# Penicillin allergy and association with ciprofloxacin coverage in community-onset urinary tract infection

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The prevalence of patients with a documented penicillin allergy is >10% in many healthcare settings in the United States.[1,2] Though up to 90% of these patients may safely tolerate penicillin, the presence of an allergy label is associated with increased use of broad-spectrum antimicrobials including fluoroquinolones, glycopeptides, and carbapenems.[2–4] In the treatment of urinary tract infections (UTIs), recent fluoroquinolone use is a demonstrated risk factor for ciprofloxacin resistance among *Escherichia coli* UTIs.[5] As part of a study aimed at developing predictive models for empiric antibiotic prescribing, we investigated the relationship between a documented penicillin-class allergy and ciprofloxacin-resistant community-onset UTIs in adult hospitalized patients. Our analysis is inclusive of all urinary pathogens.

## Methods

Using electronic health record (EHR) data from a 1,300-bed teaching hospital, we established a retrospective cohort of adult patients admitted to an inpatient unit from November 1, 2011, to June 30, 2016, with a UTI diagnosis and a positive urine culture in the first 48 hours. Only the first encounter during the study period was included. We defined the exposure as presence of a penicillin-class allergy label (eg, penicillin, amoxicillin, piperacillin) documented in the EHR, and we defined the outcome as a UTI not covered by ciprofloxacin. We included all urinary pathogens for infections where multiple pathogens were present. For UTIs with unreported ciprofloxacin susceptibilities, subject matter experts inferred susceptibility according to previously reported methods.[6]

We used modified Poisson regression with stabilized inverse probability weights (IPW) to estimate the adjusted relative risk of resistance.[7,8] Inverse probability weighting adjusted for potential measured confounders: sex, age, Elixhauser score, number of inpatient and emergency department admissions in the past year, and indicator variables for transfer from a nursing home and presence of a cephalosporin or carbapenem allergy label. We adjusted for cephalosporin and carbapenem allergy to isolate the effect of a penicillin-class allergy label. Stabilized IPW were estimated via boosted logistic regression, and covariate balance between exposure groups after weighting was evaluated by standardized differences between exposure groups using the *twang* package version 1.5 in R.[8] Analyses were conducted in Stata version 15 software (StataCorp, College Station, TX) and R version 3.4.2 software (R Foundation for Statistical Computing, Vienna, Austria).

Additionally, we examined the potential mediation effect of recent fluoroquinolone use in the relationship between a penicillin-class allergy label and lack of ciprofloxacin coverage. We estimated the total, direct, and indirect effects of prior fluoroquinolone use, adjusted by IPW, through the *mediation* package (version 4.4.6) in R.[9] This study was approved by the Institutional Review Board of the Office of Responsible Research Practices at The Ohio State University.

## Results

Among 6,361 patients admitted with community-onset UTI, 1,252 (19.7%) had a penicillin-class allergy label documented in the EHR. A total of 7,431 isolates representing 75 organisms were included in the analysis. The most prevalent organisms, which accounted for 75.9% of all isolates, were *Escherichia coli* (n = 2,797), *Enterococcus faecalis* (n = 1,281), *Klebsiella pneumoniae* (n = 876), *Pseudomonas aeruginosa* (n = 391), and *Enterococcus faecium* (n = 292). Prior to IPW, exposure groups were notably imbalanced on sex, age, and cephalosporin allergy. After IPW, all standardized differences between exposure groups were < 10%. Patients with a penicillin-class allergy label were 1.13 times more likely to have a ciprofloxacin-resistant UTI (707 of 1,252, 56.5%) compared to those without a penicillin-class allergy label (2,601 of 5,109, 50.9%; aRR, 1.13; 95% CI, 1.06–1.19). Mediation analysis revealed that 24% of the total effect of a penicillin-class allergy label on ciprofloxacin-resistant UTI was explained by fluoroquinolone use in the past 90 days, as documented in our EHR at least 24 hours prior to culture (95% CI, 0.08–0.49) (Fig. 1).

A major assumption in the development of susceptibilities for this cohort was that enterococci were not covered by ciprofloxacin if susceptibilities were not reported. However, because enterococci may be susceptible to ciprofloxacin, we reevaluated our models assuming that enterococci with missing susceptibilities were susceptible to ciprofloxacin (21% of encounters affected). Overall inference in the association of interest and mediation effect by

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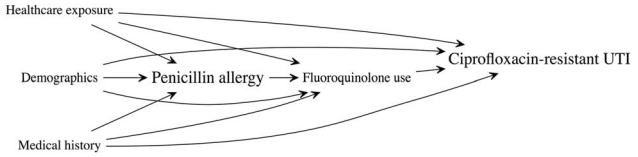


**Fig. 1.** Directed acyclic graph of the proposed association between penicillin-class allergy label and ciprofloxacin-resistant urinary tract infection (UTI), including partial mediation by recent fluoroquinolone use. Potential confounding variables accounted for in our analysis are also presented: demographics (sex and age), healthcare exposure (nursing home transfer, emergency department admissions, inpatient admissions), and medical history (Elixhauser score, cephalosporin allergy, carbapenem allergy).

fluoroquinolone use in this sensitivity analysis did not substantially change (aRR, 1.20; 95% CI, 1.09–1.31; average proportion mediated: 17%; 95% CI, 0.06–0.37).

## Discussion

Among patients presenting with a UTI, those with a penicillin-class allergy label may be at a slightly increased risk of not being covered by ciprofloxacin. Recent fluoroquinolone use partially contributes to this effect, suggesting additional mechanisms behind this association. Because we were limited to evaluating antibiotic exposures that occurred within our healthcare system, the proportion of the total effect mediated by fluoroquinolone use may have been higher than 24% if similar patterns of recent fluoroquinolone use by allergy status occurred outside of our health system. Additional mediators could include recent exposure to other antimicrobial classes that were not evaluated in this study.

Targeting areas of antibiotic overuse is key to combating resistance and improving patient outcomes through appropriate antibiotic prescribing. With respect to penicillin-class allergy labels, antimicrobial stewardship initiatives have focused on allergy confirmation through skin testing and oral challenge.[10] In many cases, patients with a documented but unconfirmed penicillin-class allergy can be de-labeled following appropriate testing.[10] Our finding that nearly 20% of patients in this cohort had a documented penicillin-class allergy highlights the potential for more accurate classification and labeling of allergies to support antimicrobial stewardship. We show that a penicillin-class allergy is a modest risk factor for ciprofloxacin resistance, which may be due in part to increased use of fluoroquinolones. This finding suggests that one possible solution to fluoroquinolone overuse would be to reassess the veracity of penicillin allergy labels at the point of care.

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