



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Original Article

Epinephrine autoinjector prescription patterns for severe anaphylactic patients in Japan: A retrospective analysis of health insurance claims data

Mikio Nakajima^{a, b, c, *}, Sachiko Ono^d, Nobuaki Michihata^e, Richard H. Kaszynski^a, Hiroki Matsui^b, Yoshihiro Yamaguchi^c, Hideo Yasunaga^b^a Emergency and Critical Care Center, Tokyo Metropolitan Hiroo Hospital, Tokyo, Japan^b Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan^c Department of Trauma and Critical Care Medicine, Kyorin University School of Medicine, Tokyo, Japan^d Department of Biostatistics & Bioinformatics, The University of Tokyo, Tokyo, Japan^e Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

ARTICLE INFO

Article history:

Received 24 November 2019

Received in revised form

6 February 2020

Accepted 29 February 2020

Available online xxx

Keywords:

Anaphylaxis

Epinephrine autoinjector

Refill

Self-inject epinephrine

Self-treatment

Abbreviations:

EAI epinephrine autoinjector
 ICD-10 the International Classification of Diseases, Tenth Revision
 IQR interquartile range

ABSTRACT

Background: Current guidelines recommend that any patient who has experienced anaphylaxis should be prescribed one or more epinephrine autoinjectors (EAI) for immediate self-treatment. However, the etiology of anaphylaxis and prescription patterns of EAI have not been widely examined in Japan.

Methods: This was a retrospective cohort study using a large Japanese claims database (JMDC, Tokyo, Japan). We included patients with severe anaphylaxis who received epinephrine in a hospital or outpatient clinic from 2011 to 2016. We extracted patients who were prescribed EAI and examined the annual trend of EAI prescription rates and refill patterns.

Results: We identified 1255 eligible patients. Among them, 361 patients (28.8%) were prescribed EAI within 30 days after their initial severe anaphylactic episode. In patients who were prescribed EAI, 65.9% were prescribed EAI from the same facility in which initial treatment was given for severe anaphylaxis. The prescription rates of EAI significantly increased from 11.1% in 2011 to 30.9% in 2016. Among patients with initial EAI prescriptions, 97.3% refilled their EAI prescriptions at least once and 40.5% refilled their prescriptions annually during the 3 year follow up period.

Conclusions: EAI prescription rates were relatively low in patients who experienced severe anaphylaxis in Japan. Physicians should prescribe EAI to all patients who were treated for anaphylaxis under their care and avoid delegating the responsibility of prescribing EAI to other facilities. Initial prescription of EAI can result in improved regular refill and dissemination practices.

Copyright © 2020, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Anaphylaxis, a relatively common encounter in the realm of emergency medicine, is a potentially life-threatening systemic reaction affecting up to 2% of the population.¹ Epinephrine (also known as adrenaline) is the cornerstone of emergency treatment for anaphylaxis; however, failure to inject epinephrine in a timely manner significantly hinders its effectiveness and may result in impaired clinical outcomes.^{2,3}

An epinephrine autoinjector (EAI) is recommended as the primary treatment in patients with anaphylaxis under the conditions of self-treatment.^{2–4} Current guidelines recommend that any patient who has experienced anaphylaxis should be prescribed one or more EAI.^{3,5} However, previous studies have demonstrated the existence of a number of barriers limiting the proper dissemination of EAI such as: low prescription rates^{3,4,6} (patients never having been prescribed EAI regardless of past severe anaphylactic episode); high costs (patients could not afford to purchase EAI); limited shelf life of 12 months (EAI was expired at the time of anaphylaxis onset); and number of doses to dispense^{7,8} (current guidelines recommend that patients at risk of anaphylaxis maintain two EAI on-hand at all times^{3,5}).

* Corresponding author. Emergency and Critical Care Center, Tokyo Metropolitan Hiroo Hospital, 2–34–10, Ebisu, Shibuya-ku, Tokyo, 150-0013, Japan.

E-mail address: mikioh@ks.kyorin-u.ac.jp (M. Nakajima).

Peer review under responsibility of Japanese Society of Allergology.

<https://doi.org/10.1016/j.alit.2020.02.008>

1323–8930/Copyright © 2020, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Although the prescription of EAls is of life-dependent importance to patients and physicians, the etiology of EAI prescription patterns have not been examined in Japan at the broad-scale level. The aim of the present study was to elucidate EAI prescription patterns in Japan using a widely utilized public health insurance database.

Methods

Data source

We conducted a retrospective cohort study using the JMDC database (JMDC Inc., Tokyo, Japan),⁹ which has been described in detail in previous reports.^{10–13} The database collects data from more than 60 insurers with approximately 5.6 million individuals registered in 2018.⁹ Most of the enrollees are employees of Japanese companies and their family members. More than 95% of the cohort were under the age of 65 in 2013.⁹ The JMDC database includes information on administrative claims data (inpatient/outpatient/pharmacy) and annual health screenings. The database also includes the following data for each patient: age; sex; dates of hospital or clinic visit; diagnoses recorded under the International Classification of Diseases, Tenth Revision (ICD-10) codes; prescription of drugs categorized according to the World Health Organization Anatomical Therapeutic Chemical classification system.

Ethics

The study was approved by the Institutional Review Board at The University of Tokyo (approval number, 10862–1). Due to the anonymous nature of the data, the requirement for informed consent was waived.

Patient selection

We retrospectively extracted data for patients with a history of severe anaphylaxis between September 2011 and December 2016 (EAI was made available under coverage of the Japanese National Health Insurance system from August 2011 in Japan). Diagnosis of anaphylaxis was defined as ICD-10 codes: T780 (diagnosis of anaphylactic reaction or shock due to adverse food reaction), and T782 (anaphylactic shock, unspecified). We enrolled patients with severe anaphylaxis defined as patients who were administered epinephrine at a hospital or outpatient clinic with the above diagnosis.

Code T886 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered) and T805 (anaphylactic shock due to serum, i.e., blood transfusion) are generally applied in cases of anaphylactic shock resulting from interventions occurring during hospitalization and therefore patients falling under these classifications were excluded from the study. When a patient develops anaphylaxis in response to contrast media, transfusion or drugs during hospitalization, the patient will receive epinephrine in the hospital; however, patients with T886 and T805 are not optimal candidates for EAI prescription as they will not routinely encounter exposure to contrast media and transfusions outside of the hospital setting. Patients who had undergone cardiac resuscitation (ICD-10 code, I46) with epinephrine were also excluded because post-cardiac arrest patients have been administered epinephrine during emergency resuscitation and therefore are generally not prescribed EAls. Patients aged 3 and under were also excluded from the study because EAls of 0.15 mg cannot be prescribed in patients whose body weight is less than 15 kg.

Exclusion criteria should be based on weight and not age. Unfortunately, because the database fails to reflect body weight, we resorted to the adoption of an age-based cut off of age 3 because the median weight of Japanese children at the age of 3 is 15 kg.

Patient characteristics

Among the patients described above, we extracted patients who were prescribed EAls (EpiPen^R 0.15 mg or 0.3 mg, Mylan EPD, Tokyo, Japan) within 30 days after their initial severe anaphylactic episode. Individual characteristics were documented for each patient regardless of whether or not the patient was prescribed an EAI. The characteristics included the following variables: age; sex; diagnosis (ICD-10 code, T780 or T-782); type of hospital in which the patient was administered epinephrine for severe anaphylaxis (outpatient clinic, non-acute care hospital, acute care hospital or academic hospital); type of facility prescribing EAI (i.e. was the patient prescribed EAI from the same facility in which the initial treatment was administered for severe anaphylaxis or a separate facility).

Trend of EAI prescription

After tallying the numbers of severe anaphylactic patients on an annual basis, the prescription rate of EAls (prevalence of EAI prescription) within a 30-day period from the initial onset of anaphylaxis was calculated.

EAI refill patterns

Among patients who were prescribed EAls, we identified patients who refilled the EAI prescription at least once after their initial prescription. We compared the characteristics of those patients who did or did not refill EAI prescriptions. Refill opportunities (patterns) were defined in brackets of 12 months after the initial dispensing of the EAI: ≤ 12 months, 13–24 months, or 25–36 months after initial EAI dispensing. In addition, we describe EAI prescription patterns in patients without an initial EAI prescription. We limited our analysis to patients who experienced severe anaphylaxis prior to December 2013 due to the required minimum follow-up period of 3 years (36 months) to observe refill patterns.

We tallied the total number of EAls that were prescribed during the defined observational periods of each individual. Next, we calculated the number of devices prescribed divided by the length of each observational period (annual basis, EAls/year) and defined this as our “annual prescription index.” A zero means no refill history, 0–1 means at least one history of refill and ≥ 1 indicates annual refilling. A histogram reflecting the annual prescription index was generated.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), and categorical variables were reported as number and percentage. Continuous variables were compared between the groups via the Wilcoxon rank-sum test, and categorical variables were compared by the chi-square test. To assess annual trends during the study period, we used the Cochran–Armitage test for proportions. Two-sided *p*-values of <0.05 were considered significant. All analyses were performed using Stata MP15 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

We identified 1255 patients within the target period after applying the inclusion and exclusion criteria. Of these patients, 361 (28.8%) were prescribed EAI within 30 days after their initial severe anaphylactic episode. The characteristics of patients with severe anaphylaxis are shown in Table 1. The patients who were prescribed EAI were significantly younger than those who were not. In the patients who were prescribed EAI, 238 patients (65.9%) were prescribed EAI from the same facility in which the initial treatment was administered for severe anaphylaxis.

Trend of EAI prescription

After EAI were approved under the Japanese universal healthcare coverage system in August 2011, the prescription rate of EAI significantly increased from 11.1% in 2011 to 30.9%, 31.9%, 30.9% in 2014, 2015 and 2016, respectively (p for trend 0.003) (Fig. 1). The sum total of the proportion of patients being prescribed EAI spanning the entire data spectrum (2011–2016) was 28.8%.

EAI refill patterns

Among patients who were prescribed EAI, 200 patients (55.4%) refilled their EAI prescriptions at least once after their initial prescription. Table 2 shows the characteristics of those patients who did or did not refill EAI prescriptions. Younger patients were more likely to refill EAI prescriptions.

Table 3 shows EAI refill patterns for severe anaphylactic patients in the cohort for ≥ 3 years. In patients with an initial EAI prescription, 40.5% refilled their prescriptions annually. Over 97% of patients refilled EAI prescriptions at least once within the 3 year follow up period. In patients without an initial EAI prescription, 16.5% were prescribed EAI after 30 days of the initial anaphylactic episode.

Table 1

Characteristics of patients with severe anaphylaxis regardless of whether or not the patient was prescribed an epinephrine autoinjector.

Variables	Initial EAI prescription [†]		P-value	
	No (n = 894)	Yes (n = 361)		
Age, years, median (IQR)	30 (12, 46)	13 (7, 37)	<0.001	
Age category, years			<0.001	
4–6	121 (13.5)	84 (23.3)		
7–12	105 (11.7)	79 (21.9)		
13–18	82 (9.2)	67 (18.6)		
19–	586 (65.5)	131 (36.3)		
Male	497 (55.6)	217 (60.1)	0.14	
Hospital category (initial anaphylactic episode)			0.007	
Outpatient clinic	223 (24.9)	61 (16.9)		
Non-acute care hospital	56 (6.3)	34 (9.4)		
Acute care hospital	553 (61.9)	242 (67.0)		
Academic hospital	62 (6.9)	24 (6.6)		
Hospital category (initial EAI prescription)				
Outpatient clinic		83 (23.0)		
Non-acute care hospital		43 (11.9)		
Acute care hospital		204 (56.5)		
Academic hospital		31 (8.6)		
EAI prescription from same facility [‡]		238 (65.9)		

EAI, epinephrine auto-injector; IQR, interquartile range.

Data are shown as n (%) otherwise specified.

[†] EAI prescription within 30 days of the initial severe anaphylactic episode.

[‡] EAI prescription from the same facility in which the initial treatment was administered for severe anaphylaxis or a separate facility.

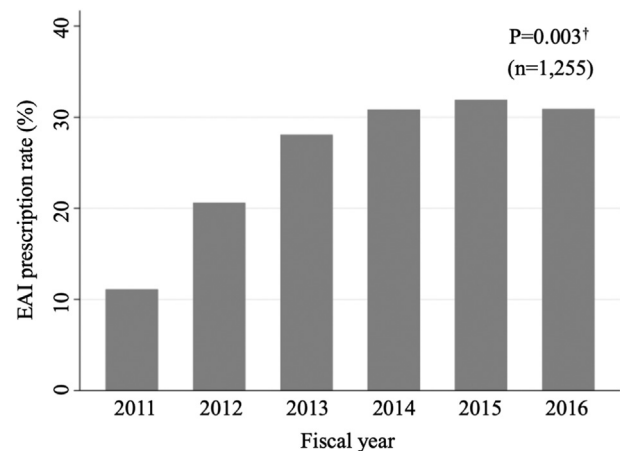


Fig. 1. Annual prescription rate of epinephrine autoinjector in patients with severe anaphylaxis. [†]Cochrane–Armitage trend test. EAI, epinephrine autoinjector.

Table 2

Characteristics of patients who were prescribed initial epinephrine autoinjectors.

Variables	Never refilled EAI (n = 161)		Refilled EAI at least once (n = 200)		p-value
Age, years, median (IQR)	24	(12, 47)	10	(6, 16)	<0.001
Age category, years					<0.001
4–6	26	(16.1)	58	(29.0)	
7–12	19	(11.8)	60	(30.0)	
13–18	25	(15.5)	42	(21.0)	
19–	91	(56.5)	40	(20.0)	
Male	98	(60.9)	119	(59.5)	0.79
Hospital category (initial anaphylactic episode)					0.84
Outpatient clinic	25	(15.5)	36	(18.0)	
Non-acute care hospital	14	(8.7)	20	(10.0)	
Acute care hospital	110	(68.3)	132	(66.0)	
Academic hospital	12	(7.5)	12	(6.0)	
Hospital category (initial EAI prescription)					0.63
Outpatient Clinic	38	(23.6)	45	(22.5)	
Non-acute care hospital	16	(9.9)	27	(13.5)	
Acute care hospital	95	(59.0)	109	(54.5)	
Academic hospital	12	(7.5)	19	(9.5)	

EAI, epinephrine auto-injector; IQR, interquartile range.

Data are shown as n(%) otherwise specified.

Figure 2 shows the distribution of the annual prescription index. The median was 0.83 EAI/year (IQR, 0.60–1.17). In 5 patients, the annual prescription index was ≥ 2 EAI/year.

Discussion

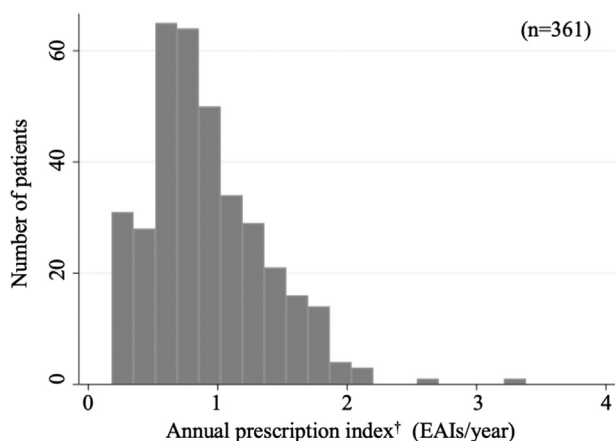
Approximately 30% of patients experiencing severe anaphylactic episode were prescribed EAI in the present study. One-third of these patients were prescribed EAI from the same facility in which initial treatment was administered for severe anaphylaxis. Among patients who were initially prescribed EAI, over half refilled their EAI prescriptions at least once. Forty percent of patients refilled their prescriptions on an annual basis. The median annual prescription index was less than one.

Although a trend analysis revealed a significant increase in the prescription rate of EAI on an annual basis, the prescription rate plateaued after 2014. An important finding to note is that even in patients who have experienced a severe anaphylactic episode necessitating an epinephrine injection, merely 30% of which were prescribed EAI within 30 days after their initial anaphylactic episode. International EAI prescription rates vary among studies:

Table 3
Initial prescription and refill patterns for epinephrine autoinjector in the cohort for ≥ 3 years.

In patients with initial EAI prescription (n = 74)					
Initial EA prescription	EAI refill opportunity (months)			n	(%)
	≤ 12	12–23	24–36		
YES	NO	NO	NO	2	(2.7)
YES	NO	NO	YES	0	(0.0)
YES	NO	YES	YES	0	(0.0)
YES	NO	YES	NO	0	(0.0)
YES	YES	NO	NO	14	(18.9)
YES	YES	NO	YES	10	(13.5)
YES	YES	YES	NO	18	(24.3)
YES	YES	YES	YES	30	(40.5)
In patients without initial EAI prescription (n = 243)					
Initial EA prescription	EAI prescription and refill opportunity (months)			n	(%)
	≤ 12	12–23	24–36		
NO	NO	NO	NO	203	(83.5)
NO	NO	NO	YES	7	(2.9)
NO	NO	YES	YES	7	(2.9)
NO	NO	YES	NO	3	(1.2)
NO	YES	NO	NO	4	(1.6)
NO	YES	NO	YES	1	(0.4)
NO	YES	YES	NO	5	(2.1)
NO	YES	YES	YES	13	(5.3)

EAI, epinephrine auto-injector.

**Fig. 2.** Histogram of the annual prescription index in severe anaphylactic patients. [†]The total number of EAI divided by the length of each observational period (per year basis). EAI, epinephrine autoinjector.

11%,¹⁴ 16%,¹⁵ 37%¹⁶ and 61%.¹⁷ Considering the international EAI prescription rates, the 30% achieved in Japan may appear deceptively average or nominal.

The Japanese healthcare system conveys a number of strategic advantages to patients which can be summed up in three parts. First, EAI is relatively affordable in terms of price (EpiPen® 0.3 mg in Japan, \$98 US dollars [\$1USD = 108JPY]). Second, the universal healthcare coverage system in Japan only requires patients to pay 10–30% of their medical fees (including medication) and therefore the actual cost of an EAI for the patient is comparably low. Third, most local government administrations offer a specialized subsidy system for children and therefore pediatric patients can often be prescribed EAI at zero or minimal cost. Thus, socio-economic barriers are negligible with respect to EAI prescriptions

in Japan. Nevertheless, even after a documented improvement from 11.1% in 2011, the EAI prescription rate remains at a minimally satisfactory 30%.

Among patients who were prescribed EAI within 30 days after their initial severe anaphylactic episode, two-thirds were prescribed EAI from the same medical facility in which the initial treatment was administered. These results underscore an advantageous prescription rate for patients who have been prescribed EAI by the same physician treating the initial anaphylactic episode. This is most likely attributed to the convenience of having an EAI prescription upon discharge. In contrast, the need for a follow-up visit to one's primary care physician or a different healthcare facility merely for the sake of obtaining an EAI would result in lower prescription rates.

In addition, there are some other plausible reasons for the low prescription rate of EAI in Japan. First, the limited shelf life of EAI is an existential barrier when considering the prescription of an EAI. When anaphylactic patients are hospitalized, EAI is generally prescribed at discharge. As a general practice, prescription medications provided to patients at the time of discharge are prepared from internal hospital pharmacies. Because of the limited shelf life and relative rarity of EAI prescriptions, the vast majority of hospitals in Japan do not routinely stock EAI. Therefore, a significant portion of patients cannot be provided EAI at discharge. Second, only physicians licensed by the manufacturer can prescribe EAI in Japan and therefore only a small number of emergency care physicians might have this authority. Third, the physician who treats the anaphylactic episode may adopt an optimistic outlook and assume that the chances of the patient ever experiencing the next severe anaphylactic episode necessitating epinephrine is low and fails to prescribe an EAI. Fourth, the cultural differences between pediatricians and internists may also contribute to the low prescription rate of EAI. Anaphylaxis is more common in children than adults. Therefore, pediatricians are more experienced with EAI prescriptions. On the other hand, internists (not including allergists) may experience more reluctance when prescribing EAI due to their lack of experience with the device. Finally, the shortage of allergists might also effect the low prescription rate of EAI in Japan.

The EAI refill patterns revealed in the present study show that among patients who were prescribed EAI on at least one occasion, less than half refilled their prescriptions annually but the majority of patients refilled their prescriptions at least once during the subsequent 3 year period. In an observational study conducted in the US, 46% of the patients refilled their prescriptions at least once and only 11% refilled consistently at all expected refill intervals during the subsequent 5 year period.¹⁸ Japanese patients may display a higher adherence to refills once they are prescribed EAI. Additionally, among patients who were not prescribed EAI following an initial anaphylactic episode, approximately 17% eventually received an EAI prescription out of necessity within 3 years of initial onset. These results suggest that the initial prescription of EAI is crucial in proper dissemination of EAI.

Although current guidelines recommend that patients at risk of anaphylaxis maintain two EAI on-hand at all times,^{3,5} virtually no patients presented with an annual prescription index ≥ 2 (EAI/year). The implication here is that only a small fraction of patients had over two EAI available at any given timeframe. A recent report revealed that 16–36% of anaphylactic patients required a second dose of epinephrine during an anaphylactic episode.¹⁹ Therefore, physicians should refrain from assuming a false sense of security by prescribing a single EAI.

The present study has several limitations. First, we may have underestimated the number of actual anaphylactic episodes. In the

present study, we detected the number of anaphylactic episodes using ICD-10 codes but because the diagnosis in the claims database is not well-validated, we adopted the combination of therapeutic management of epinephrine use in the outpatient clinic or hospital to refine our search. Previous observational studies have shown that 16–64% of anaphylactic patients received epinephrine in emergency departments.^{17,20–22} Patients were often treated with second-line therapies, including antihistamines and steroids.⁷ Anaphylactic patients who were treated using antihistamines or steroids were not included in this study. However, even among patients who were administered epinephrine, the prescription rate of EAls was low. Second, the data we retrieved did not contain the causes of the anaphylaxis. Although bee stings are the most common causes of anaphylaxis in Japan, we could not identify any specific details in the ICD-10 based diagnosis. Third, the details in which the EAI prescriptions were refilled are unknown. We assumed that the EAI prescriptions following the initial prescription was simply a refill; however, the second prescription may have been issued as a result of another anaphylactic episode. Due to the limited information available on the database, we were unable to distinguish whether the EAI was prescribed due to another anaphylactic episode or it was simply a regular refill in response to an approaching expiration date. Fourth, because this study was based on the universal healthcare coverage system in Japan, the findings may not be applicable to other countries adopting different health care provision strategies.

Conclusions

The prescription rate for EAls was relatively low in patients with severe anaphylaxis in Japan. Primary and emergency care physicians should endeavor to prescribe EAls to all patients who have experienced an anaphylactic episode under their care and avoid delegating the responsibility of prescribing EAls to other facilities. This is a critical issue to note as initial prescription of EAls resulted in improved regular refill practices.

Acknowledgements

This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan (19AA2007) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (17H04141 and 17H05077).

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

MN designed this study. MN, SO, NM and HY performed the statistical analysis. MN, RHK, SO NM and HY edited the manuscript. YY provided professional suggestions in the conduct of the study and interpretation of study results. HM and HY contributed to data collection and management. All authors participated in revision of the manuscript and approved the final manuscript.

References

- Lieberman P, Camargo CA, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of allergy, asthma and immunology epidemiology of anaphylaxis working group. *Ann Allergy Asthma Immunol* 2006;**97**:596–602.
- Simons FER, Arduoso LRF, Bil MB, El-Gamal YM, Ledford DK, Ring J, et al. Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;**127**:587–93. e1–22.
- Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: world Allergy Organization anaphylaxis guidelines. *World Allergy Organ J* 2015;**8**:32.
- Simons FER. Epinephrine auto-injectors: first-aid treatment still out of reach for many at risk of anaphylaxis in the community. *Ann Allergy Asthma Immunol* 2009;**102**:403–9.
- Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol* 2015;**115**:341–84.
- Waserman S, Avilla E, Ben-Shoshan M, Rosenfield L, Adcock AB, Greenhawt M. Epinephrine autoinjectors: new data, new problems. *J Allergy Clin Immunol Pract* 2017;**5**:1180–91.
- Fromer L. Prevention of anaphylaxis: the role of the epinephrine auto-injector. *Am J Med* 2016;**129**:1244–50.
- Järvinen KM, Sicherer SH, Sampson HA, Nowak-Węgrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 2008;**122**:133–8.
- JMDC Inc. Available from: <https://www.jmdc.co.jp>. [Accessed 9 November 2019].
- Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. *J Epidemiol* 2010;**20**:413–9.
- Ono S, Ono Y, Koide D, Yasunaga H. Association between routine nephropathy monitoring and subsequent change in estimated glomerular filtration rate in patients with diabetes mellitus: a Japanese non-elderly cohort study. *J Epidemiol* 2019. <https://doi.org/10.2188/jea.JE20180255> [Epub ahead of print].
- Okubo Y, Michihata N, Morisaki N, Kinoshita N, Miyairi I, Urayama KY, et al. Recent patterns in antibiotic use for children with group A streptococcal infections in Japan. *J Glob Antimicrob Resist* 2018;**13**:55–9.
- Ohishi M, Yoshida T, Oh A, Hiroi S, Takeshima T, Otsuka Y, et al. Analysis of antihypertensive treatment using real-world Japanese data—the retrospective study of antihypertensives for lowering blood pressure (REAL) study. *Hypertens Res* 2019;**42**:1057–67.
- Civelek E, Erkoçoğlu M, Akan A, Özcan C, Kaya A, Vezir E, et al. The etiology and clinical features of anaphylaxis in a developing country: nationwide survey. *Asian Pac J Allergy Immunol* 2017;**35**:212–9.
- Pourang D, Batech M, Sheikh J, Samant S, Kaplan M. Anaphylaxis in a health maintenance organization: international Classification of Diseases coding and epinephrine auto-injector prescribing. *Ann Allergy Asthma Immunol* 2017;**118**:186–90. e1.
- Saleh-Langenberg J, Dubois AEJ, Groenhouf F, Kocks JWH, van der Molen T, Flokstra-de Blok BMJ. Epinephrine auto-injector prescriptions to food-allergic patients in primary care in The Netherlands. *Allergy, Asthma. Clin Immunol* 2015;**11**:28.
- Sidhu N, Jones S, Perry T, Thompson T, Storm E, Melguizo Castro MS, et al. Evaluation of anaphylaxis management in a pediatric emergency department. *Pediatr Emerg Care* 2016;**32**:508–13.
- Kaplan MS, Jung SY, Chiang ML. Epinephrine autoinjector refill history in an HMO. *Curr Allergy Asthma Rep* 2011;**11**:65–70.
- Song TT, Lieberman P. Who needs to carry an epinephrine autoinjector? *Cleve Clin J Med* 2019;**86**:66–72.
- Hitti EA, Zaitoun F, Harmouche E, Saliba M, Mufarrij A. Acute allergic reactions in the emergency department: characteristics and management practices. *Eur J Emerg Med* 2015;**22**:253–9.
- Kawano T, Scheuermeyer FX, Stenstrom R, Rowe BH, Grafstein E, Grunau B. Epinephrine use in older patients with anaphylaxis: clinical outcomes and cardiovascular complications. *Resuscitation* 2017;**112**:53–8.
- Kimchi N, Clarke A, Moisan J, Lachaine C, La Vieille S, Asai Y, et al. Anaphylaxis cases presenting to primary care paramedics in Quebec. *Immun Inflamm Dis* 2015;**3**:406–10.