An analysis of characteristics of patients with exacerbation of asthma in a large university hospital in Japan

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Summary

Background: Considerable progress has been made in the management of asthma with the increasing use of inhaled corticosteroids. However, asthma exacerbation remains a problem. To analyze the characteristics of patients with exacerbation of asthma who visited our hospital in order to better understand the risk factors for fatal asthma.

Objectives: We studied 100 patients who presented at Dokkyo Medical University Hospital (DMUH) with asthma exacerbation.

Methods: Entry sheets were completed by physicians and questionnaires by patients.

Results: Before the exacerbation, the severity was assessed as Step 1 in 46% of patients, Step 2 in 15%, Step 3 in 11%, and Step 4 in 18%. With regard to primary care physicians, 45% were treated at DMUH and 36% had no primary care physicians. Among the DMUH group, the largest proportion was aged 60-69 years and was in Step 4 category. According to asthma control test (ACT) scores, disease was poorly controlled in 83%. Patients with no primary care physician were most often aged 20-39 years (p<0.01), and severity was assessed as Step 1 in 86% (p<0.01). However, 44% were poorly controlled according to ACT (p<0.05).

Conclusion: Patients could be classified into two groups: older patients with severe intractable asthma, treated by a specialist and younger patients considered to have mild asthma, half of whom had poorly controlled asthma and no primary care physician. Systems are needed that allow the emergency physicians to evaluate the need for regular treatment in patients with exacerbation because such patients often visit the hospital at night or on a non-working day. (*Asian Pac J Allergy Immunol 2010;28:242-9)*

Introduction

Exacerbation of asthma is associated with considerable healthcare costs and negatively affects the quality of life of patients and their families.[1-5] Severe exacerbation or poor management of asthma impairs quality of life and are known risk factors for death. 2770 asthma-related deaths were reported by the Ministry of Health, Labour and Welfare, Japan in 2006.[6-8] As compared with a decade ago, mortality from asthma has decreased by about 50% owing to the increasing use of inhaled corticosteroids (ICSs) and leukotriene receptor antagonists (LTRAs). However, asthma-related deaths remain a serious problem.[9]

Elimination of asthma-related deaths requires a better understanding of demographic characteristics of patients with exacerbations of asthma. Our hospital, Dokkyo Medical University Hospital (DMUH), has both an Allergy Care Unit and an Emergency Department which provides 24-hour emergency care to all patients with exacerbations of asthma. Therefore, in this study, we analyzed the demographic characteristics of patients who presented at DMUH with exacerbation of asthma.

Methods

DMUH is located 100 km north of Tokyo in the Kita-Kanto area of Japan, and is close to an

Table 1. Background of patients

		Number of patients	
Total		100	(100.0%)
Gender			
	Male	47	(47.0%)
	Female	53	(53.0%)
Severity			
	Step1	46	(46.0%)
	Step2	15	(15.0%)
	Step3	11	(11.0%)
	Step4	18	(18.0%)
	Unknown	10	(10.0%)
Primary care physician			
	DMUH	45	(45.0%)
	Other hospitals	19	(19.0%)
	None	36	(36.0%)
The time of arrival			
	Working weekday	28	(28.0%)
	Night or non-working day	72	(72.0%)

Table 2. Background of patients who answered a questionnaire

		Number of patients	
Total		45	(100.0%)
Severity			
	Step1	20	(44.4%)
	Step2	7	(15.6%)
	Step3	4	(8.9%)
	Step4	9	(20.0%)
	Unknown	5	(11.1%)
Primary care physician			
	DMUH	30	(66.7%)
	Other hospitals	6	(13.3%)
	None	9	(20.0%)
The time of arrival			
	Working weekday	17	(37.8%)
	Night or non-working day	28	(62.2%)
ACT score			
	Totally controlled	2	(4.4%)
	Well controlled	8	(17.8%)
	Poorly controlled	35	(77.8%)

expressway interchange, providing easy access for a large numbers of patients. It has 1167 beds, and about 55,000 patients attend the hospital each month from about 40 of the 47 prefectures in Japan. Additionally, about 300 ambulances and 1800 patients, including those from other prefectures, are accepted into the Emergency Department each month. DMUH is therefore the main hospital in the Kita-Kanto area.

Subjects

Study subjects were all patients who presented at DMUH with moderate or severe exacerbation of asthma. Severity was evaluated by the Global Initiative for Asthma (GINA) 2002.[10] From August 2005 to June 2006, 100 patients (mean age ± standard deviation, 44.0 ± 19.1 years) were enrolled in the study. Although this study was planned for one year from July 2005, the start was delayed one month by the progress of the ethics committee. When a patient attended our hospital more than twice for the above period, the patient was enrolled for the first visit only.

Study Design

DMUH provides 24-hour emergency care to all patients with exacerbation of asthma. Patients who arrive during the working weekday are treated by an allergist at the Allergy Care Unit, whereas those who arrive at nights or on a non-working day are treated by an emergency physician at the Emergency Department. After treatment, physicians complete entry sheets, which include information about patient medication, general health status, primary care physician, and asthma severity before the exacerbation.

Within 1 week after attending the hospital, we contacted patients by mail or telephone and asked them to complete a questionnaire regarding their medication, general health status, and primary care physician before the exacerbation of asthma. The questionnaire was provided to patients after leaving the hospital because treatment for the exacerbation of asthma took first priority. Responses were obtained from 45 patients (response rate of 45%). Physicians classified the severity of asthma based on patient symptoms according to GINA 2002: Step 1, intermittent; Step 2, mild persistent; Step 3, moderate persistent; and Step 4, severe persistent.[10] Patients scored their own condition using the Asthma Control Test (ACT).[11] An ACT score of 0 to 19 was classified as poorly controlled, a score of 20 to 24 was classified as well controlled, and a maximum score of 25 was classified as completely controlled. The study protocol was approved by the ethics committee of Dokkyo Medical University on July 21, 2005 (No 1719).

Analysis

Differences between two independent samples were tested using relative risk, 95% confidence intervals and the chi-square test.

Results

The results from the physician entry sheets and the patient questionnaires are shown in Table 1 and Table 2, respectively. Analysis of the results revealed subgroups of patients with different characteristics. The first group was divided according to time of arrival at DMUH into those arrived during "the working weekday" or those

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Table 3.Severity of asthma according to the time of arrival at hospital and the type of primary care physician noted on physician sheets

	Step 1		Step 2		Step 3		Step 4		The chi-square test	
	Prevalence %	RR (95%CI)	Prevalence %	RR (95%CI)	Prevalence %	RR (95%CI)	Prevalence %	RR (95%CI)	X^2 (*p*-value)	Subject
The time of arrival at hospital										
1. Working weekday group	35.7 (10/28)		21.4 (6/28)		14.3 (4/28)		28.6 (8/28)			
2. Night or non-working day group	50.0 (36/72)	0.71 (0.41-1.24)	12.5 (9/72)	1.71 (0.67-4.37)	9.7 (7/72)	1.47 (0.47-4.63)	13.9 (10/72)	2.06 (0.91-4.67)	5.3 (0.150)	vs "1"
The type of primary care physician										
3. DMUH group	22.2 (10/45)		17.8 (8/45)		20.0 (9/45)		40.0 (18/45)			
4. Other hospital group	26.3 (5/19)	0.84 (0.33-2.14)	31.6 (6/19)	0.56 (0.23-1.40)	5.3 (1/19)	3.80 (0.52-27.9)	0.0 (0/19)	N/A	39.7 (<0.001)	vs "3"
5. No primary care physician group	86.1 (31/36)	0.26 (0.15-0.45)	2.8 (1/36)	6.40 (0.84-48.8)	2.8 (1/36)	7.20 (0.96-54.2)	0.0 (0/36)	N/A	10.9 (0.012)	vs "3"
									16.0 (<0.001)	"4" vs "5"
									53.8 (<0.001)	"3" ~ "5"

arrived "at night or on a non-working day". According to the physician sheets, 28.0% of patients arrived during the working weekday and the remaining 72.0% at night or on a non-working day. According to the patient questionnaires, 37.8% arrived during the working weekday and 62.2% at night or on a non-working day.

The second group was divided according to care before presentation i.e. those who regularly visited the DMUH (DMUH group), those who regularly visited other hospitals (other hospital group), and those with no primary care physician (no primary care physician group). According to the physician sheets, the DMUH group comprised 45.0% of the patients, the other hospital group 19.0% of the patients and the no primary care physician group the remaining 36.0% of patients. However, from the patient questionnaires, the proportion of patients in the three groups was 66.7%, 13.3%, and 20.0%, respectively.

Analysis of the Time of Arrival at Hospital

Among those patients who arrived during the working weekday, disease severity was assessed as Step 1 in 35.7%, Step 2 in 21.4%, Step 3 in 14.3%, and Step 4 in 28.6% according to the physician sheets. Among the patients who arrived at night or on a non-working day, disease

severity was assessed as Step 1 in 50.0%, Step 2 in 12.5%, Step 3 in 9.7%, Step 4 in 13.9%, unknown in 13.9% (Table 3). Although severity was assessed as Step 1 in half of the patients who arrived at night or on a non-working day, there is no significant difference between the groups (X^2 = 5.31, *p* = 0.150) by the chi-square test. The 'unknown' group was not shown in Table 3, because relative risk could not be calculated for the working weekday group in 0.0%.

With regard to primary care physician status assessed by physician sheets among patients who arrived during the working weekday, 67.9% belonged to the DMUH group, 17.9% belonged to the other hospital group, and 14.3% belonged to the no primary care physician group. Among patients who arrived at night or on a non-working day, 36.1% belonged to the DMUH group, 19.4% to the other hospital group, and 44.4% to the no primary care physician group. Primary care physician status differed significantly between the two arrival time groups (X^2 = 9.64, *p* = 0.008) by the chi-square test. (Table 4)

With regard to treatment, more drugs were used to treat patients who arrived during the working weekday than those who arrived at night or on a non-working day, presumably because the

Table 4. The type of primary care physician according to the time of arrival at hospital noted on physician sheets

	DMUH group		Other hospital group		No primary physician group		The chi-square test	
	Prevalence %	RR (95%CI)	Prevalence %	RR (95%CI)	Prevalence %	RR (95%CI)	X^2 (*p* -value)	Subject
The time of arrival at hospital								
1. Working weekday group	67.9 (19/28)		17.9 (5/28)		14.3 (4/28)			
2. Night or non-working day group	36.1 (26/72)	1.88 (1.26-2.80)	19.4 (14/72)	0.92 (0.36-2.31)	44.4 (32/72)	0.32 (0.13-0.83)	9.6 (0.008)	vs "1"

RR: relative risk, CI: confidence interval

incidence of severe disease was higher in the former (Figure 1A). However, the ACT scores from the patient questionnaires indicated that asthma in 70.6% of patients who arrived during the working weekday was poorly controlled, compared with 82.1% of patients who arrived at night or on a non-working day. (Table 5) Thus, asthma in most of the patients in both groups was poorly controlled, with the percentages of patients with poorly controlled disease similar between the two groups (X^2=0.82, p=0.665) by the chi-square test.

### *Analysis of Primary Care Physician Status*

We analyzed differences in demographic characteristics of the DMUH group, the other hospital group and the no primary care physician. According to the physician sheets, in the DMUH group, disease severity was assessed as Step 1 in 22.2% of patients, Step 2 in 17.8%, Step 3 in 20.0%, and Step 4 in 40.0%. In the no primary care physician group, disease severity was given as Step 1 in 86.1% of patients, Step 2 in 2.8%, Step 3 in 2.8%, Step 4 in 0.0% and unknown in 5.6%. (Table 3) Therefore, the largest subgroup of patients in the DMUH group had Step 4 severity, whereas the overwhelming majority of patients in the no primary care physician group had Step 1 severity, representing a significant difference in severity between the two groups (X^2 = 10.9, *p* = 0.012) by the chi-square test. According to the patient questionnaires, the number of exacerbation episodes during the 6 months before presentation significantly differed between the DMUH group (4.35 times) and the no primary care physician group (0.75 times; p<0.01) by the Mann-Whitney U test.

From the physician sheets, it was clear that the largest subgroup of patients in the DMUH group was in the 60-69 year age groups, followed by patients aged 50-59 years (Figure 1B). Older patients thus comprised the largest subgroup. In the no primary care physician group, the overwhelming majority of patients were younger, with those in their twenties and thirties comprising the largest subgroup. The difference in the age distribution between the two groups was significant (X^2 = 25.4, p<0.001) by the chi-square test.

From the patient questionnaires, analysis of ACT scores indicated that disease was poorly controlled in 83.3% of the DMUH group, well controlled in 13.3%, and totally controlled in 3.3%. (Table 5) The high proportion of patients with poorly controlled disease in the DMUH group was attributed to the fact that most patients had Step 4 disease in this group. In the no primary care physician group, disease was poorly controlled in 44.4% of patients, well controlled in 44.4%, and totally controlled in 11.1%. (Table 5) Although most patients in the no primary care physician group had Step 1 severity, disease was poorly controlled in about half of the patients. But, disease-control status did not differ significantly between the two groups (X^2=5.49, *p* = 0.064) by the chi-square test.

Follow-Up Analysis of the No Primary Care Physician Group

We performed a follow-up survey for the no primary care physician group because ACT score indicated that disease was poorly controlled and some patients experienced exacerbations episodes during the previous 6 months, despite the fact that most had Step 1 disease. We examined the

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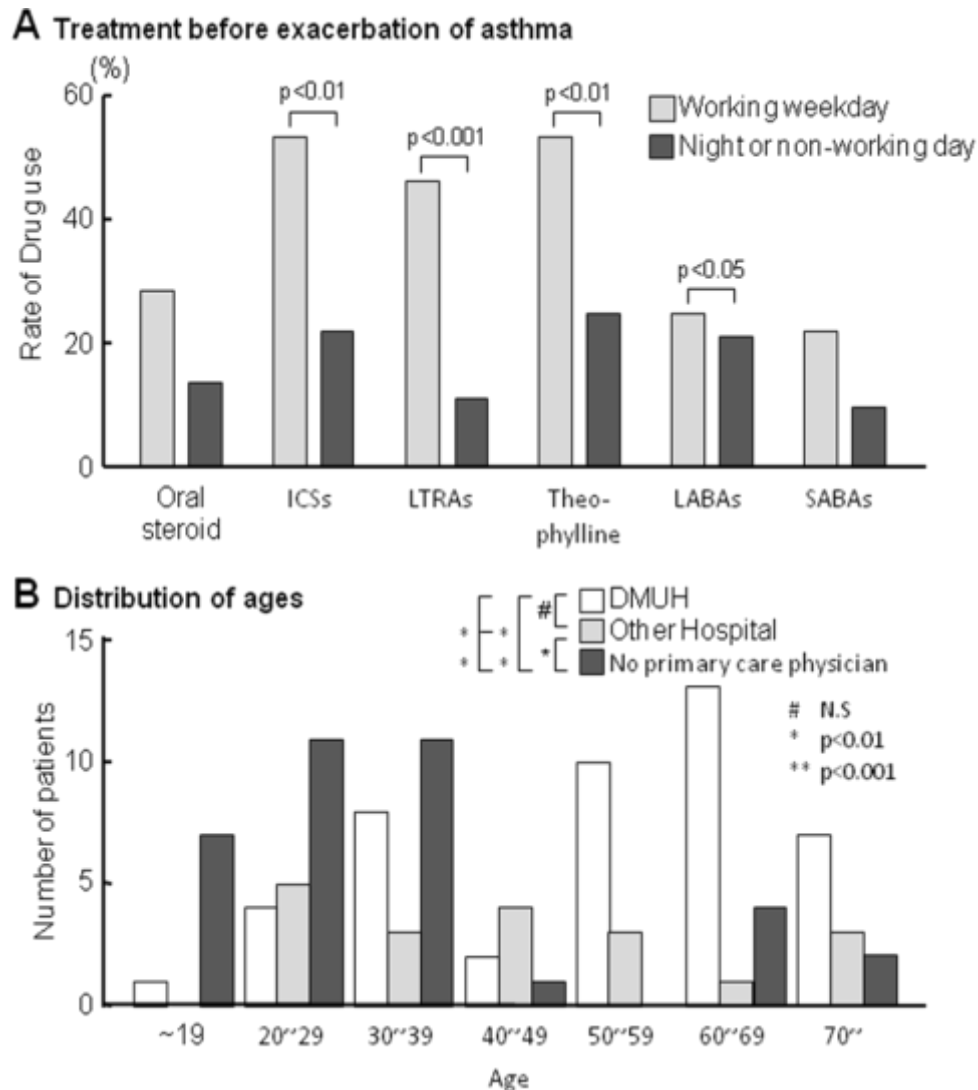
Figure 1. The treatment before exacerbation of asthma (B) according to the time of arrival at hospital noted on physician sheets. In B, there are significant differences in inhaled corticosteroids (ICSs: $X^2=9.26$, p=0.002), leukotriene receptor antagonists (LTRAs: $X^2=15.2$ p<0.001), theophylline ($X^2=7.44$ p=0.006) and long-acting beta$_2$ agonists (LABAs: $X^2=4.95$ p=0.026), but there are no significant differences in oral corticosteroid ($X^2=2.94$, p=0.086) and short-acting beta$_2$ agonists (SABAs): $X^2=2.44$ p=0.118) by the chi-square test. C is the age distribution according to the type of primary care physician noted on physician sheet. There are significant differences are noted (the DMUH vs the no primary care physician: $X^2=25.4$, p<0.001, the other hospital vs the no primary care physician: $X^2=17.0$, p=0.009 and those three groups: $X^2=38.4$, p <0.001), except the DMUH vs the other hospital ($X^2=11.0$, p=0.090) by the chi-square test

number of visits to DMUH because of exacerbations of asthma during the year following presentation. In total, 50% of patients did not visit DMUH again, and 2.8% (one patient) visited only once for exacerbation of asthma during the 1-year follow-up. The remaining 47.2% of patients regularly returned to DMUH and received treatment for their asthma at the Allergy Care Unit after presentation (Figure 2). This subgroup of patients received medication and remained stable for 1 year. No patient without a primary care physician visited DMUH repeatedly for exacerbations of asthma. We also evaluated the time of year that patients with no primary care physician visited DMUH for exacerbation of asthma. The most common months were September (22.2% of patients) and May (19%), showing that many exacerbation episodes occurred in the spring and fall. The frequency of exacerbation episodes in the fall were similar to the trend seen in Western countries.[12, 13]

Discussion

Exacerbation of asthma is associated with significant healthcare costs and diminishes the quality of life of patients and their families.[1-5] Treatment according to established guidelines is considered essential for the prevention of acute exacerbation. In addition to GINA, Japanese Guidelines for the Diagnosis and Treatment of Allergic Diseases have been published by the Japanese Society of Allergology and are revised annually.[14] However, only 18% of asthmatic patients were prescribed ICSs in 2005, suggesting that adherence to general guidelines remains inadequate in Japan.[15] The rate of treatment with ICSs is much lower in Japan than in Western countries, although prescription has increased, compared with 12% in 2000.[16] The aim of the present study was to analyze the demographic characteristics of patients with exacerbations of asthma and thereby contribute to better adherence to treatment guidelines and the elimination of asthma-related mortality.

Table 5. ACT score according to the time of arrival at hospital and the type of primary care physician noted on patient questionnaires

	Totally controlled		Well controlled		Poorly controlled		The chi-square test	
	Prevalence %	RR (95%CI)	Prevalence %	RR (95%CI)	Prevalence %	RR (95%CI)	X^2 (*p* -value)	Subject
The time of arrival at hospital								
1. Working weekday group	5.9 (1/17)		23.5 (4/17)		70.6 (12/17)			
2. Night or non-working day group	3.6 (1/28)	1.65 (0.11-26.6)	14.3 (4/28)	1.65 (0.47-5.74)	82.1 (23/28)	0.86 (0.60-1.22)	0.8 (0.665)	vs "1"
The type of primary care physician								
3. DMUH group	3.3 (1/30)		13.3 (4/30)		83.3 (25/30)			
4. Other hospital group	0.0 (0/ 6)	N/A	100.0 (6/ 6)	0.13 (0.05-0.33)	0.0 (0/6)	N/A	1.2 (0.560)	vs "3"
5. No primary care physician group	11.1 (1/ 9)	0.30 (0.02-4.33)	44.4 (4/ 9)	0.30 (0.09-0.97)	44.4 (4/9)	1.88 (0.89-3.96)	5.5 (0.064)	vs "3"
							5.0 (0.082)	"4" vs "5"
							8.0 (0.090)	"3" ~ "5"

RR: relative risk, CI: confidence interval

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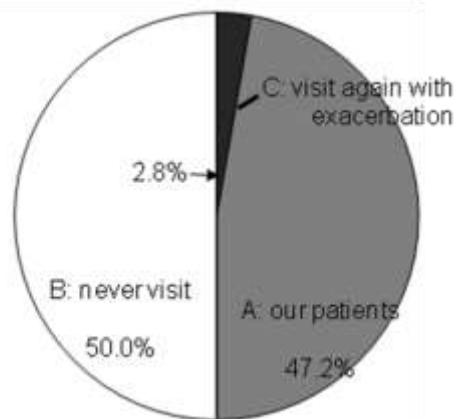
Figure 2. Analysis of the no primary care physician group for 1 year after presentation. A: they started to be treated regularly at the Allergy Care Unit in DMUH. B: they never came to DMUH with exacerbation of asthma for 1 year. C: visit to DMUH by another exacerbation of asthma without primary care physician. The half of asthmatic patients without primary care physicians started to be treated regularly in our hospital by advice from the emergency physicians

Our findings showed that two major patient groups were at risk for exacerbation of asthma. The first group consisted of patients with severe asthma. These patients were older than those in the second group and were regularly treated by allergists at the Allergy Care Unit in DMUH. Exacerbation episodes occurred frequently, despite well-designed treatment. The persistence of severe asthma and the poor response to treatment may be ascribed to the occurrence of airway remodeling before the widespread use of ICSs. Older patients who die of asthma are included in this group. Airway remodeling is a risk factor for fatal asthma, and prevention of asthma-related deaths is extremely difficult in older patients with airway remodeling.[17] The risk of multiple exacerbations and fatal asthma in such patents was noted in another Japanese study.[18]

The second group at risk for exacerbation of asthma consisted of young patients with mild asthma. These patients did not have a primary care physician for asthma because their occupational activities did not enable them to regularly consult a physician. As a consequence, these patients did not have sufficient information about asthma or understand the need for regular treatment. Additionally, they visited hospitals at night or on non-working days, only when experiencing exacerbation. Such patients claimed that their symptoms were mild. It was difficult for physicians to evaluate the real severity of their symptoms within a short time, and most patients were given a diagnosis of mild asthma. However, the ACT scores, evaluated by patient questionnaire, indicated that half of the patients with no primary care physician had poorly controlled asthma, and those without a primary care physician experienced 0.75 episodes of asthma exacerbation on average during the 6 months before presentation. These findings suggest that not all patients without a primary care physician had Step 1 disease. Poor management was a risk factor for fatal asthma, and asthma-related deaths among younger patients were likely to occur in this group.[7] Regular treatment may be able to prevent asthma-related mortality in patients with no primary care physician.

DMUH provides 24-hour emergency care to all patients with exacerbation of asthma. As mentioned earlier, patients who arrived during the working weekday were treated at the Allergy Care Unit by allergists, whereas those who arrived at night or on non-working days were treated at the Emergency Department by emergency physicians. Because emergency physicians did not provide regular treatment after therapy for the exacerbation of asthma, they instructed patients to visit the Allergy Care Unit the next day. We found from our study that some patients followed these instructions and visited the Allergy Care Unit. At the unit about half of all patients with no primary care physician required and were started on regular treatment, as prescribed by the allergist. We consider that it is very important to give advice to patients in the emergency department, as no patient without a primary care physician previously came to DMUH because of multiple exacerbations of asthma.

Many asthma-related deaths have been reported in young people who frequently used only short-acting beta$_2$ agonists (SABAs), without regular anti-inflammatory treatment.[19, 20] Because mild exacerbation can be controlled by SABAs, patients do not think it is necessary to consult

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their physicians regularly. Patients are also unaware of the risk of asthma-related death because they lack sufficient information about asthma. Thus, it is very important for asthmatic patients without primary care physicians to receive advice from the emergency physician, because most of these patients do not have a chance to consult an allergist. The educational interventions applied in emergency departments can reduce subsequent asthma-related admissions to hospital.[21] Ideally emergency physicians should evaluate the need for regular treatment and advise patients accordingly. To facilitate proper care, we intend to establish guidelines for the diagnosis and treatment of asthma for emergency physicians.

There were several limitations of our study. We showed analysis of characteristics of patients with exacerbation of asthma who visited our emergency department or allergy care unit. Patients without primary care physicians were generally younger and busy with work. Because they have often visited hospitals at night or on non-working days for exacerbation of asthma, they usually did not have a chance to consult an allergist. Such patients therefore lacked information about asthma, and their disease was often not properly evaluated, including the need for regular treatment. Most patients without primary care physicians considered their asthma to be mild, but in about half of these patients their disease was poorly controlled and they required regular treatment. Systems are needed that allow the emergency physicians to evaluate the need for regular treatment in patients with exacerbation.

Conclusions

Guidelines for diagnosis and treatment of asthma by the emergency physicians should be developed to avoid asthma-related deaths for patients without primary care physicians. Before the establishment of such guidelines, the emergency physicians should instruct patients "to visit an allergist tomorrow", as currently practiced at our hospital.

Acknowledgements

We thank Dr. Hironori Sagara (Dokkyo Medical University, Koshigaya Hospital) for his assistance.

References

1. Lane S, Molina J, Plusa T. An international observational prospective study to determine the cost of asthma exacerbations (COAX). Respir Med. 2006; 100: 434-50.
2. Skrepnek GH, Skrepnek SV. Epidemiology, Clinical and Economic Burden, and Natural History of Chronic Obstructive Pulmonary Disease and Asthma. Am J Manag Caew. 2004; 10: S129-38.
3. Andersson F, Borg S, Ståhl E. The impact of exacerbations on the asthmatic patient's preference scores. J Asthma. 2003; 40: 615-23.
4. Sugiyama K, Sugiyama T, Toda M, Yukawa T, Makino S, Fukuda T. Prevalence of asthma, rhinitis and eczema among 13-14-year-old schoolchildren in Tochigi, Japan. Allergol Int. 2000; 49: 205-11.
5. Sugiyama T, Sugiyama K, Toda M, Yukawa Y, Makino S, Fukuda T. Risk factors for asthma and allergic diseases among 13-14-year-old schoolchildren in Japan. Allergol Int. 2002; 51: 139-50.
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. Hessel PA, Mitchell I, Tough S, Green HF, Cockcroft D. Kepron W, et al. Risk factors for death from asthma. Prairie Provinces Asthma Study Group. Ann Allergy Asthma Immunol 1999; 83: 362-8.
8. Ministry of Health, Labour and Welfare Japan. Vital statistics. Ministry of Health, Labour and Welfare Japan, Tokyo, 2006
9. Suissa S, Ernst P. Use of anti-inflammatory therapy and asthma mortality in Japan. Eur Respir J. 2003; 21: 101-4.
10. National Institutes of Health, National Heart, Lung, and Blood Institute. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention – Revised 2002. National Institutes of Health Publication, Maryland, 2002
11. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus T, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004; 113: 59-65.
12. Sears MR, Johnston NW. Understanding the September asthma epidemic. J Allergy Clin Immunol. 2007; 120: 526-9.
13. Johnston NW, Sears MR. Asthma exacerbations. 1: epidemiology. Thorax. 2006; 61: 722-8.
14. Japanese Society of Allergology. Japanese Guideline for Diagnosis and Treatment of Allergic Diseases. Kyowa-Kikaku, Tokyo, 2007 . Japanese.
15. Adachi M, Ohta K, Morikawa A, Nishima S. Asthma Insights & Reality in Japan 2005. Arerugi. 2006; 55: 1340-3. Japanese.
16. Adachi M, Morikawa A, Ishihara K. Asthma insights & reality in Japan (AIRJ) Arerugi. 2002; 51: 411-20. Japanese.
17. James AL, Elliot JG, Abramson MJ, Walters EH. Time to death, airway wall inflammation and remodelling in fatal asthma. Eur Respir J. 2005; 26: 429-34.
18. Koga T, Oshita Y, Kamimura T, Koga H, Aizawa H. Characterization of patients with frequent exacerbation of asthma. Respir Med. 2006; 100: 273-8.
19. Tanihara S, Nakamura Y, Matsui T, Nishima S. A case-control study of asthma death and life-threatening attack: their possible relationship with prescribed drug therapy in Japan. J Epidemiol. 2002; 12: 223-8.
20. Sears MR, Taylor DR, Print CG, *et al*. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet. 1990; 336: 1391-6.
21. Tapp S, Lasserson TJ, Rowe BH. Education interventions for adults who attend the emergency room for acute asthma. Cochrane Database Syst Rev 18: CD003000, 2007