



Anaphylaxis in a health maintenance organization: *International Classification of Diseases* coding and epinephrine auto-injector prescribing

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ABSTRACT

Background: Accurate estimates of the incidence of anaphylaxis are limited. Current *International Classification of Diseases, Ninth Revision (ICD-9)* codes complicate accurate diagnosis of anaphylaxis and assessment of appropriate epinephrine prescribing.

Objective: To quantify the incidence and demographic character of patients with anaphylaxis-related ICD-9 codes in a large health maintenance organization and analyze epinephrine prescribing and dispensing rates. **Methods:** All patients included had at least 12 months of continuous membership over a 4-year period from January 1, 2008 to December 31, 2012 and were selected based on anaphylaxis-related ICD-9 codes (N = 159,172). This algorithm was extrapolated from a previous study that used expanded ICD-9 codes to identify more cases of anaphylaxis. Individual chart reviews found that many expanded ICD-9 codes represented unconfirmed cases of anaphylaxis and therefore were excluded, resulting in analysis of 52,405 patients.

Results: Incidence of anaphylaxis over 4 years was 2.07%, with female predominance (56.5%) over male predominance (43.5%). Epinephrine was prescribed in 16.2% of total cases. Highest rates of epinephrine prescription were for traditional ICD-9 codes 995.0 (other anaphylactic shock) and 995.60 to 995.69 (anaphylactic shock caused by food) at 49.3% and 58.6%, respectively. Of the cases in which an epinephrine auto-injector was prescribed, it was dispensed 95.9% of the time, independent of copayment amount.

Conclusion: Low epinephrine auto-injector prescribing rates in cases of anaphylaxis suggest the continued difficulty in the diagnosis of anaphylaxis and could result in suboptimal treatment of potential future episodes.

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Introduction

Although there is no universal agreement on the definition of anaphylaxis, it is a serious allergic reaction that is rapid in onset and can cause death.¹ Few studies have examined the true incidence of anaphylaxis in a large population. A recent cross-sectional

telephone survey study estimated that the prevalence of anaphylaxis is at least 1.6% of the general population.² The 3 most common reported triggers were medications, foods, and insect stings. However, existing data are not directly comparable because of lack of standardization for diagnosis of anaphylaxis.^{3–5} Thus, it remains controversial whether the incidence is actually increasing, stable, or decreasing. In addition, several factors affect hospital admission for anaphylaxis. One study observed that hospital admission rates for patients presenting with anaphylaxis tend to increase when more organ systems are involved.⁶

Epinephrine is the treatment of choice for anaphylaxis.⁷ Studies have suggested that there are obstacles to prescribing self-injectable epinephrine^{8,9} and that the prescription of epinephrine is infrequently performed in the emergency department setting.^{10–12} Simons et al¹³ surveyed survivors of anaphylaxis. They found that 27% used epinephrine during an episode vs 73% who

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Table 1

Study Population Characteristics by Anaphylaxis Diagnosis Status, Kaiser Permanente Southern California, 2008 Through 2012

	No anaphylaxis (n = 2,479,158; 97.9%)	Anaphylaxis (n = 52,405; 2.1%)	Total (N = 2,531,563)	P value	Standardized difference ^a
Length of membership					
Months, mean (SD)	120.8 (116.46)	128.0 (121.30)	121.0 (116.56)	<.01	0.06
1–<2 y, n (%)	362,859 (14.6)	6,870 (13.1)	369,729 (14.6)		
2–<4 y, n (%)	458,246 (18.5)	9,435 (18)	467,681 (18.5)		
≥4 y, n (%)	1,658,053 (66.9)	36,100 (68.9)	1,694,153 (66.9)		
Age at index date (y) ^b					
Mean (SD)	38.7 (22.21)	36.5 (23.64)	38.7 (22.24)	<.01	–0.16
<18 y, n (%)	604,363 (24.4)	16,508 (31.5)	620,871 (24.5)		
≥18 y, n (%)	1,874,761 (75.6)	35,897 (68.5)	1,910,658 (75.5)		
Sex, n (%)					
Female	1,307,289 (52.7)	29,614 (56.5)	1,336,903 (52.8)	<.01	0.08
Male	1,171,869 (47.3)	22,791 (43.5)	1,194,660 (47.2)		
Race, ethnicity, n (%)					
White, non-Hispanic	864,015 (34.9)	19,999 (38.2)	884,014 (34.9)	<.01	0.19
Black, non-Hispanic	243,997 (9.8)	6,511 (12.4)	250,508 (9.9)		
Hispanic	877,620 (35.4)	18,276 (34.9)	895,896 (35.4)		
Asian, non-Hispanic	213,808 (8.6)	4,218 (8)	218,026 (8.6)		
Other, non-Hispanic	279,718 (11.3)	3,401 (6.5)	283,119 (11.2)		

^aA standardized difference greater than 0.2 indicates a significant difference in the 2 populations with respect to the characteristic.^bIndex date is date of diagnosis of anaphylaxis. If anaphylaxis was not diagnosed, then the age was the age on January 1, 2008.

were nonusers. The nonusers cited the following major reasons for not using epinephrine at the time of anaphylaxis: use of an H₁ antihistamine, no prescription for epinephrine, and/or a perceived mild anaphylaxis episode. A prospective observational study found that only 29.9% of preschool-age children with anaphylaxis were given epinephrine.¹⁴ Kaplan et al¹⁵ described differences in the percentage of epinephrine prescribed—depending on age, causative agent, specific *International Classification of Diseases, Ninth Revision (ICD-9)* code used, and whether the patient had seen a specialist.

A retrospective study reported that current ICD-9 codes associated with clinical manifestations of anaphylaxis do not capture all individuals with the condition.¹⁰ One study reported a 58% validated increase in the capture of patients with anaphylaxis using an expanded ICD-9 Clinical Modification algorithm for anaphylaxis.¹⁶ Another study emphasized the importance of reviewing a broad range of diagnoses, less specific but still related to anaphylaxis, to define an accurate number of true cases.³ Without a standardized definition for anaphylaxis, in the setting of multiple diagnosis codes, the specific diagnosis and intervention of anaphylaxis is made difficult for clinicians. The purpose of this study was to quantify the accuracy of anaphylaxis-related ICD-9 codes in the Southern California Permanente Medical Group, describe the incidence of anaphylaxis in this population, and to analyze epinephrine prescriptions and usage in this population.

Methods

Study Design

In this retrospective cohort study, we examined the population demographic characteristics and diagnosing patterns in patients with and without anaphylaxis who had at least 12 months of continuous membership in Kaiser Permanente Southern California from January 1, 2008 through December 31, 2012. Of patients diagnosed with anaphylaxis, we also examined prescribing practices for EpiPen auto-injectors within 60 days of diagnosis.

Study Setting and Population

Kaiser Permanente Southern California is a health care system with equal access to resources covering the Southern California region. We considered all age, sex, and race and ethnic groups for this study (Table 1).

Anaphylaxis Case Definition

The traditional ICD-9 codes for anaphylaxis included 995.1 and 995.6 to 995.69. For this study, an algorithm was used to identify any patient with an anaphylaxis-related ICD-9 code. The algorithm used was modified by an algorithm used by Harduar-Morano et al¹⁶ (method II), which found that an expanded set of ICD-9 codes captured more cases of anaphylaxis than the traditional ICD-9 codes. We did not apply ICD-9 codes for the definition of symptom categories, as they did. In addition, we excluded certain ICD-9 codes that, based on manual chart review, did not support the diagnosis of anaphylaxis; these ICD-9 codes included 995.2 and 995.3.

All other ICD-9 codes were part of our expanded algorithm. Patients with more than 1 episode of anaphylaxis during this period were counted only once. Patients with appropriate ICD-9 codes (Table 2) in the emergency department setting were identified, and the anaphylaxis ICD-9 code was the primary diagnosis.

Table 2ICD-9 Code^a Use Frequency for Patients Diagnosed With Anaphylaxis at Kaiser Permanente Southern California, 2008 Through 2012

ICD-9 code	Description	n (%)
989.5	toxic effect of venom	27,248 (52.0)
995.1	angioneurotic edema not elsewhere classified	18,883 (36.0)
995.0	other anaphylactic reaction	2,121 (4.1)
E905.3	sting of hornets wasps and bees causing poisoning and toxic reactions	1,616 (3.1)
995.60	anaphylactic reaction to unspecified food	590 (1.1)
995.61	anaphylactic reaction to peanuts	590 (1.1)
995.64	anaphylactic reaction to tree nuts and seeds	548 (1.1)
995.62	anaphylactic reaction to crustaceans	202 (0.4)
995.69	anaphylactic reaction to other specified foods	187 (0.4)
995.65	anaphylactic reaction to fish	123 (0.2)
995.67	anaphylactic reaction to milk products	57 (0.1)
995.68	anaphylactic reaction to eggs	56 (0.1)
995.63	anaphylactic reaction to fruits and vegetables	48 (0.1)
E905.5	other venomous arthropods causing poisoning and toxic reactions	46 (0.1)
995.66	anaphylactic reaction to food additives	31 (0.1)
E905.9	poisoning and toxic reactions caused by unspecified animals and plants	30 (0.1)
995.4	shock to anesthesia not elsewhere classified	28 (0.1)
E905.8	poisoning and toxic reactions caused by other specified animals and plants	1 (0.0)

Abbreviation: ICD-9, *International Classification of Diseases, Ninth Revision*.^aICD-9 code 995.2 was excluded from consideration after chart review.

Data Source and Variables

Kaiser Permanente Southern California electronic health records were used to extract all variables for analysis. Specifically, we examined age at the index date, sex, race and ethnicity, total length of membership from index through the earliest date of death, discontinuation of enrollment, or the end of the study period (December 31, 2012). The index date was the date of diagnosis of anaphylaxis or the start of the study period (January 1, 2008) for patients not diagnosed with anaphylaxis. For patients with anaphylaxis, we examined whether epinephrine auto-injectors were ordered and whether the patient actually dispensed the medication order. For patients who dispensed the order, we also examined the copayment amount where available.

Statistical Analysis

Initial comparisons of the population with anaphylaxis with the population without anaphylaxis were performed using χ^2 or Fisher exact test for categorical variables and *t* test or Wilcoxon rank-sum test for continuous variables, where appropriate. Shapiro-Wilk test for normality was used to identify the best measurement of central tendency. Standardized difference scores also were estimated between these 2 groups as the standardized difference independent of sample size,¹⁷ and we used a threshold of 0.2 to indicate significant differences based on this score.

Age- and age/sex-adjusted rates of anaphylaxis diagnosis were estimated by year and across all 5 years combined. The numerator for each rate was the sum of the total number of patients who were diagnosed with anaphylaxis during the study period, and the denominator was the number of patients who were members at any stage in the year, weighted by the length of time they were a member in that year. For example, a female patient in 2010 who was a member for 3 calendar months would contribute 0.25 female-years to the 2010 denominator. Age- and sex-adjusted rates were subsequently directly standardized to the 2000 age and sex distribution of the United States.¹⁸ Use of the US Standard Population in 2000 for age and sex adjustment ensured valid comparison of the rates computed for each of the study years. SEs for the rates were estimated assuming a Poisson distribution. All rates are reported per 100,000 individuals, all tests were 2-sided, and all analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

Study Population and Characteristics

As mentioned earlier, we identified specific ICD-9 codes that required omission from our study. Certain codes were observed to account for the large number of captured cases but with a small percentage of epinephrine auto-injectors prescribed—one of them being ICD-9 code 995.3 (allergy, unspecified, not elsewhere classified). Two hundred randomly selected patients, 50 within each quartile of age and 25 from each sex, with ICD-9 code 995.3 were reviewed to validate the diagnosis of anaphylaxis and to estimate the positive predictive value of ICD-9 code 995.3 to identify true anaphylaxis. Anaphylaxis was more clearly identified based on the definition by Sampson et al¹ in the Symposium on the Definition and Management of Anaphylaxis: Summary Report and referred to in this study as “true anaphylaxis.” Briefly, Sampson et al¹ established that anaphylaxis is highly likely when there is acute onset of illness involving skin and/or mucosal tissue in conjunction with respiratory compromise, decreased blood pressure, end-organ dysfunction, or persistent gastrointestinal symptoms.

Of the 200 charts reviewed, patients meeting the case definition of anaphylaxis were 0 to 5 years old (4 patients, 8%), 6 to 18 years old (6 patients, 12%), 19 to 60 years old (4 patients, 8%), and at least

60 years old (1 patient, 2%). The low positive predictive value of 7.5% (15 cases of true anaphylaxis of the 200 randomly selected charts) suggested that the positive anaphylaxis identified by this ICD-9 code represents largely unconfirmed cases of anaphylaxis and therefore all 995.3 diagnoses were excluded from our analysis.

Harduar-Morano et al¹⁶ also included ICD-9 code 995.2 in their analysis. We reviewed the specific subsets within code 995.2 (eTable 1). In total, 71,784 fell into ICD-9 subsets of codes 995.20 to 995.29. Based on the specific descriptions of these ICD-9 codes (eg, Arthus phenomenon, adverse effect of anesthesia, failed moderate sedation during procedure), these codes were excluded. Ten cases were reviewed from each of the mentioned ICD-9 codes, none of which met the criteria for anaphylaxis.

Of the 2,531,563 members included in our analysis, we identified 52,405 (prevalence 2.07%) with anaphylaxis based on this modified, expanded algorithm using ICD-9 codes (Fig 1). Table 1 presents the demographic and membership length characteristics by anaphylaxis diagnosis status across the study period. There were no significant differences in age, sex, race and ethnicity, or length of membership of patients diagnosed with anaphylaxis vs those who were not.

Anaphylaxis Diagnosing Patterns

The frequency of anaphylaxis diagnosis codes are presented in Table 2. The highest frequency of ICD-9 code use was observed for code 989.5 (decreased blood pressure in conjunction with skin-mucosal involvement and the toxic effect of venom) at 52.0% and code 995.1 (respiratory compromise in conjunction with shock caused by angioneurotic edema) at 36.0%. ICD-9 codes 995.0 (other anaphylactic reaction) and E905.3 (sting of hornets wasps and bees causing poisoning and toxic reactions) constituted another 4.1% and 3.1%, respectively, of all anaphylactic cases identified in our study population. The remaining ICD-9 codes studied accounted for fewer than 10% of all ICD-9 codes observed.

Epinephrine Auto-Injector Prescribing Patterns

Table 3 presents the prescription patterns of patients diagnosed with anaphylaxis. Of all cases of anaphylaxis (52,405) identified, 8,418 (16.1%) were prescribed an epinephrine auto-injector within 60 days of the initial anaphylaxis encounter. For ICD-9 codes 995.0 (other anaphylactic shock) and 995.60 to 995.69 (anaphylactic shock

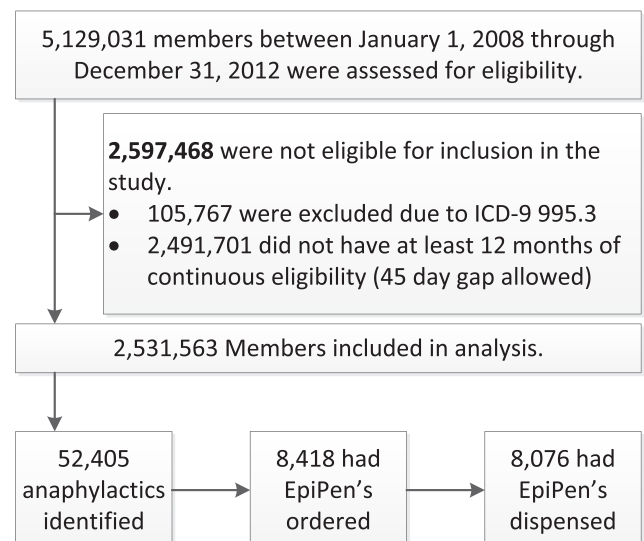


Figure 1. Study population selection flow chart. ICD-9, International Classification of Diseases, Ninth Revision.

Table 3

Study Population Prescribing Patterns in Patients With Anaphylaxis, Kaiser Permanente Southern California, 2008 Through 2012

	Anaphylaxis (n = 52,405)
Had an EpiPen order placed, n (%)	8,418 (16.1)
Patient dispensed EpiPen order, n (%)	8,076 (15.4)
Copayment (US\$)	
Mean (SD)	23.9 (27.53)
0–<10, n (%)	1,941 (24.0)
10–<20, n (%)	1,537 (19.0)
20–<30, n (%)	2,198 (27.2)
≥30, n (%)	2,398 (29.7)

caused by food), epinephrine auto-injectors were prescribed in 49.3% to 58.6% of all cases. For all remaining ICD-9 codes, epinephrine auto-injectors were prescribed in 0% to 16.2% of all cases.

Specifically, the frequency of epinephrine auto-injector ordered per ICD-9 code was 10.2% for code 989.5 (decreased blood pressure in conjunction with skin-mucosal involvement and the toxic effect of venom), 49.3% for code 995.0 (other anaphylactic shock), 16.2% for code 995.1 (respiratory compromise in conjunction with shock caused by angioneurotic edema), 7.1% for code 995.4 (skin-mucosal tissue involvement and respiratory compromise in conjunction with shock caused by anesthesia), 50.4% to 58.6% for codes 995.60 to 995.69 (anaphylactic shock caused by food), and 0% to 9.4% for codes E905.3, E905.5, E905.8, and E905.9 (cause of poisoning was a venomous animal or plant).

Of all epinephrine auto-injectors that were prescribed (8,418), 29.7% were prescribed for patients 0 to 18 years old, 70.3% for those at least 18 years old, 43.1% white patients 11.7% for black patients, 30.2% for Hispanic patients, 8.3% for Asian or Pacific Islander patients, and 6.7% for other or unknown.

Epinephrine Auto-Injector Dispensing

Of the 8,418 cases in which epinephrine auto-injector was prescribed, it was dispensed in 8,076 (95.9%). No significant ICD-9–based differences in dispensing behaviors were observed.

Of the epinephrine auto-injectors that were dispensed (8,076), 29.3% were prescribed for patients 0 to 18 years old, 70.7% for those at least 18 years old, 43.1% white patients, 11.6% for black patients, 30.3% for Hispanic patients, 8.4% for Asian or Pacific Islander patients, and 6.6% for other or unknown.

There was an overall even distribution of copayments when an epinephrine auto-injector was prescribed and subsequently dispensed in the population (\$0–<\$10, 1,941 [24%]; \$10–<\$20, 1,537 [19%]; \$20–<\$30, 2,198 [27.2%]; ≥\$30, 2,398 [29.7%]).

Distribution of Anaphylaxis Diagnosed in 2008 Through 2012

Table 4 presents the age- and age/sex-adjusted rates of anaphylaxis diagnosis across 2008 through 2012 and for all years combined. The rates are presented as adjusted by age for each sex

and combined and as age- and sex-adjusted rates. In summary, we observed some variability in the rates of diagnosis from 307.9 per 100,000 members in 2008 to 328.7 per 100,000 members in 2012. The 5-year rate of diagnosis was 314.2 per 100,000 members, but the average annual rates do not suggest an increasing trend in diagnosis.

General Population Characteristics

Of the entire Southern California Permanente Medical Group population from 2008 to 2012, 2,531,563 patients were included in the analysis (Fig 1). Two percent (52,405 patients) were identified to have anaphylaxis, which is slightly higher than in previous reports.²

Discussion

In this study, we identified 52,405 patients diagnosed with anaphylaxis, which is slightly higher than previously reported prevalence estimates of approximately 1.6.² We also found that 8,418 (16.1%) of those diagnosed were prescribed an epinephrine auto-injector within 60 days of the initial anaphylaxis encounter and an age- and sex-adjusted rate of diagnosis across all 5 years of the study period was estimated at 314.2 per 100,000 members. Previously published data have established that the socioeconomic diversity within Kaiser Permanente Southern California is reflective of the Southern California census population.¹⁹ To our knowledge, this is one of the few studies to examine anaphylaxis diagnosing and prescribing patterns in such a large cohort of patients and the first to report age- and sex-adjusted rates across multiple years.

The largest percentage of epinephrine was prescribed for classic ICD-9 code 995.0 (other anaphylactic shock) at 49.3% and codes 995.60 to 995.69 (anaphylactic shock caused by food) at an average of 56.7%. Fewer than 60% of cases coded for as anaphylactic shock were prescribed epinephrine—consistent with previous data that anaphylaxis is misdiagnosed and/or epinephrine is underprescribed in cases of true anaphylaxis.

For all other ICD-9 codes (which are the codes from the expanded algorithm), epinephrine auto-injectors were prescribed 0% to 16.2% of the time. This might indicate that the expanded algorithm does not identify true cases of anaphylaxis as accurately as previously reported. Also, previous data stated that that 58% of anaphylaxis cases remain undiagnosed if only the ICD-9 *Clinical Modification* codes for anaphylaxis are used to identify cases.¹⁶ However, applying the algorithm of Harduar-Morano et al¹⁶ did not acutely identify true cases of anaphylaxis, as suggested by our chart review of cases with the expanded ICD-9 codes. Therefore, we excluded ICD-9 codes 995.3 and 995.20 to 995.29 from our data collection and analysis.

Once epinephrine was prescribed, the medication was dispensed 95.9% of the time, from 87.5% to 100% across all ICD-9 codes. Thus, the copayment dollar amount, whether \$0 or more than \$30, did not appear to affect whether the epinephrine prescription was dispensed. However, higher copayments in the

Table 4Age- and Sex-Adjusted Rates^a of Anaphylaxis Diagnoses per 100,000 Kaiser Permanente Southern California Members Across 5 Years

Year	Age-adjusted rates per 100,000 members (SE)			Adjusted for age and sex (SE)
	Female	Male	Total	
2008	336.1 (4.6)	278.6 (4.3)	308.7 (3.1)	307.9 (3.1)
2009	338.3 (4.5)	276.1 (4.2)	309.2 (3.1)	308.4 (3.1)
2010	344.6 (4.6)	284.6 (4.3)	316.6 (3.2)	315.4 (3.1)
2011	336.2 (4.4)	282.3 (4.2)	310.9 (3.1)	309.9 (3.1)
2012	364.0 (4.6)	291.1 (4.2)	329.5 (3.1)	328.7 (3.1)
2008–2012	344.0 (2.0)	282.6 (1.9)	315.1 (1.4)	314.2 (1.4)

^aRates were adjusted to the US Census population in 2000.

current market may pose a new barrier to patients filling the prescribed epinephrine autoinjectors.

Strengths and Limitations

This study was limited only to those patients with anaphylaxis who used Kaiser Permanente Southern California health care resources. A previous survey reported up to 6.4% of patients with anaphylaxis receive no treatment and up to 27% self-treat with antihistamines. The inherent validity of using ICD-9 codes to identify patients with anaphylaxis-related events is unknown and likely not the best method to identify affected patients. However, our study was strengthened by the use of electronic health records that allowed for examination of not only diagnosing patterns but also prescribing behaviors of providers and patients. All patients had access to similar levels of care. To our knowledge, this is one of the few studies to have this advantage and the first study to examine rates of diagnosis across 5 years.

Anaphylaxis continues to be a difficult and controversial entity for diagnosis and resulting treatment. Our data support findings that anaphylaxis prevalence is approximately 2% and that epinephrine is likely under-prescribed.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.10.027>.

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eTable 1

ICD-9 Code Use Frequency for 995.2x Among KPSC Members, 2008 Through 2012

ICD-9 Code	Description	Patients	Visits
995.20	Adverse Drug Reaction	51,153	60,958
995.21	Arthus Phenomenon	32	36
995.22	Adverse Effect of Anesthesia	87	104
995.23	Unspecified Adverse Effect of Insulin	243	295
995.24	Failed Moderate Sedation During Procedure	10	14
995.27	ACE Inhibitor Sensitivity	11,547	14,873
995.29	Vaccines Adverse Reaction	8,712	11,830