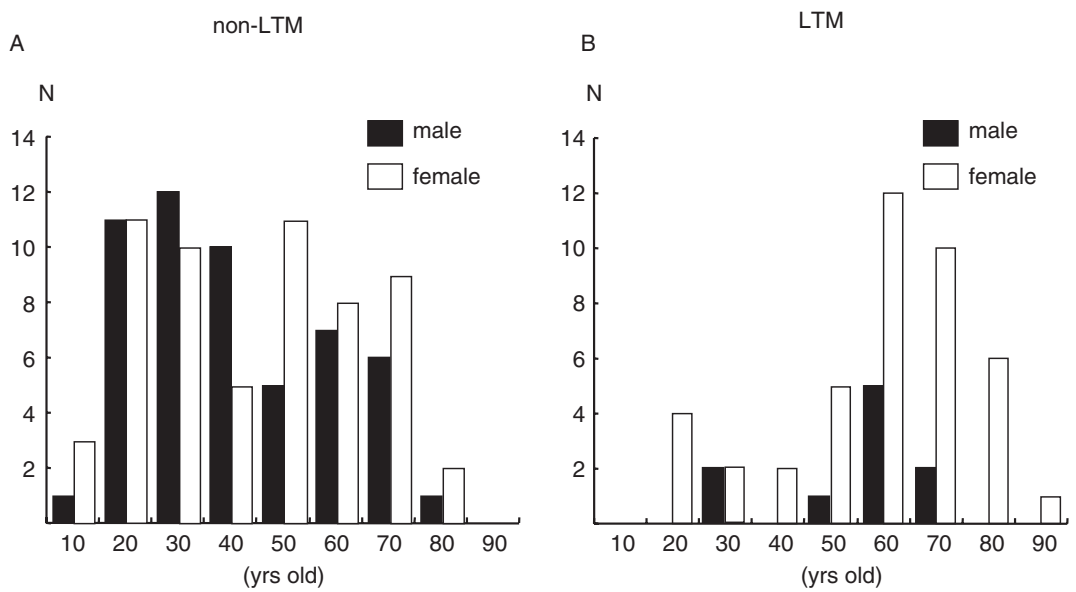


**Fig. 1** The age distribution of patients according to gender in the non-LTM group (**A**) and the LTM group (**B**), respectively.

both genders.

Figure 2A shows the causes of exacerbation by group. In both groups, airway infection was the most frequent cause (approximately 60%). Although infectious episodes can usually be observed during the summer season, they were least common in the summer in both groups and therefore no seasonal difference in airway infections between the LTM and the non-LTM groups ($P$ = 0.329) were found. The number of admissions was highest in October for the non-

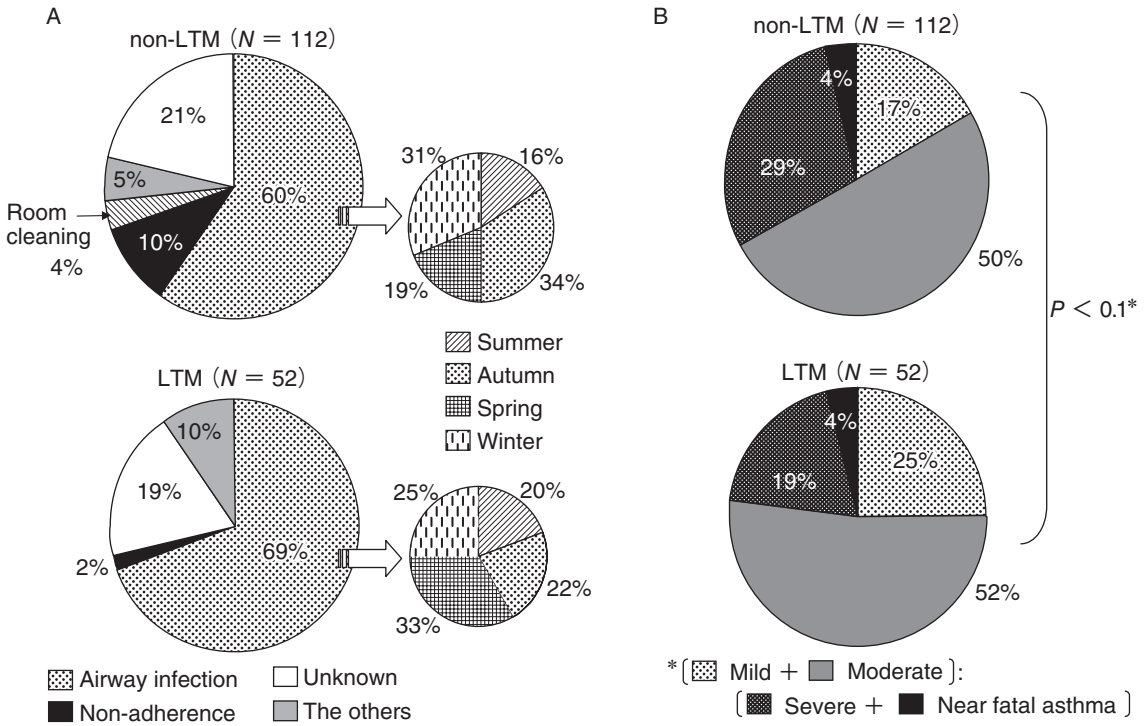


**Fig. 2** **A**: Causes of exacerbation in the LTM group and the non-LTM group, and seasonal distribution of infectious episodes. Summer: from June to August, Autumn: from September to November, Winter: from December to February, Spring: from March to May. **B**: severity of the exacerbation in the non-LTM group and the LTM group.

LTM group and in January for the LTM group; however, there was no significant difference in the overall distribution between the 2 groups (unpublished data).

Figure 2B shows the distribution of the severity of asthma exacerbations in the LTM and non-LTM groups. Moderate exacerbations accounted for 50% of the attacks in both groups. However, the proportion of severe plus near fatal exacerbations to that of mild plus moderate exacerbations tended to be higher in the non-LTM group than in the LTM group but not with statistical significance (33% vs. 23%, $P < 0.1$). The age distribution did not differ between the 2 severity groups (median 56.5 years, range, 16–98 years) in the mild plus moderate exacerbation group versus (median 45 years) (range, 19–84 years) the severe plus near fatal group ($P = 0.1919$).

Figure 3 shows the severity of pre-admission asthma exacerbation severity in both the non-LTM group and LTM group. In the non-LTM group, 37% had severe plus near fatal exacerbations, even in step 1 patients as well as step 3 & 4 patients. In the LTM group, 38% of step 3 & 4 patients had severe plus near fatal exacerbations, while only 9% of step 1 patients had severe plus near fatal exacerbations. Among the step 1 patients, the proportion of severe plus near fatal exacerbations was significantly lower in the LTM group than in the non-LTM group ($P = 0.0358$). Distributions of the severity of asthma exacerbations which were caused by infection were not significantly different between step 1 and ≧step 2 patients.

Univariate analysis to determine which factors were associated with severe plus near fatal exacerbations was performed using the following variables: smoking habits, type of asthma (allergic or not), age (over 60 years or not), LTM (yes or no), history of admission due to asthma exacerbation, cause of the exacerbation (by infection or not), and asthma control level (severity) based on symptoms or pulmonary functions. The risk of severe plus near fatal exacerbations tended to decrease with LTM (odds ratio 0.5, 95% CI; 0.225–1.110, $P = 0.0885$); and other factors did not indicate a significant relation to the severity of exacerbations.

Figure 4 shows the PEF of 29 patients in the LTM group at 1 month before admission, at the time of exacerbation, and at discharge (when the PEF values were probably at their peak). Among the step 1 patients, the PEF at the time of the exacerbation was significantly lower than 1 month before admission, and then improved to a value that was not significantly different from that at 1 month before admission. On the other hand, the PEF of other patients (i.e. ≧step 2 before admission) was significantly greater at discharge than at 1 month before admission. Furthermore, the proportion of ≧step 2 patients treated with leukotriene receptor antagonists (LTRA) appeared to be greater at the time of discharge (Ta-

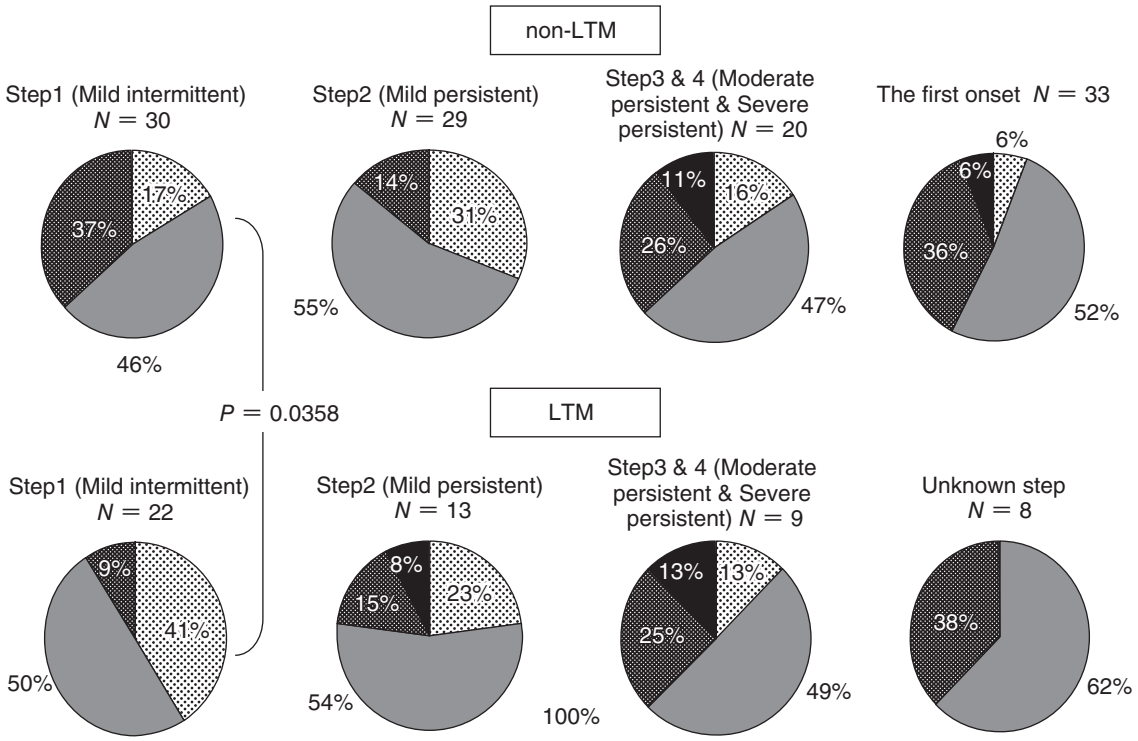


**Fig. 3** Relationship between asthma severity, characterized by daily symptoms and/or daily PEF values, and severity of the exacerbation on admission in the non-LTM group (upper) and in the LTM group (lower). Severity of asthma exacerbation: ⁙ mild, ▒ moderate, ▓ severe, and ■ near fatal.

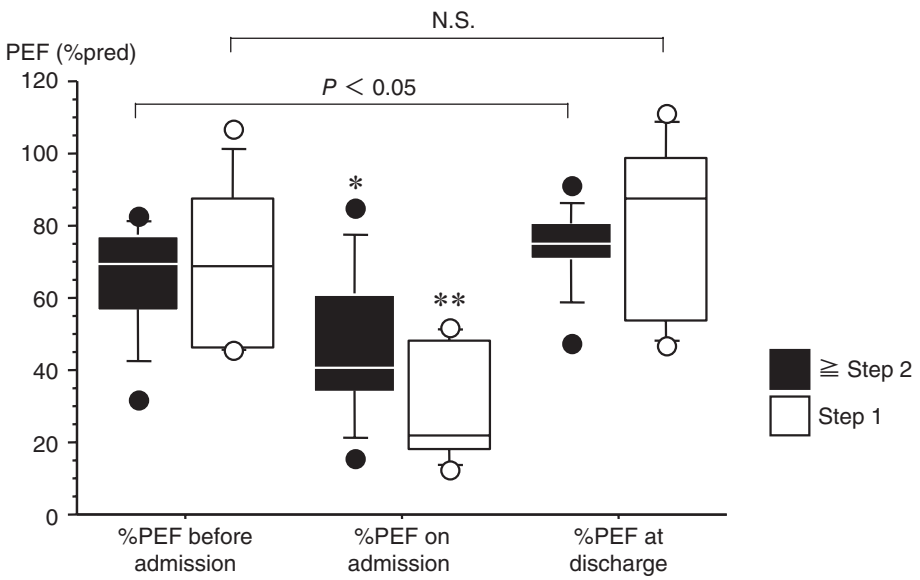


**Fig. 4** Daily best PEF values of 29 LTM group patients monitored during their clinical course. Empty squares represent the patient group with asthma severity of step 1 ($n = 13$), and solid square represents the patients group with asthma severity ≧step 2 ($n = 16$). Note that in ≧step 2 patients, PEF significantly improved after treatment of the exacerbation.

**Table 2** Therapy before and after admission in patients who had received LTM

| | Before admission | | At discharge | |
|---|---|---|---|---|
| | Step 1 | ≧Step 2 | Step 1 | ≧Step 2 |
| Dose of ICS (μgBDP/day) [median (range) ] | 800 (100－1600) | 800 (400－1600) | 800 (400－1600) | 800 (400－2000) |
| Dose of theophylline (mg/day) [median (range) ] | 300 (150－500) | 400 (100－800) | 400 (200－500) | 400 (200－600) |
| Percentage of patients given LTRA (%) | 40.9 | 43.3 | 45.5 | 53.3 |
| Percentage of patients given long acting $\beta_2$-stimulant (%) | 31.8 | 56.7 | 36.4 | 60 |

ble 2). Regardless of the status of asthma severity, the dosage of inhaled corticosteroid or theophylline was not significantly different during the clinical course.

The adherence rate after discharge is shown in Figure 5. A marked difference in adherence could be seen between the non-LTM group and the LTM group: 48% of the non-LTM patients discontinued LTM, while only 17% of LTM patients discontinued LTM ($P$ = 0.0001). The patients' responses to the questionnaire indicated that the reason for discontinuing LTM was relief of the symptoms, while some explained that they had no time or money to spare for LTM.

A multivariate analysis was used to determine the factors related to LTM status using the factors identified as significant in the univariate analysis: age, gender, occupational history, severity of asthma, and history of admission due to asthma exacerbation. As shown in Table 3, previous admission and age (over 60 years) were significant factors associated with good adherence to LTM, while male patients showed a negative association with LTM adherence (Table 3).

## DISCUSSION

The risk for hospitalization due to asthma exacerbation has been reported to be related to psychological factors[4,5] and may be predicted by a past history of hospitalization due to exacerbation, but not by previous corticosteroid inhalation therapy.[6] Furthermore, the risk for hospitalization can be decreased by exact assessment and resolution of poor adherence.[7] Since the subjects studied in the present study involved patients who required hospitalization due to asthma exacerbation, it could not be concluded that poor adherence was the factor for asthma admission, even though there were more non-LTM patients than LTM patients. Therefore, in this study, we targeted our analyses on clarifying causative factors of acute exacerbations in both groups, and clarifying clinical characteristics and background factors relevant to poor adherence by comparing the characteristics between the LTM and non-LTM patients.

The most frequent cause of asthma exacerbation in both the non-LTM and LTM groups was airway infection, although infection was not a factor associated with the severe plus near fatal exacerbations. Since airway infection was a common cause even during the summer season, measures to prevent infection due to various organisms, including the influenza virus, are essential in lowering the risk of asthma exacerbation.

It was found in the non-LTM group the proportion of severe plus near fatal exacerbations to that of mild plus moderate exacerbations tended to be higher than in the LTM group, and that 37% of step 1 patents were hospitalized due to severe and near fatal exacerbations. The following situations would be suspected in the non-LTM group as reasons for this; inappropriate on-demand use of inhaled short acting β2-agonists, poor control of allergic airway inflammations and delay in visiting emergency facilities. In the present study, univariate analysis revealed that adherence with LTM could decrease the risk of severe and near fatal exacerbations, so that maintaining adherence or improvement of poor adherence with LTM should be encouraged.

However, even in the LTM group, the rate of severe plus near fatal asthma reached 42.3% in ≧step 2 patients, whose PEF values after discharge were significantly higher than their PEF values 1 month before admission. In the present study, the asthma severity was determined based on the symptoms and/or pulmonary functions at 1 month before admission. Therefore, the findings indicate that asthma management had not been appropriate in ≧step 2 patients even in the LTM group. It has been reported that the prevalence of asthma symptoms has been substantially underestimated by healthcare professionals.[8] Thus, careful evaluation of the actual severity of asthma and prompt treatment that is appropriate for the severity of disease should always be encouraged.

In this study, LTRA or inhaled long-acting $\beta_2$-stimulants were used for improving asthma management in many patients, probably due to the previous study[9-11] reporting that including these therapies to inhaled corticosteroid (ICS) therapy was more effec-

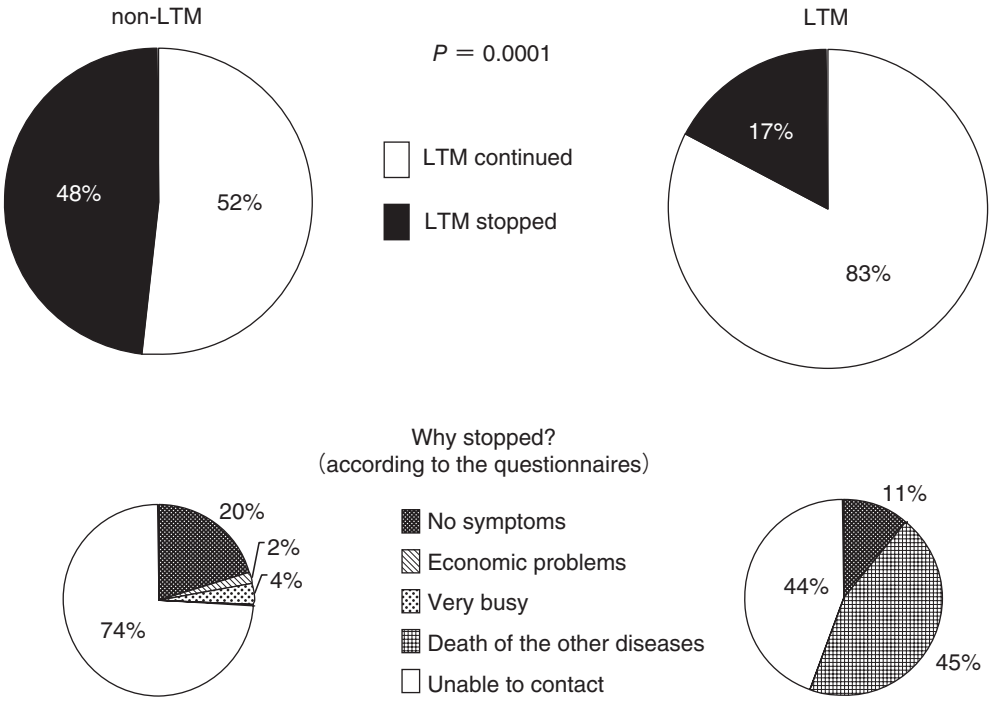


**Fig. 5** Adherence with asthma management after treatment of the exacerbation in the non-LTM group and in the LTM group.

**Table 3** Background factors related to adherence (Multivariate analysis)

| Factor | Level | Odds ratio (95%CI) | |
|---|---|---|---|
| Previous admission due to asthma exacerbation | Y/N | 3.926 (1.637－9.412) | $P < 0.003$ |
| Occupation | Y/N | 0.906 (0.358－2.293) | N.S. |
| Gender | M/F | 0.320 (0.127－0.807) | $P < 0.03$ |
| Severity of asthma (Step 1) | Y/N | 1.524 (0.661－3.517) | N.S. |
| Age ( ≧ 60 years) | Y/N | 4.646 (1.959－11.020) | $P < 0.001$ |

tive than doubling the ICS dosage for improving lung functions.

Turner[12] compared the characteristics of patients who were admitted with near fatal asthma to patients who were hospitalized due to asthma exacerbations without respiratory failure and found that there was no difference between the groups in the degree of airway obstruction or bronchial hyperresponsiveness, and that history of admission to the intensive care unit, irrespective of the severity of asthma, the failure to respond to worsening asthma was the risk factor for near fatal asthma. In the present study, gender, age, smoking habits, control level in terms of lung function and/or asthma symptoms, and history of admission due to asthma exacerbation did not appear to be risk factors for severe plus near fatal exacerbations. This is probably due to complex interactions among the various factors and/or regional differences, suggesting that epidemiological studies such as this one might be necessary in each region.

Adherence after discharge declined in the non-LTM group than in the LTM group, as expected. Reasons for poor adherence with asthma management have been considered to include: 1) the majority of patients considering themselves to have controlled asthma, while actual symptom levels show failure to reaching the levels expected by management guidelines[2,13]; 2) the patients desire fewer symptoms and no impact on daily activities but experience difficulties in receiving LTM due to several circumstantial problems (e.g. problems accessing prescriptions, cost, competing demands, etc)[2]; and 3) intentional poor adherence arises from the patients' common beliefs about illness and treatment or expectations that influence their motivation to maintain the treatment regimen.[14,15] In the present study, the following items were identified as possible factors for poor adherence: 1) no history of previous admission due to asthma exacerbation; 2) the patient is male; and 3) the patient is young (<60 years). Asthma control levels before admission and occupational history did not seem to be related to adherence. Thus, the following

countermeasures against poor adherence would be considered appropriate: 1) helping to make hospitalized patients understand that controlling asthma based on the guidelines will benefit them; 2) thorough and persistent education informing patients that relief from asthma symptoms does not imply a cure; 3) identifying the reasons for poor control in individual patients; and 4) paying particular attention to patients with risk factors that were identified to be significant in the present study. Patients may sometimes feel reluctant to talk to physicians about their economic problems or living conditions and therefore physicians should not hesitate to these issues up with their patients as the occasion demands. Indeed, identifying individual patients' goals has been shown to encourage patient involvement, which may lead to a better adherence to therapy.[16]

On the other hand, three-quarters (74%) of the non-LTM patients did not respond to the questionnaires. These non-respondents may represent a group who have poor psychological adherence or affinity to medical facilities and may make it very difficult for medical staff to successfully use the medical approach in improving such poor adherence.

Successful treatment with inhaled corticosteroids has been achieved in many patients with asthma, however it is now time to proceed to the next step in ensuring a patient's strong adherence with long-term management. In order to implement the strategies identified in this study, family doctors, to whom patients have easy access, may play an important role. In addition to a partnership between patients and healthcare staff, a medical partnership between specialists and general physicians, for example by sharing the patients' profiles and performing efficient medical care, might also be effective for maintaining strong patient adherence. Furthermore, partnerships with nursing staff and/or pharmacists may also be important. A prospective study to verify the usefulness of such a system would be appropriate.

## APPENDIX

In case of the following symptoms and signs of asthma exacerbation which did not completely respond to inhalation of rapid-acting $\beta_2$-agonist within 1–2 hours and/or systemic administration of corticosteroid:

- Symptoms not completely relieved
- PEF <70% personal best or predicted
- Hypoxemia ($O_2$ saturation <93%)

## REFERENCES


1. Ministry of Health, Labour and Welfare. *[Annual Report on Health and Welfare 2006–2007]*. 2007;34 (in Japanese).
2. Horne R, Price D, Cleland J *et al*. Can asthma control be improved by understanding the patient's perspective? *BMC Pulm Med* 2007;**7**:8.
3. Ministry of Health and Welfare, Immunology and Allergy Study Group. *[Asthma Prevention and Management Guideline 2003, Japan (Updated from: JGL 1998)]*. Tokyo: Kyowa Kikaku, 2003 (in Japanese).
4. Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (SLTA) in adults: psychological factors. *Thorax* 2002;**57**:317-22.
5. Sturdy PM, Victor CR, Anderson HR *et al*., for the Mortality and Severe Morbidity Working Group of the National Asthma Task Force. Psychological, social and health behaviour risk factors for deaths certified as asthma: a national case-control study. *Thorax* 2002;**57**:1034-9.
6. Alvarez GG, Schulzer M, Jung D, Fitzgerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. *Can Respir J* 2005;**12**:265-70.
7. Weinstein AG. Should patients with persistent severe asthma be monitored for medication adherence? *Ann Allergy Asthma Immunol* 2005;**94**:251-7.
8. Price D, Ryan D, Pearce L, Bride F. The AIR study: asthma in real life. *Asthma Journal* 1999;**4**:74-8.
9. Laviolette M, Malmstrom K, Lu S *et al*. Montelukast added to inhaled beclomethasone in treatment of asthma. *Am J Respir Crit Care Med* 1999;**160**:1862-8.
10. Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Salmeterol Study Group. *Ann Allergy Asthma Immunol* 1999;**82**:383-9.
11. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997; **337**:1412-8.
12. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma: A case-control study in hospitalized patients with asthma. *Am J Respir Crit Care Med* 1998;**157**:1804-9.
13. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**:802-7.
14. Horne R, Weinman J, Barber N, Ellicott RA, Morgan M. *Concordance, Adherence and Compliance in Medicine Taking: A Conceptual Map and Research Priorities*. London: National Coordinating Centre for NHS Service Delivery and Organization R & D NCCSDO, 2005.
15. Horne R. Compliance, adherence, and concordance; implications for asthma treatment. *Chest* 2006;**130** (Suppl): 65S-72.
16. Beck AT. *Cognitive Therapy and Emotional Disorders*. New York: International University Press, 1976.