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Clinical implications:
We confirmed the diagnosis of DHR to quinolones in a quarter of patients, mainly by DPT. We showed an over 90% match between the semiology and chronology of index reactions and those elicited by DPT. We suggest a DPT protocol of 5 doses, with 2 supplementary low doses in case of anaphylactic index reactions.

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Currently, quinolones are the second-most used antibiotic line in human medicine in Europe, after betalactams (1). Drug hypersensitivity reactions (DHR) to this group of medication are mostly immediate and moxifloxacin singles out as a trigger of life-threatening anaphylaxis (2,3).

In this study, we retrospectively describe our experience with quinolone allergy work up, including skin tests (ST) and drug provocation test (DPT). The patients (children and adults at the time of the allergy work-up) were retrieved from the Drug Allergy and Hypersensitivity Database (DAHD) (2004-2019) and from the database of the Allergy Unit of the Metz Hospital since 2015. ST were performed according to the concentrations presented in **Table E1** in both centers.

We performed a descriptive analysis of the cases then used logistic regression to search for risk factors of confirmed DHR. Variables with $p<0.15$ in univariate analysis were included in the multivariate model. Odds ratios were expressed with 95% confidence interval (95% CI). A p value < 0.05 was considered statistically significant. The R software (R 3.4.1) was used for the analysis.

To analyze DPT, we performed survival analysis to detect reactive doses (RD, expressed as a ratio between the cumulative reactive dose and the total DPT dose for a given patient; *i.e.*, the dose reached if DPT was to be completed). RD was expressed as a percentage. The studied event was occurrence of a reaction during DPT.

Quinolone DPT performed in the two centers were conducted according to an open empirical protocol, with 30-minute incremental doses, followed by a compulsory surveillance period of 1 hour 30 minutes after the last administered dose. In the Allergy Unit in Montpellier, the protocols (4) described in **Table E1** were used for an adult with no need of dose adjustment.

In cases of anaphylaxis, the first dose was 1/10 of the initial dose (e.g., 0.1 mg instead of 1 mg).

The same protocol was used for immediate (4) and mild-to-moderate nonimmediate reactions, and general DPT contraindications (namely severe cutaneous adverse reactions) were observed (5). The patients (or their parents, in case of children) gave their written informed consent to take part in this study for which approval from the local ethical committee was

granted (IRB-MTP-2020-01-202000334). In all the patients in Metz, a basophil activation test (BAT) was also performed.

One hundred fifty-nine patients (139 from Montpellier and 20 from Metz) were analyzed in this study (20 other patients, 19 from Montpellier and one from Metz were excluded due to inconclusive data). They were mostly adults (mean age: 50.6±16.4 years; two children were tested, aged six and ten). Three quarters (117, 73.6%) were female patients. The most frequently involved quinolone in the index reaction was ofloxacin (50 cases, 31.4%), followed by ciprofloxacin (42 cases, 26.4%), levofloxacin (30 cases, 18.9%) and moxifloxacin (14 cases, 8.8%). Almost half of the index reactions (71 cases, 44.4%) were immediate. Thirty-nine patients could provide precise data on chronology (range: 1-240 minutes), and in half of these cases, the reaction occurred within 20 minutes after the intake (IQR25-75: 10-30 min). The index reactions were elicited on Day 1 of exposure for most patients (median: 1, IQR25-75: 1-2). They were mainly urticarial (40.5%) or anaphylactic (20%). Only a minority of patients (15%) recalled a previous course of quinolone. Patients were tested within a median time of 48 months (IQR25-75: 8-144) after their last episode.

ST were performed in two thirds of patients (100 cases, 62.9%), and they were positive in nine of them (9% of the tested patients) (**Table E2**). Two of these patients had a DPT for an alternative quinolone (and they tolerated it). All nine had presented immediate reactions, seven with a history of anaphylaxis (five shocks) and two with urticaria/angioedema. In 31 patients, 40 DPTs were positive for different quinolones. Of note, the majority of patients were initially tested (in ST and DPT) for their culprit quinolone (91.8% match). Patients who were skin tested prior to DPT had more immediate reactions (p=0.01) than those who did not undergo ST, but there were no other differences between these groups in terms of type of initial reaction (p=0.2), type of culprit quinolone (p=0.5), previous use of quinolone (p=0.10), or confirmed hypersensitivity (p=0.5).

All in all, DHR to quinolones was confirmed in a quarter of the tested patients (40, 25.1%). **Table 1** describes in detail the characteristics of these patients. As demonstrated by multivariate analysis, several clinical predictors were independently associated with a confirmed DHR. Thus, having an immediate index reaction significantly increased the risk by 3-fold (OR=3.1, 95% CI: 1.0-9.7), anaphylaxis by 8-fold (OR=8.3, 95% CI: 1.7-38.9), but urticaria/angioedema did not (OR=3.1, 95% CI:0.8-12.1), and neither did the delay between the reaction and tests. Moxifloxacin exposure was the strongest risk factor, associated with a

13-fold increased risk of confirmed DHR (OR=13.5, 95% CI:2.8-63.9). Of all the patients with anaphylaxis in their index history, 21.2% were diagnosed by positive ST (7 cases), 36.3% by DPT (12 cases) and in 42.4%, the diagnosis of DHR was ruled out and patients tolerated the DPT with the culprit drug.

The reactions elicited during the 40 positive DPT were anaphylactic (8 DPT, 20%) or cutaneous (32 DPT, 80%). In 27 cases, the index reactions had been cutaneous, in 12 anaphylactic and in one, the patient had presented an isolated bronchospasm. Of the 12 index anaphylactic reactions who underwent a DPT, they were all captured either during DPT or during the compulsory surveillance period after DPT completion (7 anaphylaxis, 5 milder reactions) and they were treated with antihistamines H1 and corticosteroids (none received epinephrine), with no sequalae. The reactions elicited during DPT were of similar or lesser severity compared to the index reaction in all but one patient (2.5%). Indeed, although his index reaction was described as cutaneous and of delayed chronology, i.e., 6-24h after the last intake, he presented anaphylaxis at 17.1% of ofloxacin daily therapeutic dose). The global match between the chronology of the index reaction and that of the DPT was 81% (30 of the 37 DPT with both chronologies available: 26 for immediate reactions and 4 for delayed reactions). In 6 cases, there was a miss-match, with 5 non-immediate index reactions eliciting an immediate symptomatology and one presumably immediate reaction occurring late (4 hours after the last intake during DPT; this reaction turned out to be a fixed drug eruption). Thus, for immediate and non-immediate index reactions, in 96.3% and 100% of cases respectively, the patients reacted either within the same delay after the last dose, or earlier.

Figure 1 and **Table 2** shows the distribution of the events and in particular of the anaphylactic events on the Kaplan Meier curve. Visually, there were several steep drops, evocative of the occurrence of several events at close doses, namely before: RD=1%, RD=20%, RD=50% and at RD=100%. Considering this distribution, we then focused on the severity of the reactions and we could observe that in our series, anaphylaxis in DPT started at RD=0.1%. Moreover, in 75% of the cases, anaphylaxis in DPT had already occurred before RD=20%, the following thresholds for anaphylaxis being at RD=41% and RD=96.6%, respectively.

For the 20 patients explored in the Metz hospital (6 immediate and 14 non-immediate reactions), a BAT was systematically performed. It was negative in all the patients, as were ST and DPT.

Exploring quinolone DHR suspicions has become increasingly important in the last decade, with the increased use of these antibiotics. In France, and according to the National Medicine Agency surveys, fluoroquinolones are the second most used antibiotics, following beta-lactams. Our data confirm (3,5,8) that moxifloxacin is the quinolone most frequently associated with a confirmed diagnosis of DHR. The large 95% CI, however, are evocative of a small sample size.

Although non-immediate DHR to quinolones have been described and confirmed, immediate DHR are more frequent and mostly attributable to 2 mechanisms: IgE-mediated (with evidence of sIgE to quinolones (6) and via the MGRPX2 activation pathway, which would not need a previous sensitizing contact (3,9). Indeed, in our cohort, up to 45% of patients who did not recall a previous use of quinolone had a confirmed DHR following allergy work-up. However, unknown previous contact cannot be ruled out without having access to the full lifelong patient's previous health records. Moreover, quinolones are widely used in the food industry (poultry, rabbit, veal) and in fish farming (1).

ST for immediate reactions are controversial because they are considered irritant (beyond 1/100 dilutions of the IV products) (2) or having low sensitivity for non-immediate reactions, and *in vitro* tests are neither sufficiently sensitive, nor easily accessible (2,3). Therefore, DPT seems the method of choice to explore quinolone DHR. It has been suggested to perform DPT directly to an alternative quinolone and not to the culprit one, due to the potential anaphylactic risk, which materialized in 20% of DPT in our series. Nevertheless, of all the patients who had initially described anaphylaxis, the diagnosis was ruled out in up to 42.4%, proving the utility of DPT.

The DPT to quinolones used in our Units were empirical (but similar over the past 20 years) and included 5 to 7 doses, depending on the drug (preceded by a supplementary low dose in case of anaphylactic index history).
As advocated by the European Network on Drug Allergy, we initially designed our empirical DPT protocols to reach a daily therapeutic dose, instead of a single dose. The clinical relevance of the MGRPX2 activation pathway for quinolones is not known, but it could be argued that some of the positive DPT were due to too high a dose, administered in a short

time interval. While this might be true for some patients, 65% of those reacting by DPT did so at RD < 50%, which would be the equivalent of a single dose.

The dose increments usually consisted of a 2 or 3-fold increase between successive steps, allowing us to explore and detect reactions we could not have otherwise detected, had our empiric DPT been shorter. The two patients who reacted with anaphylaxis at RD=0.1% and RD=0.6% had clinical histories of anaphylaxis. We therefore consider that small doses should not be overlooked in patients with severe index reactions. Ideally, a data-driven protocol would attempt to reach at each step cumulative doses lower than those causing anaphylaxis, with the hypothesis that the reaction would thus be less severe (e.g., anaphylaxis elicited at RD=27% might be captured as urticaria at RD= 20%). Several episodes of anaphylaxis occurred within a close range of doses before RD=20%. Taking into account all these considerations, we propose the following DPT protocol: 5%-10%-15%-20%-50%, preceded by 0.1% and 0.5% in case of anaphylactic index reactions.

In a cohort of patients with a suspicion of quinolone DHR, we: (i) confirmed the diagnosis in 25.1% of cases, mainly by means of DPT; (ii) showed the good match (over 90%) between the semiology and the chronology of the index reactions and those elicited by DPT; (iii) proved the utility of the one-day DPT for both immediate and non-immediate reactions. Having analyzed the details of the reaction patterns during DPT, we suggest a DPT protocol of 5 doses, with 2 supplementary low doses in case of anaphylactic index reactions.

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Legends

Figure 1. Kaplan–Meier curve (and 95% CI in dotted lines) for the whole set of drug provocation test events.

Table 1. Characteristics of the studied population.

Table 2. Distribution of the events (and in particular the anaphylactic events on the Kaplan Meier curve). By RD=10%, two patients had reacted with anaphylaxis during DPT, one at RD=0.1% and another one at RD=0.6%; between RD=10% and RD=20%, four more cases had occurred, all at RD=17%-18%; finally, the last two cases occurred at RD=41% and RD=96%, respectively.

Figure 1. Kaplan–Meier curve (and 95% CI in dotted lines) for the whole set of drug provocation test (DPT) events. The Reactive Doses (RD) are mentioned on the X axis in percentage.

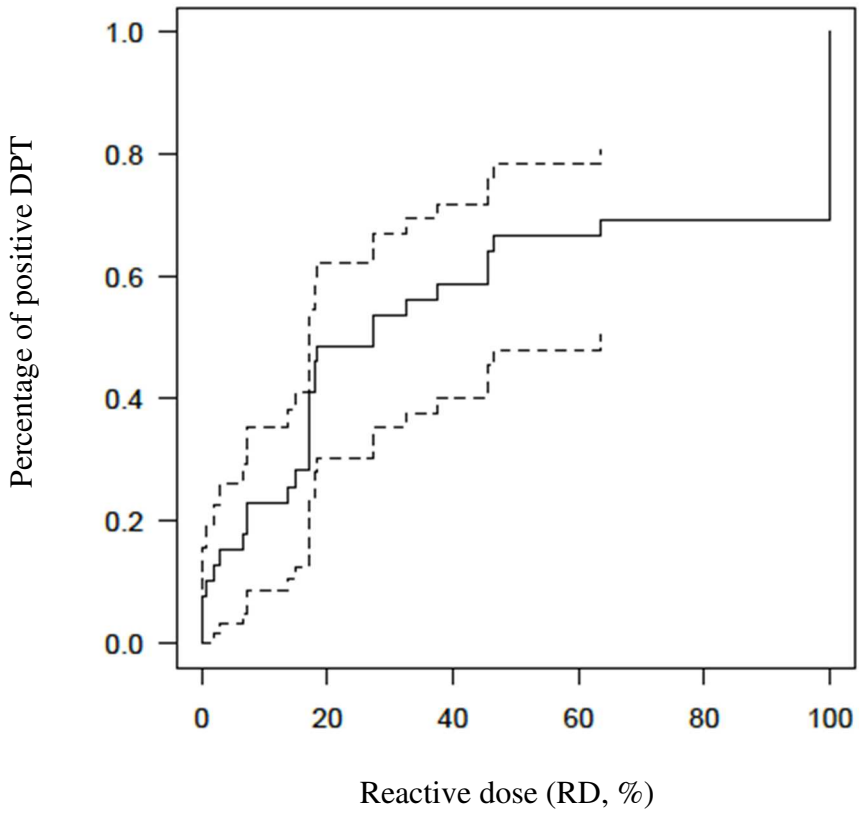

Table 1. Characteristics of the studied population.

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	Total number of patients N=159	**Patients with no DHR N=119 (%)**	**Patients with confirmed DHR** N=40 (%)	p value
Female patients	117	88 (75.2)	29 (72.5)	0.85
Symptoms and signs of index reaction°				***< 0.0001***
Urticaria and/or Angioedema	64	49 (41.5)	15 (37.5)	
Anaphylaxis	33	14 (11.8)	19 (47.5)	
w/o shock	21	9 (7.5)	12 (30)	
with shock	12	5 (4.2)	7 (17.5)	
Maculopapular exanthema	49	44 (37.2)	5 (12.5)	
Other	11	11 (9.3)	0 (0)	
Isolated bronchospasm	1	0 (0)	1 (2.5)	
Chronology of index reaction after the last ingested dose				***< 0.0001***
≤1h	57	33 (27.7)	24 (60)	
1-6h*	14	7 (5.8)	7 (17.5)	
> 6h (6-24h, >24h)	59	53 (44.5)	6 (15)	
Unknown	29	26 (21.8)	3 (7.5)	
Culprit quinolone (index reaction)				***< 0.0001***
Ciprofloxacin	42	36 (30.2)	6 (15)	
Levofloxacin	30	22 (18.5)	8 (20)	
Moxifloxacin	14	3 (2.5)	11 (27.5)	
Ofloxacin	50	38 (31.9)	12 (30)	
Other quinolone**	23	20 (16.8)	3 (7.5)	
Previous use of quinolone				***0.0015***
Yes	24	17 (14.2)	7 (17.5)	
No	40	22 (18.4)	18 (45)	
Unknown	95	80 (67.2)	15 (37.5)	
Age* (years): mean±SD	50.6±16.4	51.1±16.7	49.2±15.5	0.5
Delay# (months) between reaction and tests: median (IQR25-75)	86.8±99.5	30 (7-120)	90 (13-150)	0.09

** normally distributed variable; # not normally distributed variable; °contains one missing variable (therefore 158 patients)*
DHR, drug hypersensitivity reaction; DPT, drug provocation test; IQR, interquartile range; SD, standard deviation; ST, skin tests

p-value of comparison between the group with confirmed quinolone hypersensitivity (either by ST or by DPT) and the one whose hypersensitivity suspicion was ruled out
**For further analysis, these patients were considered in the immediate group (this choice made sense clinically and statistically).*
*** This group included: norfloxacin, lomefloxacin, pefloxacin, pipemidic acid.*

Table 2. Distribution of the events (and in particular the anaphylactic events on the Kaplan Meier curve). By RD=10%, two patients had reacted with anaphylaxis during DPT, one at RD=0.1% and another one at RD=0.6%; between RD=10% and RD=20%, four more cases had occurred, all at RD=17%-18%; finally, the last two cases occurred at RD=41% and RD=96%, respectively.

% Positive DPT	**5**	**27.5**	**47.5%**	**65%**	**100%**
Data-driven steps (RD %)	**0.1**	**10**	**20**	**50**	**100**
New DPT reactions since previous steps (cumulative cases)	2	7 (9)	10(19)	7 (26)	14 (40)
New DPT reactions with anaphylaxis since previous steps (cumulative cases)	1	1 (2)	4 (6)	1 (7)	1 (8)