

Update on Quinolone Allergy

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Abstract

Purpose of Review Quinolones are a group of synthetic antibiotics widely use as first-line treatment for many infections. There has been an increase in the incidence of hypersensitivity reactions to quinolones in recent years, likely due to increased prescription. The purpose of this review is to summarize the

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clinical pictures, the methods used for diagnosing and the management of allergic reactions to quinolones.

Recent Findings Allergic reactions to quinolones can be immediate or delayed, being anaphylaxis and maculopapular exanthema respectively the most frequent clinical entities. A precise diagnosis is particularly difficult since clinical history is often unreliable, skin tests can induce false-positive results, and commercial in vitro test are not well validated. Therefore, drug provocation testing is considered the gold standard to establish diagnosis, which is not a risk-free procedure. Cross-reactivity between quinolones is difficult to predict due to the small number of patients included in the few published studies. Moreover, hypersensitivity to quinolones has also been associated with beta-lactam and neuromuscular blocking agent allergies, although further studies are needed to understand the underlying mechanisms. Avoidance of the culprit quinolone is indicated in patients with a diagnosis of hypersensitivity to these drugs. When quinolone treatment is the only therapeutic option available, desensitization is necessary.

Summary This review summarizes the complex diagnostic approach and management of allergic reactions to quinolones.

Keywords Anaphylaxis · Basophil activation test · Drug provocation test · Maculopapular exanthema · Quinolone · Skin test

Abbreviations

AGEP	Acute generalized exanthematous pustulosis
BAT	Basophil activation test
DR	Delayed reactions
DPT	Drug provocation test
ELISA	Enzyme-linked immunosorbent assay
FDE	Fixed drug eruption
IR	Immediate reactions

IDT	Intradermal test
MPE	Maculopapular exanthema
NMBA	Neuromuscular blocking agent
RAST	Radioallergosorbent test
SPT	Skin prick test
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis

Introduction

Quinolones are a group of synthetic antibiotics with a wide range of activities against both gram-negative and gram-positive bacteria [1]. In recent years, there has been a large increase in the use of quinolones as first-line treatment, especially in immunocompromised patients which are susceptible for bacterial infections [2, 3]. The most widely used members of this group of antibiotics are the fluoroquinolones, being ciprofloxacin, the most frequently used worldwide [1].

Quinolones are generally well-tolerated antibiotics; however, adverse effects have been reported, including hypersensitivity reactions. In the last few decades, there has been an increase in the incidence of hypersensitivity reactions to quinolones [4], some of which have been severe, including anaphylactic reactions, acute exanthematic reactions, and toxic epidermal necrolysis (TEN) [5]. This increase in incidence of hypersensitivity reactions to quinolone is likely due to an increased prescription of these drugs as first-line treatment [2, 3].

Classification and Chemical Structure of Quinolones

The first quinolone antibiotic drugs were developed in the 1960s, namely nalidixic acid and cinoxacin. Their basic structure is formed by a bicyclic skeleton; the carboxylic acid and ketone groups at the 3 and 4 positions, respectively, are essential for their pharmacological activity (Fig. 1a). In order to improve their antibacterial spectra, modification by means of introduction of a fluorine atom in the chemical structure yielded the so-called fluoroquinolones. Thus, it has been established that a cyclopropyl group at position 1, a piperazinyl ring at C-7 and a halogen atom (generally fluorine) at C-6, and to a lower extent at C-8 enhance the antibacterial activity of these antibiotics.

Quinolones can be classified by different criteria: chemical structure, antibacterial spectra, and pharmacokinetic features. In this review, they are classified according to generation, which correlates with their antibacterial spectra [6] (Fig. 1b). The first generation agents display narrower spectra than the later ones.

Epidemiology and Risk Factors for Quinolone Allergy

Although hypersensitivity reactions to quinolones are considered unusual [7], their incidence has been rising, and they are now the non-beta-lactam antibiotics most frequently involved in drug hypersensitivity [4, 7, 8•] and the third leading cause of confirmed hypersensitivity to drugs [4]. Among hospitalized patients, quinolones are the second most frequent antibiotics reported in allergy/intolerance alerts [9]. This is likely due to their increased prescription and the introduction of moxifloxacin [7], which has been shown to be the most frequent trigger of quinolone reactions, followed by ciprofloxacin and levofloxacin [10••]. Most hypersensitivity reactions to quinolones are immediate reactions (IR), which are IgE-mediated. Importantly, reactions are severe for 70% of cases [10••, 11•, 12••].

On the basis of spontaneous reports of anaphylaxis induced by quinolones, in the last decades there has been an increase in the total number of cases of anaphylaxis [11•], with an estimated incidence of 1.8–2.3 per 10,000,000 days of treatment [7] and representing 4.5% of drug-induced anaphylaxis [13]. Although all quinolones have been implicated in anaphylaxis, moxifloxacin has been shown to be the most common culprit [14], followed by levofloxacin and ciprofloxacin [11•, 12••, 15]. Moreover, reactions induced by moxifloxacin were more severe, with 75% of reactions including anaphylaxis or anaphylactic shock [12••]. Though less common than IR, delayed reactions (DR), which are T cell-dependent reactions, have also been reported [16, 17, 18•, 19–22]. In this case, ciprofloxacin is the most frequent culprit drug, followed by levofloxacin and moxifloxacin [15, 23, 24].

Considering risk factors, it has been reported that 21% of penicillin-allergic patients develop allergy to non-beta-lactam antibiotics such as quinolones, compared to just 1% of those who are not penicillin allergic [25]. In fact, a previous diagnosis of IR to beta-lactam antibiotics has been shown to be a strong risk factor for developing quinolone allergy (OR 23.654; 95% CI 1.529–365.853; $p = 0.024$) [10••]. This is especially relevant for immunocompromised patients, as the prohibition of two groups of first-line antibiotics may worsen the prognosis. It is unclear whether this is due to an inherent predisposition to developing allergy or because patients diagnosed as allergic to beta-lactams are more likely to be prescribed quinolone [10••]. Moxifloxacin has been shown to increase the odds of suffering an IR by fourfold compared to those of other drugs (odd ratio [OR] 4.20; 95% confidence interval [CI] 3.19–5.55) [14]. However, ciprofloxacin has been associated with a higher risk of developing severe cutaneous DR (OR 6.9; 95% CI 1.8–27) [26] compared with those of other drugs; norfloxacin, ofloxacin, and ciprofloxacin have been associated with a higher risk of acute generalized exanthematous pustulosis (AGEP) (OR 33; 95% CI 8.5–127) [27] compared to that of other quinolone.

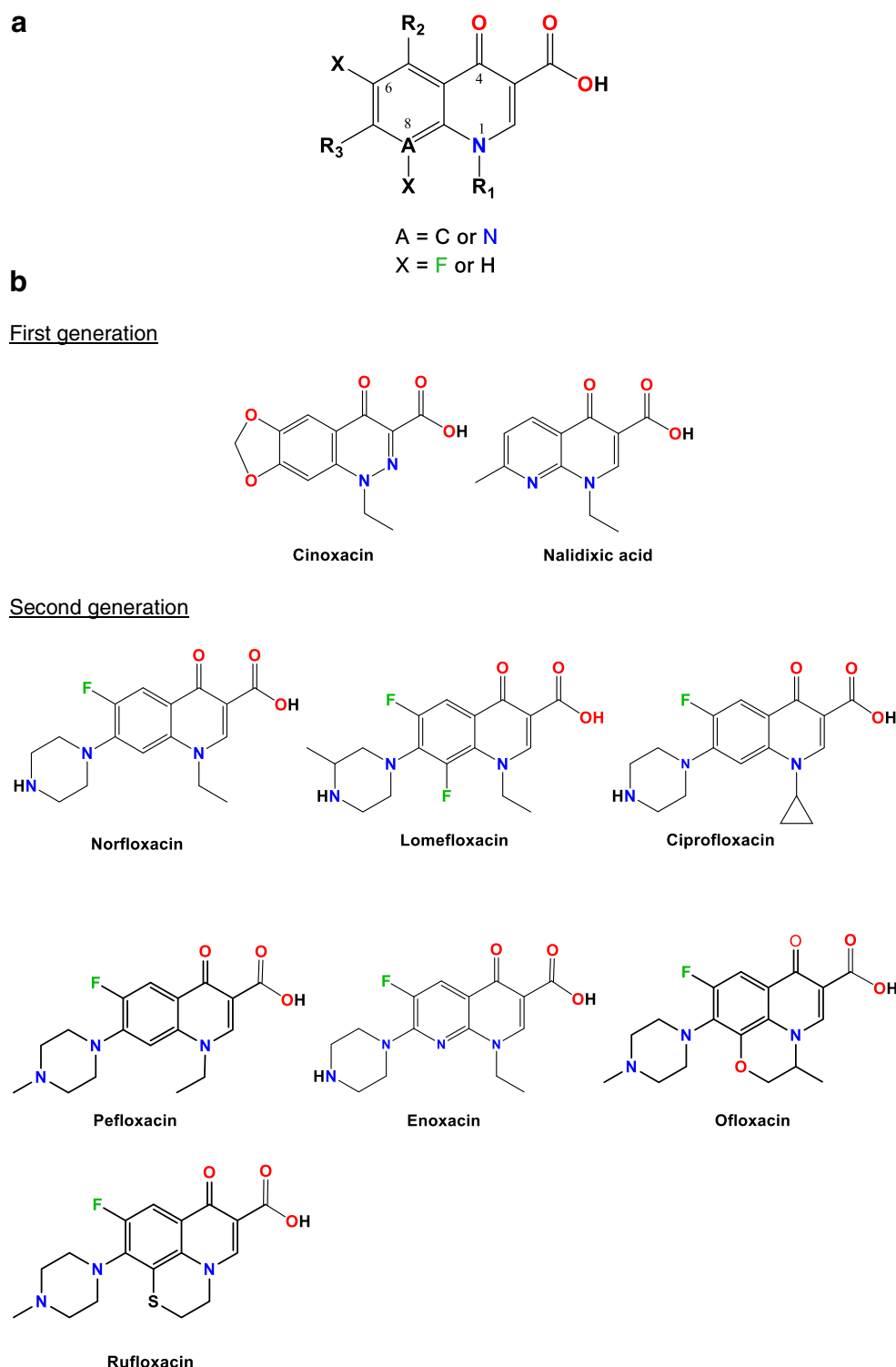


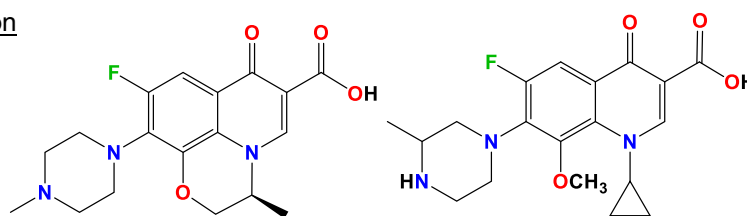
Fig. 1 **a** General chemical structure of quinolones. **b** Classification of quinolones by antibacterial spectra

The Clinical Picture

Allergic reactions to quinolones can be classified as IR if they appear within 1 h after drug intake, and DR if they appear more than 1 h after drug intake. Most published studies

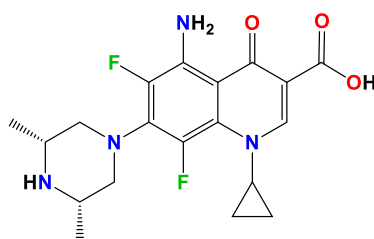
reporting IR after quinolone administration are case reports or small series [5, 16, 17, 18•, 19–21, 27–35].

Clinical entities typical for IR are urticaria with or without angioedema (31.6–85%), anaphylaxis (32.8–42.1%), and shock (13–26.3%) [35, 36••]. Any quinolone may be

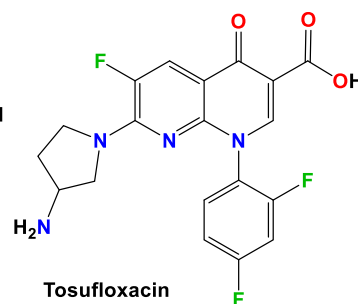
Third generation

Levofloxacin

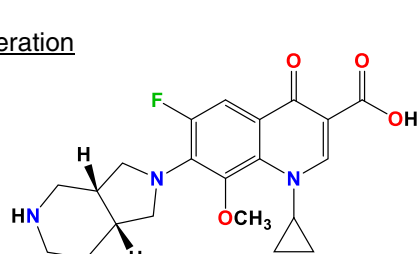
Gatifloxacin



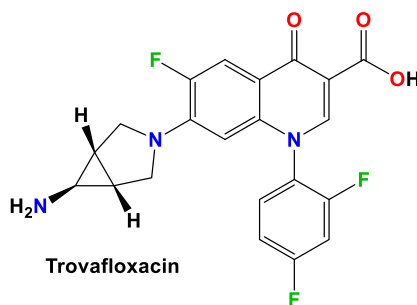
Sparfloxacin



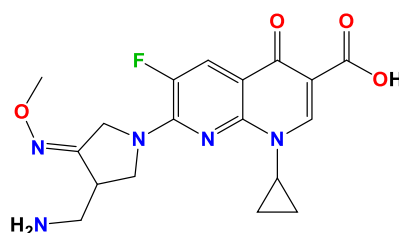
Tosufloxacin

Fourth generation

Moxifloxacin



Trovafloxacin



Gemifloxacin

Fig. 1 (continued)

involved, however, the most common triggers are ciprofloxacin (23.2–43.7%), moxifloxacin (15.4–63.2%), and levofloxacin (7.9–38.5%) [8•, 12••, 34, 35, 36••].

DR to quinolones is less common. Maculopapular exanthems (EMP), normally not severe [34], and fixed drug eruption (FDE) [22, 37, 38] are the most commonly reported reactions [18•, 34, 35, 39]. Quinolones are one of the most common drugs inducing photo allergy, representing up to 38% of cases [40]. DR can also include other less frequent entities, such as AGEP [41], Stevens-Johnson syndrome (SJS), and TEN [19, 42], hematologic disorders and organ-specific reactions [27]. The most

frequently involved quinolone in DR are ciprofloxacin, followed by moxifloxacin, ofloxacin, and levofloxacin [18•, 34, 35].

Diagnostic Procedures

Diagnosis can be performed based on clinical history and *in vivo* and *in vitro* testing. However, these methods have serious limitations and a precise diagnosis can be difficult.

Clinical History

The most reliable initial approach for evaluating allergic reactions to quinolones is a detailed clinical history (Fig. 2). This must be obtained carefully and should include the symptomatology and chronology of the symptoms (including the latency period between the last dose and the onset of symptoms and time of resolution). The time interval between both the first and last dose and the occurrence of the reaction is useful for classifying reactions as IR or DR. Other important details are as follows: age, sex, personal history of atopy and documented hypersensitivity to other drugs, family history of drug allergy, other medications taken simultaneously, how long the patient was taking the culprit drug before the reaction occurred, the last time the patient tolerated any type of quinolones, and whether the patient had previous episodes of reactions to the same drug or others belonging to the same group. The ENDA/EAACI questionnaire can be very useful to ensure these data are recorded in a uniform format [43].

However, the clinical history can be imprecise in many cases, especially when the time elapsed between the reaction and evaluation is prolonged. In this case, other diagnostic methods are needed to achieve diagnosis: skin tests, in vitro tests, and drug provocation testing (DPT).

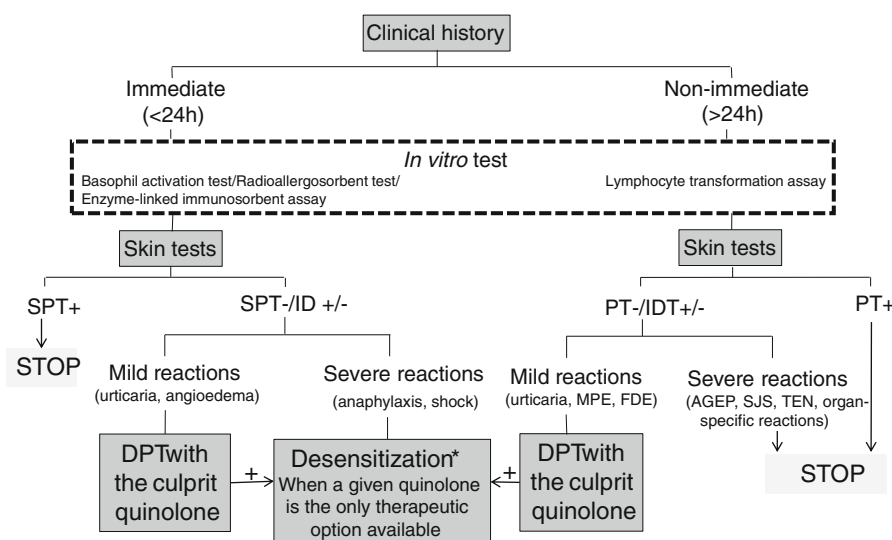
Skin Tests

Skin tests may be used for the evaluation of suspected quinolone reaction (Fig. 2); although, its utility is controversial due to both a low sensitivity and a high rate of false-positive

results because of irritant and histamine-releasing effects [27, 34, 36••, 44, 45].

For IR, the procedure generally begins with skin prick testing (SPT). If this is negative, intradermal testing (IDT) is used. SPT often gives false-negative results, while IDT can give false-negative results at low concentrations and false-positive results at high concentrations. Several authors have investigated optimal concentrations for IDT by looking for non-irritant concentrations; however, the studies give contradictory results. Barbaud et al. suggest 0.2 mg/mL for IDT with ciprofloxacin and 5 mg/mL for ofloxacin [46]. Broz et al. recommended an IDT of 1:300 to 1:1000 for ciprofloxacin [47]. In contrast, Empedrad et al. found a 100-fold dilution as always irritant in the non-sensitized control group [44]. They observed considerable variability in the response to ciprofloxacin and were unable to identify a definitive nonirritant concentration. Scherer et al. yielded $2 \text{ mg/mL} \times 10^{-3}$ as optimal threshold concentration for non-irritant IDT with ciprofloxacin [27]. Seitz et al. also found positive reactions in controls with concentrations ranging from 0.0002 to 0.2 mg/mL [34]. In the case of levofloxacin, Empedrad et al. suggested an IDT concentration of $25 \text{ mg/mL} \times 10^{-3}$ [44]. 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 [5, 31, 34]. However, some studies did not include controls and the majority was restricted to small numbers of cases. In a recent study, Uyttebroek et al. found positive IDT results in 10/14 patients and in 12/16 controls tested with a parenteral formulation of moxifloxacin hydrochloride. Two patients tested positive at the 1:1000 dilution, two

Fig. 2 Algorithm for the diagnosis and management of patients reporting hypersensitivity reactions to quinolones. *SPT* skin prick test, *IDT* intradermal test, *PT* patch test



* DPT with an alternative quinolone can be carried out if necessary according to the scarce evidence published:

- If **nalidixacid** is the culprit: DPT with levofloxacin or moxifloxacin
- If **second-generation** is the culprit: DPT with another different second-generation, levofloxacin and moxifloxacin
- If **levofloxacin** is the culprit: DPT with ciprofloxacin and moxifloxacin
- If **moxifloxacin** is the culprit: DPT with ciprofloxacin and levofloxacin

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 [42]. Sensitivity and specificity of IDT calculated in this population were 57 and 12%, respectively. Positive and negative predictive values were 36 and 25%, respectively.

The evaluation of DR is usually performed by delayed-reading IDT and patch tests [48]. These can be useful for diagnosing AGEF [41]. However, in most published cases of quinolone-induced FDE, patch tests were negative [37, 38]. Only one case report involved a positive patch test on areas of previous lesions [22]. In a retrospective study, Brajon et al. found that commercially available preparations of different quinolones diluted to 30% in water or petrolatum were non-irritant [49]. To detect photoallergic reactions, photopatch tests with UVA light can be used [50]. Moreover, scarification of the skin prior to photopatch testing to enhance drug penetration has been suggested to increase sensitivity [27]. Studies of the role of patch tests or IDT in DR to quinolones have shown contradictory results. Sensitivity ranges widely depending on the symptomatology of the reaction, diagnostic test used (IDT or patch tests), drug concentration, drug vehicle used in patch tests (petrolatum, dimethyl sulfoxide, etc.) and if the test is only performed on unaffected skin (or previously affected skin in FDE). Regarding delayed-reading IDT, 80% of quinolone allergic subjects have been reported to give positive test results, although the possibility of an irritant response cannot be ruled out [35]. It has been shown to be positive in 60% of cases with delayed-urticaria or MPE, and 66.6% of which were ultimately confirmed as allergic [35]. Regarding patch tests, results vary depending on the study; positivity of allergic subjects can range from 0 to 50% [34].

In Vitro Tests

There are currently no validated commercial in vitro tests for the evaluation of quinolone allergy. Therefore, most tests are produced in-house. The two main in vitro methods are as follows: basophil activation test (BAT) and immunoassay (radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA)).

Several studies looked at the detection of quinolone-specific serum IgE using RAST, obtaining a high specificity, although sensitivity was low, ranging from 30 to 55% [12•, 36•]. The variation in sensitivity can be attributed to the type of allergic reaction that was studied as well as the quinolone investigated. It should be taken into account that a loss of sensitivity to drugs over time has been reported for IgE-mediated hypersensitivity reactions to beta-lactams [51], dypirone [52], and neuromuscular blocking agents [53]. Therefore, it is possible that patients may give negative results

for quinolones too, if they are evaluated after a longer time period [36•].

BAT has also been employed for diagnostic purposes for hypersensitivity reactions to quinolones. Very diverse results have been reported regarding sensitivity and reliability [12•, 29, 54, 55]. One study exhibited a sensitivity of around 70% and gave positive results for 69% of cases with severe reactions [12•], whereas in another study, all patients studied showed negative results [29]. These differences may be due to differences in the culprit quinolone and the hypersensitivity reaction involved.

It therefore appears that quinolone-specific IgE and BAT are potentially useful for the diagnosis of immediate drug hypersensitivity reactions to quinolones; however, their predictive value is far from absolute [56]. They may be of some use for deciding whether to carry out quinolone DPT in allergic patients, and perhaps future work may see improvements; however, it should be pointed out that one recent study proposed that due to potential unreliability, DPT is currently necessary to identify the culprit quinolone [57].

Regarding BAT sensitivity, ciprofloxacin shows a higher sensitivity than moxifloxacin, even in the cases where moxifloxacin is the culprit drug [12•]. These findings are due to moxifloxacin being more sensitive to ambient laboratory light than ciprofloxacin during the performance of BAT, generating higher drug photodegradation, and therefore, lower amounts of drug-protein conjugates [58]. It is known that quinolones, in particular fluoroquinolones, can cause photoallergy. This is due to their photohaptenic properties; they can bind covalently to proteins upon UVA exposure, leading to immunological reactions. It has been shown that peripheral blood mononuclear cells photomodified with quinolones by means of UVA light were able to stimulate cell proliferation [59, 60].

In the particular case of photoallergic reactions, cross-reactivity among 6-fluoroquinolones has been demonstrated using a murine model [61]. An enhanced expansion of CD4⁺TCRVβ13⁺ Th1 cells was found after in vitro stimulation of immune lymph node cells with fluoroquinolones-photomodified cells, suggesting the presence of a common epitope recognized by fluoroquinolone-specific T cells, probably the piperazinyl ring at position 7 present in several fluoroquinolones such as enoxacin, norfloxacin, ciprofloxacin, and lomefloxacin.

Regarding DR, studies using the in vitro lymphocyte transformation assay have been reported, confirming T cell involvement in MPE and AGEF pathogenesis [18•, 27, 59]_ENREF_27. This technique has a higher sensitivity than patch testing, which may be in due to the complex inflammatory response in the skin, a low quinolone penetration capability through the skin or sub-optimal quinolone concentrations [18•, 62].

Drug Provocation Testing

DPT is considered the gold standard to establish or exclude the diagnosis of hypersensitivity to quinolone when no other test is available. It is also useful to choose an alternative quinolone if diagnosis is confirmed [35, 63] and to evaluate cross-reactivity in patients who are skin test or in vitro test positive (Fig. 2) [10••].

DPT should only be considered after balancing the risks and benefits for the individual patient [34], as it is not a risk-free procedure. It must be performed by trained personnel in a clinical setting, where rapid and adequate treatment can be administered if a reaction occurs [63].

DPT is usually performed in a single-blind placebo-controlled manner, although in some cases, a double-blind procedure may be necessary [63]. 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 [6, 10••, 26].

The necessity of DPT for quinolone hypersensitivity evaluation is clear given that only 7–32% of suspected IR and DR to quinolone who underwent DPT could be confirmed as allergic [34, 35], indicating that clinical history alone is often an unreliable indicator of true quinolone hypersensitivity and can lead to over-diagnosis. Moreover, a loss of sensitivity to drugs over time has been reported for IgE-mediated hypersensitivity reactions, as has been shown in immediate reactions to beta-lactams [51], dypirone [52], and neuromuscular blocking agents [53]. Therefore, the time interval between the suspected hypersensitivity reaction and the allergological study should be as short as possible to avoid false-negative results.

Cross-Reactivity

Cross-Reactivity Between Quinolones

The presence of cross-reactivity between quinolones remains a controversial issue. It has been suggested to be associated with the common quinolone structure, a 4-oxo-1,4-dihydroquinoline ring core that may act as the antigenic determinant [64], although the structure of groups bound to the C1, C5, C7, and C8 positions may also play a role.

Different patterns of cross-reactivity have been established for IRs and DRs to quinolones, although most published studies assessing cross-reactivity are case reports or small studies with few subjects. In IR, a high degree of cross-reactivity has been reported between the first- (nalidixic acid) and second-generation (norfloxacin and ciprofloxacin) quinolone [28]. Cross-reactivity among quinolones from the second generation does not always occur [16, 33, 65] despite their similar chemical structures. Differences in reactivity patterns may be due to the production of different metabolites.

Similarly, cross-reactivity between the newer quinolones (moxifloxacin) and the second (ciprofloxacin) and third generation (levofloxacin) has been suggested to be lower [5, 7, 31, 32]. Regarding levofloxacin, a low degree of cross-reactivity with ciprofloxacin has been found [8•].

In vitro studies of IR to quinolones also suggest a high level of cross-reactivity. Using Sepharose-RAST, sIgE toward more than one quinolone was detected in 63.6–80% of cases, although only 16% of these patients reported a reaction to several quinolones [12••, 36••]. Regarding BAT, positive results from more than one quinolone have been found in 48.2% of cases [12••, 58]. BAT cross-reactivity in hypersensitivity reactions to moxifloxacin was observed to be higher than in hypersensitivity to ciprofloxacin since patients allergic to moxifloxacin were positive to ciprofloxacin in most cases, whereas patients were generally not positive to moxifloxacin when ciprofloxacin was the culprit drug. This suggests that IgE can recognize the chemical structure of ciprofloxacin despite the reaction being induced by moxifloxacin [12••]. Therefore, in vitro cross-reactivity may over represent true cross-reactivity based on DPT.

In DR, different grades of cross-reactivity between quinolones from different generation have been reported for the different clinical entities [42, 66, 67]. An evaluation of the recognition of ciprofloxacin-specific T cell clones from patients who have suffered MPE [18•] showed three main patterns: clones that reacted only to ciprofloxacin; others that reacted to two related quinolones, ciprofloxacin, and norfloxacin; and clones that reacted to up to five quinolones [19, 22, 65]. A study of photo-reactivity in a murine model of photo-allergy showed cross-reactivity between six fluoroquinolones for both in vivo and in vitro responses. This suggests that photo-haptens also share a common epitope that is recognized by T cells, particularly Th1 [60]. In vitro cross-reactivity studies seem to indicate that T cells recognize a common structure whereas IgE recognizes smaller components such as side chains or smaller groups, although with lower affinity [68].

Cross-Reactivity between Quinolones and Other Drugs

In addition to the cross-reactivity between different quinolones, an important issue is the presence of concomitant allergies to other non-chemically related drugs. It has been reported that in the case of IgE-mediated reactions, patients previously diagnosed as allergic to beta-lactams are more prone to develop allergy to non-beta-lactam antibiotics (21%) than those who were not allergic (1%) [69], being previously confirmed hypersensitivity to beta-lactams, a risk factor for the development of hypersensitivity to quinolones (OR: 23.654) [10••].

Moreover, IR to quinolones has also been associated with neuromuscular blocking agent (NMBA) sensitization. Quaternary ammonium sIgE has been detected in 53% of

patients with IR to fluoroquinolones suggesting cross-reactivity with neuromuscular blocking agents [70••]; however, the clinical relevance of this finding requires investigation *in vivo*. As with NMBAs, quinolones can induce IR after a single use [11•, 70••], suggesting that sensitization was induced by another component that shares a common antigenic determinant [11•].

Management

Avoidance of the culprit quinolone is indicated in patients with a diagnosis of hypersensitivity to these drugs. Tolerance to another quinolone should be assessed if necessary, especially for patients with a previous history of hypersensitivity to other antibiotics; for these patients, the therapeutic possibilities would otherwise decrease dramatically (Fig. 2). It must be taken into account that cross-reactivity between quinolones is still not fully known due to the small numbers of patients included in the studies published so far [6, 10•, 11•, 25, 28, 29]. When a given quinolone is the only therapeutic option available, desensitization may be required. Only three cases of desensitization in patients with IR have been reported, all induced by ciprofloxacin [71–73] and confirmed by DPT or skin tests. Desensitization in patients with DR has been reported in a few cases [17, 74]. They were induced by ciprofloxacin and confirmed by DPT. Although the induction is normally temporary, one case has been described in which long-term tolerance to ciprofloxacin was achieved after the desensitization of a patient with a history of FDE-related to this drug [17].

Conclusions

The number of documented cases of hypersensitivity to quinolones has increased in the last few decades, particularly for IR and for reactions induced by moxifloxacin. Diagnosis is complex, since clinical history is often unreliable, skin tests can induce false-positive results and *in vitro* tests are not well validated. Therefore, in many cases, the only way to diagnose tolerance is with DPT, a procedure that can carry some risks. Quinolones present a variable degree of cross-reactivity that is unclear and difficult to predict. Importantly, hypersensitivity to quinolones may be influenced by allergy to other drugs such as beta-lactams and neuromuscular blocking agents, although further studies are needed to understand the underlying mechanisms and the clinical relevance.

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IA contributed to the classification and chemical structure and *in vitro* tests sections; EM contributed to the clinical reactions immediate and delayed reactions, clinical history and skin tests sections; ID contributed to the epidemiology and risk factors; drug provocation test and cross-reactivity sections. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

Conflict of Interest None of the authors have any conflict of interest, nor have they received any money for this study. Research is part of their daily activities. All authors had full access to all data and take responsibility for the integrity and accuracy of the data analysis.

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.

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- Of importance
- Of major importance

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