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Surveillance of the use of adrenaline auto-injectors in Japanese children

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AAI	adrenaline auto-injector
ELT	emergency life-saving technicians
JSPACI	The Japanese Society of Pediatric Allergy and Clinical Immunology
FDEIA	food-dependent exercise-induced anaphylaxis
ED	emergency department

ABSTRACT

Background: The appropriate usage of an adrenaline auto-injector (AAI, EpiPen[®]) is a key aspect of patient and social education in the management of anaphylaxis. However, although AAI is being prescribed increasingly frequently, there are few reports on their actual use.

Methods: The Anaphylaxis Working Group of the Japanese Society of Pediatric Allergy and Clinical Immunology requested that society members register cases in which AAI was used. Two hundred and sixty-six cases were collected from March 2014 to March 2016.

Results: The cases included 240 events of immediate-type food allergies caused by cow's milk ($n = 100$), hen's egg ($n = 42$), wheat ($n = 40$), and peanuts ($n = 11$). Exercise-related events were reported in 19 cases; however, the diagnosis of food-dependent exercise-induced anaphylaxis with a specific causative food was only made in 4 cases (wheat, $n = 2$; fish, $n = 1$; squid, $n = 1$). The frequent reasons for the causative intake included programmed intake ($n = 48$), failure to check the food labeling ($n = 43$), and consuming an inappropriate food ($n = 26$). AAI was used at schools or nurseries in 67 cases, with school or nursery staff members administering the AAI in 39 cases (58%). On arriving at the hospital, the symptom grade was improved in 71% of the cases, while grade 4 symptoms remained in 20% of the cases. No lethal cases or sequelae were reported.

Conclusions: AAI was used effectively, even by school teachers. The need to visit a hospital after the use of an AAI should be emphasized because additional treatment might be required.

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Introduction

Anaphylaxis is defined as “a serious, life-threatening generalized or systemic hypersensitivity reaction”, and “a serious allergic reaction that is rapid in onset and might cause death”.¹ The intramuscular injection of adrenaline is the first-line treatment for anaphylaxis.² Adrenaline auto-injectors (AAIs; EpiPen[®]; Pfizer Japan Inc. Tokyo) are prescribed to patients who are at risk of anaphylaxis.

In Japan, the 0.3-mg AAI was first approved for bee venom-induced anaphylaxis in 2003. The indication was expanded to food- and drug-induced anaphylaxis in 2005; at the same time, the

0.15-mg AAI was approved for children 15–30 kg in body weight. The number of AAI prescriptions dramatically increased after 2011, when AAI received national health insurance coverage. Since 2009, emergency life-saving technicians (ELTs) have been allowed to administer a prescribed AAI under medical control.

Many efforts had been made to manage children who are at risk of developing anaphylaxis in schools and nurseries.³ These efforts have included identifying students who are at risk of anaphylaxis, providing school lunches safely and—importantly—establishing a social consensus that school teachers are allowed to use AAI in case of emergencies involving students. However, despite these nationwide efforts, a fatal accident occurred in December 2012 when a student suffered from anaphylaxis after ingesting a milk product that was served in a school lunch.

This event led to the publication of the anaphylaxis guidelines by the Japanese Society of Allergy.⁴ The Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) also proposed a

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list of symptoms that are indicators for the use of AAI by individuals other than medical professionals (Table 1).³

According to a nationwide surveillance of the prescription and usage of AAI in Japan from 2003 to 2009, 51,447 AAI were prescribed, while AAI were actually used in 449 cases (0.87%).⁵ This low prevalence of AAI usage suggests that many physicians who prescribe AAI have little chance of encountering an event in which an AAI is needed. Information about situations in which an AAI was actually used may help improve the understanding of patients and attendees of social education programs.

The JSPACI organized the Anaphylaxis Working Group in 2013. This group immediately issued a statement regarding the indications for AAI usage (Table 1). The present project was then initiated to collect information on cases involving the use of AAI from members of the society.

Methods

The present survey was conducted from March 2014 to March 2016. The Aichi Pediatric Clinical Study Group (Director: Professor Seiji Kojima, Nagoya University Graduate School of Medicine) also supported this study in the Aichi area. The members of each committee are listed in Supplementary Table 1. The project was announced to the members of the JSPACI (n = 3880 in November 2014) through the society's official journal and website.

The data collection sheet was provided via the website, and JSPACI members—mostly pediatricians working in hospitals or clinics—were asked to register cases. The data collection sheet consisted of 5 pages: 3 pages were a questionnaire asking patients or their caregivers to describe the details of the event; the attending doctors were then asked to confirm the information and complete a 2-page survey. Of note, the attending doctors were asked to judge the major symptoms that led the caregiver using the AAI (Table 1) and to judge the grade of anaphylaxis³ before the use of the AAI and at the time of arrival at the hospital.

The target patients were <20 years of age when the AAI was used. The following events were reported: 1) cases involving the use of the AAI that had been prescribed by the participating doctor; 2) cases in which the physician followed the patient as a family doctor; and 3) cases involving direct consultation for treatment at the time of the event.

The report was sent to the study office (Aichi Children's Health and Medical Center) by posted mail, fax or e-mail. Duplicated reports were recognized and integrated in the study office.

The sheet did not contain any personal information about the patients. The completion of the survey form was considered to

indicate the patient's consent to participate in the study. All of the procedures of this study were approved by the ethics committee of Aichi Children's Health and Medical Center (No. 201331).

Results

Data collection

A total of 266 events (male, n = 174; female, n = 92) were collected from 52 hospitals in 23 of the 47 prefectures in Japan. Most reports came from urban prefectures (Aichi, Osaka, Tokyo, Shiga, Kanagawa). This reflected the population of children and the number of cooperative doctors in the prefectures.

The median age of the patients was 7.6 years (range 1–19 years; Fig. 1). Their grades of education were as follows: senior high school or higher (≥ 15 years old, n = 15), junior high school (12–15 years old, n = 28), primary school (6–12 years old, n = 113) and kindergarten or nursery (≤ 6 years old, n = 96). A 0.15-mg AAI was used in 196 (74%) cases, while a 0.3-mg AAI was used in 70 (26%) cases. At the time of usage, 186 (70%) of the patients were using an AAI for the first time, while 55 (21%), 13 (5%), 6 (2%), and 6 (2%) were using an AAI for the second, third, fourth and fifth time or more, respectively.

Triggers of anaphylaxis

The clinical background that led to the prescription and AAI usage was immediate food allergy in 240 cases (90%). The most frequent causative food was cow's milk (n = 100, 42%), followed by hen's egg (n = 42, 18%), wheat (n = 40, 17%), peanut (n = 11), tree nuts (n = 3), fruits (n = 2) and other foods (n = 16). The offending food was not specified in the remaining 26 cases.

Exercise after the intake of food was associated with the onset of anaphylaxis in 19 cases (7%). Among these, 6 cases were diagnosed as food-dependent exercise-induced anaphylaxis (FDEIA) to wheat (n = 3), shrimp, fish and fruit (apple and peach). However, the offending food at the event was only specified in two cases involving wheat allergy, one case of fish allergy and one case of 'shrimp allergy' in which the patient used an AAI after consuming squid. Nine cases had a clinical history of immediate food allergy to wheat (n = 6), cow's milk (n = 2) and hen's egg (n = 1), and the

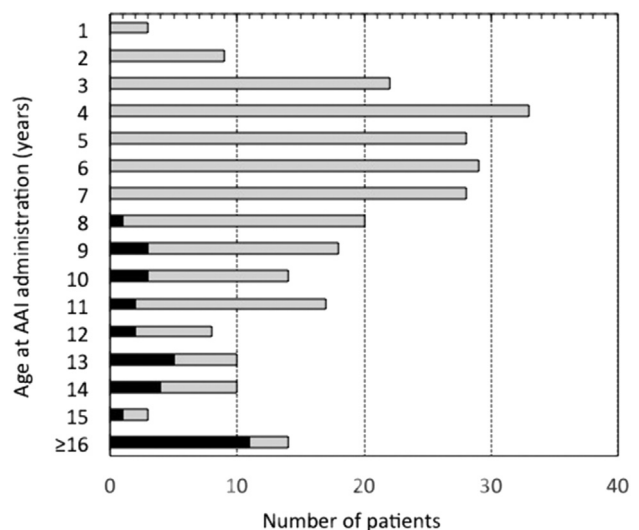


Fig. 1. Patients ages at the time of AAI usage. The distribution of the patients' ages at the time of adrenaline auto-injector (AAI) usage is shown in the bars (n = 266). Black bars indicate the number of patients who used an AAI by themselves (n = 32).

Table 1

Indications for the use of adrenaline auto-injectors by general persons (Japanese Society of Pediatric Allergy and Clinical Immunology).³

The EpiPen® should be administered to patients with suspected anaphylactic shock and for whom an EpiPen® is prescribed when the patient presents at least one of the following symptoms:	
Digestive symptoms	Repeated vomiting Persistent severe (intolerable) abdominal pain
Respiratory symptoms	Tightening in the throat or chest Husky voice Barking cough Persistent severe cough Wheezing
Systemic symptoms	Breathing difficulty Pale lips or nails Hardly palpable pulse Confusion Fatigue Incontinence

event occurred in association with exercise after the intake of the offending food. The offending food was not determined in the remaining 4 cases.

There were no cases caused by insect venom, drugs or other causes. In seven cases, an AAI was prescribed due to repeated idiopathic anaphylaxis, and the AAI was used in an event caused by an unknown trigger.

Situations surrounding the causative intake of food and the use of AAI

The causative intake of food occurred at home ($n = 138$, 52%), at school or in a nursery ($n = 61$, 23%), while eating out ($n = 24$, 9%), at a relative or friend's house ($n = 15$, 6%) and at other locations ($n = 28$). The most frequent reason for the causative intake was physician-oriented programmed intake ($n = 46$, 17%), which included oral immunotherapy for cow's milk ($n = 26$), hen's egg ($n = 10$), wheat ($n = 9$) and peanut ($n = 1$). The triggers included failure to check a food label ($n = 43$, 16%), eating an inappropriate food ($n = 26$, 10%) and young patients not understanding their intake ($n = 19$, 7%) (Table 2).

The locations in which the AAIs were used included the home ($n = 143$, 54%), at a school or nursery ($n = 67$, 25%) and in the ambulance or hospital ($n = 30$, 11%). Among the 67 cases in which an AAI was used at a school or nursery, the offending food was eaten at home ($n = 9$), as part of a programmed intake ($n = 4$) or due to failure to check the food label ($n = 2$).

The person who administered the AAI included the patient's mother ($n = 157$), the patient themselves ($n = 32$), the patient's father ($n = 22$), a school or nursery staff member ($n = 39$), an ELT ($n = 9$) and others ($n = 7$). In the 67 cases in which an AAI was used at a school or nursery, it was administered by a school or nursery staff member in 39 cases (58%), as follows: by a school nurse ($n = 22$), a nursery teacher ($n = 8$), a director ($n = 5$), or others ($n = 4$). Others who administered an AAI at school or nursery were the mother ($n = 15$), father ($n = 1$), patient themselves ($n = 7$) and ELT ($n = 5$).

The youngest patient who personally used an AAI was 8 years of age, while 11 of the 77 (14.3%) patients who were from 8 to 12 years of age used an AAI by themselves. Even among patients who were ≥ 13 years of age, only 21 of the 36 (58.3%) patients used an AAI by themselves (Fig. 1).

The posture of the patient during the use of the AAI was the supine position ($n = 129$, 48%), the sitting position ($n = 98$, 37%) and, surprisingly, the standing position ($n = 20$, 8%).

Situation during the intake of the causative food and the usage of the AAI

In the case of immediate reactions ($n = 236$), the median time between the intake and appearance of the initial symptom was

36 min (range, 1–300 min). The initial symptom was recognized within 1 h in 80% of the cases, and ≥ 2 h in 8% of the cases (Fig. 2A). The median time between the recognition of the initial symptom and the use of the AAI was 28 min (range, 0–190 min). In 74 cases, the AAI was administered within 15 min, whereas the AAI was used after 60 min in 42 cases (Fig. 2B).

During the course of the event, skin ($n = 209$), respiratory ($n = 225$), gastrointestinal ($n = 131$), neurological ($n = 79$) and cardiovascular ($n = 27$) symptoms were observed. Among the 13 symptoms listed in the JSPACI recommendation, respiratory symptoms (including breathing difficulty [$n = 106$], wheezing [$n = 102$] and persistent severe cough [$n = 89$]) were the dominant symptoms for which the caregivers decided to use an AAI, followed by systemic symptoms (fatigue [$n = 67$], Fig. 3). Nine cases used an AAI immediately after a skin symptom was observed, and the symptoms were limited to local hives in three cases.

Another medication was used before an AAI in 176 (66%) cases. These drugs included anti-histamines ($n = 162$), β_2 -stimulants ($n = 64$; oral 39, inhaler 25) and corticosteroids ($n = 50$).

Outcomes of the use of AAIs

With the exception of two cases in which the symptoms disappeared immediately, all patients visited an emergency department (ED) after the use of an AAI. Patients were transported by an ambulance in 193 (73%) cases. At the time of arrival at the hospital, the patient's symptoms had improved in 184 cases (69%), while some treatments were administered in 207 cases (78%). The additional treatments included corticosteroids ($n = 143$), anti-histamines ($n = 96$), inhalation of β_2 -stimulants ($n = 54$) and intramuscular adrenaline ($n = 21$) (Fig. 4).

The anaphylaxis grade at the time of AAI administration and on arrival at the hospital was judged by the attending physician in 256 cases (Fig. 5). Three cases were judged as grade 5 at the onset. One patient exhibited reduced consciousness after eating half an egg yolk as immunotherapy. A second patient with cow's milk allergy used a bathing powder that contained a milk product and suffered from breathlessness, incontinence and near loss of consciousness. The third patient ate one fried egg in the morning, and suffered from systemic urticaria and unconsciousness 2 h later at school. At the time of arrival at the hospital, the grade of symptoms was improved in 182 cases (71%), but was unchanged or worsened in 74 cases (28.7%). Of note, 50 cases (20%) exhibited grade 4 symptoms on arrival. After emergency treatment, 140 patients (53%) were admitted to the hospital. No lethal cases or sequelae were reported.

No cases involving the inappropriate usage or handling of an AAI were reported in this study. However, in 1 case, an 11-year-old girl felt throat tightness and fatigue without an apparent trigger at school and self-administered an AAI alone in a lavatory without any supervision.

Adverse effects of AAIs

Adverse effects were reported in association with the use of an AAI in 23 cases (8.6%). The most frequent symptom was pain at the site of injection ($n = 17$), followed by tremor of the extremities ($n = 3$), intradermal bleeding ($n = 2$) and palpitation ($n = 1$). A slash injury from the needle on the thigh was reported in one case, as the patient had not been properly restrained by the caregivers.

There were 24 cases ≤ 3 years of age, and most of them were considered to have a body weight of <15 kg at the time of prescription. Among these 24 cases, 2 reported pain at the site of the injection, but no other adverse effects were reported.

Table 2
The most commonly reported reasons for the causative intake of allergens.

Reasons for causative intake	n
Programmed intake (including oral immunotherapy)	46
Failure to check the food label	43
Eating an inappropriate food	26
A young patient not understanding their intake	19
Exercise after the intake of an allergen	16
The intake of an unexpected food	16
Contamination during the cooking procedure	12
Eating another person's dish	11
Being served by an unfamiliar person	9
The intake of an excessive amount of allergen	8
Being sick at the time of the intake	5
Others	31
Unknown	25

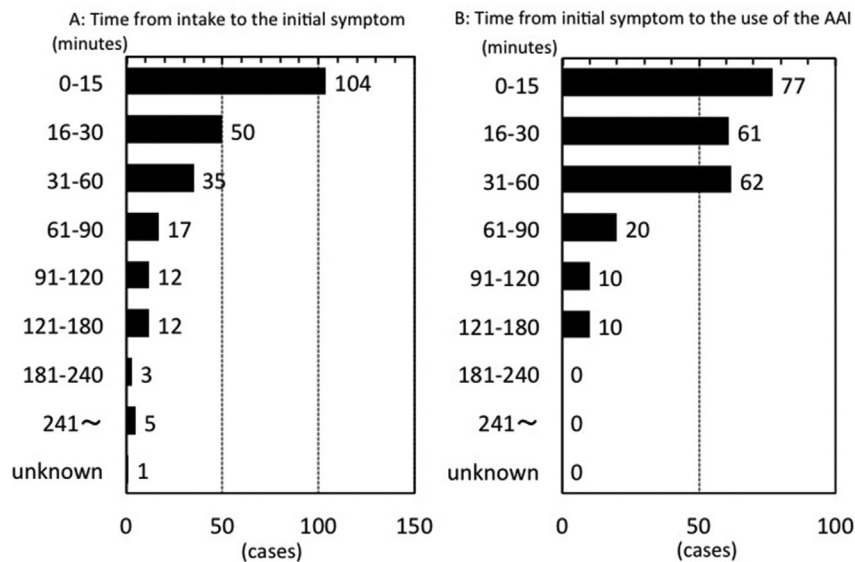


Fig. 2. Time interval of events. **A:** The time between the intake of the allergen and the recognition of the initial symptom. **B:** The time between the recognition of the symptom and the use of the AAI (minutes). The reports of 240 immediate reactions were analyzed.

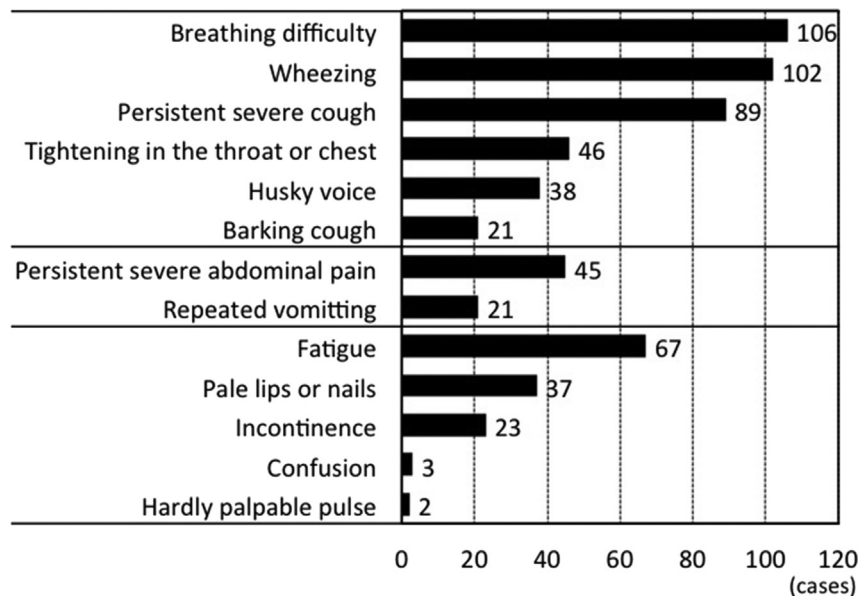


Fig. 3. Major symptoms associated with the decision to use an AAI. Those who administered an AAI ($n = 266$) were asked to choose the major symptom(s) that led to the decision to use an AAI among the 13 symptoms for which the JSPACI recommends the use of an AAI.

All of these adverse effects were associated with the physiological action of adrenaline or the intramuscular injection, and the patients quickly recovered without the need for treatment.

Discussion

AAIs are widely prescribed and used worldwide, but there are few reports of cases involving the use of AAIs. The actual situation regarding AAI usage offers valuable information concerning social education,⁶ especially for school personnel.⁷ However, even physicians who prescribe AAIs are not familiar with how AAIs are actually used.⁸

In the present study, we collected 266 cases in which AAIs were used to treat children. This study did not focus on the frequency of AAI usage in relation to the number of AAI prescriptions.⁵ Nakata

et al. reported on 1177 AAIs prescribed to 442 patients over an 8-year period at a single institution and collected 25 cases (2.1% per prescription) in which AAIs were used.⁹ In a study from western Japan, Korematsu *et al.* reported that AAIs were prescribed to 1330 patients in 1 year, and 83 patients (6% of the prescribed patients) actually used an AAI.¹⁰

The present study did not focus on the appropriate usage of AAIs in the event of anaphylaxis. The European Anaphylaxis Registry¹¹ reported that AAIs were used in 12% of patients prior to visiting to an ED with anaphylaxis, whereas AAIs were not used in 14% of cases despite having been prescribed an AAI. Recently, a shocking report published from a representative pediatric ED in Japan, noted that no patients were administered an AAI before arrival at the ED among the 217 patients who were treated at that location for anaphylaxis from 2011 to 2014.¹²

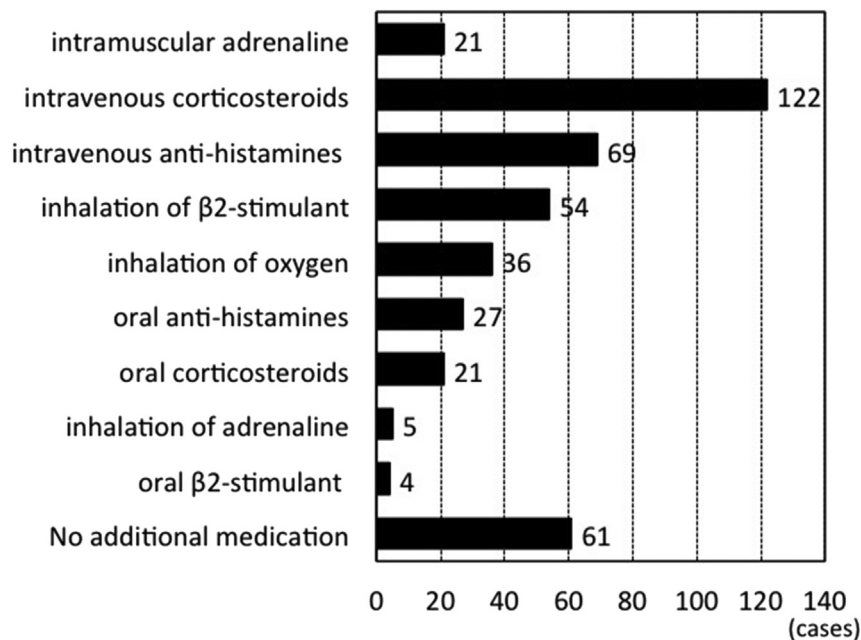


Fig. 4. Additional treatments at the hospital.

Although we did not exclude cases involving insect or drug allergies, with the exception of 7 cases of idiopathic anaphylaxis, all of the collected cases were caused by food allergies. This age-related trend was consistent with a report from the European Anaphylaxis Registry,¹¹ which noted that food allergy accounted for 88% of the anaphylaxis cases in preschool (<6 years) children, and 57% of children of 6–12 years of age. It is also true that most cases of anaphylaxis caused by drug¹³ and insect stings¹⁴ occurred in adulthood.

Cow's milk was the causative food in >40% of the cases. This frequency differed from that reported by the European Registry,¹¹ which reported that peanut was the most common causative food, followed by cow's milk and hen's egg. A nationwide survey¹⁵ showed that hen's egg (39%) was the most frequent causative food of immediate-type allergic reactions in Japan; this was followed by cow's milk (21.8%). The reason for this difference might be that cow's milk provokes respiratory symptoms more frequently and

rapidly¹⁶ than hen's egg; thus, patients with cow's milk allergies tend to decide to use AAI more frequently.

The primary trigger of the event was most often a physician-oriented programmed intake of the allergenic food, including oral immunotherapies.¹⁷ A meta-analysis of oral immunotherapy revealed that it was associated with an increased risk of systemic reactions in comparison to controls under complete elimination; thus, the risk of oral immunotherapy cannot be over-emphasized.¹⁸ The present data might be somewhat biased, as most of the participating doctors were allergy specialists who were involved in oral immunotherapies.¹⁹ As such, more investigations into safer procedure is needed. Failure to check food label²⁰ and eating an inappropriate food were also associated with the accidental intake. Importantly, anaphylaxis may occur after arrival at a school or nursery following the intake of an allergenic food at home in the morning.

The time course from the causative intake to the use of the AAI was relatively slow compared with that caused by insect venom.⁵ Although AAI should be used within 30 min in cases of severe anaphylaxis,²¹ AAI were used later than 30 min after the recognition of the initial symptom in 102 cases. In most cases, mild cutaneous or respiratory symptoms were observed at first and then lapsed slowly. In such situations, the caregivers have time to prepare the AAI and call an ambulance first, as according to the official database of the Fire and Disaster Management Agency, the average time until the arrival of an ambulance in Japan was 8.6 min in 2016. However, AAI should be used immediately when any of the symptoms proposed by the JSPACI are observed (Table 1).

AAI were administered by school or nursery staff members in more than half of the events that occurred at schools or nurseries. Even among patients of junior high school age or older, AAI were administered by caregivers in more than 50% of cases. Self-injection is difficult, even for adolescent patients,²² especially when they are in an emergent situation. Special training²² or a specially designed AAI device²³ may improve the usage ability; however, the usage of AAI by bystanders should always be allowed, even for adolescent and adult patients.

There were no cases in which an AAI was used to treat a patient to whom an AAI had not been prescribed, which is not legally

Anaphylaxis grade on hospital arrival	5	-	-	-	-	-	-
	4	-	-	1	2	46	1
	3	-	-	1	16	17	-
	2	-	-	6	21	43	1
	1	-	2	7	16	37	1
	0	-	3	6	8	21	-
		0	1	2	3	4	5
Anaphylaxis grade at the administration of the AAI							

Fig. 5. Change in the grade of anaphylaxis. The grade of anaphylaxis symptoms³ before the use of the AAI and on hospital arrival was judged by the attending physician in the 256 cases. The gray columns indicate the number of cases in which the grade was unchanged on hospital arrival.

allowed in Japan. Unassigned AAI is available for children who have a first-time anaphylactic reaction in public schools in Chicago, IL, USA²¹; however, this system seems to be associated with some problems.²⁴ The major issue is that many school nurses are responsible for multiple schools. The second is the limited situations in which an unassigned AAI could be administered. However, despite these issues, 38 AAIs were administered during the 2012–2013 inaugural year, and 55.0% of them were administered for first-time anaphylactic events.²⁵

The 13 symptoms for which the JSPACI recommends the use of an AAI seem to be appropriate. This recommendation does not require two symptoms to determine that anaphylaxis has occurred; only one is sufficient.¹ Furthermore, it does not include “skin” symptoms, as these are observed in more than 90% of patients with anaphylaxis,¹⁵ and skin symptoms are not an inherent indication for adrenaline injection. Respiratory symptoms were the most frequent reason for deciding to use an AAI, while “confusion” and “hardly palpable pulse”, both suggestive of anaphylaxis shock, were rarely recognized. The judgment of the general condition might be difficult without objective markers, such as blood pressure or SpO₂.

The outcome of AAI usage resulted in an improvement of the symptoms in almost 70% of the cases, with 23% of cases requiring no additional treatment. However, grade 4 symptoms remained on hospital arrival in 20% of cases, and additional intramuscular adrenaline was administered in 8% of cases. This confirms the need to visit an ED immediately after the use of an AAI, because the effect of the AAI may be transient, and a prolonged or late reaction²⁶ might occur even after the initial symptoms disappear. We identified 2 cases that took 45 min to arrive at the hospital after the use of AAI and required a second adrenaline injection at the hospital. Those events occurred at a festival and in a hotel, suggesting the need to have a second AAI close at hand in situations where emergency medical services are not sufficient.

The present study revealed the actual situations in which AAIs were administered to children in Japan. AAIs were used safely and appropriately in most cases, and school teachers were able to manage students promptly. Physicians who prescribe AAIs should recognize these situations and encourage caregivers to use them appropriately.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.07.002>.

Conflict of interest

ME received honorarium from DBV Technologies and Pfizer. The rest of the authors have no conflict of interest.

Authors' contributions

KI planned the study design and was responsible for finalizing the manuscript. MO equally contributed to writing the draft of the manuscript. NK, TM, TN and SS contributed to the data collection, reviewing reports and the statistical analysis. ME supervised the study as the chief of the working group.

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