Ann Allergy Asthma Immunol 122 (2019) 401–406

Contents lists available at ScienceDirect

Trends in hospitalizations related to anaphylaxis, angioedema, and urticaria in the United States

Pragya Shrestha, MD [*]; Rashmi Dhital, MD [*]; Dilli Poudel, MD [*,†]; Anthony Donato, MD [*]; Paras Karmacharya, MD [*,‡]; Timothy Craig, DO [§]

[*] Department of Internal Medicine, Reading Hospital-Tower Health System, West Reading, Pennsylvania
[†] Division of Rheumatology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
[‡] Division of Rheumatology, Mayo Clinic, Rochester, Minnesota
[§] Division of Pulmonary, Allergy, and Critical Care Medicine, Penn State College of Medicine, Hershey, Pennsylvania

ARTICLE INFO

Article history:
Received for publication November 27, 2018.
Received in revised form February 1, 2019.
Accepted for publication February 2, 2019.

ABSTRACT

Background: Data on the prevalence of allergic disorders over time are limited. Recent studies have noted marked increase in the prevalence of allergic conditions in different parts of the world.
Objective: To examine time trends in the prevalence of anaphylaxis, angioedema, and urticaria in the United States.
Methods: Using the largest inpatient National Inpatient Sample data in the United States from 2001 to 2014, adults admitted with a primary diagnosis of anaphylaxis, angioedema, or urticaria were identified based on *International Classification of Diseases, Ninth Revision* codes. Yearly distribution of hospital admissions was stratified per different age groups, and yearly trends of hospitalizations related to anaphylaxis, angioedema, and urticaria were calculated.
Results: Although an increasing trend in the rate of hospitalizations was seen for angioedema (annual percentage change [APC], 4.48), a decreasing trend (APC, −2.19) was observed for urticaria-related hospitalizations. Overall anaphylaxis-related hospitalizations were noted to be stable, but a significant increasing trend was observed among those aged 5 to 14 years (APC, 4.19), mostly because of the subgroup of food-related hospitalizations (APC, 5.86). Angioedema-related hospitalizations were highest among the 35- to 64-year age group (APC, 5.38).
Conclusion: An increasing trend of hospitalizations has been observed for allergic conditions, with varying age distribution according to the nature of eliciting agent and susceptibility of different age groups. Although angioedema has been observed as an increasing problem in older populations, food-induced anaphylaxis is an increasing concern in the younger population.
© 2019 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Allergic disorders are common clinical disorders with high rates of health care use.[1] Studies from developed countries have suggested an increasing prevalence of allergic diseases.[2–4] However, the data on the epidemiology of anaphylaxis, angioedema, and urticaria are limited, with only small cohort studies available.[1,4] Recent studies from the United Kingdom and Australia have noted a marked increase in hospitalizations related to urticaria, angioedema, and anaphylaxis.[1,4] Epidemiologic study and incidence data of these conditions, however, depend on several factors, including diagnostic criteria used, variation in patient surveys, disease incidence in the general population, and diagnostic awareness among physicians. In this study, we sought to assess the trends in the incidence rates of hospitalization for these allergic conditions (anaphylaxis, angioedema, and urticaria) in the United States as a marker of disease prevalence using a large inpatient database.

Methods

This retrospective study was performed using the Nationwide Inpatient Sample database for the years 2001 to 2014. The Nationwide Inpatient Sample database is the largest inpatient database in the United States and is part of the Healthcare Cost and Utilization Project, sponsored by Agency for Healthcare Research and Quality. Approximately 8 million to 9 million hospitalizations are sampled each year, which, when weighted, is estimated to be

Reprints: Pragya Shrestha, MD, Division of Internal Medicine, Reading Hospital-Tower Health System, Reading, PA 19610; E-mail: sh.pragya@gmail.com.
Disclosures: Authors have nothing to disclose.
Funding: none.

https://doi.org/10.1016/j.anai.2019.02.003
1081-1206/© 2019 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Table 1
Baseline characteristics of Patients Admitted With Anaphylaxis, Angioedema, and Urticaria in the United States (2001-2014)

Variable	Year													
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Total No. of discharges with any allergic diagnosis (anaphylaxis, angioedema, urticaria) (weighted)	37,187,646	37,804,054	38,220,591	38,661,786	39,163,834	39,450,216	39,541,948	39,885,120	39,434,956	39,008,298	38,590,733	36,484,846	35,597,792	35,358,818
Anaphylaxis														
No. of discharges (weighted)	14,685	16422	15725	17132	17026	16667	15725	15704	16254	16667	16037	16290	16044	14,840
Patients hospitalized, %	0.04	0.04	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.05	0.04
Females, %	51.6	51.7	51.32	49.3	49.01	50.03	52	50	50	50.4	51.04	50.09	51.5	52
Age, median (range), y	48 (32-67)	48 (32-66)	47 (32-65)	46 (28-63)	46 (25-62)	45 (26-62)	47 (28-62)	48 (28-64)	48 (27-62)	47 (24-62)	49 (29-62)	47 (25-62)	47 (26-62)	47 (24-62)
Angioedema														
No. of discharges (weighted)	12,078	12,405	12,506	13,134	12,780	14,450	14,882	16,137	17,455	19,723	20,179.3	19,210.01	18,735	18,050
Patients hospitalized, %	0.03	0.03	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.05	0.05	0.05	0.05	0.05
Females, %	65	66	62	62	61	60.7	61	60	59.2	58.09	57.5	57.13	58.3	58.23
Age, median (range), y	61 (46-73)	61 (46-72)	59 (44-71)	59 (45-72)	60 (45-73)	59 (45-72)	60 (47-72)	60 (47-71)	59 (46-71)	60 (48-72)	60 (47-72)	59 (48-71)	59 (47-71)	59 (48-70)
Urticaria														
No. of discharges (weighted)	4062	3805	4062	3795	3728	3937	3684	3812	3460	3445	3389	2890	2600	2255
Patients hospitalized, %	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Females, %	65	66	63	65	62.1	64.4	63	61.23	60.3	63	67.5	63	63.5	61.42
Age, median (range), y	45 (25-64)	44 (24-60)	42 (20-59)	42 (22-58)	40 (16-58)	42 (16-60)	42 (17-59)	41 (17-59)	42 (21-62)	41 (20-60)	45 (23-61)	41 (15-58)	43 (17-59)	40 (18-58)

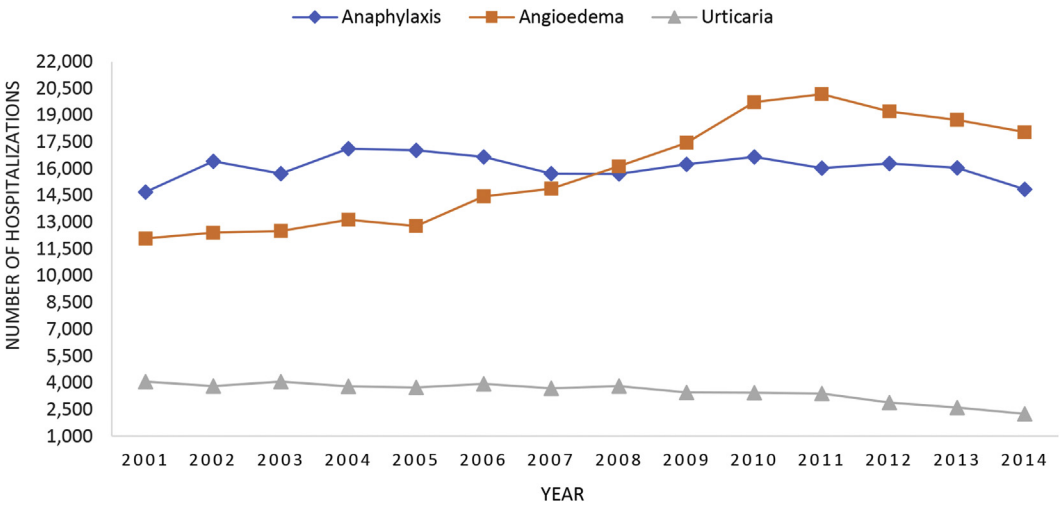


Figure 1. Anaphylaxis, angioedema, and urticaria hospitalization trends in the United States, 2001 to 2014.

greater than 35 million hospitalizations annually. It is designed to approximate a 20% stratified sample of all US hospitals.[5] *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD 9-CM*) codes were used to identify all patients discharged between January 1, 2001, and December 31, 2014, with a principal diagnoses of anaphylaxis (*ICD-9-CM* codes 995.0, 995.60-995.69, 999.40, 999.41, 999.41-999.42,999.49, 989.50, E905.0-E905.9, 995.20-995.24, 995.27, 995.29, V138.1, V150.6), angioedema (*ICD-9 CM* codes 277.6, 995.1), and urticaria (*ICD-9-CM* codes 708.0-708.9, 995.1). Only principal discharge diagnoses for these conditions were used to maximize the validity of the case definition.[6] Yearly distribution of hospital admissions was stratified per age groups (<5, 5-14, 15-34, 35-64, and ≥65 years). Anaphylaxis was further categorized into food-related and non–food-related anaphylaxis. Stata software, version 13.0 (StataCorp), Microsoft Excel 2016, and Joinpoint Regression Program, version 4.5.0.1 were used to calculate and plot yearly hospitalization trends for anaphylaxis, angioedema, and urticaria. Calculations were performed on weighted samples, and statistical significance was set at $P \leq .05$ (2-tailed).

Results

Between 2001 and 2014, a total of 446,942 hospital admissions for anaphylaxis, angioedema, and urticaria were coded in the United States (Table 1). Overall, a slightly higher female predominance was noted (anaphylaxis, 50.72%; angioedema, 60.35%; and urticaria, 63.00%). Trends of hospital admissions are depicted in Figure 1.

There were 221,724 hospitalizations for angioedema during the study period. Most angioedema-related hospitalizations were observed in the year 2011, with 20,179 admissions. Rate of admissions was highest in persons aged 35 to 64 years and lowest in children younger than 5 years (Fig 2A). The number of angioedema hospitalizations increased progressively from 12,078 in 2001 to 18,050 in 2014, with an overall increasing trend (annual percentage change [APC], +4.48) (Fig 3A). Admission trends were highest among the 35- to 64-year age group (APC, +5.38). Although overall hospitalizations were highest among the white population (115,101) (eFigure 1), a significant increase in the rate of hospital admissions for angioedema was seen among the black population (APC, +12.01 vs +3.67 in whites) through 2001 to 2014 (eFigure 2).

From 2001 to 2014, there was a significant decrease in the rate of hospital admissions for urticaria in all age groups (Fig 4A). The greatest decrease was in those 65 years and older (APC, −3.95), followed by the 35- to 64-year age group (APC, −3.7) (Fig 5A). However, the age group that was related to a higher number of admissions with urticaria was 5 to 14 years, with approximately 3 to 4 times higher admission proportions among total hospitalizations per year.

Anaphylaxis-related hospitalizations had no significant change (Fig 2B). However, the highest numbers of admissions were seen

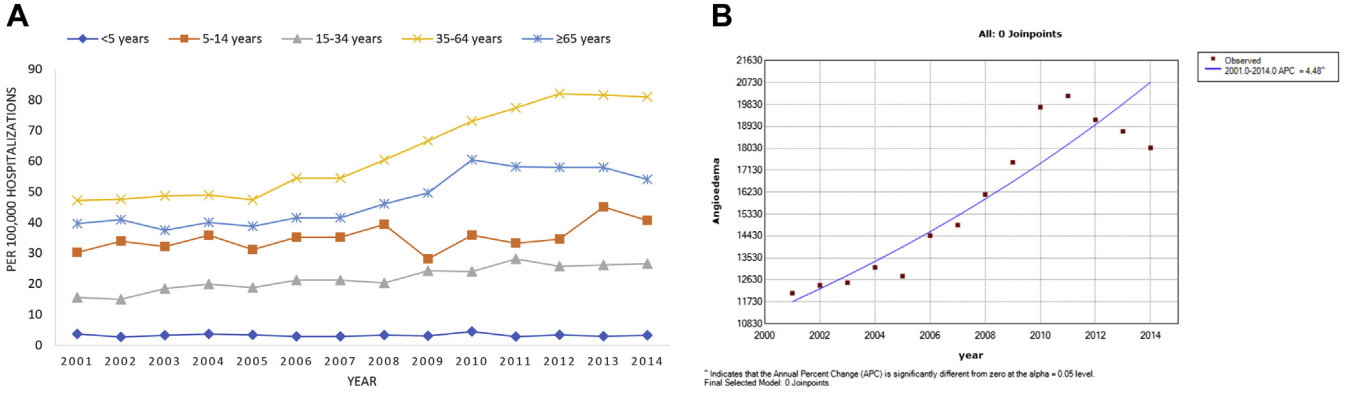


Figure 2. Angioedema-related hospitalization trends in the United States, 2001 to 2014. A, Hospitalizations by age; B, Join-Point regression analysis of trends.

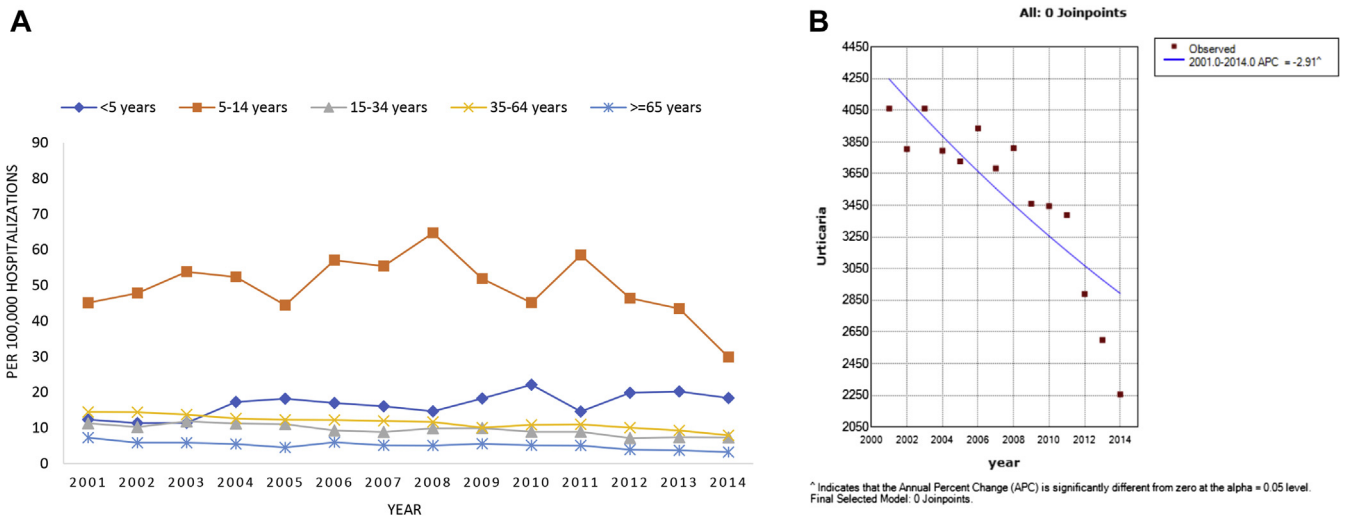


Figure 3. Urticaria-related hospitalization trends in the United States, 2001 to 2014. A, Hospitalizations by age; B, Join-Point regression analysis of trends.

in the 5- to 14-year age group, followed by the 35- to 64-year age group (Fig 3B). Significant increases in the rate of admissions were also seen in the same group, with an APC of 4.19 during the years of study. An increasing trend in the group younger than 5 years was noted (APC, 3.85), with a probable increase in occurrence in the following years. As expected, food-related anaphylaxis was highest among those younger than 5 years followed by those 5 to 14 years old (Fig 4B). However, remarkable increases in the rate of admissions with APCs of 5.86 and 5.63 were observed in those 5 to 14 and 15 to 34 years old, respectively, again, showing high susceptibility in children 5 to 14 years old. Non–food-related anaphylaxis was highest among those 65 years and older, with a stable rate of admissions during the study years in most age groups (Fig 5B).

Discussion

In this study, we observed a trend of increasing hospitalizations for angioedema, decrease in hospitalizations for urticaria, and no significant change in hospitalizations related to anaphylaxis in the United States during the years 2001 to 2014. This finding is in contrast to prior studies in the United Kingdom by Gupta et al[1] and Sheikh et al[7] and in Australia by Poulos et al[4] (1993-2005), where increasing trends were noted for all these conditions over time. The increasing trend in angioedema hospitalizations that we identified was consistent with a 1990 to 2003 US (New York) study by Lin et al.[8] Those authors also observed an association of urticaria with angioedema admissions, which they speculated was a possible contributing factor in its upward trend in angioedema admissions,[8] in contrast to our decrease in urticaria-related admissions in all age groups. The discrepancy with these studies might be secondary to a different demographic population or a new shift in the trends because our data analyzed more recent years.

The overall incidence of angioedema-related hospitalization seems to be mostly affected by a sharp increase in hospitalizations among the 35- to 64-year age group (APC, +5.38%), with a median (SD) age at presentation of 59.64 (19) years. This age range is similar to

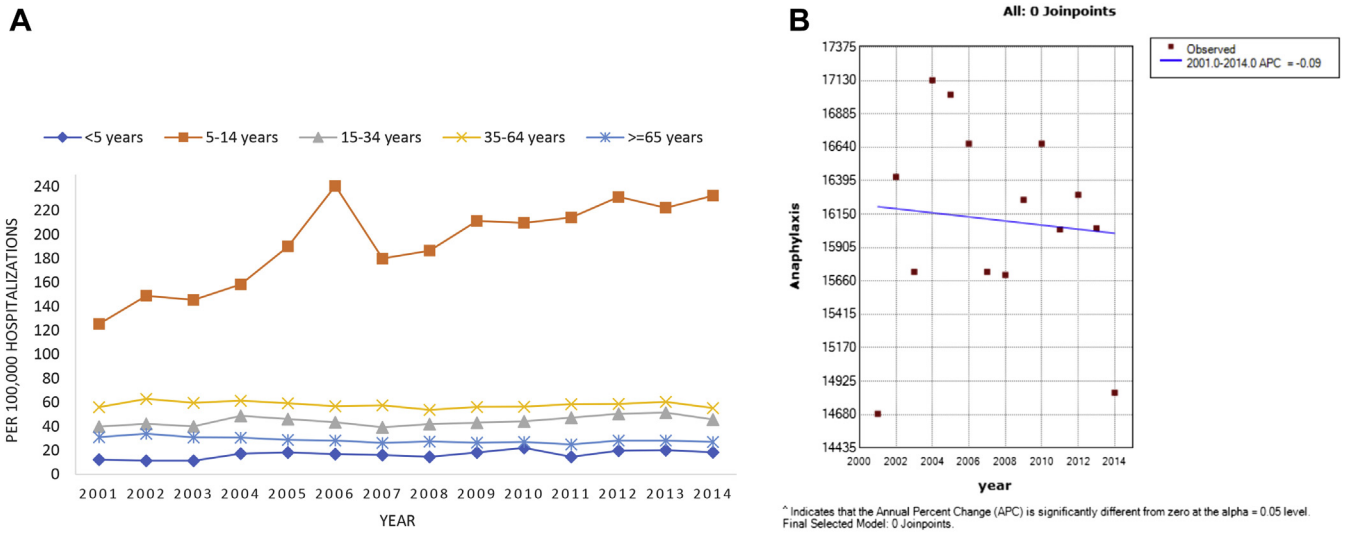


Figure 4. Anaphylaxis-related hospitalization trends in the United States, 2001 to 2014. A, Hospitalizations by age; B, Join-Point regression analysis of trends.

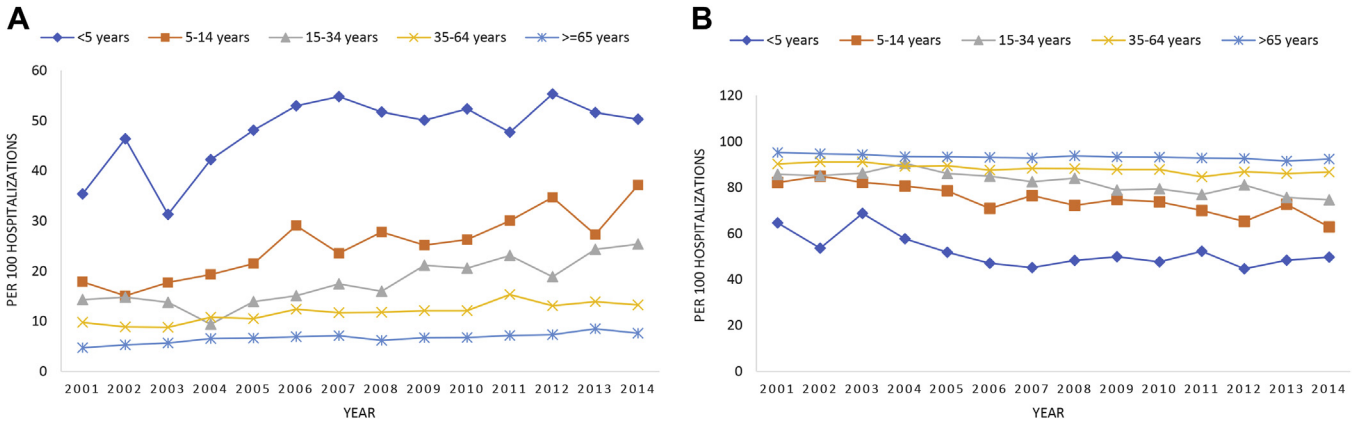


Figure 5. Food-related (A) and non–food-related (B) anaphylaxis hospitalization trends by age in the United States, 2001 to 2014.

reports of angioedema admissions with a diagnosis of hypertension associated with angiotensin-converting enzyme inhibitors (ACEIs[4,8] reported from Austria, Australia, and the United States.[8] ACEIs are some of the most commonly prescribed antihypertensives in the United Staets, accounting for 35% of all hypertension prescriptions to more than 40 million patients.[9] The overall incidence of ACEI-related angioedema is 0.1% to 0.7%.[10] A US national health survey reported an increase in overall antihypertensive prescriptions from 63.5% in 2001 to 77.3% in 2010,[12] with an increase in ACEI use by 31%. ACEI was found to be the second most commonly used antihypertensive drug class in 2001 to 2010 after calcium channel blockers.[12] ACEI-associated angioedema occurs within 1 month of prescription in 0.7% and another 0.23% during the first year along with higher associations among patients with history of nonsteroidal anti-inflammatory drug allergies.[11] Whether a stricter blood pressure control management as per new guidelines by the governing bodies or increasing use of medications, such as acetylsalicylic acid,[4] as a preventive care has any bearing on this trend would be subject for further studies.

We observed an overall decreased rate of admissions for urticaria with significant rate change in all age groups. Although no significant trend was observed over the years, the highest prevalence of urticaria was seen among the younger age group of 5 to 14 years. A study performed by Jackson et al[13] in 2013 found an increasing trend in allergic conditions among children younger than 18 years, which included urticaria among the skin allergy conditions.[13] This study found skin allergy to be more common in children compared with food allergy, but a consistent decreasing trend with increase in age was also noted.[13]

Our study found a relatively stable hospitalization trend for anaphylaxis. However, a significant increase in food-related anaphylaxis hospitalizations was observed. Food-related anaphylaxis was noted to be highest among the younger than 5-year age group, but an increasing trend was observed for the 5- to 14-year and 15- to 34-year age groups (Table 2). Although the specific foods leading to hospitalization for anaphylaxis were not known, prior studies have found that peanut and tree nut allergies were the common associations in younger patient populations in terms of nut allergies,[14,15] followed by milk and shellfish.[16] Trends in non–food-related anaphylaxis composed of anaphylaxis related to medications, vaccines, blood and blood product transfusion, and venom remained stable overall (Table 3).

The primary strength of this study arises from the use of a large database to observe any trends in allergic conditions. There were several limitations to our study. The main limitation is that hospitalizations may only represent a proportion of the incident cases of these conditions and that better management may decrease rates of hospitalizations despite increasing prevalence. Patients presenting to urgent care settings or managed in the outpatient settings would have been missed by our analysis. The data used in this study are based on reported hospitalization data and discharge codes, so uncoded or undiagnosed cases of anaphylaxis could have resulted in an underestimation of the true hospitalization incidence. The possibility of overreporting is also possible because 1 person may present with all 3 diagnosis. Although the use of hospitalization data represents only a proportion of prevalent cases, the large rate of increase or decrease in admissions likely reflects an existing disease pattern.

We observed an increasing trend in hospitalizations for angioedema, a decrease in hospitalizations for urticaria, and no significant change in hospitalizations related to anaphylaxis in the years 2001 to 2014 in the United States. An overall increase in angioedema-related hospitalization seems to be accounted for by a sharp increase in hospitalizations among the 35- to 64-year age group, and angioedema appears to mirror the trends of ACEI use.[8,12] An increasing trend of angioedema-related hospitalization among the black population was noted, which needs further

Table 2
Food-Related and Non–Food-Related Anaphylaxis Admissions in the United States (2001-2014)

Variable	Year													
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
No. of discharges with food-related anaphylaxis	1583	1757	1625	2027	2316	2585	2373	2252	2584	2747	2828	2830	2915	2780
Age, median, y	37	35	36	37	28	27	30	30	28	24	34	25	29	24
No. of discharges with non–food-related anaphylaxis	16,985	16,261	15,622	13,964	12,911	11,478	11,995	13,132	12,085	11,565	9521	9205	8815	8365
Age, median, y	50	50	49	47	47	47	48	51	50	50	52	50	50	50

Table 3
Non–Food-Related Anaphylaxis Admissions in the United States (2001-2014)

Variable	Year													
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Serum related	3422	3070	2702	3141	2983	2432	2849	2607	2752	3299	2193	2695	2375	2430
Medications related	13,563	13,191	12,920	10,823	9928	9046	9146	10,525	9333	8266	7328	6510	6435	5935
Venom related	0	0	0	0	0	0	0	0	0	0	0	0	0	5

study to look at possible genetic predisposition for this occurrence. Food-related anaphylaxis is an important cause of morbidity in children and appears to be increasing in the United States and many other developed countries.[1,4] More studies are needed to investigate the association of these trends in hospitalization rates with changes in allergen sensitization and triggers in community.

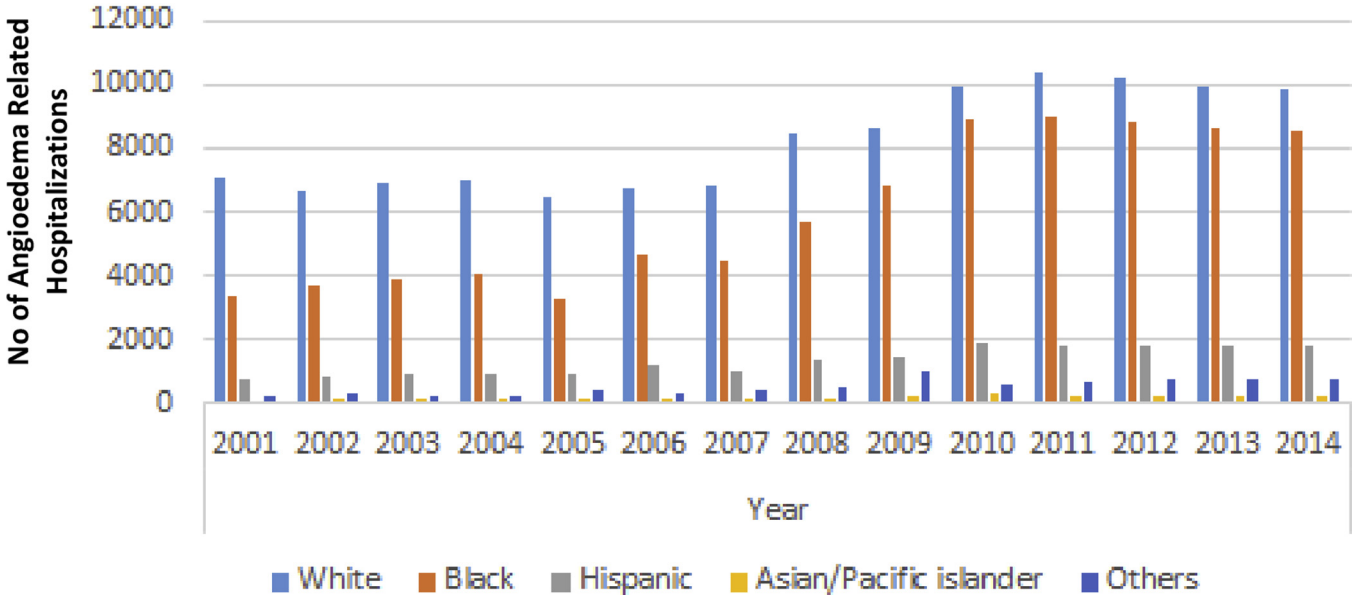
Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2019.02.003.

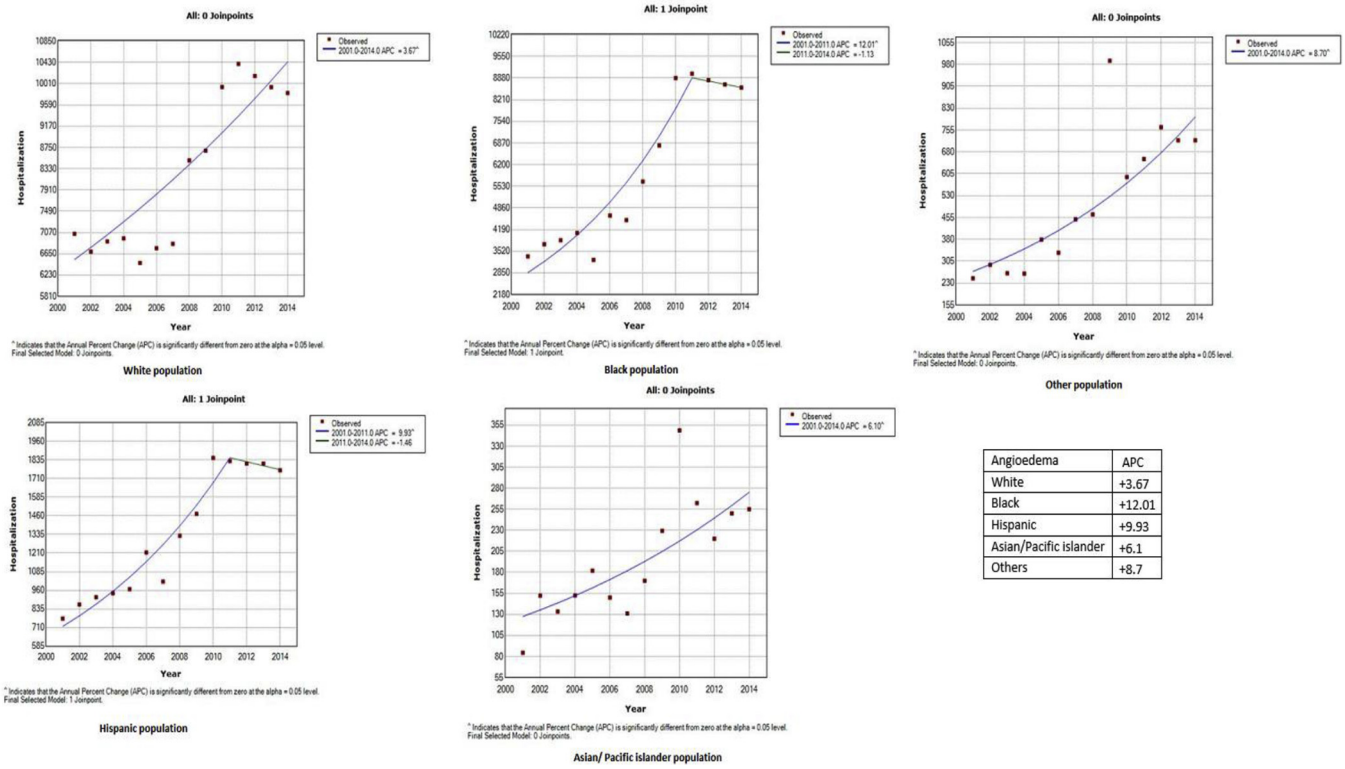
References

1. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax*. 2007;62(1):91–96.
2. Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol*. 2015;135(4):956–963.e1.
3. Wood RA, Camargo CA, Lieberman P, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin Immunol*. 2014;133(2):461–467.
4. Poulos LM, Waters A-M, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. *J Allergy Clin Immunol*. 2007;120(4):878–884.
5. HCUP-US NIS Overview. https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed December 3, 2017.
6. Patel NJ, Deshmukh A, Pant S, et al. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. *Circulation*. 2014;129(23):2371–2379.
7. Sheikh A, Alves B. Age, sex, geographical and socio-economic variations in admissions for anaphylaxis: analysis of four years of English hospital data. *Clin Exp Allergy*. 2001;31(10):1571–1576.
8. Lin RY, Cannon AG, Teitel AD. Pattern of hospitalizations for angioedema in New York between 1990 and 2003. *Ann Allergy Asthma Immunol*. 2005;95(2):159–166.
9. Ma J, Lee KV, Stafford RS. Changes in antihypertensive prescribing during US outpatient visits for uncomplicated hypertension between 1993 and 2004. *Hypertension*. 2006;48(5):846–852.
10. Messerli FH, Nussberger J. Vasopeptidase inhibition and angio-oedema. *Lancet*. 2000;356(9230):608–609.
11. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension. *Circulation*. 2012;126(17):2105–2114.
12. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology of ACE inhibitor angioedema utilizing a large electronic health record. *J Allergy Clin Immunol Pract*. 2017;5(3):744–749.
13. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. *NCHS Data Brief*. 2013;(121):1–8.
14. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010;125(6):1322–1326.
15. Allergy Statistics. The American Academy of Allergy, Asthma & Immunology. https://www.aaaai.org/about-aaaai/newsroom/allergy-statistics. Accessed July 1, 2018.

Supplementary Data



eFigure 1. Racial distributions of angioedema-related hospitalizations, United States, 2001 to 2014.



Angioedema	APC
White	+3.67
Black	+12.01
Hispanic	+9.93
Asian/Pacific islander	+6.1
Others	+8.7

eFigure 2. Join-Point regression analysis of trends of angioedema-related hospitalizations by race in the United States, 2001-2014. APC, annual percentage change.