



Antimicrobial-associated anaphylaxis at a tertiary care medical city

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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, 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, which required hospitalization in 23.8% of the cases and ICU admission in 19% of the cases. **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 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 in the United States of America (USA) was estimated to be approximately 50–2000 episodes per 100,000 persons or a lifetime prevalence of 0.05–2.0% [2], and data from the European Anaphylaxis Registry shows that antimicrobials account 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 USA 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 70% had received penicillin previously, with the majority of cases leading to death within 15 min [7].

Besides mortality, the consequences of drug-related anaphylaxis have infrequently been described. In a population-based 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 and that (5%) of women died, (38%) required intensive care admission and (19%) had one or more additional severe maternal morbidities [8].

In the pre-surgical setting, it was commonly thought that muscle relaxants were the main offenders, however in a study that identified cases of anaphylaxis during surgery that occurred over a period of 11 years at a hospital in the USA; anaphylaxis was more commonly elicited by antibiotics [9]. Similar results were reported from a large study in the UK [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 (17.4%) were triggered by drugs; with the majority being antibiotics [11]. Besides this study, our literature search revealed only one 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; which is not well described, particularly in an in-patient setting in our region. Therefore, the objective of our study was to describe the incidence and undesirable outcomes of antimicrobial-

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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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 2100 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

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).

2.4. Data collection

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).

2.5. Outcomes

We intend to determine the rate of anaphylaxis per 100,000 exposure, data on antimicrobial prescriptions was obtained from the pharmacy electronic system. We also determined the most commonly implicated antimicrobials/classes, and describe the demographics and potential risk factors of patients.

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

- Mortality related to anaphylaxis (defined as death due to anaphylaxis)
- The infection-related mortality (defined as death that could be attributed to the infectious disease to which the antibiotic that caused anaphylaxis was indicated for)
- Hospital admission (defined as any patient who was admitted to the hospital as a direct consequence of their anaphylaxis episode)
- Intensive Care Unit (ICU) admission (defined as any patient who was admitted to the ICU as a direct consequence of their anaphylaxis episode)

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

- Percentage of patients that switched to a less effective antimicrobial for the infection being treated (defined as switching from a first line to a second line antimicrobial as per our institution's antimicrobial guidelines).
- Percentage of patients that switched to a broader spectrum antimicrobial (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].

2.6. 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. 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%.

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 3656 of which 117 (3.2%) were antimicrobial induced anaphylaxis; of these, 42 cases of 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.

Of the 42 events included, anaphylaxis occurred in a total of 40 patients, one patient had two separate anaphylaxis events involving two different drugs, and in another patient two antibiotics were administered at the same time and the culprit was not ruled out. Complete details of overall ADRs over the same study period have been published [15].

3.1. Demographics

Of the 40 patients included, (22/40, 55%) were female and the median age was 51 ± 25.4 years of which only (6/40, 15%) were pediatric patients. History of asthma was recorded in eleven participants (11/40, 27.5%). History of other allergies was recorded in 15 patients (15/40, 37.5%), which included mainly other drugs and food allergies.

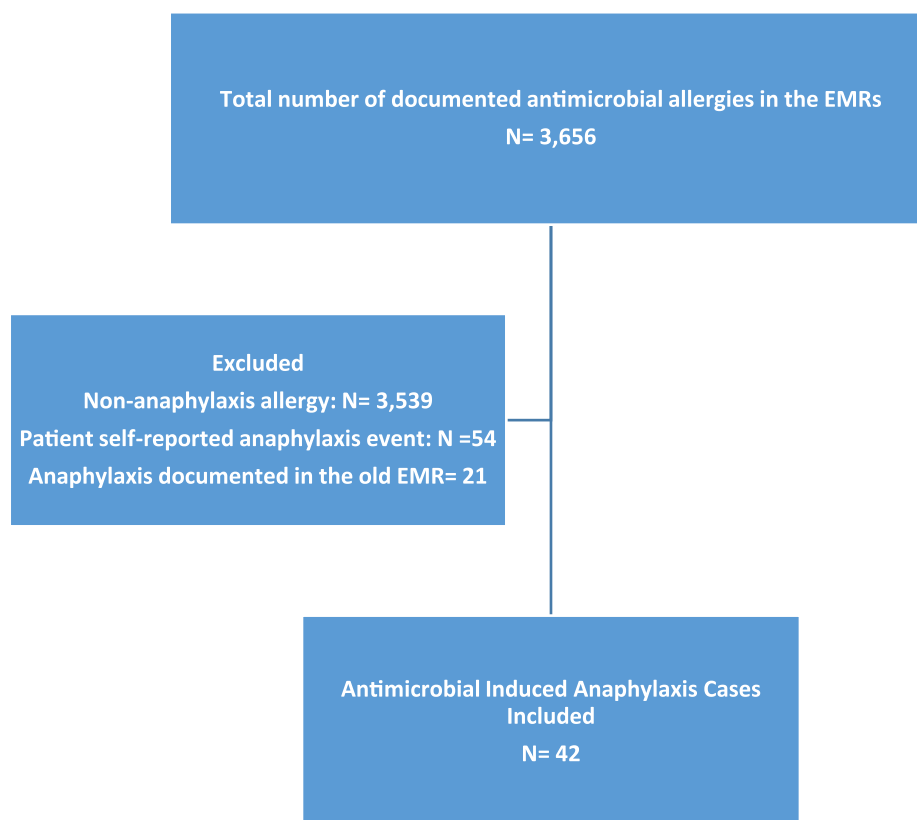


Fig. 1. Patient Selection. Abbreviations: EMR: Electronic Medical Record.

Thirteen (13/40, 32.5%) patients were on a beta-blocker, and eight (8/40, 20%) were on an ACEI/ARB. See [Table 1](#) for demographics.

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

[Fig. 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. Hospital and ICU admission

In (10/42, 23.8%) of the episodes anaphylaxis was the reason for admission, and in (8/42, 19%) of the cases required ICU admission.

Five patients suffered a cardiac arrest (5/42, 11.9%) and a code blue was activated in 14 cases (14/42, 33.3%).

3.5. Therapeutic changes

In eleven of the cases patients were switched to a less effective antimicrobial (11/42, 26.19%) 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%). None of the predictors for infection-related mortalities were significant besides code-blue activation (P 0.035). See [Tables 2 and 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 of 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 [\[16\]](#). Although different in design, compared to our study this incidence also 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 and 0.51 per million/year, with antimicrobials being the leading causal drug [\[17\]](#). In our study period, there was one drug anaphylaxis related mortality; this is in line

Table 1

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

Variable Name	Level	n = 42
Age, median (Q1 – Q3), years		49 (31–76)
		Frequency (%)
Age	Less than 65 years	29 (69.05%)
	65 years or more	13 (30.95%)
Gender	Female	22 (52.38%)
	Male	20 (47.62%)
Death related to the anaphylactic event	No	41 (97.62%)
	Yes	1 (2.38%)
Infection-Related Mortality	No	37 (88.1%)
	Yes	5 (11.9%)
Cardiac Arrest	No	37 (88.1%)
	Yes	5 (11.9%)
Code blue activated	No	28 (66.67%)
	Yes	14 (33.33%)
Switch to less effective antimicrobial	No	31 (73.81%)
	Yes	11 (26.19%)
Switch to a broader spectrum antimicrobial	No	29 (69.05%)
	Yes	13 (30.95%)
Underwent a desensitization	No	42 (100%)
Asthma	No	31 (73.81%)
	Yes	11 (26.19%)
Atopic dermatitis	No	42 (100%)
Other allergies	No	27 (64.29%)
	Yes	15 (35.71%)
Beta-blockers	No	29 (69.05%)
	Yes	13 (30.95%)
ACEI/ARB	No	34 (80.95%)
	Yes	8 (19.05%)
Concomitant drugs during anaphylaxis	No	39 (92.86%)
	Yes	3 (7.14%)

*Fisher exact test is used

with reports from other countries where fatalities in hospitalized anaphylaxis cases are very uncommon [18,19,20].

Low mortality rates could be explained by the easily identifiable anaphylaxis symptoms, which are rapid in onset and easily identifiable. 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 allergy has been brought to question [21]. 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 [22,23].

Over the past couple of years while transitioning to a new EHR system we identified multiple problems with allergy documentation and how it contributed to treatment decisions.

We, therefore, initiated the allergy documentation improvement

project, here are some of the actions taken:

- Developed electronic reminders prompting physicians to update patient's allergies on each patient visit
- Implemented system modifications to the allergy section under EHRs to include: drug names rather than drug classes, the addition of a section describing in detail the time to onset and symptoms encountered, and relevant drugs tolerated (e.g. patient allergic to amoxicillin but tolerated ceftriaxone).
- We are also developing a tool to upload real-life allergy photos of a patient's allergic skin reaction, to be saved under the EHR of patients, this would ease differentiating mild vs severe rashes and rule out severe forms of allergies where re-challenging is unsafe

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 [24]. 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 [25].

The rate of ceftriaxone-induced anaphylaxis was higher in our study 48.9 (95% CI: 19.0–125.6) cases per 100,000 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) [26], this difference in incidence may suggest a genetic predisposition 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* [27]. 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 a second line agent replaces ceftriaxone.

In our study 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.

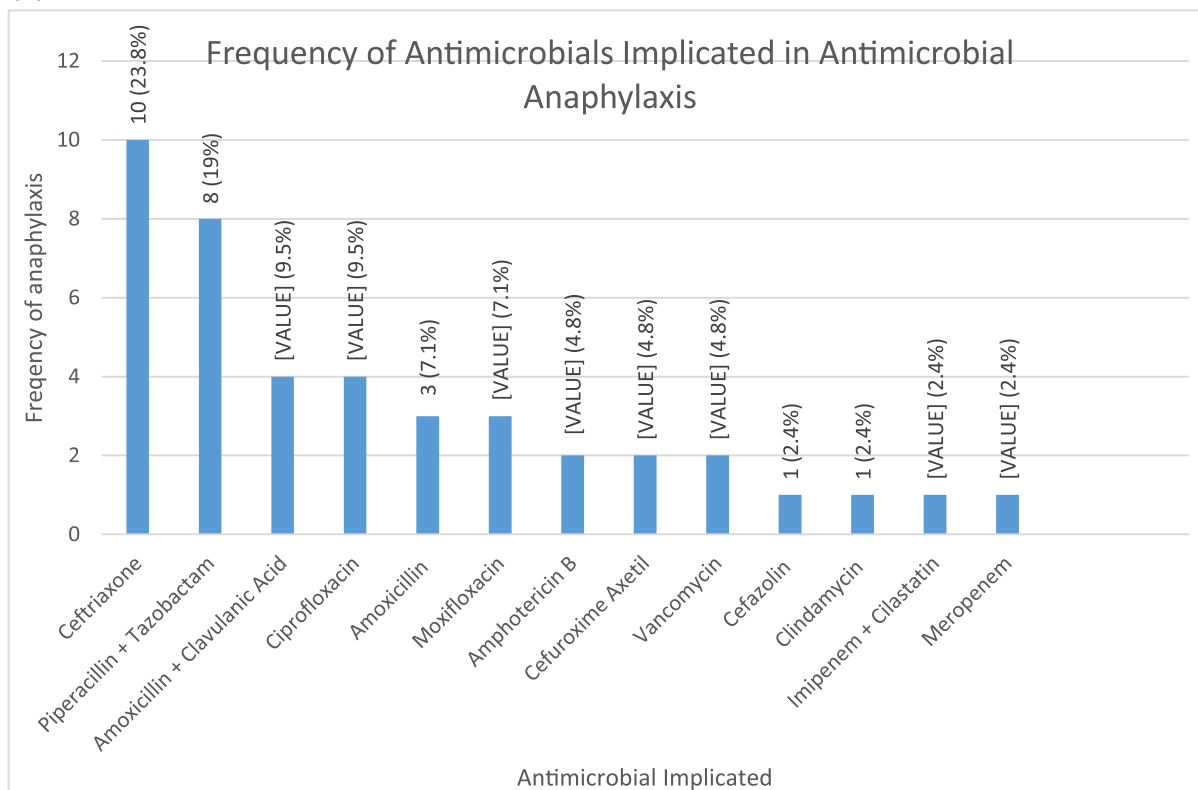
Severe allergic reactions can drive prescribers away from their first empiric choice and broader spectrum antibiotics, which in turn contribute to the burden of antimicrobial resistance. Hospitalization and ICU admission have both morbidity and economic consequences, and was considerably high in our study.

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 [28,29,30], prescribers may need to more frequently weigh the benefit of a desensitization approach vs switching to a less favorable

(a)



(b)

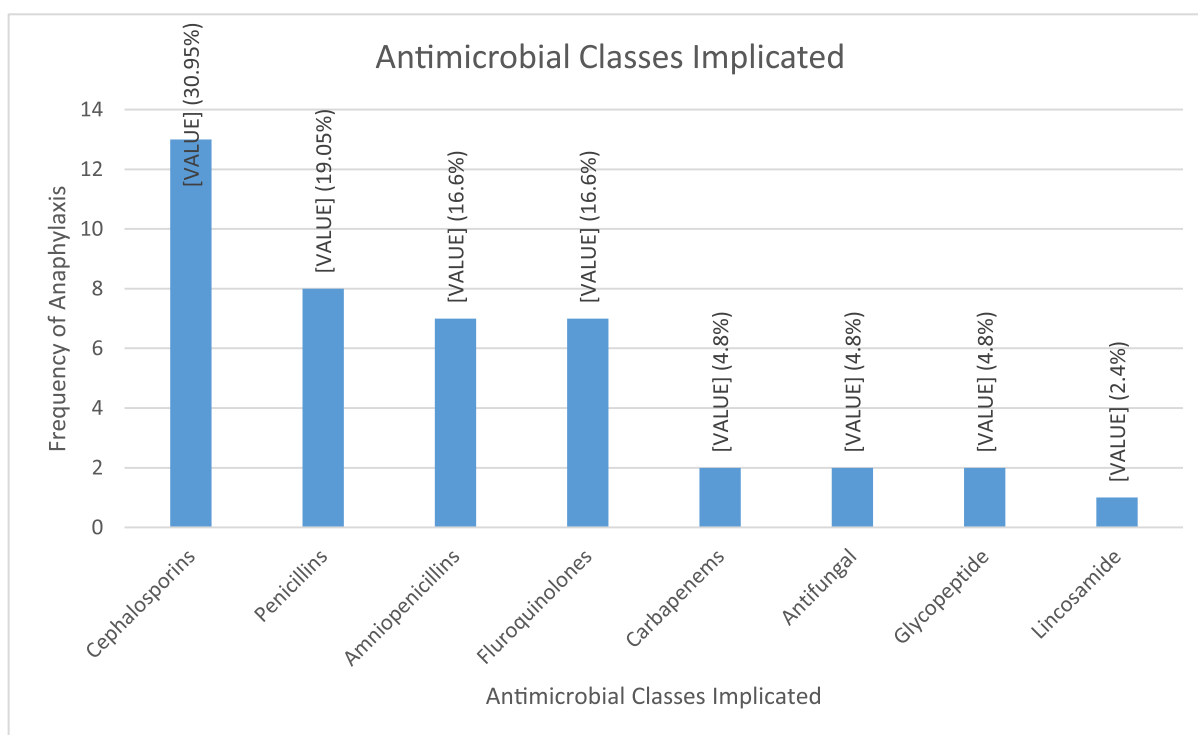


Fig. 2. (a) Anaphylaxis episodes per implicated individual antimicrobial. All implicated antimicrobials (N = 42). (b) Anaphylaxis episodes per antimicrobial class.

Table 2
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
Age		Frequency (%)	Frequency (%)	
	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 broad spectrum antimicrobial	No	25 (86.21%)	4 (13.79%)	1
	Yes	12 (92.31%)	1 (7.69%)	
Underwent desensitization	No	37 (88.1%)	5 (11.9%)	0.303
	Yes	11 (100%)	0 (0%)	
Asthma	No	26 (83.87%)	5 (16.13%)	0.639
	Yes	14 (93.33%)	1 (6.67%)	
Atopic dermatitis	No	23 (85.19%)	4 (14.81%)	0.162
	Yes	10 (76.92%)	3 (23.08%)	
Beta-blockers	No	27 (93.1%)	2 (6.9%)	1
	Yes	10 (88.24%)	4 (11.76%)	
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 3
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 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%.

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.

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 hospitalization; further research into measures to predict and manage antimicrobial anaphylaxis could serve antimicrobial stewardship programs.

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CRediT authorship contribution statement

Laila Carolina Abu Esba: Conceptualization, Data curation, Formal analysis, Methodology, Writing. **Faisal Aqeel Al Sehli:** Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Transparency declarations

None to declare.

Ethics statement

Ethics approval was obtained from the Institutional Review Board ethics approval was granted by King Abdullah International Medical Research Center's (KAIMRC) (RC19/339/R).

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