

Original Article

Clinical Characterization and Diagnostic Approaches for Patients Reporting Hypersensitivity Reactions to Quinolones

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What is already known about this topic? Quinolones can induce hypersensitivity through several mechanisms, being the third most common drug associated with hypersensitivity, and the second most frequent drug inducing both IgE-mediated hypersensitivity and severe anaphylaxis. The optimal diagnostic approach remains a controversial topic.

What does this article add to our knowledge? The risk of having quinolone hypersensitivity is higher for immediate reactions, particularly for moxifloxacin-induced anaphylaxis. The basophil activation test has a higher sensitivity than skin test. Drug provocation tests can be useful to identify safe alternative quinolones.

How does this study impact current management guidelines? We propose an algorithm for diagnosing quinolone-induced reactions, which should be classified according to the interval between drug intake and reaction onset, using a 6-hour threshold. The algorithm includes skin, basophil activation, and drug provocation tests as necessary.

BACKGROUND: Quinolones are the second most frequent cause of hypersensitivity reactions (HSRs) to antibiotics. A marked increase in the number of patients with HSRs to quinolones has been detected.

OBJECTIVE: To describe the clinical characteristics of patients with HSRs to quinolones and present methods for their diagnosis.

METHODS: Patients attending the allergy unit due to reactions suggestive of HSRs to quinolones were prospectively evaluated between 2005 and 2018. Diagnosis was achieved using clinical history, skin tests (STs), basophil activation tests (BATs), and drug provocation tests (DPTs) if ST and BAT results were negative.

RESULTS: We included 128 subjects confirmed as having HSRs to quinolones and 42 found to be tolerant. Anaphylaxis was the most frequent entity in immediate HSRs and was most commonly induced by moxifloxacin. Patients were evaluated a median of 150 days (interquartile range, 60-365 days) after the reaction. Of patients who underwent ST and BAT, 40.7% and 70%, respectively, were positive. DPT with a quinolone was performed in 48 cases, giving results depending on the culprit drug: when moxifloxacin was involved, 62.5% of patients gave a positive DPT result to ciprofloxacin, whereas none reacted to levofloxacin. The risk of HSR was 96 times higher in subjects who reported moxifloxacin-induced anaphylaxis and 18 times

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Abbreviations used

BAT- Basophil activation test
DPT- Drug provocation test
HSR- Hypersensitivity reaction
IR- Immediate reaction
IV- Intravenous
NIR- Nonimmediate reaction
OR- Odds ratio
PT- Patch test
SPT- Skin prick test
ST- Skin test

higher in those reporting immediate reactions compared with clinical entities induced by quinolones other than moxifloxacin and nonimmediate reactions.

CONCLUSIONS: The diagnosis of HSR to quinolones is complex. The use of clinical history is essential as a first step. BAT shows higher sensitivity than STs. DPTs can be useful for finding safe alternative quinolones. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Adverse drug reaction; Anaphylaxis; Basophil activation test; Ciprofloxacin; Drug provocation test; Hypersensitivity; Levofloxacin; Moxifloxacin; Quinolones; Skin tests

INTRODUCTION

Quinolones are antibiotics that are commonly prescribed for their effectiveness against gram-positive and gram-negative bacteria.¹⁻³ Adverse effects occur in 2% to 10% of people taking quinolones; however, most of them are mild, mainly affecting the gastrointestinal or central nervous system.^{3,4} Quinolones can induce hypersensitivity reactions (HSRs)⁵ through IgE-mediated reactions (immediate reactions [IRs]) and T-cell-dependent reactions (nonimmediate reactions [NIRs]).^{6,7} In addition, quinolones may cause HSRs in drug-naïve patients.^{8,9} A mechanism of mast cell activation via occupation of the human mast-related G-protein receptor X2 has been described for IRs^{10,11} occurring in patients without previous exposure to quinolones.¹²

Although the absolute risk of an HSR related to quinolones is low (44.0 emergency department visits/100,000 prescriptions; 95% CI, 34.8-53.3),⁸ quinolones are the third most frequent drug associated with HSRs¹³ in general, and the second most frequent in IgE-mediated HSRs. They are also the second most frequent cause of alert activation for antibiotic allergy in electronic hospital records¹⁴ and severe drug-induced anaphylaxis.^{13,15} In recent years, an increase in the percentage of patients with HSRs to these drugs has been detected, ranging from 0.54% in 2005 to 6.85% in 2010.¹³ This is likely due to their increased prescription over the last decades.¹⁶ The incidence of anaphylaxis induced by quinolones has been estimated to be 1.8 to 23 per 10 million days of treatment,^{17,18} and the prevalence of cutaneous adverse reaction to be 0.09%.¹⁹ Quinolones are also one of the main triggers of acute generalized exanthematous pustulosis, photosensitivity, and vasculitis.²⁰

HSRs to quinolones appear in an important percentage of patients (23%) previously diagnosed as allergic to betalactams: in fact, betalactam-allergic patients have a 17 times higher risk of

reacting to quinolones than those nonallergic. This represents an important health problem because it greatly decreases the therapeutic options available.¹⁶ In a large study of inpatients with common infections requiring antibiotic treatment, quinolone allergy occurred in 5.4% of patients who were already sensitive to betalactams,²¹ leading to important restrictions for antibiotic prescription and subsequently poor prognosis of their infections.

The optimal diagnosis of quinolone HSRs is still a matter of debate. The value of skin tests (STs) is uncertain, and they have shown false-positive results when quinolones are tested at high concentration.²²⁻²⁵ The presence of specific IgE to quinolones has been reported using the sepharose radioimmunoassay, with a sensitivity of 54.5%.²⁶ The basophil activation test (BAT) has shown promising results for the diagnosis of patients with IRs to quinolones.²⁷⁻²⁹ However, other studies have contradicted these findings.^{30,31} The criterion standard, therefore, is the drug provocation test (DPT). However, this is not free of risk and not advisable in cases where the reaction might be severe.

The aim of this study was to describe the clinical characteristics of a large group of patients with quinolone-induced HSRs and present methods for their diagnosis.

METHODS

Patients

We prospectively evaluated patients with symptoms suggestive of HSR to quinolones who had been referred to the Allergy Unit of the University Regional Hospital of Málaga, the University Hospital of Salamanca, and the University Hospital La Fe of Valencia over a period of 13 years (2005-2018).

Inclusion criteria. Patients 14 years or older in whom the allergological study was completed were included and classified into 2 groups: (1) patients confirmed as having HSRs to quinolones (by positive STs, BATs, or DPT results) and (2) patients confirmed as being nonallergic (tolerant) because they tolerated a DPT with the suspected culprit quinolone.

Exclusion criteria. Patients younger than 14 years; patients in whom the allergological study was not completed and so the diagnosis could not be confirmed as being neither allergic nor tolerant to quinolones; pregnant or breast-feeding patients; patients taking beta-blockers or angiotensin-converting enzyme inhibitors or with contraindications for epinephrine administration; patients who had acute infections and/or underlying cardiac, hepatic, or renal diseases that contraindicated DPTs; and subjects with psychosomatic disorders were excluded.

Clinical history

Patients were asked about their reaction symptoms,³² the interval between drug intake and reaction onset, the number of episodes, the interval between their last reaction and the study, and the presence of other underlying diseases. If a reported reaction occurred within 6 hours after quinolone intake, the reaction was classified as IR; when this interval was longer, it was considered an NIR.^{5,32}

Skin testing

For reactions suggestive of an IR, skin prick tests (SPTs) were carried out as described³³ using ciprofloxacin (at 0.02 and 0.2 mg/mL), levofloxacin (at 0.05 and 0.5 mg/mL), and moxifloxacin (1 tablet of 400 mg suspended in NaCl). Intradermal tests were

not performed to avoid false-positive results because nonspecific histamine release by quinolones has been reported.^{34,35}

For reactions suggestive of an NIR, patch tests (PTs) were carried out and evaluated as described³³ by mixing powdered quinolone (ciprofloxacin, levofloxacin, and moxifloxacin) in petrolatum at 30% w/w.

Basophil activation test

In patients with a suspected IR, BATs were performed as described previously,²⁷ using ciprofloxacin (2 and 0.2 mg/mL), levofloxacin (4 and 2 mg/mL), moxifloxacin (2, 0.2, and 0.1 mg/mL), norfloxacin (2, 0.2, and 0.1 mg/mL), ofloxacin (4, 2, 0.2 and 0.1 mg/mL), and lomefloxacin (4, 2, 0.2, and 0.1 mg/mL).

Drug provocation test

DPTs with ciprofloxacin, levofloxacin, and moxifloxacin were performed in a single-blind manner if ST and BAT results were negative³⁶: placebo capsules were given at different times on the first day; increasing doses of quinolones were administered orally at intervals of 60 minutes (5, 20, 100 mg for ciprofloxacin and levofloxacin; 5, 30, 65 mg for moxifloxacin) on the second day. If these did not produce a reaction, 3 further doses of quinolones were given on the third day: 125, 125, 250 mg (accumulative dose 500 mg) for ciprofloxacin and levofloxacin; 100, 100, 200 mg (accumulative dose 400 mg) for moxifloxacin. The 3 test days were separated by 1 week. If cutaneous and/or respiratory symptoms or alterations in vital signs appeared, the procedure was stopped and the symptoms were evaluated and treated. If no symptoms appeared during graded challenge, the therapeutic dose was achieved. This was then followed by taking the full dose at home, starting 24 hours after the graded challenge. Before beginning the DPT procedure, patients were stable and their FEV₁ had to be at least 80% of the predicted value, with an absolute volume of at least 1.5 L. Medications were stopped before DPT according to international guidelines.³⁶

Statistical analysis

Data analysis was performed using χ^2 analysis to test differences in nominal variables between groups, the Fisher test was used when there were no criteria for using the χ^2 test, and the Mann-Whitney test was used for quantitative variables. All reported *P* values represented 2-tailed tests, with values less than .05 considered statistically significant. A logistic regression analysis was performed to establish the characteristics associated with the diagnosis of HSR or tolerance to quinolones and with the diagnosis of immediate anaphylaxis. The following variables were analyzed: sex, age, time interval between drug intake and the onset of the reaction, symptoms experienced, drugs involved, time interval between drug reaction and study, and number of episodes.

The study was conducted according to the principles of the Declaration of Helsinki. All the participants were informed orally about the study and signed the corresponding informed consent.

RESULTS

A total of 612 patients with a clinical history suggestive of an HSR to quinolones were evaluated. Of these, full diagnosis could not be achieved for 442 patients: 361 patients who gave a negative ST result and a negative BAT result could not undergo DPT to quinolones because of age, comorbidities, or because it was contraindicated because of potential severity of the reaction; 78 did not give consent for the allergological tests (STs, BAT, and/or DPTs); and 3 were excluded because of pregnancy. For

the remaining 170 patients, a full diagnosis could be achieved: 128 were confirmed as having HSRs to quinolones and 42 as nonallergic (tolerant) to quinolones.

Clinical data of the subjects included in the study

The 170 included subjects with confirmed diagnosis had a median age of 53 years (interquartile range, 40-63.25 years), and 126 (74.1%) were female. Most cases reported only 1 previous episode induced by quinolone intake, except for 2 cases who reported 2 previous IRs. As such, the patients included in the study reported a total of 172 previous reactions: 120 IRs and 52 NIRs, with the percentage of IRs higher in those confirmed as having HSRs compared with the tolerant group (73.8% vs 19%; *P* < .0001) (Table I). Most reported reactions were induced by oral quinolones (142 [82.5%]), the rest by the intravenous (IV) route (30 [17.4%]). In terms of the symptoms of reported reactions, the percentage of anaphylaxis reactions was higher in subjects confirmed as having HSRs (*P* < .0001), whereas urticaria (*P* = .0004), local reaction at the site of IV administration (*P* = .0001), and maculopapular exanthema (*P* = .03) were more frequently reported by subjects who were found to be tolerant (Table I). Moxifloxacin was the most frequent culprit quinolone in patients with confirmed HSRs; ciprofloxacin was more frequent in subjects confirmed as tolerant (*P* < .0001 and *P* = .001, respectively) (Table I). In subjects confirmed as having HSRs, most cases of anaphylaxis were induced by moxifloxacin (52.9%; *P* = .002); urticaria and angioedema were mostly induced by ciprofloxacin (48.8% and 66.7%, respectively), although these differences were not found to be statistically significant (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). For those found to be tolerant, ciprofloxacin was the most frequent cause of both urticaria and angioedema (69.2% and 66.7%, respectively), as well as of local reactions at the site of IV administration (66.7%) (*P* > .05) (Table E1).

The logistic regression analysis showed that the risk of being confirmed as having HSRs was higher for cases who reported moxifloxacin-induced anaphylaxis (odds ratio [OR], 96.16; 95% CI, 6.172-Inf; *P* = .009) and for those reporting IRs (OR, 18.856; 95% CI, 5.196-271.449; *P* < .0001) compared with cases who reported other symptoms induced by other quinolones and NIRs. Moreover, the risk for being confirmed as having HSRs decreased when ciprofloxacin was the culprit (OR, 0.107; 95% CI, 0.002-0.741; *P* = .04) and the symptoms reported were maculopapular exanthema, fixed drug eruption, urticaria, angioedema (OR, 0.053; 95% CI, 0-0.452; *P* = .03), or a local reaction at the site of IV administration (OR, 0.001; 95% CI, 0-0.016; *P* = .0006). No significant associations were found for the other variables, and there were no interactions between variables.

Analysis of the patients confirmed as suffering HSRs to quinolones

In patients confirmed as having HSRs, a total of 112 reported reactions (73.8%) were IRs and 18 (26.2%) NIRs. No differences were found when comparing age, sex, atopy, allergen sensitization, and underlying diseases between IR and NIR groups (data not shown).

Anaphylaxis was the most frequent reported symptom among IRs (*P* < .0001) and urticaria among NIRs (*P* > .05) (Table II). It is of note that the 7 (25%) patients reporting reactions within the interval of 1 to 6 hours showed symptoms compatible with

TABLE I. Clinical data for the reactions reported by the subjects included in the study, comparing cases confirmed as having HSRs to quinolones and those confirmed as tolerant to these drugs

Clinical data for the historical reactions	HSR (n = 130)	Tolerant (n = 42)	P
Historical reaction symptoms, n (%)			
Anaphylaxis	70 (53.8)	—	<.0001
Urticaria	41 (31.5)	26 (61.9)	.0004
AE	12 (9.2)	6 (14.3)	.3522
FDE	4 (3.1)	—	.5732
MPE	3 (2.3)	4 (9.5)	.03
Local reaction at the site of IV administration	—	6 (14.3)	.0001
Drugs involved in historical reactions, n (%)			
Ciprofloxacin	49 (37.7)	28 (66.7)	.001
Levofloxacin	21 (16.2)	10 (23.8)	.2618
Moxifloxacin	52 (40)	2 (4.8)	<.0001
Norfloxacin	3 (2.3)	2 (4.8)	.5967
Ofloxacin	1 (0.8)	—	>.999
Pipemidic acid	2 (1.5)	—	>.999
Unknown	2 (1.5)	—	>.999
Time interval intake-reaction (min), median (interquartile range)	30 (11.25-60)	7200 (2880-8640)	<.0001
Time interval intake-reaction ≤ 1 h, n (%)	112 (73.8)	8 (19)	<.0001
Time interval intake-reaction > 1 h, n (%)	18 (26.2)	34 (81)	
Administration route, n (%)			
Oral	109 (83.8)	33 (78.6)	.4335
IV	21 (16.1)	9 (21.4)	
No. of episodes, median (interquartile range)	1 (1-1)	1 (1-1)	.08

AE, Angioedema; FDE, fixed drug eruption; MPE, maculopapular exanthema.

TABLE II. Clinical data for the reported reactions in cases confirmed as having HSRs to quinolones

Clinical data for the historical reactions	IR (%)	NIR, n (%)	P
Historical reaction symptoms, n (%)			
Anaphylaxis	70 (62.5)	—	<.0001
Urticaria	34 (30.4)	7 (38.9)	.4696
AE	8 (7.1)	4 (22.2)	.04
FDE	—	4 (22.2)	.0002
MPE	—	3 (16.7)	.002
Drugs involved in historical reaction, n (%)			
Ciprofloxacin	42 (37.5)	7 (38.9)	.9101
Levofloxacin	17 (15.2)	4 (22.2)	.451
Moxifloxacin	46 (41.1)	6 (33.3)	.5339
Norfloxacin	2 (1.8)	1 (5.6)	.3629
Ofloxacin	1 (0.9)	—	>.999
Pipemidic acid	2 (1.8)	—	>.999
Unknown	2 (1.8)	—	>.999

AE, Angioedema; FDE, fixed drug eruption; MPE, maculopapular exanthema.

anaphylaxis. Moxifloxacin was the most frequent quinolone involved in IRs and ciprofloxacin in NIRs (41.1% and 38.9%, respectively) (Table II). Anaphylaxis was induced primarily by moxifloxacin in IRs (52.9%; OR, 2.935; 95% CI, 1.418-6.075; $P = .003$), whereas most urticaria and angioedema was induced by ciprofloxacin (52.9% and 75%, respectively). Considering NIRs, moxifloxacin was the culprit in most cases reporting urticaria (42.8%) and ciprofloxacin in angioedema reporting cases (50%) (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

www.jaci-inpractice.org). The time interval between intake and onset of the reaction was shorter when the drug was administered by an IV route compared with the oral route (5 [interquartile range, 5-10] minutes vs 30 [interquartile range, 15-60] minutes, $P = .005$). This comparison was also statistically significant when ciprofloxacin was the culprit (IV route: 5 [5-10] minutes; oral route: 30 [18.7-165] minutes; $P = .01$) (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Methods used for diagnosis

The median time interval between the reaction and the study was 150 days (interquartile range, 60-365 days; mean, 560.3 ± 1028.4 days). No differences were found between IRs and NIRs. STs were performed on 54 subjects, BATs on 76, and DPTs on 48. No differences were found when comparing the clinical characteristics of patients undergoing the different tests (data not shown).

Skin tests. SPTs were performed on 48 patients and PTs on 6, of which results for 22 were positive: 20 SPTs and 2 PTs. Of those with positive SPT results, 13 (43.33%) were positive to moxifloxacin, 7 (8.53%) to ciprofloxacin, and 6 (9.83%) to levofloxacin (Table III). When ciprofloxacin was the suspected culprit drug, SPT results to ciprofloxacin were positive in 16.7% of the tests and levofloxacin in 22.2%; when levofloxacin was the suspected culprit, 25% of SPT results were positive to levofloxacin and 80% to moxifloxacin. Finally, when the suspected culprit was moxifloxacin, 100% of SPT results were positive to moxifloxacin and 6.2% to ciprofloxacin (Table III). Regarding the symptomatology of the reported reactions, the highest percentage of positive ST results was found for anaphylaxis (53.8%),

TABLE III. Results of SPTs according to the drugs involved and the drug tested

Drugs involved; positive cases/cases in which the test was performed (%)	Drugs tested; positive cases/cases in which the test was performed (%)			
	Ciprofloxacin	Levofloxacin	Moxifloxacin	Total
Ciprofloxacin	3/18 (16.7)	2/9 (22.2)	—	5/27 (18.5)
Levofloxacin	0/8	2/8 (25)	4/5 (80)	6/21 (28.6)
Moxifloxacin	1/16 (6.2)	0/9	7/7 (100)	8/34 (23.5)
Norfloxacin	0/1	0/1	—	0/2
Pipemidic acid	2/2 (100)	1/1 (100)	1/1 (100)	4/4 (100)
Unknown	1/1 (100)	1/1 (100)	1/1 (100)	3/3 (100)
Total	7/46 (15.2)	6/29 (20.7)	13/14 (92.8)	

TABLE IV. Results of BATs according to the drugs involved and the drug tested

Drugs involved; positive cases/cases in which the test was performed (%)	Drugs tested; positive cases/cases in which the test was performed (%)						
	Ciprofloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin	Lomefloxacin	Total
Ciprofloxacin	20/25 (80)	9/19 (47.4)	12/20 (60)	5/6 (83.3)	2/6 (33.3)	4/6 (66.7)	24/26 (92.3)
Levofloxacin	8/11 (72.7)	5/11 (45.45)	2/10 (20)	1/1 (100)	—	0/1	10/12 (83.3)
Moxifloxacin	26/34 (76.5)	12/26 (46.2)	20/32 (62.5)	9/10 (90)	8/10 (80)	6/10 (60)	32/35 (91.4)
Norfloxacin	1/1 (100)	0/1	0/1	—	—	—	1/1 (100)
Ofloxacin	1/1 (100)	0/1	1/1	—	—	—	1/1 (100)
Unknown	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Total	56/73 (76.7)	26/59 (44.1)	35/65 (53.8)	15/18 (83.3)	10/17 (58.8)	10/18 (55.5)	

followed by urticaria (33.3%). Although the interval between the last quinolone-induced reaction and the study was shorter in patients with positive ST results compared with negative, no statistical difference was found (90 [interquartile range, 60-240] vs 120 [interquartile range, 60-172.5] days; $P = 1$).

Basophil activation test. The BAT result was positive in 68 (89.5%) cases. A total of 56 (76.7%) cases were positive to ciprofloxacin, 35 (53.8%) to moxifloxacin, 26 (44.1%) to levofloxacin, 15 (83.3%) to norfloxacin, 10 (58.8%) to ofloxacin, and 10 (55.5%) to lomefloxacin (Table IV). When ciprofloxacin was the culprit, BAT result to ciprofloxacin was positive in 80%, to moxifloxacin in 60%, and to levofloxacin in 47.4%; when levofloxacin was the culprit, BAT result was positive to ciprofloxacin in 72.7%, to levofloxacin in 45.4%, and to moxifloxacin in 20%; finally, when the culprit drug was moxifloxacin, BAT result was positive to ciprofloxacin in 76.5%, to moxifloxacin in 62.5%, and to levofloxacin in 46.2% (Table IV). BAT result was positive in 48 of 49 (97.9%) cases reporting anaphylaxis, in 13 of 18 (72.2%) cases of urticaria, and in 5 (100%) cases of angioedema. Although the interval between the historical quinolone reaction and whether the patients were found to be allergic or not in the study was shorter in patients who gave a positive BAT result compared with negative, no statistical differences were found (150 [interquartile range, 60-365] vs 395 [interquartile range, 60-1003.7] days; $P = .9909$).

Drug provocation test. We performed 58 DPTs in 48 patients. A total of 34 DPTs with the culprit quinolone were carried out in cases with negative ST and BAT results, all of which were positive: 23 in IR (16 with ciprofloxacin, 3 with levofloxacin, and 4 with moxifloxacin) and 11 in NIR (5 with ciprofloxacin, 2 with levofloxacin, and 4 with moxifloxacin).

When the benefit was considered to outweigh the risk, we carried out DPTs with an alternative quinolone in 24 cases; this was positive for 13 of these (11 IR and 2 NIR) (Table V). When ciprofloxacin was the culprit, DPT result to levofloxacin was positive in 60%; when levofloxacin was the culprit, DPT result was positive to ciprofloxacin in 40%; when the culprit drug was moxifloxacin, DPT result was positive to ciprofloxacin in 62.5%; and no case reacted to levofloxacin (Table V). In all cases, DPTs with quinolones induced mild symptoms (pruritus and wheals localized on different parts of the body) that disappeared 1 to 48 hours after administering antihistamine and corticosteroid treatment.

DISCUSSION

Although HSRs to quinolones represent an important health problem,²¹ no large-scale study of patients suffering from them exists. To our knowledge, this is the largest published series of HSRs to quinolones to date. In our study, more than 50% of patients reported anaphylaxis, most of whom suffered from IRs, in agreement with previously published short series.^{24,26,27,30,34} Moreover, data suggest that the risk of an HSR is different depending on the quinolone. Analyses of spontaneous reports implicate that moxifloxacin triggers anaphylaxis in a higher proportion of cases than levofloxacin or ciprofloxacin,^{8,9,37} which is in line with our results. Indeed, the risk of experiencing anaphylaxis was 2.2-fold higher when moxifloxacin was the culprit, which agrees with previously published data.^{8,9,37} This may be due to the expanded use of quinolones or increased immunogenicity to newer quinolones.

The interval between drug intake and the appearance of symptoms is crucial for evaluating allergic reactions to drugs. Historically, reactions occurring less than 1 hour after drug intake are considered IRs, and those occurring after an hour are

TABLE V. Results of DPTs performed according to the drugs involved and the drug tested

Drugs involved in historical reaction; positive cases/cases in which the test was performed (%)	Drugs used in DPT; positive cases/cases in which the test was performed (%)		
	Ciprofloxacin	Levofloxacin	Moxifloxacin
Ciprofloxacin	21/21	3/5 (60)	—
Levofloxacin	2/5 (40)	5/5	0/1
Moxifloxacin	5/8 (62.5)	0/2	8/8
Norfloxacin	1/1 (100)	1/1 (100)	—
Unknown	—	1/1 (100)	—

considered NIRs.^{5,38} The former are thought to be induced by an IgE-mediated response, although an alternative non-IgE-dependent mechanism may also be involved.^{10,11} For the latter, the underlying mechanism remains a matter of debate, especially for those with a time interval of 1 to 6 hours after drug intake.³⁹⁻⁴¹ For betalactam antibiotics, the mechanism has been proposed to be non-IgE-dependent, because some evidence suggests that these reactions are mediated by T cells.^{40,41} However, for met-amizole, a study of reactions occurring 1 to 8 hours after intake using BAT support an IgE-mediated mechanism.⁴² However, to our knowledge, this mechanism has not yet been studied for quinolones. In this study, we have observed that around 25% of patients reported anaphylaxis 1 hour after quinolone intake, and more than 40% of them showed positive results via BAT or SPT, suggesting that an IgE mechanism is likely. The interval between drug administration and reaction onset may be related to the production of as-yet unidentified metabolites and the route of administration. However, most patients in our study took the quinolone orally and no differences could be found in terms of the administration route when considering drugs involved and symptoms reported. As such, we would suggest that the classification of reactions as IR or NIR based solely on a 1-hour cutoff does not sufficiently reflect the extension of the pathophysiology of the reactions.

The diagnosis of HSRs to quinolones is still a matter of debate. A detailed clinical history is crucial as a first approach. We found that the chance of being confirmed as having an HSR to quinolones was 96 times higher in patients who reported moxifloxacin-induced anaphylaxis and 18 times higher in those reporting IRs. This risk decreased when ciprofloxacin was the culprit and the symptoms experienced in the reported reaction were maculopapular exanthema, fixed drug eruption, urticaria, angioedema, or a local reaction at the site of the administration of the drug. Concerning STs, there is controversy regarding their utility. Some authors consider they are useful, with a sensitivity of 71%, specificity of 86%, and positive and negative predictive values of 50% and 94%, respectively, having been reported previously.²⁴ However, other studies suggest that STs are not valid because they can produce false-negatives,^{34,35} potentially missing important reactions and putting patients at risk; moreover, they can produce a large number of false-positive results when tested at high concentrations, which is attributed to nonspecific histamine release by quinolones due to mast cell activation.^{35,43-48} We decided not to perform intradermal tests in our patients on the basis of this consideration. In our study, we found a low sensitivity for STs in general, although it was higher for severe reactions (anaphylaxis) and when levofloxacin and ciprofloxacin were the culprits.

We found the BAT to be useful for the diagnosis of patients with IRs to quinolones.²⁷⁻²⁹ However, other studies have shown contradictory results.^{30,31} Here, BAT gave a higher percentage of positive results than STs, agreeing with previous studies.^{27,28} This is important, because if BATs can be used to confirm diagnosis instead of DPTs in some cases, this will reduce patient risk. This is particularly useful here, given that the most common clinical entity induced by quinolones is anaphylaxis.

Although cross-reactivity among quinolones remains a controversial issue, DPTs could be useful to find safe alternative quinolones. A high degree of cross-reactivity has been reported between the first- and second-generation quinolones.²² Regarding the second-generation, cross-reactivity does not always occur within this group,^{43,45,49} which may be due to the production of different metabolites. The same phenomenon can occur for the newer (moxifloxacin) and the second- (ciprofloxacin) and third-generation (levofloxacin) quinolones.⁵⁰⁻⁵² A low degree of cross-reactivity has been found between levofloxacin and ciprofloxacin.³⁴ In our study, 60% of the patients who reported reactions induced by levofloxacin tolerated ciprofloxacin in DPT and 40% of cases tolerated levofloxacin when the reactions were induced by ciprofloxacin. DPT with levofloxacin was carried out for 2 cases who reported moxifloxacin-induced reactions, with neither patient experiencing an adverse reaction. On the basis of data obtained from our large series of cases, we propose an algorithm for the diagnosis of quinolone-induced HSRs, as described in Figure 1.

A limitation of this study is the high percentage of patients for whom we were not able to confirm the diagnosis because of contraindication or patient refusal. This could be the reason why the number of cases confirmed as tolerant in our series is low. However, despite this, our results show relevant differences in clinical characteristics comparing tolerant and cases confirmed as HSRs, highlighting the importance of a detailed clinical history as an initial approach for diagnosis. Another limitation of our study is that ST, BAT, and DPT could not be performed for all patients and with all quinolones, that PT was carried out at a 30% dilution in petrolatum, which could increase the rate of false-negative results, and that the time interval between the reaction and the allergy evaluation was not uniform in all patients. However, our aim was to describe the role and utility of the different diagnostic methods used in a large group of patients in real allergological practice, not finding differences in the clinical characteristics when comparing groups of patients on the basis of results for ST, BAT, and DPT.

The accurate diagnosis of quinolone-induced HSRs is an important issue not only due to their frequency, as described above, but also because an important percentage of patients who report quinolone-induced HSRs report previous reactions to

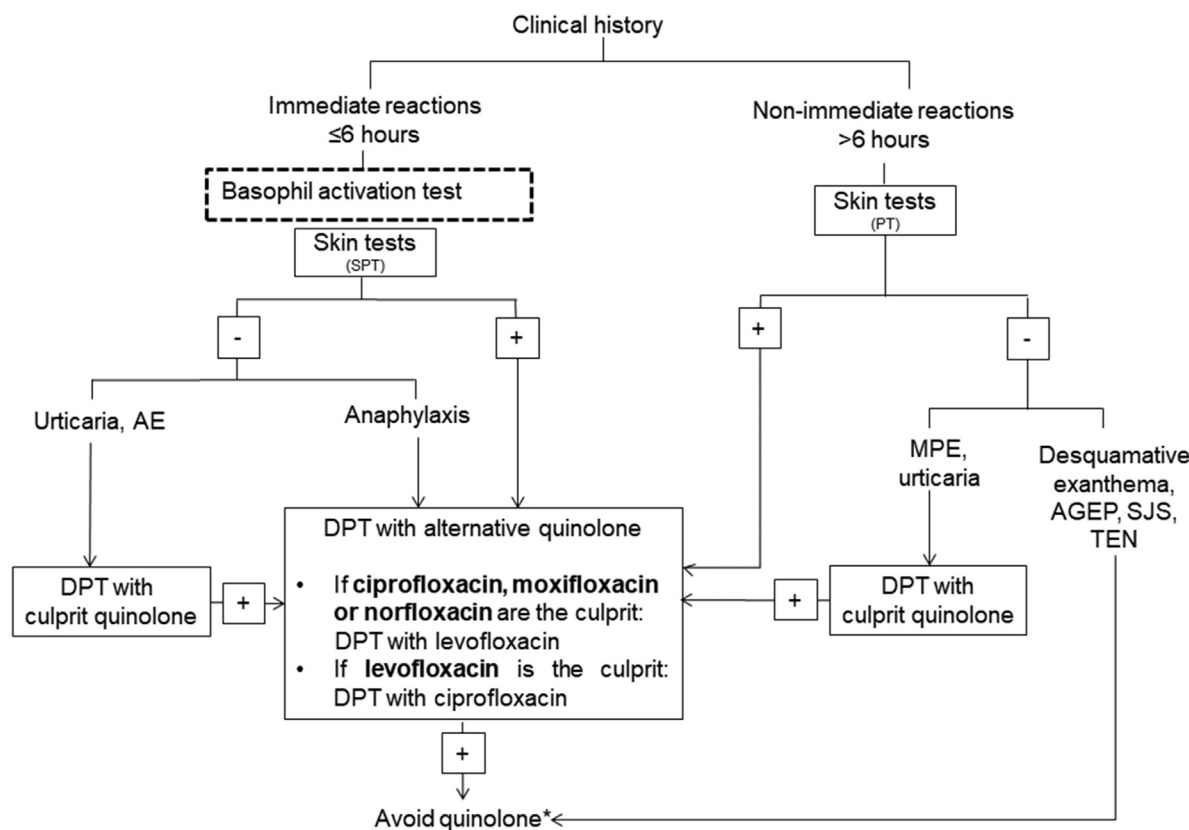


FIGURE 1. Algorithm proposed for the diagnosis of quinolone induced-HSRs. AE, Angioedema; AGEP, acute generalized exanthematous pustulosis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

beta-lactams, drastically reducing their therapeutic options.¹⁶ Referring patients with quinolone-induced HSRs for a full allergological evaluation is crucial to confirm or dismiss their reported allergy.

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TABLE E1. Analysis of the drug involved in each reaction according to the symptoms reported for cases confirmed as having HSR to quinolones and those confirmed as tolerant

Drug	HSR					Tolerant			
	Anaphylaxis	Urticaria	AE	FDE	MPE	Urticaria	AE	MPE	Local reaction at IV site administration
Ciprofloxacin	18 (25.7)	20 (48.8)	8 (66.7)	1 (25)	2 (66.7)	18 (69.2)	4 (66.7)	2 (50)	4 (66.7)
Levofloxacin	12 (17.1)	6 (14.6)	2 (16.7)	—	1 (33.3)	4 (15.4)	2 (33.3)	2 (50)	2 (33.3)
Moxifloxacin	37 (52.9)	11 (26.8)	2 (16.7)	2 (50)	—	2 (7.7)	—	—	—
Norfloxacin	—	2 (5.8)	—	1 (25)	—	2 (7.7)	—	—	—
Ofloxacin	1 (1.4)	—	—	—	—	—	—	—	—
Pipemidic acid	1 (1.4)	1 (2.4)	—	—	—	—	—	—	—
Unknown	1 (1.4)	1 (2.4)	—	—	—	—	—	—	—
<i>P</i>	.002	.2366	.3949	.2391	.4201	.2759	.8126	.5244	.8126

AE, Angioedema; *FDE*, fixed drug eruption; *MPE*, maculopapular exanthema.

The percentages are given for the symptoms reported (columns).

TABLE E2. Quinolones involved in the reported reactions according to the symptoms experienced in cases confirmed as having HSRs to quinolones

Drug	IR, n (%)			NIR, n (%)			
	Anaphylaxis	Urticaria	AE	Urticaria	AE	FDE	MPE
Ciprofloxacin	18 (25.7)	18 (52.9)	6 (75)	2 (28.6)	2 (50)	1 (25)	2 (66.7)
Levofloxacin	12 (17.1)	4 (11.8)	1 (25)	2 (28.6)	1 (25)	—	1 (33.3)
Moxifloxacin	37 (52.8)	8 (23.5)	1 (25)	3 (42.8)	1 (25)	2 (50)	—
Norfloxacin	—	2 (5.9)	—	—	—	1 (25)	—
Ofloxacin	1 (1.4)	—	—	—	—	—	—
Pipemidic acid	1 (1.4)	1 (2.9)	—	—	—	—	—
Unknown	1 (1.4)	1 (2.9)	—	—	—	—	—
<i>P</i>	0.001	0.01	0.3937	0.6894	1	0.2154	0.511

AE, Angioedema; *FDE*, fixed drug eruption; *MPE*, maculopapular exanthema.

TABLE E3. Comparison of time interval between drug intake and the onset of the reaction for oral and IV routes, according to the quinolone involved and the symptoms reported in the reaction

Clinical data for the historical reactions	Time interval between drug intake and reaction onset (min), median (interquartile range)		
	Oral	IV	<i>P</i>
Drugs involved			
Ciprofloxacin	30 (18.7-165)	5 (5-10)	.01
Levofloxacin	30 (17.5-240)	—	—
Moxifloxacin	30 (10-30)	—	—
Norfloxacin	27.50 (26.2-28.75)	—	—
Ofloxacin	17.5 (11.2-23.75)	—	—
Pipemidic acid	70 (45-95)	—	—
Unknown	20 (15-25)	—	—
Symptoms experienced in reported reactions			
Anaphylaxis	30 (10-30)	7.5 (5-10)	.04
Urticaria	30 (30-120)	5 (5-5)	.1479
AE	600 (240-2880)	17.5 (11.2-23.7)	.118
FDE	1740 (1170-2310)	—	—
MPE	720 (660-1800)	—	—

AE, Angioedema; FDE, fixed drug eruption; MPE, maculopapular exanthema.