

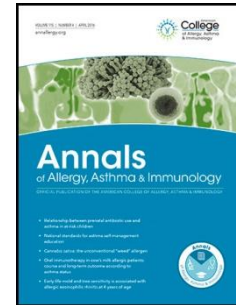
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Concordance with Anaphylaxis Care Guidelines and the Impact on Healthcare Resource Utilization in the USA

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26 *Abbreviations used*

27 EAI - Epinephrine auto-injector

28 ED - Emergency department

29 HCRU - Healthcare resource utilization

30 IQR - Interquartile range

31 SD - Standard deviation

32 US/USA - United States of America

33

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For patients who have experienced anaphylaxis, United States (US) guidelines recommend first-line therapy with epinephrine to prevent fatalities, as well as prescription of an epinephrine auto-injector (EAI), referral to an allergist/immunologist, and training to identify and avoid the responsible allergen.¹⁻³ However, adherence to these guidelines is low⁴⁻⁶ and generally, patients face increased healthcare resource utilization (HCRU) and associated costs.⁴

We evaluated concordance with pre-event and post-discharge care guidelines and HCRU among adults (age ≥ 18 years) and children (age < 18 years) using inpatient or emergency department (ED) claims for anaphylaxis in the MarketScan[®] Commercial Claims and Encounters (Commercial) and Medicare Supplemental and Coordination of Benefits databases. These databases comply with the Health Insurance Portability and Accountability Act of 1996. As this study was comprised of de-identified data, it was exempt from review and approval by an institutional review board. Patients were selected if they had ≥ 1 claim for anaphylaxis between January 1, 2009, and December 31, 2012, and continuous medical/pharmaceutical coverage for ≥ 1 year pre-index (baseline period) and post-index (follow-up period). The first claim during that period was recorded as index date but patients might have had an event prior to the baseline

period. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis algorithm was used to identify claims for anaphylaxis, including food-induced anaphylaxis (eTable 1) and features of non-food-based anaphylactic syndrome sufficient to make a diagnosis of anaphylaxis (eTable 2). Patients were excluded if the symptoms were a result of direct venom toxicity from an animal or plant rather than anaphylaxis. Analyses were performed using SAS 9.4 (SAS Institute, Cary NC). No statistical comparisons were performed. Mean (standard deviation [SD]) were calculated for continuous variables, median (interquartile range, IQR) for non-normally distributed data.

Baseline and demographic characteristics are shown in eTable 3. Of 15,316 eligible patients, 11,389 (74%) were adults and 3,927 (26%) were children. Ages at index event ranged throughout the lifespan, including patients <2 and ≥65 years of age.

Endpoint results are shown in Table 1. Before the index event, only 16% of patients had ≥1 EAI fill (11% of adults, 32% of children; mean duration [SD] between EAI fill and event: 4.6 [3.5] months) and 11% have visited an allergist (8% of adults, 21% of children). Thus, many patients were not prepared for the index event and were therefore at greater risk of anaphylaxis-related medical events, costly ED visits, and hospital admissions. Overall, median annual treatment costs (IQR) in the follow-up period were almost twice as high for patients without (\$23,045 [\$8,988–60,929]) vs. patients with a pre-index EAI fill for 12 (\$12,603 [\$5,592–31,640]) or 18 months (Table 1) before the event. Similarly, median hospitalization costs (IQR) in the follow-up period were higher for patients without (\$50,660 [\$21,506–115,000]) vs. patients with a prescription (\$40,396 [\$19,073–106,879]). Although, after occurrence of an anaphylactic event, guidelines strongly recommend prescription of an EAI (2 doses recommended because a second dose is required in 12% to 36% of patients) and referral to a medical specialist,^{1–3} only about half of all

patients (53%; 46% of adults, 76% of children) had EAI fills in the follow-up period and 27% (23% of adults, 42% of children) visited an allergist, with the mean number of visits decreasing from baseline to follow-up (Table 1). The numbers of patients with post-discharge EAI fills and post-discharge visits to medical specialists were still suboptimal, indicating inadequate adherence to guidelines. However, the need to follow post-discharge care guidelines and adequately equip patients to deal with future episodes is highlighted by the finding that 18% of patients (16% of adults, 24% of children) experienced a subsequent anaphylaxis event. Suboptimal levels of EAI prescription fills and visits to allergists were also reported in studies that assessed claims in the Truven Health MarketScan databases between 2002 and 2008. Only 54% of adults and 83% of children with food-induced anaphylaxis received ≥ 1 EAI prescription and even fewer consulted an allergist (22% of adults, 43% of children) after the event.^{5,6} A reason for guideline non-adherence might be a lack of knowledge of anaphylaxis among non-allergist healthcare professionals, other caregivers, and patients.⁷⁻¹⁰ One study demonstrating the need to improve non-allergist's knowledge of anaphylaxis reported that only 56% of 468 US pediatricians correctly diagnosed anaphylaxis and identified epinephrine as the appropriate medication when being presented a child's symptoms after ingesting peanut.⁸ Potential reasons for inadequate use of EAIs by patients and caregivers include lack of training, inconsistent advice from healthcare professionals, the belief that emergency services would be available if required, concerns as to how the device may be perceived in public, and inconvenience to carry the EAI.^{7, 9, 10}

Details on types and causes of anaphylaxis-related medical events and interventions are also provided in Table 1. Acute respiratory failure (6%) and hypotension (8%), and cardiorespiratory/resuscitative interventions (36%) were more frequent in adults without than in

adults with a fill in the previous 12 months (3% and 4%, and 27%, respectively). Details on the most common secondary adverse events are shown in eTable4.

This study is subject to limitations common to all studies that utilize retrospective claims data, such as potential coding errors, physician misdiagnosis, and incomplete data. It is unknown whether patients who had an EAI fill actually used it in the event of an anaphylaxis and whether patients received a fill without using their insurance. Furthermore, the data came from an insured population (private and government sponsored) in the US, and thus may not be completely applicable to uninsured individuals.

In conclusion, this retrospective study of real world data demonstrates that patients in this population were not prepared for anaphylactic events and therefore were at risk for life threatening anaphylaxis due to suboptimal maintenance of EAI prescriptions and visits to allergists. Care guidelines were inadequately followed after the index event. Therefore, it may be necessary to improve educational programs and safety information delivered to healthcare professionals, patients, and caregivers, including the use of EAI to treat anaphylaxis. This may help improve patient outcomes and reduce healthcare costs.

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Respiratory events	1,797 (18.1)	277 (11.0)	202 (16.6)	136 (11.0)	248 (16.9)	146 (10.3)
Hypotension	761 (7.7)	37 (1.5)	46 (3.8)	8 (0.6)	55 (3.7)	8 (0.6)
Cardiac arrest	45 (0.5)	3 (0.1)	6 (0.5)	1 (0.1)	6 (0.4)	1 (0.1)

Number of patients with anaphylaxis-related interventions (%)

Cardiorespiratory/ resuscitative interventions	3,574 (36.0)	133 (5.3)	322 (26.5)	45 (3.6)	385 (26.2)	56 (3.9)
Intubation	257 (2.6)	7 (0.3)	14 (1.2)	1 (0.1)	17 (1.2)	1 (0.1)
Laryngoscopy/ tracheostomy	296 (3.0)	8 (0.3)	22 (1.8)	1 (0.1)	27 (1.8)	1 (0.1)
CPR	17 (0.2)	–	2 (0.2)	1 (0.1)	3 (0.2)	1 (0.1)
Epinephrine administration	1,151 (11.6)	454 (18.1)	135 (11.1)	172 (13.8)	169 (11.5)	202 (14.2)

Abbreviations: CPR, Cardiopulmonary resuscitation; EAI, Epinephrine auto-injector; IQR, Interquartile range; SD, Standard deviation.

^a Events occurred within 1-week on or after the index date.

170 **Electronic Supplementary Tables**

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171 **eTable 1** Anaphylaxis Codes

ICD-9-CM Code	Description
Method I	
995.6	Anaphylactic reaction due to unspecified food
995.60	Anaphylactic reaction due to unspecified food
995.61	Anaphylactic reaction due to peanuts
995.62	Anaphylactic reaction due to crustaceans
995.63	Anaphylactic reaction due to fruits and vegetables
995.64	Anaphylactic reaction due to tree nuts and seeds
995.65	Anaphylactic reaction due to fish
995.66	Anaphylactic reaction due to food additives
995.67	Anaphylactic reaction due to milk products
995.68	Anaphylactic reaction due to eggs
995.69	Anaphylactic reaction due to other specified food
995.0	Other anaphylactic reaction
Method II	
995.1	Angioneurotic edema, not elsewhere classified
995.2	Unspecified AE of drug medicinal and biological substance not elsewhere classified
995.3	Allergy, unspecified, not elsewhere classified
995.4	Shock due to anesthesia, not elsewhere classified
989.5	Toxic effect of venom
E905	Venomous animals/plants
E905.3	Sting of hornets, wasps, and bees causing poisoning and toxic reactions
E905.5	Other venomous arthropods causing poisoning and toxic reactions
E905.8	Poisoning and toxic reactions caused by other specified animals and plants

E905.9 Poisoning and toxic reactions caused by unspecified animals and plants

172 Abbreviations: AE, Adverse effect; ICD-9-CM, International Classification of Diseases, Ninth Revision,

173 Clinical Modification.

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177 **eTable 2** Features of Anaphylactic Syndrome

Anaphylactic syndrome description and ICD-9-CM code
Skin-mucosal tissue involvement (conjunctival edema [ICD-9-CM code 372.73], edema of eyelid [374.82], edema of pharynx or nasopharynx [478.25], edema of larynx [478.6], pruritus of genital organs [698.1], other specified pruritic conditions [698.8], unspecified pruritic disorder [698.9], flushing [782.62], allergic urticaria [708.0], idiopathic urticaria [708.1], urticaria due to cold and heat [708.2], dermatographic urticaria [708.3], vibratory urticaria [708.4], cholinergic urticaria [708.5], other specified urticaria [708.8], urticaria, unspecified [708.9]) in conjunction with shock due to anesthesia (995.4)
Respiratory compromise (extrinsic asthma, unspecified [493.00], extrinsic asthma with status asthmaticus [493.01], extrinsic asthma with (acute) exacerbation [493.02], asthma, unspecified type, unspecified [493.90], asthma, unspecified type, with status asthmaticus [493.91], asthma, unspecified type, with (acute) exacerbation [493.92], acute respiratory failure [518.81], other pulmonary insufficiency, not elsewhere classified [518.82], respiratory abnormality, unspecified [786.00], hyperventilation [786.01], orthopnea [786.02], apnea [786.03], Cheyne-Stokes respiration [786.04], shortness of breath [786.05], tachypnea [786.06], wheezing [786.07], other respiratory abnormalities [786.09], stridor [786.1]) in conjunction with shock due to anesthesia (995.4) or angioneurotic edema (995.1)
Reduced blood pressure (hypotension, orthostatic [458.0], iatrogenic hypotension [458.2], other specified hypotension [458.8], hypotension, unspecified [458.9], symptom, syncope and collapse [780.2]) in conjunction with skin-mucosal involvement (see above), angioneurotic edema (995.1), the toxic effect of venom (989.5), or an E-code indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9)

Reduced blood pressure (see above) and gastrointestinal symptoms (allergic gastroenteritis and colitis [558.3], nausea with vomiting [787.01], vomiting alone [787.03], abdominal pain, unspecified site [789.00], abdominal pain, right upper quadrant [789.01], abdominal pain, left upper quadrant [789.02], abdominal pain, right lower quadrant [789.03], abdominal pain, left lower quadrant [789.04], abdominal pain, periumbilic [789.05], abdominal pain, epigastric [789.06], abdominal pain, generalized [789.07], abdominal pain, other specified site [789.09]) in conjunction with an unspecified adverse effect due to the correct administration of a drug, medicinal, and biologic substance (995.2), or an unspecified allergic reaction (995.3)

Reduced blood pressure (see above) and skin-mucosal tissue involvement (see above) in conjunction with an unspecified adverse effect due to the correct administration of a drug, medicinal, and biologic substance (995.2), or an unspecified allergic reaction (995.3)

Respiratory compromise (see above) and reduced blood pressure (see above) in conjunction with an unspecified adverse effect due to the correct administration of a drug, medicinal, and biologic substance (995.2), or an unspecified allergic reaction (995.3)

Respiratory compromise (see above) and gastrointestinal symptoms (see above) in conjunction with an unspecified adverse effect due to the correct administration of a drug, medicinal, and biologic substance (995.2), an unspecified allergic reaction (995.3), skin-mucosal involvement (see above), the toxic effect of venom (989.5), or an E-code indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9)

Respiratory compromise (see above) and skin-mucosal tissue involvement (see above) in conjunction with an unspecified adverse effect due to the correct administration of a drug, medicinal, and biologic substance (995.2), an unspecified allergic reaction (995.3), the toxic effect of venom (989.5), or an E-code indicating the cause of poisoning was a venomous

animal/plant (E905, E905.3, E905.5, E905.8, E905.9)

Gastrointestinal symptoms (see above) and skin-mucosal tissue involvement (see above) in conjunction with an unspecified adverse effect due to the correct administration of a drug, medicinal, and biologic substance (995.2), an unspecified allergic reaction (995.3), the toxic effect of venom (989.5), or a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9)

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical

Modification.

Source: Harduar-Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. *J Allergy Clin Immunol*. 2010;126:98–104.

186 **eTable 3** Patient Demographics

	All patients	Adults	Children
	N=15,316	N=11,389	N=3,927
Sex, N (%)			
Male	6,853 (44.7)	4,559 (40.0)	2,294 (58.4)
Female	8,463 (55.3)	6,830 (60.0)	1,633 (41.6)
Age at index, N (%)			
<2 years	180 (1.2)	—	180 (4.6)
2–5 years	1,174 (7.7)	—	1,174 (29.9)
6–11 years	1,166 (7.6)	—	1,166 (29.7)
12–17 years	1,407 (9.2)	—	1,407 (35.8)
18–34 years	2,619 (17.1)	2,619 (23.0)	—
35–44 years	1,999 (13.1)	1,999 (17.6)	—
45–54 years	2,651 (17.3)	2,651 (23.3)	—
55–64 years	2,597 (17.0)	2,597 (22.8)	—
≥65 years	1,523 (9.9)	1,523 (13.4)	—
Payer, N (%)			
Commercial	13,793 (90.1)	9,866 (86.6)	3,927 (100.0)
Medicare Supplemental	1,523 (9.9)	1,523 (13.4)	—
Plan type, N (%)			
Basic/major medical	—	—	—
Comprehensive	856 (5.6)	830 (7.3)	26 (0.7)
EPO	170 (1.1)	122 (1.1)	48 (1.2)
HMO	3,030 (19.8)	2,204 (19.4)	826 (21.0)
POS	1,425 (9.3)	988 (8.7)	437 (11.1)
PPO	8,054 (52.6)	5,952 (52.3)	2,102 (53.5)
POS with capitation	75 (0.5)	57 (0.5)	18 (0.5)
CDHP	447 (2.9)	301 (2.6)	146 (3.7)
HDHP	218 (1.4)	143 (1.3)	75 (1.9)
Unknown	1,041 (6.8)	792 (7.0)	249 (6.3)
Region, N (%)			
Northeast	3,196 (20.9)	2,228 (19.6)	968 (24.7)
North central	3,676 (24.0)	2,756 (24.2)	920 (23.4)
South	5,258 (34.3)	4,079 (35.8)	1,179 (30.0)
West	2,917 (19.1)	2,158 (18.9)	759 (19.3)
Unknown	269 (1.8)	168 (1.5)	101 (2.6)
Comorbidities of interest, N (%)			
Allergic rhinitis	2,719 (17.8)	1,730 (15.2)	989 (25.2)
Asthma	4,145 (27.1)	2,627 (23.1)	1,518 (38.7)

Cardiovascular disease	1,627 (10.6)	1,560 (13.7)	67 (1.7)
COPD	834 (5.5)	811 (7.1)	23 (0.6)
Depression	1,566 (10.2)	1,413 (12.4)	153 (3.9)
Eczema	355 (2.3)	278 (2.4)	77 (2.0)
Hypertension	4,551 (29.7)	4,535 (39.8)	16 (0.4)
History of allergies	1,526 (10.0)	861 (7.6)	665 (16.9)
Psychiatric disease	27 (0.2)	27 (0.2)	—
Stroke	334 (2.2)	333 (2.9)	1 (0.0)
Thyroid disease	1,465 (9.6)	1,427 (12.5)	38 (1.0)
Encounter, N (%)			
ED	12,370 (80.8)	8,852 (77.7)	3,518 (89.6)
Inpatient	1,988 (13.0)	1,780 (15.6)	208 (5.3)
ED to inpatient	958 (6.3)	757 (6.6)	201 (5.1)
Enrollment, years			
Prior to index date			
Mean (SD)	2.48 (1.10)	2.51 (1.11)	2.39 (1.06)
Median	2.25	2.30	2.14
(interquartile range)	(1.55–3.30)	(1.57–3.36)	(1.49–3.11)
Post index date			
Mean (SD)	2.82 (1.23)	2.80 (1.23)	2.87 (1.23)
Median	2.59	2.57	2.65
(interquartile range)	(1.87–3.61)	(1.84–3.59)	(2.00–3.67)

Abbreviations: CDHP, Capital district physicians' health plan; COPD, Chronic obstructive pulmonary disease; ED, Emergency department; EPO, Exclusive provider organization; HDHP, High deductible health plan; HMO, Health maintenance organization; POS, Point of service; PPO, Preferred provider organization; SD, Standard deviation.

194 **eTable 4** Frequency of Secondary AEs (Incidence $\geq 5\%$ in Any Group)

AE	All patients N (%) 15,316 (100)	Adults n (%) 11,389 (100)	Child ren n (%) 3,927 (100)
Shortness of breath	2,314 (15.1)	2,045 (18.0)	269 (6.9)
Unspecified essential hypertension	2,288 (14.9)	2,279 (20.0)	—
Asthma, unspecified type, unspecified	2,137 (14.0)	1,410 (12.4)	727 (18.5)
Allergy, unspecified, not elsewhere classified	1,709 (11.2)	1,339 (11.8)	370 (9.4)
Other respiratory abnormalities	1,436 (9.4)	1,192 (10.5)	244 (6.2)
Swelling, mass, or lump in head and neck	1,369 (8.9)	1,060 (9.3)	309 (7.9)
Urticaria, unspecified	1,347 (8.8)	948 (8.3)	399 (10.2)
Other anaphylactic reaction	1,145 (7.5)	875 (7.7)	270 (6.9)
Allergic urticaria	1,119 (7.3)	791 (6.9)	328 (8.4)
Angioneurotic edema, not elsewhere classified	1,112 (7.3)	967 (8.5)	145 (3.7)
Rash and other nonspecific skin eruption	1,012 (6.6)	723 (6.3)	289 (7.4)
Unspecified pruritic disorder	888 (5.8)	746 (6.6)	142 (3.6)
Syncope and collapse	861 (5.6)	796 (7.0)	65 (1.7)
Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled	740 (4.8)	733 (6.4)	—
Tobacco use disorder	584 (3.8)	578 (5.1)	—
Hypotension, unspecified	594 (3.9)	569 (5.0)	25 (0.6)
Wheezing	504 (3.3)	275 (2.4)	229 (5.8)

195 Abbreviations: AE, Adverse event.

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