

Epinephrine Autoinjector Refill History in an HMO

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Abstract Epinephrine can be lifesaving in episodes of anaphylaxis, yet it is underprescribed and underused. Tracking of epinephrine refills over time for patients with a diagnosis of anaphylaxis has not been reported. This study reports on the refill history of 14,677 patients in a large HMO who received an initial dispensing of EpiPen (Dey Pharma, Basking Ridge, NJ) or EpiPen Jr between 2000 and 2006. A total of 6,776 (46%) refilled at least once. Twenty-five percent of the patients who were in the cohort for 5 years or more refilled multiple times, and 11% refilled consistently at all expected refill times. Infants through children 12 years of age were more likely to receive a refill dispensing (63%) compared with teenagers and adults (40%). The most common *ICD-9* codes that were linked to the initial epinephrine dispensing were allergic disorder (37%), miscellaneous anaphylaxis/angioedema (23%), hymenoptera/insect bite or sting (14%), and specific or nonspecific food allergy (11%). A total of 79% of patients with a food-related *ICD-9* code and 59% of patients with an insect sting-related *ICD-9* code refilled epinephrine at least once. An opportunity exists to identify system-based as well as personal barriers in an ongoing effort to provide patients at risk with the tools and empowerment that could reduce their risk during life-threatening anaphylactic reactions.

Keywords Anaphylaxis · Severe allergic reaction · Epinephrine autoinjector

Introduction

Even though the frequency of life-threatening or fatal anaphylactic reactions is low, the potential for worsening severity with subsequent reactions has been reported [1]. Every year, 8% of patients with a prior anaphylactic episode experienced another episode [2]. Injectable epinephrine is the primary treatment for severe anaphylactic reactions, yet it is underprescribed and underused in the community and in emergency settings. Simons and coworkers [3•] reported on the use of epinephrine in patients who had been prescribed self-injectable epinephrine (SIE) and had experienced a subsequent anaphylactic reaction. A total of 500 (27%) of the 1,885 survey participants had used epinephrine. Epinephrine users were more likely to have experienced respiratory or shock-type symptoms; to have had peanut, fish, or insect sting exposure; and to be asthmatic and thus required asthma medication on the day of the event [3•]. Haymore [4] reviewed medical records at a military hospital to determine the rate of epinephrine use in cases of anaphylaxis. Epinephrine was administered in 50% of the cases, the same rate as treatment with H2 blockers and less than H1 blockers and corticosteroids. SIE was prescribed in 29% of the cases, and an allergy referral was made in 29% of the cases [4]. Simons [5•] reviewed the evidence base for the use of epinephrine in anaphylaxis, including treatment in community settings, identification of patients who need an autoinjector prescription, current use of autoinjectors, why physicians fail to prescribe autoinjectors for patients with anaphylaxis, and why patients fail to self-inject epinephrine during an anaphylactic episode.

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The purposes of this study were to examine the refill history for epinephrine autoinjectors in a group of patients in a large HMO and characterize patients who are more likely to refill epinephrine over time. Because EpiPen (Dey Pharma, Basking Ridge, NJ) and EpiPen Jr represent more than 98% of the epinephrine autoinjector dispensings in the HMO, only those devices were considered in selecting the cohort. This was a descriptive retrospective study.

Methods

The study cohort was identified from administrative data. Patients must have had an initial dispensing of EpiPen or EpiPen Jr between January 1, 2000, and December 31, 2006. Refill information and medical records were analyzed through the first quarter of 2009. To be eligible for inclusion, patients must have had continuous membership in the HMO and received prescriptions from a Health Plan pharmacy from the time of initial dispensing to the end of the data collection period. Refill opportunities were defined every 12 to 23 months after the initial dispensing and assigned as refill year 1 to 2, 3 to 4, or 5 years or more after the initial dispensing. Patients who were in the cohort for the longest period of time (initial dispensing from 2000–2002) had the opportunity to refill in years 1 to 2, years 3 to 4, and greater than 5 years after the initial dispensing, while those in the cohort for the shortest period of time (initial dispensing in 2006) had the opportunity to refill only in years 1 to 2 after the initial dispensing. Continuous membership was defined as no gaps longer than 4 months in any 12-month rolling period. Two-year segments were chosen for refill opportunities to allow for expiration dates that exceeded 1 year.

The databases used were Pharmacy Information Management System (to identify patients with initial EpiPen dispensings and track refills) and a membership database (to identify continuous membership). Electronic health records (EHRs) were used to identify patients who had been dispensed an EpiPen or EpiPen Jr and a matching *ICD-9* code to the EpiPen dispensings. A query tool to identify the cohort that incorporated all the databases was constructed, and a spreadsheet was created to include age, epinephrine refill dates, *ICD-9* codes linked to the epinephrine dispensings, and dispensing provider.

The database was analyzed for the number of repeat dispensings and in which time frame after the initial dispensing the refill occurred. *ICD-9* codes at the time of the initial dispensing were recorded. The relationship of refill history to *ICD-9* codes was examined, including the relationship of specific *ICD-9* codes to refill history for SIE during all eligible refill periods. Refill history was also examined in relation to age at first dispensing, causative

agent, and whether or not a patient had seen a specialist. Repeat use of an *ICD-9* code that was associated with the initial SIE dispensing did not necessarily mean that the encounter associated with a subsequent dispensing was for another anaphylactic event. The functionality of the EHR requires that every order for medication be linked to an *ICD-9* code for the encounter to be closed electronically. Coding guidelines require *ICD-9* codes to be supported by text in the provider's note for that encounter. We assumed that addressing a history of anaphylaxis reflected in the encounter coding would enhance the behavior of renewing an SIE prescription.

Study Questions

1. What percentage of patients refilled EpiPen at least once?
2. What percentage of patients eligible to refill in any given time period after the initial dispensing refilled in year 1 to 2, 3 to 4, and 5 or greater?
3. What percentage of patients refilled in every time period in which they were eligible to refill?
4. Which *ICD-9* codes were associated with EpiPen dispensings?
5. Do the following factors affect EpiPen refill history: age of the patient, *ICD-9* code for the initial dispensing event, or allergist versus other provider as the ordering provider?

Results

Between January 1, 2000, and December 31, 2006, 14,677 patients had an initial dispensing of SIE in the form of EpiPen or EpiPen Jr: 1,685 patients in the year 2000 and 2,046, 1,957, 2,123, 2,017, 2,086, and 2,763 patients in the subsequent years through 2006. During the course of the study period, 6,776 (46%) refilled (received a dispensing) at least once. Patients who were in the cohort the longest had the opportunity to refill in years 1 to 2, 3 to 4, year 5 or greater after the initial dispensing. Those in the cohort the shortest time had the opportunity to refill only in the year 1 to 2 time frame. A total of 5,790 of 14,677 (39%) eligible patients refilled in the 1- to 2-year period after the initial dispensing; 3,130 of 9,828 (32%) eligible patients refilled in the 3- to 4-year period, and 1,081 of 5,688 (19%) in the 5-year-or-greater period.

Of those 5,688 patients who were in the cohort for 5 years or more, 2,514 (43%) refilled in the 1- to 2-year follow-up period; 2,049 (35%) refilled in the third or fourth year, and 1,724 (30%) refilled in the fifth year or longer

after the initial dispensing. A total of 4,140 patients were in the study for 4 years but not longer. Of these patients, 1,556 (38%) refilled in year 1 or 2, and 1,079 (26%) refilled in year 3 or 4. Of the 4,849 patients in the cohort for only 2 years, 1,720 (35%) refilled. When examined by age, 1,386 (67%) patients who were 0 to 6 years old at the time of initial dispensing ($n=2,060$) had at least one refill during the study period; 728 of 1,272 (57%) of the 7- to 12-year-olds, and 4,190 of 10,314 (40%) of patients older than 17 years of age had at least one refill (Table 1).

In the entire cohort of 14,677 patients, 6,776 (46%) refilled at least once. Of these patients who ever refilled, 5,800 (86%) refilled in the first time period (year 1–2) after the initial dispensing. Of the total of 5,688 patients were in the cohort for 5 years or more, 2,955 (52%) refilled at least once in any of the three time periods (year 1–2, year 3–4, or years ≥ 5), but not necessarily in the first time period. A total of 641 (11%) refilled in two of the three time periods, and 792 (14%) refilled across all three time periods. A total of 2,481 (44%) of the patients who were in the cohort the longest refilled in the first eligible time period (year 1–2), and 1,315 (53%) of these patients refilled in at least two of the three time periods, as opposed to 119 of 475 patients (25%) who did not refill in the first time period (Table 2).

Consistency of refilling across all eligible time periods differed by age: 241 (12%) of 2,060 0- to 6-year-olds, 158 (12%) of 1,272 7- to 12-year-olds, and 634 (6%) of 10,314 of those older than 17 years of age. The 13- to 17-year age group was not analyzed based on the assumption that school-age children would be more likely to have SIEs required in their school emergency kits, and among the group between 13 and 17 years of age, school enrollment cannot be relied upon as a factor driving epinephrine autoinjector dispensing.

The leading anaphylaxis diagnostic codes associated with the initial EpiPen or EpiPen Jr dispensing were allergic disorder (37% of all initial dispensings), various anaphylaxis/angioedema codes (21%), hymenoptera anaphylaxis/insect sting or bite (14%), food allergy (11%), and chronic or autoimmune urticaria (7%). The leading diagnostic codes in patients who ever refilled EpiPen or EpiPen Jr were allergic disorders (33%), food/food additives

Table 2 Refill patterns for EpiPen for patients in the cohort for ≥ 5 years

Refill year 1–2	Refill year 3–4	Refill year ≥ 5	Total, n (%)
No	No	Yes	118 (2)
No	Yes	No	258 (5)
No	Yes	Yes	119 (2)
Yes	No	No	1,166 (20)
Yes	No	Yes	72 (1)
Yes	Yes	No	451 (8)
Yes	Yes	Yes	792 (14)
No	No	No	2,733 (46)

(21%), various anaphylaxis/angioedema codes (19%), insect stings or bites (14%), urticaria (8%), and others (7%) (Fig. 1). These percentages were different when an allergist was the prescribing provider. The three leading diagnostic codes for allergist-prescribed dispensings were food/food additive (48%), various anaphylaxis/angioedema codes (27%), and insect sting/bite (9%) (Fig. 1).

Patients were eligible to be included in the cohort if they had ever filled a prescription for EpiPen or EpiPen Jr. A total of 79% of 2,027 patients with a code for food or food additive allergy refilled at least once, as did 79% of 68 patients with a code for anaphylaxis/shock, 67% of 9 patients with a code for latex allergy, 59% of 1,790 patients for an insect sting or bite, 57% of 1,123 for urticaria, 53% of 189 for specific drug allergy, 52% of 4,707 for an allergic disorder, 49% of 816 for adverse drug reaction, and 48% of 303 for other miscellaneous anaphylaxis and angioedema codes.

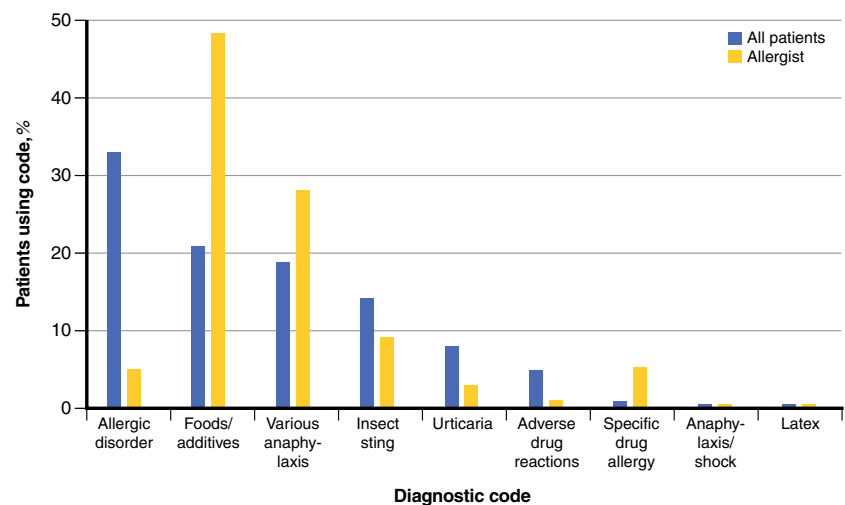
Discussion

This is a descriptive study of the refill histories for 14,667 unique patients who were dispensed EpiPen or EpiPen Jr between the beginning of 2000 and the end of 2006. Data have been analyzed through 2008. Forty-six percent of patients refilled at least once. The study was designed to evaluate the number of unique dispensing events, not the

Table 1 EpiPen refill history by age group at the time of initial fill

	Age group		
	0–6 y	7–12 y	>17 y
Total with initial fill, n (%)	2,060	1,272	10,314
Never, n (%)	674 (33)	544 (43)	6,124 (60)
Refill in 1 or 2 time periods, n (%)	1,145 (55)	570 (45)	3,556 (34)
Refill in all 3 time periods, n (%)	241 (12)	158 (12)	634 (6)
Ever, n (%)	1,386 (67)	728 (57)	4,190 (40)

Fig. 1 ICD-9 codes in patients who ever refilled. The rate of different diagnostic codes linked to epinephrine autoinjector refills is depicted for allergists and nonallergist providers. Allergists tended to use more anaphylaxis-specific codes to reflect the event or the causative agent



total number of dispensed units. We did not look at how often epinephrine injectors were ordered but not filled. Johnson and Parker [6] examined the rate at which epinephrine self-injector prescriptions were unfilled and characterized those patients who did not fill their prescriptions in a population of patients receiving care at a military medical center. Eighty-two percent of 769 patients filled at least one prescription. Those patients were more likely to be older than 55 years of age or preschool through high school age [6]. This is complementary to our findings that preschool through elementary school-age children were more likely to refill EpiPen prescriptions (Table 1). We did not specifically look at the age group 55 years of age and older. These patients were lumped with patients older than 17 years of age in the data analysis.

This was a unique study that tracked the refill history of a cohort of patients over an extended period of time. We could not find similar studies in the literature. Campbell et al. [7] reviewed medical records from two large community emergency departments representing visits over a 10-year period. Using anaphylaxis-related ICD-9 codes and detailed chart reviews, as well as randomly chosen charts of individuals with related diagnoses, 211 cases were identified that fit the criteria for anaphylaxis. Of the 64% who were discharged home, 36.6% were prescribed SIE, and only 31% were referred to an allergist. Treatment with epinephrine in the emergency department and having an insect sting as the reason for the encounter were significantly associated with receiving a prescription for SIE. Age younger than 18 years was the only factor associated with referral to an allergist [7].

Individuals in our cohort the longest had the opportunity to refill three times (or more if replacement units were needed sooner than the expiration date). Individuals in the cohort for the shortest period of time had the opportunity to refill once (year 1–2).

As mentioned, a total of 46% of the patients refilled at least once. This number includes 4,849 patients who were in the cohort for no more than 2 years. If they are observed longer, they may refill in a later time period, as suggested by the refill patterns for those patients in the cohort for 5 years or longer (Table 2). Although 1166 (20%) of 5,688 patients who were in the cohort the longest refilled only in the first eligible time period, 495 (9%) refilled at least once but did not refill in the first eligible time period. Of the 5,688 patients, 377 (7%) refilled in the second or third time period, and 118 (2%) refilled only in the third time period. Projecting these refill patterns to the 4,849 patients who were in the cohort the shortest, an additional 729 patients may have refilled if they had been in the cohort for 5 years or longer. This would increase the number of patients who would potentially refill at least once to 7505 (51% of 14,677 patients).

Thirty-nine percent of the patients refilled in year 1 to 2 after the initial dispensing. The refill rate then declined further during the other time periods. A total of 2,481 (44%) of 5,688 patients in the cohort the longest refilled in at least the first time period. A total of 1,315 (53%) refilled in at least two of the three time periods if they had refilled in year 1 to 2 after the initial dispensing, as opposed to 119 patients (4%) who did not refill in the first time period. The rate of refilling in all three time periods if a patient refilled in year 1 to 2 was 32%. This is an important finding. It appears that patients refilling in the first 1- to 2-year period after the initial dispensing were more likely to refill in subsequent time periods and more likely to refill consistently. A post hoc analysis of individual electronic records is being done to characterize the patients who refilled in the first time period, those who consistently refilled across all three time periods, and those who did not refill in any of the three time periods to explore the relationship between age and gender, type of symptoms during the initial event or

subsequent events, initial *ICD-9* code, agent causing the event, visit to a specialist after the initial dispensing, number of repeat encounters with an anaphylaxis-related *ICD-9* code, refill behavior for other chronic medications, and co-pay issues.

ICD-9 codes for anaphylaxis are limited for use in clinical research and accurate documentation of acute allergic events. Many of the codes for anaphylaxis contain the terminology *anaphylactic shock*. In this study, when data analysis is limited to patients with *ICD-9* codes more typically associated with anaphylactic events and linked to the initial dispensing, we found that rates for at least one refill ranged from 48% to 78%. Providers may reject the use of an *ICD-9* code that has the term *anaphylactic shock* when treating a patient with a severe allergic reaction who is normotensive. They may elect to use a code of convenience. Another issue appeared in our preliminary review of individual EHRs. There were several instances in which providers linked EpiPen refills to the *ICD-9* code for essential hypertension. In our EHR system, a prescription or procedure must be linked to an *ICD-9* code for the encounter to be closed. It appears that in these cases, the link was made to expedite the closure, and the provider did not take the time to enter the proper historical *ICD-9* link to the EpiPen dispensing. How this affects subsequent dispensings of EpiPen is unknown. The dispensing likely was correct and the documentation inaccurate.

Our early, limited record review of patients in the cohort for whom an EHR is available from the time of the initial dispensing event reveals several cases in which the likelihood of anaphylaxis is low. This may result in a lower refill rate and may explain the difference in the leading *ICD-9* codes for initial dispensing versus leading *ICD-9* codes for patients who ever refilled.

There were several limitations to this study. The study population consisted of members of an HMO with an integrated electronic medical record and may not be representative of the general population. We did not examine the rate of appropriate epinephrine prescriptions written at the time of the anaphylaxis encounter (over- and underprescribing) or the refill history for other chronic medications as a marker of patient self-care behavior. We made an assumption of the date of the first dispensing. Once patients were identified by EpiPen dispensings, their continuous membership was examined for as far back as 2000. The earliest dispensing of EpiPen was assumed to be the first dispensing. We looked at the rate of refilling EpiPen by *ICD-9* code in patients who ever refilled. We did not look at the rate of EpiPen orders or dispensings using the *ICD-9* code as the base criterion.

The study was not designed to examine how many EpiPen orders for initial or refill prescriptions went unclaimed. Johnson and Parker [6] found that 18% of their

patients did not claim an ordered prescription for an epinephrine autoinjector. This number may be an underestimate, as they looked at the number of patients who did not claim their prescription and not the number of total unclaimed orders. Patient or parent attitudes about administering epinephrine were not assessed. Reluctance to use epinephrine may influence subsequent refill behavior. Kim et al. [8] reported that in a group of children prescribed EpiPen, 42% had anaphylaxis, but only 8% received EpiPen. In a community study, Simons et al. [3•] described epinephrine use in patients who had an epinephrine autoinjector and had experienced subsequent anaphylaxis. Factors associated with the likelihood of epinephrine use were identified [3•]. In these studies, factors associated with epinephrine autoinjector use were discussed. Attitudes regarding perceived risk, fear of epinephrine use, lack of proper patient education and empowerment, and prior use of an epinephrine autoinjector influence comfort level for using epinephrine and perhaps refill behaviors.

Conclusions

To our knowledge, no study like this has been reported. The database that we used is robust, and factors associated with refill behavior are identified. Using the spreadsheet created for this study, we can now explore the appropriateness of an EpiPen dispensing. The snapshot created by this study is a first step in exploring factors that may influence epinephrine autoinjector prescribing patterns and refill behaviors for patients in an ongoing effort to enhance emergency preparedness for patients at risk.

Disclosure Dr. Kaplan has served on an advisory board for Dey Pharma. Drs. Jung and Chiang reported no potential conflicts of interest relevant to this article.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Vander Leek TK, Liu AH, Stefanski K, et al.: The natural history of peanut allergy in young children and in association with serum peanut specific IgE. *J Pediatr* 2000, 137:749–755.
2. Mullins RJ: Anaphylaxis: risk factors for recurrence. *Exp Allergy* 2003, 33:1033–1040.
3. • Simons, FER, Clark S, Camargo CA: Anaphylaxis in the community: learning from the survivors. *J Allergy Clin Immunol* 2009, 124:301–306. *This article offers insight into the barriers that affected the decisions of patients or their caretakers to use or not to*

- use epinephrine. The information is useful in helping to design patient education programs for populations at risk of anaphylaxis.*
4. Haymore BR: Anaphylaxis and epinephrine prescribing patterns in a military hospital: underutilization of the intramuscular route. *Allergy Asthma Proc* 2005, 26:361–365.
 5. • Simons KJ: Epinephrine and its use in anaphylaxis: current issues. *Curr Opin Allergy Clin Immunol* 2010, 10:354–361. *This is an excellent review of epinephrine use in the community, including prescribing behaviors of providers. It explores the question of who may need an autoinjector and why patients elect not to self-inject.*
 6. Johnson TL, Parker AL: Rate of retrieval of self-injector epinephrine prescriptions: a descriptive report. *Ann Allergy Asthma Immunol* 2006, 97:694–697.
 7. Campbell RL, Luke A, Weaver AL, et al.: Prescriptions for self-injectable epinephrine and follow-up referral in emergency department patients presenting with anaphylaxis. *Ann Allergy Asthma Immunol* 2008, 101:631–636.
 8. Kim JS, Sinacore JM, Pongracic JA: Parental use of EpiPen for children with food allergies. *J Allergy Clin Immunol* 2005, 116:164–168.