Fluoroquinolone Use and Methicillin-Resistant
Staphylococcus aureus Isolation Rates in Hospitalized
Patients: A Quasi Experimental Study

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(See the editorial commentary by Hota on pages 785–7)

Background. We investigated the possible association between fluoroquinolone use and the rate of methicillin-
resistant Staphylococcus aureus (MRSA) recovery from consecutive hospitalized patients.

Methods. We conducted a nonrandomized, prospective, controlled interventional “fluoroquinolone-free” study
at 4 large teaching hospitals in northwest France, catering to a total of 5,882,600 persons. During the intervention
period (January through December 2001), fluoroquinolone use was prohibited at 1 of the 4 hospitals (Caen
Hospital), unless no effective alternative was available. Three university hospitals were used as controls because
they had similar preintervention rates of MRSA.

Results. During the intervention period (2001), the annual rate of fluoroquinolone use decreased from 54 to
5 defined daily doses per 1000 patients per day at Caen Hospital and remained stable in the control hospitals. At
the end of the intervention, the rate of MRSA isolation was significantly lower at Caen Hospital than at the control
hospitals (353 [32.3%] of 1093 S. aureus isolates were MRSA, compared with 2495 [36.8%] of 6787 isolates; odds
ratio, 0.82; 95% confidence interval, 0.69–0.99; P = .036), as determined on the basis of a marginal model that
took into account within-hospital clustering. In a before-after time series analysis, compared with forecasted rates,
there was a significant downward trend in observed monthly rates of MRSA isolation at Caen Hospital at the end
of the intervention.

Conclusion. This quasi experimental study confirms the association between fluoroquinolone use and MRSA
isolation among hospitalized patients.

Several studies performed in the 1970s revealed that antimicrobials were often used inappropriately in hos-
itals and that overuse of antimicrobials contributed to the emergence of drug-resistant nosocomial pathogens
[1, 2]. The introduction of fluoroquinolones in French hospitals in the 1980s coincided with the emergence of
fluoroquinolone-resistant Staphylococcus aureus and with the spread of multidrug-resistant staphylococcal
strains [3, 4]. Initial emergence of fluoroquinolone re-
sistance in individual patients was commonly attributed
to the so-called “selective pressure” exerted by this class
of antimicrobials.

The prevalence of nosocomial methicillin-resistant S.
aureus (MRSA) isolation has now reached worrying
levels. The main cause is the presence of MRSA in at-
risk hospitalized patients and dissemination from per-
son to person; this “colonization pressure,” when com-
bined with antibiotic pressure, is one of the most
important causes of MRSA colonization and subse-
quent infection in hospitalized patients, especially
among those hospitalized in intensive care units [5–7].

Recent independent investigations have suggested
that there is a strong correlation between fluoroquin-
Fluoroquinolone use and predisposition to colonization or infection with MRSA, but not with colonization or infection with methicillin-susceptible S. aureus [8–11]. To test the possibility that significant restriction of fluoroquinolone exposure at a given hospital leads to a reduction in the rate of methicillin resistance among S. aureus isolates, we conducted a prospective, nonrandomized, controlled intervention trial.

**METHODS**

**Study Design**

We conducted a 12-month quasi experimental intervention trial at Caen University Hospital, a 1572-bed institution located in northwest France. Three other hospitals were used as controls. They were matched with Caen Hospital by geographic location (the hospitals were located in Haute-Normandie Hospital, which is 125 km from Caen; Nord-Pas de Calais, which is 385 km from Caen; and north of Paris, 225 km from Caen), medical service provision (acute care including medical, surgical, and obstetrical services; medical and surgical intensive care units; and teaching hospital status), and preintervention prevalence of MRSA among S. aureus isolates (to within ±6% of the baseline rate in Caen). Two other hospitals were considered but were not included because their baseline MRSA rates were <30%. The intervention consisted of a 1-year period of restriction (from 1 January 2001 to 31 December 2001) on the use of all quinolones at Caen Hospital. No changes in antimicrobial policy were implemented for the purposes of the study in the 3 control hospitals.

The effects of fluoroquinolone restriction were analyzed in 2 ways. First, we compared the rate of MRSA isolation (defined as the number of MRSA isolates/number of S. aureus isolates tested × 100) in the intervention hospital and the 3 control hospitals before (1 January 1997 to 31 December 2000) and during the intervention period (the year 2001). Second, we performed a before-after analysis of changes in the monthly rate of MRSA isolation in the intervention hospital. For this purpose, we also analyzed changes in the incidence density of hospital-acquired MRSA infections (defined as the number of MRSA infections/1000 patient-days), which had been prospectively monitored by the infection-control team since 1 April 1998. The study protocol was approved by a local and a national ethics committee.

**Data Collection**

**Antibiotic use.** In the 4 participating hospitals, the total fluoroquinolone use rate by each ward was recorded by the central pharmacies and aggregated for each hospital into defined daily doses (DDDs) per 1000 bed-days, as recommended by the World Health Organization [12], the year before and during the intervention period.

**Definition of MRSA prevalence.** MRSA prevalence rates were calculated for all S. aureus isolates recovered from patients admitted to the 4 hospitals during 1997–2001. Isolates recovered by surveillance cultures for detection of MRSA carriage, including nasal swab cultures, were not used to calculate MRSA prevalence rates. When multiple clinical isolates were obtained from a given patient, duplicates were eliminated on the basis of antimicrobial susceptibility patterns.

**Definition of nosocomial infection.** The monthly incidence density of hospital-acquired infections by MRSA and extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae (ESBL-EB) was routinely collected from the Caen hospital surveillance system, as recommended by French national hygiene guidelines. A new case was defined as a case in a patient with no previous history of MRSA or ESBL-EB colonization or infection who was infected with MRSA or ESBL-EB no less than 48 h after hospital admission. Rates of vancomycin-resistant enterococci were not collected, because vancomycin-resistant enterococci were not endemic in France either before or after the intervention.

**Fluoroquinolone Prescription Policy**

From 1 January 2001 through 31 December 2001, all patients admitted to Caen Hospital who qualified for oral or parenteral fluoroquinolone therapy received an alternative antimicrobial drug. The choice of drug was based on a protocol validated by local infectious diseases experts and distributed to all antibiotic prescribers, including residents and senior physicians. Depending on the patient’s characteristics and the site of infection, substitute antimicrobials included a β-lactam (amoxicillin, amoxicillin plus clavulanate, cefotaxime, or ceftriaxone) alone or combined with an aminoglycoside (netilmicin, tobramycin, or amikacin); an oral streptogramin (pristinamycin); a macrolide (erythromycin, roxithromycin, or spiramycin), alone or combined with a β-lactam; and trimethoprim-sulfamethoxazole. Rifampin, tetracycline, and clindamycin were also available. Rates of use of the substitute antibiotics are shown in table 1.

If no effective alternative was available for a particular patient, an infectious diseases consultant had to approve a fluoroquinolone prescription. No specific programs to reduce fluoroquinolone use were implemented in the control hospitals during the intervention period.

**Infection Control**

The measures recommended by French national guidelines for the prevention of nosocomial infections were implemented in the 4 study hospitals several years before the study began. In brief, prevention measures consisted of identifying reservoirs, preventing cross-transmission between patients, and routine identification of carriers in units with a high risk of transmission. In particular, all patients infected with MRSA or ESBL-
EB were isolated in single-bed rooms with reinforced hygiene measures. Nasal swab specimens were obtained at the time of admission from all patients admitted to the intensive care units in all 4 hospitals, to identify MRSA carriers. For obvious ethical reasons, the hospitals involved in this study were not discouraged from promoting measures aimed at reducing cross-transmission. In addition, implementation of a hand hygiene campaign in control hospitals to reduce the MRSA rate would confound the results toward no effect of fluoroquinolone class restriction (i.e., null hypothesis). A hand hygiene campaign based on alcoholic hand-rubs was implemented in several departments of control hospital A, including medical intensive care units, in July 2000. The volume of alcohol-based hand-rub used in this hospital almost doubled during the second half of 2001, relative to the same period in 2000. Details of this successful intervention on MRSA rates have been reported elsewhere [13]. Alcoholic hand-rubs were introduced in May 2001 in hospital B and before January 2001 at Caen Hospital, where surgical hand disinfection was evaluated [14].

**Antibiotic Resistance Survey**

In the 4 hospitals, antibiotic susceptibility was routinely determined by the agar disk diffusion technique on the basis of the latest yearly recommendations of the Antimicrobial Testing Committee of the French Society for Microbiology. Methicillin resistance was screened with oxacillin disks on Mueller-Hinton medium supplemented with salt. The tested fluoroquinolones were ofloxacin for staphylococci and ofloxacin and ciprofloxacin for gram-negative bacilli. When an Enterobacteriaceae isolate was found to have intermediate resistance or to be resistant to a third-generation cephalosporin (i.e., cefotaxime, cefazidime, or cefepime), it was also tested by the double disk synergy test; isolates were considered to produce ESBL if synergism was noted between third-generation cephalosporins and the amoxicillin-clavulanate combination.

**Statistical Analysis**

The primary outcome measure was the rate of methicillin resistance. The statistical unit of analysis was the *S. aureus* isolate. Because restriction of fluoroquinolone use was applied to multiple individuals in the same hospital, and because outcome was measured at the level of the individual patient, we took into account a possible clustering effect. We thus used a generalized estimating equation (the Genmod procedure with Repeated statement in SAS software, version 9.1) to compare MRSA rates (Fisher’s exact test assumes that all observations are independent).

In the before-after analysis, we used the methods popularized by Box and Jenkins [15] for time series analysis, because adjacent observation of MRSA rates taken over time are dependent. This method has been proposed for evaluation of the temporal relationship between antibiotic use and resistance [16]. First, the normal distribution of the series was tested with the Kolmogorov-Smirnov method. Second, as changes in the monthly MRSA rate and in the monthly incidence density of hospital-acquired MRSA infections showed a decreasing trend and chaotic behavior, we used log transformation and differencing to allow stationarity of the time series. We examined the series autocorrelations and partial autocorrelations to identify autoregressive and moving average behaviors. The terms “autoregressive” and “moving average” refer to the influence of past values and their abrupt changes on the current value (for example, monthly MRSA rates). For MRSA rates and incidences of MRSA infection, ARIMA(1,1,1) models were adjusted. We then used these ARIMA models to forecast expected values of the outcomes during the intervention. Finally, observed values were compared with the 95% CIs of the expected values.

P values of <0.05 were considered to be statistically significant. All tests were 2-sided. Computations were done with SAS software, version 9.1 (SAS Institute).

**RESULTS**

**Hospital Characteristics and Fluoroquinolone Use**

Caen University Hospital cares for a population of 1,422,400 people, 22.8% of whom are at least ≥60 years old. The corresponding figures for control hospitals A, B, and C are
Table 2. Hospital characteristics and fluoroquinolone use before and after fluoroquinolone class restriction.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>No. of beds</th>
<th>Occupancy index</th>
<th>No. of DDDs/1000 bed-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control hospital A</td>
<td>1130</td>
<td>0.84</td>
<td>84.8</td>
</tr>
<tr>
<td>Control hospital B</td>
<td>1777</td>
<td>0.82</td>
<td>85.4</td>
</tr>
<tr>
<td>Control hospital C</td>
<td>2761</td>
<td>0.68</td>
<td>89.2</td>
</tr>
<tr>
<td>Caen hospital</td>
<td>1572</td>
<td>0.79</td>
<td>53.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of DDDs/1000 bed-days</th>
<th>Occupancy index</th>
<th>No. of beds</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>53.6</td>
<td>0.79</td>
<td>1572</td>
</tr>
<tr>
<td>2001</td>
<td>5.2</td>
<td>0.77</td>
<td>1519</td>
</tr>
</tbody>
</table>

NOTE. DDD, defined daily dose.

1,205,000 (13.4%), 1,780,200 (19.5%), and 2,555,000 (18.1%), respectively.

Table 2 shows the baseline characteristics of the 4 hospitals during the intervention period and during the previous year. From 1 January 2001 through 31 December 2001, the rate of use of fluoroquinolones (essentially ofloxacin and ciprofloxacin) at Caen Hospital decreased by 90.3%, compared with the previous year, to an average of rate of 5.2 DDDs per 1000 bed-days. Fluoroquinolone use remained stable or increased in the control hospitals (table 2).

Hospital-Controlled Analysis
From 1 January 1997 through 31 December 2000 (i.e., the baseline evaluation period), 25,228 nonsurveillance isolates of *S. aureus* were recovered in the 4 hospitals. The rates of MRSA were 980 (31.5%) of 3112 *S. aureus* isolates, 2247 (37.4%) of 6002 *S. aureus* isolates, 4261 (36.8%) of 11,589 *S. aureus* isolates, and 1627 (36.0%) of 4525 *S. aureus* isolates at hospitals A, B, and C and at Caen Hospital, respectively. Only hospital A had a significantly lower prevalence of MRSA than Caen hospital *(P < .001)*. Overall, the rates of MRSA did not differ between Caen Hospital and the control hospitals (36.0% vs. 36.2%; *P* = not significant).

A total of 7880 *S. aureus* isolates were collected during the intervention period. During this period, the rate of MRSA was significantly lower at Caen Hospital than at the control hospitals (353 [32.3%] of 1093 isolates and 2495 [36.8%] of 6787 isolates, respectively; OR, 0.82; 95% CI [adjusted for within-hospital correlation], 0.68–0.99; *P* = .036).

Time Series Analysis
**Methicillin resistance.** The forecasted values of the ARIMA models were linear, with large 95% CIs, as expected by the absence of seasonality and the chaotic behavior of the data. The observed monthly prevalence of MRSA was lower than expected in the ARIMA model in July (23% vs. 24%) and December 2001 (22% vs. 24%), as shown in figure 1. The observed incidence density of hospital-acquired MRSA infections (figure 2) remained within the 95% CI forecast. The observed incidence was lowest 2 months after the end of the intervention (0.284 cases per 1000 patient-days in February 2002) and was less than the lower limit of the 95% CI forecast (0.291 cases per 1000 patient-days).

**Resistance to other antimicrobials.** Changes in quinolone resistance correlated strongly with changes in methicillin resistance among *S. aureus* isolates (data not shown). No decrease in the rate of quinolone resistance was observed among gram-negative bacilli, such as *Pseudomonas aeruginosa* and *Escherichia coli*, during the fluoroquinolone restriction period at Caen Hospital. However, we observed a time-limited high incidence of hospital-acquired infection by ESBL-producing *Klebsiella pneumoniae* from May to August 2001 (from 0.354 to 0.310 cases per 1000 patient-days, respectively) (figure 3).

**DISCUSSION**
In this nonrandomized, prospective, hospital-controlled study, we observed a significant association between restriction of fluoroquinolone use during a 12-month period (90.3% reduction in use) and a decrease in the rate of MRSA isolation. These findings were supported by time series analysis of MRSA isolation rates and nosocomial MRSA incidence rates before and after fluoroquinolone restriction. The results of this prospective quasi experimental study are in keeping with those of retrospective ecological and case-control studies in European and American hospitals [11, 17–19]. The baseline prevalences of MRSA found in this study were very similar to those reported elsewhere in France during the same period [20].

This prospective intervention study used 2 different controls—namely, comparable hospitals with similar baseline rates of MRSA and the intervention hospital before the intervention. In the latter analysis, we compared not only the rates of MRSA but also the incidence of MRSA infection per 1000 patient-days, to adjust for the number of days at risk. Regardless of the control group and the parameter, we consistently observed a decrease in the rate of MRSA isolation during fluoroquinolone restriction.

This study has a number of limitations. First, our design was...
not a cluster randomized, controlled trial. Consequently, statistical association does not necessarily imply causality. Confounding variables included regression to the mean, maturation effects, and differences in comorbidity among the patients studied in the intervention and control hospitals. However, the use of a mixed design that combined elements of both internal and external comparisons increased the potential for making a causal inference [21]. The population-based design of the study, which included all consecutive patients originating from a geographically defined area and admitted to teaching hospitals with similar baseline MRSA rates, tends to limit the impact of such individual differences.

The relatively modest reduction in MRSA rates during the intervention period, from 36.0% to 32.3%, might be explained by 2 factors. First, fluoroquinolone use rates in the intervention hospital were low at baseline, compared with the control hospitals and with American hospitals [18, 19]. Second, some patients may have received fluoroquinolones previously on an outpatient basis. It is likely, however, that the colonization pressure exerted by inpatient fluoroquinolone treatment would...
Fluoroquinolone Restriction and MRSA Rates

have had a stronger impact on the incidence of nosocomial MRSA infection, as we observed in this study and others have observed previously [22]. The significant reduction in the incidence of MRSA isolation observed in February 2002 may have resulted from a prior reduction in MRSA colonization. Additional studies with transfer function of the ARIMA models are warranted to better explore the lagged effect of fluoroquinolone restriction. However, because use of both ofloxacin and ciprofloxacin was restricted, we are unable to speculate on the respective role of each drug. A causal association between fluoroquinolone use and increasing MRSA rates is also supported by the results of several laboratory studies summarized elsewhere [11, 23].

We do not believe that fluoroquinolone use should be drastically restricted to stop the spread of MRSA. During our intervention period, we observed an increased incidence of ESBL-EB infection, possibly owing to increased pressure exerted by cephalosporins that were used to replace fluoroquinolones. A previous prospective time-controlled analysis [24] reported a 44% reduction in ESBL-EB isolation following an 80% restriction of cephalosporin use, together with an increase in the rate of imipenem-resistant P. aeruginosa. This effect, known as “squeezing the balloon” [25], underscores the limits of systematic drug class restriction, because it may lead to the emergence of other class resistance patterns.

Fluoroquinolones are widely used for their activity on a broad spectrum of bacteria and for their excellent oral bioavailability. Inappropriate fluoroquinolone use should, however, be identified and reduced [26–28]. Our quasi experimental study provides additional evidence that inappropriate fluoroquinolone use may not only have financial implications, but may also increase bacterial resistance, as previously suggested by observational studies [8–11, 17–19, 29, 30]. Our results support the implementation of programs designed to optimize fluoroquinolone prescription and thereby to help control the spread of MRSA.

FRENCH FLUOROQUINOLONE-FREE STUDY GROUP

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