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3

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6

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56

57 **ABSTRACT**

58 **Background:** Quinolones are the second most frequent cause of hypersensitivity  
59 reactions (HSRs) to antibiotics ~~after betalactams~~. A marked increase in the number of  
60 patients with HSRs to quinolones has been detected.

61 **Objective:** To describe the clinical characteristics of patients with HSRs to quinolones  
62 and present methods for their diagnosis.

63 **Methods:** Patients attending the allergy unit due to reactions suggestive of HSRs to  
64 quinolones were prospectively evaluated between 2005-2018. Diagnosis was achieved  
65 using clinical history, skin tests (STs), ~~the~~ basophil activation tests (BATs), and drug  
66 provocation tests (DPTs) if ST and BAT were negative as necessary.

67 **Results:** We included 128 subjects confirmed as having HSRs to quinolones and 42  
68 found to be tolerant. Anaphylaxis was the most frequent entity in immediate HSRs and  
69 was most commonly induced by moxifloxacin. Patients were evaluated a median of 150  
70 days (interquartile range: 60-365) after the reaction. Of patients who underwent ST and  
71 BAT, 40.74% and 70% respectively were positive. DPT with a quinolone was  
72 performed in 48 cases, giving ~~different~~ results depending on the culprit drug: when  
73 moxifloxacin was involved the culprit, 62.5% of patients gave a positive DPT to  
74 ciprofloxacin, whilst none reacted to levofloxacin. The risk of HSR was 96 times higher  
75 in subjects who reported moxifloxacin-induced anaphylaxis and 18 times higher in  
76 those reporting immediate reactions compared to clinical entities induced by quinolones  
77 other than moxifloxacin and non-immediate reactions.

78 **Conclusions:** The diagnosis of HSR to quinolones is complex. The use of clinical  
79 history is essential as a first step. BAT shows higher sensitivity than STs. DPTs can be  
80 useful for finding safe alternative quinolones.

81

82 **What is already known about this topic?**

83 Quinolones can induce hypersensitivity through several mechanisms, being the third  
84 most common drug associated with hypersensitivity, and the second most frequent drug  
85 inducing both IgE-mediated hypersensitivity and severe anaphylaxis. The optimal  
86 diagnostic approach remains a controversial topic.

87 **What does this article add to our knowledge?**

88 The risk of having quinolone hypersensitivity is higher for immediate reactions,  
89 particularly for moxifloxacin-induced anaphylaxis. The basophil activation test has a  
90 higher sensitivity than skin test. Drug provocation testing can be useful to identify safe  
91 alternative quinolones.

92 **How does this study impact current management guidelines**

93 We propose an algorithm for diagnosing quinolone-induced reactions, which should be  
94 classified according to the interval between drug intake and reaction onset, using a 6  
95 hour threshold. The algorithm includes skin, basophil activation, and drug provocation  
96 tests as necessary.

97

98 **KEYWORDS:** Adverse drug reaction; Anaphylaxis; Basophil activation test;  
99 Ciprofloxacin; Drug provocation test; Hypersensitivity; Levofloxacin; Moxifloxacin;  
100 Quinolones; Skin tests.

101

102 **ABBREVIATIONS:** Acute generalized exanthematous pustulosis (AGEP); Basophil  
103 activation test (BAT); Drug provocation test (DPT); Fixed drug eruption (FDE);  
104 Hypersensitivity reaction (HSR); Immediate reaction (IR); Intravenous (IV);  
105 Maculopapular exanthema (MPE); Non-immediate reaction (NIR); Skin prick test  
106 (SPT).

107

108

109 **INTRODUCTION**

110 Quinolones are antibiotics that are commonly prescribed for their effectiveness against  
111 Gram (+) and Gram (-) bacteria<sup>1-3</sup>. Adverse effects occur in 2-10% of people taking  
112 quinolones, however most of them are mild, mainly affecting the gastrointestinal or  
113 central nervous systems<sup>3,4</sup>. Quinolones can induce hypersensitivity reactions (HSRs)<sup>5</sup>  
114 through IgE-mediated reactions (immediate reactions, IRs) and T-cell dependent  
115 reactions (non-immediate reactions, NIRs)<sup>6,7</sup>. In addition, quinolones may also cause  
116 HSRs in drug-naïve patients<sup>8,9</sup>. A mechanism of mast cell activation via occupation of  
117 the human Mast-related G-protein receptor X2 (MRGPRX2) has been described for  
118 IRs<sup>10,11</sup> occurring in patients without previous exposure to quinolones<sup>12</sup>.

119 Although the absolute risk of an HSR related to quinolones is low (44.0 (95% CI: 34.8–  
120 53.3) emergency department visits/100,000 prescriptions)<sup>8</sup>, quinolones are the third  
121 most frequent drug associated with HSRs<sup>13</sup> in general, and the second most frequent in  
122 IgE-mediated HSRs. They are also the second most frequent cause of alert activation for  
123 antibiotic allergy in electronic hospital records<sup>14</sup> and severe drug-induced  
124 anaphylaxis<sup>13,15</sup>. In recent years, an increase in the percentage of patients with HSRs to  
125 these drugs has been detected, ranging from 0.54% in 2005 to 6.85% in 2010<sup>13</sup>. This is  
126 likely due to their increased prescription over the last decades<sup>16</sup>. The incidence of  
127 anaphylaxis induced by quinolones has been estimated to be 1.8–23 per 10 million days  
128 of treatment<sup>17,18</sup> and the prevalence of cutaneous adverse reaction to be 0.09%<sup>19</sup>.  
129 Quinolones are also one of the main triggers of acute generalized exanthematous  
130 pustulosis (AGEP), photosensitivity and vasculitis<sup>20</sup>.

131 HSRs to quinolones appear in an important percentage of patients (23%) previously  
132 diagnosed as allergic to betalactams: in fact, betalactam allergic patients have a 17 times  
133 higher risk of reacting to quinolones than those non-allergic. This represents an  
134 important health problem as it greatly decreases therapeutic options available<sup>16</sup>. In a  
135 large study of inpatients with common infections requiring antibiotic treatment,  
136 quinolone allergy occurred in 5.4% of patients who were already sensitive to  
137 betalactams<sup>21</sup>, leading to important restrictions for antibiotic prescription and  
138 subsequently poor prognosis of their infections.

139 The optimal diagnosis of quinolone HSRs is still a matter of debate. The value of skin  
140 tests (STs) is uncertain, and they have shown false positive results when quinolones are  
141 tested at high concentration<sup>22-25</sup>. The presence of specific IgE to quinolones has been  
142 reported using the sepharose radioimmunoassay, with a sensitivity of 54.5%<sup>26</sup>. The

143 basophil activation test (BAT) has shown promising results for the diagnosis of patients  
144 with IRs to quinolones<sup>27-29</sup>. However, other studies have contradicted these findings<sup>30,31</sup>.  
145 The gold standard, therefore, is the drug provocation test (DPT). However, this is not  
146 free of risk and not advisable in cases where the reaction might be severe.  
147 The aim of this study was to describe the clinical characteristics of a large group of  
148 patients with quinolone-induced HSRs and present methods for their diagnosis.  
149

## 150 **METHODS**

### 151 **Patients**

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

156 *Inclusion criteria.* Patients  $\geq 14$  years-old in whom the allergological study was  
157 completed were included and classified in two groups: A) Patients confirmed as having  
158 HSRs to quinolones (by positive STs, BATs or DPTs); and B) Patients confirmed as  
159 being non-allergic (tolerant) as they tolerated a DPT with the suspected culprit  
160 quinolone.

161 *Exclusion criteria.* Patients  $< 14$  years-old; patients in whom the allergological study  
162 was not completed so that the diagnosis could not be confirmed as being neither allergic  
163 nor tolerant to quinolones: pregnant or breastfeeding patients; patients taking beta-  
164 blockers or ACE inhibitors or with contraindications for epinephrine administration;  
165 patients who had acute infections and/or underlying cardiac, hepatic or renal diseases  
166 that contraindicated DPTs; and subjects with psychosomatic disorders.

### 167 **Clinical history**

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

### 173 **Skin testing**

174 For reactions suggestive of an IR, skin prick tests (SPTs) were carried out as described<sup>33</sup>  
175 using ciprofloxacin (at 0.02 and 0.2 mg/ml), levofloxacin (at 0.05 and 0.5 mg/ml), and  
176 moxifloxacin (one tablet of 400 mg suspended in NaCl). Intradermal tests were not  
177 performed to avoid false positive results as non-specific histamine release by quinolones  
178 has been reported<sup>34,35</sup>.

179 For reactions suggestive of an NIR, patch tests (PTs) were carried out and evaluated as  
180 described<sup>33</sup> by mixing powdered quinolone (ciprofloxacin, levofloxacin, and  
181 moxifloxacin) in petrolatum at 30% w/w.

### 182 **Basophil activation test**



183 In patients with a suspected IR, BATs were performed as described previously<sup>27</sup>, using  
184 ciprofloxacin (2 and 0.2 mg/ml), levofloxacin (4 and 2 mg/ml), moxifloxacin (2, 0.2 and  
185 0.1 mg/ml), norfloxacin (2, 0.2 and 0.1 mg/ml), ofloxacin (4, 2, 0.2 and 0.1 mg/ml), and  
186 lomefloxacin (4, 2, 0.2 and 0.1 mg/ml).

### 187 **Drug provocation test**

188 DPTs with ciprofloxacin, levofloxacin, and moxifloxacin were performed in a single  
189 blind manner if skin tests and BATs were negative<sup>36</sup>: placebo capsules were given at  
190 different times on the first day; increasing doses of quinolones were administered orally  
191 at intervals of 60 min (5, 20, 100 mg for ciprofloxacin and levofloxacin; 5, 30, 65 mg  
192 for moxifloxacin) on the second day. If these did not produce a reaction, three further  
193 doses of quinolones were given on the third day: 125, 125, 250 mg (accumulative dose  
194 500 mg) for ciprofloxacin and levofloxacin; 100, 100, 200 mg (accumulative dose 400  
195 mg) for moxifloxacin. The three test days were separated by 1 week. If cutaneous and/or  
196 respiratory symptoms or alterations in vital signs appeared, the procedure was stopped  
197 and the symptoms were evaluated and treated. If no symptoms appeared during graded  
198 challengedrug administration, the therapeutic dose of quinolone was achieved. T and  
199 this was then followed by taking the full 2 days at maximum dose at home, starting after  
200 a gap of 24 hours after the graded challenge. Before beginning the DPT procedure,  
201 patients were stable and their forced expiratory volume in 1s had to be at least 80% of  
202 the predicted value, with an absolute volume of at least 1.5 L. Medications were stopped  
203 before DPT according to international guidelines<sup>36</sup>.

### 204 **Statistical analysis**

205 Data analysis was performed using Chi-square analysis to test differences in nominal  
206 variables between groups, the Fisher test was used when there were no criteria for using  
207 the Chi-square test and the Mann–Whitney test was used for quantitative variables. All  
208 reported p values represented two-tailed tests, with values <0.05 considered statistically  
209 significant. A logistic regression analysis was performed to establish the characteristics  
210 associated with the diagnosis of HSR or tolerance to quinolones and with the diagnosis  
211 of immediate anaphylaxis. The following variables were analysed: gender, age, time  
212 interval between drug intake and the onset of the reaction, symptoms experienced, drugs  
213 involved, time interval between drug reaction and study, and number of episodes.

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



218 **RESULTS**

219 A total of 612 patients with a clinical history suggestive of an HSR to quinolones were  
220 evaluated. Of these, full diagnosis could not be achieved for 442 patients: 361 patients  
221 that gave a negative ST and negative BAT could not undergo DPT to quinolones due to  
222 age, comorbidities or because it was contraindicated due to the potential severity of the  
223 reaction; 78 did not give consent for the allergological tests (STs, BAT and/or DPTs);  
224 and 3 were excluded due to pregnancy. For the remaining 170 patients a full diagnosis  
225 could be achieved: 128 were confirmed as having HSRs to quinolones and 42 as non-  
226 allergic (tolerant) to quinolones.

227 **Clinical data of the subjects included in the study**

228 The 170 included subjects with confirmed diagnosis had a median age of 53  
229 [interquartile range: 40–63.25] years, and 126 (74.1%) were female. The majority of  
230 cases reported only one previous episode induced by quinolone intake, except for 2  
231 cases who reported 2 previous IRs. As such, the patients included in the study reported a  
232 total of 172 previous reactions: 120 IRs and 52 NIRs, with the percentage of IRs higher  
233 in those confirmed as having HSRs compared to the tolerant group (73.8% vs 19%;  
234  $p<0.0001$ ) (Table 1). Most reported reactions were induced by oral quinolones (142;  
235 82.5%), the rest by intravenous route (30;17.4%). In terms of the symptoms of reported  
236 reactions, the percentage of anaphylaxis reactions was higher in subjects confirmed as  
237 having HSR ( $p<0.0001$ ); whereas urticaria ( $p=0.0004$ ), local reaction at the site of IV  
238 administration ( $p=0.0001$ ) and MPE ( $p=0.03$ ) were more frequently report by subjects  
239 that were found to be as tolerant (Table 1). Moxifloxacin was the most frequent culprit  
240 quinolone in patients with confirmed HSRs; ciprofloxacin was more frequent in subjects  
241 confirmed as tolerant ( $p<0.0001$  and  $p=0.001$ , respectively) (Table 1). In subjects  
242 confirmed as having HSRs, most cases of anaphylaxis were induced by moxifloxacin  
243 (52.9%;  $p=0.002$ ); urticaria and angioedema were mostly induced by ciprofloxacin  
244 (48.8% and 66.7%, respectively), although these differences was not found to be  
245 statistically significant (Table E1). For those found to be tolerant, ciprofloxacin was the  
246 most frequent cause of both urticaria and angioedema (69.2% and 66.7%, respectively),  
247 as well as of local reactions at the site of IV administration (66.7%) ( $p>0.05$ ) (Table  
248 E1).

249 The logistic regression analysis showed that the risk of being confirmed as HSR was  
250 higher for cases who reported moxifloxacin-induced anaphylaxis (OR: 96.16; CI: 6.172-  
251 Inf;  $p=0.009$ ) and for those reporting IRs (OR: 18.856; CI: 5.196-271.449;  $p<0.0001$ )

252 compared to cases who reported other symptoms induced by other quinolones and  
253 NIRs. Moreover, the risk for being confirmed as HSR decreased when ciprofloxacin  
254 was the culprit (OR: 0.107; CI: 0.002-0.741; p=0.04) and the symptoms reported were  
255 MPE, FDE, urticaria, angioedema (OR: 0.053; CI: 0-0.452; p=0.03), or a local reaction  
256 at the site of IV administration (OR: 0.001; CI: 0-0.016; p=0.0006). No significant  
257 associations were found for the other variables, and there were no interactions between  
258 variables.

### 259 **Analysis of the patients confirmed as suffering HSRs to quinolones**

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

264 Anaphylaxis was the most frequent reported symptom among IRs (p<0.0001) and  
265 urticaria among NIRs (p>0.05) (Table 2). It is of note that the 7 (25%) of patients  
266 reporting reactions within the interval of 1-6 hours showed symptoms compatible with  
267 anaphylaxis. Moxifloxacin was the most frequent quinolone involved in IRs and  
268 ciprofloxacin in NIRs (41.1% and 38.9%, respectively) (Table 2). Anaphylaxis was  
269 induced primarily by moxifloxacin in IRs (52.9%; OR=2.935 (IC:1.418-6.075),  
270 p=0.003) whereas most urticaria and angioedema was induced by ciprofloxacin (52.9%  
271 and 75%, respectively). Considering NIRs, moxifloxacin was the culprit in most cases  
272 reporting urticaria (42.8%) and ciprofloxacin in angioedema reporting-cases (50%)  
273 (Table E2). The time interval between intake and onset of the reaction was shorter when  
274 the drug was administered by an IV route compared to the oral route (5 [IR: 5-10]  
275 minutes vs 30 [IR: 15-60] minutes, p=0.005). This comparison was also statistically  
276 significant when ciprofloxacin was the culprit (IV route: 5 [5-10] minutes; oral route: 30  
277 [18.7-165] minutes; p=0.01) (Table E3).

### 278 **Methods used for diagnosis**

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

### 284 ***Skin tests***

285 SPTs were performed on 48 patients and PTs on 6, of which 22 were positive: 20 SPTs  
286 and 2 PTs. Of the positive SPTs, 13 (43.33%) were positive to moxifloxacin, 7 (8.53%)  
287 to ciprofloxacin, and 6 (9.83%) to levofloxacin (Table 3). When ciprofloxacin was the  
288 suspected culprit drug, SPTs to ciprofloxacin were positive in 16.7% of the tests and  
289 levofloxacin in 22.2%; when levofloxacin was the suspected culprit, 25% of SPTs were  
290 positive to levofloxacin and 80% to moxifloxacin. Finally, when the suspected culprit  
291 was moxifloxacin, 100% of SPTs were positive to moxifloxacin and 6.2% to  
292 ciprofloxacin (Table 3). Regarding the symptomatology of the reported reactions, the  
293 highest percentage of positive ST results was found for anaphylaxis (53.8%), followed  
294 by urticaria (33.3%). Although the interval between the last quinolone-induced reaction  
295 and the study was shorter in patients with positive STs compared to negative, no  
296 statistical difference was found (90 [interquartile range: 60-240] vs 120 [interquartile  
297 range: 60-172.5] days; p=1).

#### 298 ***Basophil activation test***

299 The BAT was positive in 68 (89.5%) of cases. A total of 56 (76.7%) cases were positive  
300 to ciprofloxacin, 35 (53.8%) to moxifloxacin, 26 (44.1%) to levofloxacin, 15 (83.3%) to  
301 norfloxacin, 10 (58.8%) to ofloxacin and 10 (55.5%) to lomefloxacin (Table 46). When  
302 ciprofloxacin was the culprit, BAT to ciprofloxacin was positive in 80%, to  
303 moxifloxacin in 60% and to levofloxacin in 47.4%; when levofloxacin was the culprit,  
304 BAT was positive to ciprofloxacin in 72.7%, to levofloxacin in 45.4% and to  
305 moxifloxacin in 20%; finally, when the culprit drug was moxifloxacin, BAT was  
306 positive to ciprofloxacin in 76.5%, to moxifloxacin in 62.5% and to levofloxacin in  
307 46.2% (Table 46). BAT was positive in 48 out of 49 (97.9%) cases reporting  
308 anaphylaxis, in 13 out of 18 (72.2%) cases of urticaria and in 5 (100%) cases of  
309 angioedema. Although the interval between the historical quinolone reaction and  
310 whether the patients were found to be allergic or not in the study was shorter in patients  
311 who gave a positive BAT compared to negative, no statistical differences were found  
312 (150 [interquartile range: 60-365] vs 395 [interquartile range: 60-1003.7] days;  
313 p=0.9909).

#### 314 ***Drug provocation test***

315 We performed 58 DPTs in 48 patients. A total of 34 DPTs with the culprit quinolone  
316 were carried out in cases with negative ST and BAT, all of which were positive: 23 in  
317 IR (16 with ciprofloxacin, 3 with levofloxacin, and 4 with moxifloxacin) and 11 in NIR  
318 (5 with ciprofloxacin, 2 with levofloxacin, and 4 with moxifloxacin). When the benefit

319 was considered to outweigh the risk, we carried out DPTs with an alternative quinolone  
320 in 24 cases, this was positive for 13 of these (11 IR and 2 NIR) (Table 5). When  
321 ciprofloxacin was the culprit, DPT to levofloxacin was positive in 60%; when  
322 levofloxacin was the culprit, DPT was positive to ciprofloxacin in 40%; when the  
323 culprit drug was moxifloxacin, DPT was positive to ciprofloxacin in 62.5%, and no case  
324 reacted to levofloxacin (Table 5). In all cases DPTs with quinolones induced mild  
325 symptoms (pruritus and wheals localized on different parts of the body) that  
326 disappeared 1-48 hours after administering antihistamine and corticosteroid treatment.

## 327 **DISCUSSION**

328 Although hypersensitivity reactions (HSRs) to quinolones represent an important health  
329 problem<sup>21</sup>, no large-scale study of patients suffering from them exists. To our  
330 knowledge, this is the largest published series of HSRs to quinolones to date. In our  
331 study, more than the 50% of patients reported anaphylaxis, most of whom suffered from  
332 immediate reactions (IRs), in agreement with previously published short  
333 series<sup>24,26,27,30,34</sup>. Moreover, data suggests that the risk of an HSR is different depending  
334 on the quinolone. Analyses of spontaneous reports implicate moxifloxacin triggers  
335 anaphylaxis in a higher proportion of cases than levofloxacin or ciprofloxacin<sup>8,9,37</sup>,  
336 which is in line with our results. Indeed, the risk of experiencing anaphylaxis was 2.2-  
337 fold higher when moxifloxacin was the culprit, which agrees with previously published  
338 data<sup>8,9,37</sup>. This may be due to the expanded use of quinolones or increased  
339 immunogenicity to newer quinolones.

340 The interval between drug intake and the appearance of symptoms is crucial for  
341 evaluating allergic reactions to drugs. Historically, reactions occurring less than one  
342 hour after drug intake are considered IRs, and those occurring after an hour are  
343 considered NIRs<sup>5,38</sup>. The former are thought to be induced by an IgE-mediated response,  
344 although an alternative non-IgE dependent mechanism may also be involved<sup>10,11</sup>. For  
345 the latter, the underlying mechanism remains a matter of debate, especially for those  
346 with a time interval of 1 to 6 hours after drug intake<sup>39-41</sup>. For betalactam antibiotics, the  
347 mechanism has been proposed to be non-IgE dependent, as some evidence suggests that  
348 these reactions are T-cell mediated<sup>40-41</sup>. On the other hand, for metamizole, a study of  
349 reactions occurring 1–8 hours after intake using basophil activation testing support an  
350 IgE-mediated<sup>42</sup>. However, to our knowledge, this mechanism has not yet been studied  
351 for quinolones. In this study, we have observed that around 25% of patients reported  
352 anaphylaxis 1 hour after quinolone intake, and more than 40% of them showed positive

353 results via BAT or SPT, suggesting that an IgE mechanism is likely. The interval  
354 between drug administration and reaction onset may be related to the production of as-  
355 yet unidentified metabolites and the route of administration. However, most patients in  
356 our study took the quinolone orally and no differences could be found in terms of  
357 administration route when considering drugs involved and symptoms reported. As such,  
358 we would suggest that the classification of reactions as IR or NIR based solely on a 1  
359 hour cut-off does not sufficiently reflect the extension of the pathophysiology of the  
360 reactions.

361 The diagnosis of HSRs to quinolones is still a matter of debate. A detailed clinical  
362 history is crucial as a first approach. We found that the chance of being confirmed as  
363 having an HSR to quinolones was 96 times higher in patients who reported  
364 moxifloxacin-induced anaphylaxis and 18 times higher in those reporting IRs. This risk  
365 decreased when ciprofloxacin was the culprit and the symptoms experienced in the  
366 reported reaction were MPE, FDE, urticaria, angioedema or a local reaction at the site  
367 of the administration of the drug. Concerning STs, there is controversy regarding their  
368 utility. Some authors consider they are useful, with a sensitivity of 71%, specificity of  
369 86%, and positive and negative predictive values of 50% and 94%, respectively having  
370 been reported previously<sup>24</sup>. However, other studies suggest that STs are not valid  
371 because they can produce false-negatives<sup>34,35</sup>, potentially missing important reactions  
372 and putting patients at risk, moreover they can also produce a large number of false-  
373 positive results when tested at high concentrations, which is attributed to non-specific  
374 histamine release by quinolones due to mast cell activation<sup>35,43-48</sup>. We decided not to  
375 perform intradermal tests in our patients based on this consideration. In our study, we  
376 found a low sensitivity for STs in general, although it was higher for severe reactions  
377 (anaphylaxis) and when levofloxacin and ciprofloxacin were the culprits.

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

384 Although cross-reactivity among quinolones remains a controversial issue, DPTs could  
385 be useful to find safe alternative quinolones. A high degree of cross-reactivity has been  
386 reported between the first- and second- generation quinolones<sup>22</sup>. Regarding the second

387 generation, cross-reactivity does not always occur within this group<sup>43,45,49</sup>, -which may  
388 be due to the production of different metabolites. The same phenomenon can occur for  
389 the newer (moxifloxacin) and the second- (ciprofloxacin) and third-generation  
390 (levofloxacin) quinolones<sup>50-52</sup>. A low degree of cross-reactivity has been found between  
391 levofloxacin and ciprofloxacin<sup>34</sup>. In our study, 60% of the patients who reported  
392 reactions induced by levofloxacin tolerated ciprofloxacin in DPT and 40% of cases  
393 tolerated levofloxacin when the reactions were induced by ciprofloxacin. DPT with  
394 levofloxacin was carried out for 2 cases who reported moxifloxacin-induced reactions,  
395 with neither patient experiencing an adverse reaction. Based on the data obtained from  
396 our large series of cases, we propose an algorithm for the diagnosis of quinolone-  
397 induced HSRs, as described in Figure 1.

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

411 The accurate diagnosis of quinolone-induced HSRs is an important issue not only due to  
412 their frequency, as described above, but also due to the fact that an important percentage  
413 of patients that report quinolone-induced HSRs report previous reactions to betalactams,  
414 drastically reducing their therapeutic options<sup>16</sup>. Referring patients with quinolone-  
415 induced HSRs for a full allergological evaluation is crucial to confirm or dismiss their  
416 reported allergy.

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573 Table 1. Clinical data for the reactions reported by the subjects included in the study, comparing cases confirmed as having HSRs to quinolones  
 574 and those confirmed as tolerant to these drugs. AE: Angioedema. FDE: Fixed drug eruption. HSR: Hypersensitivity reaction. MPE:  
 575 Maculopapular exanthema.  
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		HSR n=130	Tolerant n=42	p
Historical reaction symptoms; n (%)	Anaphylaxis	70 (53.8)	-	<0.0001
	Urticaria	41 (31.5)	26 (61.9)	0.0004
	AE	12 (9.2)	6 (14.3)	0.3522
	FDE	4 (3.1)	-	0.5732
	MPE	3 (2.3)	4 (9.5)	0.03
	Local reaction at the site of intravenous administration	-	6 (14.3)	0.0001
Drugs involved in historical reactions; n (%)	Ciprofloxacin	49 (37.7)	28 (66.7)	0.001
	Levofloxacin	21 (16.2)	10 (23.8)	0.2618
	Moxifloxacin	52 (40)	2 (4.8)	<0.0001
	Norfloxacin	3 (2.3)	2 (4.8)	0.5967
	Ofloxacin	1 (0.8)	-	1
	Pipemidic acid	2 (1.5)	-	1
	Unknown	2 (1.5)	-	1

Time interval intake-reaction, median (IR) (min)		30 (11.25-60)	7200 (2880-8640)	<0.0001
Time interval intake-reaction ≤1h; n (%)		112 (73.8)	8 (19)	<0.0001
Time interval intake-reaction >1h; n (%)		18 (26.2)	34 (81)	
Administration route; n (%)	Oral	109 (83.8)	33 (78.6)	0.4335
	Intravenous	21 (16.1)	9 (21.4)	
Number of episodes, median (IR)		1 (1-1)	1 (1-1)	0.08

Table 2. Clinical data for the reported reactions in cases confirmed as HSRs to quinolones. AE: Angioedema. FDE: Fixed drug eruption. MPE: Maculopapular exanthema.

		Immediate	Non-immediate	p
		n (%)	n (%)	
Historical reaction symptoms; n (%)	Anaphylaxis	70 (62.5)	-	<0.0001
	Urticaria	34 (30.4)	7 (38.9)	0.4696
	AE	8 (7.1)	4 (22.2)	0.04
	FDE	-	4 (22.2)	0.0002
	MPE	-	3 (16.7)	0.002
Drugs involved in historical reaction; n (%)	Ciprofloxacin	42 (37.5)	7 (38.9)	0.9101
	Levofloxacin	17 (15.2)	4 (22.2)	0.451
	Moxifloxacin	46 (41.1)	6 (33.3)	0.5339
	Norfloxacin	2 (1.8)	1 (5.6)	0.3629
	Ofloxacin	1 (0.9)	-	1
	Pipemidic acid	2 (1.8)	-	1
	Unknown	2 (1.8)	-	1

Table 3. Results of SPTs according to the drugs involved and the drug tested.

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



Table 4. Results of BATs according to the drugs involved and the drug tested.

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

Table 5. Results of DPTs performed according to the drugs involved and the drug tested.

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

## **FIGURE LEGENDS**

**Figure 1.** Algorithm proposed for the diagnosis of quinolone induced-HSRs. AGEP: Acute generalized exanthematous pustulosis. DPT: Drug provocation test. PT: Patch test. SJS: Stevens-Johnson syndrome. SPT: Skin prick test. TEN: Toxic epidermal necrolysis.

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3

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6

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56

57 **ABSTRACT**

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

61 **Objective:** To describe the clinical characteristics of patients with HSRs to quinolones  
62 and present methods for their diagnosis.

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

67 **Results:** We included 128 subjects confirmed as having HSRs to quinolones and 42  
68 found to be tolerant. Anaphylaxis was the most frequent entity in immediate HSRs and  
69 was most commonly induced by moxifloxacin. Patients were evaluated a median of 150  
70 days (interquartile range: 60-365) after the reaction. Of patients who underwent ST and  
71 BAT, 40.7% and 70% respectively were positive. DPT with a quinolone was performed  
72 in 48 cases, giving results depending on the culprit drug: when moxifloxacin was  
73 involved, 62.5% of patients gave a positive DPT to ciprofloxacin, whilst none reacted to  
74 levofloxacin. The risk of HSR was 96 times higher in subjects who reported  
75 moxifloxacin-induced anaphylaxis and 18 times higher in those reporting immediate  
76 reactions compared to clinical entities induced by quinolones other than moxifloxacin  
77 and non-immediate reactions.

78 **Conclusions:** The diagnosis of HSR to quinolones is complex. The use of clinical  
79 history is essential as a first step. BAT shows higher sensitivity than STs. DPTs can be  
80 useful for finding safe alternative quinolones.

81

82 **What is already known about this topic?**

83 Quinolones can induce hypersensitivity through several mechanisms, being the third  
84 most common drug associated with hypersensitivity, and the second most frequent drug  
85 inducing both IgE-mediated hypersensitivity and severe anaphylaxis. The optimal  
86 diagnostic approach remains a controversial topic.

87 **What does this article add to our knowledge?**

88 The risk of having quinolone hypersensitivity is higher for immediate reactions,  
89 particularly for moxifloxacin-induced anaphylaxis. The basophil activation test has a  
90 higher sensitivity than skin test. Drug provocation testing can be useful to identify safe  
91 alternative quinolones.

92 **How does this study impact current management guidelines**

93 We propose an algorithm for diagnosing quinolone-induced reactions, which should be  
94 classified according to the interval between drug intake and reaction onset, using a 6  
95 hour threshold. The algorithm includes skin, basophil activation, and drug provocation  
96 tests as necessary.

97

98 **KEYWORDS:** Adverse drug reaction; Anaphylaxis; Basophil activation test;  
99 Ciprofloxacin; Drug provocation test; Hypersensitivity; Levofloxacin; Moxifloxacin;  
100 Quinolones; Skin tests.

101

102 **ABBREVIATIONS:** Acute generalized exanthematous pustulosis (AGEP); Basophil  
103 activation test (BAT); Drug provocation test (DPT); Fixed drug eruption (FDE);  
104 Hypersensitivity reaction (HSR); Immediate reaction (IR); Intravenous (IV);  
105 Maculopapular exanthema (MPE); Non-immediate reaction (NIR); Skin prick test  
106 (SPT).

107

108

109 **INTRODUCTION**

110 Quinolones are antibiotics that are commonly prescribed for their effectiveness against  
111 Gram (+) and Gram (-) bacteria<sup>1-3</sup>. Adverse effects occur in 2-10% of people taking  
112 quinolones, however most of them are mild, mainly affecting the gastrointestinal or  
113 central nervous systems<sup>3,4</sup>. Quinolones can induce hypersensitivity reactions (HSRs)<sup>5</sup>  
114 through IgE-mediated reactions (immediate reactions, IRs) and T-cell dependent  
115 reactions (non-immediate reactions, NIRs)<sup>6,7</sup>. In addition, quinolones may also cause  
116 HSRs in drug-naïve patients<sup>8,9</sup>. A mechanism of mast cell activation via occupation of  
117 the human Mast-related G-protein receptor X2 (MRGPRX2) has been described for  
118 IRs<sup>10,11</sup> occurring in patients without previous exposure to quinolones<sup>12</sup>.

119 Although the absolute risk of an HSR related to quinolones is low (44.0 (95% CI: 34.8–  
120 53.3) emergency department visits/100,000 prescriptions)<sup>8</sup>, quinolones are the third  
121 most frequent drug associated with HSRs<sup>13</sup> in general, and the second most frequent in  
122 IgE-mediated HSRs. They are also the second most frequent cause of alert activation for  
123 antibiotic allergy in electronic hospital records<sup>14</sup> and severe drug-induced  
124 anaphylaxis<sup>13,15</sup>. In recent years, an increase in the percentage of patients with HSRs to  
125 these drugs has been detected, ranging from 0.54% in 2005 to 6.85% in 2010<sup>13</sup>. This is  
126 likely due to their increased prescription over the last decades<sup>16</sup>. The incidence of  
127 anaphylaxis induced by quinolones has been estimated to be 1.8–23 per 10 million days  
128 of treatment<sup>17,18</sup> and the prevalence of cutaneous adverse reaction to be 0.09%<sup>19</sup>.  
129 Quinolones are also one of the main triggers of acute generalized exanthematous  
130 pustulosis (AGEP), photosensitivity and vasculitis<sup>20</sup>.

131 HSRs to quinolones appear in an important percentage of patients (23%) previously  
132 diagnosed as allergic to betalactams: in fact, betalactam allergic patients have a 17 times  
133 higher risk of reacting to quinolones than those non-allergic. This represents an  
134 important health problem as it greatly decreases therapeutic options available<sup>16</sup>. In a  
135 large study of inpatients with common infections requiring antibiotic treatment,  
136 quinolone allergy occurred in 5.4% of patients who were already sensitive to  
137 betalactams<sup>21</sup>, leading to important restrictions for antibiotic prescription and  
138 subsequently poor prognosis of their infections.

139 The optimal diagnosis of quinolone HSRs is still a matter of debate. The value of skin  
140 tests (STs) is uncertain, and they have shown false positive results when quinolones are  
141 tested at high concentration<sup>22-25</sup>. The presence of specific IgE to quinolones has been  
142 reported using the sepharose radioimmunoassay, with a sensitivity of 54.5%<sup>26</sup>. The

143 basophil activation test (BAT) has shown promising results for the diagnosis of patients  
144 with IRs to quinolones<sup>27-29</sup>. However, other studies have contradicted these findings<sup>30,31</sup>.  
145 The gold standard, therefore, is the drug provocation test (DPT). However, this is not  
146 free of risk and not advisable in cases where the reaction might be severe.  
147 The aim of this study was to describe the clinical characteristics of a large group of  
148 patients with quinolone-induced HSRs and present methods for their diagnosis.  
149

## 150 **METHODS**

### 151 **Patients**

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

156 *Inclusion criteria.* Patients  $\geq 14$  years-old in whom the allergological study was  
157 completed were included and classified in two groups: A) Patients confirmed as having  
158 HSRs to quinolones (by positive STs, BATs or DPTs); and B) Patients confirmed as  
159 being non-allergic (tolerant) as they tolerated a DPT with the suspected culprit  
160 quinolone.

161 *Exclusion criteria.* Patients  $< 14$  years-old; patients in whom the allergological study  
162 was not completed so that the diagnosis could not be confirmed as being neither allergic  
163 nor tolerant to quinolones: pregnant or breastfeeding patients; patients taking beta-  
164 blockers or ACE inhibitors or with contraindications for epinephrine administration;  
165 patients who had acute infections and/or underlying cardiac, hepatic or renal diseases  
166 that contraindicated DPTs; and subjects with psychosomatic disorders.

### 167 **Clinical history**

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

### 173 **Skin testing**

174 For reactions suggestive of an IR, skin prick tests (SPTs) were carried out as described<sup>33</sup>  
175 using ciprofloxacin (at 0.02 and 0.2 mg/ml), levofloxacin (at 0.05 and 0.5 mg/ml), and  
176 moxifloxacin (one tablet of 400 mg suspended in NaCl). Intradermal tests were not  
177 performed to avoid false positive results as non-specific histamine release by quinolones  
178 has been reported<sup>34,35</sup>.

179 For reactions suggestive of a NIR, patch tests (PTs) were carried out and evaluated as  
180 described<sup>33</sup> by mixing powdered quinolone (ciprofloxacin, levofloxacin, and  
181 moxifloxacin) in petrolatum at 30% w/w.

### 182 **Basophil activation test**

183 In patients with a suspected IR, BATs were performed as described previously<sup>27</sup>, using  
184 ciprofloxacin (2 and 0.2 mg/ml), levofloxacin (4 and 2 mg/ml), moxifloxacin (2, 0.2 and  
185 0.1 mg/ml), norfloxacin (2, 0.2 and 0.1 mg/ml), ofloxacin (4, 2, 0.2 and 0.1 mg/ml), and  
186 lomefloxacin (4, 2, 0.2 and 0.1 mg/ml).

### 187 **Drug provocation test**

188 DPTs with ciprofloxacin, levofloxacin, and moxifloxacin were performed in a single  
189 blind manner if skin tests and BATs were negative<sup>36</sup>: placebo capsules were given at  
190 different times on the first day; increasing doses of quinolones were administered orally  
191 at intervals of 60 min (5, 20, 100 mg for ciprofloxacin and levofloxacin; 5, 30, 65 mg  
192 for moxifloxacin) on the second day. If these did not produce a reaction, three further  
193 doses of quinolones were given on the third day: 125, 125, 250 mg (accumulative dose  
194 500 mg) for ciprofloxacin and levofloxacin; 100, 100, 200 mg (accumulative dose 400  
195 mg) for moxifloxacin. The three test days were separated by 1 week. If cutaneous and/or  
196 respiratory symptoms or alterations in vital signs appeared, the procedure was stopped  
197 and the symptoms were evaluated and treated. If no symptoms appeared during graded  
198 challenge, the therapeutic dose was achieved. This was then followed by taking the full  
199 dose at home, starting 24 hours after the graded challenge. Before beginning the DPT  
200 procedure, patients were stable and their forced expiratory volume in 1s had to be at  
201 least 80% of the predicted value, with an absolute volume of at least 1.5 L. Medications  
202 were stopped before DPT according to international guidelines<sup>36</sup>.

### 203 **Statistical analysis**

204 Data analysis was performed using Chi-square analysis to test differences in nominal  
205 variables between groups, the Fisher test was used when there were no criteria for using  
206 the Chi-square test and the Mann–Whitney test was used for quantitative variables. All  
207 reported p values represented two-tailed tests, with values <0.05 considered statistically  
208 significant. A logistic regression analysis was performed to establish the characteristics  
209 associated with the diagnosis of HSR or tolerance to quinolones and with the diagnosis  
210 of immediate anaphylaxis. The following variables were analysed: gender, age, time  
211 interval between drug intake and the onset of the reaction, symptoms experienced, drugs  
212 involved, time interval between drug reaction and study, and number of episodes.

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



216 **RESULTS**

217 A total of 612 patients with a clinical history suggestive of an HSR to quinolones were  
218 evaluated. Of these, full diagnosis could not be achieved for 442 patients: 361 patients  
219 that gave a negative ST and negative BAT could not undergo DPT to quinolones due to  
220 age, comorbidities or because it was contraindicated due to the potential severity of the  
221 reaction; 78 did not give consent for the allergological tests (STs, BAT and/or DPTs);  
222 and 3 were excluded due to pregnancy. For the remaining 170 patients a full diagnosis  
223 could be achieved: 128 were confirmed as having HSRs to quinolones and 42 as non-  
224 allergic (tolerant) to quinolones.

225 **Clinical data of the subjects included in the study**

226 The 170 included subjects with confirmed diagnosis had a median age of 53  
227 [interquartile range: 40–63.25] years, and 126 (74.1%) were female. The majority of  
228 cases reported only one previous episode induced by quinolone intake, except for 2  
229 cases who reported 2 previous IRs. As such, the patients included in the study reported a  
230 total of 172 previous reactions: 120 IRs and 52 NIRs, with the percentage of IRs higher  
231 in those confirmed as having HSRs compared to the tolerant group (73.8% vs 19%;  
232  $p<0.0001$ ) (Table 1). Most reported reactions were induced by oral quinolones (142;  
233 82.5%), the rest by intravenous route (30;17.4%). In terms of the symptoms of reported  
234 reactions, the percentage of anaphylaxis reactions was higher in subjects confirmed as  
235 having HSR ( $p<0.0001$ ); whereas urticaria ( $p=0.0004$ ), local reaction at the site of IV  
236 administration ( $p=0.0001$ ) and MPE ( $p=0.03$ ) were more frequently report by subjects  
237 that were found to be as tolerant (Table 1). Moxifloxacin was the most frequent culprit  
238 quinolone in patients with confirmed HSRs; ciprofloxacin was more frequent in subjects  
239 confirmed as tolerant ( $p<0.0001$  and  $p=0.001$ , respectively) (Table 1). In subjects  
240 confirmed as having HSRs, most cases of anaphylaxis were induced by moxifloxacin  
241 (52.9%;  $p=0.002$ ); urticaria and angioedema were mostly induced by ciprofloxacin  
242 (48.8% and 66.7%, respectively), although these differences was not found to be  
243 statistically significant (Table E1). For those found to be tolerant, ciprofloxacin was the  
244 most frequent cause of both urticaria and angioedema (69.2% and 66.7%, respectively),  
245 as well as of local reactions at the site of IV administration (66.7%) ( $p>0.05$ ) (Table  
246 E1).

247 The logistic regression analysis showed that the risk of being confirmed as HSR was  
248 higher for cases who reported moxifloxacin-induced anaphylaxis (OR: 96.16; CI: 6.172-  
249 Inf;  $p=0.009$ ) and for those reporting IRs (OR: 18.856; CI: 5.196-271.449;  $p<0.0001$ )

250 compared to cases who reported other symptoms induced by other quinolones and  
251 NIRs. Moreover, the risk for being confirmed as HSR decreased when ciprofloxacin  
252 was the culprit (OR: 0.107; CI: 0.002-0.741; p=0.04) and the symptoms reported were  
253 MPE, FDE, urticaria, angioedema (OR: 0.053; CI: 0-0.452; p=0.03), or a local reaction  
254 at the site of IV administration (OR: 0.001; CI: 0-0.016; p=0.0006). No significant  
255 associations were found for the other variables, and there were no interactions between  
256 variables.

### 257 **Analysis of the patients confirmed as suffering HSRs to quinolones**

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

262 Anaphylaxis was the most frequent reported symptom among IRs (p<0.0001) and  
263 urticaria among NIRs (p>0.05) (Table 2). It is of note that the 7 (25%) of patients  
264 reporting reactions within the interval of 1-6 hours showed symptoms compatible with  
265 anaphylaxis. Moxifloxacin was the most frequent quinolone involved in IRs and  
266 ciprofloxacin in NIRs (41.1% and 38.9%, respectively) (Table 2). Anaphylaxis was  
267 induced primarily by moxifloxacin in IRs (52.9%; OR=2.935 (IC:1.418-6.075),  
268 p=0.003) whereas most urticaria and angioedema was induced by ciprofloxacin (52.9%  
269 and 75%, respectively). Considering NIRs, moxifloxacin was the culprit in most cases  
270 reporting urticaria (42.8%) and ciprofloxacin in angioedema reporting-cases (50%)  
271 (Table E2). The time interval between intake and onset of the reaction was shorter when  
272 the drug was administered by an IV route compared to the oral route (5 [IR: 5-10]  
273 minutes vs 30 [IR: 15-60] minutes, p=0.005). This comparison was also statistically  
274 significant when ciprofloxacin was the culprit (IV route: 5 [5-10] minutes; oral route: 30  
275 [18.7-165] minutes; p=0.01) (Table E3).

### 276 **Methods used for diagnosis**

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

### 282 **Skin tests**

283 SPTs were performed on 48 patients and PTs on 6, of which 22 were positive: 20 SPTs  
284 and 2 PTs. Of the positive SPTs, 13 (43.33%) were positive to moxifloxacin, 7 (8.53%)  
285 to ciprofloxacin, and 6 (9.83%) to levofloxacin (Table 3). When ciprofloxacin was the  
286 suspected culprit drug, SPTs to ciprofloxacin were positive in 16.7% of the tests and  
287 levofloxacin in 22.2%; when levofloxacin was the suspected culprit, 25% of SPTs were  
288 positive to levofloxacin and 80% to moxifloxacin. Finally, when the suspected culprit  
289 was moxifloxacin, 100% of SPTs were positive to moxifloxacin and 6.2% to  
290 ciprofloxacin (Table 3). Regarding the symptomatology of the reported reactions, the  
291 highest percentage of positive ST results was found for anaphylaxis (53.8%), followed  
292 by urticaria (33.3%). Although the interval between the last quinolone-induced reaction  
293 and the study was shorter in patients with positive STs compared to negative, no  
294 statistical difference was found (90 [interquartile range: 60-240] vs 120 [interquartile  
295 range: 60-172.5] days; p=1).

#### 296 ***Basophil activation test***

297 The BAT was positive in 68 (89.5%) of cases. A total of 56 (76.7%) cases were positive  
298 to ciprofloxacin, 35 (53.8%) to moxifloxacin, 26 (44.1%) to levofloxacin, 15 (83.3%) to  
299 norfloxacin, 10 (58.8%) to ofloxacin and 10 (55.5%) to lomefloxacin (Table 4). When  
300 ciprofloxacin was the culprit, BAT to ciprofloxacin was positive in 80%, to  
301 moxifloxacin in 60% and to levofloxacin in 47.4%; when levofloxacin was the culprit,  
302 BAT was positive to ciprofloxacin in 72.7%, to levofloxacin in 45.4% and to  
303 moxifloxacin in 20%; finally, when the culprit drug was moxifloxacin, BAT was  
304 positive to ciprofloxacin in 76.5%, to moxifloxacin in 62.5% and to levofloxacin in  
305 46.2% (Table 4). BAT was positive in 48 out of 49 (97.9%) cases reporting  
306 anaphylaxis, in 13 out of 18 (72.2%) cases of urticaria and in 5 (100%) cases of  
307 angioedema. Although the interval between the historical quinolone reaction and  
308 whether the patients were found to be allergic or not in the study was shorter in patients  
309 who gave a positive BAT compared to negative, no statistical differences were found  
310 (150 [interquartile range: 60-365] vs 395 [interquartile range: 60-1003.7] days;  
311 p=0.9909).

#### 312 ***Drug provocation test***

313 We performed 58 DPTs in 48 patients. A total of 34 DPTs with the culprit quinolone  
314 were carried out in cases with negative ST and BAT, all of which were positive: 23 in  
315 IR (16 with ciprofloxacin, 3 with levofloxacin, and 4 with moxifloxacin) and 11 in NIR  
316 (5 with ciprofloxacin, 2 with levofloxacin, and 4 with moxifloxacin). When the benefit

317 was considered to outweigh the risk, we carried out DPTs with an alternative quinolone  
318 in 24 cases, this was positive for 13 of these (11 IR and 2 NIR) (Table 5). When  
319 ciprofloxacin was the culprit, DPT to levofloxacin was positive in 60%; when  
320 levofloxacin was the culprit, DPT was positive to ciprofloxacin in 40%; when the  
321 culprit drug was moxifloxacin, DPT was positive to ciprofloxacin in 62.5%, and no case  
322 reacted to levofloxacin (Table 5). In all cases DPTs with quinolones induced mild  
323 symptoms (pruritus and wheals localized on different parts of the body) that  
324 disappeared 1-48 hours after administering antihistamine and corticosteroid treatment.

## 325 **DISCUSSION**

326 Although hypersensitivity reactions (HSRs) to quinolones represent an important health  
327 problem<sup>21</sup>, no large-scale study of patients suffering from them exists. To our  
328 knowledge, this is the largest published series of HSRs to quinolones to date. In our  
329 study, more than the 50% of patients reported anaphylaxis, most of whom suffered from  
330 immediate reactions (IRs), in agreement with previously published short  
331 series<sup>24,26,27,30,34</sup>. Moreover, data suggests that the risk of an HSR is different depending  
332 on the quinolone. Analyses of spontaneous reports implicate moxifloxacin triggers  
333 anaphylaxis in a higher proportion of cases than levofloxacin or ciprofloxacin<sup>8,9,37</sup>,  
334 which is in line with our results. Indeed, the risk of experiencing anaphylaxis was 2.2-  
335 fold higher when moxifloxacin was the culprit, which agrees with previously published  
336 data<sup>8,9,37</sup>. This may be due to the expanded use of quinolones or increased  
337 immunogenicity to newer quinolones.

338 The interval between drug intake and the appearance of symptoms is crucial for  
339 evaluating allergic reactions to drugs. Historically, reactions occurring less than one  
340 hour after drug intake are considered IRs, and those occurring after an hour are  
341 considered NIRs<sup>5,38</sup>. The former are thought to be induced by an IgE-mediated response,  
342 although an alternative non-IgE dependent mechanism may also be involved<sup>10,11</sup>. For the  
343 latter, the underlying mechanism remains a matter of debate, especially for those with a  
344 time interval of 1 to 6 hours after drug intake<sup>39-41</sup>. For betalactam antibiotics, the  
345 mechanism has been proposed to be non-IgE dependent, as some evidence suggests that  
346 these reactions are T-cell mediated<sup>40-41</sup>. On the other hand, for metamizole, a study of  
347 reactions occurring 1–8 hours after intake using basophil activation testing support an  
348 IgE-mediated<sup>42</sup>. However, to our knowledge, this mechanism has not yet been studied  
349 for quinolones. In this study, we have observed that around 25% of patients reported  
350 anaphylaxis 1 hour after quinolone intake, and more than 40% of them showed positive

351 results via BAT or SPT, suggesting that an IgE mechanism is likely. The interval  
352 between drug administration and reaction onset may be related to the production of as-  
353 yet unidentified metabolites and the route of administration. However, most patients in  
354 our study took the quinolone orally and no differences could be found in terms of  
355 administration route when considering drugs involved and symptoms reported. As such,  
356 we would suggest that the classification of reactions as IR or NIR based solely on a 1  
357 hour cut-off does not sufficiently reflect the extension of the pathophysiology of the  
358 reactions.

359 The diagnosis of HSRs to quinolones is still a matter of debate. A detailed clinical  
360 history is crucial as a first approach. We found that the chance of being confirmed as  
361 having an HSR to quinolones was 96 times higher in patients who reported  
362 moxifloxacin-induced anaphylaxis and 18 times higher in those reporting IRs. This risk  
363 decreased when ciprofloxacin was the culprit and the symptoms experienced in the  
364 reported reaction were MPE, FDE, urticaria, angioedema or a local reaction at the site  
365 of the administration of the drug. Concerning STs, there is controversy regarding their  
366 utility. Some authors consider they are useful, with a sensitivity of 71%, specificity of  
367 86%, and positive and negative predictive values of 50% and 94%, respectively having  
368 been reported previously<sup>24</sup>. However, other studies suggest that STs are not valid  
369 because they can produce false-negatives<sup>34,35</sup>, potentially missing important reactions  
370 and putting patients at risk, moreover they can also produce a large number of false-  
371 positive results when tested at high concentrations, which is attributed to non-specific  
372 histamine release by quinolones due to mast cell activation<sup>35,43-48</sup>. We decided not to  
373 perform intradermal tests in our patients based on this consideration. In our study, we  
374 found a low sensitivity for STs in general, although it was higher for severe reactions  
375 (anaphylaxis) and when levofloxacin and ciprofloxacin were the culprits.

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

382 Although cross-reactivity among quinolones remains a controversial issue, DPTs could  
383 be useful to find safe alternative quinolones. A high degree of cross-reactivity has been  
384 reported between the first- and second- generation quinolones<sup>22</sup>. Regarding the second

385 generation, cross-reactivity does not always occur within this group<sup>43,45,49</sup>, which may  
386 be due to the production of different metabolites. The same phenomenon can occur for  
387 the newer (moxifloxacin) and the second- (ciprofloxacin) and third-generation  
388 (levofloxacin) quinolones<sup>50-52</sup>. A low degree of cross-reactivity has been found between  
389 levofloxacin and ciprofloxacin<sup>34</sup>. In our study, 60% of the patients who reported  
390 reactions induced by levofloxacin tolerated ciprofloxacin in DPT and 40% of cases  
391 tolerated levofloxacin when the reactions were induced by ciprofloxacin. DPT with  
392 levofloxacin was carried out for 2 cases who reported moxifloxacin-induced reactions,  
393 with neither patient experiencing an adverse reaction. Based on the data obtained from  
394 our large series of cases, we propose an algorithm for the diagnosis of quinolone-  
395 induced HSRs, as described in Figure 1.

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

409 The accurate diagnosis of quinolone-induced HSRs is an important issue not only due to  
410 their frequency, as described above, but also due to the fact that an important percentage  
411 of patients that report quinolone-induced HSRs report previous reactions to betalactams,  
412 drastically reducing their therapeutic options<sup>16</sup>. Referring patients with quinolone-  
413 induced HSRs for a full allergological evaluation is crucial to confirm or dismiss their  
414 reported allergy.

415

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568 quinolones: moxifloxacin cross-reactivity. *Journal of investigational allergology &*  
569 *clinical immunology*. 2005; 15(2): 146-9.

570 Table 1. Clinical data for the reactions reported by the subjects included in the study, comparing cases confirmed as having HSRs to quinolones  
571 and those confirmed as tolerant to these drugs. AE: Angioedema. FDE: Fixed drug eruption. HSR: Hypersensitivity reaction. MPE:  
572 Maculopapular exanthema.  
573  
574

		HSR n=130	Tolerant n=42	p
Historical reaction symptoms; n (%)	Anaphylaxis	70 (53.8)	-	<0.0001
	Urticaria	41 (31.5)	26 (61.9)	0.0004
	AE	12 (9.2)	6 (14.3)	0.3522
	FDE	4 (3.1)	-	0.5732
	MPE	3 (2.3)	4 (9.5)	0.03
	Local reaction at the site of intravenous administration	-	6 (14.3)	0.0001
Drugs involved in historical reactions; n (%)	Ciprofloxacin	49 (37.7)	28 (66.7)	0.001
	Levofloxacin	21 (16.2)	10 (23.8)	0.2618
	Moxifloxacin	52 (40)	2 (4.8)	<0.0001
	Norfloxacin	3 (2.3)	2 (4.8)	0.5967
	Ofloxacin	1 (0.8)	-	1
	Pipemidic acid	2 (1.5)	-	1
	Unknown	2 (1.5)	-	1

Time interval intake-reaction, median (IR) (min)		30 (11.25-60)	7200 (2880-8640)	<0.0001
Time interval intake-reaction ≤1h; n (%)		112 (73.8)	8 (19)	<0.0001
Time interval intake-reaction >1h; n (%)		18 (26.2)	34 (81)	
Administration route; n (%)	Oral	109 (83.8)	33 (78.6)	0.4335
	Intravenous	21 (16.1)	9 (21.4)	
Number of episodes, median (IR)		1 (1-1)	1 (1-1)	0.08

Table 2. Clinical data for the reported reactions in cases confirmed as HSRs to quinolones. AE: Angioedema. FDE: Fixed drug eruption. MPE: Maculopapular exanthema.

		Immediate	Non-immediate	p
		n (%)	n (%)	
Historical reaction symptoms; n (%)	Anaphylaxis	70 (62.5)	-	<0.0001
	Urticaria	34 (30.4)	7 (38.9)	0.4696
	AE	8 (7.1)	4 (22.2)	0.04
	FDE	-	4 (22.2)	0.0002
	MPE	-	3 (16.7)	0.002
Drugs involved in historical reaction; n (%)	Ciprofloxacin	42 (37.5)	7 (38.9)	0.9101
	Levofloxacin	17 (15.2)	4 (22.2)	0.451
	Moxifloxacin	46 (41.1)	6 (33.3)	0.5339
	Norfloxacin	2 (1.8)	1 (5.6)	0.3629
	Ofloxacin	1 (0.9)	-	1
	Pipemidic acid	2 (1.8)	-	1
	Unknown	2 (1.8)	-	1

Table 3. Results of SPTs according to the drugs involved and the drug tested.

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

Table 4. Results of BATs according to the drugs involved and the drug tested.

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

Table 5. Results of DPTs performed according to the drugs involved and the drug tested.

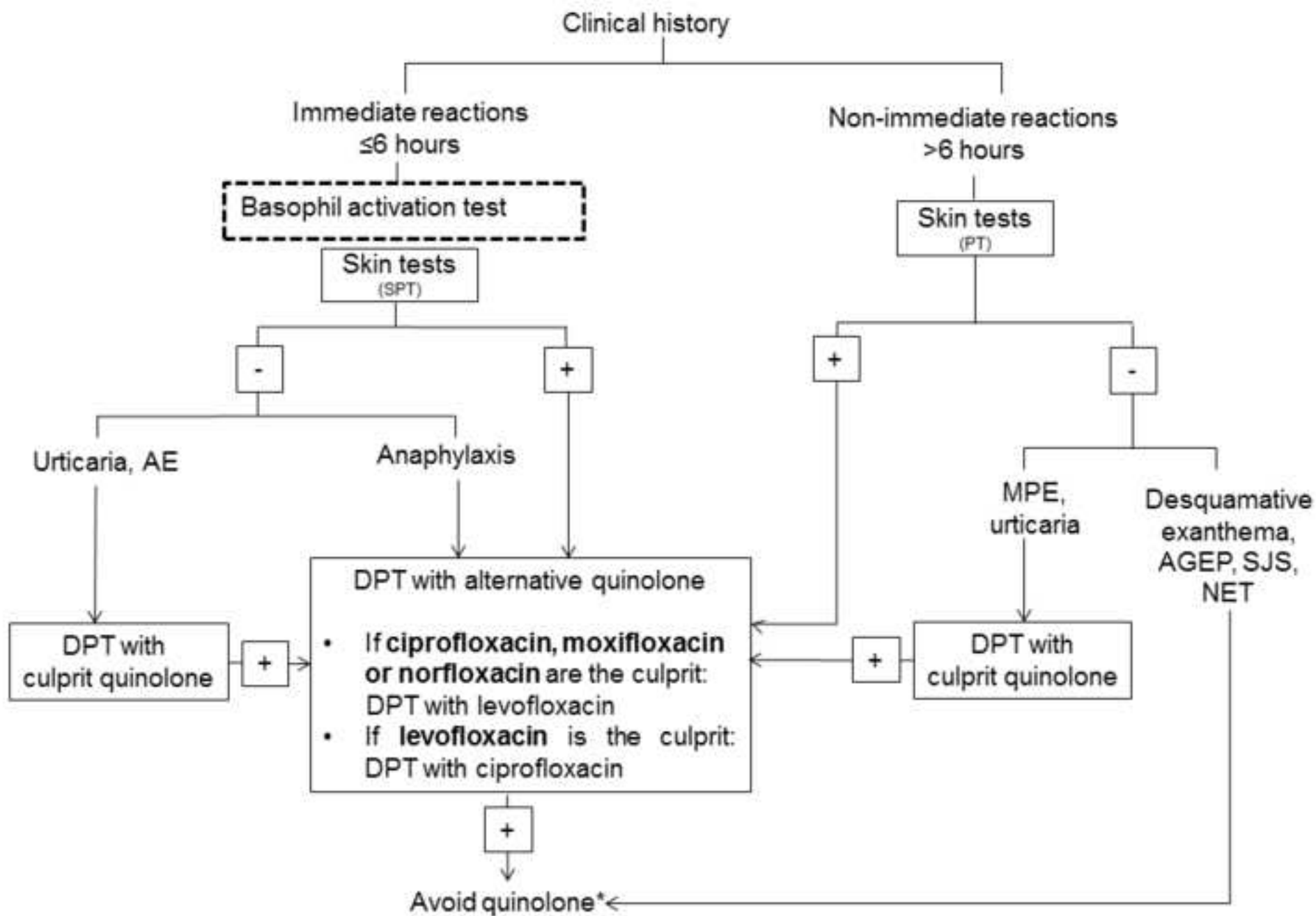
		Drugs used in DPT; positive cases/cases in which the test was performed (%)		
		Ciprofloxacin	Levofloxacin	Moxifloxacin
Drugs involved in historical reaction; positive cases/cases in which the test was performed (%)	Ciprofloxacin	21/21	3/5 (60%)	-
	Levofloxacin	2/5 (40%)	5/5	0/1
	Moxifloxacin	5/8 (62.5%)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



## **FIGURE LEGENDS**

**Figure 1.** Algorithm proposed for the diagnosis of quinolone induced-HSRs. AGEP: Acute generalized exanthematous pustulosis. DPT: Drug provocation test. PT: Patch test. SJS: Stevens-Johnson syndrome. SPT: Skin prick test. TEN: Toxic epidermal necrolysis.





\*When a given quinolone is the only therapeutic option available, desensitization could be indicated

Table E1. Analysis of the drug involved in each reaction according to the symptoms reported for cases confirmed as having HSR to quinolones and those confirmed as tolerant. The percentages are given for the symptoms reported (columns). AE: Angioedema. FDE: Fixed drug eruption. HSR: Hypersensitivity reaction. IV: Intravenous. MPE: Maculopapular exanthema.

	HSR					Tolerant			
	Anaphylaxis	Urticaria	AE	FDE	MPE	Urticaria	AE	MPE	Local reaction at IV site administration
Ciprofloxacin	18 (25.7)	20 (48.8)	8 (66.7)	1 (25)	2 (66.7)	18 (69.2)	4 (66.7)	2 (50)	4 (66.7)
Levofloxacin	12 (17.1)	6 (14.6)	2 (16.7)	-	1 (33.3)	4 (15.4)	2 (33.3)	2 (50)	2 (33.3)
Moxifloxacin	37 (52.9)	11 (26.8)	2 (16.7)	2 (50)	-	2 (7.7)	-	-	-
Norfloxacin	-	2 (5.8)	-	1 (25)	-	2 (7.7)	-	-	-
Ofloxacin	1 (1.4)	-	-	-	-	-	-	-	-
Pipemidic acid	1 (1.4)	1 (2.4)	-	-	-	-	-	-	-
Unknown	1 (1.4)	1 (2.4)	-	-	-	-	-	-	-
p	0.002	0.2366	0.3949	0.2391	0.4201	0.2759	0.8126	0.5244	0.8126

Table E2. Quinolones involved in the reported reactions according to the symptoms experienced in cases confirmed as HSR to quinolones. . AE: Angioedema. FDE: Fixed drug eruption. MPE: Maculopapular exanthema.

	Immediate; n (%)			Non-immediate; n (%)			
	Anaphylaxis	Urticaria	AE	Urticaria	AE	FDE	MPE
Ciprofloxacin	18 (25.7)	18 (52.9)	6 (75)	2 (28.6)	2 (50)	1 (25)	2 (66.7)
Levofloxacin	12 (17.1)	4 (11.8)	1 (25)	2 (28.6)	1 (25)	-	1 (33.3)
Moxifloxacin	37 (52.8)	8 (23.5)	1 (25)	3 (42.8)	1 (25)	2 (50)	-
Norfloxacin	-	2 (5.9)	-	-	-	1 (25)	-
Ofloxacin	1 (1.4)	-	-	-	-	-	-
Pipemidic acid	1 (1.4)	1 (2.9)	-	-	-	-	-
Unknown	1 (1.4)	1 (2.9)	-	-	-	-	-
p	0.001	0.01	0.3937	0.6894	1	0.2154	0.511

Table E3. Comparison of time interval between drug intake and the onset of the reaction for oral and intravenous routes, according to the quinolone involved and the symptoms reported in the reaction. AE: Angioedema. FDE: Fixed drug eruption. MPE: Maculopapular exanthema.

		Time interval between drug intake and reaction onset mediane (IR) minutes		
		Oral	Intravenous	p
Drugs involved	Ciprofloxacin	30 (18.7-165)	5 (5-10)	0.01
	Levofloxacin	30 (17.5-240)	-	-
	Moxifloxacin	30 (10-30)	-	-
	Norfloxacin	27.50 (26.2-28.75)	-	-
	Ofloxacin	17.5 (11.2-23.75)	-	-
	Pipemidic acid	70 (45-95)	-	-
	Unknown	20 (15-25)	-	-
Symptoms experienced in reported reactions	Anaphylaxis	30 (10-30)	7.5 (5-10)	0.04
	Urticaria	30 (30-120)	5 (5-5)	0.1479
	AE	600 (240-2880)	17.5 (11.2-23.7)	0.118
	FDE	1740 (1170-2310)	-	-
	MPE	720 (660-1800)	-	-