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Predictors of epinephrine dispensing and allergy follow-up after emergency department visit for anaphylaxis

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ABSTRACT

Background: National guidelines recommend that patients with anaphylaxis be prescribed an epinephrine auto-injector (EAI) and referred to an allergy/immunology (A/I) specialist.

Objective: To evaluate guideline concordance and identify predictors of EAI dispensing and A/I follow-up in patients with anaphylaxis treated in the emergency department (ED).

Methods: We identified patients seen in the ED for anaphylaxis from 2010 through 2014 from an administrative claims database using an expanded *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code algorithm.

Results: Of 7,790 patients identified, 46.5% had an EAI dispensed and 28.8% had A/I follow-up within 1 year after discharge. On multivariable analysis, those 65 years or older (odds ratio [OR] 0.35, 95% confidence interval [CI] 0.30–0.41) and with a medication trigger (OR 0.24, 95% CI 0.21–0.28) had a lower likelihood of EAI dispensing. Those younger than 5 years (OR 2.67, 95% CI 2.15–3.32) and with food (OR 1.40, 95% CI 1.24–1.59) or venom (OR 4.48, 95% CI 3.51–5.72) triggers had a higher likelihood of EAI dispensing. Similarly, for A/I follow-up, the likelihood was lower for age 65 years or older (OR 0.46, 95% CI 0.39–0.54) and medication trigger (OR 0.66, 95% CI 0.56–0.78) and higher for age younger than 5 years (OR 3.15, 95% CI 2.63–3.77) and food trigger (OR 1.39, 95% CI 1.22–1.58).

Conclusion: Overall, 46.5% of patients with anaphylaxis in the ED had EAI dispensing and 28.8% had A/I follow-up. Patient age and triggers were associated with likelihood of EAI dispensing and A/I follow-up. Post-ED visit anaphylaxis management can be improved, with the potential to decrease future morbidity and mortality risk.

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Introduction

Anaphylaxis is a life-threatening systemic allergic reaction¹ associated with a persistent risk of recurrence. Mullins² estimated that 1 in 12 patients with a history of anaphylaxis will have a

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subsequent episode. National and international guidelines published by the Joint Task Force on Practice Parameters and the World Allergy Organization^{3–5} recommend that, after an emergency department (ED) visit or hospitalization for anaphylaxis, patients should be prescribed an epinephrine auto-injector (EAI) and be referred for follow-up to an allergy/immunology (A/I) specialist. However, studies suggest that post-ED discharge guideline recommendations are not routinely followed, with only approximately 45% of patients being discharged with a prescription for EAI and only approximately 21.6% of patients being referred to an A/I specialist.⁶ Reasons for low EAI dispensing and A/I follow-up are likely multifactorial and include high out-of-pocket costs for EAI⁷ and A/I referrals, a limited availability of allergy specialists, and the potential requirement for preauthorization from the primary care physician to obtain a specialist referral.^{7,8}

Having an EAI and following up with an A/I specialist are key tools used to prevent and manage subsequent anaphylaxis events.

For example, from a clinical standpoint, A/I follow-up provides an opportunity to identify triggers and provide anaphylaxis education, including strategies for avoiding triggers and what to do in case of a severe allergic reaction. Patients also can be considered for additional therapies beyond avoidance, including venom immunotherapy for those with venom anaphylaxis and desensitization protocols if the medication trigger is needed in the future. Prevention of future anaphylaxis is key and could help limit the substantial financial burden of allergies and anaphylaxis. Although studies examining the overall economic burden of anaphylaxis nationally are lacking, it is likely profound. A study by Patel et al⁹ examining the total economic burden of food allergy and food-related anaphylaxis alone in the United States estimated the costs to be approximately half a billion dollars. Beyond the clinical and financial implications, EAI dispensing and A/I follow-up can have humanistic implications by relieving potential patient and caregiver anxiety. A study by Bollinger et al¹⁰ examining the impact of food allergy on the daily activities of children and parents found that 41% of parents reported that food allergy had a significant impact on their overall stress levels and affected their family social activities. Having an EAI and A/I specialist counseling can help to alleviate those anxieties and, in this way, can improve quality of life for these patients.

Given poor rates of postdischarge EAI prescriptions and A/I follow-up, it is important to identify associated risk factors for lack of EAI prescribing and A/I follow-up and to create targeted strategies for improving them. The objective of this study was to identify predictors associated with EAI dispensing and A/I follow-up in patients seen in the ED for anaphylaxis from 2010 through 2014.

Methods

Data Source

The OptumLabs Data Warehouse (Cambridge, Massachusetts), which includes administrative claims data for more than 100 million privately insured and Medicare Advantage enrollees in the United States,¹¹ was used for this study. The database contains longitudinal health information during the past 20 years and covers multiple domains, including enrollee information (insurance plan, sex, age, dates of eligibility), pharmacy claims (prescribing physician, pharmacy, prescription dispensing data, days of supply, dosages), and medical claims (including *International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* diagnosis codes, *ICD-9-CM* procedure codes, *Current Procedural Terminology 4* procedure codes, Healthcare Common Procedure Coding System procedure codes, site of service codes, standardized costs, and provider specialty codes).¹² This study involved analysis of pre-existing, de-identified data and was deemed exempt from institutional review board approval.

Study Population

To identify the analytic cohort of ED visits for anaphylaxis, we used 2 methods validated by the algorithm of Harduar-Morano et al.¹³ Method 1 identified patients who had *ICD-9-CM* diagnosis codes for anaphylactic shock (995.60–995.69 and 995.0). Method 2 identified patients through a validated algorithm of *ICD-9-CM* codes of symptom combinations necessary to make the diagnosis of anaphylaxis.

Using this method, we identified visits that occurred from 2005 through 2014; from those initially identified, we limited the dataset to visits from January 1, 2010 through December 31, 2014 to minimize effects related to changes in practice over time. Patients were excluded if they did not have medical insurance and pharmacy coverage at the time of the ED visit and during the 1 year before (pre-index) and 1 year after discharge date (post-index).

Methods and Measurements

This study adhered to the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) Statement.¹⁴ Demographic characteristics, triggers, and ED disposition were obtained from the claim for the index event. Post-index EAI prescription dispensing and A/I visits were identified. Comorbid conditions and ED outcomes (ED discharge or observation within an ED observation unit or in the hospital, non-intensive care unit hospital admission, and intensive care unit admission) were identified by professional claims listed in eTable 1. A/I visits were identified by *Current Procedural Terminology 4* codes, and EAI prescription dispensing was identified by medication name and drug class.

Statistical Analysis

All statistical analyses were performed using SAS 9.3 (SAS Institute, Inc, Cary, North Carolina). Patient characteristics (age, sex, and census region) were expressed as counts and percentages. Multivariable logistic regression was used to evaluate independent predictors of EAI dispensing and A/I follow-up. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). All significance tests were 2-sided, and a *P* value less than .01 was considered statistically significant. A sensitivity analysis was conducted excluding patients identified by method 2, which is based on signs and symptoms of anaphylaxis and might not be specific for the diagnosis. An additional analysis was conducted by separating patients by age, specifically children and adolescents (<18 years) from adults (≥18 years).

Results

Patient Demographics and Clinical Characteristics

From 2005 through 2014, 65,946 unique ED visits for anaphylaxis were identified using method 1 or 2 of the Harduar-Morano algorithm.⁹ After excluding patients seen from 2005 through 2009 and those without medical and pharmacy coverage for 1 year before and after the index event, 7,790 patients seen from 2010 through 2014 were included in the cohort (Fig 1). Most anaphylaxis-related ED visits involved patients 35 to 64 years old (40.2%), and most patients (58.6%) were female (Table 1). The cohort was primarily from the Southern United States census region (46.7%), followed by the Midwest (27.0%). Comorbid conditions included cardiac disease in 36.5% of patients (including hypertension, coronary atherosclerosis, and congestive heart failure) and atopy (25.0% with asthma and 14.5% with eczema; Table 1).

Overall, 26.2% of cases were associated with food, 12.6% were related to medication, and 3.3% were from insect venom, with the remaining cases caused by unknown or unspecified triggers (57.9%; Table 1). Most patients (85.2%) were discharged from the ED or observed (in ED observation units or in-hospital observation); 8.5% were admitted to the intensive care unit and 6.3% were non-intensive care unit inpatient admissions.

EAI Dispensing

Of the 7,790 patients, 3,623 (46.5%) had an EAI dispensed (Table 1). On multivariable analysis (Table 2), independent risk factors associated with a lower likelihood of EAI dispensing included older age (35–64 years old: OR 0.83, 95% CI 0.76–0.92; ≥65 years old: OR 0.35, 95% CI 0.30–0.41), Southern region (OR 0.86, 95% CI 0.80–0.94), medication trigger (OR 0.24, 95% CI 0.21–0.28), and cardiac disease (OR 0.85, 95% CI 0.80–0.91; *P* < .001 for all comparisons). In contrast, factors associated with a higher likelihood of EAI dispensing on multivariable analysis included young age (0–4 years old: OR 2.67, 95% CI 2.15–3.32; 5–17 years

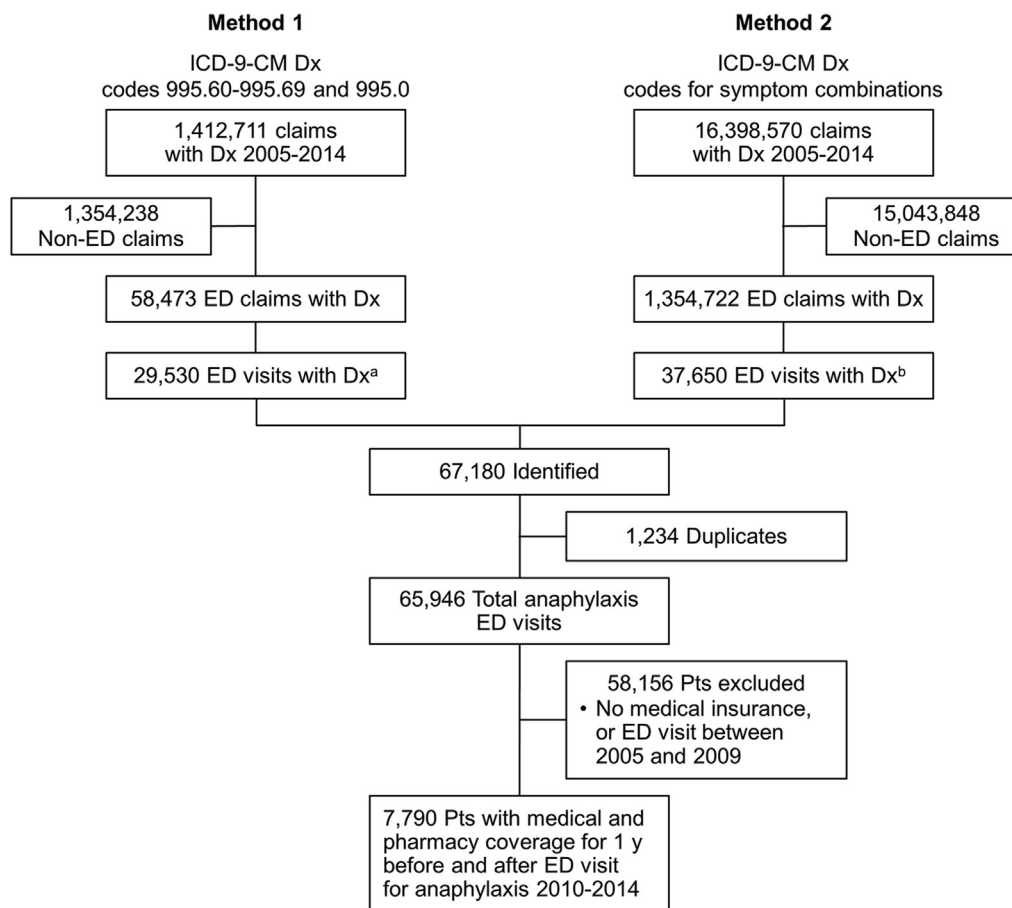


Figure 1. Flowchart of cohort identification. ^{a,b}More than 1 claim can be associated with a single ED visit. Dx, diagnosis; ED, emergency department; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; Pts, patients. (Adapted from Motosue MS, Bellolio MF, Van Houten HK, et al. Increasing emergency department visits for anaphylaxis, 2005–2014. *J Allergy Clin Immunol Pract.* 2017;5:171–175.e3. Used with permission.)

old: OR 1.51, 95% CI 1.33–1.72), food trigger (OR 1.40, 95% CI 1.24–1.59), venom trigger (OR 4.48, 95% CI 3.51–5.72), and pre-index event EAI dispensing (OR 1.43, 95% CI 1.32–1.54; $P < .001$ for all comparisons).

A/I Follow-up

In our cohort, 2,244 patients (28.8%) had A/I follow-up (Table 1). On multivariable analysis (Table 2), risk factors associated with a low likelihood of A/I follow-up included older age (35–64 years old: OR 0.78, 95% CI 0.71–0.86; ≥ 65 years old: OR 0.46, 95% CI 0.39–0.54), medication trigger (OR 0.66, 95% CI 0.56–0.78), and cardiac disease (OR 0.84, 95% CI 0.78–0.90; $P < .001$ for all comparisons). Independent factors associated with a higher likelihood of A/I follow-up on multivariable analysis included younger age (0–4 years old: OR 3.15, 95% CI 2.63–3.77; 5–17 years old: OR 1.31, 95% CI 1.16–1.48), food trigger (OR 1.39, 95% CI 1.22–1.58), asthma (OR 1.19, 95% CI 1.12–1.26), eczema (OR 1.22, 95% CI 1.13–1.31), pre-index event A/I visit (OR 1.70, 95% CI 1.38–2.09), and EAI dispensing (OR 1.37, 95% CI 1.28–1.48; $P < .001$ for all comparisons).

Sensitivity Analysis

For the sensitivity analysis, 3,745 of the 7,790 patients were identified by method 1 (more specific for the diagnosis of anaphylaxis) and were included. Multivariable analysis of this cohort of patients demonstrated similar associations as those seen with the full cohort (eTable 2). An additional analysis was done by separating adults (≥ 18 years; eTable 3) from children and

adolescents (< 18 years; eTable 4). In comparing the total cohort analysis with that of the separate analyses of children and adults, we found similar results.

Discussion

In this study of nearly 8,000 patients seen in the ED for anaphylaxis, 47% had EAI dispensing and 29% had A/I follow-up within 1 year after discharge. Independent predictors associated with low likelihood of EAI dispensing and A/I follow-up included older age, medication trigger, and cardiac disease. In contrast, younger age, food trigger, and pre-index visit EAI dispensing were associated with higher likelihood of postdischarge EAI dispensing and A/I follow-up. These findings highlight the disparities in anaphylaxis care and opportunities for emergency providers to improve post-ED visit anaphylaxis management, thereby lowering the risk of future morbidity and mortality. To our knowledge, this is the first study to examine predictors of EAI dispensing and A/I follow-up in a nationwide cohort of patients seen in the ED for all causes of anaphylaxis in the United States.

Few studies have reported rates of EAI prescriptions and A/I follow-up in patients in an ED with anaphylaxis from all causes. However, our results are similar to those published by Landsman-Blumberg et al¹⁵ who conducted a similar study that evaluated postdischarge outcomes in adults with food-induced anaphylaxis and found that 54% of adult patients filled EAI prescriptions and 22% visited an A/I specialist. In a separate analysis, Landsman-Blumberg et al⁷ examined rates of EAI dispensing and A/I visits in

Table 1
Demographic and Clinical Characteristics of Patients by EAI Dispensing and A/I Follow-up

Variable	EAI dispensing, n (%)		P value	A/I follow-up, n (%)		P value	Total (N = 7,790), n (%)
	Yes (n = 3,623)	No (n = 4,167)		Yes (n = 2,244)	No (n = 5,546)		
Age (y)			<.001			<.001	
0–4	379 (10.5)	76 (1.8)		306 (13.6)	149 (2.7)		455 (5.8)
5–17	897 (24.8)	367 (8.8)		577 (25.7)	687 (12.4)		1,264 (16.2)
18–34	683 (18.9)	694 (16.7)		368 (16.4)	1,009 (18.2)		1,377 (17.7)
35–64	1,347 (37.2)	1,788 (42.9)		780 (34.8)	2,355 (42.5)		3,135 (40.2)
≥65	317 (8.7)	1,242 (29.8)		213 (9.5)	1,346 (24.3)		1,559 (20.0)
Sex			<.001			.17	
Female	1,960 (54.1)	2,606 (62.5)		1,288 (57.4)	3,278 (59.1)		4,566 (58.6)
Male	1,663 (45.9)	1,561 (37.5)		956 (42.6)	2,268 (40.9)		3,224 (41.4)
ED visit year			.002			.73	
2010	606 (16.7)	803 (19.3)		387 (17.2)	1,022 (18.4)		1,409 (18.1)
2011	832 (23.0)	910 (21.8)		507 (22.6)	1,235 (22.3)		1,742 (22.4)
2012	913 (25.2)	1,044 (25.1)		574 (25.6)	1,383 (24.9)		1,957 (25.1)
2013	897 (24.8)	902 (21.6)		528 (23.5)	1,271 (22.9)		1,799 (23.1)
2014	375 (10.4)	508 (12.2)		248 (11.1)	635 (11.4)		883 (11.3)
Census region			<.001			<.001	
Midwest	960 (26.5)	1,142 (27.4)		602 (26.8)	1,500 (27.0)		2,102 (27.0)
Northeast	534 (14.7)	490 (11.8)		336 (15.0)	688 (12.4)		1,024 (13.1)
South	1,585 (43.7)	2,052 (49.2)		979 (43.6)	2,658 (47.9)		3,637 (46.7)
West	544 (15.0)	483 (11.6)		327 (14.6)	700 (12.6)		1,027 (13.2)
Trigger			<.001			<.001	
Food	1,439 (39.7)	605 (14.5)		811 (36.1)	1,233 (22.2)		2,044 (26.2)
Medication	180 (5.0)	803 (19.3)		135 (6.0)	848 (15.3)		983 (12.6)
Venom	204 (5.6)	52 (1.2)		40 (1.8)	216 (3.9)		256 (3.3)
Other	1,800 (49.7)	2,707 (65.0)		1,258 (56.1)	3,249 (58.6)		4,507 (57.9)
Charlson index			<.001			<.001	
0	1,946 (53.7)	1,548 (37.1)		1,100 (49.0)	2,394 (43.2)		3,494 (44.9)
1	834 (23.0)	721 (17.3)		603 (26.9)	952 (17.2)		1,555 (20.0)
≥2	843 (23.3)	1,898 (45.5)		541 (24.1)	2,200 (39.7)		2,741 (35.2)
Comorbid conditions							
Cardiac disease	804 (22.2)	2,037 (48.9)	<.001	498 (22.2)	2,343 (42.2)	<.001	2,841 (36.5)
Diabetes mellitus	300 (8.3)	624 (15.0)	<.001	191 (8.5)	733 (13.2)	<.001	924 (11.9)
Asthma	968 (26.7)	978 (23.5)	.001	741 (33.0)	1,205 (21.7)	<.001	1,946 (25.0)
Eczema	623 (17.2)	504 (12.1)	<.001	496 (22.1)	631 (11.4)	<.001	1,127 (14.5)
A/I visit (prior 12 mo)			<.001			<.001	
No	3,619 (97.9)	4,061 (99.2)		2,265 (96.8)	5,415 (99.3)		7,680 (98.6)
Yes	71 (2.0)	39 (0.9)		69 (3.1)	41 (0.7)		110 (1.4)
EAI dispensing (prior 12 mo)			<.001			<.001	
No	2,861 (77.4)	3,798 (92.8)		1,742 (74.5)	4,917 (90.2)		6,659 (85.5)
Yes	814 (22.5)	317 (7.6)		580 (25.8)	551 (9.9)		1,131 (14.5)
ED disposition			<.001			<.001	
ED discharge or observation	3,295 (90.9)	3,341 (80.2)		2,005 (89.3)	4,631 (83.5)		6,636 (85.2)
Inpatient (non-ICU) admission	169 (4.7)	325 (7.8)		130 (5.8)	364 (6.6)		494 (6.3)
ICU admission	159 (4.4)	501 (12.0)		109 (4.9)	551 (9.9)		660 (8.5)

Abbreviations: A/I, allergy/immunology; EAI, epinephrine auto-injector; ED, emergency department; ICU, intensive care unit.

children seen in the ED with food-induced anaphylaxis and reported the frequency of EAI dispensing (83%) and specialist visits (43%). Campbell et al¹⁶ reported that 36.6% of patients seen in the ED for anaphylaxis were prescribed self-injectable epinephrine and 31.3% were referred to an allergist. In other food-induced anaphylaxis studies, postdischarge outcomes in those with food-specific anaphylaxis have reported rates of EAI prescriptions ranging from 16% to 39% and rates of A/I referral ranging from 12% to 18%.^{17,18}

Older age, cardiovascular disease, and medication trigger were associated with low likelihood of A/I follow-up. A/I follow-up care is important for postdischarge management of anaphylaxis, as shown by a study¹⁹ exploring outcomes of A/I consultation and finding that up to 35% of patients seen in the ED can have an alteration in the diagnosis or suspected trigger. Through specialized evaluation, A/I providers can refine the diagnosis, provide appropriate risk assessment, and educate patients on avoidance strategies.^{3,20} Efforts to increase awareness of the importance of postdischarge A/I follow-up among ED and primary care providers and patients and the community are essential. Patient education and implementation of ED-based referral systems such as that described by Messina et al²¹ could remove barriers associated with post-ED specialty follow-up.

Age at least 35 years, cardiovascular disease, and medication trigger also were independently associated with a lower likelihood of EAI dispensing. Delayed administration of epinephrine has been associated with increased mortality.²² The association of poor rates of EAI dispensing in older patients has been previously described. Campbell et al²³ reported that patients at least 50 years old are less likely to be prescribed an EAI compared with those younger than 50 years. Our study was unable to discern whether the low dispensing rates were due to the provider not prescribing an EAI or the patient not filling the prescription.

From a health care perspective, older patients, especially the elderly, represent a high-risk population. Many of these patients often have underlying cardiovascular disease that impairs their compensatory mechanisms and makes them susceptible to treatment complications. In our cohort, cardiovascular disease was independently associated with a low likelihood of EAI dispensing. Administration of epinephrine in patients with cardiovascular disease has some risk, given its effects on vasoconstriction, heart rate, and vascular resistance.²⁴ Apprehension of providers to prescribe an EAI could stem from prior reports linking administration of epinephrine to cardiac complications, including myocardial infarction²⁵ and angina.²⁶ However, these associations might not be

Table 2Multivariable Predictors of EAI Dispensing and A/I Follow-up in Patients With Anaphylaxis in the ED^a (N = 7,790)

Variable	EAI dispensing		A/I follow-up	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, y				
0–4	2.67 (2.15–3.32)	<.001	3.15 (2.63–3.77)	<.001
5–17	1.51 (1.33–1.72)	<.001	1.31 (1.16–1.48)	<.001
18–34	ref		ref	
35–64	0.83 (0.76–0.92)	<.001	0.78 (0.71–0.86)	<.001
≥65	0.35 (0.30–0.41)	<.001	0.46 (0.39–0.54)	<.001
Female sex	0.98 (0.93–1.03)	.39	1.07 (1.02–1.13)	.01
Census region				
Midwest	ref		ref	
Northeast	1.09 (0.98–1.23)	.12	1.06 (0.94–1.19)	.32
South	0.86 (0.80–0.94)	<.001	0.92 (0.85–1.00)	.048
West	1.10 (0.98–1.23)	.11	1.02 (0.91–1.15)	.75
Trigger				
Unspecified	ref		ref	
Food	1.40 (1.24–1.59)	<.001	1.39 (1.22–1.58)	<.001
Venom	4.48 (3.51–5.72)	<.001	0.77 (0.59–1.00)	.053
Medication	0.24 (0.21–0.28)	<.001	0.66 (0.56–0.78)	<.001
Cardiac disease	0.85 (0.80–0.91)	<.001	0.84 (0.78–0.90)	<.001
Diabetes mellitus	0.92 (0.85–1.00)	.06	1.00 (0.91–1.10)	.99
Asthma	0.98 (0.92–1.04)	.45	1.19 (1.12–1.26)	<.001
Eczema	1.05 (0.98–1.14)	.17	1.22 (1.13–1.31)	<.001
Allergy consult (prior 12 mo)	1.27 (1.02–1.58)	.04	1.70 (1.38–2.09)	<.001
EAI dispensing (prior 12 mo)	1.43 (1.32–1.54)	<.001	1.37 (1.28–1.48)	<.001
ED disposition				
Inpatient (non-ICU) admission	ref		ref	
ED discharge/observation	1.10 (0.99–1.23)	.68	0.97 (0.86–1.08)	.56
ICU admission	0.89 (0.77–1.04)	.14	0.89 (0.76–1.05)	.17

Abbreviations: A/I, allergy/immunology; CI, confidence interval; EAI, epinephrine auto-injector; ED, emergency department; ICU, intensive care unit; OR, odds ratio; ref, reference group.

^aMultivariable analysis was adjusted for year of visit.

truly cause-and-effect, because cardiac complications can be part of the anaphylactic event.³ Numerous mast cells are present in the adventitia of large and small coronary arteries in normal, healthy persons. During an anaphylactic event, cardiac mast cells are activated and release mediators such as histamine, prostanooids, and platelet-activating factor. These mediators cause decreased coronary blood flow, induce arrhythmias, and can lead to cardiac arrest.²⁷ In patients with ischemic heart disease, cardiac mast cells are the main constituents of atherosclerotic plaques,^{24,27} and this most likely contributes to the increased risk of near-fatal reactions previously reported in these patients.²⁸

Moreover, the risk of adverse cardiovascular events associated with epinephrine appears dependent on the route and dose administered. Campbell et al²⁹ reported that the risk of cardiovascular complications and overdose was significantly higher with intravenous bolus epinephrine administration. Epinephrine, when appropriately dosed and given intramuscularly through an EAI, is believed to be a safe therapy for anaphylaxis.³⁰ There are currently no absolute contraindications to epinephrine use in the management of anaphylaxis.^{24,31} The use of epinephrine in patients with cardiovascular disease is complex, and recommendations are ill defined. Current national guidelines³ recommend consideration of risks vs benefits for these patients but do not further explain how to properly assess risk. Additional studies examining the safety of epinephrine in those with cardiac disease and in older patients are needed to create more concrete recommendations and perhaps develop a risk-assessment score to better guide providers.

Medication trigger was associated with lower odds of EAI dispensing. The necessity of EAI dispensing in those with medication-related anaphylaxis represents an important issue not specifically addressed in current guidelines. Current guidelines recommend that all patients after an acute anaphylactic event be prescribed an EAI and further recommend that patients fill the

prescription immediately because of the potential risk of biphasic reactions. In a recent review, biphasic reactions were reported in approximately 3% of adults and up to 15% of children.³² Although not frequent, if biphasic reactions do occur, up to 50% will require epinephrine.³² However, the necessity of an EAI for patients with medication trigger is unclear given that medications can be avoided. EAI necessity can be further decreased in those monitored in an observation or inpatient setting. Further research examining outcomes of patients with medication-related anaphylaxis are necessary to define their appropriate postdischarge care.

In contrast to adults, children and adolescents were more likely to have A/I follow-up and an EAI prescription. Reasons for this are unclear but could reflect the benefits of caregiver support, because their care is often overseen by parents and other family members. Caregivers provide psychosocial support, which has been associated with improved outcomes related to treatment adherence.³³ Incorporation of family members and others as part of a patient's social network can serve as an effective tool to increase concordance of post-ED discharge outcomes in adults.

In our study, food and venom triggers were associated with high likelihoods of EAI dispensing. In contrast to medications, venom and food are harder to avoid, and thus providers and patients might be more apt to prescribe and fill prescriptions, respectively. Interestingly, although patients with food-related anaphylaxis were more likely to have A/I follow-up, this was not true for patients with venom-related anaphylaxis. These patients could benefit the most from A/I follow-up given the potential for disease-modifying venom immunotherapy.^{34,35} Venom immunotherapy is 75% to 98% effective in preventing sting anaphylaxis.³⁶ Further studies examining barriers between guideline recommendations and patient and physician behaviors are needed.

With regard to EAI dispensing, our study also showed regional variation: patients from the South census region were less likely to

have EAI dispensing. Camargo et al.³⁷ reported regional differences in EAI prescriptions in the United States, with the South having the lowest rates of EAI prescriptions (3 prescriptions per 1,000 persons vs 8–12 EAI prescriptions per 1,000 persons elsewhere). Although not addressed by Camargo et al.,³⁷ our findings would question whether regional practice variations contributed to their findings. Additional studies examining geographic variations are important.

In our cohort, preventive anaphylaxis care in the form of pre-index event EAI dispensing was positively associated with post-ED discharge A/I follow-up and EAI dispensing. This could reflect access; once resources are made available to a patient, access after a subsequent event is most likely easier. This also could explain why patients in our cohort with a pre-index event A/I visit and those with atopic diseases such as asthma and eczema also were more likely to have A/I follow-up. Although pre-index event EAI dispensing and A/I visits have been associated with a lower risk of severe anaphylaxis requiring hospitalization,²⁸ the effect of both on the risk of a recurrent event is unclear. Given that EAI dispensing and A/I visits are recommended for prevention of future episodes, studies establishing their effect on the frequency and severity of subsequent episodes are needed.

This study has several limitations. First, as a claims data study, the data were not created or collected to answer the specific research question, and possible limitations include misclassification bias, unmeasured confounding, missing data, and changing eligibility over time. Second, the study population was composed of Medicare Advantage and privately insured patients and was limited to those with medical and pharmacy coverage 12 months before and after the index event; thus, the cohort might not accurately reflect the general population of the United States. Third, the study was based on ICD-9-CM diagnosis codes, with limitations in the validity of case ascertainment. Because anaphylaxis has been shown to be underdiagnosed,^{38–40} we used an ICD-9-CM–based diagnostic algorithm with the specific ICD-9-CM anaphylaxis codes to mitigate the impact of anaphylaxis underdiagnosis. The coding algorithm captures cases that would not have been identified by specific ICD-9-CM anaphylaxis codes alone. This method has been used in studies looking at postdischarge outcomes related to EAI dispensing and A/I visits^{7,15} and in others examining severe anaphylaxis.^{28,41} Fourth, we could not distinguish whether low rates of EAI dispensing were a factor of the providers not prescribing EAI or the patients not filling their prescriptions. Despite these limitations, this is the first study to examine predictors of the postdischarge outcomes of EAI dispensing and A/I follow-up in a large cohort of patients seen in the ED for all causes of anaphylaxis.

In conclusion, in this large and diverse cohort, younger age, food trigger, and pre-index event EAI dispensing and A/I follow-up were associated with a higher likelihood of concordance with recommended postdischarge anaphylaxis care. In contrast, older age, medication trigger, and history of cardiac disease were associated with a lower likelihood of the same outcomes, which demonstrates differences in anaphylaxis care. Further studies examining predictors of postdischarge outcomes will be important in addressing deficiencies in and creating strategies for improvement of anaphylaxis care.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anaai.2017.08.005>.

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eTable 1

Professional Claims

Description of diagnosis	Professional claims
Triggers	
Food	693.10, 995.6x, and 995.7
Medication	693.0, 995.2x, 995.4, E930.x, and E931.x
Venom	989.5, E905.3, E905.5, E905.8, and E905.9
Other	not categorized in above 3 groups
Cardiac disease	
Hypertensive disease	401.x, 402.xx, 404.xx, and 405.xx
Coronary atherosclerosis	414.00–414.05
Congestive heart failure	428.x
Asthma	493.xx except 493.93
Eczema	691.8, 692.xx except 692.97
Allergy/immunology visit before index event	CPT codes 99201–99205, 99211–99215, and 99241–99245 and provider specialty
ICU admission	
Intensive care	revenue codes 20x
Coronary care	revenue codes 210, 211, 212, 214, and 219

Abbreviations: CPT, Current Procedural Terminology; ICU, intensive care unit.

eTable 3

Multivariable Predictors of EAI Dispensing and A/I Follow-up for Adult Patients (≥18 Years)

Variable	EAI dispensing, OR (95% CI)	A/I follow-up, OR (95% CI)
Age, y		
18–34	ref	ref
35–64	0.99 (0.85–1.14)	1.17 (1.00–1.37)
≥65	0.42 (0.34–0.52)	0.70 (0.56–0.88)
Female sex	0.95 (0.84–1.06)	1.24 (1.08–1.42)
Census region		
Midwest	ref	ref
Northeast	1.07 (0.88–1.29)	1.00 (0.81–1.24)
South	0.91 (0.79–1.04)	0.93 (0.80–1.08)
West	1.06 (0.88–1.28)	0.99 (0.80–1.22)
Trigger		
Unspecified	ref	ref
Food	1.98 (0.17–2.29)	0.99 (0.84–1.16)
Venom	7.08 (5.03–9.96)	0.54 (0.36–0.80)
Medication	0.38 (0.31–0.46)	0.46 (0.37–0.57)
Cardiac disease	0.72 (0.63–0.83)	0.70 (0.60–0.82)
Diabetes mellitus	0.84 (0.71–0.99)	1.03 (0.85–1.24)
Asthma	1.00 (0.87–1.14)	1.45 (1.26–1.68)
Eczema	1.11 (0.93–1.32)	1.45 (1.21–1.74)
Allergy consult (prior 12 mo)	1.71 (1.02–2.87)	3.14 (1.89–5.20)
EAI dispensing (prior 12 mo)	1.84 (1.53–2.23)	2.43 (2.02–2.93)
ED disposition		
Inpatient (non-ICU) admission	ref	ref
ED discharge/observation	1.18 (0.93–1.50)	0.88 (0.68–1.14)
ICU admission	0.90 (0.67–1.21)	0.80 (0.58–1.11)

Abbreviations: A/I, allergy/immunology; CI, confidence interval; EAI, epinephrine auto-injector; ED, emergency department; ICU, intensive care unit; OR, odds ratio; ref, reference group.

eTable 2Multivariable Predictors of EAI Dispensing and A/I Follow-up Excluding Patients Identified by Method 2⁹ (n = 3,745)^a

Variable	EAI dispensing		A/I follow-up	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (y)				
0–4	3.30 (2.48–4.39)	<.001	3.41 (2.76–4.22)	<.001
5–17	1.80 (1.51–2.15)	<.001	1.66 (1.42–1.93)	<.001
18–34	ref		ref	
35–64	0.77 (0.68–0.89)	<.001	0.76 (0.66–0.87)	<.001
≥65	0.30 (0.24–0.38)	<.001	0.37 (0.28–0.48)	<.001
Female sex	1.01 (0.93–1.09)	.85	1.09 (1.01–1.17)	.03
Census region				
Midwest	ref		ref	
Northeast	0.98 (0.83–1.14)	.76	0.98 (0.84–1.14)	.79
South	0.82 (0.73–0.93)	.001	0.97 (0.86–1.09)	.57
West	1.40 (1.18–1.66)	<.001	1.04 (0.89–1.22)	.61
Trigger				
Unspecified	ref		ref	
Food	0.97 (0.82–1.15)	.72	1.24 (1.04–1.47)	.02
Venom	3.21 (2.26–4.55)	<.001	0.78 (0.55–1.11)	.17
Medication	0.45 (0.35–0.59)	<.001	0.83 (0.61–1.13)	.24
Cardiac disease	0.89 (0.81–0.99)	.03	0.89 (0.79–1.00)	.04
Diabetes mellitus	0.94 (0.84–1.07)	.35	1.03 (0.90–1.18)	.70
Asthma	1.00 (0.92–1.10)	.97	1.10 (1.01–1.20)	.02
Eczema	0.98 (0.88–1.09)	.67	1.15 (1.04–1.27)	.005
Allergy consult (prior 12 mo)	1.24 (0.94–1.63)	.12	1.91 (1.49–2.46)	<.001
EAI dispensing (prior 12 mo)	1.21 (1.09–1.34)	<.001	1.19 (1.08–1.30)	<.001
ED disposition				
Inpatient (non-ICU) admission	ref		ref	
ED discharge/observation	1.38 (1.17–1.62)	<.001	1.06 (0.88–1.27)	.54
ICU admission	0.90 (0.71–1.13)	.35	0.84 (0.64–1.11)	.22

Abbreviations: A/I, allergy/immunology; CI, confidence interval; EAI, epinephrine auto-injector; ED, emergency department; ICU, intensive care unit; OR, odds ratio; ref, reference group.

^aMultivariable analysis was adjusted for year of visit.**eTable 4**

Multivariable Predictors of EAI Dispensing and A/I Follow-up for Children and Adolescents (<18 Years)

Variable	EAI dispensing, OR (95% CI)	A/I follow-up, OR (95% CI)
Age (y)		
0–4	1.71 (1.26–2.32)	2.21 (1.74–2.82)
5–17	ref	ref
Female sex	0.95 (0.75–1.20)	0.94 (0.77–1.15)
Census region		
Midwest	ref	ref
Northeast	1.46 (0.99–2.16)	1.20 (0.88–1.65)
South	0.86 (0.65–1.15)	0.87 (0.68–1.12)
West	1.54 (1.03–2.29)	1.09 (0.79–1.49)
Trigger		
Unspecified	ref	ref
Food	2.69 (2.10–3.44)	0.99 (0.80–1.23)
Venom	4.48 (1.70–11.83)	0.56 (0.26–1.20)
Medication	0.30 (0.17–0.52)	0.49 (0.28–0.85)
Cardiac disease	0.52 (0.08–3.54)	0.30 (0.03–2.79)
Diabetes mellitus	1.17 (0.50–2.71)	0.66 (0.32–1.33)
Asthma	0.81 (0.62–1.05)	1.31 (1.05–1.63)
Eczema	1.08 (0.79–1.47)	1.67 (1.30–2.15)
Allergy consult (prior 12 mo)	1.50 (0.66–3.41)	2.23 (1.11–4.47)
EAI dispensing (prior 12 mo)	2.54 (1.89–3.42)	1.33 (1.07–1.67)
ED disposition		
Inpatient (non-ICU) admission	ref	ref
ED discharge/observation	0.68 (0.36–1.26)	0.65 (0.38–1.11)
ICU admission	4.54 (0.5–40.99)	0.80 (0.24–2.67)

Abbreviations: A/I, allergy/immunology; CI, confidence interval; EAI, epinephrine auto-injector; ED, emergency department; ICU, intensive care unit; OR, odds ratio; ref, reference group.