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Relationship between hospital antibiotic use and quinolone resistance in *Escherichia coli*

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SUMMARY

Background: The relationship between the hospital use of various classes of antibiotics and resistance of *Escherichia coli* to quinolones remains debated. Our aim was to study the relationship between the hospital use of 16 classes of antibacterial agents and the incidence of quinolone-resistant *E. coli* isolates.
Methods: Antibiotic use and resistance data were collected from 36 hospitals. Incident rate ratios (IRR) were assessed using negative binomial regression.
Results: The incidence of quinolone-resistant isolates was independently associated with the consumption of tetracyclines (IRR 1.139, 95% CI 1.030–1.259), first- and second-generation cephalosporins (IRR 1.007, 95% CI 1.002–1.013), third-generation cephalosporins (IRR 1.029, 95% CI 1.010–1.048), and quinolones (IRR 1.007, 95% CI 1.000–1.014). These associations were independent from the type of patient served.
Conclusions: The level of hospital use of quinolones influences the incidence of quinolone resistance in *E. coli* hospital isolates. The consumption of two other classes of antibiotics, cephalosporins and tetracyclines, is also associated with quinolone resistance.

1. Introduction

Conflicting results have been published on the relationship between the hospital use of antibacterial agents and resistance to quinolones in *Escherichia coli* hospital isolates, partly because inappropriate statistical methods have been used to study this issue. Statistical methods suited to the analysis of the relationship between antibiotic use and resistance include time series analysis and to a lesser extent cross-sectional studies.[1,2] Conversely, it is not appropriate to use correlation or linear regression on time series.[1,2] Most previous studies have focused on the relationship between the use of quinolones and resistance to quinolones. If we only consider studies based on either time series analysis or a cross-sectional design, the relationship between the hospital use of quinolones and quinolone resistance in *E. coli* remains insufficiently proven, as three studies have found a statistically significant association and two have not.[2–6] Firm conclusions cannot be drawn from other studies that have analyzed time series using correlation or linear regression.[7–10]

Moreover, the relationship between quinolone resistance and the use of other classes of antibiotics has been poorly investigated. Indeed, one study demonstrated a relationship between quinolone resistance and the use of quinolones, piperacillin/tazobactam, and carbapenems in univariate analysis, but without testing the independence of these associations.[4] Firm conclusions cannot be drawn from other studies that have analyzed time series using correlation analysis.[8,10] Hence, the influence of the hospital use of various classes of antibacterial agents on resistance of *E. coli* to quinolones has to be established with more certainty. This debate is crucial, because if antimicrobial consumption really influences resistance to quinolones in *E. coli*, it implies that antimicrobial restrictions in hospitals may help to control it. In this study, we aimed to assess the relationship between the hospital use of various classes of antibiotics and quinolone resistance in *E. coli* isolates in a network of 36 hospitals.

2. Methods

Antibiotic use and resistance data were collected from 36 acute care hospitals of the Pays de la Loire region, France, during the year 2009. Antibiotic quantities were converted to defined daily doses

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(DDD) per 1000 patient-days for each hospital, as recommended by the World Health Organization Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no). Antibacterial agents were grouped into 16 classes, adapted from the Anatomical Therapeutic Chemical (ATC) classification system: (1) beta-lactamase-resistant penicillins (J01CF), (2) amoxicillin (J01CA04) (ampicillin is not commercially available in France), (3) amoxicillin/ampicillin and enzyme inhibitor (J01CR01 and J01CR02), (4) ticarcillin and piperacillin with or without enzyme inhibitor (J01CA12, J01CA13, J01CR03, J01CR05), (5) first- and second-generation cephalosporins (J01DB, J01DC), (6) third-generation cephalosporins (J01DD) excluding ceftazidime, (7) anti-pseudomonal cephalosporins including ceftazidime (J01DD02) and fourth-generation cephalosporins (J01DE), (8) carbapenems (J01DH), (9) tetracyclines (J01A), (10) sulfonamides and trimethoprim (J01E), (11) macrolides, lincosamides, and streptogramins (J01F), (12) aminoglycosides (J01G), (13) quinolones (J01 M), (14) glycopeptides (J01XA), (15) imidazole derivatives (J01XD), and (16) other antibacterial agents.

Each participating hospital provided the number of non-duplicate *E. coli* isolates from all clinical sites (e.g., blood and urine) and all hospital units, and the number of pathogens with resistance to nalidixic acid. Duplicate isolates were defined on the basis of two criteria: (1) culture from the same patient during the study period, and (2) identical pattern of susceptibility to amoxicillin, co-amoxiclav, ceftriaxone, co-trimoxazole, and nalidixic acid. The incidence density of resistant isolates was calculated as the ratio of the number of resistant isolates to the number of patient-days in the whole hospital. Susceptibility tests were done and interpreted as recommended by the French Society for Microbiology 2009 guidelines (http://www.sfm-microbiologie.org/UserFiles/file/CASFM/casfm_2009-1.pdf). Non-susceptibility to quinolones was defined by a minimum inhibitory concentration (MIC) of nalidixic acid >16 mg/l or an inhibition diameter <15 mm. Non-susceptibility to ceftriaxone was defined by a MIC >2 mg/l or inhibition diameter <23 mm.

Descriptive statistics were expressed as the median with 25th–75th percentiles (interquartile range, IQR). The structure of antimicrobial use was analyzed using principal component analysis (PCA). The relationship between antibiotic use and the incidence density of resistant isolates was assessed using negative binomial regression. Results were expressed as the incident rate ratio (IRR), which is the relative risk of incidence density between two hospitals that differ by 1 DDD/1000 patient-days. RRmax was defined as IRR^d, where d is the difference between the maximal and minimal consumptions of the considered antibacterial class. The relationship between the incidence density of resistance and the use of every class of antibacterial agent was tested in univariate analysis. Then, with the same type of regression model, we conducted a multivariable analysis on antibiotic classes that were associated ($p \leq 0.10$) with resistance in the univariate analysis. Significant classes of antibacterial agents were selected by a backward procedure with an α threshold fixed to 5%. The statistical analysis was performed using R software, version 2.14.2011-12-16 (http://CRAN.R-project.org).

3. Results

The median number of hospital beds was 214 (IQR 145–373). The cumulated number of patient-days was 4 212 540 during the year 2009. The median percentages of patient-days for each hospital were distributed across the following activities: medical 23.5% (IQR 0–33.8%), surgical 17.0% (IQR 2.6%–55.9%), critical care 0 (IQR 0–1.2%), pediatrics 0 (IQR 0–2.3%), obstetrics 5.0% (IQR 0–8.0%), rehabilitation 12.3% (IQR 0–24.8%), long-term care 0 (IQR 0–19.5%), and psychiatry 0 (IQR 0–0). The median number of patient-days per hospital was 63 440 (IQR 42 898–113 984). Antibiograms of 23 614 isolates were collected. The median number of isolates per hospital was 285 (IQR 139–570). The median percentage of quinolone-resistant *E. coli* (QREC) was 15.3% (IQR 11.1–17.9%) and the median incidence density of QREC was 0.66 isolates/1000 patient-days (IQR 0.38–0.97). Total antibiotic use ranged from 145.1 to 615.6 DDD/1000 patient-days (Figure 1). The consumption of antibacterial agents is reported in Table 1. The structure of consumption of 16 classes of antimicrobials was analyzed using PCA (Figure 2). The score plot (Figure 2A) showed that our study sample was rather homogeneous. First and second principal components explained 51.1% and 18.7%, respectively, of total observed variance, and were mostly associated with the use of amoxicillin/ampicillin ± enzyme inhibitor, imidazoles, quinolones, aminoglycosides, first- and second-generation cephalosporins, third-generation cephalosporins, macrolides, lincosamides, and streptogramins, and amoxicillin (Figure 2B).

In univariate analysis, the incidence of QREC was significantly associated with the use of eight different classes of antibiotics: amoxicillin/ampicillin with enzyme inhibitor, first- and second-generation cephalosporins, third-generation cephalosporins, tetracyclines, aminoglycosides, quinolones, glycopeptides, and imidazoles (Table 2). Four antibacterial classes remained independently associated with the incidence of QREC isolates: tetracyclines, first- and second-generation cephalosporins, third-generation cephalosporins, and quinolones (Table 3). Using the model, the baseline incidence (i.e., in a theoretical hospital without the use of any of these classes) would be 0.22 QREC isolates for 1000 patient-days. Using the example of quinolone use, the IRR should be interpreted as follows: the incidence of QREC increases by 1.0072-fold when the quinolone use increases by 1 DDD/1000 patient-days. RRmax should be considered as the relative risk of incidence density between the hospitals with the highest and lowest consumption. For instance, the relative risk of QREC incidence was 2.7 for quinolone use.

Additionally, we checked if the incidence of QREC was a function of the type of patient served. First, we tested the relationship between the incidence of QREC and the percentage of patients-days in eight different activities (medical, surgical, pediatrics, obstetrics, critical care, rehabilitation, long-term care, and psychiatry) using negative binomial regression. In univariate analysis, three activities – surgical, rehabilitation, and long-term care – were linked with the incidence of QREC at $p \leq 0.10$. These variables were added to the eight classes of antibiotics previously selected for the multivariable analysis. The final model did not retain any type of activity. Thus, the links between the incidence of QREC and the use of tetracyclines, first- and second-generation

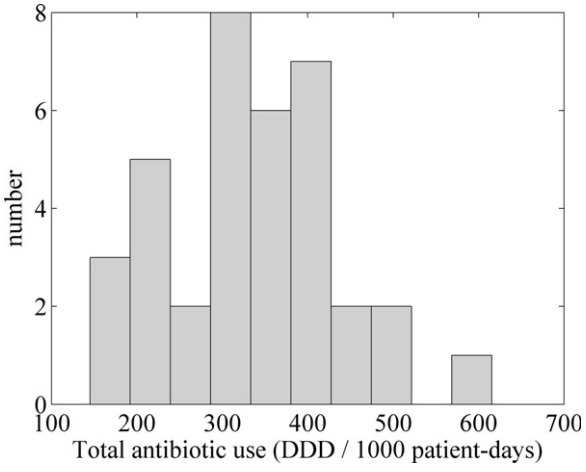

Figure 1. Distribution of total antibiotic use in 36 hospitals.

Table 1
Use of the main classes of antibacterial agents in 36 hospitals

Class	Median consumption (IQR), DDD/1000 patient-days
beta-Lactamase-resistant penicillins	7.67 (3.83–12.18)
Amoxicillin	52.43 (34.20–74.95)
Amoxicillin/ampicillin + EI	124.67 (81.19–146.81)
Ticarcillin/piperacillin ± EI	0.41 (0–2.25)
First- and second-generation cephalosporins	14 (1.02–41.43)
Third-generation cephalosporins[a]	14.34 (7.14–19.79)
Anti-pseudomonal cephalosporins	0.58 (0.20–1.96)
Carbapenems	1.37 (0.29–2.61)
Tetracyclines	0.8 (0.18–1.65)
Sulfonamides	3.68 (1.87–5.31)
Macrolides, lincosamides, streptogramins	12.38 (9.58–16.13)
Aminoglycosides	7.44 (3.54–16.74)
Quinolones	47.05 (33.04–56.03)
Glycopeptides	2.42 (1.37–4.35)
Imidazoles	10.94 (4.87–17.09)
Other antibiotics	7.61 (5.02–15.96)
Total antibiotic use	334.1 (257.76–386.72)

DDD, defined daily dose; EI, enzyme inhibitor; IQR, interquartile range.
[a] Excluding ceftazidime.

cephalosporins, third-generation cephalosporins, and quinolones were independent from the type of patient served.

The use of third-generation cephalosporins is a known risk factor for resistance to ceftriaxone, and we confirmed this with our own data (data not shown).[2,4,10,11] Furthermore, there was a strongly significant association between resistance to ceftriaxone and resistance to quinolones ($p < 0.0001$). Therefore, we constructed a new model, including the use of tetracyclines, first- and second-generation cephalosporins, third-generation cephalosporins, and quinolones, and resistance to ceftriaxone as predictors, and resistance to quinolones as the predicted variable. The consumption of first- and second-generation cephalosporins and the use of third-generation cephalosporins remained significantly associated with resistance to quinolones, independently from the incidence of resistance to ceftriaxone.

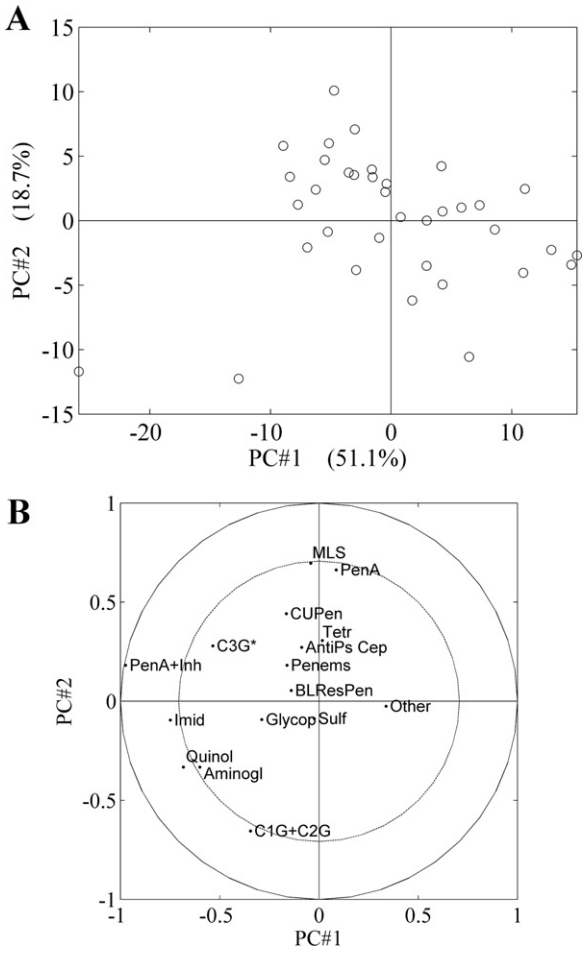

Figure 2. Principal component analysis of the use of 16 antimicrobial classes in 36 hospitals. (A) Score plot of first and second principal components; each point represents a hospital. (B) Correlation loading plot of first and second principal components, showing the correlation between antimicrobial use and principal component scores; the outer and inner circles indicate 100% and 50% explained variance, respectively. (BLResPen, beta-lactamase-resistant penicillins; PenA, amoxicillin; PenA + Inh, amoxicillin/ampicillin and enzyme inhibitor; CUP, ticarcillin and piperacillin with or without enzyme inhibitor; C1G + C2G, first- and second-generation cephalosporins; C3G*, third-generation cephalosporins excluding ceftazidime; AntiPs cep, anti-pseudomonal cephalosporins; Penems, carbapenems; Tetr, tetracyclines; Sulf, sulfonamides and trimethoprim; MLS, macrolides, lincosamides, and streptogramins; Aminogl, aminoglycosides; Quinol, quinolones; Glyco, glycopeptides; Imid, imidazole derivatives; Other, other antibacterial agents.).

4. Discussion

Resistance to nalidixic acid was selected as a marker of resistance to quinolones, because it is the first step before resistance to fluoroquinolones.[12] Resistance rates to nalidixic acid and to ciprofloxacin were significantly correlated in our study sample (Pearson's $R = 0.83$, $p < 0.0001$). Resistance to nalidixic acid is clinically relevant in France, as French guidelines recommend not treating urinary tract infections with any fluoroquinolone if the isolate is resistant to nalidixic acid but susceptible to fluoroquinolones, to limit the risk of selecting fluoroquinolone-resistant mutants during therapy.[13]

We found that the incidence of QREC isolates was independently associated with the hospital use of quinolones. This result is in accordance with three previous studies.[3,4,6] Another study in the USA used the same design as ours and found no correlation between the hospital use of quinolones in 17 hospitals and the resistance rate to quinolones.[5] Different statistical power may account for the discrepancy with our study, as we used a larger panel of hospitals. Consequently, we consider that the level of hospital use of quinolones convincingly influences the incidence of quinolone resistance in *E. coli* hospital isolates.

The relationship between QREC and extended-spectrum cephalosporin use in the hospital setting has previously been suggested.[10] We also found that the incidence of QREC was associated with third-generation cephalosporin use. This relationship persisted independently from the incidence of resistance to ceftriaxone. However, our study was not designed to demonstrate causality. As *E. coli* are less often resistant to third-generation cephalosporins than to quinolones, infections due to QREC may be treated with third-generation cephalosporins. Hence, the use of third-generation cephalosporins might be higher *because* the incidence of QREC has increased. Additional studies using time series analysis are needed to clarify this issue.

Conversely, first- and second-generation cephalosporins and tetracyclines are not used to treat infections due to QREC. Hence, our study suggests that these two classes of antibiotics may also select for resistance to quinolones in *E. coli* hospital isolates. Resistance to tetracyclines is not routinely tested in *E. coli* hospital isolates. However, resistance to quinolones is plausibly associated with resistance to tetracyclines, and this may explain why the use of tetracyclines is linked to the incidence of QREC.

Surprisingly, the effect of quinolone use on QREC incidence – expressed as the IRR – was not higher than the effect of other classes selected in the final model. Indeed, the QREC incidence

Table 2
Univariate analysis of the relationship between hospital use of major classes of antibacterial agents and incidence of quinolone-resistant *E. coli* isolates

Class	IRR (95% CI)	Pearson's Rho
beta-Lactamase-resistant penicillins	1.0112 (0.9807–1.0427)	0.1084
Amoxicillin	1.0018 (0.9946–1.0091)	0.0719
Amoxicillin/ampicillin + EI	1.0054 (1.0011–1.0098)	0.3941
Ticarcillin/piperacillin ± EI	1.0124 (0.9280–1.1044)	0.0290
First- and second-generation cephalosporins	1.0079 (1.0012–1.0146)	0.4289
Third-generation cephalosporins[a]	1.0461 (1.0254–1.0671)	0.4981
Anti-pseudomonal cephalosporins	1.0419 (0.9598–1.1311)	0.1387
Carbapenems	1.0438 (0.9789–1.1129)	0.1673
Tetracyclines	1.1627 (1.0259–1.3177)	0.3480
Sulfonamides	1.0003 (0.9646–1.0373)	−0.0107
Macrolides, lincosamides, streptogramins	1.0090 (0.9759–1.0432)	0.0782
Aminoglycosides	1.0415 (1.0218–1.0616)	0.5946
Quinolones	1.0140 (1.0059–1.0220)	0.5567
Glycopeptides	1.0611 (1.0155–1.1088)	0.4424
Imidazoles	1.0484 (1.0248–1.0725)	0.5243
Other antibiotics	1.0161 (0.9957–1.0368)	0.2200

CI, confidence interval; EI, enzyme inhibitor; IRR, incidence rate ratio. Incident rate ratios were computed using negative binomial regression; correlations between the incidence of quinolone-resistant *E. coli* and antibiotic use were also analyzed using Pearson's method.
[a] Excluding ceftazidime.

Table 3
Multivariable analysis of the relationship between hospital use of major classes of antibacterial agents and incidence of quinolone-resistant *E. coli* isolates

	IRR (95% CI)	RRmax[a]
First- and second-generation cephalosporins	1.0072 (1.0019–1.0126)	2.3
Third-generation cephalosporins[b]	1.0287 (1.0095–1.0482)	2.9
Tetracyclines	1.1387 (1.0296–1.2594)	2.1
Quinolones	1.0072 (1.0001–1.0144)	2.7

CI, confidence interval; IRR, incidence rate ratio. The pseudo-R^2 was 0.07.
[a] RRmax = IRR^d, where d is the difference between the maximal and minimal consumptions of the considered antibacterial class.
[b] Excluding ceftazidime.

between two hospitals that differed by 1 DDD/1000 patient-days for quinolones and tetracyclines, increased by 1.0072 and 1.1387, respectively. However, as tetracyclines were far less used than quinolones and cephalosporins, the effects of the four classes in the final model – expressed as RRmax – were roughly similar, ranging from 2.1 to 2.9.

Our study sample included all private and public acute care hospitals of an administrative region of 3 500 000 inhabitants, providing various types of care, e.g., mostly medical, mostly surgical, mostly obstetric, or mixed activities. The relationship between QREC and the consumption of cephalosporins, quinolones, and tetracyclines remained after taking into account the type of patient served, thus reinforcing our results.

Our study has several limitations. First, as discussed above, our cross-sectional design can demonstrate an association between antimicrobial use and resistance, but not causality. Second, we cannot be sure that hospitals are totally independent entities, as they may share some clinical practice guidelines, opinion leaders, and patients. However, hospitals in this study were totally independent from an administrative point of view, and showed great variations in the types of patient served and antimicrobial consumption. Third, our model explained a limited fraction of the variability of the incidence of QREC. We consider that the risk of over-fitting the model was acceptable, considering the ratio between sample size and number of predictors, the confidence intervals of the IRRs, the values of RRmax, and the biological plausibility of our results. Fourth, we could not exclude community-acquired isolates from our data. However, the inclusion of community-acquired isolates would probably lead to an underestimate of the magnitude of the association between hospital use of antimicrobials and bacterial resistance. Hence, our conclusions should remain acceptable.

It has previously been shown that restricting the community use of ciprofloxacin is associated with a decreased resistance rate of *E. coli* to quinolones in the community.[14] Furthermore, a 2-year intervention that decreased the hospital use of quinolones reduced the rate of resistance to quinolones in *E. coli* in a stepwise manner, although it was unable to reverse the increasing trend of resistance during the intervention.[15] Longer interventions may be necessary to decrease the incidence of QREC in hospitals. Moreover, if future studies designed for causation confirm that quinolone resistance in *E. coli* is at least partly due to the hospital use of cephalosporins or tetracyclines, interventions aimed at decreasing the incidence of QREC by restricting antibiotic use may have to take into account every involved class of antimicrobials.

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Conflict of interest: The authors have no conflicts of interest to declare.

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