Published in final edited form as:

J Allergy Clin Immunol Pract. 2019 January ; 7(1): 103–111. doi:10.1016/j.jaip.2018.06.010.

Drug-induced Anaphylaxis Documented in Electronic Health Records

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Abstract

Background—Although drugs represent a common cause of anaphylaxis, few large population-based studies of drug-induced anaphylaxis have been performed.

Objective—To describe the epidemiology and validity of reported drug-induced anaphylaxis in the electronic health records (EHRs) of a large United States healthcare system.

Methods—Using EHR drug allergy data from two large tertiary care hospitals from 1995–2013, we determined the population prevalence of anaphylaxis including anaphylaxis prevalences over time, and the most commonly implicated drugs/drug classes reported to cause anaphylaxis. Patient risk factors for drug-induced anaphylaxis were assessed using a logistic regression model. Serum tryptase and allergist visits were used to assess the validity and follow up of EHR-reported anaphylaxis.

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Conflicts of Interest

ND is a St. John's University post-doctoral fellow with Daiichi Sankyo, Inc. RD is an MCPHS University post-doctoral fellow with Sanofi Genzyme. AS, MT, DWB, KGB, and LZ report no conflicts of interest.

Results—Among 1,756,481 patients, 19,836 (1.1%) reported drug-induced anaphylaxis: Penicillins (45.9 per 10,000), sulfonamide antibiotics (15.1 per 10,000), and nonsteroidal anti-inflammatory drugs (NSAIDs) (13.0 per 10,000) were most commonly implicated. Patients with white race (odds ratio [OR] 2.38, 95% CI 2.27–2.49), female sex (OR 2.20, 95% CI 2.13–2.28), systemic mastocytosis (OR 4.60, 95% CI 2.66–7.94), Sjögren’s syndrome (OR 1.94, 95% CI 1.47–2.56), and asthma (OR 1.50, 95% CI 1.43–1.59) had an increased odds of drug-induced anaphylaxis. Serum tryptase was performed in 135 (<1%) anaphylaxis cases and 1,587 patients (8.0%) saw an allergist for follow-up.

Conclusion—EHR-reported anaphylaxis occurred in approximately 1% of patients, most commonly from penicillins, sulfonamide antibiotics and NSAIDs. Females, whites, and patients with mastocytosis, Sjögren’s syndrome, and asthma had an increased risk of reporting drug-induced anaphylaxis. The majority of EHR-reported drug-induced anaphylaxis was not confirmed with tryptase testing or specialist evaluation.

Keywords

drug; IgE; allergy; epidemiology; electronic health records; hypersensitivity

Introduction

Anaphylaxis is a severe and life-threatening allergic reaction.¹ The majority of hospital admissions for anaphylaxis in adults are triggered by drugs,² and about one in 2,700 hospitalized patients suffers drug-induced anaphylaxis.^{3,4} Although many studies on adverse reactions to drugs have been published, data specifically describing drug-induced anaphylaxis are sparse.^{5–8}

Previous studies investigating anaphylaxis epidemiology in the US used billing codes to broadly determine causes of anaphylaxis (e.g. drug, food, and venom), but lacked information on specific causative drugs or drug classes.^{4,9,10} Other drug allergy studies focused on reactions due to a single drug or drug class, or assessed all types of drug hypersensitivity reactions.¹¹ Drug allergy studies using large allergy repositories or electronic health record (EHR) allergy lists to describe drug allergy have been infrequent;^{6,9,12} furthermore, studies that investigate associations with drug anaphylaxis have been limited in scope and/or sample size.^{9,13}

We used a data repository containing patients’ allergy history documented in the allergy module of the EHR to describe the epidemiology of drug-induced anaphylaxis in a large healthcare system over the past 18 years.

Methods

Settings and Data Collection

Data were collected from Partners HealthCare System (PHS), an integrated healthcare delivery network in the Greater Boston area that includes Brigham and Women’s Hospital (BWH) and Massachusetts General Hospital (MGH). At PHS, patient allergy information captured by the EHR allergy module was integrated into the Partners’ Enterprise-wide

Allergy Repository (PEAR),¹⁴ resulting in a longitudinal allergy record accessible across the healthcare network. Included patients had allergies that were either observed by clinicians directly in the healthcare setting or reported by patients as having occurred previously. Because entries may or may not have been confirmed by clinical reasoning or diagnostic testing, we use ‘reported allergies’ and ‘reported anaphylaxis’ throughout the manuscript text.

Patients who visited BWH and/or MGH between 1995 and 2013 were included in this study. Drug allergy information from PEAR included the ‘allergen’ (i.e., culprit drug), allergy status (i.e., active or inactive), date/time reported or updated, and reaction(s). Reactions, which included side effects, toxicities, and hypersensitivity reactions, were entered using either a predefined pick list (e.g., anaphylaxis, hives, rash, etc.) or as free-text. Patients were considered to have reported anaphylaxis if the reaction recorded in PEAR was either coded ‘anaphylaxis’ or a free-text entry that mapped to ‘anaphylaxis’ because of synonyms (e.g., anaphylactic reaction, anaphylactic) or a misspelling (e.g., anapylatic, anapalaxis).

Patients’ demographics were obtained from EHR demographic tables. Comorbidities of interest included systemic mastocytosis, Sjögren’s syndrome, asthma, chronic obstructive pulmonary disease (COPD), endometriosis, inflammatory gastric disorders, lupus erythematosus, rheumatoid arthritis, multiple sclerosis, psychiatric disorders, hyperthyroidism, allergic rhinitis, and hypothyroidism,^{15–18} which were identified using the EHR’s problem list and the Agency for Healthcare Research and Quality Clinical Classifications Software¹⁹ and were considered present if one or more instance was entered at any time prior to the first anaphylaxis recorded date.

To determine the validity of EHR allergy list documentation of anaphylaxis, we used tryptase laboratory data from 2009 to 2013 retrieved from the EHR’s laboratory data section. This time-frame was identified because of testing availability at PHS. For all patients who had a serum tryptase drawn within 1 week of anaphylaxis recorded date, free-text notes within the EHR were manually reviewed to retrieve anaphylaxis causative agent and tryptase order time. We defined a positive tryptase as tryptase > 11.4 ng/mL, mature tryptase > 1 ng/mL, or beta tryptase > 1 ng/mL.²⁰ We determined if the tryptase was drawn in the appropriate time window, defined as within three hours from reported anaphylactic reaction date/time.

Using encounter tables, we also determined whether patients with reported anaphylaxis had follow-up with a PHS Allergy/Immunology specialist within the study period, and specifically within 30 days of anaphylaxis recorded date. Frequencies of tryptase test usage and specialist follow-up were also displayed over time.

Data Analysis

Prevalence was compared by sex and race/ethnicity using chi-square tests. We examined comorbidities between patients with and without drug-induced anaphylaxis using chi-square tests. We created a multivariable logistic regression model to identify independent risk factors for drug-induced anaphylaxis. The model was built using univariable screening that identified potential imbalances between patients with and without drug-induced anaphylaxis.

Sex, race/ethnicity, and all variables with $p < 0.05$ in the model were included in the final multivariable model.

Prevalence was calculated by specific drug and drug class overall, and over time. Drugs were grouped using the American Hospital Formulary Service Pharmacologic-Therapeutic Classification of drug classes.²¹ In our results, we display drugs that comprised at least 1% of reported anaphylaxis cases, or were pre-specified as clinically important from prior allergy literature.²² The incidence of drug-induced anaphylaxis was calculated as the number of patients with reported drug-induced anaphylaxis out of the total number of patients in PEAR each year.

Statistical analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Inc. Cary, NC, USA). $P < 0.05$ was considered statistically significant.

This study was approved by the Partners Institutional Review Board.

Results

General Description of Population

Of 1,756,481 patients, 622,152 (35.4%) of patients had at least one reported drug allergy; 19,836 (1.1%) had at least one reported case of drug-induced anaphylaxis (Table I), with a total of 24,970 reported cases of drug anaphylaxis.

Most patients in the total population were white (70.4%) and female (57.9%). Other races were less common: Hispanic (8.1%), black (7.1%), and Asian (4.1%).

Prevalence Rates of Reported Anaphylaxis by Drugs and Drug Classes

Penicillins (45.9 per 10,000 patients, $n=8,071$), sulfonamide antibiotics (15.1 per 10,000, $n=2,656$), nonsteroidal anti-inflammatory drugs (NSAIDs) (13.0 per 10,000, $n=2,274$), and opiates (9.8 per 10,000, $n=1,727$) were the most common drug class causes of anaphylaxis (Table II). Other antibiotics such as cephalosporins (6.1 per 10,000, $n=1,078$), macrolides (3.8 per 10,000, $n=659$), and fluoroquinolones (3.7 per 10,000, $n=641$) were also common. Codeine (3.6 per 10,000, $n=633$), morphine (2.8 per 10,000, $n=490$), and erythromycin (2.4 per 10,000, $n=420$) were the most commonly reported individual drug allergens.

All drug classes and individual drugs that triggered anaphylaxis were more common in females than males (Table II). Penicillins (55.8 per 10,000 vs. 32.4 per 10,000, $p < 0.01$), sulfonamide antibiotics (21.9 per 10,000 vs. 5.8 per 10,000, $p < 0.01$), and NSAIDs (16.2 per 10,000 vs. 8.5 per 10,000, $p < 0.01$) were also the most common drug classes causing anaphylaxis in females.

Most of the drug classes causing anaphylaxis were more prevalent in white patients (Table II), with penicillins (52.9 per 10,000 in whites vs. 25.5 per 10,000 in non-whites), sulfonamide antibiotics (18.6 per 10,000 in whites vs. 4.9 per 10,000 in non-whites), and NSAIDs (14.3 per 10,000 in whites vs. 9.4 per 10,000 in non-whites) also having the highest prevalence (all $p < 0.01$). Individual drug allergens that were more prevalent in whites included codeine (4.4 per 10,000 vs. 1.1 per 10,000), morphine (3.2 per 10,000 vs. 1.4 per

10,000), erythromycin (3.0 per 10,000 vs. 0.8 per 10,000), and amoxicillin (2.4 per 10,000 vs. 0.8 per 10,000).

Angiotensin-converting enzyme (ACE) inhibitors were more common causes of anaphylaxis in black patients (2.7 per 10,000 in blacks vs. 1.2 per 10,000 in non-blacks, $p < 0.01$). No drug class or individual drug allergen was significantly more prevalent in Hispanic patients, Asian patients, or patients of other race/ethnicity.

Drug Anaphylaxis Incidence and Culprit Agents over Time

The number of patients with drug anaphylaxis increased over the study period (Figure 1A). The number of patients ranged from approximately 100 – 320 early in the study with a steep increase in 2004, which had 1,480 patients. The number of patients decreased the following year (582 patients in 2005), but subsequently rose until the end of the study period in 2013 (4,603 patients). The total number of patients included in PEAR each year also saw a similar increase in 2004 (126,517 patients) and steadily increased until the end of the study period (324,860 patients). The incidence rate of drug-induced anaphylaxis remained between about 0.75–1.1% for most of the study period with the exception of two increases in 2004 (1.2%) and 2010 (1.3%), but reached the highest rate in the last year of the study (1.4% in 2013) (Figure 1B).

The rate of reported drug anaphylaxis due to penicillins decreased in recent years (Figure 1C), but remained the most commonly reported drug causing anaphylaxis, representing 27.8% of drug-induced anaphylaxis in 2013. The percentage of reported sulfonamide antibiotic anaphylaxis was largely constant around 10% over time, and represented the second most commonly reported antibiotic-induced anaphylaxis (10.3% in 2013). After increases in 1995 (5.7%) and 1996 (7.6%), the percentage of reported cephalosporin anaphylaxis was relatively constant at approximately 4%.

NSAIDs were consistently the most commonly reported analgesic/anesthetic related anaphylaxis (Figure 1D). In recent years, however, the percentage of reported NSAID anaphylaxis decreased slightly (11.8% in 2010 and 10.6% in 2013). The frequency of reported opiate anaphylaxis generally remained between 5–10% of drug-induced anaphylaxis.

In the last 10 years, phenothiazines comprised about 1–2% of reported drug anaphylaxis (Figure 1E). Anaphylaxis from antineoplastics and monoclonal antibodies remained comparatively low, but demonstrated an increase in the later years of the study period. ACE inhibitor anaphylaxis increased over time to 1.4% in 2013.

Demographic and Comorbid Associations for Patients with Reported Drug-Induced Anaphylaxis

White race (OR 2.38, 95% CI 2.27–2.49) and female sex (OR 2.20, 95% CI 2.13–2.28) were associated with an increased odds of drug-induced anaphylaxis (Table I). Patients with systemic mastocytosis had increased odds of reporting drug anaphylaxis (OR 4.60, 95% CI 2.66–7.94). Sjögren's syndrome (OR 1.94, 95% CI 1.47–2.56), asthma (OR 1.50, 95% CI 1.43–1.59), COPD (OR 1.48, 95% CI 1.32–1.66), and endometriosis (OR 1.42, 95% CI

1.23–1.65) were also associated with an increased odds of drug-induced anaphylaxis. Hypothyroidism (OR 0.85, 95% CI 0.80–0.91) and allergic rhinitis (OR 0.88, 95% CI 0.82–0.95) were associated with decreased odds of reporting drug anaphylaxis.

Validation and Follow-up

Among 17,242 cases of drug-induced anaphylaxis from 2009 through 2013, 135 (0.8%) had a tryptase performed within 1 week of anaphylaxis recorded date (Figure 2). Of those, 88 (65.2%) had a testing time known and 25.2% were positive. Among tryptase tests with an identifiable time drawn, 29 (33.0%) were drawn within 3 hours of the presumptive anaphylactic reaction. Tryptase tests drawn within 3 hours were ordered largely for suspected anaphylactic reactions to intravenous antibiotics (n=13, 30.2%), chemotherapeutic agents (n=6, 14.0%), and general anesthetics (n=5, 11.6%).

Tryptase testing was more frequent when assessing less stringent time-frames: Using a 30 day time-frame from anaphylaxis recorded date resulted in 1.2% having the test performed with 22.7% being positive and a 180 day time-frame resulted in 2.3% having the test performed with 21.5% being positive. Over time, the rate of tryptase testing within 1 week of anaphylaxis remained constant each year; rates did not exceed about 1% (Figure 3A).

Among 19,836 patients with reported anaphylaxis from 1995 through 2013, 1,587 (8.0%) patients saw an allergist/immunologist after the anaphylaxis recorded date, with 286 (1.4%) patients seen within 30 days of the anaphylaxis entry. Rates of allergist/immunologist follow-up within 30 days of anaphylaxis fluctuated over the study period but generally stayed within 1–2% each year (Figure 3B).

Discussion

Using one of the largest populations assessed to date, we identified that 1.1% of patients report drug-induced anaphylaxis in the EHR allergy list, and found that whites and women were over twice as likely to develop anaphylaxis compared to non-whites or men. Other independent risk factors for reported drug-induced anaphylaxis included systemic mastocytosis, Sjögren's, asthma and COPD. Overall, penicillins, sulfonamide antibiotics, NSAIDs, and opiates were the most common drugs associated with documented anaphylaxis. Finally, we found that nine out of ten EHR anaphylaxis reports were unverified in our health care system, with <1% having a tryptase test drawn and only 8% of patients seen by Allergy/Immunology.

Similar to prior studies, we found that much of drug-induced anaphylaxis was attributed to antibiotics, with beta-lactam classes the most common antibiotic class culprit.^{23–25} In our study, penicillins were the most commonly attributed drug class, with amoxicillin as the most common causative drug, which also corroborates prior data from other populations.^{25,26} Sulfonamide antibiotics, macrolide antibiotics, fluoroquinolones, and tetracyclines were also identified as common drugs that cause anaphylaxis.

Analgesics such as NSAIDs and opiates were also common drug classes reported to cause anaphylaxis. NSAIDs (13.0 per 10,000) were the third most common class with ibuprofen

being among the most commonly reported individual drugs. NSAIDs cause several types of hypersensitivity reactions, including pseudoallergic reactions related to the cyclooxygenase inhibiting mechanism of the drug.^{27,28} It is likely that some documented NSAID anaphylactic reactions were pseudoallergic, or immunoglobulin E (IgE)-independent anaphylactic reactions, rather than IgE-mediated anaphylactic reactions. Opiates are also known to elicit pseudoallergic reactions that result from their direct effect on mast cells.²² Opiates were a common drug class reported to cause anaphylaxis in our study (9.8 per 10,000). However, opiate reactions have not been as common of a culprit for anaphylaxis as other drug classes in recent studies, despite opiate prescription use increasing in the US.^{9,23,29}

Almost all of the drug classes and individual drug allergens were significantly more common in female patients. This, too, is consistent with other studies that found the majority of drug anaphylaxis populations to be female.^{26,30,31} In this study, all but one drug class (i.e., ACE inhibitors) was significantly more common in white patients. ACE inhibitors cause an accumulation of bradykinin, with resultant angioedema in 0.1–0.7% of patients; ACE inhibitor angioedema accounts for 20–40% of all angioedema emergency visits each year.^{32–35} Severe ACE inhibitor angioedema may be entered by health professionals as anaphylaxis given that oropharyngeal swelling causes shortness of breath and other systemic symptoms.³⁶ While our data are consistent with a prior study that found a higher risk of medication-induced anaphylaxis in white patients,¹⁰ another study identified that African-American race was associated with fatal drug-induced anaphylaxis.⁹ Additional studies are needed to further assess whether this racial disparity may be partially explained by the increased risk of ACE inhibitor angioedema in black patients, which has been widely reported in past studies of hypertension treatment in black patients.^{37–39} Regardless, severe immediate reactions from ACE inhibitors warrant increased attention, especially as their use has expanded.^{40,41}

The trend analysis demonstrated that while reported penicillin anaphylaxis declined over time since 2006, it remained the most commonly reported drug causing anaphylaxis. Sulfonamide antibiotic anaphylaxis remained the second most commonly reported antibiotic causing anaphylaxis over the entire study period. Penicillin was the first antibiotic discovered, and was released in the 1940s. Penicillins cause both adverse and hypersensitivity reactions, and with much of the early administrations given intramuscularly, syncopal events were challenging to distinguish from anaphylactic events.⁴² Penicillin allergy anaphylaxis prevalence may have declined over time because of newer, less allergenic formulations, administrations through oral and intravenous routes^{43,44}, shifts away from penicillin use to other antibiotics^{45,46}, and/or expanded penicillin allergy testing motivated by antibiotic stewardship initiatives.⁴⁷ Although temporal trends on drug-induced anaphylaxis have not been reported using similar methodology, declines in reported penicillin allergies have been reported elsewhere.^{5,48} Despite sulfonamide antibiotics being the 5th most prescribed antibiotic in the US (behind penicillins, cephalosporins, macrolides, and fluoroquinolones),⁴⁹ it was the 2nd most commonly reported antibiotic anaphylaxis in our study. Further research is warranted to determine if sulfonamide antibiotics have a higher risk of anaphylaxis compared to other antibiotics.

Several diseases were significantly associated with reported drug-induced anaphylaxis, most notably systemic mastocytosis, a disease characterized by increased mast cell burden, which was associated with a 4-fold increased odds of drug induced anaphylaxis.^{50,51} While not surprising, this finding supports current clinical recommendations for patients with systemic mastocytosis, including avoidance of drugs that are mast cell activators (e.g., vancomycin and opioids).^{52,53} Pulmonary diseases, such as asthma and COPD, were found to be associated with a 50% increased odds of anaphylaxis. While asthma has been documented as a risk factor for anaphylaxis in prior studies,^{54,55} COPD has not. Mechanistically, patients with asthma or COPD may have anaphylaxis documented more often because of underlying—and potentially unrelated—wheezing or hypoxemia, or they may simply have a lower threshold for pulmonary findings that are consistent with a systemic allergic reaction. We found that Sjögren's syndrome also had increased odds of reported drug-induced anaphylaxis. An association between Sjögren's syndrome and antibiotic allergies was previously identified.^{56,57}

By using tryptase and allergy encounters available in our healthcare system, we found that the vast majority of patients with reported drug-induced anaphylaxis did not have confirmed anaphylaxis. Indeed, only 1% had tryptase ordered at any time (33% of tests ordered during the correct time window) and 8% saw an allergist in the study period (1.4% within 30 days of anaphylaxis). While some of this lack of verification and follow-up may be due to patients reporting historical anaphylaxis episodes, other studies have similarly found low rates of allergy follow-up after anaphylaxis.⁸ Of the tryptase tests that were drawn, approximately 20–25% of tests were positive, but only one-third were drawn in the correct time-frame. Since the optimal time for serum tryptase testing is within two hours of a reaction and the tryptase value decreases after four hours, data may have been different if more tests were drawn within the correct time-frame.⁵⁸ Overall, our findings emphasize the importance of educating all front-line non-allergist providers that care for patients with drug-induced anaphylaxis regarding the value of tryptase testing and subsequent Allergy/Immunology evaluation.

This study has a number of important limitations. Described cases, while informative to drug anaphylaxis epidemiology, may not have had anaphylaxis. EHR reported anaphylaxis cases were largely not confirmed, as shown by the low rates of tryptase tests and allergist follow-up. We assessed comorbidities retrospectively using problem list data, which could result in misclassification. Although included diseases were documented before anaphylaxis was documented, it is possible that the anaphylaxis may have occurred before it was documented in the EHR (e.g. new patients to the hospital that report a historical, remote anaphylactic reaction). This temporal limitation also makes it difficult to measure the effects of age, healthcare setting, or socioeconomic status on drug-induced anaphylaxis. While we used EHR allergy module entries to identify anaphylaxis, other studies have largely used diagnosis codes to identify and study anaphylaxis.^{7,59,60} Although using codes may be more specific, culprit allergen details are lacking. We included only coded and free-text anaphylaxis reports, which may have missed anaphylaxis cases with different coded reactions, such as patients with separate coded reactions (e.g., shortness of breath, hives, hypotension) that would have met the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network definition for anaphylaxis.³⁶ However, we justify

this method given that we could not verify that the multiple reactions occurred at the same time. These data were taken from two large tertiary-care academic hospitals in the Greater Boston area with urban and predominantly white populations with relatively high medical acuity, so this population may not be representative of a broader patient population.

In conclusion, we analyzed drug-induced anaphylaxis in a large health care system; 1% of patients reported anaphylaxis and females and whites had more than twice the risk of anaphylaxis compared to men and non-whites. We found that antibiotics were most commonly reported to cause anaphylaxis with other notable classes including NSAIDs and opiates. Similar to ACE inhibitor angioedema, reported ACE inhibitor anaphylaxis was more common in black patients. As drug usage and allergies to certain medications have been increasing, so have reports of drug anaphylaxis. The increasing number of drug anaphylaxis reports emphasizes the need to verify reported drug-induced anaphylaxis, which would require considerable efforts to increase use of tryptase testing and allergy consultation.

Acknowledgments

Funding

This work was supported by Agency for Healthcare Research and Quality (AHRQ) R01HS022728, the National Institute of Allergy and Infectious Diseases (NIAID) K01AI125631, and the American Academy of Allergy, Asthma and Immunology (AAAAI) Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the AHRQ, NIAID/NIH, nor the AAAAI Foundation.

The authors would like to thank Yu Li, MS for her research assistance.

Abbreviations

EHR	Electronic Health Record
PHS	Partners HealthCare System
BWH	Brigham and Women's Hospital
MGH	Massachusetts General Hospital
PEAR	Partners' Enterprise-wide Allergy Repository
COPD	Chronic Obstructive Pulmonary Disease
NSAID	Nonsteroidal Anti-Inflammatory Drug
ACE	Angiotensin-Converting Enzyme
IgE	Immunoglobulin E

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Highlights

What is already known about this topic?

The majority of hospital admissions for anaphylaxis are due to drugs, and about one in 2,700 hospitalized patients suffers drug-induced anaphylaxis.

What does this article add to our knowledge?

Using drug-induced anaphylaxis reports in electronic health records (EHRs), we found that 1.1% of patients reported drug-induced anaphylaxis. Penicillins, sulfonamide antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common culprits. Female sex, white race, systemic mastocytosis, Sjögren's syndrome, asthma, and COPD were risk factors for anaphylaxis. Most EHR-reported anaphylaxis remained unconfirmed.

How does this study impact current management guidelines?

Patient-specific risk factors can be used clinically in discussion with patients about drug-induced anaphylaxis. Findings emphasize the need to verify EHR-reported anaphylaxis with tryptase testing and allergy evaluation.

A.

B.

C.

D.

E.

Figure 1.

Drug anaphylaxis over time. (A) Number of patients with reported drug-induced anaphylaxis and total number of patients in Partners' Enterprise-wide Allergy Repository (PEAR) each year for the study period. (B) Incidence rate of drug-induced anaphylaxis during the study period. (C–E) Drug-induced anaphylaxis reports for each drug class out of total drug-induced anaphylaxis reports each year during the study period. (C) Antibiotic anaphylaxis. (D) Analgesic or anesthetic anaphylaxis. (E) Other drug-associated anaphylaxis.

Figure 2.

Tryptase testing in drug-induced anaphylaxis cases from 2009 until 2013. Of 17,242 cases of drug-induced anaphylaxis, 135 had a tryptase test within 1 week of anaphylaxis recorded date.

A.

B.

Figure 3.

Tryptase testing and allergy/immunology specialist follow-up over time. (A) Rate of tryptase testing each year (number of tryptase tests out of number of drug anaphylaxis reports) within 1 week of anaphylaxis entry. (B) Rate of allergy/immunology specialist follow-up each year (number of patients with follow-up out of number of drug anaphylaxis patients) within 30 days of anaphylaxis entry.

Table I

Demographic and comorbid associations in patients with reported drug-induced anaphylaxis

Risk Factors	Total Population n (%)	Drug-induced Anaphylaxis n (%)		Adjusted OR (95% CI) [‡]
Demographic	(n=1,756,481)	Yes (n=19,836)	No (n=1,736,645)	
White race	1,236,131 (70.4)	16,321 (82.3)	1,219,810 (70.2)	2.38 (2.27, 2.49)
Female sex	1,017,343 (57.9)	14,668 (73.9)	1,002,675 (57.7)	2.20 (2.13, 2.28)
Comorbidity				
Systemic mastocytosis	219 (0.01)	14 (0.07)	205 (0.01)	4.60 (2.66, 7.94)
Sjögren's syndrome	2,215 (0.1)	55 (0.3)	2,160 (0.1)	1.94 (1.47, 2.56)
Asthma	147,795 (8.4)	1,914 (9.7)	145,881 (8.4)	1.50 (1.43, 1.59)
Chronic obstructive pulmonary disease	22,255 (1.3)	350 (1.8)	21,905 (1.3)	1.48 (1.32, 1.66)
Endometriosis	10,328 (0.6)	198 (1.0)	10,130 (0.6)	1.42 (1.23, 1.65)
Inflammatory gastric disorders [*]	36,894 (2.1)	369 (1.9)	36,525 (2.1)	1.33 (1.16, 1.52)
Lupus erythematosus	30,366 (1.7)	273 (1.4)	30,093 (1.7)	1.25 (1.04, 1.49) [§]
Rheumatoid arthritis	41,427 (2.4)	425 (2.1)	41,002 (2.4)	1.18 (1.04, 1.34)
Multiple sclerosis	7,758 (0.4)	113 (0.6)	7,645 (0.4)	1.12 (0.92, 1.36) ^{//}
Psychiatric disorders [†]	130,441 (7.4)	1,436 (7.2)	129,005 (7.4)	1.12 (1.05, 1.19)
Hyperthyroidism	39,356 (2.2)	343 (1.7)	39,013 (2.3)	1.02 (0.88, 1.18) [¶]
Allergic rhinitis	80,474 (4.6)	744 (3.8)	79,730 (4.6)	0.88 (0.82, 0.95)
Hypothyroidism	137,183 (7.8)	1,401 (7.1)	135,782 (7.8)	0.85 (0.80, 0.91)

^{*} Inflammatory gastric disorders included Crohn's disease and ulcerative colitis.

[†] Psychiatric disorders included schizophrenia, personality disorders, and anxiety disorders.

[‡] P<0.01 unless otherwise specified.

[§] P=0.02

^{//} P=0.25

[¶] P=0.81

Table II

Prevalence of drug-induced anaphylaxis by sex and race/ethnicity

Drug/Drug Class Anaphylaxis	Total [†] n=1,756,481 n (%)	Sex ^{§§}		Race/Ethnicity ^{¶¶}				
		Male n=739,009 n (%)	Female n=1,017,343 n (%)	White n=1,236,131 n (%)	Black n=124,620 n (%)	Hispanic n=142,790 n (%)	Asian n=71,670 n (%)	Other n=32,086 n (%)
Penicillins	8,071 (45.9)	2,396 (32.4)	5,675 (55.8)	6,542 (52.9)	335 (26.9)	355 (24.9)	148 (20.7)	107 (33.4)
Amoxicillin	347 (2.0)	72 (1.0)	275 (2.7)	297 (2.4)	12 (1.0)	7 (0.5)	7 (1.0)	4 (1.3)
Sulfonamide Antibiotics	2,656 (15.1)	427 (5.8)	2,229 (21.9)	2,296 (18.6)	63 (5.1)	54 (3.8)	33 (4.6)	32 (10.0)
Trimethoprim/Sulfamethoxazole	300 (1.7)	52 (0.7)	248 (2.4)	245 (2.0)	14 (1.1)	15 (1.1)	4 (0.6)	4 (1.3)
NSAIDs	2,274 (13.0)	626 (8.5)	1,648 (16.2)	1,765 (14.3)	128 (10.3)	162 (11.4)	40 (5.6)	18 (5.6)
Ibuprofen	324 (1.8)	81 (1.1)	243 (2.4)	250 (2.02)	25 (2.01)	17 (1.2)	6 (0.8)	3 (0.9)
Naproxen	167 (1.0)	37 (0.5)	130 (1.3)	137 (1.1)	5 (0.4)	8 (0.6)	2 (0.3)	1 (0.3)
Opiates	1,727 (9.8)	357 (4.8)	1,370 (13.5)	1,446 (11.7)	67 (5.4)	53 (3.7)	14 (2.0)	18 (5.6)
Codeine	633 (3.6)	118 (1.6)	515 (5.1)	541 (4.4)	20 (1.6)	15 (1.1)	4 (0.6)	1 (0.3)
Morphine	490 (2.8)	92 (1.2)	398 (3.9)	393 (3.2)	25 (2.0)	13 (0.9)	6 (0.8)	7 (2.2)
Meperidine	253 (1.4)	61 (0.8)	192 (1.9)	226 (1.8)	2 (0.2)	6 (0.4)	3 (0.4)	3 (0.9)
Cephalosporins	1,078 (6.1)	274 (3.7)	804 (7.9)	923 (7.5)	27 (2.2)	26 (1.8)	17 (2.4)	12 (3.7)
Cephalexin	201 (1.1)	38 (0.5)	163 (1.6)	167 (1.4)	8 (0.6)	11 (0.8)	1 (0.1)	2 (0.6)
Cefaclor	136 (0.8)	37 (0.5)	99 (1.0)	120 (1.0)	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.3)
Macrolides	659 (3.8)	113 (1.5)	546 (5.4)	582 (4.7)	18 (1.4)	17 (1.2)	7 (1.0)	7 (2.2)
Erythromycin	420 (2.4)	69 (0.9)	351 (3.5)	372 (3.0)	10 (0.8)	8 (0.6)	6 (0.8)	7 (2.2)
Fluoroquinolones	641 (3.7)	136 (1.8)	505 (5.0)	546 (4.4)	10 (0.8)	27 (1.9)	10 (1.4)	8 (2.5)
Ciprofloxacin	265 (1.5)	53 (0.7)	212 (2.1)	224 (1.8)	3 (0.2)	9 (0.6)	3 (0.4)	4 (1.3)
Levofloxacin	223 (1.3)	39 (0.5)	184 (1.8)	185 (1.5)	5 (0.4)	13 (0.9)	3 (0.4)	3 (0.9)
Phenothiazines	394 (2.2)	57 (0.8)	337 (3.3)	334 (2.7)	12 (1.0)	7 (0.5)	4 (0.6)	4 (1.2)
Prochlorperazine	348 (2.0)	45 (0.6)	303 (3.0)	296 (2.4)	10 (0.8)	7 (0.5)	4 (0.6)	3 (0.9)
Tetracyclines	356 (2.0)	49 (0.7)	307 (3.0)	300 (2.4)	14 (1.1)	10 (0.7)	4 (0.6)	2 (0.6)
Tetracycline	142 (0.8)	26 (0.4)	116 (1.1)	123 (1.0)	3 (0.2)	2 (0.1)	2 (0.3)	0 (0.0)
Antineoplastics	261 (1.5)	53 (0.7)	208 (2.0)	225 (1.8)	9 (0.7)	3 (0.2)	8 (1.1)	4 (1.2)
Local Anesthetics	254 (1.4)	60 (0.8)	194 (1.9)	219 (1.8)	7 (0.6)	8 (0.6)	2 (0.3)	2 (0.6)

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		Male n=739,009 n (%)	Female n=1,017,343 n (%)	White n=1,236,131 n (%)	Black n=124,620 n (%)	Hispanic n=142,790 n (%)	Asian n=71,670 n (%)	Other n=32,086 n (%)
Lidocaine	137 (0.8)	37 (0.5)	100 (1.0)	117 (1.0)	6 (0.5)	7 (0.5)	1 (0.1)	0 (0.0)
Angiotensin-converting enzyme Inhibitors	237 (1.4)	87 (1.2)	150 (1.5)	176 (1.4)	34 (2.7)	5 (0.4)	2 (0.3)	2 (0.6)
Monoclonal Antibodies	206 (1.2)	53 (0.7)	153 (1.5)	180 (1.5)	7 (0.6)	6 (0.4)	1 (0.1)	4 (1.2)
General Anesthetics	118 (0.7)	34 (0.5)	84 (0.8)	98 (0.8)	4 (0.3)	5 (0.4)	2 (0.3)	2 (0.6)
Other	2,804 (16.0)	597 (8.1)	2,207 (21.7)	2,352 (19.0)	108 (8.7)	107 (7.5)	49 (6.8)	29 (9.0)
Vancomycin	151 (0.9)	33 (0.5)	118 (1.2)	131 (1.1)	3 (0.2)	1 (0.1)	3 (0.4)	1 (0.3)

* per 10,000 patients.

[†]For all total proportions, the 95% confidence margin was less than +/- 0.01.

[‡]All drug classes and individual drugs were significantly more prevalent in females with p<0.01 except for ACE inhibitors (p=0.09).

[§]Sex information was missing for 129 patients.

[¶]All drug classes and individual drugs were significantly more prevalent in white patients compared to non-white patients except for ACE inhibitors, which were significantly more prevalent in Black patients compared to non-black patients (p<0.01).

^{††}All drug classes and individual drugs had a p <0.01 except for ibuprofen (p=0.01).

^{‡‡}Race/ethnicity was unknown in 149,184 (8.5%) patients.