Antimicrobial-Associated Anaphylaxis Consequences on Infection Related Mortality and Prolonged Hospitalization

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Research Article

Keywords: Allergy, Antimicrobial, Anaphylaxis, Antimicrobial stewardship

Posted Date: February 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-243846/v1

Abstract

Background: Antimicrobial-associated anaphylaxis occurs at different rates and can lead to worsening infection-related outcomes, we sought to describe the incidence and complications of such episodes at a tertiary care hospital.

Method: A retrospective cohort study was conducted between January 2016 and December 2019. Cases of antimicrobial-associated anaphylaxis were identified using the hospital's electronic healthcare records. Outcomes included: mortality related to anaphylaxis, infection-related mortality, prolonged hospitalization and impact on antimicrobial prescribing.

Results: The estimated rate of antimicrobial-associated anaphylaxis was 18.6 (95% CI: 11.8 –29.5) cases per 100,000 exposures. Prolonged hospitalization was seen in 52.4% of the cases, and major predictors for prolonged hospitalization were a switch to a more toxic antimicrobial (P 0.029) and switch to a broader spectrum antimicrobial (P 0.033).

Conclusion: Implications from antimicrobial-associated anaphylaxis is beyond the episode itself, and can be associated with poor clinical outcomes such as infection-related mortality and prolonged hospitalization.

1. Introduction:

Anaphylaxis as defined by the European Academy of Allergy and Clinical Immunology is a severe, life-threatening, generalized, or systemic hypersensitivity reaction [1]. The incidence of anaphylaxis was estimated by the American College of Allergy, Asthma, and Immunology, Epidemiology of Anaphylaxis Working Group to be approximately 50 to 2,000 episodes per 100,000 persons or lifetime prevalence of 0.05–2.0% [2].

Data from the European Anaphylaxis Registry showed that antimicrobials accounted for 26% of anaphylaxis cases in elderly patients [3]. Recent studies report an increase in the rate of medication-related anaphylaxis mortality in different countries [4, 5].

Penicillin associated fatal anaphylaxis was described to occur at a rate of 0.002% among the United States (US) general population and is estimated to account for 400 penicillin- anaphylactic related deaths annually [6].

In a study of 151 anaphylactic related fatalities following penicillin administration, authors reported that 14% had a history of allergies of some kind, 70% had received penicillin previously, and one third experienced prior allergic reactions. With the majority of cases leading to death within 15 minutes [7]. This highlights the importance of proper allergy history documentation, and also indicates that previous tolerance to penicillin cannot be used as an indicator of safety, as anaphylaxis type reactions are

prompted by an immunologic response involving immunoglobulin E (IgE) which necessitates a previous exposure.

The consequences of drug-related anaphylaxis have been described in two clinical settings pre-surgical and during pregnancy [8, 9, 10]. In a population-based descriptive study using the United Kingdom Obstetric Surveillance System, the complications of anaphylaxis during pregnancy was assessed, results showed that out of the cases included, antibiotics were the main culprit, (5%) of women died, (38%) required intensive care admission and (19%) had one or more additional severe maternal morbidities. There were no infant mortalities; however, in those infants whose mother had anaphylaxis before delivery (41%) required neonatal intensive care unit admissions [8].

In the pre-surgical setting, the event of anaphylaxis can be more problematic due to the complex setting and multiple medications that are initiated simultaneously, it is often difficult to identify the true culprit. It was commonly thought that muscle relaxants were the main offenders in this setting, however in a study that identified cases of anaphylaxis during surgery that occurred over a period of 11 years at a tertiary hospital in the US; anaphylaxis was more commonly elicited by antibiotics [9]. Similar results were reported from a large study in the UK, where the most common causes of perioperative anaphylaxis were antibiotics [10].

In Saudi Arabia a cross-sectional study of medical records reported a period prevalence of anaphylaxis among emergency department (ED) admissions of 0.00026% out of 617,401 ED admissions; of which only 17.4% were triggered by drugs; with the majority being antibiotics [11]. Besides this study, our literature search revealed only another study in Saudi Arabia that described the demographics of patients being prescribed adrenaline auto-injectors for anaphylaxis [12].

There are likely geographical differences in the incidence of antimicrobial-related anaphylaxis, mainly due to differences in antimicrobial selection, preferences, epidemiology of infections, and local resistance patterns; therefore, there is a need to better understand this risk on both a country and institutional level.

The landscape of anaphylaxis associated specifically with antimicrobials is not well described, particularly in an in-patient setting. Therefore, the objective of our study was to describe the incidence and undesirable outcomes of antimicrobial-associated anaphylaxis.

2. Methods:

2.1 Study Design & Setting: A retrospective cohort study was conducted between January 2016 and December 2019 at a tertiary care hospital with a bed capacity of 2,100 beds. Cases of antimicrobial-associated anaphylaxis were identified using the hospital's electronic healthcare records (EHRs), which documents patient's drug allergies under a specific field. The search terms used included anaphylaxis and anaphylactic shock. Cases identified then underwent further chart review assessment based on our inclusion and exclusion criteria (see below).

All patient's medical records were reviewed to ensure that antimicrobials were the suspected culprit in the documented anaphylaxis.

2.2 Inclusion Criteria

Inclusion criteria: adult and pediatric patients, with antimicrobial-associated anaphylaxis documented or reported during hospitalization, with a clear description of signs and symptoms documented in patient's chart; that met one of the three following description (based on National Institute of Health 2006 definition) [13]

1. Acute onset (within minutes to hours of exposure) of a skin or mucosal involvement with at least one of the following: respiratory compromise and/or reduced blood pressure with associated target-organ dysfunction
2. Two or more of the following occurring rapidly (minutes to hours of exposure) after exposure of a likely allergen: skin or mucosal tissue involvement, respiratory compromise, decreased blood pressure with associated target organ dysfunction, or tenacious gastrointestinal symptoms.
3. Reduced blood pressure occurs after exposure (for infants and children, decreased age-specific systolic blood pressure or a greater than 30% decrease from baseline; for adults, systolic blood pressure of less than 90 mm Hg or greater than a 30% decrease from baseline.)

2.3 Exclusion criteria:

Patients with cutaneous-only reactions, delayed cutaneous reactions, anaphylaxis cases that occurred outside the hospital, and anaphylaxis documented in the old health information system (due to lack of electronic documentation of the event).

Patients with antimicrobial anaphylaxis meeting inclusion criteria had their demographics collected which included: age, gender, route of antimicrobial used, history of asthma/atopic dermatitis, history of other allergies (food or drugs), underwent a desensitization protocol, use of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEIs/ARBs).

2.4 Outcomes

We intend to determine the rate of anaphylaxis, and the most commonly implicated antimicrobials/classes. While describing the demographics and potential risk factors of patients.

To assess the impact of the antimicrobial-associated anaphylaxis we assessed:

- Mortality related to anaphylaxis
- The infection-related mortality in patients with a reported anaphylaxis
- Prolonged hospitalization (defined as one or more days than anticipated based on the type of infection, and assessed by two independent expert clinical pharmacists)

To assess the impact on antimicrobial prescribing we assessed the following:

- Percentage of patients that switched to a less effective antimicrobial for the infection being treated
- Percentage of patients that switched to a more toxic antimicrobial
- Percentage of patients that switched to a broader spectrum antimicrobial

The switch to a less effective antimicrobial was defined as switching from a first line to a second line antimicrobial as per our institution's antimicrobial guidelines. A switch to a more toxic antimicrobial was based on two independent clinical pharmacists' reviews and were individualized to each patient based on the overall morbidities and the type of infection (e.g. switching to a nephrotoxic agent in a patient with underlying renal impairment), disputes were further discussed until agreement was reached between the reviewers.

The antimicrobial spectrum of activity was deemed broader based on the spectrum of activity tables in Sanford antimicrobial therapy guide (digital content updated December 29, 2019) [14].

2.5 Statistical analysis

Basic statistical analysis via SAS (Institute Inc. Cary, NC, USA), was performed with biostatistician support. We used mean and standard deviation (SD) to summarize the continuous variables and frequency, and percentage to summarize the categorical variables. We used the t-test to compare the average age among the patients that had a prolonged hospitalization to those who are not. A Chi-square test was used to compare the categorical variables across the groups. Fisher exact test was used when the Chi-square test is invalid due to lower expected cross-tabulation cell frequencies. All analyses were conducted using the SAS software package 9.4 (SAS Institute, Cary, NC).

Bivariate analysis for infection related mortality: Fisher exact test was used to compare the infection related mortality and other covariates due to lower expected cross tabulation cell frequencies. Binary logistic regression with firth correction is used to estimate the odds ratio. The estimate of area under the curve of the fitted model is 77.3%.

Binary logistic regression with maximum likelihood estimation was used to estimate the odds ratio of prolonged hospitalization. The estimate of area under the curve of the fitted model is 80.7 %.

The institutional review board (IRB) at King Abdullah International Medical Research Center (KAIMRC) (Protocol RC19/339/R) approved this study, and is performed in accordance with the Declaration of Helsinki. No consent form was required by the Ministry of National Guard Health Affairs ethics committee.

3. Results:

Between Jan 2016 and Dec. 2019, the total number of documented antimicrobial allergies in the EMRs was 3,656 of which 117 (3.2%) were antimicrobial induced anaphylaxis; of these, 42 patients that had a documented antimicrobial induced anaphylaxis met the inclusion criteria and the case definition, notably 54 (46%) of the cases were patient self-reported and were therefore excluded. See Fig. 1 for patient selection.

3.1 Demographics

Of the 42 cases that were included, (22/42, 52%) were female and the median age was 51 ± 25.4 years of which only (6/42, 14%) were pediatric patients. History of asthma was recorded in eleven participants (11/42, 26.19%). History of other allergies was recorded in 15 patients (15/42, 35.7%), which included mainly other drugs and food allergies. Thirteen (13/42, 30.9%) patients were on a beta-blocker, and eight (8/42, 19%) were on an ACEI/ARB. See Table 1 for demographics.

Table 1
Demographics and outcomes in patients with antimicrobial-induced anaphylaxis and Bivariate Analysis for Prolonged Hospitalization

Variable Name	Level	*n* = 42	Prolonged hospitalization		P value
			No (n = 20)	Yes (n = 22)	
Age, median (Q1 – Q3), years		49 (31–76)	46 (25.5–57.5)	62 (39–79)	0.208
		Frequency (%)	Frequency (%)	Frequency (%)	
Age					
	Less than 65 years	29 (69.05%)	16 (55.17%)	13 (44.83%)	0.143
	65 years or more	13 (30.95%)	4 (30.77%)	9 (69.23%)	
Gender					
	Female	22 (52.38%)	13 (59.09%)	9 (40.91%)	0.119
	Male	20 (47.62%)	7 (35%)	13 (65%)	
Death related to the anaphylactic event					
	No	41 (97.62%)	19 (46.34%)	22 (53.66%)	0.476*
	Yes	1 (2.38%)	1 (100%)	0 (0%)	
Infection-Related Mortality					
	No	37 (88.1%)	18 (48.65%)	19 (51.35%)	1*
	Yes	5 (11.9%)	2 (40%)	3 (60%)	
Cardiac Arrest					
	No	37 (88.1%)	18 (48.65%)	19 (51.35%)	1*
	Yes	5 (11.9%)	2 (40%)	3 (60%)	
Code blue activated					

*Fisher exact test is used

Variable Name	Level	*n* = 42	Prolonged hospitalization		P value
			No (n = 20)	Yes (n = 22)	
	No	28 (66.67%)	15 (53.57%)	13 (46.43%)	0.245
	Yes	14 (33.33%)	5 (35.71%)	9 (64.29%)	
Switch to less effective antimicrobial					
	No	31 (73.81%)	17 (54.84%)	14 (45.16%)	0.116
	Yes	11 (26.19%)	3 (27.27%)	8 (72.73%)	
Switch to a more toxic antimicrobial					
	No	22 (52.38%)	14 (63.64%)	8 (36.36%)	0.029
	Yes	20 (47.62%)	6 (30%)	14 (70%)	
Switch to a broader spectrum antimicrobial					
	No	29 (69.05%)	17 (58.62%)	12 (41.38%)	0.033
	Yes	13 (30.95%)	3 (23.08%)	10 (76.92%)	
Underwent a desensitization					
	No	42 (100%)	20 (47.62%)	22 (52.38%)	
Asthma					
	No	31 (73.81%)	16 (51.61%)	15 (48.39%)	0.384
	Yes	11 (26.19%)	4 (36.36%)	7 (63.64%)	
Atopic dermatitis					
	No	42 (100%)	20 (47.62%)	22 (52.38%)	

*Fisher exact test is used

Variable Name	Level	*n* = 42	Prolonged hospitalization		P value
			No (n = 20)	Yes (n = 22)	
Other allergies					
	No	27 (64.29%)	15 (55.56%)	12 (44.44%)	0.167
	Yes	15 (35.71%)	5 (33.33%)	10 (66.67%)	
Beta-blockers					
	No	29 (69.05%)	14 (48.28%)	15 (51.72%)	0.899
	Yes	13 (30.95%)	6 (46.15%)	7 (53.58%)	
ACEI/ARB					
	No	34 (80.95%)	18 (52.94%)	16 (47.06%)	0.155
	Yes	8 (19.05%)	2 (25.00%)	6 (75.00%)	
Concomitant drugs during anaphylaxis					
	No	39 (92.86%)	20 (51.28%)	19 (48.72%)	0.233*
	Yes	3 (7.14%)	0 (0%)	3 (100%)	
*Fisher exact test is used					

3.2 Rate of Antimicrobial Anaphylaxis

In an estimated 100,000 antimicrobial prescriptions during the period of the study, the estimated rate of antimicrobial-associated anaphylaxis was 18.6 (95% CI: 11.8 – 29.5) cases per 100,000 exposures.

3.3 Frequency of implicated antimicrobials

Figure 2 shows the frequency of antimicrobials implicated in antimicrobial anaphylaxis and the number of anaphylaxis episodes according to each antimicrobial class. Overall, ceftriaxone induced anaphylaxis was the most frequently implicated antimicrobial (10/42 episodes, 23.8%). The estimated incidence for ceftriaxone was 48.9 (95% CI: 19.0 – 125.6) cases per 100,000 exposures.

3.4 Prolonged Hospitalization

The prevalence of prolonged hospitalization as a result of the anaphylaxis was 52.38% (95% CI: 37.32 – 66.64). Five patients suffered a cardiac arrest (5/42, 11.9%) and a code blue was activated in 14 cases (14/42, 33.3%).

The major predictors for prolonged hospitalization per antimicrobial anaphylaxis episode were found to be associated with a switch to a more toxic antimicrobial (P 0.029) and switch to a broader spectrum antimicrobial (P 0.033). See Table 1 and 2.

Table 2
Odds Ratio for Prolonged Hospitalization*

Effect	OR (95% Confidence Limits)	P-Value
Age – 65 years or more	2.208 (0.393–12.398)	0.3682
Gender - Male	3.628 (0.713–18.472)	0.1206
Switch to less effective antimicrobial - Yes	2.113 (0.361–12.352)	0.4064
Switch to more toxic antimicrobial - Yes	1.831 (0.246–13.638)	0.5551
Switch to broad spectrum antimicrobial - Yes	4.015 (0.416–38.717)	0.2293
Asthma - Yes	1.233 (0.22–6.904)	0.8113
Other allergies - Yes	1.702 (0.354–8.175)	0.5068
***Binary logistic regression with maximum likelihood estimation is used to estimate the odds ratio. The estimate of area under the curve of the fitted model is 80.7 %.**		

3.5 Therapeutic Changes

In eleven of the cases patients were switched to a less effective antimicrobial (11/42, 26.19%), 20 switched to a more toxic antimicrobial (20/42, 47.62%), and (13/42, 30.9%) patients switched to a broader spectrum antimicrobial. In (11/42, 26.2%) patients no antimicrobial was prescribed after the anaphylaxis episode (excluding two patients who died shortly after the anaphylaxis episode before switching to another antimicrobial). None of the patients underwent a desensitization attempt.

3.6 Mortality Associated with Antimicrobial Anaphylaxis Episodes

The outcomes in patients with antimicrobial associated anaphylaxis are shown in Table 1. There was only one mortality 1 (1/42, 2.38%) related directly to an anaphylaxis event which involved amphotericin B, this patient did not have a history of asthma or atopy, no history of other allergies, he was on a beta-blocker, and was immunocompromised. There were five infection-related mortalities (5/42, 11.9%), of which 3 were switched to a more toxic antimicrobial, and the other 2 cases died shortly after the episode and were not switched to any other antimicrobial in between the time of the anaphylaxis episode and

death. None of the predictors for infection-related mortalities were significant besides code-blue activation (P 0.035). See Table 3 and 4.

Table 3
Bivariate Analysis for Infection Related Mortality*

Variable name	Level	Infection related mortality		P value
		No (*n* = 37)	Yes (*n* = 5)	
Age, median (Q1 – Q3), years		49 (26–75)	62 (46–79)	0.172
		Frequency (%)	Frequency (%)	
Age				
	Less than 65 years	26 (89.66%)	3 (10.34%)	0.637
	65 years or more	11 (84.62%)	2 (15.38%)	
Gender				
	Female	20 (90.91%)	2 (9.09%)	0.656
	Male	17 (85%)	3 (15%)	
Cardiac arrest				
	No	34 (91.89%)	3 (8.11%)	0.099
	Yes	3 (60%)	2 (40%)	
Code blue activated				
	No	27 (96.43%)	1 (3.57%)	0.035
	Yes	10 (71.43%)	4 (28.57%)	
Switch to less effective antimicrobial				
	No	27 (87.1%)	4 (12.9%)	1
	Yes	10 (90.91%)	1 (9.09%)	
Switch to more toxic antimicrobial				
	No	20 (90.91%)	2 (9.09%)	0.656
	Yes	17 (85%)	3 (15%)	
Switch to broad spectrum antimicrobial				
	No	25 (86.21%)	4 (13.79%)	1
	Yes	12 (92.31%)	1 (7.69%)	

***Fisher exact test is used to compare the infection related mortality and other covariates due to lower expected cross tabulation cell frequencies.**

Variable name	Level	Infection related mortality		P value
		No (*n* = 37)	Yes (*n* = 5)	
Underwent desensitization				
	No	37 (88.1%)	5 (11.9%)	
Asthma				
	No	26 (83.87%)	5 (16.13%)	0.303
	Yes	11 (100%)	0 (0%)	
Atopic dermatitis				
	No	37 (88.1%)	5 (11.9%)	
Other allergies				
	No	23 (85.19%)	4 (14.81%)	0.639
	Yes	14 (93.33%)	1 (6.67%)	
Beta-blockers				
	No	27 (93.1%)	2 (6.9%)	0.162
	Yes	10 (76.92%)	3 (23.08%)	
ACE/ARB inhibitors				
	No	30 (88.24%)	4 (11.76%)	1
	Yes	7 (87.5%)	1 (12.5%)	

***Fisher exact test is used to compare the infection related mortality and other covariates due to lower expected cross tabulation cell frequencies.**

Table 4
Odds ratio for Infection Related Mortality*

Effect	OR (95% Confidence Limits)	P Value
Age – 65 years or more	2.683 (0.3-23.966)	0.3769
Gender - Male	1.404 (0.209–9.447)	0.727
Switch to less effective antimicrobial - Yes	0.525 (0.044–6.247)	0.6098
Switch to more toxic antimicrobial - Yes	4.214 (0.457–38.828)	0.2043
Switch to broad spectrum antimicrobial - Yes	0.213 (0.015–2.96)	0.2494
Asthma - Yes	0.198 (0.012–3.152)	0.2512
Other allergies - Yes	0.797 (0.102–6.257)	0.8295
***Binary logistic regression with firth correction is used to estimate the odds ratio. The estimate of area under the curve of the fitted model is 77.3%.**		

4. Discussion:

The rate of antimicrobial associated anaphylaxis in the two large healthcare facilities included in this study was 18.6 (95% CI: 11.8 – 29.5) cases per 100 000 exposures. Compared to a large national study from the UK which reported an overall incidence of reported antibiotic-induced anaphylaxis was 4.0 per 100 000 exposures, where the highest incidence was seen with teicoplanin (16.4 per 100 000 exposures) then co-amoxiclav (8.7 per 100 000 exposures), our incident seems higher and involves different antibiotics [10].

In a US population-based study utilizing EHRs of patients with active healthcare plans over a period of 9 years, out of 7,449,076 patients assessed; they found only 1 of 1543 (0.065%) oral and 1 of 1030 (0.097%) parenteral confirmed penicillin-associated anaphylaxis [15]. Although different in design, compared to our study this incidence seems much less than that reported in our study.

Epidemiological data from different countries have reported a drug anaphylaxis fatality rate of between 0.05–0.51 per million/year, with antimicrobials being the leading causal drug [16]. In our study period, there was one drug anaphylaxis related mortality; this is in line with reports from other countries where fatalities in hospitalized anaphylaxis cases are very uncommon [17, 18, 19].

Low mortality rates could be explained by the easily identifiable anaphylaxis symptoms, which are rapid in onset and classic. In addition to the availability of anaphylactic kits in almost all areas within the hospital and familiarity of staff in managing anaphylaxis events.

Interestingly the majority of antimicrobial anaphylaxis documented in the EHRs which were excluded from our study, were patient self-reported. This may have implications on antimicrobial choices and

infection outcomes; as the accuracy of patient-reported antimicrobial allergy history has been brought to question [20]. This finding raises the need for better tools to identify, document, and classify patient's allergies, in order to facilitate the decision process should the patient have a forthcoming need for an antimicrobial. De-labeling patients that may not be truly allergic to antimicrobials has been of interest lately, with successful experiences reported [21, 22].

Our study is the first in the region to explore the epidemiology and outcomes of antimicrobial anaphylaxis. A key finding was that unlike other studies where penicillins/aminopenicillins have been reported to be the most frequently implicated antimicrobial class in antimicrobial anaphylaxis; in our setting cephalosporins were the top implicated antimicrobials, driven mainly by anaphylaxis associated with ceftriaxone.

The International Collaborative Study of Severe Anaphylaxis reports an incidence of parenteral cephalosporin-associated anaphylaxis of 5.7 cases per 100 000 exposures [23]. While the real-world frequency of anaphylaxis from 12 California hospitals reports a lower incidence of 0.6 cases per 100 000 exposures with oral cephalosporins and 1.6 per 100 000 exposures with parenteral cephalosporin [24].

The rate of ceftriaxone-induced anaphylaxis was higher in our study 48.9 (95% CI: 19.0 – 125.6) cases per 100000 exposures. Such high incidence has been reported in a Korean study of 76 cephalosporin-induced anaphylaxis where the highest incidence was reported with ceftriaxone (9.2 per 100 000 exposures) [25], this difference in incidence may suggest a genetic predisposition to this reaction to ceftriaxone in these two populations.

Ceftriaxone is a third-generation parenteral cephalosporin and an essential antibiotic that is listed as a first-line agent for multiple susceptible organisms including N. gonorrhea, N. meningitides, and H.influenzae [26]. It is generally considered well tolerated with no dose adjustments required in patients with renal or hepatic impairment. Therefore, besides the high incidence of ceftriaxone anaphylaxis and implications of managing an episode, poor infection-related outcomes should be expected in cases where ceftriaxone were to be replaced by a second line agent.

In our study in 26.2% of the cases, the patient's antimicrobial was discontinued after the anaphylaxis event with no further orders for any other antimicrobial; out of which, the majority were initiated empirically, and none were associated with mortality. Although assessing antimicrobial appropriateness was out of the scope of this study, it is startling to say that in almost a quarter of the cases antimicrobials may have been prescribed unnecessarily.

A switch to a more toxic antimicrobial, and/or a broader spectrum antimicrobial were predictors of prolonged hospitalization in our study. As a severe allergic reaction drives prescribers away from their first empiric choice this outcome is foreseen and expected. Prolonged hospitalization has both morbidity and economic consequences and was significantly high in the population studied here > 50%. However,

interpretation should be made cautiously since we did not control confounders such as disease severity due to the small sample size.

In the five infection-related mortality cases, one patient's culture grew carbapenem-resistant Klebsiella pneumoniae with the OXA48 gene detected while the other four patient's cultures did not grow any resistant organisms. Possibly indicating that mortality was driven by adverse drug toxicity rather than a drug-bug mismatch.

In none of the cases was desensitization attempted, although desensitization is an effective approach to patients with a clear IgE type reaction. There are multiple published desensitization protocols [27, 28, 29], prescribers may need to more frequently weigh the benefit of a desensitization approach vs switching to a less favorable antimicrobial.

5. Study Limitations:

Case definition: we only included patients that had explicitly an anaphylaxis episode recorded in their files, this could have excluded other cases where the symptoms of anaphylaxis were documented such as hypotension, shortness of breath, and/or collapse but the term anaphylaxis was not explicitly used. The prolonged hospital stay was subjectively assessed by the authors.

6. Conclusion:

Implications of antimicrobial-associated anaphylaxis are beyond the episode itself, and can be associated with poor clinical outcomes such as infection-related mortality and prolonged hospitalization, further research into measures to predict and manage antimicrobial anaphylaxis could sever antimicrobial stewardship programs.

Authors certify that there were no funding sources to complete this project, and have no conflict of interests

7. Abbreviations:

ACEIs/ARBs: angiotensin converting enzyme inhibitors or angiotensin II receptor blockers

ADR: Adverse Drug Reaction

ED: emergency department

EHRs: electronic healthcare records

IgE: immunoglobulin E

US: United States

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Figures

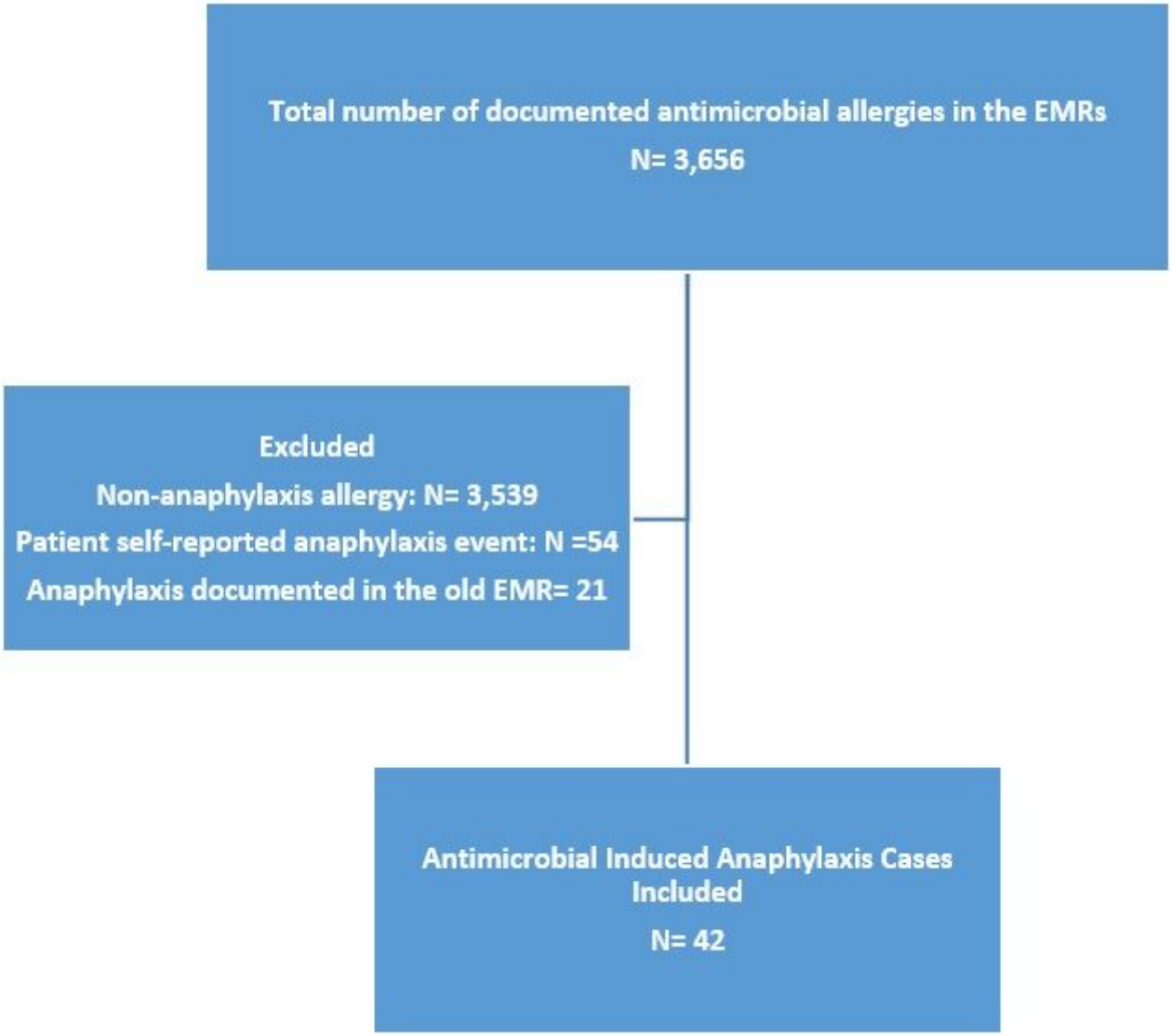
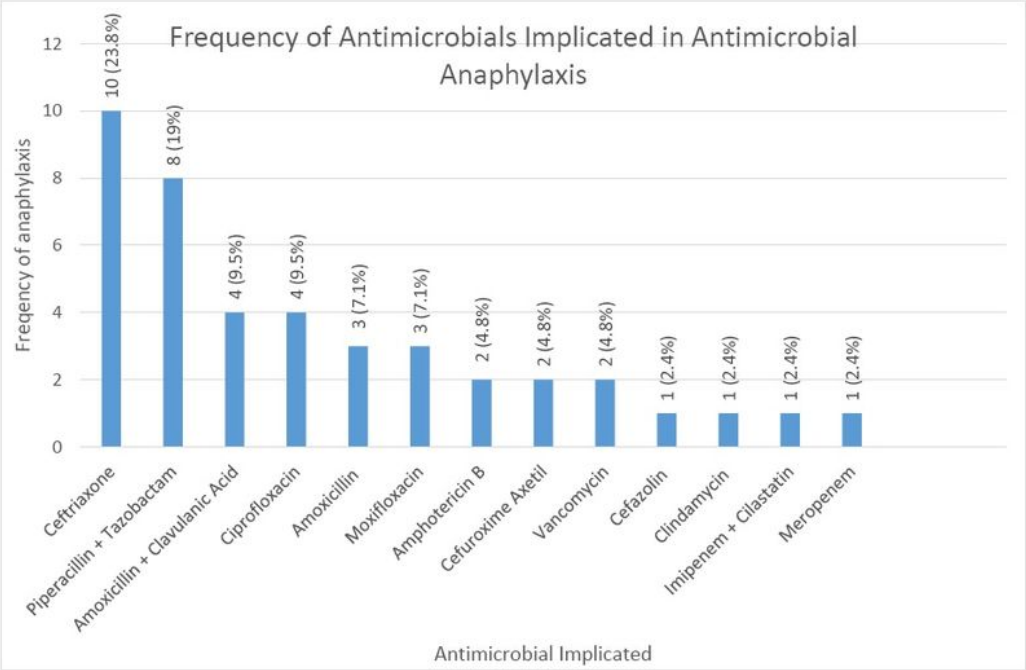


Figure 1

Patient Selection. Abbreviations: EMR: Electronic Medical Record

(a)



(b)

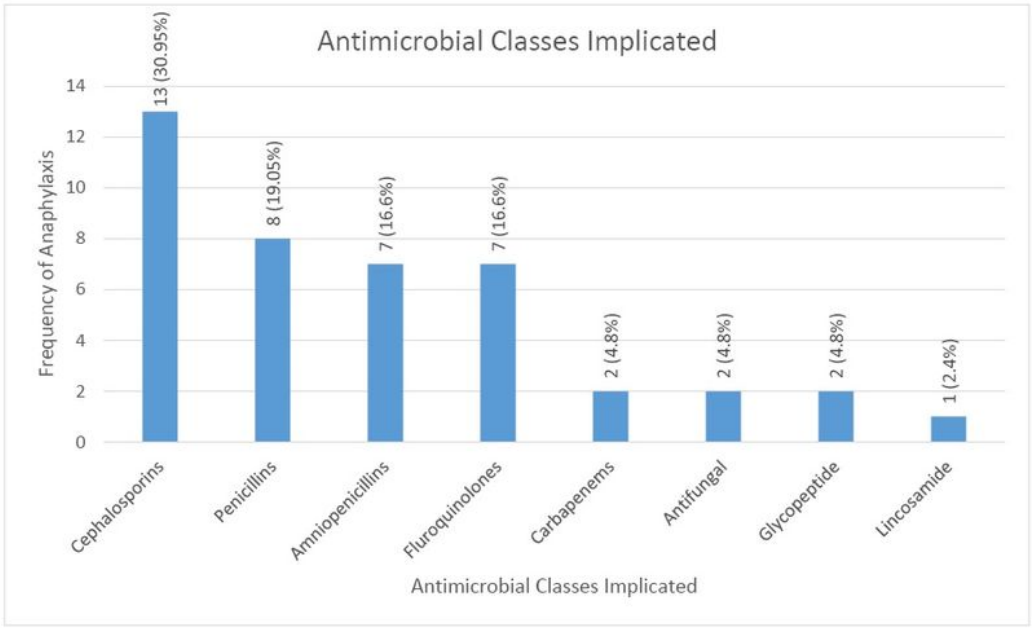


Figure 2

(a) Anaphylaxis episodes per implicated individual antimicrobial. All implicated antimicrobials (N=42). (b) Anaphylaxis episodes per antimicrobial class.