



Quinolone-Induced Anaphylaxis

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Abstract

Purpose of review Quinolones are the second most common antibiotic class that may induce IgE and non-IgE-mediated immediate hypersensitivity reactions. The prevalence of true quinolone allergy still remains unknown, but its incidence has increased in recent years, probably due to the extensive utilization of this antibiotic class and the introduction of moxifloxacin.

Recent findings Quinolones may also induce nonallergic reactions through the MRGPRX2 receptor. The diagnosis of hypersensitivity reactions to quinolones is complex, since clinical history is often doubtful, skin tests can induce false-positive results, and in vitro tests are not well validated. Therefore, in many cases, the only way to confirm or rule out the diagnosis is drug provocation test, a procedure that carries some risks. Quinolones present a variable degree of cross-reactivity that is undetermined and difficult to predict, and desensitization may be required in patients with no other antibiotic options.

Summary This review critically analyzed the existing data on quinolone allergy, highlighting the recent advances in its diagnosis and management. Further studies are needed to increase the knowledge in the field and to improve patients' care.

Introduction

Quinolones are synthetic antibiotics that inhibit DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria, inducing DNA cleavage and rapid killing of susceptible bacteria [1•]. Due to their broad-spectrum activity, excellent tissue and intracellular penetration, high bioavailability, and, generally, good oral-tolerability, the use of quinolones as first-line therapy increased in recent years [1•].

Fluoroquinolones are the most widely used members of this group of antibiotics, being ciprofloxacin, moxifloxacin, and levofloxacin the most frequent used worldwide [1•]. However, adverse effects have been

observed, including hypersensitivity reactions (HR) [2•]. As a result, the European Medicines Agency published a statement “Disabling and potentially side effects lead to suspension or restrictions of quinolone and fluoroquinolones antibiotics” in November 2018 [3]. An increase of HR to quinolones in the last decades is reported, some reactions being severe, including anaphylaxis [2•].

In this review, we emphasize the immediate hypersensitivity reactions (IHR) to quinolones, including anaphylaxis.

Classification and chemical structure of quinolones

Quinolones are classified into four generations based on their chemical structure, antibacterial activity, and pharmacokinetic properties [1•]. Their basic structure consists of a bicyclic skeleton with the carboxylic acid and ketone groups at the third and fourth positions, respectively (Fig. 1). Nalidixic acid was the first quinolone antibiotic that was developed in 1960s [2•]. The fluorination of the original molecule yielded the fluoroquinolones, with chemical

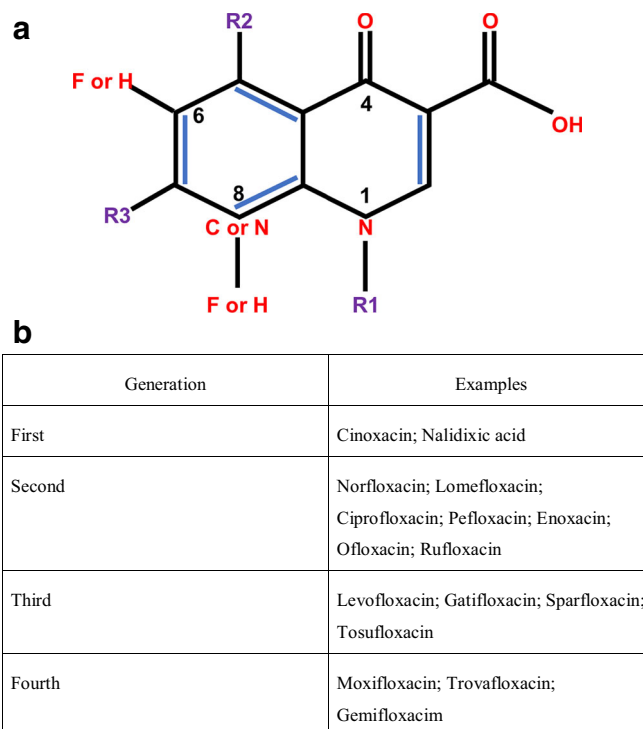


Fig. 1. **a** Basic chemical structure of quinolones. **b** Classification of quinolones by antibacterial spectra [2•]

modifications at positions N-1, C-7, and C-8 [1•]. Fluoroquinolone medicines consist of ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, and rifloxacin [3]. Although most quinolones, with the exception of moxifloxacin, are not subject to extensive hepatic metabolism, a small proportion of them may be converted to reactive intermediates in the liver, which may interact with proteins and generate covalent hapten-protein conjugates, triggering specific immune reactions [4•].

Epidemiology and risk factors

The prevalence of quinolone allergy in the general population is unknown. A recent retrospective study reported quinolone allergy in about 2% of hospitalized patients, and the most commonly documented reactions were hives and rash [5]. Quinolones are now the most frequently non-beta-lactam antibiotics involved in drug hypersensitivity and the third leading cause of confirmed HR to drugs [2•].

Most HR to quinolones are immediate (IHR), which are severe in 70% of the cases. In the last decades, there has been an increase in the total numbers of anaphylaxis to quinolones, with an estimated incidence of 1.8–2.3 per 10,000,000 days of treatment, corresponding to 4.5% of the drug-induced anaphylaxis [2•]. This is most likely associated with the expanded use of quinolones and/or the introduction of moxifloxacin, which appears to be more reactive than other quinolones [4, 6].

The risk of anaphylaxis may be different among quinolones, and studies showed that moxifloxacin is the culprit of 52.1–63% of all quinolone-anaphylaxis, followed by levofloxacin, 13–35.7%, and ciprofloxacin, 7.1–28.9% [7•]; however, a cohort study performed in the USA using a large claim database found no difference in the incidence of anaphylaxis across quinolones [8]. Moreover, moxifloxacin has induced more severe reactions, with 75% of them being anaphylaxis or anaphylactic shock [2•].

Previous history of beta-lactam allergy was shown to be a strong risk factor to develop quinolone allergy [4•]. Another study showed that 21% of patients with history of IgE-mediated allergy to penicillin also reported allergic reactions to non-beta-lactams compared with only 1% of individuals with no drug allergy history [9]. Additionally, a higher incidence of intravenous contrast reaction was observed in patients with quinolone allergy (6%) compared with those with penicillin allergy (2%) [10]. Moxifloxacin has been shown to increase the odds of suffering an IHR by fourfold compared with those of other quinolones (odd ratio [OR] 4.20; 95% confidence interval [CI] 3.19–5.55) [11].

Giavina-Bianchi et al. concluded that the excess of mast cells and their MRGPRX2 receptors in patients with mastocytosis may induce anaphylaxis on activation by quinolones. Based on the current knowledge and on this case report, it is advisable to be cautious when prescribing quinolones for patients with mastocytosis until further studies address this issue [12••].

Pathogenesis and natural history

There is evidence for both immunoglobulin E (IgE) and non-IgE mechanisms involved in IHR to fluoroquinolones. IgE-mediated activation of

mast cells via Fcε receptor-1 is the hallmark of classical Gell and Coombs type I hypersensitivity reaction. IHR to drugs and other agents that are non-IgE-mediated have been referred as pseudoallergic and/or anaphylactoid reactions. There is plenty evidence, from in vitro studies and rodent models, that some non-IgE-mediated anaphylactic reactions result from stimulation of mast cell MRGPR receptors. This class of G protein-coupled receptors consists of about 40 members classified into 9 separate families, A–H and X. MRGPRX1 and MRGPRX2 are expressed in primates, on neurons and mast cells, respectively. MRGPRX2 appears to play a role in human non-IgE-mediated acute drug HR [13].

Non-specific mast cell degranulation may be induced by interaction with the surface receptor MRGPRX2. Cationic substances acting as basic secretagogues activate mouse mast cells, in vitro and in vivo, through a single receptor, the Mrgprb2, which is ortholog of the human MAS-related G protein-coupled receptor-X2 (MRGPRX2). Several basic exogenous substances have been involved in MRGPRX2-mediated mast cell activation according to in vitro studies (Fig. 2). Neuromuscular blocking agents and all fluoroquinolones have a tetrahydroisoquinoline motif, which can bind and activate this receptor. The secretagogue compound 48/80, vespid mastoparan, opioids, and icatibant are other examples of agonists of MRGPRX2 [12••]. Non-IgE-mediated reactions through the MRGPRX2 receptor may occur during the first drug exposure since prior sensitization is not necessary [14••].

The fluoroquinolones increase intracellular Ca²⁺ mobilization in MRGPRX2/HEK293 cells, and enhanced β-hexosaminidase and histamine secretion in LAD2 cells (LAD2 cells that closely resemble primary human mast cells) [15]. The increased Ca²⁺ concentration in the cytoplasm may activate STIM1, which is the endoplasmic reticulum (ER) Ca²⁺ sensor, and

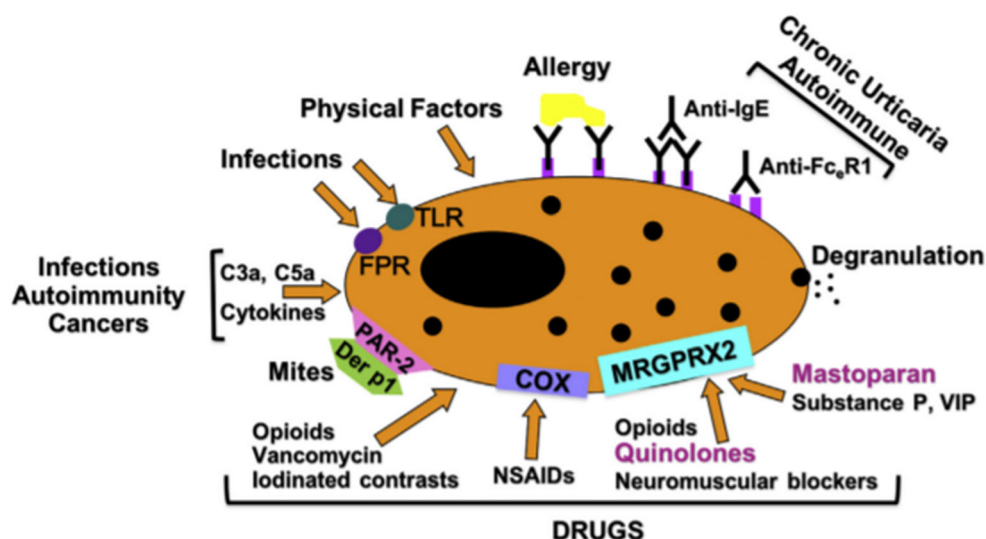


Fig. 2. Mechanisms of mast cell activation. Reprinted from *The Journal of Allergy and Clinical Immunology: In Practice*, Vol 7/Issue 6, Pedro Giavina-Bianchi, Danilo Gois Gonçalves, Andressa Zanandréa, Raísa Borges de Castro, Laila Sabino Garro, Jorge Kalil, Mariana Castells, Anaphylaxis to quinolones in mastocytosis: Hypothesis on the mechanism, 2089–2090, Copyright (2019), with permission from Elsevier

STIM1 could act on Orai1, which is the Ca^{2+} channel protein in the plasma membrane [16]. One of the mechanisms of fluoroquinolone-derived mast cells activation via MRGPRX2 and increasing intracellular Ca^{2+} concentration may be accomplished by activating STIM1 and Orai1 [14]. Protonation nitrogen atom may be the crucial structure for fluoroquinolones triggered anaphylactoid reaction via MRGPRX2. Meanwhile, the substituent of the nitrogen atom can affect the electrical properties of the whole compound [14].

Regarding IgE-mediated IHR, there is some evidence that fluoroquinolone-specific IgE declines over time, implying that some patients could lose their allergy if not re-exposed to the drug for a period of time [17••]. Based on a small number of studies of patient with IHR to fluoroquinolones who underwent graded challenge with the culprit drug, most patients tolerated the drug upon re-exposure. Unfortunately, the time elapsed between the reaction and challenge was not specified [18, 19].

Manifestations of quinolone allergy

Characteristic IHR to quinolones, induced by IgE-mediated and non-IgE-mediated mast cell degranulation, include urticaria with or without angioedema (31.6–85%), anaphylaxis (32.8–42.1%), and shock (13–26.3%) [2•]. Among the quinolones, moxifloxacin has been reported to have the highest incidence of IHR. Urticaria was more frequently observed, at a rate of 31.6–85% for patients on moxifloxacin, than anaphylaxis, which was reported at a rate of 13–42% [20]. Another study confirmed that urticaria is the most common clinical manifestation of IHR to quinolones [16]. However, even type I Kounis syndrome has been described, which is characterized by histamine-induced coronary artery spasm as a consequence of extensive vasodilation and low cardiac output [21].

Giavina-Bianchi and colleagues recently reported a case of a woman with recurrent severe anaphylaxis over a 7-year period. The first three reactions were due to stinging insects, while the other two were induced by ciprofloxacin. The authors observed flushing, laryngeal edema, and syncope in the episodes of anaphylaxis to ciprofloxacin. Only after 7 years from the first anaphylaxis, the patient had the diagnoses of indolent systemic mastocytosis, a disease associated with anomalous proliferation and accumulation of mast cells in different tissues and which has a lifetime anaphylaxis risk of 50%. The authors suggested that the excess of mast cells and their MRGPRX2 receptors in patients with mastocytosis may be a risk for anaphylaxis induced by quinolones [12••].

Evaluation and diagnosis

The evaluation of drug HR typically begins with a thorough clinical history, which should include the details of the symptoms, the timing of the reaction in relation to the causative agent, the timing passed since the reaction, and any relevant substance ingestion, taken concurrently and/or since the reaction [22]. Additionally, the patient's current medication list, allergy history, and previous exposure to the same or any quinolone agent should be reviewed. A thorough

patient history can aid to identify a true HR, the type and severity of this reaction, and the need for diagnostic tests [22].

Evaluation for fluoroquinolones' allergy is not indicated in every patient, being more helpful in patient who report less severe IHR, such as pruritic rashes, urticaria, or angioedema, than full anaphylaxis, and who are likely to require fluoroquinolones in the future. After a complete clinical history, *in vivo* and *in vitro* tests are essential in the algorithm to assess quinolone allergy. In recent years, studies have evaluated several diagnostic tests, including skin tests, drug provocation tests (DPT), and laboratory tests [1, 23, 24]. Skin testing and *in vitro* tests have displayed low sensitivity and specificity, limiting their diagnostic utility. Also, it is advisable, if possible, to wait 4–6 weeks to perform skin testing or drug challenge after an episode of anaphylaxis [17, 18].

Skin testing

The value of skin testing remains a subject of debate. Its utility is controversial due to both unknown sensitivity and a high rate of false-positive results because of irritant and histamine-releasing effects. Most studies showed that quinolones can induce false-positive results due to the capacity of some quinolones to activate mast cells, inducing histamine release [7, 18]. It is also important to note that late or delayed reactions can occur with intradermal skin tests and should always be assessed [24].

Regarding IHR, skin testing generally begins with skin prick test (SPT) followed by intradermal test (IDT) in the case the SPT is negative. Several authors have investigated optimal concentrations for IDT by looking for non-irritant concentrations; however, the studies give contradictory results [25–28].

For moxifloxacin, non-irritant concentrations for SPT vary between 1 and 20 mg/mL, and for IDT between 0.004 and 0.05 mg/mL [18, 29]. The best concentration of moxifloxacin for use in skin testing is not entirely clear. A study using 3 concentrations of a parenteral formulation of moxifloxacin hydrochloride in the IDT found positive results in 10/14 patients and in 12/16 controls tested. Two patients tested positive at the 1:1000 dilution, two patients at the 1:100 dilution, and six patients at the 1:10 dilution. Of the 16 controls, two tested positive at the 1:100 dilutions and 12 individuals at the 1:10 dilution. Sensitivity and specificity of IDT calculated in this population were 57% and 12%, respectively. Positive and negative predictive values were 36% and 25%, respectively [30].

Performing IDT with ciprofloxacin in normal volunteers with 1/10, 1/50, and 1/100 dilutions of the 2 mg/mL ciprofloxacin regular solution, false-positive test results were observed 100%, 31%, and 0% of the time, respectively. Therefore, if the aim of skin testing is good specificity, we should use the 1/100 dilution to perform IDT with ciprofloxacin. However, there are not enough data with real allergic patients to ciprofloxacin showing that the 1/100 dilution has good sensitivity to diagnose allergic reactions. Other studies suggest the use of lower concentrations in the IDT, but this, according to our experience, is not necessary. On the other hand, higher concentrations may be irritative, inducing false-positive test results, and they should not be used [31].

A small number of studies provide information about the utility of skin testing to identify patients at risk of quinolones IHR. In the largest study, fluoroquinolone SPT had a negative predictive value of 93%, sensitivity of 50%, and specificity of 93% [18].

In vitro tests

Development of in vitro tests is important due to the low specificity of skin testing and to be used in severe cases of life-threatening IHR. The most common in vitro tests that have been used with promising results in the diagnosis of IHR to quinolones are radioimmunoassays (RIA) and basophil activation tests (BAT) [6, 32]. These tests are recommended to be performed prior to the in vivo tests in high-risk patients, including patients with history of life-threatening reactions [2, 33].

RIA for quinolone IgE-mediated allergy have presented low sensitivity, varying from 31.6 to 54.5%, and high specificity. Higher serum-specific IgE levels were found in patients evaluated within a few months after the IHR, while patients showing negative results were generally evaluated after a longer time [2]. Studies have shown the utility of BAT for evaluating quinolone-allergic reactions, with sensitivity ranging from 50 to 100%, which can be explained by several factors such as patient's medication therapy, the quinolone involved in the reaction, the quinolone used in the test, and the choice of basophil activation markers used during the test [33••]. Ciprofloxacin showed higher sensitivity than moxifloxacin in the BAT, even in the cases where moxifloxacin was the culprit drug. These findings may be due to moxifloxacin being more sensitive to ambient laboratory light than ciprofloxacin, generating higher drug photodegradation [7]. When moxifloxacin was the culprit drug, addition of other quinolone to the tests increased the sensitivity of BAT from 41.7 to 79.2%, and of specific IgE from 17 to 29.2%.

Patients developing IHR to moxifloxacin may only show positive in vitro tests to ciprofloxacin, which was introduced on the market earlier and might be the original sensitizer. Therefore, patients with positive in vitro tests only to ciprofloxacin should be considered allergic to moxifloxacin [7].

Drug provocation test

DPT is considered the "gold standard" for establishing or excluding the diagnosis of quinolone allergy, but the test is time consuming, associated with costs, and involves the risk of induction of new severe reactions. They are also useful to choose an alternative quinolone and to evaluate cross-reactivity in patients who have skin test or in vitro test positive to a specific quinolone [2].

DPT must be performed by trained personnel in a clinical setting, where rapid and adequate treatment can be administered if a reaction occurs [34]. Doses and the number of steps used in DPT vary depending on the study, ranging from a single dose [3] to escalating doses until the therapeutic dose is achieved [2•]. Fluoroquinolone-graded challenge typically starts with 1/100 or 1/1000 of the full dose and includes two to four steps until the full dose is reached. The degree of caution is determined by the patient's risk stratification, including the severity of the initial reaction and the time elapsed since the reaction [18].

The need of DPT in quinolone IHR evaluation is verified given that only 7–32% of suspected immediate and delayed HR to quinolone, which underwent DPT, were confirmed [18, 19], showing that clinical history alone may be inaccurate to identify true quinolone IHR and can lead to over-diagnosis. Moreover, a loss of sensitivity to drugs over time has been observed for IgE-mediated HR, as has been reported in IHR to beta-lactams, dypirone, and neuromuscular blocking agents [2•]. Therefore, the time elapsed between the suspected HR and the allergological evaluation should be as short as possible to avoid false-negative results.

Cross-reactivity

The presence of cross-reactions between quinolones in IHR remains a controversial issue. Cross-reactivity might be associated with the common quinolone structure, a 4-oxo-1, 4-dihydroquinoline ring core that may act as the major antigenic determinant, although the structure of groups bound in the C1, C5, C7, and C8 positions may also play a role [2•]. In IHR, a high degree of cross-reactivity has been reported between the first- (nalidixic acid) and second-generation (norfloxacin and ciprofloxacin) quinolones. Cross-reactivity among quinolones from the second generation does not always occur despite their similar chemical structures. Differences in reactivity patterns may be due to the production of different metabolites [2, 35, 36]. Cross-reactivity between the newer (moxifloxacin) and the second- (ciprofloxacin) and third-generation (levofloxacin) quinolones has been suggested to be lower [2, 20]. In relation to levofloxacin, a low degree of cross-reactivity with ciprofloxacin has been observed [37].

The report of three cases of IHRs to moxifloxacin showed a lack of cross-reactivity among moxifloxacin and ciprofloxacin since all patients were able to tolerate the oral DPTs to ciprofloxacin as well as a full course of this drug. The lack of cross-reactivity may be explained by moxifloxacin's unique side chain [38]. Another study evaluated 12 patients who had IHR, including four anaphylaxis, after oral intake of quinolones. Most of the ciprofloxacin reactive patients tolerated levofloxacin, and most of the levofloxacin reactive patients tolerated ciprofloxacin. In addition, the patients who reacted to moxifloxacin tolerated ciprofloxacin and levofloxacin. This study highlighted the lack of cross-reactivity among quinolones and suggested levofloxacin as a safer alternative in cases of reaction to first-, second-, or fourth-generation quinolones [37].

Several studies have assessed cross-reactivity among quinolones, but few have evaluated cross-reactivity between quinolones and other classes of antibiotics. Furthermore, IHR to quinolones has also been associated with neuromuscular blocking agent (NMBA) sensitization. Quaternary ammonium specific IgE has been detected in 53% of patients with IHR to fluoroquinolones suggesting cross-reactivity with neuromuscular blocking agents [32]; however, the clinical relevance of this finding requires *in vivo* investigation. Similar to the NMBAs, quinolones can induce IHR during the first administration [32], suggesting a non-IgE-mediated reaction or that sensitization might be induced by another substance that shares a common antigenic determinant [2•].

Management

Quinolone IHR management is based on three essential principles: discontinuation of the offending agent, initiation of an alternative agent, and supportive care. Tolerance to another quinolone should be assessed if necessary, especially for patients without a good antibiotic alternative for the case [2•]. It must be taken into account that cross-reactivity between quinolones is still not fully known due to the lack of robust studies published so far. When a given quinolone is the only therapeutic option available, desensitization may be required. Few cases of desensitization in patients with IHR induced by ciprofloxacin and confirmed by DPT or skin tests have been reported [2, 39, 40].

Conclusions

Quinolones are the second most common antibiotic class associated with IHRs, which may be IgE-mediated or not. The prevalence of true quinolone allergy still remains unknown, but its incidence has increased in recent decades, probably due to the extensive utilization of this antibiotic class and the introduction of moxifloxacin.

The description of a novel mechanism of drug-induced mast cell degranulation through the MRGPRX2 receptor modified the current management of drug IHR, and quinolones should be avoided by patients with a known history of mastocytosis. Quinolones IHR diagnosis is complex, since clinical history is often doubtful, skin tests can induce false-positive results, and *in vitro* tests are not well validated. Therefore, in many cases, the only way to confirm or rule out the diagnosis is DPT, a procedure that carries some risks.

Quinolones present a variable degree of cross-reactivity that is unclear and difficult to predict, and desensitization may be required in patients with no other antibiotic options. Further studies assessing quinolones allergy are needed to increase the knowledge in the field and to improve patients' management.

Compliance with ethical standards

Conflict of interest

Nathalia Coelho Portilho, Marcelo Vivolo Aun, Jorge Kalil, and Pedro Giavina-Bianchi declare that they have no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. • McGee EU, et al. Quinolone allergy. Pharmacy (Basel). 2019
Enlightening review regarding quinolone allergy.
2. • Doña I, et al. Update on Quinolone Allergy. Curr Allergy Asthma Rep. 2017;17:56
Enlightening review regarding quinolone allergy.
3. European Medicines Agency-Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolones antibiotics. EMA/ 795349/2018.
4. • Blanca-Lopes N, et al. Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved. Clin. Exp. Allergy. 2013;43:560–7
Epidemiologic study of quinolone allergy.
5. Wall GC, Taylor MJ, Smith HL. Prevalence and characteristics of hospital inpatients with reported fluoroquinolone allergy. Int J Clin Pharm. 2018;40:890–4.
6. Salas M, Barrionuevo E, Fernandez TD, Ruiz A, Andreu I, Torres MJ, et al. Hypersensitivity reactions to fluoroquinolones. Curr Treat Opt Allergy. 2016;3:129–46.
7. • Aranda A, Mayorga C, Ariza A, Dona I, Rosado A, Blanca-Lopez N, et al. In vitro evaluation of IgE-mediated hypersensitivity reactions to quinolones. Allergy. 2011;66:247–54
Study evaluating *in vitro* tests in the diagnosis of allergy to quinolones.
8. Johannes CB, Ziyadeh N, Seeger JD, Tucker E, Reiter C, Faich G. Incidence of allergic reactions associated with antibacterial use in a large, managed care organisation. Drug Saf. 2007;30:705–13.
9. Sullivan TJ, Ong RC, Gilliam LK. Studies of the multiple drug allergy syndrome. J Allergy Clin Immunol. 1989;83:270.
10. Demir S, Unal D, Olgac M, Akdeniz N, Aktas-Cetin E, Gelincik A, et al. An unusual dual hypersensitivity reaction to moxifloxacin in a patient. Asia Pac Allergy. 2018;8:e26.
11. Salvo F, Polimeni G, Cutroneo PM, et al. Allergic reactions to oral drugs: a case/non-case study from an Italian spontaneous reporting database (GIF). Pharmacol Res. 2008;58(3–4):202–7.
12. •• Giavina-Bianchi P, Gois Gonçalves D, Zanandrea A, Borges de Castro R, Sabino Garro L, Kalil J, et al. Anaphylaxis to quinolones in mastocytosis: hypothesis on the mechanism. J Allergy Clin Immunol Pract. 2019;7:2089–90
Case report assessing the mechanism of hypersensitivity reaction to quinolones.
13. Weiler CR. Mastocytosis, Quinolones, MRGPRX2, and Anaphylaxis. J Allergy Clin Immunol Pract. 2019.
14. •• Liu E, et al. Mast cell-mediated hypersensitivity to fluoroquinolones is MRGPRX2 dependent. Int Immunopharmacol. 2019;70:417–27
Study assessing the mechanism of mast cell activation by quinolones.
15. Holowka D, Wilkes M, Stefan C, Baird B. Roles for Ca²⁺ mobilization and its regulation in mast cell functions: recent progress. Biochem Soc Trans. 2016;44(2):505–9.
16. Kulthanan K, Chularojanamontri L, Manapajon A, Dhana N, Jongjarearnprasert K. Cutaneous adverse reactions to fluoroquinolones. Dermatitis. 2011;22:155–60.
17. •• Manfredi M, Severino M, Testi S, Macchia D, Ermini G, Pichler WJ, et al. Detection of specific IgE to quinolones. J Allergy Clin Immunol. 2004;113(1):155
Study evaluating specific IgE in the diagnosis of allergy to quinolones.
18. Seitz CS, Bröcker EB, Trautmann A. Diagnostic testing in suspected fluoroquinolone hypersensitivity. Clin Exp Allergy. 2009 Nov;39(11):1738–45.
19. •• Venturini DM, Lobera LT, Del Pozo G, Blasco AS, González MI. In vivo diagnostic tests in adverse reactions to quinolones. J Investig Allergol Clin Immunol. 2007;17(6):393–8
Study evaluating *in vivo* tests in the diagnosis of allergy to quinolones.
20. Blanca-Lopez N, Andreu I, Torres Jaen MJ. Hypersensitivity reactions to quinolones. Curr Opin Allergy Clin Immunol. 2011;11:285–91.
21. Nunez G, Marmol A, Villarejo B, Vergara S, Gonzalez E, Ariza R. Kounis syndrome after levofloxacin intake: a clinical report and cross-reactivity study. J Investig Allergol Clin Immunol. 2016;26:335–6.
22. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. Lancet. 2019;393:183–98.
23. Valdivieso R, Pola J, Losada E, Subiza J, Armentia A, Zapata C. Severe anaphylactoid reaction to nalidixic acid. Allergy. 1988;43:71–3.
24. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57:45–51.
25. Barbaud A, Trechot P, Reichert-Penetrat S, Commun N, Schmutz JL. Relevance of skin tests with drugs in investigating cutaneous adverse drug reactions. Contact Dermatitis. 2001;45(5):265–8.
26. Broz P, Harr T, Hecking C, et al. Nonirritant intradermal skin test concentrations of ciprofloxacin, clarithromycin, and rifampicin. Allergy. 2012;67(5):647–52.

27. Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol*. 2003;112(3):629–30.
28. Scherer K, Bircher AJ. Hypersensitivity reactions to fluoroquinolones. *Curr Allergy Asthma Rep*. 2005;5(1):15–21.
29. Sanchez-Morillas L, Rojas Perez-Ezquerro P, Reano-Martos M, Laguna-Martinez JJ, Gomez-Tembleque P. Systemic anaphylaxis caused by moxifloxacin. *Allergol Immunopathol*. 2010;38(4):226–7.
30. Uyttebroek AP, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Moxifloxacin hypersensitivity: uselessness of skin testing. *J Allergy Clin Immunol Pract*. 2015;3(3):443–5.
31. Giavina-Bianchi P, Gonçalves DG, Borges de Castro R, Zanandrea A, Weiler CR. *J Allergy Clin Immunol Pract*. 2020;8(1):426–7.
32. Rouzaire P, Nosbaum A, Mullet C, et al. Immediate allergic hypersensitivity to quinolones associates with neuromuscular blocking agent sensitization. *J Allergy Clin Immunol Pract*. 2013;1(3):273–9 e1.
- 33.●● Fernandez TD, Ariza A, Palomares F, Montanez MI, Salas M, Martin-Serrano A, et al. Hypersensitivity to fluoroquinolones: the expression of basophil activation markers depends on the clinical entity and the culprit fluoroquinolone. *Medicine*. 2016;95:e3679
- Study evaluating BAT in the diagnosis of allergy to quinolones.
34. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy*. 2003;58(9):854–63.
35. Alonso MD, Martin JA, Quirce S, Davila I, Lezaun A, Sanchez CM. Fixed eruption caused by ciprofloxacin with cross-sensitivity to norfloxacin. *Allergy*. 1993;48(4):296–7.
36. Lozano Ayllon M, Gomez Martinez M, Mosquera MR, Laguna Martinez JJ, Orta Martiartu M. Fernandez de Miguel C. fixed eruption caused by ciprofloxacin without cross-sensitivity to norfloxacin. *Allergy*. 1995;50(7):598–9.
37. Lobera T, Audicana MT, Alarcon E, Longo N, Navarro B, Munoz D. Allergy to quinolones: low cross-reactivity to levofloxacin. *J Investig Allergol Clin Immunol*. 2010;20(7):607–11.
38. Chang B, Knowles S, Weber E. Immediate hypersensitivity to moxifloxacin with tolerance to ciprofloxacin: report of three cases and review of the literature. *Ann Pharmacother*. 2010;44:740–5.
39. Lantner RR. Ciprofloxacin desensitization in a patient with cystic fibrosis. *J Allergy Clin Immunol*. 1995;96(6 Pt 1):1001–2.
40. Erdem G, Staat MA, Connelly BL. Anaphylactic reaction to ciprofloxacin in a toddler: successful desensitization. *Pediatr Infect Dis J*. 1999;18:563–4.

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