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Population-based incidence of new ampicillin, cephalexin, cefaclor, and sulfonamide antibiotic “allergies” in exposed individuals with and without preexisting ampicillin, cephalexin, or cefaclor “allergies”

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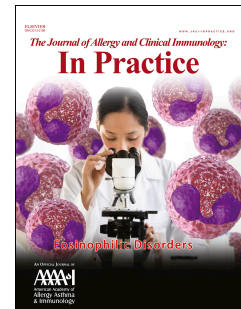
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**Population-based incidence of new ampicillin, cephalexin, cefaclor, and
sulfonamide antibiotic “allergies” in exposed individuals with and without
preexisting ampicillin, cephalexin, or cefaclor “allergies”**

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41

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43 Adverse drug reaction
44 Allergy
45 Ampicillin
46 Cephalexin

47 Cefaclor
48 Electronic health record
49 Hypersensitivity
50 Intolerance
51 Penicillin
52 Sulfonamide antibiotic

53

54

55 **Abbreviations**

56 ACC ampicillin, cephalexin, and cefaclor
57 EHR electronic health record
58 KPNC Kaiser Permanente Northern California
59 KPSC Kaiser Permanente Southern California

Abstract

Background: There is a theoretical concern, unconfirmed by population-based challenge data, that clinically-significant immunologically-mediated hypersensitivity occurs between beta-lactams sharing side chains.

Objective: Determine the population-based “allergy” incidence associated with the use of beta-lactams sharing exact R1 side chains, [ampicillin, cephalexin, and cefaclor (ACC)], with or without a current ACC “allergy” or a sulfonamide antibiotic “allergy” for comparison.

Methods: All courses of ACC and trimethoprim-sulfamethoxazole, used by any Kaiser Permanente California members in 2017 and 2018, with follow-up through January 2019, were identified along with their preexisting antibiotic “allergy” status and all new antibiotic-specific “allergies” reported within 30 days of course initiation.

Results: There were 1,167,713 courses of ACC administered to individuals with no sulfonamide antibiotic or ACC “allergy” and 4,771 (0.41%) new ACC “allergies” were reported. There were 130,032 courses of ACC administered to individuals with a sulfonamide antibiotic “allergy” and no ACC “allergy” and 904 (0.70%) new ACC “allergies” were reported. There were 5,958 courses of ACC administered to individuals with an ACC “allergy”, 2,341 who also had sulfonamide antibiotic “allergy”, and 52 (0.87%) new ACC “allergies” were reported.

83

84 **Conclusion:** The incidence of new ampicillin, cephalexin, or cefaclor “allergy” reports is
85 minimally and non-specifically increased when a preexisting ACC or sulfonamide
86 antibiotic “allergy” exists over the baseline incidence in the population. This argues
87 against clinically-significant immunologically-mediated cross-reactivity between beta-
88 lactams sharing exact side chains in individuals with pre-existing, but unconfirmed,
89 beta-lactam “allergy”. Any previously reported, even unrelated, antibiotic “allergy”
90 appears to be a risk factor for reporting a new antibiotic “allergy”.

Highlights Box

1. What is already known about this topic?

Anecdotally, many individuals with a history of a beta-lactam “allergy” have been noted to tolerate alternative beta-lactams, even those sharing exact side chains.

2. What does this article add to our knowledge?

This is the first population-based data on real world exposures of beta-lactams sharing exact side chains in individuals with beta-lactam allergies associated with those specific side chains.

3. How does this study impact current management guidelines?

This provides more evidence that warnings not to use beta-lactams, even those sharing exact side chains, in individuals with beta-lactam “allergies” can be deleted.

Introduction

There is significant morbidity associated with avoiding use of an indicated beta-lactam antibiotic, such as ampicillin or cephalexin, when it is the drug of choice.¹ This increased morbidity includes treatment failures, increased acquisition of drug resistant infections, and longer hospitalizations.²

It is already widely accepted that all individuals with a penicillin “allergy”, and probably any oral cephalosporin “allergy”, should have their “allergies” evaluated.¹⁻³ Most individuals with benign histories of delayed-onset rashes or other histories not compatible with anaphylaxis or other serious cutaneous or systemic adverse reaction can be safely challenged with a single therapeutic dose, and passing such a challenge is adequate to confirm current tolerance.⁴ Direct observation for 1 hour is adequate to confirm acute tolerance. We have previously shown that an additional 5 days of observation is needed to confirm the absence of a clinically significant T-cell mediated delayed-onset hypersensitivity.⁴ A rostrum article reviewing the historical events and misguided reasoning that led to the antiquated warning not to use cephalosporins in the setting of a penicillin “allergy” has recently been published.⁵

We recently published an analysis of the outcomes associated with completely removing the penicillin-cephalosporin cross-reactivity alert previously seen by providers using the electronic health record (EHR) system in Kaiser Permanente Southern California (KPSC).⁶ This cross-reactivity alert warned against using any cephalosporin

in the setting of a penicillin “allergy”. The outcomes in KPSC were compared to Kaiser Permanente Northern California (KPNC) where the warning was retained.⁶ Removing the default EHR warning resulted in decreased use of second-line antibiotics among patients with a penicillin “allergy” without any significant differences in overall adverse antibiotic-associated reactions or specific serious cephalosporin-associated morbidities.⁶ Removing the warning did not significantly reduce the known morbidities associated with an unconfirmed penicillin allergy.⁶

Immunologically-mediated cross-reactivity between beta-lactams sharing identical side chains has been suspected based on skin testing and immunochemistry results since the 1970s, but population-based challenge data confirming this suspicion is lacking.^{1,7}

The fear is often that anaphylaxis might occur with re-exposure to a beta-lactam that shares an exact side chain, even if anaphylaxis did not occur with the index exposure.⁵

Cephalosporin- and penicillin-associated anaphylaxis is much rarer than commonly feared.^{8,9} Only 1 in 260 to 1 in 1543 newly reported cephalosporin or penicillin “allergies” are confirmed to be anaphylaxis.^{8,9}

In our previous publications there were 4,112 (0.51%) reports of a new cephalixin “allergy” after 811,400 cephalixin exposures with 4 cases of anaphylaxis identified.⁸ There were 35 (0.54%) reports of a new cefaclor “allergy” after 6,459 cefaclor exposures and no cases of anaphylaxis identified.⁸ There were 204 (0.76%) reports of a new ampicillin/penicillin “allergy” after 26,766 exposures to oral ampicillin and no

cases of anaphylaxis were identified.⁹ There were 376 (0.34%) reports of a new ampicillin/penicillin “allergy” after 111,285 parenteral ampicillin or ampicillin-sulbactam exposures and only one case of ampicillin-sulbactam-associated anaphylaxis identified.⁹ We also noted that in 6,404 courses of cephalosporins administered to individuals with another cephalosporin “allergy” there were only 45 (0.70%) new cephalosporin “allergies” reported and no episodes of anaphylaxis identified.⁸ In summary the baseline population-based rates of anaphylaxis with ampicillin, cephalexin, and cefaclor exposures is very low.^{8,9}

In neither report did we specifically evaluate the incidence of new antibiotic “allergies” reported in individuals with and without an ACC “allergy” who received an ACC. We noted incidentally in our recent report that there were several thousand individuals with a record of an “allergy” to ampicillin, cephalexin, and/or cefaclor who then subsequently received one or more of these antibiotics.⁶ Ampicillin, cephalexin, and cefaclor (ACC) share the same 2-amino-2-phenylacetamido group at position 6 of the penam ring and position 7 of the cepham ring respectively.⁷ If there was clinically significant IgE-mediated or T-cell mediated hypersensitivity cross-reactivity based on the identical side-chain, then there should be a significantly increased rate of new “allergies” reported within 30 days of exposure in these individuals, over and above the usual higher rates of new “allergies” reported in any individuals with any pre-existing antibiotic or other drug “allergy” history.⁸⁻¹⁰ We chose to use trimethoprim-sulfamethoxazole as a completely unrelated control because it is typically the second most commonly reported antibiotic “allergy”.³

Methods

The data used in this analysis were extracted and assembled as part of a previous retrospective, observational study of a natural experiment which included all members enrolled in either the KPSC or KPNC health plans who received an antibiotic between January 1, 2017 and December 31, 2018.⁶ During this period, the health plans had about 9 million members, broadly representative of the state of California.^{11,12} Some of this cohort, those KPSC members who were treated with ampicillin between January 1, 2017 and December 31, 2017 have been previously reported on in part.⁹ The institutional review boards of KPSC and KPNC approved this study and waived the requirement for informed consent for this preexisting data only study.⁶

The data were extracted from existing health plan and care delivery sources including ambulatory and hospital-based electronic health records (EHR), claims, and other administrative data such as health plan membership. We included outcome data through January 31, 2019 to allow for 30 days of follow-up time after courses starting through December 31, 2018. Patients were excluded from the analysis if the gender was missing in the source data; if the birth date was missing or was obviously inaccurate (occurring after the first antibiotic course); or if the death date was obviously inaccurate (occurring before the first antibiotic course).

The original dataset included all oral and parenteral dispenses or administrations (in the ambulatory or hospital setting) for twelve antibiotic categories, excluding antibiotic use

outside of membership periods. Multiple periods of exposure to the same drug by the same route were combined into the same course if they were separated by fewer than 2 days. Exposure periods for outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply.

In the current analysis we included the 1,800,663 courses of ampicillin, cephalexin, cefaclor, and trimethoprim-sulfamethoxazole for which the patient had at least 30 days of membership after the course start date. These courses were used by 1,235,847 unique individuals, of whom 1,433 contributed courses both with and without an ACC "allergy" due to their change in ACC "allergy" status over the two-year study interval.

The presence of a drug "allergy" was defined based on entries in the EHR allergy field, rather than requiring confirmed IgE- or T-cell-mediated hypersensitivity.⁸⁻¹⁰ Periods of "allergies" were calculated based on the patient's complete antibiotic "allergy" history. The patient's antibiotic "allergy" status was calculated as of the day before the start date for each antibiotic course. New antibiotic "allergies" following ampicillin, cephalexin, or cefaclor courses were defined as new "allergy" records matching the generic name (ampicillin, cephalexin, or cefaclor) within 30 days of the start of the course. New antibiotic "allergies" following trimethoprim-sulfamethoxazole courses were defined as new "allergy" records specifically for "sulfamethoxazole" or for the more general "sulfonamide antibiotics" within 30 days of the start of the course. If a new "allergy" record appeared in the follow-up windows for multiple courses, it was assigned to the course(s) on the most recent date.

220

221 Statistical analyses were conducted using SAS Enterprise Guide, version 7.1 (SAS
222 Institute). Statistical significance was assessed based on p values from Fisher's exact
223 tests (for pairs of categorical variables), chi-squared tests (for 3 or more categorical
224 variables), or t tests (for continuous variables).

Results

The demographics of study subjects are displayed in Table 1. Study subjects with an ACC “allergy” were more likely to be female and were on average 11.2 years older than individuals without an ACC “allergy” ($p < 0.0001$ for both comparisons).

The number of new antibiotic “allergies” after ampicillin, cephalexin, cefaclor, and trimethoprim-sulfamethoxazole courses in individuals with no sulfonamide antibiotic or ACC “allergy”, a sulfonamide antibiotic “allergy” but no ACC “allergy”, and an ACC “allergy” are displayed in Table 2. Having any “allergy” even an unrelated trimethoprim-sulfamethoxazole “allergy” is the primary risk factor for having a higher rate of new antibiotic “allergy” reports.

The total number of new “allergies” associated with combined ACC exposures and underlying ACC or sulfonamide antibiotic “allergy” history status are displayed in Table 3. There were significantly more new ACC “allergies” reported after exposure in both individuals with a sulfonamide antibiotic “allergy” or an ACC “allergy” compared to individuals without either a sulfonamide antibiotic “allergy” or an ACC “allergy”. There was no significant difference in the number of new ACC “allergies” reported between individuals with a sulfonamide antibiotic “allergy” (but no ACC “allergy”) or an ACC “allergy”. There were 2,341 courses of an ACC used in the ACC “allergy” group by individuals who also had a sulfonamide antibiotic “allergy”.

Among the 23,843 courses of ACCs and trimethoprim-sulfamethoxazole administered to ACC “allergic” individuals there were 5,039 (21.13%) given to ampicillin “allergic” individuals, 16,703 (70.05%) given to cephalexin “allergic” individuals, and 1,790 (7.51%) given to cefaclor “allergic” individuals. There were 210 (0.88%) courses given to dual ampicillin and cephalexin “allergic” individuals, 22 (0.09%) given to dual ampicillin and cefaclor “allergic” individuals, and 73 (0.31%) given to dual cephalexin and cefaclor “allergic” individuals. Finally, there were 6 (0.03%) courses given to individuals with “allergies” to ampicillin, cephalexin, and cefaclor.

There was a total of 1,776,820 courses of ampicillin, cephalexin, cefaclor, or trimethoprim-sulfamethoxazole given to individuals with no ACC “allergy”. This included 131,586 (7.41%) courses given to individuals with a sulfonamide antibiotic “allergy”.

There was a total of 479,075 courses of trimethoprim-sulfamethoxazole given to individuals without an ACC “allergy”. This included 1,554 (0.32%) courses of trimethoprim-sulfamethoxazole given to individuals with a sulfonamide antibiotic “allergy”. There was a total of 17,885 courses of trimethoprim-sulfamethoxazole given to individuals with an ACC “allergy”, including 354 (1.98%) courses given to individuals with both an ACC and a sulfonamide antibiotic “allergy”.

There were 2,873 courses of cephalexin or cefaclor given to people with an ampicillin “allergy” and in 35 (1.22%) was a new cephalexin or cefaclor “allergy” reported within the next 30 days. There were 998 courses of ampicillin given to people with a

cephalexin or cefaclor “allergy” and in 8 (0.80%) was a new ampicillin “allergy” reported within the next 30 days.

The rate of new antibiotic “allergy” reports after trimethoprim-sulfamethoxazole exposures was 1.83% in the non-ACC “allergy” cohort compared to 3.18% (74% higher) in the ACC “allergy” cohort ($p < 0.0001$).

There were 23 courses of ampicillin given to people with an ampicillin “allergy”, 1,656 courses of cephalexin given people with a cephalexin “allergy” and 6 courses of cefaclor given to people with a cefaclor “allergy”. It was not possible to determine how many had their “allergy” removed within 30 days of exposure, or if they noted a new adverse reaction, because this data was not extracted out of the EHR as part of the dataset used for this paper.

Discussion

We noted that the incidence of new ampicillin, cephalexin, cefaclor, or sulfonamide antibiotic “allergy” reports was increased in individuals with a preexisting ampicillin, cephalexin, or cefaclor “allergy” but not in a side-chain restricted fashion. This argues against a clinically-significant immunologically mediated cross-reactivity between beta-lactams sharing side chains in individuals with pre-existing, but unconfirmed, beta-lactam “allergy”.^{6,7,9} Having an ACC “allergy” was associated with an increased rate of reporting a new “allergy” after trimethoprim-sulfamethoxazole use compared to those not reporting an ACC “allergy”. We again noted the approximate doubling in the risk of reporting a new antibiotic “allergy” when there is any preexisting antibiotic “allergy” reported compared to what is typically seen in unselected individuals.^{8-10,20,21} We noted an elevated risk of a new ACC “allergy” report in patients with preexisting ACC “allergy” and in patients with preexisting sulfonamide antibiotic “allergy” (but no preexisting ACC “allergy”), compared to patients without a preexisting ACC or sulfonamide antibiotic “allergy”. There was no significant difference in the risk of a new ACC “allergy” report when comparing patients with preexisting ACC “allergy” to patients with preexisting sulfonamide antibiotic “allergy” (but no preexisting ACC “allergy”). In summary, any previously reported antibiotic “allergy” appears to be a significant risk factor for reporting a new “allergy”.

Rarely do individuals with suspected hypersensitivity reactions associated with the use of ampicillin, cephalexin, or cefaclor have their index events confirmed to be clinically

significant ampicillin-, cephalexin-, or cefaclor-specific IgE- or T-cell-mediated hypersensitivity by skin testing or challenge.¹ Even more rarely have they been challenged with or given therapeutic courses of beta-lactams that share exact side chains after confirming a specific beta-lactam hypersensitivity.⁵

Only a small minority, typically less than 5%, of individuals with any beta-lactam “allergy” are confirmed via testing to have clinically significant IgE-mediated or Tcell-mediated hypersensitivity.² If the index reaction was anaphylaxis, which is extremely rare as noted previously, or urticaria starting within 1 hour of the first dose and clearing within 1 day, then clinically significant IgE-mediated acute-onset hypersensitivity is much more likely to be confirmed by appropriate skin testing or challenge.¹³ We know that about 97 to 98% of individuals with a penicillin “allergy” will tolerate an oral challenge with a therapeutic dose of a penicillin without any acute or delayed-onset hypersensitivity event.^{2,4}

From what little published data there is on this topic, it appears that only a minority of individuals with confirmed cephalexin, cefaclor, or ampicillin hypersensitivity will have reactions associated with challenges to other members of this group of beta-lactams that share exact or very similar side chains. Thus, it is not surprising that we noted no clinically-significant increased rate of new “allergy” reports in our cohort of unconfirmed ACC “allergy” with re-exposures to an alternative ACC.

Audicana and coworkers in 1994 reported on a group of 7 individuals with history of acute-onset hypersensitivity associated with the use of ampicillin.¹⁴ There were 4 with a history compatible with anaphylaxis and 3 with benign rashes. There were 5 who were skin test positive to ampicillin and 2 were additionally skin test positive to cephalexin. There were 5 who were oral cephalexin challenge negative, one was cephalexin oral challenge positive, manifest with benign urticaria only, and one was not challenged due to cephalexin skin test positivity.

Romano and coworkers in 1997 reported on a cohort of 48 highly selected individuals with a history of ampicillin-associated urticaria, 9 (19%), or anaphylaxis, 39 (81%).¹⁵ All were confirmed to have immediate- or delayed-onset hypersensitivity using penicillin and ampicillin skin testing. Most were only skin test positive to penicillin determinants. They identified 10 (21%) individuals positive to both penicillin and ampicillin and only 3 (6.3%) individuals whose hypersensitivity was restricted specifically to ampicillin-specific determinants. None of these individuals were subsequently challenged or treated with cephalexin or cefaclor.

Phillips and co-workers reported in 2001 on a cohort of 16 individuals with histories of delayed-onset reactions to an ampicillin skin test, but who tolerated an acute oral penicillin challenge.¹⁶ They were subsequently patch tested with ampicillin and cephalexin and only 5 (31%) individuals were positive to both. There were 2 ampicillin patch test positive patients given a 5-day cephalexin challenge and 4 ampicillin patch

test positive patients given a single dose cefaclor challenge and none of these patients reacted to the challenges.

We have similarly reported on a cohort of 24 individuals with acute-onset oral amoxicillin-associated challenge reactions and an additional 10 individuals with delayed-onset oral amoxicillin-associated challenge reactions seen between 2010 and 2017.¹⁷ Amoxicillin has a very similar side chain to ampicillin, cephalexin, and cefaclor, differing only by a hydroxyl group attached to the benzene ring. There were no cephalexin- or cefaclor-associated adverse reactions occurring in the 13 (38.2%) individuals in this cohort who were exposed to 53 total therapeutic courses of cephalexin and one of cefaclor.

Romano and coworkers in 2015 using skin testing identified 3 individuals confirmed to be cephalexin hypersensitive and 13 individuals confirmed to be cefaclor hypersensitive.¹⁸ Two of the 3 individuals who were skin test positive to cephalexin were also skin test positive to ampicillin. Only 2 of the 13 individuals positive to cefaclor were skin test positive to ampicillin. These were a highly selected group given that 3 of the cefaclor and 1 of the cephalexin skin positive subjects had anaphylaxis as their index reaction. In their entire cohort of 102 subjects with any confirmed cephalosporin allergies, 83 (81.4%) of who had anaphylaxis as their index reaction, there were 4 who were skin test positive to ampicillin, 7 were skin test positive to cephalexin, and 16 were skin test positive to cefaclor. Four of these individuals were skin test positive to both

cephalexin and cefaclor. No challenges were done with ampicillin in those skin test positive to cephalexin or cefaclor, even if ampicillin skin test negative.

Stone and coworkers in 2021 reported on 136 individuals with cephalexin-associated index reactions and 33 with cefaclor-associated index reactions in a combined cohort of 328 suspected cephalosporin allergic individuals.¹⁹ In the combined cohort there were 245 (74.7%) with an immediate-onset and 83 (25.3%) with delayed-onset index cephalosporin-associated reactions and 240 (73.2%) who also carried an unconfirmed penicillin “allergy”. They did not perform any skin testing using cephalexin or cefaclor to confirm these specific hypersensitivities. There were 11 (8.0%) individuals with cephalexin-associated index reactions who were skin test-positive to ampicillin and none of those with cefaclor-associated index reactions were ampicillin skin test-positive. They used cephalexin for all their oral cephalosporin challenges, and none were positive. They did not perform any oral ampicillin challenges in those who were ampicillin skin test negative to confirm tolerance.

We did not note higher rates of new “allergy” reports with exposure to beta-lactams sharing identical side chains compared to our historical data on population-based rates, without specific beta-lactam “allergy” histories.²¹ The overall rate of new ampicillin “allergies” reported here in individuals without an ACC “allergy”, 0.26% per course, or with an ACC “allergy”, 0.79%, are both lower than the global population-based numbers noted in our previous work.⁹ In our patient population it can be estimated that less than 5% (“optimistic”) or even less than 1% (“pessimistic”) of all ACC “allergy” cases could

potentially have a clinically-significant immunologically-mediated hypersensitivity to an ACC. Thus, even in individuals with specific ACC “allergies” who are then treated with another ACC antibiotic, there is no clinically-significant increased risk of reporting a new “allergy” over background population-based risks.

We have previously noted that as many as 2% of individuals with a penicillin “allergy” are given a penicillin in any year, and only a very small fraction have their penicillin “allergy” removed.³ We again noted the use of specific antibiotics by patients with an active “allergy” listed to that antibiotic. Monitoring the EHR to identify uneventful antibiotic re-exposures could potentially result in the removal of many of these apparently inaccurate antibiotic “allergies”.³

A weakness in this report was the inability to determine exactly how many individuals had their antibiotic “allergies” removed in a timely fashion (within 30 days) after tolerating re-exposure to the implicated antibiotic or if re-exposures resulted in a new unreported adverse reaction. Since this dataset was collected for another purpose, we did not extract this data out of the EHR, because it was not part of the previous analysis. We were also unable to adjust our results based on the reasons individuals were using antibiotics. We were unable to identify adverse reactions that were not reported in the drug “allergy” fields, but we also consider these to be clinically insignificant events, because they do not alter future antibiotic usage decisions.

The rare individuals with a good history for ampicillin, cephalexin, or cefaclor-associated anaphylaxis should be evaluated by Allergy/Immunology and proceed with an appropriate work-up to confirm or refute the suspected acute-onset potentially life-threatening hypersensitivity.^{1,2}

The practical application of our observations is that the risk of using an alternative ACC in groups of people with an unconfirmed ACC “allergy” is very low. Given the significant morbidity associated with avoiding a beta-lactam antibiotic when it is the antibiotic of choice, if ampicillin, cephalexin, or cefaclor is the drug of choice for a confirmed infection and the person has a low-risk ACC “allergy”, and the relative safety, serious consideration should be given to using ampicillin, cephalexin, or cefaclor with one hour of direct observation after the first dose.²²⁻²⁴ Formal testing to confirm a true ACC allergy should also be done as soon as practically possible.¹

We did not see evidence that individuals with unconfirmed “allergies” to ampicillin, cephalexin, or cefaclor have increased new “allergy” reports after using these antibiotics that share identical R1 side chains. There is a higher rate of new antibiotic “allergies” noted with exposures to all antibiotics, even completely unrelated antibiotics, in individuals with any antibiotic “allergy” in their record.

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Table 1: Study subject demographics

	All unique patients	Patients contributing courses with no ACC allergy	Patients contributing courses with ACC allergy
Patients	1,235,847	1,222,045	15,235
Gender Female (%)	818,630 (66.2)	807,574 (66.1)	12,231 (80.3)
Age (years) at first antibiotic exposure (SD)	44.4 (23.6)	44.3 (23.6)	55.5 (21.2)
Unique patients with ampicillin exposure (total courses)	59,711 (65,372)	58,901 (64,353)	824 (1,019)
Unique patients with cephalexin exposure (total courses)	934,036 (1,237,293)	930,937 (1,232,384)	3,431 (4,909)
Unique patients with cefaclor exposure (total courses)	844 (1,038)	829 (1,008)	17 (30)

Unique patients with trimethoprim-sulfamethoxazole exposure (total courses)	390,632 (496,960)	379,026 (479,075)	11,998 (17,885)
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528 Note: 1,433 of the 1,235,847 unique patients contributed courses both with and without
529 an ACC allergy to the analysis, due to a change in allergy status during the study
530 interval.

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Table 2: New drug allergies reported

	No sulfonamide “allergy” and no ACC “allergy”	Sulfonamide “allergy” and no ACC “allergy”	ACC “allergy”
Ampicillin exposure			
Total courses	60,855	3,498	1,019
[New “allergies”]	[152]	[15]	[8]
(%)	(0.25)	(0.43)	(0.79)
Cephalexin exposure			
Total courses	1,106,059	126,325	4,909
[New “allergies”]	[4,616]	[884]	[44]
(%)	(0.42)	(0.70)	(0.90)
Cefaclor exposure			
Total courses	799	209	30
[New “allergies”]	[3]	[5]	[0]
(%)	(0.38)	(2.39)	(0.00)

Trimethoprim- sulfamethoxazole exposure			
Total courses	477,521	1,554	17,885
[New “allergies”]	[8,744]	NA	[568]
(%)	(1.83)	(NA)	(3.18)

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Table 3. New “allergies” associated with combined ACC exposures and underlying ACC or sulfonamide antibiotic “allergy” history

		No sulfonamide antibiotic or ACC “allergy” ^a	Sulfonamide antibiotic “allergy” and no ACC “allergy” ^b	ACC “allergy” ^c
Ampicillin, cephalixin, or cefaclor exposure	Total courses [New “allergies”] (%)	1,167,713 [4,771] (0.41)	130,032 [904] (0.70)	5,958 [52] (0.87)

The difference between columns a and b is statistically significant ($p < 0.0001$)

The difference between columns a and c is statistically significant ($p < 0.0001$)

The difference between columns b and c is not statistically significant ($p = 0.11$)