



Prevalence and characteristics of hospital inpatients with reported fluoroquinolone allergy

Geoffrey C. Wall¹ · Matthew J. Taylor² · Hayden L. Smith³

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Abstract

Background Fluoroquinolone (quinolones) antibiotics are commonly prescribed worldwide. Hypersensitivity reactions to these agents have been reported, but little systematic data exists concerning prevalence, types of reactions, or associated factors. **Objective** To identify the prevalence of patients reporting an allergy to quinolones, types of reactions claimed, and patient information associated with allergy. **Setting** A tertiary 370 bed level 1 trauma center, located in a Midwestern City in the United States. **Method** A retrospective cohort study was conducted. Included in the study were all unique patients 18 years or older admitted to our hospital in 2016 with a length of stay ≥ 24 h. Collected data elements included types of reaction, other drug allergies claimed, and patient characteristics. As a comparator group, an equal sized random sample of patients admitted during the same period reporting penicillin allergy was identified. **Main Outcome Measure** prevalence and descriptors of quinolone allergy. **Results** There were 327 patients with a quinolone allergy and 317 patients with a penicillin allergy used as the study sample. Hospital prevalence rate for quinolone allergy was 2%. Hives, rash, and nausea/vomiting were the most common reported reactions. These patients tended to be older than penicillin allergy patients and had an association with concomitant intravenous contrast allergy. Tendonitis or tendon rupture was reported in quinolone patients. **Conclusion** The prevalence of patients claiming a quinolone allergy in the study hospital was 2%. Common hypersensitivity reactions were reported. Data tended to support a possible association between intravenous contrast allergy and quinolone allergy.

Keywords Antibiotic allergies · Antimicrobial stewardship · Fluoroquinolone · Hospital inpatients · Penicillin · United States

Impacts on practice

- Quinolone drug allergy, although infrequent, is not rare with roughly 2% of all hospital inpatients claiming such an allergy.
- Taking an accurate history of fluoroquinolone drug allergies is imperative since there are no ex vivo or in vitro tests that exist to confirm quinolone hypersensitivity.
- Providers should proceed with caution when prescribing fluoroquinolones to patients with an unknown reaction type and at risk for tendinitis, since tendon-/muscle-related adverse effects have been associated with patients claiming a quinolone allergy.
- Patient variables associated with an undiagnosed fluoroquinolone allergy included older age and the number of reported antibiotic allergies compared to patients with a claimed penicillin allergy.

Introduction

Hospital inpatients often report a past hypersensitivity reaction to one or more drugs, frequently antimicrobials. In recent years, with the rise of antimicrobial stewardship programs, it has been noted that claimed allergies can have a serious and often untoward effect on antibiotic selection [1]. For example, patients with recorded beta-lactam allergies

✉ Geoffrey C. Wall
geoff.wall@drake.edu

¹ College of Pharmacy and Health Sciences, Drake University, 2507 University Ave., Des Moines, IA 50310, USA

² PGY-2 Internal Medicine Resident, Iowa Methodist Medical Center, Des Moines, IA, USA

³ Iowa Methodist Medical Center, Des Moines, IA, USA

are likely to be treated with secondary choice, more toxic, broad-spectrum, and more expensive antibiotics [2]. In addition to the direct effects to patients there is a concern that claimed antibiotic allergies may even be a driver of local resistance rates [3]. Therefore, prevalence, characteristics, diagnosis and registration of allergy against antibiotics should be documented as accurately as possible.

While much of this information has been accomplished in patients who claim an allergy to penicillin, little work has been done with other types of antibiotic allergies. In particular the fluoroquinolone (e.g., quinolone drugs including: ciprofloxacin; levofloxacin; and moxifloxacin) class of antibacterials are now among the most prescribed non-beta lactam antibiotics with an annual usage approaching 33 million prescriptions in the United States [4]. These drugs are routinely used for a variety of infections including urinary tract and respiratory. With the increase in their use comes increased exposure of the general patient population to this drug class and, potentially, an increase in the number of patients with a quinolone hypersensitivity reaction. Yet, little is known of general prevalence of quinolone allergy, the patient characteristics associated with it, and any differences in these characteristics compared to the other patients with antimicrobial drug allergy—especially in hospitalized patients. Unfortunately, unlike penicillin allergy, no easy, validated ex vivo or in vitro tests exist to confirm quinolone hypersensitivity [5]. This limitation drives prescribers to rely on patient history alone to determine if such an allergy exists. This can be important not only for consideration of re-prescribing the “culprit” drug, but also any other drug in the class, as at least some evidence suggests the degree of cross-reactivity to the different quinolone drugs may be high [6]. To date the only published trial data examining characteristics of patients claiming a quinolone allergy was published in 2013. The study was conducted in a Spanish allergy clinic and found that patients with quinolone allergy had three factors associated with this reaction, including a history of allergy to beta-lactam antibiotics, a severe, immediate reaction with the culprit drug, and receipt of the quinolone moxifloxacin [7]. To address the paucity of available information describing quinolone hypersensitivity, the aim of the presented retrospective study was to report the prevalence, characteristics, and intolerances of hospital inpatients claiming a quinolone allergy and secondarily contrast them with those of patients claiming a penicillin allergy.

Ethics approval

The presented study was approved by the local Institutional Review Board (Approval Number IM2017-029) and granted a Waiver of Consent.

Method

A retrospective cohort study was conducted with a secondary comparator group. Included in the study were all unique patients 18 years or older admitted to a tertiary 370 bed level 1 trauma center, located in a Midwestern City in the United States, in 2016 with a length of stay ≥ 24 h. Patients had to have any of the following key terms or corresponding trade names listed in the allergy field of their medical record: ciprofloxacin; levofloxacin; ofloxacin; moxifloxacin; fluoroquinolones; or quinolones. A comparator group was constructed consisting of an equal sized random sample of patients admitted during the same time period with any of the following key terms or commercial formulations listed in the allergy field of their medical record: PCN; penicillin; penicillin G; amoxicillin; ampicillin; ampicillin-sulbactam; nafcillin; dicloxacillin; piperacillin; or previous trade names or combination products (e.g., amoxicillin/clavulanate).

Exclusion criteria included an allergy which could not be corroborated within the medical record for the indexed medical visit and patients claiming both a penicillin and quinolone drug allergy. The electronic medical records for included patients were reviewed for information on: age; gender; number of claimed drug allergies; presence or absence of other allergic diseases (e.g., asthma, allergic rhinitis); quinolone or penicillin drug listed as allergic agent; type of reaction (e.g., hives, rash, shortness of breath, etc., if documented); and assessment of whether the claimed drug reaction may be immunologic in nature (e.g., diarrhea is considered an adverse reaction but not usually considered an immunologic or hypersensitivity reaction). Also a history of latex or intravenous contrast allergies were recorded and all final decisions on whether a reaction was immunologic was based on investigator consensus. These latter two allergies were chosen to be included in the study due to them being commonly reported by hospital inpatients.

Study analyses were primarily descriptive in nature with continuous variables presented as medians and interquartile ranges (IQR), while categorical data were presented as counts and percentages. The prevalence of patients at the study hospital who claimed quinolone allergy was calculated based on the total numbers of unique patient encounters with a claimed allergy over total number of hospital inpatients during study year. Collected data on patient and allergy characteristics were contrasted between those patients with a claimed quinolone or penicillin allergy. Age differences were analyzed using exact Monte Carlo test and categorical data examined using multiple logistic regression, which controlled for covariate imbalances (i.e., age) between the allergy groups (i.e., quinolones and

penicillins). Revealed significant differences between drug allergy groups were reported with adjusted odds ratios (OR) with 95% confidence intervals (CI). External data adjustments were used to conduct a sensitivity analysis of the required magnitude of an unknown confounder equally associated with the reported reaction and drug group (OR_{sen}), which would have been large enough to nullify the significance of reported OR.

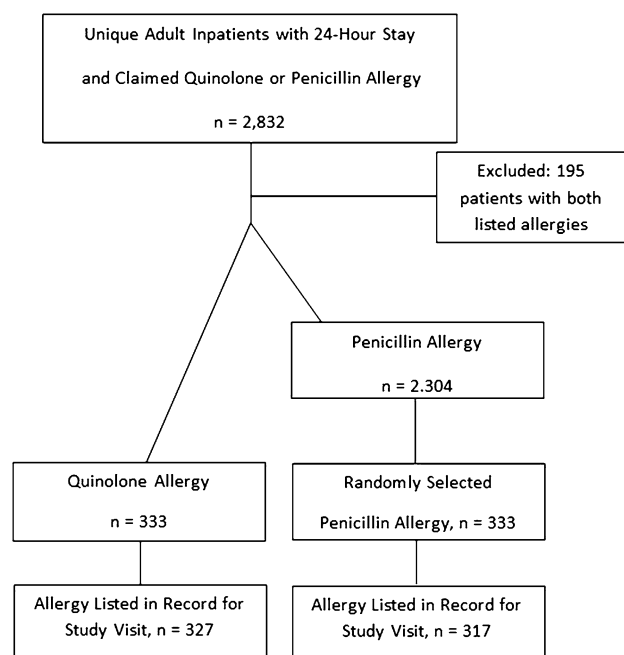


Fig. 1 Eligible study sample of patients with a hospital admission ≥ 24 h and a reported quinolone or penicillin allergy

Results

During the 1 year study period there were 3618 inpatient admissions with a listed allergy related to a quinolone and/or penicillin. This initial sample represented 2832 unique patients (Fig. 1). After application of the exclusion criteria and the removal of 195 patients who claimed both a quinolone and a penicillin allergy, the final study sample included 327 patients reporting solely a quinolone allergy. These patients represented 2% (95% CI 1.7, 2.2%) of all adult hospital admissions with a length of stay ≥ 24 h during the study year. Also of these patients, 309 (95%) had 1 drug listed from that antibiotic class and 18 (5%) had 2 drugs listed. Thus 5% of total inpatients who claimed an allergy to a quinolone also claimed reactions to more than one drugs in that class. The study comparator group consisted of a random sample of patients claiming a penicillin allergy during the same time period, resulting in 317 patients. Of these patients, 307 (97%) had 1 drug listed from that antibiotic class and 10 (3%) had 2 drugs listed.

A review of quinolone allergy patients in comparison to the subsample of penicillin allergy patients revealed they tended to be older (median age 70 vs. 52 years), but had a comparable gender distribution (Table 1). Patients with a reported quinolone allergy were more likely to have other listed drug allergies compared to the penicillin group (i.e., 67% penicillin allergy patients had only that drug listed under allergies vs. 33% of quinolone allergy patients had only that single drug listed under allergies). For the quinolone reactions, 90 (28%) patients were classified as type I hypersensitivity reaction and 76 (23%) patients were classified as type IV hypersensitivity reaction. For the penicillin reactions, 139 (44%) patients were classified as type I hypersensitivity reaction and 91 (32%) patients were classified as type IV hypersensitivity reaction. Types of allergy reactions are listed in Table 2. Most of the listed reactions in

Table 1 Characteristics of patients claiming a quinolone allergy versus penicillin allergy

Patient characteristic	Quinolone allergy, n=327	Penicillin allergy, n=317	P value*
Age (years, median)	70 (IQR: 57, 82)	52 (IQR: 35, 77)	< 0.001 [#]
Gender (female)	220 (67%)	211 (67%)	0.2529
Contrast allergy	18 (6%)	6 (2%)	0.0500 [#]
Atopic dermatitis	11 (3%)	13 (4%)	0.6182
Latex allergy	9 (3%)	15 (5%)	0.4707
Allergic rhinitis	36 (11%)	37 (12%)	0.5164
Asthma	37 (11%)	40 (13%)	0.7316
Other atopic disease	2 (1%)	2 (1%)	0.7405

IQR interquartile range

*Continuous variable examined using exact Monte Carlo test and categorical variables examined with multiple logistic regression controlling for patient age

[#]Statistically significant

Table 2 Reported reactions by patients claiming either a quinolone or penicillin allergy

Patient characteristic	Quinolone allergy, n = 327	Penicillin allergy, n = 317	P value*
Anaphylaxis	12 (4%)	28 (9%)	0.0211 [#]
Hives	57 (17%)	104 (33%)	0.0011 [#]
Itching	20 (6%)	13 (4%)	0.2843
Nausea/vomiting	43 (13%)	17 (5%)	0.0031 [#]
Swelling	18 (6%)	13 (4%)	0.1330
Throat swelling	10 (3%)	1 (0%)	0.0088 [#]
Any swelling	18 (6%)	13 (4%)	0.4638
Rash	61 (19%)	89 (28%)	0.0051 [#]
Syncope	3 (1%)	0 (0%)	0.2490

*Based on multiple logistic regression controlling for patient age

[#]Statistically significant

the medical record's allergy field were not considered immunologic (e.g., tendon pain/tendonitis for quinolones). When reviewing immunologic reactions, quinolone allergy patients had 0.57 (95% CI 0.12, 0.79; OR_{sen} 1.5) times lower odds for reported anaphylaxis than penicillin allergy patients; hives 0.47 (95% CI 0.13, 0.64; OR_{sen} 1.6) times lower; and rash 0.39 (95% CI 0.11, 0.58; OR_{sen} 1.5) times lower. However, throat swelling had a 16.7 (95% CI 2.0, 138.0; OR_{sen} 3.4) times greater odds of being reported in patients claiming a quinolone allergy than penicillin. Considering non-immunologic reactions, nausea and/or vomiting had a 2.5 (95% CI 1.4, 4.5; OR_{sen} 2.1) times greater odds of being reported in quinolone allergy patients. Although it was not an a priori listed measure in the study, tendon-related muscle-related adverse effects in patients claiming a quinolone allergy was 28%.

Patients with a history of atopic or allergic disease as well as those claiming an allergy to latex or contrast are listed in Table 1. Eleven percent of patients claiming an allergy to quinolone had a concomitant history of asthma or allergic rhinitis. Generally concomitant atopic disease prevalence was low between the two claimed drug allergy groups. Intravenous contrast allergy had a 2.6 (95% CI 1.01, 6.76; OR_{sen} 1.11) times greater odds of being reported in quinolone allergy patients than penicillin allergy patients. There were no other significant differences between the two drug allergy groups in any other atopic diseases or other allergies.

Discussion

To the authors' knowledge, this is the first study conducted in the United States presenting information on this topic in the inpatient setting. The presented study described the prevalence of fluoroquinolone allergies and related

characteristics, revealing a 2% prevalence. When comparing claimed quinolones allergy patients to those claiming penicillin allergies, the former group tended to be older, have more listed drug allergies, and were more likely to claim a contrast dye allergy. In addition, 28% of patients with a claimed quinolone allergy reported a tendon-related muscle-related adverse effect.

The only other published study on this topic found in a literature search was a retrospective Spanish trial conducted in 2013, which compared immediate and non-immediate reactions including anaphylaxis, urticarial, and exanthema reactions. The sample was comprised of patients attending an outpatient allergy clinic. The study found that in patients claiming fluoroquinolone allergies, hypersensitivity was more often confirmed in those with allergies to beta-lactam antibiotics, immediate reactions, and moxifloxacin [7].

In the presented study, patients claiming fluoroquinolone allergies compared to those claiming penicillin allergies tended to be older with a median age more than 10 years higher. This is likely multifactorial including inaccurate parental reporting of allergies, especially penicillin in children, the higher likelihood of being treated with penicillin at a younger age for infections (as fluoroquinolones are generally not used in the pediatric population), and that older patients tend to be exposed to more and different courses of antimicrobials [8]. Interestingly, it was found that patients who claimed allergies to fluoroquinolone claim more total drug allergies. Fluoroquinolone patients had greater odds of a drug allergy than penicillin patients; with approximately 70% of those who claimed fluoroquinolone allergies listing 5 or more different allergies compared to 30% of patients with penicillin allergies. It is possible that such patients have what has been termed "multiple drug hypersensitivity syndrome" which develops as a result of massive T-cell stimulation against chemically different antibiotics [9]. Unfortunately testing to confirm this syndrome is complex and may not be available in areas without advanced allergy/immunology clinicians. Patients who claimed a quinolone allergy were more likely to also claim intravenous contrast dye allergy. The clinical significance of this association is unclear and routine screening of patients for IV contrast allergies before prescribing quinolone antibiotics would not be recommended. It should be noted that both contrast allergy and quinolone allergy may both have a mechanistic component of anaphylactoid reactions—that they may bind directly to mast cells rather than use immunoglobulins as an intermediary to cause mast cell content release [10–12]. Quinolone allergy mechanisms can also be similar to that of other drug allergies (i.e., IgE or T cell mediated) [12]. Types of reactions were similar to those patients who claimed a penicillin allergy with dermatologic and gastrointestinal manifestations, which were the most common reactions. Life-threatening reactions were not reported more frequently in the quinolone group

compared to the penicillin allergy group. There was a lower relative frequency of quinolone reactions being classified as either type 1 or 4 hypersensitivity reactions. Type 2 and 3 hypersensitivity reactions were not classified in this study given a lack of detailed description in the allergy fields.

A serious side effect of fluoroquinolones that all clinicians should monitor for is the development of tendonitis or tendon rupture. The incidences of either of these are reported between 0.01 and 0.4% in the United States [12]. In the presented study, patients claiming tendon-related adverse effects as an “allergy” was not uncommon. This may reinforce the boxed warning of all drugs in the fluoroquinolone class and encourages vigilance for both clinicians and patients using these drugs. It also emphasizes the importance of a thorough review of adverse events and allergy history in patients.

This study was the first United States based review performed entirely within the hospital setting, and compared claimed fluoroquinolone allergies to a subset of penicillin allergies. Limitations of the study are related to the use of secondary data. Reported allergies and reactions may be missing in the medical record. Given the unreliability of skin testing outside of experimental settings, [13] there were no viable options to confirm claimed allergies to this class of antibiotics, other than oral challenge which may endanger the patient [6, 14]. Successful desensitization to quinolones has been reported in the literature, but is time and resource intensive and does involve some small risk [14]. Given the widespread use of this class of antibiotic and our findings that a small but significant percentage of inpatients claim an allergy to quinolones, we feel that further research into developing practical testing for true quinolone allergy is needed. Since this is a retrospective study relying on documentation in the medical records at one institution, larger representative samples based on multiple institutions may help understand and define the prevalence and risk factors associated with quinolone allergies.

Conclusion

The prevalence of a reported quinolone allergy at the study hospital was 2%, tendonitis or tendon rupture was reported as an allergy, and the pattern of purported hypersensitivities were relatively similar to the penicillin comparator group. With continued antibiotic resistance and a focus on antimicrobial stewardship, prescribers continually need to make difficult antibiotic selections in the allergy setting. A thorough allergy history and understanding of characteristics in patients claiming quinolone allergy may better help clinicians utilize optimal agents.

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