Adverse reactions associated with oral and parenteral use of cephalosporins: A retrospective population-based analysis

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Background: Few studies have provided population-based, route-specific data on allergy to cephalosporin or incidence of serious adverse drug reactions (ADRs).
Objective: We investigated the incidence of new reports of cephalosporin-associated "allergy" and serious ADRs.
Methods: We identified all members of the Kaiser Permanente Southern California health plan given cephalosporins (from January 1, 2010, through December 31, 2012), all new reports of cephalosporin-associated allergy, and all serious ADRs.
Results: There were 622,456 health plan members exposed to 901,908 courses of oral cephalosporins and 326,867 members exposed to 487,630 courses of parenteral cephalosporins over the 3-year study period. New reports of allergy to cephalosporin were more frequent among women (0.56%; 95% CI, 0.54% to 0.57%) than among men (0.43%; 95% CI, 0.41% to 0.44%) per course ($P < .0001$). The most frequent serious cephalosporin-associated ADRs were *Clostridium difficile* infection within 90 days (0.91%), nephropathy within 30 days (0.15%), and all-cause death within 1 day (0.10%). None correlated with history of drug allergy. Physician-documented cephalosporin-associated anaphylaxis occurred with 5 oral exposures (95% CI, 1/1,428,571-1/96,154) and 8 parenteral exposures (95% CI, 1/200,000-1/35,971) ($P = .0761$). There were 3 documented cephalosporin-associated serious cutaneous adverse reactions (95% CI, 0-1 in 217,291). All were associated with the use of another antibiotic at the same time as cephalosporin.
Conclusions: Cephalosporins are widely and safely used, even in individuals with a history of penicillin allergy. Physician-documented cephalosporin-associated anaphylaxis and serious cutaneous adverse reactions are rare compared with *C difficile* infection within 90 days, nephropathy within 30 days, and all-cause death within 1 day. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Adverse drug reaction, allergy, cephalosporin,* Clostridium difficile*, death, hemolytic anemia, hospitalized, oral, outpatient, nephropathy, parenteral, serious cutaneous adverse reaction, Stevens-Johnson syndrome*

Abbreviations used
ADR: Adverse drug reaction
EHR: Electronic health record
ICD-9: *International Classification of Diseases, Ninth Revision*
RR: Relative risk
SCAR: Serious cutaneous adverse reaction
SJS: Stevens-Johnson syndrome

Cephalosporins are the most commonly used antibiotic in patients hospitalized in the Kaiser Permanente Health Care Program.[1] Cephalosporins are widely used to prevent infections in patients undergoing surgery and in outpatients with genitourinary tract, upper respiratory tract, and skin infections. However, there are few infections for which cephalosporins are the antibiotic of choice. The use, and specifically overuse, of cephalosporins has been associated with adverse drug reactions (ADRs),[2] ranging from rashes and diarrhea to anaphylaxis, serious cutaneous adverse reactions (SCARs), hemolytic anemia, nephropathy, *Clostridium difficile* infection, and death.

The rate of anaphylaxis associated with parenteral cephalosporin exposure has been assumed to be greater than that associated with oral use, but this has never been comprehensively demonstrated in a large, diverse population.[3] The relative frequencies of serious cephalosporin-associated ADRs are poorly understood. Many physicians still fear cephalosporin-associated anaphylaxis in individuals with a history of penicillin "allergy," rather than serious and frequent morbidity from *C difficile* infection.

Cephalosporins are currently widely, safely, and appropriately used in individuals with histories of penicillin allergy, despite concerns about immune cross-reactivity with both drugs.[3] One reason cephalosporins are safely used could be that only a small minority of individuals with histories of penicillin allergy show responses to penicillin in skin tests or with oral challenges.[4] There are doubts about a potential small increase in the rate of serious allergic reactions to cephalosporins among individuals with proven IgE-mediated allergy to penicillin.[5]

There have been a number of studies, involving as many as tens of thousands of individuals, of the incidence of antibiotic-associated ADRs. These reported new cases of allergy and anaphylaxis, but most of these studies focused on penicillins and sulfonamides—classes of antibiotics with the highest prevalence of allergy.[6-8] In 1983, Alanis and Weinstein[9] reviewed adverse reactions associated with the use of oral penicillins and cephalosporins in the preceding 30 years but provided no data on parenteral cephalosporin-associated ADRs.[9]

We reported new cases of antibiotic allergy in 411,543 individuals in 2007.[10] We noted that 0.60% of male outpatients (95% CI, 0.47% to 0.72%) and 1.08% of female outpatients

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(95% CI, 0.96% to 1.21%) who received cephalosporin (almost all oral) reported a new allergy to the drug within 1 year after each course of use. In a study of 2,375,424 patients seen during 2009, we associated sex, age, medication use, and history of drug allergy with future reports of antibiotic allergy.[11]

We now aim to provide a descriptive report of the real-world frequency of new reports of cephalosporin-associated "allergies" or serious ADRs, including physician-documented anaphylaxis and SCARs, along with reports of hemolytic anemia and nephropathy within 30 days, *C difficile* infection within 90 days, and all-cause death within 1 day.

METHODS

The Kaiser Permanente Southern California Institutional Review Board reviewed and approved this project.

All individuals who received health care from Kaiser Permanente in Southern California between January 1, 2010, and December 31, 2012, were potential cohort members. Subsets of these individuals have been previously reported on, in part.[1] Individuals of unknown sex were not included (n = 3133, 0.078%). There is 1 electronic health record (EHR) system used by Kaiser Permanente in Southern California, called Health Connect (Epic Systems Corporation, Verona, Wis). Health Connect links all health care provided in the outpatient and inpatient settings with pharmacies.

Clinical visits were defined as an outpatient visit and included visits to medical offices, urgent care centers, infusion centers, or emergency rooms; these also included phone calls or electronic (e)-visits (via direct Health Connect electronic messages) or admission to 1 of 12 Kaiser Permanente Southern California hospitals. A small fraction of the cohort may have received health care outside the network, but if medications used or any ADRs experienced were entered into Health Connect via an e-visit or future in-person visit, the event was captured for this study.

All cephalosporin antibiotics used by the cohort during the study interval were identified. All cephalosporin use was linked to an outpatient visit, e-visit, or hospitalization. Drug class allergies were determined as previously described.[11] The maximum number of drug class allergies possible was set as 24.

A *course of a cephalosporin* was defined as any oral or parenteral exposure to a specific cephalosporin by 1 systemic route. Parenteral exposures included intravenous, intramuscular, subcutaneous, intradermal, intraosseous, intraperitoneal, and intravesicular injections or infusions. Any exposure to the same cephalosporin by the same route within 36 hours was considered to be the same course. We collected data on active drug allergies noted in the EHR for each individual on the day before the use of each cephalosporin class antibiotic. Any serious, or clinically significant, reproducible IgE-, IgG-, or T-cell–mediated cephalosporin-associated ADRs, occurring because of pre-existing immunologic reactivity to cephalosporins or cross-reactivity with penicillins, would be expected to be manifest within 5 days of the exposure and could therefore be attributed to that course. To allow for potential new sensitization, we identified all new cephalosporin class antibiotic allergy entries made within 30 days of each cephalosporin use. These methods differ from those we published previously and should more accurately link drug allergy entries with specific cephalosporin courses.[10]

The following algorithms were used to identify cephalosporin-associated serious ADRs, including physician-documented anaphylaxis and SCARs, hemolytic anemia, nephropathy, *C difficile* infection, and death. We identified all individuals for whom a diagnosis of anaphylaxis (*International Classification of Diseases, Ninth Revision* [ICD-9] 995.0) was coded within 1 day of starting a course of cephalosporin, along with all intramuscular epinephrine administrations made within 1 day of starting the cephalosporin course. It was not possible to reliably identify intravenous use of epinephrine in the operating room. An EHR review was then performed to verify that anaphylaxis occurred and met the current working definition.[12] The EHR review was also used to rule out the possibility that an alternate medication caused the anaphylaxis episode. Physician-documented SCARs were identified by using the following ICD-9 codes, entered in the EHR up to 30 days after each course of cephalosporin began: erythema multiforme major (ICD-9 695.14), Stevens-Johnson syndrome (SJS) (ICD-9 695.13), toxic epidermal necrolysis (ICD-9 695.15), and drug reaction with eosinophilia and systemic symptoms (ICD-9 995.27). Drug reaction with eosinophilia and systemic symptoms cases were required to have more than 10% eosinophilia, with 500 or more eosinophils/μL, and increased levels of liver enzymes within 30 days of the implicated starting does of cephalosporin.

An EHR review was then performed to verify that the coded SCAR diagnosis was correct and that biopsy analyses supported the diagnosis, as well as to rule out the use of another medication at the same time as the implicated cephalosporin. Potential cases of cephalosporin-associated hemolytic anemia were identified on the basis of a combination of hemoglobin levels newly below 8 gm/dL, associated with lactate dehydrogenase levels of more than 2000 U/L, within 30 days of starting the implicated cephalosporin course, along with the lack of a previous diagnosis of anemia, sepsis, or renal failure.

EHRs were reviewed to confirm cases and determine clinical outcomes. Cephalosporin-associated nephropathy was identified in individuals who had new increases of more than 3.0 mg/dL in serum creatinine levels, within 30 days of starting the implicated cephalosporin course, and no history of increased serum creatinine levels (>1.3 mg/dL) or chronic kidney disease (ICD-9 codes 580 through 589 or 250.4) in the preceding 90 days. EHRs were reviewed to determine clinical outcomes. We identified all new-onset cases of clinically significant *C difficile* infection (verified by the first use of ICD-9 code 8.45 as a diagnosis) or a new positive result from a laboratory test for *C difficile*, toxin, or culture, within 90 days of using a cephalosporin. Finally, we identified all individuals who died from all causes within 1 day of starting a course of cephalosporin.

All statistical analyses were conducted with SAS EG 4.3. Percentages and odds ratios were calculated on categorical outcomes. Means and SDs were calculated on continuous variables. Statistical significance was assessed on the basis of categorical variables using chi-square tests and *t* tests for continuous variables. All *P* values of less than .05 were considered to be statistically significant. Unadjusted relative risks (RRs) for the adverse outcomes in oral and parenteral cephalosporins were computed from 2 × 2 tables. Adjusted RRs were computed with Poisson regression models adjusting for age, sex, and cephalosporin generation. The primary outcome measures were new cephalosporin allergy reports within 30 days and incidence rates of serious cephalosporin-associated ADRs, including physician-documented anaphylaxis with the first-course exposure; physician-documented SCARs, hemolytic anemia, or nephropathy within 30 days; *C difficile* infection within 90 days; and all-cause death within 1 day.

RESULTS

There were 3,999,290 total unique individuals with at least 1 health plan visit during the 3-year study period (from January 1, 2010, through December 31, 2012). There were 462,225 individuals (11.6% of total) with at least 1 hospitalization during the study interval. There were 2,848,001 individuals (71.2% of total) with only an outpatient visit during the study interval. There were 7767 individuals (0.19% of total) with only an e-visit during the study interval. The demographic characteristics of all health plan members, at their index visit during the study interval, who were hospitalized during the study interval were compared with those of health plan members who were not hospitalized (Table I).

Female patients had almost twice as many baseline drug class allergies as did male patients. Hospitalized and nonhospitalized women were more likely than men to receive oral cephalosporins and had a higher baseline prevalence of penicillin or cephalosporin allergies. Penicillin allergy was noted on the day before the index visit in 6.3% of nonhospitalized individuals, 9.9% of hospitalized individuals, and 6.8% of all health plan members. A cephalosporin allergy was noted on the day before the index