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INVITED ARTICLE

Immediate Hypersensitivity to Fluoroquinolones: A Cohort Assessing Cross-Reactivity

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Background. Fluoroquinolones are the second-most prescribed antimicrobial and are frequently associated with causing hypersensitivity reactions. Existing evidence regarding cross-reactivity of fluoroquinolones is limited, offering clinicians little guidance in understanding the implications of selecting an in-class alternative among patients with histories of allergic reactions to fluoroquinolones. The aim of this study was to compare the frequency of immediate hypersensitivity reactions to ciprofloxacin, levofloxacin, and/or moxifloxacin among patients with a history of immediate hypersensitivity to a different fluoroquinolone.

Methods. This retrospective chart review included adult patients with a history of an immediate hypersensitivity reaction to ciprofloxacin, levofloxacin, and/or moxifloxacin and a documented prescription for a different fluoroquinolone. The primary outcome was documentation of a hypersensitivity reaction upon second fluoroquinolone exposure.

Results. A total of 321 cases met inclusion criteria. Of these cases, 2.5% experienced an immediate hypersensitivity reaction after second fluoroquinolone exposure to ciprofloxacin, levofloxacin, and/or moxifloxacin. Within the ciprofloxacin, levofloxacin, and moxifloxacin index allergy cohorts, the frequency of cross-reactivity was 2.5%, 2.0%, and 5.3%, respectively.

Conclusions. Our data suggest that patients with a history of immediate hypersensitivity reaction to ciprofloxacin, levofloxacin, and/or moxifloxacin are at low risk of experiencing a cross-reaction when exposed to a different fluoroquinolone. Avoidance of all fluoroquinolones in this patient population may not be warranted.

Keywords. allergy; ciprofloxacin; IgE-mediated; levofloxacin; moxifloxacin.

Fluoroquinolones are commonly prescribed in the acute and ambulatory care settings [1, 2]. In the acute care setting, fluoroquinolones are frequently used when transitioning from intravenous (IV) to oral antibiotics as they have been shown to shorten hospital stays while maintaining similar clinical outcomes [3, 4]. Fluoroquinolones are also second only to β-lactams in frequency of causing hypersensitivity reactions [5]. However, fluoroquinolone allergy testing has not advanced as much as β-lactam allergy testing. For example, skin testing techniques to assess for penicillin allergy are reliable and have demonstrated a near 99% negative predictive value [6]. The accuracy of negative skin test results for fluoroquinolone allergy vary from 50% to 75% negative predictive value [7, 8]. Immunoglobulin E (IgE) tests, basophil activation tests, and other in vitro allergy assessment methods are similarly unreliable. Without a reliable alternative, the validity of patients' fluoroquinolone allergies is difficult to determine without subjecting them to drug provocation tests. The provocation test entails administration of an oral dose of the potentially immunogenic agent. The necessity of challenging patients' allergic responses to fluoroquinolones with dose administrations entails a degree of risk and discomfort for the patient. This, coupled with relatively small sample sizes, may contribute to the general paucity of high-quality fluoroquinolone allergy studies. The cross-reactivity of fluoroquinolones, therefore, has also been inadequately characterized in the available literature.

Data regarding potential cross-reactivity of fluoroquinolones are derived primarily from small case studies, some of which use unreliable allergy assessment methods [9–13]. The objective of this study is to explore fluoroquinolone cross-reactivity rates by investigating immediate hypersensitivity reactions in patients with a history of a fluoroquinolone allergy and exposure to an alternative fluoroquinolone agent.

METHODS

Participants

This retrospective study was reviewed and approved by the Colorado Multiple Institutional Review Board. Data from the electronic health records (EHRs) of all adult patients within the University of Colorado Health (UCHealth) system

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(inpatient and outpatient) between 1 January 2012 and 1 January 2021 were collected. A query tool within the EHR was used to identify potential participants. Patients were included if they were aged 18–89 years; had a history of an immediate hypersensitivity reaction to systemic formulations of either ciprofloxacin, levofloxacin, and/or moxifloxacin (herein defined as index fluoroquinolone allergy); and had a documented prescription for a different fluoroquinolone (herein defined as second fluoroquinolone). Patients were excluded if the second fluoroquinolone was prescribed and no further documentation existed in the EHR, the second fluoroquinolone exposure occurred outside of the UCHealth system and patient response was not communicated to a UCHealth clinician, or the index fluoroquinolone allergy reaction history did not represent symptoms associated with immediate hypersensitivity reactions [14]. Symptoms of immediate hypersensitivity reactions included but were not limited to respiratory distress, hypotension, angioedema, nonfacial edema, anaphylaxis, and/or hives.

Data Collection

This retrospective chart review was documented within the Research Electronic Data Capture system (REDCap). Baseline characteristics collected included demographics, index fluoroquinolone allergy and associated immediate reaction(s), comprehensive allergy history, and comorbidities associated with the immune system including autoimmune and immunosuppressive diseases. Data regarding second fluoroquinolone exposure were also collected, including medication, formulation, prescription setting (inpatient vs outpatient), and concurrent immunomodulatory medications at the time of second fluoroquinolone exposure. Patients included in the study were sorted into cohorts based on their earliest reported fluoroquinolone allergy. Within each index fluoroquinolone allergy cohort, there were 2 study arms, 1 for each second fluoroquinolone exposure. For example, within the index ciprofloxacin allergy cohort, there was a levofloxacin exposure arm and moxifloxacin exposure arm. If a patient was exposed to 2 fluoroquinolones beyond the index fluoroquinolone allergy, both exposures were recorded individually as 2 separate events. For any patients in whom the primary outcome was found, a screening of the EHR was performed to determine if any medications new to the patient were administered within 24 hours of symptom onset.

Outcomes

The primary outcome was immediate hypersensitivity reaction to a second fluoroquinolone other than the index fluoroquinolone allergy. Immediate hypersensitivity was defined as any symptoms associated with immediate hypersensitivity reactions that occurred within 24 hours after first-dose systemic exposure of either ciprofloxacin, levofloxacin, or moxifloxacin as documented within the EHR [14]. For inpatients, all notes in the EHR were screened for symptoms associated with immediate hypersensitivity for 3 days after second fluoroquinolone exposure or until discharge if <3 days. For outpatients, all notes within the EHR were screened for immediate hypersensitivity symptoms between the time of second fluoroquinolone exposure and a follow-up visit with the prescriber. Secondary outcomes included similarity of reaction symptoms between index fluoroquinolone allergy and second fluoroquinolone and need for medical intervention for the treatment of immediate hypersensitivity reactions.

Statistical Analysis

Patients were divided into 3 cohorts according to their index fluoroquinolone allergy (ciprofloxacin, levofloxacin, or moxifloxacin). Within each cohort the frequency of immediate hypersensitivity reactions to second fluoroquinolone was compared. Baseline categorical variables were compared among subgroups using a 2-sided Fisher exact test. Continuous baseline variables were compared using a 2-tailed independent sample *t* test. The primary outcome of immediate hypersensitivity reaction between each index fluoroquinolone allergy subgroup was analyzed using a 2-sided Fisher exact test. Statistical significance was defined as $P < .05$. Univariable logistic regression was used to assess risk factors for immediate reaction to second fluoroquinolones, with statistical significance determined by a 95% confidence interval (CI). Statistical analysis was performed using SPSS software version 27.

RESULTS

Cohort Characteristics

The final sample size included 321 cases of second fluoroquinolone exposures from 310 patients. Index ciprofloxacin allergy cases were screened for inclusion (n = 307), resulting in 157 cases. Index levofloxacin allergy cases were screened for inclusion (n = 330), resulting in 145 cases, and screened for inclusion (n = 57), resulting in 19 cases. Reasons for exclusion were receipt of second fluoroquinolone not documented (n = 204), nonsystemic dosage form (n = 84), index fluoroquinolone allergy described as a nonallergy (n = 51), absence of documentation within the EHR after receipt of second fluoroquinolone prescription (n = 18), index fluoroquinolone allergy not an immediate hypersensitivity reaction (n = 10), record found in alternate cohort (n = 5), or reaction to second fluoroquinolone did not occur within 24 hours of administration (n = 1). In total, 25.7% of cases met inclusion criteria. Baseline variables between study arms of each cohort were not statistically significant (Table 1).

Primary Outcome: Immediate Hypersensitivity Reaction Upon Exposure to Second Fluoroquinolone

Immediate hypersensitivity reactions to a second fluoroquinolone occurred in 8 (2.5% [95% CI, 1.2%–4.9%]) of the 321 cases included in the study. In the ciprofloxacin allergy cohort, 157

Table 1. Characteristics of Patients With Histories of Immediate Hypersensitivity Reactions to a Fluoroquinolone Who Received a Different Fluoroquinolone

Characteristic	Ciprofloxacin Index Allergy		Levofloxacin Index Allergy		Moxifloxacin Index Allergy	
	Levofloxacin (n = 147)	Moxifloxacin (n = 10)	Ciprofloxacin (n = 135)	Moxifloxacin (n = 10)	Levofloxacin (n = 12)	Ciprofloxacin (n = 7)
Age, y, mean ± SD	56.7 ± 16.1	56.2 ± 12.2	57.6 ± 17.1	62.4 ± 9.5	60.0 ± 12.9	66.3 ± 16.5
Female sex	124 (84.4)	8 (80.0)	102 (75.6)	8 (80.0)	10 (83.3)	5 (71.4)
Race/ethnicity						
White	123 (83.7)	9 (90.0)	111 (82.2)	9 (90.0)	10 (83.3)	7 (100.0)
Hispanic	15 (10.2)	0 (0.0)	15 (11.1)	0	1 (8.3)	0 (0.0)
African American	6 (4.1)	0 (0.0)	7 (5.2)	1 (10.0)	0 (0.0)	0 (0.0)
Asian	2 (1.4)	1 (10.0)	2 (1.5)	0	0 (0.0)	0 (0.0)
Reaction to index FQ						
Respiratory distress	14 (9.5)	1 (10.0)	26 (19.3)	0 (0.0)	3 (25.0)	2 (28.6)
Angioedema	16 (10.9)	1 (10.0)	15 (11.1)	0 (0.0)	3 (25.0)	1 (14.3)
Nonfacial edema	33 (22.4)	3 (30.0)	23 (17.0)	1 (10.0)	2 (16.7)	2 (28.6)
Anaphylaxis	13 (8.8)	0 (0.0)	26 (19.3)	2 (20.0)	3 (25.0)	1 (14.3)
Hives	89 (60.5)	7 (70.0)	58 (43.0)	7 (70.0)	4 (33.3)	3 (42.9)
Other	6 (4.1)	0 (0.0)	5 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
Allergen history						
Non-FQ antimicrobial	109 (74.1)	9 (90.0)	97 (71.9)	5 (50.0)	11 (91.7)	5 (71.4)
Other medications	86 (58.5)	5 (50.0)	87 (64.4)	7 (70.0)	10 (83.3)	6 (85.7)
Environmental	37 (25.2)	2 (20.0)	32 (23.7)	3 (30.0)	2 (16.7)	1 (14.3)
Food	26 (17.7)	1 (10.0)	20 (14.8)	1 (10.0)	1 (8.3)	2 (28.6)
Concurrent immunomodulatory medications						
Corticosteroid (systemic)	27 (18.4)	1 (10.0)	22 (16.3)	4 (40.0)	6 (50.0)	2 (28.6)
Chemotherapy	3 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antihistamine (systemic)	20 (13.6)	0 (0.0)	20 (14.8)	0 (0.0)	1 (8.3)	2 (28.6)
Antibody-based targeted therapy	2 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)	1 (8.3)	1 (14.3)
Other	18 (12.2)	0 (0.0)	17 (12.6)	1 (10.0)	1 (8.3)	0 (0.0)
Comorbidities						
Immunosuppressive disease	9 (6.1)	1 (10.0)	14 (10.4)	2 (20.0)	1 (8.3)	0 (0.0)
Autoimmune disease	45 (30.6)	2 (20.0)	44 (32.6)	2 (20.0)	7 (58.3)	5 (71.4)
Second FQ exposure						
Oral route	111 (75.5)	8 (80.0)	111 (82.8)	10 (100.0)	9 (75.0)	7 (100.0)
Outpatient prescription	74 (50.3)	6 (60.0)	94 (69.6)	8 (80.0)	6 (50.0)	5 (71.4)

Data are presented as No. (%) unless otherwise indicated. No significant difference was found between any outcomes ($P \geq .05$).

Abbreviations: FQ, fluoroquinolone; SD, standard deviation.

Table 2. Frequency of Immediate Hypersensitivity Reactions to Second Fluoroquinolone Exposure, Type of Reaction, and Supportive Care Administered

	Ciprofloxacin Index Allergy		Levofloxacin Index Allergy		Moxifloxacin Index Allergy	
Type of Reaction	Levofloxacin (n = 147)	Moxifloxacin (n = 10)	Ciprofloxacin (n = 135)	Moxifloxacin (n = 10)	Levofloxacin (n = 12)	Ciprofloxacin (n = 7)
HSR to second FQ	4 (2.7)	0 (0.0)	3 (2.2)	0 (0.0)	1 (8.3)	0 (0.0)
Respiratory distress	3 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	…	…
Angioedema	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nonfacial edema	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Hives	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	…	…
Other	1 (0.7)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Same reaction to both index and second FQ	2 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)	1 (8.3)	0 (0.0)
Medical intervention						
Epinephrine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antihistamine	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Corticosteroid	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as No. (%) unless otherwise indicated. No significant difference was found between any outcomes ($P \geq .05$).

Abbreviations: FQ, fluoroquinolone; HSR, hypersensitivity reaction.

exposures resulted in 4 (2.5% [.7%–6.3%]) immediate hypersensitivity reactions, all of which were found in the levofloxacin exposure arm. Of the 145 exposures examined in the levofloxacin allergy cohort, 3 (2.0% [.4%–5.9%])) resulted in an immediate hypersensitivity reaction, all of which were found in the ciprofloxacin exposure arm. Within the moxifloxacin allergy cohort, 19 exposures resulted in 1 (5.3% [95% CI, .0–26.5%]) immediate hypersensitivity reaction, found in the levofloxacin arm (Table 2).

Six of the 8 cases that experienced immediate hypersensitivity reactions were female with a median age of 60.5 years (Table 3). The median number of medication allergies beyond fluoroquinolones was 3 (interquartile range, 2.5–8.5). Four of the 8 immediate hypersensitivity reaction symptoms were the same as the index fluoroquinolone reaction symptoms on record.

A univariable logistic regression was used to assess risk factors for an immediate hypersensitivity reaction to a second fluoroquinolone, including index fluoroquinolone allergy, index fluoroquinolone reaction symptom, age, sex, number of additional medication allergies, and autoimmune comorbidities. No variables were statistically significant.

DISCUSSION

The study included 321 cases in which 310 patients had a history of an immediate hypersensitivity reaction to ciprofloxacin, levofloxacin, and/or moxifloxacin and received a different fluoroquinolone. Eight of 321 cases experienced an immediate hypersensitivity reaction to a second fluoroquinolone, resulting in a cross-reactivity frequency of 2.5% (95% CI, 1.1%–4.9%).

Table 3. Demographic and Cross-Reaction Descriptions of Primary Outcome Patients

Patient Number	Age, y/ Sex	Index FQ Allergy: Reaction	Number of Additional Medication Allergies	Autoimmune Diseases	New Medications at Time of Second FQ Exposure	Second FQ, Route	Reaction to Second FQ
1	43/F	Ciprofloxacin: SOB	10	Allergic rhinitis	None	Levofloxacin, oral	Throat swelling, SOB
2	68/F	Ciprofloxacin: hives	17	Rheumatoid arthritis	None	Levofloxacin, oral	Nonfacial edema, SOB
3	49/F	Ciprofloxacin: anaphylaxis	3	None	None	Levofloxacin, oral	SOB, hypotension
4	72/F	Ciprofloxacin: throat swelling, swelling (unspecified)	0	None	None	Levofloxacin, oral	Hives
5	56/F	Levofloxacin: SOB	2	None	None	Ciprofloxacin, oral	Hypotension, severe headache, jitteriness
6	72/F	Levofloxacin: hives	3	None	None	Ciprofloxacin, oral	Swollen tongue
7	46/M	Levofloxacin: anaphylaxis, throat swelling, rash, fever, sore muscles	7	None	None	Ciprofloxacin, intravenous	Rash, neuropathy
8	65/M	Moxifloxacin: swelling	3	None	None	Levofloxacin, oral	Nonfacial edema

All patients shown in this table were of White race.

Abbreviations: F, female; FQ, fluoroquinolone; M, male; SOB, shortness of breath.

Cross-reactivity among the ciprofloxacin and levofloxacin cohorts were similar at 2.5% and 2.0%, respectively. The frequency of cross-reactivity in the moxifloxacin cohort was 5.3% and difficult to interpret due to the small sample size of the cohort.

The frequency of cross-reactivity in our study is lower than what was found in a prospective cross-sectional study by Demir et al, who assessed fluoroquinolone cross-reactivity among 54 patients with a history of fluoroquinolone hypersensitivity [8]. Similar to our study, patients were excluded if their hypersensitivity reaction occurred >24 hours after drug exposure. Patients underwent drug provocation tests of both index and alternative fluoroquinolone. Of 30 patients with a history of hypersensitivity to ciprofloxacin, 9 patients (30.0%) cross-reacted to moxifloxacin and 7 (23.3%) cross-reacted to levofloxacin. Of the 12 patients with a history of hypersensitivity to moxifloxacin, 1 (8.3%) cross-reacted to ciprofloxacin and 1 (8.3%) cross-reacted to levofloxacin. Out the 4 patients with a history of hypersensitivity to levofloxacin, 1 (25.0%) cross-reacted to moxifloxacin. Drug provocation test with ciprofloxacin was not reported in this arm. The authors found an overall cross-reactivity frequency of 5% among the 5 fluoroquinolones included: ciprofloxacin, moxifloxacin, levofloxacin, ofloxacin, and gemifloxacin [8]. Contrary to our study, patients with nonimmediate hypersensitivity reactions, such as fixed drug eruptions and maculopapular drug eruptions, were included whereas patients with comorbid diseases, such as uncontrolled asthma, were excluded. These differences may explain why the cross-reactivity frequencies differ.

Other available evidence that uses oral challenge or exposure to analyze fluoroquinolone cross-reactivity is primarily offered by case reports and small studies. Several publications reported cross-reactivity when a patient sensitive to one fluoroquinolone was administered another [11, 12, 15, 16], while other studies reported either no or low rates of cross-reactivity [13, 17–19]. The varying results and conclusions of these studies are likely attributed to the inclusion of different types of hypersensitivity reactions and small sample sizes. Our study differs because it includes a larger sample size that focuses on immediate hypersensitivity reactions.

Cross-reactivity among fluoroquinolones may be attributed to structural similarities of the core ring or the side chains bound to positions N1, C7, and C8 as seen in Figure 1 [20]. The differences in side chains bound to these positions can affect the spectrum of activity and adverse effect profile of each fluoroquinolone. These structural changes are also used to classify the fluoroquinolones into generations. Ciprofloxacin and levofloxacin both have a piperazinyl ring at C7. This piperazinyl side chain is altered by ultraviolet A irradiation, which could cause the formation of a common allergenic fluoroquinolone-protein complex and may explain the photoallergic cross-reactivity observed between ciprofloxacin and levofloxacin [21]. This reasoning does not explain the results of our study as photoallergic reactions are delayed hypersensitivity reactions, and our study specifically focused on immediate hypersensitivity reactions. The structure of moxifloxacin is noticeably unique to that of ciprofloxacin and levofloxacin as it has a methoxy group on C8. This distinction has led some to predict low rates of cross-reactivity of moxifloxacin with other in-class agents and to suggest using moxifloxacin as a safe therapeutic alternative in patients hypersensitive to other fluoroquinolones [10]. Our results do not support this prediction as moxifloxacin did not have the lowest cross-reactivity rate compared to ciprofloxacin and levofloxacin. Ciprofloxacin, levofloxacin, and moxifloxacin all share a 4-oxo-1,4-dihydroquinoline ring core with a fluorine atom attached to position 6. Given this common ring structure, it is hypothesized that a patient allergic to one fluoroquinolone would also be allergic all other fluoroquinolones [10]. The low incidence of cross-reactivity in our study suggests that the fluoroquinolone core is not commonly the antigenic component of fluoroquinolone molecules.

Interestingly, immediate-type reactions to fluoroquinolones are more often mediated via a mechanism that is triggered independently of IgE antibody activation, and are instead due to direct activation of mast cells through Mas-related G protein-coupled receptor X2 (MRGPRX2) [22]. An important distinction between the 2 reaction mechanisms is that, while IgE-antibody reactions tend to occur even with miniscule exposure to the antigen, MRGPRX2-mediated reactions are dose-dependent, and many medications have established half maximal effective concentration (EC_{50}) values [23–28]. A recent study by Krantz et al proposed new intradermal test criteria followed by single-dose oral challenge—200 mg, 250 mg, and 250 mg for moxifloxacin, levofloxacin, and ciprofloxacin, respectively—that they used for de-labeling of fluoroquinolone drug allergy [29]. The authors acknowledge, however, that the low-dose oral challenge standard to allergy testing may not

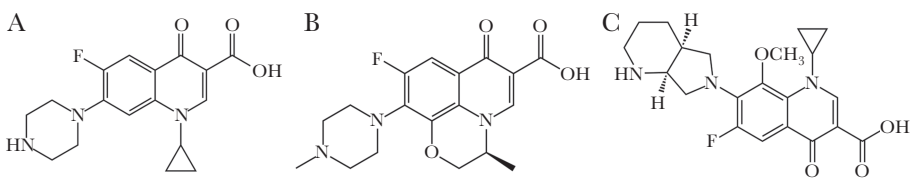

Figure 1. Chemical structure of 3 fluoroquinolones: ciprofloxacin (*A*), levofloxacin (*B*), and moxifloxacin (*C*).

account for the dose-dependent nature of non-IgE-mediated reactions. While the retrospective nature of our study does not allow the confirmatory testing of reaction mechanism (ie, IgE-mediated vs MRGPRX2-mediated), the outcomes offer a clinically important perspective on the likelihood of immediate reaction to a therapeutic dose of an alternate fluoroquinolone in the setting of a fluoroquinolone allergy label in a patient's EHR.

Given its retrospective nature, our study inherently has several limitations that may have impacted our results. Inaccurate reporting of index fluoroquinolone allergies by patients may have contributed to the lower cross-reaction rates seen in our study. Blanca-López et al reported that hypersensitivity among patients with a fluoroquinolone allergy is more often confirmed if the patient experienced an immediate reaction [30]. We addressed the possibility of false allergy reports by limiting inclusion criteria to patients who reported serious immediate hypersensitivity reactions, as opposed to more ambiguous symptoms, such as gastrointestinal discomfort. It is also possible that some cross-reactions to a second fluoroquinolone exposure were not accounted for in our study due to those patients seeking care for their hypersensitivity reaction outside of the UCHealth system. We tried to minimize this impact by including patients if they subsequently communicated a reaction to second fluoroquinolone exposure to a UCHealth provider despite receiving medical intervention for that reaction elsewhere. Several patients were excluded from the study for reporting an index allergy or having a second exposure to nonsystemic dosage forms of moxifloxacin, particularly ophthalmic formulations. The resulting small sample size limits the ability to interpret the cross-reactivity of moxifloxacin with other fluoroquinolones.

Our study is hypothesis-generating and prospective data from a large sample size are necessary to establish causality. Future research is needed to identify risk factors for hypersensitivity reactions as they appear unpredictable even in the setting of prior immediate hypersensitivity reactions. Beyond clinical risk factors, perhaps genotypic risk factors could predict cross-reactivity. Pirmohamed explains that several drug-induced hypersensitivity reactions have evidence supporting a genetic predisposition [31]. For example, HLA-A29, HLA-B12, and HLA-DR7 have been associated with the development of toxic epidermal necrolysis upon receipt of sulfonamides. Current research in this area is limited to small studies.

CONCLUSIONS

Given the high utilization of fluoroquinolones to treat numerous infections, the prevalence of fluoroquinolone allergy is second only to β-lactams. The low cross-reactivity frequency found in this study should increase clinician confidence in attempting a test dose or oral challenge among patients with a history of immediate allergy to fluoroquinolones. Comprehensive education about likelihood of hypersensitivity and symptom management should be provided in these scenarios.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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