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Can fluoroquinolones be safely used in patients with immediate hypersensitivity reaction to penicillin?

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Abstract

Objective: The aim of this study was to evaluate whether fluoroquinolone antibiotics, which are structurally distinct from penicillins, can be safely prescribed as alternatives for patients with a history of immediate-type hypersensitivity reactions (HSRs) to penicillin in the absence of multidrug allergy and without the need for provocation testing.

Methods: We conducted a retrospective analysis of the medical records of patients who presented to the Erciyes University Adult Immunology and Allergy Outpatient Clinic with a documented history of penicillin allergy between 2015 and 2024. Inclusion criteria for immediate hypersensitivity to penicillin included at least one of the following: (1) a history of at least two separate immediate HSRs to the same penicillin; or (2) positive results from penicillin G/V (Penicillin G and Penicillin V) serum-specific immunoglobulin E (SsIgE) and/or skin prick testing. Patients who met these criteria and subsequently underwent oral provocation testing with fluoroquinolone antibiotics were included in the study.

Results: This study included 76 patients (72% female, mean age: 45.63 ± 11.76 years), 47.4% of whom had comorbid allergic diseases. The diagnosis was primarily based on clinical history (80%), while the remainder were confirmed by SsIgE testing, skin tests, or drug provocation. A history of urticaria-angioedema was reported in 59.2% of the patients, while 40.8% had a history of anaphylaxis. Following oral provocation testing with fluoroquinolones, only two patients (2.6%) developed mild, self-limited urticaria or angioedema, without systemic involvement.

Conclusions: Our study demonstrates a low positive rate (2.6%) for fluoroquinolone oral provocation testing among patients with penicillin allergy. These findings suggest that fluoroquinolones may be a viable and safe alternative in patients with a confirmed penicillin hypersensitivity and no history of multidrug allergy, and may be considered without prior provocation testing in selected cases.

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Introduction

Drug hypersensitivity reactions (DHRs) are most commonly triggered by beta-lactam (BL) antibiotics, as shown in multiple studies.^{1,2} Among these, penicillin is mainly the culprit, accounting for 5% to 10% of all reported drug allergies.³ In contrast, while fluoroquinolone hypersensitivity reactions (HSRs) are less prevalent, their incidence is increasing—ranging from 0.4% to 2%—and they have become the leading cause of non-BL antibiotic-related HSRs.⁴ The rate of HSRs to fluoroquinolones (regardless of immediate or delayed type) rose markedly from 0.54% in 2005 to 6.85% in 2010.⁵ One hospital-based study reported a 2% prevalence of fluoroquinolone allergy among its inpatients.⁶

The diagnostic approach to penicillin hypersensitivity includes a detailed clinical history, supported by in vitro testing (e.g., basophil activation test [BAT], serum-specific immunoglobulin E [SsIgE]), skin prick tests (SPTs), and drug provocation tests (DPTs).⁷ In confirmed cases of BL allergy, non-BL antibiotics—such as fluoroquinolones, aminoglycosides, imidazoles, macrolides, and lincosamides—are generally recommended as alternatives⁸; however, some of these agents may have lower efficacy, higher costs, or increased risk of adverse drug reactions compared to penicillin.^{9,10}

Fluoroquinolones are synthetic antibiotics with a broad-spectrum activity against both gram-positive and gram-negative bacteria.⁶ Their core chemical structure, consisting of a bicyclic ring with carboxylic acid and ketone functional groups at positions 3 and 4, respectively, is chemically and pharmacologically unrelated to penicillin.^{11,12} As a result, the necessity of oral provocation testing with fluoroquinolones in patients with penicillin allergy remains debatable. Given the limited number of studies addressing whether a history of penicillin allergy increases the risk of fluoroquinolone hypersensitivity, this testing may lead to unnecessary patient anxiety, resource use, and healthcare costs—particularly in patients with a well-defined, single drug allergy to penicillin.

Therefore, the aim of this study was to assess the rate of immediate-type HSRs to fluoroquinolones identified through DPTs in patients with confirmed penicillin allergy, in order to evaluate their safety in alternative antibiotics.

Methods

We conducted a retrospective review of medical records of patients who presented to the Erciyes University Division of Allergy and Clinical Immunology Outpatient Clinic with a documented history of penicillin allergy evaluated between 2015 and 2024.

Patients were excluded if they had:

- Uncertain reactions to penicillin (e.g., confounded by food intake or viral infections)
- Delayed-type HSRs
- A history of multiple drug hypersensitivity
- Incomplete/inaccessible medical records

Eligible participants were adults (≥ 18 years) who met one of the following criteria:

- A history of at least two distinct immediate HSRs to penicillin antibiotics occurring at different times. Immediate

reactions were defined as symptoms typically occurring within 1 hour of drug administration, though onset could occasionally be delayed up to 6 hours.

- A single immediate HSR confirmed by SsIgE and/or skin testing.

Penicillin allergy was diagnosed according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines using clinical history, SsIgE levels, and skin testing when necessary. Clinical history assessment focused on prior exposure to BL antibiotics, followed by hypersensitivity symptoms such as urticaria, anaphylaxis, respiratory symptoms, or other typical manifestations.¹

SsIgE levels were measured using the ImmunoCAP fluoroenzyme immunoassay system (Thermo Fisher Scientific, Uppsala, Sweden), and a cut-off value of ≥ 0.35 kU/L was used to define SsIgE positivity.

Skin testing was performed following the current EAACI guideline recommendations, including both SPTs and intradermal tests. The reagents used included benzylpenicilloyl-polylysine (PPL), a minor determinant mixture (MDM), Determination of Allergen Potential (DAP)-penicillin (0.04 mg + 0.5 mg/vial), penicillin G, amoxicillin (20 mg/flacon), and clavulanic acid (20 mg/flacon), all from Diater (Madrid, Spain). In patients with negative SPT results, an oral provocation test with 500/125 mg amoxicillin/clavulanate was performed, followed by a 2-hour observation period.¹ An induration of ≥ 3 mm was considered a positive result.

To identify a safe alternative, all patients underwent a single blind, placebo-controlled oral challenge with levofloxacin (500 mg). The DPTs were conducted in a single blind, placebo-controlled manner. The challenge was performed in incremental doses: 50, 125, 250, and 500 mg. Doses were administered at 30-minute intervals, and patients were monitored for 45 minutes following the final dose.¹³ Both blood pressure and heart rates were measured before and after each dose.

The following variables were analyzed: age, sex, diagnostic method, reaction type, onset time, comorbidities, personal allergic history, and family history of drug hypersensitivity.

The study protocol was approved by the Erciyes University Ethics Committee (Approval date: September 18, 2024; Approval number: 2024/183).

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean \pm standard deviation (SD), depending on their distribution. Descriptive statistics were applied to summarize patient demographics and clinical characteristics. The chi-square test was used for categorical variables and the one-sample t-test was applied to compare continuous parametric variables. A p-value of < 0.05 was considered statistically significant.

Results

A total of 255 patients with a history of penicillin allergy were screened, of whom 76 met the study criteria and

underwent fluoroquinolone oral provocation testing. The diagnostic distribution of these patients is detailed in Figure 1.

Seventy-two percent were female ($n = 55$) with a mean age of 45.6 ± 11.8 years. Comorbid allergic diseases were present in 47.4% of the patients. Additionally, 44 patients had non-allergic comorbidities, most commonly cardiovascular and endocrinological disorders. A family history of drug hypersensitivity was reported in 22 patients (28.9%). Detailed clinical characteristics are summarized in Table 1.

Eighty percent of diagnoses were based on clinical history, while the remainder were confirmed by SsIgE, skin tests or provocation. Among the cohort, 45 (59.2%) patients had a history of urticaria-angioedema and 31 (40.8%) had experienced anaphylaxis following penicillin exposure.

Two (2.6%) patients developed urticaria or angioedema during fluoroquinolone provocation testing; both were considered positive reactions. Both reactions were mild, limited to the skin, and resolved spontaneously without systemic involvement or medication. Both patients had negative SsIgE to penicillin; their initial reactions had occurred approximately 3 years before the provocation test. The initial clinical presentations were consistent with immediate-type hypersensitivity, characterized by urticaria developing within one hour of drug intake. One patient had hypertension and the other had asthma and allergic rhinitis.

Discussion

Our study showed that in patients with a history of immediate-type HSRs to penicillin, the positivity rate of oral

provocation tests conducted with fluoroquinolones to identify safe alternative antibiotics was 2.6%. Considering that immediate-type HSRs to fluoroquinolones in the general population range from 0.4% to 2%,¹³ this suggests that there is no significant increase in immediate-type HSRs to fluoroquinolones in patients with penicillin allergy.

A study conducted in the United States reported that quinolone allergy of any severity presenting to the emergency department occurred at a rate of 44 per 100,000 prescriptions.¹⁴ The incidence of fluoroquinolone-induced anaphylaxis is estimated to be 1.8-2.3 per 10 million days of treatment,¹⁵ accounting for 4.5% of drug-induced anaphylaxis,¹⁶ while the prevalence of cutaneous adverse reactions is estimated at 0.09%.¹⁷ Additionally, a study involving inpatients determined the prevalence of quinolone HSRs to be 2%.⁶ Quinolones rank as the third most common drugs associated with HSRs overall and the second most common in IgE-mediated HSRs.¹⁷ Although all quinolones have been linked to anaphylaxis, moxifloxacin has been identified as the most frequent causative agent, followed by levofloxacin and ciprofloxacin.¹⁸⁻²⁰

In our study, the observed quinolone allergy rate of 2.6% in patients with a history of immediate-type HSR to penicillin appears to be a slight but not significant increase compared to rates in the general population reported by other studies.

Risk factors for specific drug-induced early HSRs include chronic urticaria, diabetes, cardiovascular morbidity, advanced age, race, and gender.²¹⁻²³ Regarding chemotherapy agents, research has demonstrated that disease severity, histologic type, previous drug allergies, and cumulative dose may contribute to the risk of HSRs.^{24,25} Considering these general risk factors and the fact that DPT is not

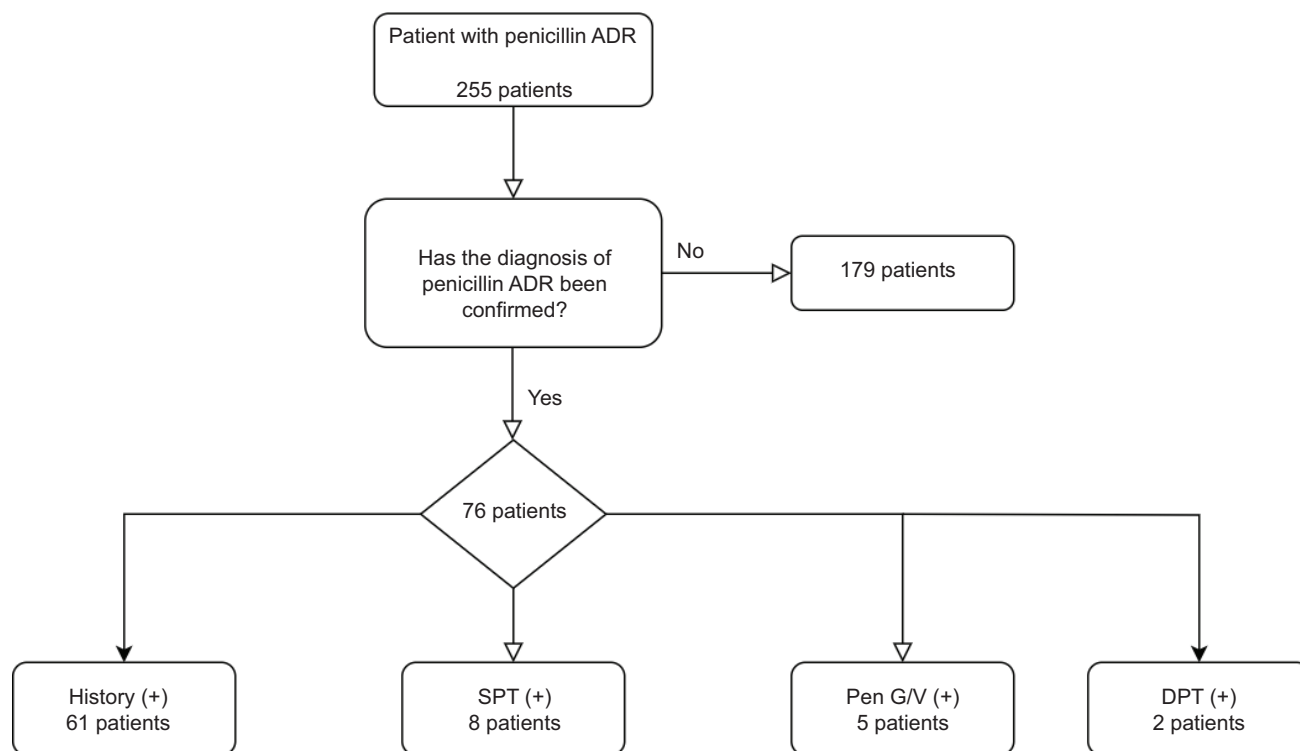


Figure 1 Flow chart of patients with penicillin antibiotic hypersensitivity. ADR: Adverse Drug Reaction; DPT: Drug Provocation Test; SPT: Skin Prick Tests.

Table 1 Clinical characteristics of patients with penicillin allergy.

Age at first reaction, years (mean \pm SD)	33.49 \pm 14.43
Atopic comorbidities, n (%)	
Asthma/allergic rhinitis	23 (30.3%)
Urticaria/angioedema	13 (17.1%)
Time since last reaction, years (mean \pm SD)	4.53 \pm 4.06
Onset time after drug intake, minutes (mean \pm SD)	43.09 \pm 56.6
Number of allergic episodes (mean \pm SD)	2.95 \pm 1.47
Serum total IgE, IU/mL (mean \pm SD) (normal range: 0-100)	190.72 \pm 377.76

routinely performed due to associated risks, the slight increase in quinolone hypersensitivity observed in patients with a history of early type HSR solely to penicillin—without multiple drug allergies—suggests that quinolones may be directly prescribed as an alternative to penicillin, without the need for DPT.

A literature review shows that antibiotic consumption increased by 36% between 2000 and 2010, with the most significant increases observed for cephalosporins, broad-spectrum penicillins, and fluoroquinolones.²⁶ This increase has been accompanied by a rise in HSRs to quinolones, partly due to their growing use as first-line therapy, especially in patients susceptible to bacterial infections.^{5,27} Consequently, fluoroquinolones have become the most prevalent cause of non-BL antibiotic-related HSRs.^{11,12} According to guidelines from the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology, HSRs to quinolones have increased tenfold in recent years, partly attributed to more frequent prescriptions and the introduction of potentially more immunogenic quinolones such as moxifloxacin.²⁸ A study in Spain further reported an increase in patients with HSRs to quinolone group drugs from 0.54% in 2005 to 6.85% in 2010, likely due to increased prescribing.⁵ These studies demonstrate an increasing prevalence of quinolone allergies independent of penicillin allergy.

Although chemically unrelated, one published study observed that a history of HSRs to BL may be a risk factor for fluoroquinolone hypersensitivity.¹² In this study, patients with immediate and nonimmediate reactions to quinolones were divided into two groups, and clinical history, BAT, or DPT confirmed the diagnosis. BAT was performed in all patients with immediate-type HSRs leading to diagnosis in 36% of cases; DPT was performed in BAT-negative patients. Notably, 23.19% of patients with confirmed quinolone hypersensitivity had a prior HSR to BLs, indicating that patients with BL allergy were 4.5 times more likely to react to quinolones than those without.¹²

In a study conducted in Türkiye, the prevalence of an additional drug allergy in patients with quinolone hypersensitivity was 46.3%, with BLs (37.1%) and nonsteroidal anti-inflammatory drugs (NSAIDs) (18.5%) being the most common culprits.²⁹ These findings suggest that previous BL allergy may pose a risk for quinolone allergy; however, many patients in those studies had multiple drug allergies. In contrast, our study included only patients with a single drug

allergy to penicillin, focusing on those undergoing DPT with quinolones to identify alternative antibiotics. To our knowledge, this methodological approach has not been applied in previous studies. Aligning with our study, a large database analysis of patients with MDHS found no association between BL and quinolone DHRs, with most reported reactions being late-type HSR.³⁰ Another study showed that the development of penicillin allergy and non-BL antibiotic allergy were not associated in retrospectively evaluated patients.³¹

The paper on hypersensitivity to BLs published by EAACI recommends the use of non-BL antibiotics for emergency treatment in patients with a history of early type reactions to BLs.¹ Similarly, the American Academy of Allergy, Asthma, and Immunology (AAAAI) recommends alternative agents based on microbial susceptibility in patients with a history of early or late-type penicillin reactions without prior testing.³² In accordance with these recommendations, our findings support the notion that routine oral provocation testing with quinolones is not necessary in patients with a single drug allergy to penicillins.

This study has several limitations. Primarily, its retrospective nature and limited sample size constitute the main constraints. Nevertheless, the data reflect real-world clinical practice. Another limitation is that the diagnosis of immediate-type hypersensitivity to penicillin was predominantly based on patient history, which raises the risk of overdiagnosis in the absence of confirmatory testing. However, the study included only patients with a clear history of immediate-type HSRs to penicillin occurring on at least two separate occasions without concurrent use of other drugs or food intake. Patients with suspicious histories or only one hypersensitivity episode were excluded, enhancing diagnostic reliability.

In conclusion, our study did not demonstrate a significant increase in immediate-type hypersensitivity to fluoroquinolones among patients with a history of immediate-type HSRs to penicillin compared to the general population. These findings suggest that fluoroquinolones may represent a relatively safe alternative in such patients, particularly in urgent situations requiring antibiotic therapy. However, given the retrospective nature of the study and the potential severity of DHRs, the decision to forego oral provocation testing should be made cautiously and on a case-by-case basis. When appropriately applied, this approach may help reduce unnecessary delays, procedural costs, healthcare resource utilization, and treatment postponement. Future prospective studies are warranted to confirm these findings and to support evidence-based recommendations for the safe use of fluoroquinolones in this population.

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Authors Contribution

Elif Açar (EA), Murat Türk (MT), Serpil Köylüce (SK), Hatice Eylül Bozkurt Yılmaz (HEBY), Serhat Şeker (SŞ), Elif Aktaş

Yapıcı (EAY) and İnsu Yılmaz (IY) contributed equally to the study. All authors participated in the study conception and design, data collection, data analysis, and interpretation of results. EA drafted the initial manuscript. MT, SK, HEBY, SŞ, EAY, and IY critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of Interest

IY is or recently was a speaker and/or advisor for Abdi İbrahim, AstraZeneca, Chiesi, GSK, and Novartis. MT is or recently was a speaker and/or advisor for Abdi İbrahim, AstraZeneca, Chiesi, GSK, Novartis, ROXALL, and Vem ilaç. All other authors have no relevant conflicts of interest concerning this work.

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