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Drug Allergy (MJ Torres Jaén, Section Editor)

Hypersensitivity Reactions to Fluoroquinolones

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Opinion statement

Fluoroquinolones (FQs) are important antibiotics for the treatment of a wide range of infectious diseases. However, while FQs are generally well-tolerated, both IgE and T cell-mediated hypersensitivity reactions can occur. Moreover, there has been an increase in the prevalence of these reactions in recent decades, probably due to higher levels of consumption. The diagnosis of allergy to FQs is complex and is based on clinical history, skin tests (STs), and determination of the drug-specific IgE using both immunoassays and basophil activation tests (BATs). However, these approaches have sub-optimal sensitivity and specificity: clinical history can be unreliable and overestimate the incidence of reactions, STs show a high rate of false positives, and in vitro tests have low sensitivity. Therefore, drug provocation testing is currently the best method to establish diagnosis; however, it carries certain risks and should be avoided for cases with a history of severe reactions. In order to improve the sensitivity and specificity of in vivo and in vitro methods, it is crucial to fully characterize the FQ antigenic determinants that are recognized by the immunological system. Current data indicate that groups at the C2–C6 positions of their chemical structure may form part of the antigenic determinant recognized by IgE. Moreover, their photostability can affect protein reactivity and therefore the

formation of the hapten-carrier. All of these factors influence IgE and T cell recognition, the clinical response, and cross-reactivity and are the key for improving diagnostic methods. Additionally, a previous diagnosis of hypersensitivity to β-lactams has been reported to be a risk factor for FQ hypersensitivity, and this significantly decreases the therapeutic options for treating infectious diseases. Therefore, further studies are needed to obtain an accurate diagnosis, taking into account cross-reactivity, and to find alternative treatments.

Introduction

Fluoroquinolones (FQs) are synthetic antibiotics that emerged in the late 1980s with the addition of a fluorine side chain (at C6) to the original quinolone structure. Ciprofloxacin is the most frequently used FQ worldwide [1, 2]. Their chemical structure comprises an eight-membered, nitrogen-containing heterocyclic aromatic ring with a ketone group at position C4 and a carboxylic group at position C3. The main ring contains one nitrogen atom at position C1 (quinolones), while the second ring can contain another nitrogen atom at position C8 and analogs have different groups at positions C2, C6, C7, or C8 (Table 1). FQs have a wide range of activities against both Gram-negative and Gram-positive bacteria [1] and are classified into four generations with differing antibacterial spectra [3] (Table 1). The first generation includes 1-alkyl-4-quinolone-carboxilic acid structures and their corresponding 1,8-naphthyridine derivatives, such as nalidixic acid and cinoxacin (Gram-negative spectrum). The addition of fluorine at position 6 and the dialkylamino chain at position C7 of the quinolone structure yield the second, third, and fourth generations, with a broader antimicrobial spectrum (extended from Gram-negative to Gram-positive bacteria coverage) and improved pharmacokinetic properties [4, 5]. Moxifloxacin, a fourth-generation FQ, is widely used due to its Gram-positive activity [3], lower resistance rate than levofloxacin and lower phototoxicity and risk of adverse effects [6, 7].

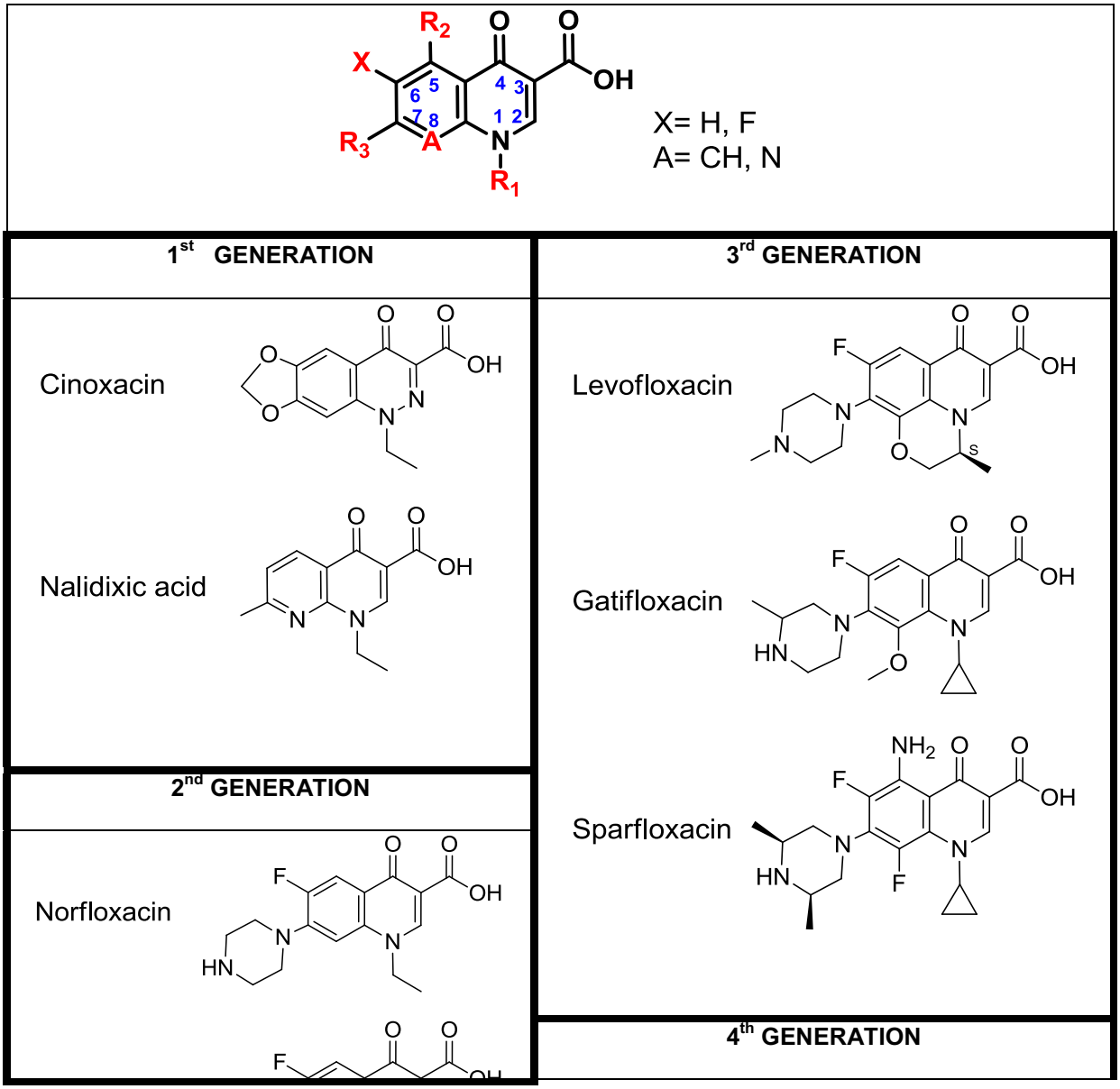
Although FQs are generally safe and have been considered well-tolerated antibiotics, adverse effects have been reported involving hypersensitivity and phototoxicity [8]. In the last few decades there has been an increase in documented hypersensitivity reactions to FQs, some of which have been severe, including anaphylactic reactions, acute exanthematic reactions, and toxic epidermal necrolysis (TEN) [9].

Fluoroquinolone hypersensitivity: an increasing problem

FQs are the most frequently involved non-β-lactam antibiotics in drug hypersensitivity and the incidence of reactions has been rising [10–12, 13•]. In Spain, the prevalence of hypersensitivity to quinolones has increased from 0.54 to 6.85 %, making them the third most common cause of drug hypersensitivity after non-steroidal anti-inflammatory drugs (NSAIDs) and β-lactams [10]. This is likely due to increased prescription and the introduction of moxifloxacin [12], which has been shown to be the most frequent cause of FQ reactions, followed by ciprofloxacin and levofloxacin [14••].

Immediate reactions (IRs), which are IgE-mediated reactions, are the most common, with 70 % of cases being severe [14••, 15•, 16••]. Though less common, delayed reactions (DRs), which are T cell-dependent reactions, have also been reported and include maculopapular exanthema (MPE) [17, 18••], fixed drug eruptions (FDEs) [19, 20], acute generalized exanthematic pustulosis (AGEP) [18••] and Stevens-Johnson syndrome (SJS)/TEN [18••, 21–24]. It

Table 1. Chemical structure of quinolones and classification into four generations

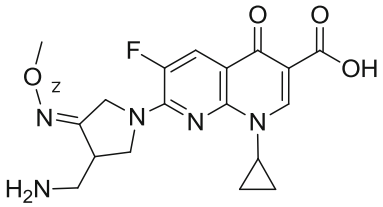
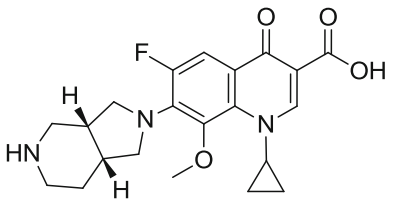
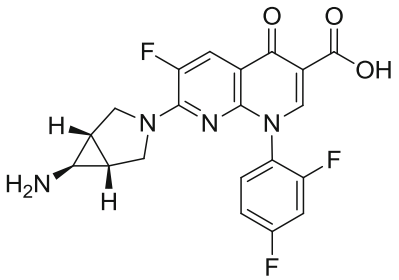


should be noted that due to the photosensitivity of FQs, a proportion of T cell reactions are photoallergic reactions [25].

Epidemiology of immediate hypersensitivity to fluoroquinolones

The incidence of FQ-induced anaphylaxis is on the increase, and is estimated to be 1.8–2.3 per 10,000,000 days of treatment [12]. Although all quinolones

Table 1. (continued)

	Gemifloxacin 
	Moxifloxacin 
	Trovafloxacin 

have been involved in anaphylaxis, moxifloxacin has been shown to be the most common culprit (odds ratio [OR] 4.20; 95 % confidence interval [CI] 3.19–5.55) [26]. The corresponding rates per 1 million defined daily doses based on crude estimates of exposure were 3.3, 0.6, and 0.2 for moxifloxacin, levofloxacin, and ciprofloxacin, respectively [9]. Studies in the Spanish, Italian, and German population have shown that the most frequently involved FQ in severe IRs, anaphylaxis, or anaphylactic shock was moxifloxacin (54–75 % of cases), followed by levofloxacin (15–35.7 %), and ciprofloxacin (7.1–54 %) [15•, 16••, 27].

Epidemiology in delayed hypersensitivity to fluoroquinolones

FQs have also been reported to elicit DRs, with MPE being the most common manifestation (28–39.7 %) and ciprofloxacin the major culprit, responsible for 33.3–34.9 % of all reported allergic reactions to drugs, followed by levofloxacin (19.5–32.3 %) and moxifloxacin (13.5–20.4 %) [27, 28]. They have also been associated with the development of FDE, with ciprofloxacin again the most frequent culprit [24, 29–32], followed by norfloxacin [19, 24] and levofloxacin [33, 34], and more severe DRs [35–39]. In particular, norfloxacin, ofloxacin, and ciprofloxacin have been associated with a high risk of AGEP (OR 33; 95 % CI 8.5–127) [36, 37]. FQs have also been shown to be associated with risk of SJS/TEN induction (OR 10; 95 % CI 2.6–38) in a large retrospective analysis

[38] and new data from EuroSCAR (European Study of Severe Cutaneous Adverse Reactions) showed similar results (OR 6.9; 95 % CI 1.8–27) [39]. The FQ most commonly responsible for inducing TEN is ciprofloxacin [22, 40–44], followed by levofloxacin [21, 22, 42, 44] and moxifloxacin [45–47]. Finally, FQs have been shown to be amongst the most common causes of idiosyncratic acute liver injury induction, another type of T cell-mediated reaction [48].

Risk factors

Evaluation of the factors involved in reactions to FQs using multivariate analysis showed that IRs were the most prevalent (OR 52.493; 95 % CI 6.621–416.200; $p = 0.001$) [14••] and identified a previous diagnosis of IRs to β-lactams as a strong risk factor (OR 23.654; 95 % CI 1.529–365.853; $p = 0.024$) [14••]. The increased co-occurrence of IRs to two non-chemically related antibiotics was previously described by Sullivan et al. as multiple drug allergy syndrome, since they found that 21 % of patients allergic to penicillin developed allergy to non-β-lactam antibiotics in comparison with just 1 % of those who were not allergic [49]. However, it is unclear whether this is due to an inherent predisposition to developing an allergy or because those patients who were diagnosed as allergic to β-lactams were more likely be prescribed FQs [50]. However, no association with other highly prescribed drugs, such as NSAIDs, has been detected [14••].

The challenge of diagnosis of fluoroquinolone hypersensitivity

Diagnosis of FQ hypersensitivity can be made based in part on clinical history, skin tests (STs), and determination of the specific IgE (sIgE). However, several of these approaches have sub-optimal sensitivity and specificity and drug provocation testing (DPT) is generally accepted as the best way to establish diagnosis [21, 51, 52].

Skin tests

There is controversy regarding the usefulness of STs for diagnosing IRs to FQs. In one study, STs (prick, intradermal, or patch) were found to be useful for the diagnosis as a negative ST can predict a negative DPT in 94 % of cases and only 5 % of patients with negative STs had a positive DPT [53]. However, specificity was low with a large number of false-positive results in controls and a positive result in STs only predicted 50 % of DPT positivity [53].

Other authors indicate that STs are not valid since they produce false-negative results [13•, 52, 54] and also positive results in control subjects [21, 29, 31, 52]. Reasons for these false-positive results are not completely clear but they could be due to the capacity of FQs to trigger direct histamine release by mast cells [55]. It has recently reported that this could occur through the non-specific activation of the receptor MRGPRX2 [56].

In order to avoid false-positive results, some authors have suggested optimal, "non-irritating" FQ concentrations for intradermal testing (IDT) in a group of healthy subjects [37, 57]. However, positive reactions were still found for some control subjects at ciprofloxacin concentrations as low as 0.0002–0.2 mg/mL [17].

In a recent study performed in a large number of patients with suspected

allergy to FQs, 56 % of cases had a positive ST and only 14.8 % of these showed a positive DPT. The ST specificity was very low (46.5 %) and the positive and negative predictive values were 14.8 % and 95.2 %, respectively [58]. All of these data indicate the limited value of STs for the evaluation of hypersensitivity to FQs because of their low sensitivity and high rate of false-positive results.

The evaluation of DRs is usually performed by delayed-reading IDT and patch tests (PTs). IDT has been shown to be positive in 60 % of cases with suspected DRs, 66.6 % of which were ultimately confirmed as allergic [53]. In a study in six patients with MPE and AGEP related to ciprofloxacin, moxifloxacin, and norfloxacin, positive PTs to ciprofloxacin were observed in three patients [18••]; in another study, PTs were shown to be positive for more than 50 % of cases with AGEP [37].

No positive PTs could be obtained in a study of 37 patients with FDEs [17]. However, this may be due to the fact that the tests were performed in non-affected skin. There is currently one report of a positive PT in a patient with FDEs related to ciprofloxacin, which was performed in lesional skin and in which the patient showed negative results when testing normal skin [24]. Thus, is our view that for FQ reactions, PTs should be performed on the lesional skin in addition to the conventional upper back.

Other reasons for the negative PTs could be the performance of the test during the refractory period (<2 weeks after the resolution of the reaction), sensitization to FQ metabolites rather than to the native drug, the drug concentration used, and the limited penetration capacity of the drug [59].

In photoallergic reactions, photopatch tests with ultraviolet A (UVA) light exposure can be performed. Moreover, scarification of the skin prior to photopatch testing to enhance drug penetration has been suggested to increase sensitivity [37, 60].

In vitro tests

There is no commercial test for the in vitro determination of the sIgE to quinolones. Two studies using quinolones coupled to an epoxy-activated sepharose 6B as the solid phase (sepharose-radioimmunoassay [RIA]) have found a high specificity, although sensitivity varied: 54.5 vs. 28.9 % [16••, 61••]. These discrepancies could be attributed to the quinolone involved and the type of reaction: in the study by Manfredi et al. [61••], there was a higher frequency of urticaria (85 %) than anaphylactic shock (13 %), whereas two-thirds of the cases in the study by Aranda et al. [16••] were severe reactions. Regarding the culprit drug, in the first study the most frequently involved FQs were ciprofloxacin (29 %) and cinoxacin (29 %), whereas in the second study moxifloxacin (63.2 %) and ciprofloxacin (28.9 %) were more common [16••, 61••]. Although no correlation was found between the level of sIgE and the severity of the reaction, significantly higher sIgE levels were found in patients evaluated within 8 months of the reaction than in those evaluated more than 8 months after the reaction. In addition, patients with negative results showed a higher time interval between the reaction and test [61••].

BATs have been shown to be useful for in vitro evaluation of FQ hypersensitivity [16••, 62, 63]. This is important in order to avoid the performance of DPT, particularly if we take into account the high rate of acute reactions to FQs, with anaphylactic shock occurring in 24 % and anaphylaxis in 42 % [14••]. In one study, BAT showed a sensitivity of 71 % and, more importantly, it was positive in 69 % of cases with severe reactions [16••]. Moreover, BAT has also been shown to

have an excellent negative predictive value since all 15 patients with negative BAT also showed negative DPT [62]. These results suggest that BAT is a valuable tool in making the decision of whether to perform DPT in FQ-allergic patients.

It has been shown that BAT sensitivity depends on the culprit FQs and also on those included in the test. Indeed, in those cases with a reaction to ciprofloxacin, BAT sensitivity did not change with the inclusion of other FQs, whereas in moxifloxacin-allergic patients, BAT sensitivity increased from 41.7 to 79.2 % after adding ciprofloxacin [16••]. This suggests that moxifloxacin-hypersensitive patients were previously sensitized to ciprofloxacin, which is in agreement with the fact that moxifloxacin was introduced to the market at a later date [16••].

In general, BAT with ciprofloxacin shows a higher sensitivity than with moxifloxacin, even in cases where moxifloxacin is the culprit drug [16••]. This observation can be explained by differences in chemical structure and behavior upon light exposure, which influence the quinolone-protein conjugates and thus affect BAT results [64]. In fact, photodegradation under laboratory light conditions can occur during BAT, especially for moxifloxacin. These results correlate with the lower positivity for BAT with moxifloxacin in light (17.9 %) than in dark (35.7 %) conditions whilst positivity for ciprofloxacin (46.4 %) does not change [64].

In vitro studies of DRs to FQs have been performed using the lymphocyte transformation test [18••, 65] and confirm T cell involvement in MPE and AGEP pathogenesis [18••, 37]. Moreover, a higher sensitivity of this technique was found than for PTs, which could be due to aspects of the complex inflammatory response in the skin but also to a low FQ penetration capacity through the skin or the use of a low FQ concentration [18••, 66].

Finally, in photoallergy it has been demonstrated that peripheral blood mononuclear cells photomodified with quinolones using UVA light were able to stimulate homologous cell proliferation [65, 67].

Drug provocation tests

Despite the above-mentioned progress in other testing methods, DPT is still considered the gold standard for the diagnosis of FQ hypersensitivity [51, 53]. However, since this test can provoke reactions, a risk–benefit assessment is necessary [17].

The necessity of DPT for quinolone hypersensitivity evaluation is clear given that only 11.8–32 % of patients with a suggestive clinical history had a positive DPT and could therefore be confirmed as allergic [17, 68]. This indicates that the clinical history alone is often unreliable and can lead to over-diagnosis. One reason for this could be that signs first interpreted as hypersensitivity, such as urticaria or exanthema, are really due to infectious agents [17, 69].

The immunochemistry of fluoroquinolones

Different in vivo and in vitro approaches have found evidence of IgE and T cells specific to quinolones in IRs and DRs, respectively, suggesting an immunological mechanism for FQ-induced hypersensitivity [16••, 18••, 61••, 63, 67]. The current understanding of how drugs interact with the immunological system and induce allergic reactions is based on the hapten hypothesis, which proposes that drugs must bind covalently to proteins and produce hapten-carrier conjugates that will be recognized by either sIgE or T cells [70–72]. However, the exact quinolone

structure, whether consisting of the native drug or metabolites that initially interact with the immunological system, remains unknown and establishing this could be very important in improving the actual diagnostic methods.

Antigenic determinants

FQs can be metabolized by oxidation, reduction, or hydrolysis (phase I reactions) and conjugation with an endogenous substance such as glucuronic acid, acetic acid, sulphuric acid, or an amino acid (phase II reactions) [73]. Their immunogenicity could be explained by the formation of conjugates through a glucuronide at C3, occurring in a similar way for ciprofloxacin, levofloxacin, and moxifloxacin [1]. Moreover, it has been shown that the pattern of reactivity is mainly influenced by the amino-heterocyclic moiety at C7, which differs among these FQs. Thus, the diazabicyclic ring in moxifloxacin is more reactive than piperazine in ciprofloxacin or a methyl-modified piperazine in levofloxacin at the same position [1, 14••, 74] (Fig. 1a).

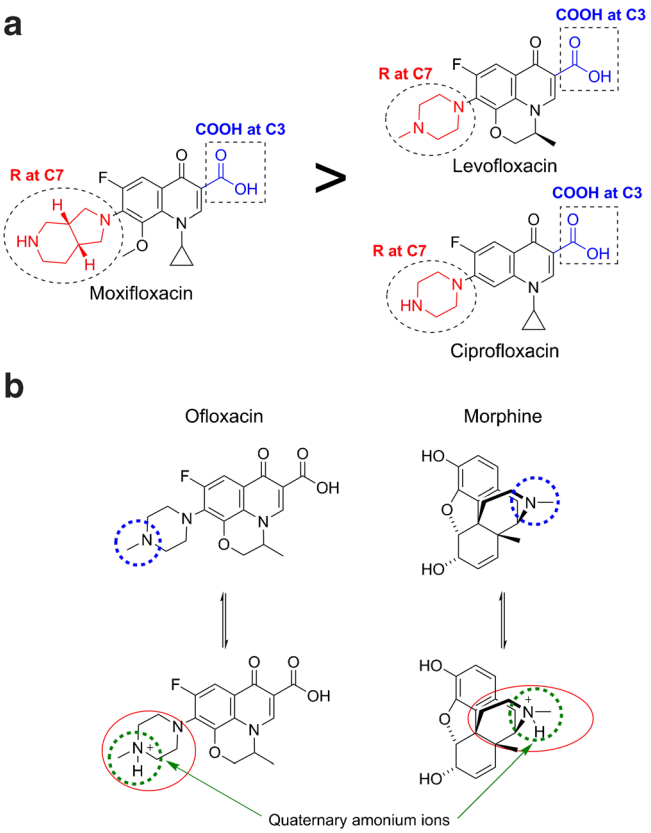


Fig. 1. **a** The pattern of reactivity of fluoroquinolones is influenced by the amino-heterocyclic moiety at C7: the diazabicyclic ring in moxifloxacin, piperazine in ciprofloxacin, and methyl-modified piperazine in levofloxacin. **b** Substituted or quaternary ammonium ion determinant (*in green*) derived from protonation of tertiary amine (*in blue*). Quaternary ammonium of neuromuscular blocking agentsis also present in some quinolones such as ofloxacin, in which the substituent at C7 is a piperazine. Specific IgE could recognize not only quaternary ammonium ions but also neighboring structures. The piperazine structure (*in red*) of ofloxacin is very similar to the nitrogen 6-member ring of morphine (*in red*).

The antigenic determinant of quinolones has been described based on in vitro studies of sIgE recognition. Data obtained with RIA-sephadex in patients with hypersensitivity to cinoxacin showed consistently negative results with this quinolone versus positive results with other quinolones. However, it was possible to detect cinoxacin sIgE in the sera of patients with hypersensitivity to cinoxacin by inhibition assays when this quinolone was used in the fluid phase. These results suggest that groups at positions from C2 to C6 of quinolones form part of the antigenic determinant since most quinolones have the capacity to bind to the carrier protein via the side chain at position C7; however, for cinoxacin, which lacks a side chain at position C7, binding is through the carboxyl group at position 3 [18••, 61••] (Table 1).

In the case of DRs to FQs, the generation of T cell clones specific to ciprofloxacin or norfloxacin in patients with quinolone-induced MPE has shown that, in contrast to IgE, recognition of the drug by these cells does not require covalent binding of the quinolone with proteins, indicating that both IgE and T cells could react with different quinolone structures [18••]. Moreover, T cells recognized the quinolones with no need for metabolism or processing, although the possibility that the T cells were stimulated by different quinolone metabolites of cannot be excluded [18••].

Photoadducts

UVA light exposition induces photodegradation of FQs, making them more prone to binding covalently to proteins and therefore able to induce a photoallergic response [67, 75, 76]. This has been studied in experimental models where it has been demonstrated that murine T cells react to Langerhans cells photomodified by quinolones [67, 77, 78]. An enhanced expansion of $CD4^{+}TCRV\beta13^{+}$ T helper (Th) 1 cells has been found after in vitro stimulation of immune lymph node cells with FQ-photomodified cells, which are recognized by FQ-specific T cells. Moreover, cross-reactivity amongst six FQs has been demonstrated, suggesting the presence of a common epitope (probably the piperazinyl ring at position 7) [77].

Photodegradation can be modulated by the nature of the substituents bound to the quinolone structure and produced by a variety of photochemical processes, such as generation of singlet oxygen, production of superoxide, defluorination, decarboxylation at C3, or oxidation of the amino group at C7 [79–81]. The protein photobinding capacity can also depend on the piperazinyl ring at the C7 position [82, 83].

Reactive intermediates generated by heterolytic defluorination from the triplet state of FQs (specifically aryl cations) have been observed in ciprofloxacin, norfloxacin, and lomefloxacin, making them effective in photobinding to human serum albumin (HSA) as compared with enoxacin and no binding for cinoxacin (a non-fluorinated analog) [84–86]. However, interactions between the FQ singlet excited state and albumin seem to be key for the formation of FQ-HSA conjugates [87]. Aside from the quinolone structure, photostability will depend on the characteristics of the biological environment [79, 80]. For example, high photodegradation for moxifloxacin compared with ciprofloxacin was found in whole blood, whereas no differences could be observed in aqueous solution [64].

On the other hand, the phototoxicity of FQs can inversely influence their photoimmunogenicity [88–90]. The phototoxicity of FQ can be associated with

the fluorine at the C8 position, as is the case for sparfloxacin and lomefloxacin. In contrast, ciprofloxacin and norfloxacin, which do not possess this fluorine at C8, showed a higher photoallergy capacity than sparfloxacin [91, 92]. Although the reasons for this inverse relation are not known, it could be due to the reduction in the antigen-presenting ability of photomodified cells such as Langerhans cells [67].

Treatment options for patients with fluoroquinolone hypersensitivity

The increase in hypersensitivity to FQs reduces the therapeutic possibilities for managing infectious diseases dramatically, especially in patients with a previous history of hypersensitivity to other antibiotics. It is therefore crucial to get an accurate diagnosis of hypersensitivity, including cross-reactivity, to avoid the prescription of other antibiotics that may be more toxic, induce bacterial resistance, and be more expensive for the healthcare system.

Cross-reactivity between fluoroquinolones

Fluoroquinolone cross-reactivity: in vivo studies

It is widely thought that cross-reactivity is associated with the common FQ structure, a 4-oxo-1,4-dihydroquinoleine ring core, although the groups bound to C1, C5, C7, and C8 positions may also play a role. However, studies assessing cross-reactivity are often poorly described: most are case reports or small studies with few subjects and mainly performed for IRs. DPT has been used to establish a diagnosis as well as to evaluate cross-reactivity or to choose an alternative, safer quinolone. Different patterns of cross-reactivity for both IRs and DRs to quinolones have been established [13•, 18••, 37].

The first study was performed with first- (nalidixic acid) and second-generation (norfloxacin and ciprofloxacin) quinolones and found a high degree of cross-reactivity [21]. However, others found a lack of cross-reactivity among quinolones from the second generation, i.e., ciprofloxacin and norfloxacin, despite them having similar chemical structures [19, 31]. This may be due to the production of different metabolites interacting with the immunological system in different ways.

Moxifloxacin, a fourth-generation FQ, differs from ciprofloxacin mainly at positions C7 and C8. At C7, ciprofloxacin has an unsubstituted six-membered piperazine ring whereas moxifloxacin presents a five-membered diazabicyclic ring, and at C8 ciprofloxacin does not have any side chain whereas moxifloxacin has a methoxy group (CH_3O). There are several studies analyzing the cross-reactivity of moxifloxacin with other quinolones (ciprofloxacin, ofloxacin, levofloxacin, norfloxacin) that demonstrate good tolerance to levofloxacin and ciprofloxacin [9, 93–95], indicating that the cross-reactivity of moxifloxacin to other quinolones is low. However, these authors also showed that a positive reaction to moxifloxacin could occur

in patients with ciprofloxacin allergy [94], indicating that cross-reactivity is not necessarily a bilateral phenomenon [12]. Considering levofloxacin, which is the levogyre form of ofloxacin, a low degree of cross-reactivity with ciprofloxacin has been found, indicating that it could be a valid alternative for patients with IRs to FQs [13•].

In DRs, a high cross-reactivity has been found in FDEs caused by ciprofloxacin with norfloxacin and ofloxacin [96] and those caused by levofloxacin with moxifloxacin [93] and ofloxacin [34]. On the other hand, a large study demonstrated around 10 % cross-reactivity between gemifloxacin and ciprofloxacin in patients with MPE [97]. Moreover, in TEN induced by moxifloxacin and trovafloxacin, differing degrees of tolerance to levofloxacin and ciprofloxacin have been found [45–47].

Fluoroquinolone cross-reactivity: in vitro studies

In vitro studies in both IRs [16••, 61••] and DRs [18••] to quinolones also suggest a high level of cross-reactivity. Using Sepharose-RIA, sIgE toward more than one quinolone was detected in 80 % of cases (24 of 30), although only 16 % of these patients reported a reaction to several quinolones, indicating that in vitro cross-reactivity can be over-estimated [61••]. A similar level of in vitro cross-reactivity (63.6 %) has also been found by others [16••].

Regarding BATs, positive results from more than one quinolone have been found in 48.2 % of cases [16••]. Interestingly, BAT cross-reactivity in hypersensitivity 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 not often positive to moxifloxcin when ciprofloxacin was the culprit drug [16••, 64]. This suggests that IgE specifically recognizes the chemical structure of ciprofloxacin despite the reaction being induced by moxifloxacin. We do not have an explanation for this phenomenon, although it seems to indicate that IgE specifically recognizes the drug of first exposure (ciprofloxacin), as has been demonstrated with β-lactams, reflecting an anamnestic immune response [98–100].

The evaluation of the recognition of ciprofloxacin-specific T cell clones from patients who have suffered MPE from this drug [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. These patterns can be found in the in vivo response to quinolones [21, 24, 31]. The photoreactivity of T cells to modified FQ derivatives in mice showed a wide cross-reactivity among six FQs in both in vivo and in vitro responses, suggesting that photohaptens also share a common epitope (probably the piperazinyl ring at position 7) that is recognized by T cells, particularly Th1 [67, 88].

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 small groups, although with lower affinity [101, 102].

The general conclusion obtained from in vivo and in vitro studies is that there is high cross-reactivity among quinolones, particularly between first- and second-generation quinolones [13•, 93, 94]. However, it is very difficult to predict the reaction pattern, and thus a precise evaluation of these patients should be performed and it is recommended that

a DPT be carried out before considering another quinolone as a safe alternative [13•, 53, 63, 103].

Cross-reactivity with penicillins

In addition to the cross-reactivity between different quinolones, an important issue is the presence of concomitant allergies to other, non-chemically related antibiotics. A recent article showed that, in the case of IgE-mediated reactions, a previously confirmed hypersensitivity to β-lactams is a risk factor for the development of hypersensitivity to FQs [14••]. As mentioned earlier, this was originally named multiple drug allergy syndrome [49, 104] when it was first described that patients previously diagnosed as allergic to β-lactams had a higher propensity to develop an allergy to non-β-lactam antibiotics (21 %) than those who were not allergic (1 %) [49]. This association could be explained by the high probability of FQs being prescribed to patients previously diagnosed as allergic to β-lactams [14••], an alteration in the immune response to haptens, or a predisposition to allergic reactions [49, 105].

Regarding DRs, polysensitivity to chemically unrelated drugs, although rare, has been reported in FDE [106–108] for several groups of drugs including β-lactams, anticonvulsants, trimethoprim, sulfamethoxazole, and tenoxicam, with lesions located on the same or separate areas [109]. Recently, a case of FDE related to amoxicillin and quinolones has been reported [110••].

Contain the piperazine cycle

Apart from antibiotics, FQs have been also associated with neuromuscular blocking agent (NMBA) sensitization [111••]. In a recent report, a higher percentage of cases with sIgE to quaternary ammonium was found in patients with hypersensitivity to FQs (53 %) than in patients with no confirmed allergy (11 %). Although the clinical relevance remains unclear, it could be related to the fact that, similar to NMBAs, FQs can induce IRs in 43 % of patients after the first use [15•, 111••]. This suggests the presence of sIgE induced by other components that share chemical structures with quinolones. Although quinolones do not have quaternary ammonium determinants, they contain piperazine cycle, which on protonation could mimic substituted ammonium explaining the IgE cross-reactivity (Fig. 1b). However, molecular modelling could not demonstrate the presence of common epitopes between quinolones and NMBAs [111••].

The presence of IgE against tertiary and quaternary ammonium ions could be relatively frequent in patients with drug allergy and in the general population (9.3 %) [112, 113]. This suggests that for those drugs that can induce allergic reactions after the first exposure, as happens with NMBAs and quinolones, the presence of the so-called natural antibodies that may be specific to environmental chemicals, i.e., phosphorylcholine, should be considered.

Desensitization

In some infectious diseases, and especially when allergy to other antibiotics has been previously confirmed, FQs may be the only therapeutic option available. In these cases, clinical tolerance induction may be required. Desensitization to FQs has to date been performed mainly for IRs but also for DRs to ciprofloxacin [114–117]. Although the induction is normally temporary, only lasting a few days, a 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 [20].

Conclusions

The documented hypersensitivity to FQs has increased in the last few decades, with moxifloxacin being the most frequent cause of severe IRs and ciprofloxacin the most frequent cause of DRs. Since clinical history is often unreliable and STs can produce false-positive results, especially in IRs, there is a need to perform DPT for the hypersensitivity evaluation of FQs. In vitro tests, immunoassays, and BAT can help but show low sensitivity, probably because of the limited knowledge about the antigenic determinants of FQs, including the possibility of inducing photoadducts. FQs present a variable degree of cross-reactivity with other FQs, as demonstrated by in vivo and in vitro tests. Importantly, hypersensitivity to FQs can present concomitantly with allergies to other drugs such as β-lactams and NMBAs, although further studies are needed to understand the underlying mechanism of this.

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Compliance with Ethical Standards

Conflicts of Interest
Dr. Maria Salas declares that she has no conflict of interest.
Dr. Esther Barrionuevo declares that she has no conflict of interest.
Dr. Tahia Diana Fernandez declares that she has no conflict of interest.
Dr. Arturo Ruiz declares that he has no conflict of interest.
Dr. Immaculada Andreu declares that she has no conflict of interest.
Dr. Maria Jose Torres declares that she has no conflict of interest.
Dr. Cristobalin Mayorga declares that he has 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.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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This is the first study where polysensitization to NMBA and quinolones has been described. The authors found a high prevalence of quaternary ammonium sensitization in patients with immediate hypersensitivity to quinolone. Although the clinical relevance of this finding should be further analyse, this could raise some explanation in those cases of drug hypersensitivity that happens after the first drug exposition.

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