10.1111/j.1469-0691.2005.01287.x

Bactericidal activity of fluoroquinolones against plasmid-mediated QnrA-producing *Escherichia coli*

The recent article in *CMI* by Rodriguez-Martinez *et al.* [1] reported the effect of Qnr on the MICs of nalidixic acid and fluoroquinolones. The Qnr determinant (recently named QnrA) has been known to be plasmid-mediated since 1998 [2], and is now reported increasingly worldwide [3]. QnrA binds to the subunits of DNA gyrase [4], and confers, in terms of MICs, resistance to nalidixic acid and decreased susceptibility to fluoroquinolones [1]. However, the effect of QnrA on the bactericidal activity of fluoroquinolones has not been reported previously.

In order to investigate this effect, we performed time-kill studies to analyse the bactericidal activity of ofloxacin and ciprofloxacin, two fluoroquinolones used extensively for treating Gram-negative infections. The QnrA-positive strain used was *Escherichia coli* J53 (pQR1), in which the QnrA determinant was located on the 180-kb plasmid pQR1, transferred by conjugation from clinical isolate *E. coli* Lo, with *E. coli* J53 as control [3]. The MICs of ofloxacin and ciprofloxacin for *E. coli* J53 (pQR1) were 1 mg/L and 0.25 mg/L, respectively [3]. The materials and methods used were as described previously [5]. Antibiotic concentrations used in killing experiments were two-, four- and eight-fold higher than the MICs. Viable counts

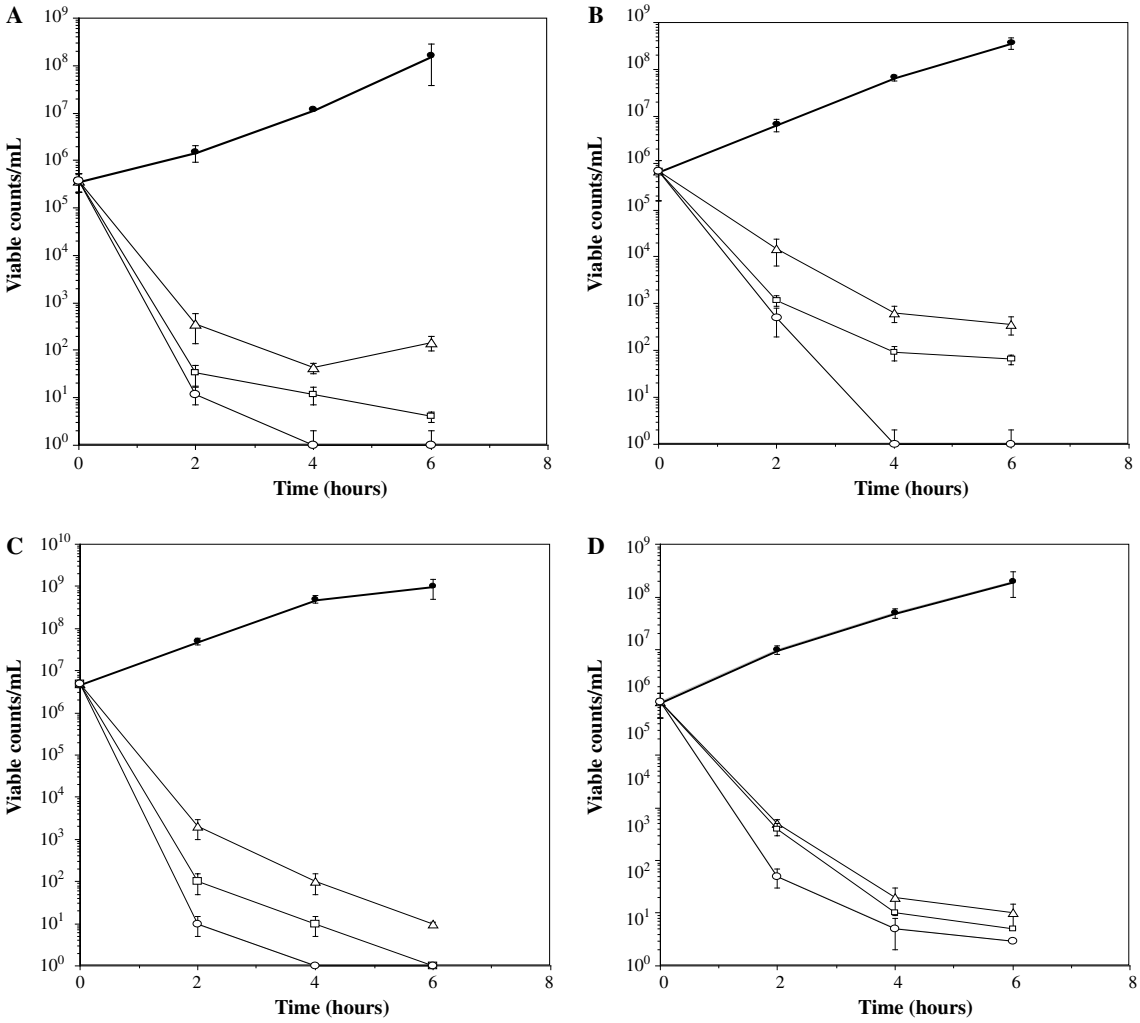

Fig. 1. Bactericidal kinetics of ofloxacin (A) and ciprofloxacin (B) against Qnr-producing *Escherichia coli* J53 (pQR1), and of ofloxacin (C) and ciprofloxacin (D) against *E.coli* J53. Symbols indicate inhibitory concentrations as follows: triangles, 2 × MIC; squares, 4 × MIC; open circles, 8 × MIC. Each point corresponds to the mean ± SD of three independent determinations.

were performed after 0, 2, 4 and 6 h. A bactericidal effect was defined as a ≥ 3 $\log_{10}$ (99.9% killing) reduction in CFU compared with the initial test inoculum. Colony counts were determined and averaged from each sample.

The results are presented in Fig. 1. Ofloxacin and ciprofloxacin showed bactericidal activity against *E. coli* J53 (pQR1) at concentrations two-, four- and eight-fold higher than the MICs, beginning after incubation for 2 h and 4 h for ofloxacin and ciprofloxacin, respectively. These results indicated that transfer of QnrA into *E. coli* J53 did not modify the bactericidal activity of ofloxacin and ciprofloxacin.

Martínez-Martínez *et al.* [2] reported that QnrA may enhance selection of higher levels of quinolone resistance [2]. The low level of resistance conferred by QnrA may allow the bacterial population to reach a concentration at which secondary chromosomal mutations for higher levels of quinolone resistance may occur. However, the bactericidal activity of fluoroquinolones remained unchanged. Our results indicate that, in the absence of additional chromosome-encoded quinolone resistance mechanisms, QnrA-positive enterobacterial isolates may remain susceptible to the bactericidal effect of fluoroquinolones. Animal infection models, as well as clinical studies, may provide further evidence to support these in-vitro results.

ACKNOWLEDGEMENTS

This work was funded by a grant from the Ministère de l'Education Nationale et de la Recherche (UPRES-EA3539), Université Paris XI, Paris, France, and by the European Community (6th PCRD, LSHM-CT-2003-503-335). We are grateful to L. Gutmann for fruitful discussion. LP is a researcher from INSERM, France.

*H. Mammeri, L. Poirel and P. Nordmann**
Service de Bactériologie-Virologie,
Hôpital de Bicêtre,
Assistance Publique/Hôpitaux de Paris,
Faculté de Médecine Paris-Sud,
Université Paris XI,94275 K.-Bicêtre, France
*E-mail: nordmann.patrice@bct.ap-hop-paris.fr

REFERENCES

1. Rodriguez-Martinez JM, Conejo MC, Martinez-Martinez L, Cano ME, Velasco C, Pascual A. Evaluation of antimicrobial susceptibility of bacteria containing the *qnr* gene and FOX-5 β-lactamase by four automated systems. *Clin Microbiol Infect* 2005; **11**: 402–404.
2. Martínez-Martínez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. *Lancet* 1998; **351**: 797–799.
3. Mammeri H, Van De Loo M, Poirel L, Martínez-Martínez L, Nordmann P. Emergence of plasmid-mediated quinolone resistance in *Escherichia coli* in Europe. *Antimicrob Agents Chemother* 2005; **49**: 71–76.
4. Tran JH, Jacoby GA, Hooper DC. Interaction of the plasmid-encoded quinolone resistance protein Qnr with *Escherichia coli* DNA gyrase. *Antimicrob Agents Chemother* 2005; **49**: 118–125.
5. McCloskey L, Moore T, Niconovich N *et al*. In vitro activity of gemifloxacin against a broad range of recent clinical isolates from the USA. *J Antimicrob Chemother* 2000; **45**(suppl 1): 13–21.

10.1111/j.1469-0691.2005.01272.x

Correct use of the term 'pan-drug-resistant' (PDR) Gram-negative bacteria

We congratulate Hsueh *et al.* for their recent publication in *CMI* regarding 'pan-drug-resistant' nosocomial *Pseudomonas aeruginosa* infections [1]. However, we would like to express our disagreement with the use of the term 'pan-drug-resistant' (PDR) in this article. We believe that this term should not be used for Gram-negative bacteria that are susceptible to polymyxins. This practice causes confusion among clinicians because it suggests an absence of antimicrobial agents for the management of infections caused by these bacteria, while a potential salvage option is available in the form of intravenous polymyxins.

An isolate of *P. aeruginosa* should be defined as 'pan-drug-resistant' if it is resistant to all seven available anti-pseudomonal classes of antimicrobial agents, namely anti-pseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones, aminoglycosides and polymyxins [2]. Several recent studies have used the term 'pan-drug-resistant' despite the fact that the isolates had not been tested for their susceptibility to polymyxins [3–5]. For example, a mortality rate of 60% was reported in a study of patients with 'pan-drug-resistant' *Acinetobacter baumannii* infections from Taiwan; however, the isolates were not tested for their in-vitro susceptibility to polymyxins. Furthermore, no polymyxin was used to treat the patient population studied [3,4]. Several studies have now shown that intravenous polymyxins may be useful for the treatment of patients with infections caused by Gram-negative bacteria with in-vitro susceptibility to these antibiotics, even if