MAJOR ARTICLE

Relationship between Fluoroquinolone Use and Changes in Susceptibility to Fluoroquinolones of Selected Pathogens in 10 United States Teaching Hospitals, 1991–2000

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We retrospectively examined the relationship between fluoroquinolone use and the susceptibilities of 11 bacterial pathogens to fluoroquinolones in 10 US teaching hospitals from 1991 through 2000. Statistical significance was determined by 2-way analysis of variance, with the number of isolates tested each year as a weighting factor. The analysis of baseline–to–end point change in the percentage of susceptibility and the slope of the regression line (trend line) for logit percentage of susceptibility showed that the overall percentage of susceptibility to fluoroquinolones decreased significantly during the study period ($P < .05$) and that change in percentage of susceptibility was significantly related to change in fluoroquinolone use ($P < .05$). Particularly notable were the decreases in the susceptibilities of *Pseudomonas aeruginosa, Proteus mirabilis,* and *Escherichia coli* (decreases of 25.1%, 11.9%, and 6.8%, respectively).

Since their introduction <2 decades ago, fluoroquinolone antibacterial agents have come to play a major role in the prevention and treatment of bacterial infections. Recent reports have raised concern about the increasing prevalence and magnitude of bacterial resistance to the fluoroquinolone antibacterials [1–13]. Hospital clinicians and administrators are particularly alarmed by the decrease in susceptibility to fluoroquinolones and other antibacterial agents, because bacterial resistance leads not only to longer and more costly hospital stays but also to increased morbidity and death rates [14]. An association between the intensity of antibacterial use and the development of bacterial resistance has been recognized [15, 16]. To further explore this relationship, we retrospectively examined the degree of fluoroquinolone use and the susceptibilities of selected pathogens to fluoroquinolones in US teaching hospitals from 1991 through 2000.

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METHODS

Data collection. Ten teaching hospitals were selected for participation in the study on the basis of their ability to provide retrospective data on their use of fluoroquinolone antibacterials and to furnish in vitro sus-

ceptibility data based on hospital antibiograms for isolates of 11 pathogens *(Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Enterobacter aerogenes, Acinetobacter* species, *Serratia marcescens, Citrobacter* species, *Stenotrophomonas maltophilia,* and *Staphylococcus aureus).* Each hospital completed survey forms that requested data for 1991 through 2000. Ten hospitals and a 10-year time period were examined as a means of minimizing analytic bias due to susceptibility and drug use. One hundred four hospital-pathogen combinations were collected. For 99 of these combinations, susceptibility data were available from ⩾8 years.

To control for the number of fluoroquinolone doses dispensed and the diversity of the patient populations exposed to fluoroquinolones, the degree of fluoroquinolone use was expressed as the number of defined daily doses per 1000 patient-days (use density rate [UDR]), which was calculated as follows: ([pooled annual use or purchase of fluoroquinolones in grams/defined daily dose in grams]/pooled number of patient-days) × 1000. The defined daily doses, which were based on the manufacturers' prescribing information, were as follows: intravenous ciprofloxacin, 800 mg; oral ciprofloxacin, 1000 mg; intravenous gatifloxacin, 400 mg; oral gatifloxacin, 400 mg; intravenous levofloxacin, 500 mg; oral levofloxacin, 500 mg; oral norfloxacin, 400 mg; intravenous ofloxacin, 400 mg; oral ofloxacin, 400 mg; intravenous trovafloxacin, 300 mg; and oral trovafloxacin, 200 mg.

Annual reports on percentage of isolates susceptible to a particular drug (percentage of susceptibility) for the 11 study pathogens were requested for inpatients, regardless of their location in the hospital. Also requested was the total number of bacterial isolates tested annually for each quinolone-pathogen combination. Data on susceptibilities classified as "intermediate" were to be excluded. One hospital included both outpatient and inpatient data in its data set and reported susceptibilities classified as "intermediate" in the "susceptible" category of its microbiology reports. Statistical analyses done with and without the data from this hospital, however, yielded similar results at all stages. Two hospitals did not exclude duplicate isolates, but because data were obtained from large numbers of isolates for each of the study pathogens, this is unlikely to have greatly affected the study results.

Microbiologic testing. Pathogen susceptibility was determined by the clinical microbiology laboratories of each hospital, according to the guidelines of the NCCLS, by the Kirby-Bauer disk diffusion method or by Vitek (bioMérieux) or MicroScan (Dade Behring) automated susceptibility testing instruments.

Statistical analysis. The primary objectives of the statistical analysis were to examine changes over time in the UDRs of the fluoroquinolones and in the percentages of susceptibility of the study pathogens and to determine the relationship between these 2 variables. The fluoroquinolones used by the hospitals changed during the study period, and therefore the primary statistical analysis examined the combined percentages of susceptibility to all of the fluoroquinolones and total UDRs. The combined percentage of susceptibility for a given pathogen was calculated as the weighted mean of all susceptibility percentages calculated for that pathogen in a given year, with the numbers of isolates tested as weights. The total UDR was defined as the sum of the UDRs recorded for all fluoroquinolones in a given year.

For each combination of pathogen and hospital, numerical features were computed from the sequence of susceptibilities over time. The 2 features analyzed were percentage change in annual percentage of susceptibility from the beginning to the end of the study period (baseline–to–end point change) for each hospital and each pathogen and slope of the least-squares regression line (trend line) for logit susceptibility against time, without adjustment for serially correlated errors.

These features were analyzed by means of weighted least squares to fit a regression model that included the categorical variables of pathogen and hospital and continuous variables for the interaction of pathogen with absolute change in fluoroquinolone UDR. The weights used were the estimated variances for each pathogen-hospital combination, which were estimated in the feature-extraction stage of the analysis. Because the UDR was the same for all pathogens at a given hospital, the main effect of UDR is confounded with the effects of individual hospitals in this model. This model is, effectively, a 2-way analysis of variance (ANOVA).

The data show evidence of a heavy-tailed error distribution. To allow for this, residual normal quantile plots and the DFFITS statistic were used to identify potential outliers. To remove observations with disproportionate influence on the model, indicator variables equaling 1 for the influential observation and 0 for all other observations were introduced into the regression model to fit these observations exactly, thereby eliminating their influence on the other model coefficients. Indicator variables were introduced to mask the most influential residuals. $P < .05$ was considered to be statistically significant.

RESULTS

The 10 hospitals selected for participation in the study ranged in size from 381 to 1389 beds. Three were located in the Northeast, 2 were in the Midwest, 4 were in the South, and 1 was in the West. Hospital characteristics are presented in table 1.

The fluoroquinolones used by the participating hospitals during the study period were ciprofloxacin, gatifloxacin, levofloxacin, norfloxacin, ofloxacin, and trovafloxacin. Seven hospitals reported grams of fluoroquinolone dispensed and 3 reported grams of fluoroquinolone purchased for use in the

Table 1. Characteristics of hospitals included in a survey of fluoroquinolone use and changes in susceptibility to fluoroquinolones.

Hospital	Location	No. of beds	No. of ICU beds	Susceptibility testing method[a]
1	Urban	925	125	MicroScan
2	Urban	819	58	MicroScan
3	Urban	934	141	Vitek
4	Suburban	629	79	Vitek
5	Urban	677	109	Vitek
6	Urban	452	42	Vitek
7	Urban	381	18	Kirby-Bauer
8	Urban	1389	117	Vitek, Kirby-Bauer
9	Urban	400	60	Kirby-Bauer
10	Urban	813	70	Vitek

NOTE. ICU, intensive care unit.

[a] The Microscan instrument is manufactured by Dade Behring, and the Vitek instrument is manufactured by bioMérieux.

calculation of their annual UDRs. The fluoroquinolone UDRs and baseline–to–end point changes in UDR for the hospitals are shown in table 2. Only 2 hospitals provided UDRs for the entire 10-year study period. One hospital provided UDRs for 7 years, 2 supplied UDRs for 6 years, and 5 supplied UDRs for 5 years.

Table 3 shows the baseline–to–end point changes in the percentage of susceptibility to fluoroquinolones of the study pathogens for each of the study hospitals. Mean percentage changes from baseline to end point in percentage of susceptibility, by pathogen and by hospital, are presented in tables 4 and 5.

The mean percentage changes in percentage of susceptibility of all of the pathogens except *E. aerogenes, Acinetobacter* species, and *Citrobacter* species decreased during the study period (table 4). The mean percentage decreases in percentage of susceptibility for *P. aeruginosa, P. mirabilis,* and *E. coli* are particularly noteworthy (25.1%, 11.9%, and 6.8%, respectively). All but 2 of the hospitals had a decrease in mean percentage of susceptibility to the study pathogens (table 5). These 2 hospitals had outlier organism values (*Citrobacter* species at hospital 2 and *Acinetobacter* species at hospital 1). It is noteworthy that hospital 2 is the only hospital that had a decrease in fluoroquinolone use over the study period.

Baseline–to–end point changes in the mean trend-line slopes for logit susceptibility, by pathogen and by hospital, are shown in tables 6 and 7. The trend lines for percentage of susceptibility for all 11 pathogens and all 10 hospitals generally slope downward, but only for *E. coli* and *P. mirabilis* and hospitals 1, 5, and 8 are all of the trend lines downward-sloping.

The weighted regression analysis of variance revealed statistically significant differences among the pathogens in percentage change in percentage of susceptibility ($P < .0001$). Differences among hospitals also were significant ($P = .0066$), which suggests that hospital characteristics other than UDR influenced susceptibility during the study period. The interaction between pathogen and change in absolute UDR also is a significant variable ($P = .0081$), which indicates that changes in susceptibility on a percentage scale are affected by changes in UDR. The linear relationship between the percentage change in percentage of susceptibility and change in UDR was significant for *P. aeruginosa* ($P = .0400$) and *E. coli* ($P = .0021$).

In fitting the regression model, outlying observations for *P. aeruginosa* at hospital 6 and for *P. mirabilis* at hospital 2 were masked by indicator variables. Estimated skewness ($b_1 = -0.307$) and kurtosis ($b_2 = 0.355$) of the residuals did not indicate a systematic departure from the normal distribution.

The regression analysis of the slopes of the trend lines (regression lines for mean logit susceptibility as a function of time) revealed that slope is significantly affected by hospital ($P = .0019$), pathogen ($P = .0001$), and the interaction of pathogen and change in UDR ($P = .0070$). The trend-line slopes were

Table 2. Fluoroquinolone use density rates (UDRs) and change from baseline to end point in UDR in a survey of development of resistance to fluoroquinolones in 10 US teaching hospitals.

	UDR in indicated year											
Hospital	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	Mean UDR ± SD	Change in UDR (%)
1	…	…	…	…	92.5	61.4	100.1	124.3	121.8	169.2	115.4 ± 39.3	76.8 (83.0)
2	…	…	…	…	55.1	62.4	61.4	94.8	81.6	40.1	68.1 ± 21.0	−15.0 (−27.2)
3	57.2	74.2	84.9	9.9	98.4	83.3	94.0	56.5	106.6	86.8	85.5 ± 18.5	29.7 (51.9)
4	52.0	57.9	54.3	53.3	51.1	64.4	67.6	88.4	93.5	72.6	77.3 ± 12.9	20.5 (39.4)
5	…	…	…	…	…	248.0	240.4	193.2	250.8	296.2	245.7 ± 36.6	48.1 (19.4)
6	…	…	…	…	…	672.5	738.9	775.0	580.0	860.9	725.4 ± 106.0	188.4 (28.0)
7	…	…	…	8.2	21.8	17.6	12.0	13.3	16.0	16.0	14.9 ± 2.3	7.8 (95.0)
8	…	…	…	…	…	38.6	41.9	48.7	77.1	90.0	59.2 ± 2.9	51.4 (133.3)
9	…	…	…	…	…	52.3	64.4	94.8	153.3	168.7	106.7 ± 2.2	116.4 (222.5)
10	…	…	…	…	…	33.2	35.4	96.3	109.7	121.7	79.1 ± 41.9	87.8 (264.8)

Table 3. Change from baseline to end point in percentage of susceptibility to fluoroquinolones.

Pathogen	Change in percentage of susceptibility in indicated hospital, % (susceptibility in year 2000)									
	1	2	3	4	5	6	7	8	9	10
Escherichia coli	−4.2 (95)	−2.5 (97)	−11.1 (88)	−7.5 (92)	−2.9 (96)	−15.3 (83)	−16.1 (84)	−3.0 (97)	−4.0 (95)	−1.0 (99)
Pseudomonas aeruginosa	−32.6 (59)	18.2 (73)	−8.1 (68)	−23.4 (72)	−25.2 (52)	−23.7 (71)	−60.7 (35)	−23.4 (59)	−27.9 (57)	−44.4 (55)
Klebsiella pneumoniae	−6.1 (92)	2.7 (96)	3.3 (94)	−3.6 (94)	−6.3 (83)	−3.6 (95)	22.5 (83)	−7.29 (89)	−11.8 (86)	−2.5 (98)
Proteus mirabilis	−11.0 (86)	0.0 (99)	−18.4 (80)	−5.6 (93)	−12.0 (88)	−1.0 (99)	−43.7 (54)	−8.1 (91)	−11.0 (89)	−8.5 (92)
Enterobacter cloacae	−4.4 (94)	3.7 (84)	−10.4 (86)	−4.2 (92)	−12.0 (86)	−5.8 (90)	−5.6 (84)	−12.2 (86)	−0.4 (94)	−15.0 (85)
Enterobacter aerogenes	−6.0 (88)	17.4 (94)	5.4 (97)	…	−8.2 (89)	−2.6 (96)	…	−8.2 (90)	16.2 (83)	−3.0 (97)
Acinetobacter species	…	−6.6 (84)	−26.9 (49)	296.9 (64)	−34.3 (52)	−1.1 (93)	−11.8 (31)	−33.0 (54)	0.0 (74)	−30.1 (69)
Serratia marcescens	2.1 (91)	−9.8 (84)	3.3 (95)	−3.1 (93)	−4.8 (83)	−2.0 (97)	−5.6 (94)	−13.2 (79)	…	−2.0 (99)
Citrobacter species	…	87.5 (91)	5.0 (84)	−5.3 (…)	−7.5 (84)	−8.3 (89)	−1.6 (91)	−3.3 (89)	−7.0 (93)	−31.0 (…)
Stenotrophomonas maltophilia	−48.1 (27)	−40.0 (34)	−60.7 (…)	−8.6 (74)	2.5 (…)	−30.0 (59)	22.6 (82)	−16.7 (40)	−28.4 (…)	32.6 (57)
Staphylococcus aureus	−31.2 (50)	−40.7 (48)	−10.6 (59)	−11.5 (54)	−50.0 (40)	−57.9 (40)	9.03 (34)	−45.5 (48)	−3.8 (…)	…

negative for all of the pathogens included in the study, indicating an overall decrease in susceptibility during the 10-year study period. The linear relationship between trend-line slope and change in absolute UDR was significant for *P. aeruginosa* ($P = .0077$), *K. pneumoniae* ($P = .0400$), and *S. aureus* ($P < .0001$).

In fitting the regression model, outlying observations for *E. coli* and *P. aeruginosa* at hospital 7 and for *S. aureus* at hospital 1 were masked by indicator variables. Estimated skewness ($b_1 = -0.371$) and kurtosis ($b_2 = 0.315$) of the residuals did not indicate a systematic departure from the normal distribution.

DISCUSSION

Statistical significance in our study was determined by the use of an ANOVA regression model with the variables hospital, pathogen, and interaction of pathogen and change in absolute UDR. All 3 variables were found to contribute significantly to change in percentage of susceptibility of the study pathogens. Both the baseline–to–end point ANOVA and the trend-line ANOVA showed a significant relationship between overall change in combined fluoroquinolone UDR and change in percentage of susceptibility to fluoroquinolones. Except for *P. aeruginosa,* the statistical significances of the associations between UDR and the susceptibilities of the individual study organisms, as determined in the baseline–to–end point analysis and the trend-line analysis, did not agree with one another. This may be attributable to the fact that the former analysis focused on 2 data points only, whereas the latter was based on up to 10 data points over the course of the study period.

The hospital variable also was significant in both of the analyses, probably because of differences among hospitals in factors such as infection-control measures, patient populations, geographic location, and fluoroquinolone doses used. As mentioned above, the equation used to calculate UDR substitutes a defined daily dose for the actual dose. It is possible that the fluoroquinolone doses varied among the study hospitals and that this variation contributed to the significance of the hospital variable in the ANOVA regression. Friedrich et al. [17] report that the susceptibility of a pathogen to an antibacterial agent may be reduced by the use of other antibacterials in the same hospital. Differences in overall antibacterial use, therefore, may have contributed to the significance of hospital as a variable in our analysis. Further study is needed to determine whether there is an association between the UDRs of other classes of antibacterials, including cephalosporins, aminoglycosides, and carbapenems, and changes in bacterial susceptibility to fluoroquinolones.

It is noteworthy that the only hospital that showed a decrease in UDR (27.2%; table 2) was also the only hospital to report an increase in the susceptibility to fluoroquinolones of *P. aeruginosa* (18.2%; table 3). The 25.1% decrease in the mean percentage of susceptibility of *P. aeruginosa* found in our study is

Table 4. Percentage change from baseline to end point in percentage of susceptibility to fluoroquinolones, by pathogen.

Pathogen	No. of hospitals	Change in percentage of susceptibility, %	
		Mean ± SD	Range
Escherichia coli	10	−6.8 ± 5.5	−16.1 to −1.0
Pseudomonas aeruginosa	10	−25.1 ± 20.7	−60.7 to 18.2
Klebsiella pneumoniae	10	−1.3 ± 9.5	−11.8 to 22.5
Proteus mirabilis	10	−11.9 ± 12.4	−43.7 to 0.0
Enterobacter cloacae	10	−6.6 ± 5.8	−15.0 to 3.7
Enterobacter aerogenes	8	1.4 ± 10.45	−8.2 to 17.4
Acinetobacter species	9	17.0 ± 105.8	−34.3 to 296.9
Serratia marcescens	9	−3.8 ± 5.27	−13.2 to 3.3
Citrobacter species	9	3.2 ± 33.11	−31.0 to 87.5
Stenotrophomonas maltophilia	10	−17.4 ± 30.08	−60.7 to 32.6
Staphylococcus aureus	9	−26.8 ± 23.34	−57.9 to 9.0

Table 5. Percentage change from baseline to end point in percentage of susceptibility to fluoroquinolones, by hospital.

Hospital	No. of pathogens	Change in percentage of susceptibility, %	
		Mean ± SD	Range
1	9	−15.7 ± 17.2	−48.1 to 2.1
2	11	2.8 ± 34.1	−40.7 to 87.5
3	11	−11.8 ± 19.3	−60.7 to 5.4
4	10	22.4 ± 96.6	−23.4 to 296.9
5	11	−14.6 ± 15.6	−49.5 to 2.5
6	11	−13.7 ± 17.6	−57.9 to −1.0
7	10	−9.1 ± 26.5	−60.7 to 22.6
8	11	−15.8 ± 13.2	−45.5 to −3.0
9	10	−7.8 ± 13.2	−28.4 to 16.2
10	10	−10.5 ± 21.5	−44.4 to 32.6

especially worrisome, because only a limited number of antibacterial agents are available for the treatment of infections caused by this organism. Also of concern is the mean decrease in the susceptibility of *E. coli* (6.8%), because this confirms reports that resistance to fluoroquinolones is increasing among community-acquired pathogens [1]. The increase in resistance of *E. coli* to fluoroquinolones may be the result of an increase in the use of these agents in the treatment of uncomplicated infections, such as cystitis [2, 18], or of other infections that results in colonization and infection with fluoroquinolone-resistant strains.

The high mean decreases in percentage of susceptibility to fluoroquinolones of *P. aeruginosa* and *E. coli* found in our study confirm the findings of other recent studies. At a large university hospital, Chan-Tack [8] found that the susceptibility of *P. aeruginosa* to ciprofloxacin decreased from 85% to 69% over the course of an 8-year period. In a summary of the data collected for the period January 1992 through June 2001, the National Nosocomial Infections Surveillance System [9] reported that the resistance to fluoroquinolones of *P. aeruginosa* in patients in intensive care units increased from ~12% to ~27%. In their discussion of the prevalence of resistance to antimicrobials in the 23 Project ICARE hospitals, Fridkin et al. [11] reported that the mean resistance to ciprofloxacin of *P. aeruginosa* and *E. coli* in patients other than those in intensive care units increased significantly, from 17.2% to 23.9% and from 1.4% to 2.5%, respectively, between 1996 and 1999. Ena et al. [2] noted a significant increase (from 3% to 20%) between 1990 and 1996 in the resistance to ciprofloxacin of *E. coli* isolated from urine specimens collected in a community hospital in Spain. In their report on data obtained from hospital laboratories in England and Wales, Livermore et al. [12] cite a statistically significant increase between 1990 (0.8%) and 1999 (3.7%) in the mean resistance to ciprofloxacin of bloodstream isolates of *E. coli*.

When interpreting the results of our study, it must be borne in mind that the data on both percentage of susceptibility and UDR are aggregates for the 6 fluoroquinolones studied. In addition, the fluoroquinolones prescribed within each hospital changed over the study period. Consequently, conclusions cannot be drawn for the use of a single fluoroquinolone but only for total fluoroquinolone use.

A possible confounding factor in our study is the fact that 7 of the hospitals reported the amount of fluoroquinolone dispensed and 3 reported the amount of fluoroquinolone purchased for use in calculating the UDR. However, because both dispensing and purchasing data were reported in grams, rather than as a dollar value, and because errors are equally likely to occur in recording each type of information, both methods were included in the study.

The results of our study and the findings of a number of recent studies [1–13] confirm 2 generally accepted principles with regard to the development of bacterial resistance to antibacterial agents: bacterial resistance develops with time, and the greater the use of an antibacterial, the greater and more rapid will be the decrease in pathogen susceptibility [9]. Resistance to an antibacterial that develops in one person, furthermore, may affect other persons in that individual's environment. Because there is no counterselective pressure, resistance decreases very slowly, even if exposure of the organism to the antibacterial agent ceases. Factors such as local prescribing policies for antibacterials, patient characteristics, clonal spread of resistant pathogens, adherence to infection-control guidelines, and the inappropriate use of antibacterials result in geographic variation in susceptibility rates among hospitals [9]. It must be pointed out, however, that factors such as unsuitable pharmacodynamics, inappropriate dosage, prolonged antibac-

Table 6. Mean trend-line slope for logit susceptibility to fluoroquinolones, by pathogen.

Pathogen	No. of hospitals	Change in trend-line slope, %	
		Mean ± SD	Range
Escherichia coli	10	−0.25 ± 0.12	−0.47 to −0.06
Pseudomonas aeruginosa	10	−0.13 ± 0.08	−0.24 to 0.01
Klebsiella pneumoniae	10	−0.06 ± 0.14	−0.25 to 0.15
Proteus mirabilis	10	−0.20 ± 0.07	−0.36 to −0.13
Enterobacter cloacae	10	−0.10 ± 0.14	−0.41 to 0.05
Enterobacter aerogenes	8	−0.02 ± 0.16	−0.29 to 0.21
Acinetobacter species	9	−0.02 ± 0.13	−0.19 to 0.23
Serratia marcescens	9	−0.01 ± 0.06	−0.07 to 0.08
Citrobacter species	9	−0.05 ± 0.21	−0.39 to 0.26
Stenotrophomonas maltophilia	10	−0.05 ± 0.16	−0.29 to 0.23
Staphylococcus aureus	9	−0.11 ± 0.16	−0.34 to 0.17

Table 7. Mean trend-line slope for logit susceptibility to fluoroquinolones, by hospital.

Hospital	No. of pathogens	Change in trend-line slope, %	
		Mean ± SD	Range
1	9	−0.18 ± 0.09	−0.34 to −0.03
2	11	−0.04 ± 0.18	−0.32 to 0.26
3	11	−0.06 ± 0.14	−0.29 to 0.26
4	10	0.10 ± 0.16	−0.38 to 0.23
5	11	−0.11 ± 0.10	−0.36 to −0.01
6	11	−0.12 ± 0.10	−0.34 to 0.01
7	10	−0.04 ± 0.19	−0.47 to 0.23
8	11	−0.13 ± 0.07	−0.26 to −0.04
9	10	−0.05 ± 0.18	−0.25 to 0.21
10	10	−0.12 ± 0.21	−0.41 to 0.20

terial therapy, inadequate infection-control practices, severity of illness, and underlying disease also can contribute to the emergence of resistance [19–21]. One or more of these factors may have confounded our examination of the relationship between fluoroquinolone use and the development of resistance.

The statistical analysis of our aggregate hospital data documents the relationship between increasing fluoroquinolone use and decreasing susceptibility to fluoroquinolones of common gram-negative bacteria and *S. aureus.* We observed that susceptibility decreases not only in difficult-to-treat organisms, such as *P. aeruginosa,* but also in more common organisms, such as *E. coli.* These findings have important implications for the treatment of bacterial infections. If the use of fluoroquinolones continues to increase, both the prevalence and degree of reduced susceptibility to these agents can be expected to increase as well. To preserve the efficacy of the fluoroquinolones, therefore, efforts should be made to limit their use to infections for which they offer a clear therapeutic advantage over other antibacterials and to select the dose and duration of treatment that are most effective for the indication.

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