Review Article

Treatment and management of severe asthma in childhood through to young adult patients: 12th Japanese Society of Allergology Meeting, Spring Clinical Meeting, Lecture of the Chairman

Sankei Nishima
National Minami Fukuoka Chest Hospital, Fukuoka-shi, Japan

ABSTRACT

Asthma treatments have changed radically due to elucidation of morbidity and development of medicine/treatment strategies. The Global Initiative for Asthma consists of a six-part asthma management program and seven defined states for controlled asthma worldwide. However, considering the present status of asthma in infants through to young adult patients, it is extremely difficult to implement these ideal programs and to attain their goals. At the Pediatric Unit in the National Minami Fukuoka Chest Hospital, the number of out-patients and patients hospitalized due to asthma attacks increased continuously from 1975 until 1987 at respective rates of 4.9-fold (from 466 to 2295 patients) and 10.6-fold (from 118 to 1245 cases). Thereafter, the number of out-patients has remained stable (1999 patients in 1997), while the number of hospitalizations has decreased (766 in 1997). However, the age-specific distribution of hospitalized patients has changed remarkably. There are two peaks: one in the infant population and another in older elementary school students. In the past, the incidence of hospitalization was higher among older elementary school students, although now the situation has been reversed, with as many as 53.6% (323 patients) of patients aged between 0 and 3 years of age being hospitalized in 1999 and more patients being identified with complications. This reversal could be largely attributable to the fact that whereas strong medications and therapies, such as round the clock therapy with theophylline, disodium cromoglycate inhalation and inhalation of steroids, have become standard treatments for older elementary school children with asthma, these therapies, especially steroid inhalation, may be difficult to use for the treatment of infants and, therefore, pediatricians are hesitant to use these treatment strategies. The elevated incidence rate of asthma and its higher incidence in younger children may also be an underlying cause. In contrast, asthma mortality at our pediatric unit has never increased, on average one patient yearly, and most of these cases were deaths at home or deaths on the way to hospital. With regard to asthma death statistics in Japan, a sudden increase in deaths due to asthma was noted among children aged 10–14 years in the 1960s, whereas no such increase in deaths due to asthma has been noted since the 1970s. This suggests a big step ahead in terms of the treatment and management of children with bronchial asthma. However, the long-term prognosis of severe childhood refractory asthma is not good. In our prognosis study on severe asthma patients who were hospitalized 20 years ago, 27.2% experienced remission and 12.7% died, and residual impaired pulmonary function was noted in many cases. Among the 24 cases of death, we have been notified that 20 cases of sudden death were patients aged between 10 and 29 years of age. The mortality rate in patients aged 15–29 years in Japan increased threefold during the subsequent 10 years from 1980. Although this rate has apparently started to decrease in the past 5 years, compared with the
estimated bronchial asthma incidence rate from the International Study of Asthma and Allergies in Childhood (ISAAC) study, the bronchial asthma mortality rate in Japan is definitely higher than in Western countries. These data suggest difficulty in the management of adolescent and young adult patients with severe asthma, who often have a psychological/social/economic handicap. The relatively high asthma mortality rate in Japan may be attributable to: (i) a greater number of patients with severe asthma; (ii) the poor medical supply system; (iii) a lack of asthma education for both physicians and patients; and (iv) problematic treatment regimens. In present paper, the first point is discussed in relation to the ISAAC study, the second point is discussed with regard to the system for outpatients’ overnight visits, the third point is discussed with regard to the educational/cooperative system involving school and society, and the fourth point is discussed in terms of treatments with steroids inhalation and β-adrenergic receptor agonists. In conclusion, the overall control of bronchial asthma can certainly be achieved more easily now, as seen by the reduction in the number of hospitalizations from asthma attacks and the year-round number of patients with severe asthma. However, infant asthma patients do not show this tendency and this requires investigation into treatment regimens involving morbidity analysis and early interventions. In addition, severe childhood refractory asthma presents various current and future problems. In fact, these patients are facing many problems, such as long-term use of multiple medications, disturbances to everyday life, obstacles to higher education/work, an inadequate system of emergency night visits and a lack of understanding in society. Therefore, establishment of a system for true total care with early long-term vision and social consciousness is strongly desired. Asthma mortality is a serious problem that requires the establishment of a large, long-term project in order to investigate the cause of the relatively high mortality rate among asthma patients in Japan and to propose measures against this.

Key words: adolescence, asthma death, bronchial asthma, epidemiology, infantile asthma, young adult.

INTRODUCTION

The prevalence of allergic diseases, including bronchial asthma, has been increasing worldwide. Taking into account the recent increase in the mortality due to bronchial asthma among the young population in Japan, analysis of the disease and the development of measures against the mortality are urgently required. In addition, the increased hospitalization rate for infant asthmatics and the lack of an appropriate treatment regimen for this group of patients are dawning as other problems requiring investigation.

Based on data from an analysis of the present status of infant asthmatics, trends and characteristics of clinical symptoms in adolescent through to young adult patients, long-term prognosis in pediatric patients with severe asthma who have been hospitalized for long periods, the pulmonary functional perspective in young patients with severe bronchial asthma and mortality in young asthma patients, including my own views on Global Initiative for Asthma (GINA) guidelines1 and the Japanese guidelines for the treatment of asthma in adult patients (JGL ‘98),2 the following paper discusses the treatment and management of patients with severe asthma, ranging from infants through to young adults.

THE SHIFT IN THE NUMBER OF PEDIATRIC ASTHMA PATIENTS AND AGE-SPECIFIC DISTRIBUTION

Looking at the number of pediatric asthma patients in National Minami Fukuoka Chest Hospital, the number of out-patients subsequent to 1984 has been between 2000 and 2500 annually. The number of patients hospitalized due to asthma attacks, which once amounted to 1280, has started to decrease in recent years. There are two peaks for hospitalization rates: one in the adolescent population and one in the infant population. The figures show that of the 16 791 asthma patients who were hospitalized and received treatment during the 24 years between 1974 and 1997, there were 1.34-fold more boys than girls (Fig. 1).

Dividing these 24 years into three 8 year periods (1974–1981, 1982–1989, and 1990–1997), we can see a significant increase in the number of younger patients hospitalized in the most recent 8 year period, whereas a significant decrease is observed in the number of school children hospitalized (Fig. 2).

A particular characteristic in this shift of the incidence of hospitalization is observed: the incidence of hospitalization of younger patients because of asthma attacks has not decreased but, rather, has shown an increase in terms of absolute values. This increase in hospitalization is characterized by a high complication rate with
respiratory tract infections, such as upper respiratory tract infection, bronchitis and pneumonia. The rate of complications with infections was higher and more significant in infants (Fig. 3).

The number of young adult patients with asthma has been increasing; however, this may be a matter of the clinical course of asthma. Because patients with mild, moderately severe or severe asthma may improve as they become older, if we work in the same pediatrics office for a long time, we would be able to see a greater number of patients with severe asthma to a certain extent; that is to say, we would naturally end up seeing a greater number of older patients in the pediatrics department. We conducted two epidemiological surveillances on approximately 50,000 elementary school children in 11 prefectures of western Japan between 1982 and 1992. In these studies, the prevalence rate for asthma had been decreasing gradually in both boys and girls in the 1st through to the 6th grades in the past, whereas in 1992, the rate of decrease had slowed down and the prevalence rates, at the end of the surveillance, had even been higher for all grades (Fig. 4). Data from other regions in Japan also showed the same pattern as our data. This may be one of the reasons for the greater number of older patients with bronchial asthma observed in pediatrics.

In our recent surveillance of elementary school children using the American Thoracic Society–Division of Lung Diseases (ATS-DLD) questionnaire (Japanese version/revision), the results indicated a prevalence rate of asthma of approximately 5% in almost every region. In Japan, the ISAAC study was conducted in Fukuoka City. The 12 month prevalence of asthma symptoms among 1st graders and junior high school 2nd graders was 17 and 13%, respectively. Japan has the highest prevalence rate of asthma symptoms in children in all south-east Asia (Fig. 5).

The ISAAC study used a rough definition of the disease. Therefore, some patients who did not have bronchial asthma may have been included in this ‘wheeze’ group.

In contrast, despite epidemiologic data that showed no

Fig. 1 Annual changes in acute hospitalizations for asthma from 1974 to 1997, Division of Pediatrics, National Minami Fukuoka Chest Hospital. (closed square), females (n = 7163); (open square), males (n = 9628).
variation in the age-specific incidence rate for asthma symptoms, the age-specific rates for recipients of asthma treatment showed a different pattern. The number of recipients of asthma treatment gradually decreased in the 1–4-, 5–9-, 0- and 10–14-year-old age groups, while the number of recipients of asthma treatment in the 15 years or older age group showed a rapid decrease. This may be one of the outstanding problems in the treatment and management of young adult patients with severe bronchial asthma, as I will now discuss.

DIFFERENCES IN ASTHMA TREATMENT BETWEEN PEDIATRIC AND INTERNAL MEDICINE UNITS

A study was conducted on the patient distribution in the pediatric and internal medicine units of three major hospitals in Japan (National Minami Fukuoka Chest Hospital, National Sagamihara Hospital and Doai Memorial Hospital). The results were as follows: a greater percentage of patients aged between 15 and 19 years had visited the pediatric unit (62.4%) and a greater percentage of patients aged between 20 and 24 years had been shifted to the internal medicine unit (30.0% of these patients had visited the pediatric unit), whereas most patients over 30 years of age had visited the internal medicine unit. This makes the problem of treatment more complicated in young adult asthmatics.

These three institutions, together with some other institutions (Kinki Medical School, Tamana Chuo Hospital, National Children’s Hospital and Kyushu University), have organized the Adolescent Asthma Research Group. This group has conducted a study on a total of 170
patients, consisting of 69 male patients and 101 female patients aged 12–22 years. Ideally, the severity of asthma should be equal when the adolescent patient is assessed by the internal medicine and pediatric severity standard classification systems. However, the equality rate in this study was 73%. In some cases in which the severity of the disease was assessed differently between the pediatric and internal medicine units, it was found that internists tended to judge the severity of the patients’ asthma milder than pediatricians. This is to say that up to one-quarter of all patients had been judged differently, being considered as having severe asthma by a pediatrician but moderately severe asthma by an internist, or moderately severe asthma by a pediatrician but mild asthma by an internist. This is the group of patients who may encounter serious problems when they are transferred from pediatric care to internal medicine care.

The therapeutic score is an important issue when considering whether an internal medicine classification or a pediatric classification should be used to determine the severity of asthma in adolescent patients. The Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) has recently made a proposal regarding therapeutic scores. When the internal medicine severity classification was used in adolescent/young adult patients, the therapeutic score did not necessarily work as well as the classification, whereas patients more severe asthma were given higher therapeutic scores when the pediatric severity classification was used. However, there remains a further question of when the internal medicine severity classification should start to be used, with no conclusions provided from the Adolescent Asthma Research Group study.

We questioned all directors of JSPACI as to what drug therapy should be administered to patients with Step 2: Mild Persistent and Step 3: Moderate Persistent Asthma in the guidelines. Compared with adult patients, the difference was apparent in pediatric patients with Step 2 asthma, to whom no steroid inhalation is administered but high-dose disodium cromoglycate (DSCG) inhalation...
is used instead. Steroid inhalation was not frequently used in patients with mild Step 3 asthma either. No steroids were administered orally to children with Step 3 asthma. In particular, this suggests that steroid use is the outstanding issue in terms of differences between pediatric treatment of asthma and internal medicine treatment of asthma.

**PROBLEMS RELATED TO SCHOOLWORK AND SOCIAL WORK**

For adolescents through to young adult patients with asthma, their schoolwork is another underlying problem in terms of the substantial social/psychological problems resulting from their condition. Asthmatic children with uncontrollable severe asthma often receive institutionalized therapy in Japan. The average school absence rate in institutionalized patients 20 years ago was approximately 15%. Nevertheless, a recent study reported a school absence rate of over 25%. This is a serious problem because, with regard to the school absence rate and school records for elementary and junior high school-age out-patients, the more severe the disease, the higher the absence rate; this results in a poorer school record, which is more significant for patients at the junior high school level than for patients of elementary school age. As a result, a greater number of underachievers, who cannot achieve their potential level at school based on their intelligence and achievement deviations, is found at higher grades.

In addition, in a survey of long-term prognosis of institutionalized patients with severe asthma, various psychosocial problems were identified. These include problems in gaining higher education, getting a job and daily life; patients who remain symptomatic have a tendency to face more serious problems. A considerable
number of young adult patients continue to consulting with physicians and receive medical therapy.

**PECULIARITY OF CLINICAL SYMPTOMS IN ADOLESCENT/YOUNG ADULT PATIENTS**

The clinical symptoms in young adult asthma patients differ from those in younger children, middle-aged and older patients. As pointed out already, there are differences in the age distribution of patients hospitalized due to asthma attacks; there was a peak in the younger childhood population and another in the adolescent population. Cases complicated with respiratory infections were concentrated in the infant population. This suggests that fewer adolescent patients with severe asthma attacks have worsened due to complications with respiratory infection (Fig. 3).

Atelectasis in asthma patients, particularly that of the middle lobe, is common and occurs overwhelmingly in younger children, whereas only a few cases of atelectasis are found in older children with asthma. In contrast, mediastinal emphysema and subcutaneous emphysema, called air leak syndrome, are concentrated in the young adult population.\(^{15}\)

**LONG-TERM PROGNOSIS OF PATIENTS WITH SEVERE CHILDHOOD ASTHMA WHO HAVE HAD LONG-TERM HOSPITALIZATION (INSTITUTIONALIZED THERAPY)**

We conducted the fourth surveillance by questionnaires and interviews in 1996 to examine the long-term prognosis of patients with severe bronchial asthma who have had long-term hospitalization (institutionalized therapy).

Subjects comprised a total of 127 patients with bronchial asthma who had been admitted and discharged from the National Minami Fukuoka Chest Hospital during the 4.5 years subsequent to 1974. The average age of asthma onset was 2.6 years and the age on admission was 8.5 years. A total of four surveys were performed from 1980 through to 1996.\(^{13}\)

In the data submitted in 1996, a total of 48 patients were aged between 24 and 35 years, with a mean age of 29.5 ± 2.8 years. The remission rates in the past studies

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**Fig. 5** 12 month prevalences of self-reported asthma symptoms from written questionnaires (13–14-year-olds; from ISAAC\(^{4}\)).
were 15.7–40.9%; however, the rate among the 48 patients of the 1996 study was 27.2%, which is relatively low for a long-term observation (Table 1). In our study, the important result was a mortality rate of 12.7%, approximately 40-fold higher than that of asthma patients in this age group in Japan. In the recent yearly asthma status, there were some patients who had never had attacks, whereas a great number of patients remained symptomatic and many were treated with steroid inhalation.

Looking at the hospital visits status, 64.6% of patients were still consulting with physicians; half at the internal medicine unit and the other half at the pediatrics unit.

Results of pulmonary function measurements were as follows: percentage forced vital capacity (%FVC) 102.2 ± 15.9%; percentage forced expiratory volume (%FEV₁.₀) in 1 s 84.8 ± 17.2%; percentage peak expiratory flow (%PEF) 80.6 ± 26.3%; and percentage V₅₀ 50.3 ± 25.5%. A greater decrease in %PEF in young adult subjects who have had long-term hospitalization compared with patients with childhood severe asthma was noted (Fig. 6). Some patients were well controlled, while a considerable number of patients continued to have low pulmonary function values. We compared serum IgE levels in patients at a mean age of 9 years on discharge and 20 years later. The mean IgE value at age 9.1 years was 202.5 ± 1362.5 IU/mL, whereas the value dropped to 529.4 ± 445.9 IU/mL at 28.4 years, with only one patient of 16 cases showing an elevated value of serum IgE. The total IgE values decreased to nearly one-quarter of the level 20 years ago.

When we investigated elementary school children and compared the IgE value distribution in these children with a healthy population, asthma patients and wheezy children were characterized by a large peak distribution at 1000–2000 IU/mL and only a small peak at 500–1000 IU/mL. The IgE value, in general, decreased after the age of 20 years. To understand this, we considered that this pattern may be attributable to differences in house

<table>
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<th>Survey</th>
<th>n (response rate, %)</th>
<th>Age (years)</th>
<th>Remission</th>
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<th>Prognosis (%)</th>
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<td>1980</td>
<td>115 (90.6)</td>
<td>13</td>
<td>15.7</td>
<td>57.3</td>
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<td>1984</td>
<td>109 (85.8)</td>
<td>17</td>
<td>33.0</td>
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<td>1990</td>
<td>93 (73.2)</td>
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<td>1996</td>
<td>48 (37.8)</td>
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In 1980 and 1984, patients were studied 3 years after institutionalized therapy; in 1990, patients were studied 15 years after institutionalized therapy; in 1996, patients were studied 22 years after institutionalized therapy.
dust mite environments between the past and present rather than individually reduced values. However, in the results of the long-term follow-up study, an early individual total IgE decrease has been suggested, which may reflect a decrease in IgE-mediated immunity/allergic reactions in individuals.

I will now discuss the part played by menstruation, pregnancy and birth. Our data did not show any effect of menarche on asthma status: unchanged 70.6% at the time, improved 23.5% and growing worse 5.9%. Because the mean age of the female subjects was 26 years, menstrual asthma may be detected, yet the rate of menstrual asthma was rather low at 23.5%, 60% of which consisted of premenstrual asthma patients.

Regarding asthma in pregnancy, Gilbert has reported that one-third of patients will improve, one-third will remain unchanged and one-third will become worse. The data of our study have indicated that 66.7% of asthma patients improved due to pregnancy and one-third of these have been doing well during the postnatal period; no aggravated case due to pregnancy has been reported in 17 subjects.

Whether asthma is a handicap for marriage and what will happen in the future are questions that we often hear from patients and their parents. Fortunately, in the group of patients who were concerned about asthma before marriage, only one case (3.4%) was reported to have negative consequences, preventing people from getting married. Twenty-six babies have been born to married patients and for this group of babies the prevalence rate of allergic diseases was found to be 34.6%, while the prevalence rate of asthma was 15.4%. Data from epidemiologic surveillance in the western regions of Japan indicate that the rate of asthma patients in families with a history of asthma was 9% in 1982 and 12% in 1992; therefore, the rates for subjects in our survey were a little higher. However, the study in the western Japan was conducted on elementary school children, whereas a great number of preschool children have been involved in our study. Therefore, the asthma prevalence rate among offspring of patients with severe asthma may be higher than in out-patients with asthma.

**PULMONARY FUNCTION OF YOUNG ADULT PATIENTS WITH SEVERE BRONCHIAL ASTHMA**

As discussed previously, the pulmonary function of patients who had experienced long-term hospitalization therapy 20 years ago were, unfortunately, not good (Fig. 6). Measurements of FVC were normal, %PEF and %FEV\(_{1.0}\) were rather lower and V\(_{50}\) was apparently equivalent to that of patients with severe asthma. Among the elementary school children classified into four groups as children with no asthma, children with mild asthma, children with moderately severe asthma and children with severe asthma, all subjects showed greater than 100% in %PEF, 90% in %FEV\(_{1.0}\), which was somewhat lower, and a group of severe asthma patients showed 50% in %V\(_{50}\) (Fig. 7). The subjects in this study showed values nearly equivalent to those of children with severe asthma except for %PEF.
values, which were lower. Namely, the low %PEF values in young adult patients were apparently different from those of severe asthma patients at elementary school age.

We performed pulmonary function tests after the administration of epirrenamine hydrochloride, subcutaneous injection, to four groups of patients: a group of patients who have been doing well after hospitalization through to a group of patients who were receiving medication but still experiencing attacks. The results observed for $V_{50}$ showed that some patients who were not doing well had an initial percentage value less than 50% and that even patients who were doing fairly well had values as low as 60%. The incidence of patients whose pulmonary function values were elevated to greater than 80% of predicted values after the administration of the bronchodilator were low for $V_{50}$ overall and this was significant in patients who were not doing well. We have experienced few cases of patients’ ventilatory function in small airway parameters recovering to 100% after administration of bronchodilator. To my understanding, before 20 years of age, airway constriction may persist continuously in patients with severe asthma, even when the patients are in a good stable condition; this is supported by the recent chronic airway inflammation theory.18,19

We compared three groups of patients, namely a group of patients who had died of asthma, a group of patients with episodes of severe attacks and a group with mild asthma, aged 13–15 years with the same background. The data indicated that, compared with mild cases, the group of patients who died of asthma had apparently lower $V_{50}$ values.20 There was no difference between the severe-type group and those patients who died of asthma and this could be a serious problem because it means that we are not able to distinguish the group at risk of death from other groups by pulmonary function values before the asthma attack that leads to their death. The results of pulmonary function tests of patients at a mean age of 30 years, who were questioned in the follow-up study, were nearly equivalent to those of patients who had died of asthma. These patients were therefore considered as a high-risk group and will require adequate treatment and regular management.

Patients with severe asthma can easily develop airway constriction (i.e. exercise-induced asthma (EIA) or exercise-induced bronchospasm (EIB)).21,22 Patients with mild, moderately severe and severe asthma are clearly more apt to develop EIB than healthy children (Fig. 8).22 The airways of these patients are extremely sensitive and this becomes an impediment in their activity of daily living (ADL) and quality of life (QOL). As a result, junior high school students with severe asthma are inferior to the national average in terms of back muscle strength,

Fig. 8 Maximal percentage fall in (a) forced vital capacity (FVC), (b) peak expiratory flow (PEF) and (c) $V_{50}$ in asthmatic children (A, normal; B, mild asthma; C, moderate asthma; D, severe asthma) by bicycle ergometer.22 *P < 0.01, †P < 0.005.
repeating sideways jumps and grip strength, and their physical performance is not comparable. We are unable to recommend vigorous exercise to severe asthma patients with a high EIB tendency without premedication. At our hospital, we have been performing swimming training, which is less likely to cause EIB, all year round in order to strengthen these patients physically as well as to improve their bronchial hypersensitivity.

**Asthma Mortality**

Incidents of mortality from asthma for the entire Japanese population have been decreasing gradually over the past 10 years to approximately 5.0 cases per 100,000. In the past, sudden deaths of boys aged 10–14 years became a worldwide issue from 1965 through the 1970s, and it still remains vividly in our memory. These sudden deaths were first reported in England and Wales and the mortality rate among boys aged 10–14 years in Japan was elevated to sevenfold. However, this rate has decreased to 0.4–0.5 in the 5 years subsequent to 1970. Asthma mortality has been said to be increasing recently, but cases of this in the population aged 10–14 years, which became an international issue in 1970, has not increased in Japan (Fig. 9). However, mortality in the population group ranging from 15 to 29 years took an apparently different course. In 1980, mortality in both males and females in this age group had started to increase and then continued increasing to threefold the previous rate in the subsequent 10 years. In the population older than 30 years, asthma mortality showed only a little increase. The recent increase in asthma mortality in the 15–29-year-old age group was peculiar. However, the mortality rate in this age group has been decreasing since 1995.

We have unfortunately experienced death in 26 asthma patients during the past 26 years among the patients registered at the Pediatric Unit of National Minami Fukuoka Chest Hospital. The most recent death occurred in June 1996. Two patients died from malignant tumors, two patients experienced sudden death due to unknown causes and other patients died of asthma. We have analyzed a total of 24 patients, including these two

![Image](https://example.com/image.png)

**Fig. 9** Asthma mortality in three age groups (○, 5–34 years; ●, 10–14 years; □, 15–29 years) in Japan from 1960 to 1999.
sudden-death patients because they had severe asthma. The age distribution in the 24 patients who died ranged from 3 to 29 years, with a mean age of 15.5 ± 7.4 years. Fourteen cases were males. There was an apparent difference in the age distribution between cases of death from asthma and patients with near-fatal asthma (NFA) in the Minami Fukuoka Chest Hospital. Although a greater number of NFA patients were distributed in the younger age group, the mortality in this age group was low and showed a similar tendency to the national data published by Japanese Society of Pediatric Allergy Asthma Mortality Committee. The data of our hospital indicated a greater number of NFA attacks in young children. A significant difference was observed in the 22 severe patients, accounting for 92% of a total of 24 of patients, whereas in the data of the Asthma Mortality Committee, the rate of severe asthma patients was as low as 32.6%. Patients with severe asthma in NFA cases have amounted to 65.5% in Minami Fukuoka Hospital as well, whereas the national surveillance rate was 35.4%. In addition, there was an important difference in the place of death between our 24 patients and those of the national surveillance. In most of our cases, patients had already died on their way to hospital. As a result, death from asthma in pediatric patients in our hospital were characterized by death from asthma attacks in young adult patients outside the hospital. Another characteristic was that the mean age of the most recent 13 patient deaths was 19.6 years, showing a shift to a group of older patients. These marked differences between data in our hospital and those of the national surveillance are a problem that needs to be solved in order to investigate the cause of asthma mortality and to plan an appropriate management regimen.

Examining the risk factors for asthma mortality and NFA, delayed visits to hospitals and an overreliance on β-adrenergic receptor agonists metered dose inhaler (MDI)/nebulizer have been indicated as contributing factors. Among 10 cases of death in our patients in whom the use of β-adrenergic receptor agonists could be traced, 70% may have been overreliant, which is higher compared with cases of NFA. Among the β-adrenergic receptor agonists in use, there is some concern about the use of fenoterol; there are some points that should be noted with regard to the use of β-adrenergic receptor agonists MDI in Japan. To look at the number of β-adrenergic receptor agonist MDI canisters sold yearly from 1985 to 1995, almost the same amount of fenoterol, procaterol and salbutamol has been sold, whereas the amount of isoproterenol MDI sold decreased slightly in 1995, even though the frequent occurrence of asthma mortality in 1965–1970 was considered to be associated with the use of isoproterenol MDI. The reason for this may be that once a patient starts to use a specific vigorous β-adrenergic receptor agonist MDI, it cannot be easily changed to another medication. Among our out-patients, a considerable number of patients may certainly resist our efforts to change their medication. Although there are various guidelines for asthma treatment, the actual β₂-adrenergic receptor agonist MDI usage status in Japan seems to be working unrelated to the cautions indicated in the recent guidelines before 1998.

The well-known data from New Zealand are contrary to expectations. The data from the Japanese Society of Pediatric Allergy Asthma Mortality Committee showed nearly the same results as the New Zealand studies and the Saskatchewan study. However, because the Japanese data were not constant in terms of background factors and were of an insufficient level in terms of evidence-based medicine (EBM), we are unable to come to any conclusions (Table 2).

The reasons for mortality concentrated around adolescents through to young adults may be because of the following.

1. The shift of initiative for the treatment from a physician or family members to the patient himself/herself results in a disturbance in appropriate therapy.
2. Daytime hospital visits on an out-patient basis may become difficult due to increased schoolwork or workload, resulting in fewer, intermittent visits.
3. The pathophysiology may be altered by more frequent air leak syndrome complications or menstrual influences.
4. It may be hard for a patient to adapt to either internal medicine or pediatrics either physically or psychologically.
5. Starting to live alone makes it difficult to get support from others.

Particularly regarding the fifth point, male patients are more likely to be isolated without any support, which may become a big problem. The asthma management guidelines for adolescents through to young adult patients with intractable asthma should be set separately. To set up separate guidelines, important points to consider include how to judge the severity of the asthma, adjustments in the understanding of medical staff and family of the patients, compliance, education of school/workplace and identification of high-risk patients.
CONSIDERATIONS IN GINA

I am going to point out some points for consideration in the asthma management program GINA.

The six-part asthma management program consists of the following.

1. Educating patients to develop a partnership in asthma management.
2. Assessing and monitoring asthma severity with symptom and lung function measurements.
3. Avoiding or controlling asthma triggers.
4. Establishing medication plans for long-term management.
5. Establishing plans for managing exacerbations.
6. Providing regular follow-up care.

With regard to the second point, monitoring asthma severity, asthma attacks are classified into mild, moderate and severe, drawing lines at 80 and 60% in terms of %PEF values and at 45 mmHg in $P_aCO_2$. However, the question is whether this could actually be applied to childhood asthma patients or not. According to data from our study examining changes in patients admitted from asthma attacks subsequent to β-adrenergic receptor agonist inhalation, the %PEF values of admitted patients may be as low as 30% and, even after the β-adrenergic receptor agonist inhalation, these values increase to approximately 40%. However, patients may be discharged with values of 60–80% after β-adrenergic receptor agonist inhalation. Therefore, if we follow and apply the GINA guidelines, which indicate we should admit patients with %PEF values of 60% or less after β-adrenergic receptor agonist inhalation, a considerable number of patients would have to be admitted (Fig. 10).

Similarly, another question is whether or not 45 mmHg $P_aCO_2$ could be correctly applied to children. The six condition-specific $P_aCO_2$ values are measured when asthma is under control, rhonchi with auscultation, mild attack, moderate attacks, severe attacks and severe attacks with disturbance of consciousness. We can find that even patients who are under a severe attack never have a value greater than 45 mmHg on average and when the value is greater than 45 mmHg the patient may be in a very serious condition with agitation or disturbance of consciousness (Fig. 11). Therefore, the standard value of 45 mmHg is very risky it is to be applied to preteen or younger patients and should be lowered to 40 mmHg.

Another consideration is about point 3, ‘Environmental control measures’ in the asthma management program of GINA. Sporik et al. have suggested that infants who are exposed to house dust mite at birth have a greater chance of developing allergies. There is no doubt that patient education about their environment is important. In fact, we have been giving instructions, such as using air-conditioning systems, caution regarding bed clothes, methods of house cleaning, wider storage space and not keeping animals indoors. However, it is difficult for many patients to follow all these instructions and I will show how difficult it is using cats as an example. According to the data of the Petfoods Industry Association (T Ooki, Secretary General Petfoods Industry Association, pers. comm., 1995), 10.6% of Japanese households now have cats; 8.0% are estimated to keep cats in the house. However, data on our pediatric out-patients indicate that a considerable number of older asthma patients often keep cats and as high as 64.7% of patients who have cats ($n = 51$) were sensitized, whereas 21.2% of patients who did not have cats were sensitized. Even though we give instructions to not keep cats, a significant number of patients, in fact, still keep cats. Considering an ideal environment, some lifestyle changes are required and, in addition, great deal of energy is required, either economically or timewise, which makes it difficult to follow the instructions. Thus, we cannot help but rely only on medications. Without any insurance coverage, a 3 day period

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<tr>
<th>Table 2</th>
<th>Proportion of cases (asthma deaths) and controls prescribed fenoterol in studies in New Zealand, Saskatchewan and Japan</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total deaths</td>
</tr>
<tr>
<td>First New Zealand study$^{29}$</td>
<td>117</td>
</tr>
<tr>
<td>Second New Zealand study$^{29}$</td>
<td>58</td>
</tr>
<tr>
<td>Third New Zealand study$^{30}$</td>
<td>112</td>
</tr>
<tr>
<td>Saskatchewan study$^{31}$</td>
<td>44</td>
</tr>
<tr>
<td>Japanese study$^{39}$</td>
<td>30</td>
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</tbody>
</table>

*Market share; this study did not include a formal control group. OR, odds ratio; CI, confidence interval.
Fig. 10  Changes in pulmonary function before and after isoproterenol inhalation on admission (○) and at discharge (●). Data are the mean±SEM. FVC, forced vital capacity; FEV₁₀, forced expiratory volume in 1 s; PEF, peak expiratory flow; MMF, maximal mid-expiratory flow.

Fig. 11  Arterial blood gases in asthmatic children. 0, no rhonchi of auscultation; 1, rhonchi only; 2, mild attack; 3, moderate attack; 4, severe attack; 5, respiratory failure with disturbance of consciousness. *P < 0.005.
hospitalization of asthma patients may cost up to US$700–800, which may be an economic burden on frequently hospitalized patients, making it harder to improve the life environment; thus, the vicious cycle develops.

The GINA defines controlled asthma as: (i) minimal (ideally no) chronic symptoms; (ii) minimal (infrequent) exacerbations; (iii) minimal (ideally no) need for pro re nata (p.r.n.; as needed) \( \beta_2 \)-adrenergic receptor agonist; (iv) no limitations on activities; (v) (near) normal PEF and PEF circadian variation of less than 20%; (vi) minimal (or no) adverse effects from medicine; and (vii) physical and psychological status are kept normal. The questions are, for example, whether it is possible to keep PEF circadian variation less than 20% or whether it is appropriate for the standard to be applied to children that asthma severity is assessed as paroxysmal with over 80% \%PEF, chronic–severe with less than 60% and mild with a circadian variation of less than 20%. As previously discussed, %PEF values in children, even in severe-type asthma patients, could be averaged over 100%. In our study, in the group of patients with a mean age of 30 years, 80% of PEF measurements were obtained when no attacks were observed. Therefore, the value of 80% in the GINA guidelines is not appropriate, at least for patients younger than adolescents, and cannot be applied to childhood asthma patients. Pulmonary function measurements in some childhood patients may show dynamic changes and it is very difficult to keep PEF circadian variation of less than 20% in patients with severe asthma, even when the patient’s asthma appears to be well controlled.

As I have mentioned, although various ideals are indicated in the treatment and management guidelines of GINA, we must, unfortunately, face many underlying problems when we try to apply these guidelines uniformly, especially to young adult patients who often have complex backgrounds.

CONCLUSIONS

Overall, the control of childhood bronchial asthma could certainly be more easily achieved now. However, patients with severe intractable asthma remain problematic. These patients face many problems, such as long-term use of multiple medications, disturbances in QOL, obstacles in higher education/work, an inadequate system of emergency night visits and a lack of understanding in society. The establishment of a system for true total care with early long-term vision and social consciousness is strongly desired.

REFERENCES


