Improvement of gram-negative susceptibility to fluoroquinolones after implementation of a pre-authorization policy for fluoroquinolone use: A decade-long experience

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Abstract

Objective: Due to concerns over increasing fluoroquinolone (FQ) resistance among gram-negative organisms, our stewardship program implemented a preauthorization use policy. The goal of this study was to assess the relationship between hospital FQ use and antibiotic resistance.

Methods: We performed a retrospective analysis of FQ susceptibility of hospital isolates for 5 common gram-negative bacteria: Acinetobacter spp., Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa. Primary endpoint was the change of FQ susceptibility. A Poisson regression model was used to calculate the rate of change between the preintervention period (1998–2005) and the postimplementation period (2006–2016).

Results: Large rates of decline of FQ susceptibility began in 1998, particularly among P. aeruginosa, Acinetobacter spp., and E. cloacae. Our FQ restriction policy improved FQ use from 173 days of therapy (DOT) per 1,000 patient days to <60 DOT per 1,000 patient days. Fluoroquinolone susceptibility increased for Acinetobacter spp. (rate ratio [RR], 1.038; 95% confidence interval [CI], 1.005–1.072), E. cloacae (RR, 1.028; 95% CI, 1.013–1.044), and P. aeruginosa (RR, 1.013; 95% CI, 1.006–1.020). No significant change in susceptibility was detected for K. pneumoniae (RR, 1.002; 95% CI, 0.996–1.008), and the susceptibility for E. coli continued to decline, although the decline was not as steep (RR, 0.981; 95% CI, 0.975–0.987).

Conclusions: A stewardship-driven FQ restriction program stopped overall declining FQ susceptibility rates for all species except E. coli. For 3 species (ie, Acinetobacter spp, E. cloacae, and P. aeruginosa), susceptibility rates improved after implementation, and this improvement has been sustained over a 10-year period.

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A retrospective, quasi-experimental analysis of FQ susceptibility among 5 common hospital isolates: *Acinetobacter species*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. We included clinical isolates from all body sites, including blood, skin or soft tissue, respiratory tract, urinary tract, and sterile cultures from the clinical microbiology laboratory from inpatient and emergency department locations. Any organism with the same susceptibility pattern from the same patient was only included once per calendar year. The minimum inhibitory concentration (MIC) for each isolate was determined by Microscan (Beckman Coulter, Carlsbad, CA). Susceptibility breakpoints were determined using Microscan MIC breakpoints in accordance with US Clinical and Laboratory Standards Institute (CLSI) guidelines. Volume of antimicrobial use is reported in days of FQ therapy per 1,000 patient days.

**Antibiotic restriction program**

In October 2005, as recommended by the ASP, the Pharmacy and Therapeutics Committee at UAB Hospital instituted a restriction policy requiring prior authorization for FQ. As part of this policy, our antimicrobial inpatient formulary was first streamlined from levofloxacin, gatifloxacin, moxifloxacin, and ciprofloxacin to moxifloxacin and ciprofloxacin as the only FQs available. All inpatient providers were required to obtain ASP approval for empiric use of an FQ (with the exception of moxifloxacin for use for community-acquired pneumonia). Fluoroquinolone use was permitted for treating gram-negative infections if culture results were available and the bacterial isolate was susceptible to an FQ. Prior to the availability of computer physician order entry (CPOE; 2008), FQ prescriptions were manually reviewed by clinical pharmacists. After implementation of CPOE, providers were required to document reason for the use of FQ or to document approval by the ASP ID attending physician. Any data point prior to January 1, 2006 was considered to have occurred during the preintervention period, and any data point after was considered to have occurred during the postintervention period.

**Statistical analysis**

To determine whether the annual trends in susceptibility were different in the periods prior to and following implementation of the stewardship program (ie, 1998–2005 vs 2006–2016), a Poisson regression including an interaction between time period and continuous time was used to estimate rate ratios (RRs) and associated 95% confidence intervals (CIs) for the annual rate of change in susceptibility for each of the 2 time periods. A likelihood ratio test of the interaction between period and continuous year was used to examine whether the slopes of the annual rate of change in susceptibility differed statistically between periods. Poisson models were created for overall susceptibility as well as species-specific susceptibility. All Poisson models accounted for dispersion utilizing a dispersion parameter calculated as the division of the model deviance by degrees of freedom. For all analyses, *P* < .05 was considered statistically significant, and SAS version 9.4 software (SAS Institute, Cary, NC) was used for all analyses.

**Results**

**Fluoroquinolone use**

Inpatient FQ use steadily increased from 1998 to 2004 and peaked at 173 days of therapy (DOT) per 1,000 patient days in 2004 (Fig. 1). Following the implementation of the FQ restriction program in October 2005, there was a precipitous drop in FQ use from 2006 to 2007: usage declined from 141 to 52 DOT per 1,000 patient days. From 2007 and continuing through 2016, the rate of FQ use remained below 60 DOT per 1,000 patient days. The lowest period of use was in 2016, with 36 DOT 1,000 patient days. The FQ restriction policy resulted in a decrease in FQ use with a subsequent increase in third- and fourth-generation cephalosporin use. The average number of positive cultures of the 5 total isolates studied increased from 2,615 per year before the policy was implemented. However, a net total decrease was observed for all common parenteral anti–gram-negative antimicrobials, including β-lactamase inhibitors such as piperacillin-tazobactam and ampicillin or sulbactam, cephalosporins, aminoglycosides, and carbapenems.
Fluoroquinolone susceptibility

The FQ susceptibilities were assessed for 5 common gram-negative organisms: Acinetobacter spp, E. cloacae, E. coli, K. pneumoniae, and P. aeruginosa (Table 1, Figure 2). In the preintervention period (1998–2005), all 5 isolates had decreasing rates of susceptibility to FQs. Acinetobacter spp susceptibility declined from 76% to 35% (annual trend RR, 0.871; 95% CI, 0.833–0.912); E. cloacae susceptibility declined from 99% to 55% (annual trend RR, 0.898; 95% CI, 0.870–0.926); E. coli susceptibility declined from 99% to 71% (annual trend RR, 0.952; 95% CI, 0.941–0.964); K. pneumoniae susceptibility declined from 94% to 80% (annual trend RR, 0.976; 95% CI, 0.964–0.989); and P. aeruginosa susceptibility declined from 72% to 50% (annual trend RR 0 (annual trend R Rn 0.937; 95% CI, 0.923–0.951) (Tables 1 and 2).

Comparing the annual trends between the preimplementation and postimplementation periods, overall, a decreasing annual trend of the FQ susceptibility rates was observed during 1998–2005 (RR, 0.935; 95% CI, 0.918–0.954). Following the implementation of the restriction policy, the annual trend was flat (RR, 1.000; 95% CI, 0.990–1.009), a difference that was statistically significant between the 2 periods (P < .0001) (Table 2). When examining trends by organism, a significant difference in the annual trends between the preimplementation and postimplementation periods was observed for all 5 gram-negative organisms (P < .0001 for all organisms except K. pneumoniae, which had a P = .0002). Specifically, following the implementation of the restrictive policy, susceptibility increased for Acinetobacter spp (RR, 1.038; 95% CI, 1.005–1.072), E. cloacae (RR, 1.028; 95% CI, 1.013–1.044), and P. aeruginosa (RR, 1.013; 95% CI, 1.006–1.020). The annual trend of K. pneumoniae did not increase in the postimplementation period, though it did remain flat (RR, 1.002; 95% CI, 0.996–1.008), and the trend of E. coli continued to decrease though not as sharply (RR, 0.981; 95% CI, 0.975–0.987).

Discussion

Our study demonstrates either cessation in (K. pneumoniae) or reversal of (Acinetobacter spp, E. cloacae, and P. aeruginosa) FQ resistance for hospital isolates which correlates with the implementation of an FQ restriction policy within the hospital that has been sustained for more than a decade. Interestingly, the FQ resistance rates not only stabilized, we also observed a reemergence of overall population susceptibility for certain species. The timing of these improvements varied, but we observed a 10% improvement in FQ susceptibilities within the first 2 years of implementing the restriction program for these 4 classically healthcare-associated pathogens.

In contrast, E. coli isolates continued to demonstrate decreasing FQ susceptibility despite declining FQ use, although at a notably slower rate compared to the preimplementation period. Although some stewardship programs have shown more success in improving hospital E. coli resistance rates, these studies were followed for shorter periods, focused on only 1 type of isolate, excluded isolates from primary care, or focused on nosocomial infections alone. Langford et al25 found that selectively withholding FQ susceptibility results on cultures involving E. coli significantly halted the increase in the resistance rate. Interestingly, these researchers did not observe a significant change in P. aeruginosa susceptibility rates despite a decrease in FQ use.24,25 These mixed observations demonstrate that reversing the resistance trends in gram-negative bacteria is a very complex process, especially with respect to enteric bacteria such as E. coli, and that antimicrobial restriction programs are likely be more effective if both inpatient and outpatient settings are targeted. However, these restriction programs were only followed for 2–3 years, while our ongoing FQ restriction program has been sustained for more than a decade.

Although our FQ restriction program did not result in an improvement of susceptibility to E. coli, we were able to demonstrate an improvement in the rate of the decline in susceptibility. We hypothesize that the continued decline in FQ

Fig. 2. Linear annual trends in fluoroquinolone-susceptibility rates before and after implementation of a policy requiring prior authorization for fluoroquinolone prescription.
| Organism                      | Preintervention | Postintervention |
|------------------------------|-----------------|------------------|
|                              | 1998            | 1999  | 2000  | 2001  | 2002  | 2003  | 2004  | 2005  | 2006  | 2007  | 2008  | 2009  | 2010  | 2011  | 2012  | 2013  | 2014  | 2015  | 2016  |
| Acinetobacter spp Isolates   | 62/181          | 135/177 | 106/165 | 109/120 | 109/170 | 95/225 | 87/292 | 157/449 | 111/245 | 78/182 | 149/395 | 78/182 | 128/418 | 121/184 | 121/245 | 74/182 | 66/132 | 45/87 |
|                              | %               | 76    | 76    | 74    | 76    | 74    | 76    | 76    | 74    | 76    | 74    | 76    | 74    | 76    | 74    | 76    | 74    | 76    | 74    |
| Enterobacter cloacae Isolates| 25/25           | 291/316 | 216/254 | 216/260 | 184/322 | 162/260 | 126/262 | 206/375 | 155/262 | 187/341 | 276/349 | 293/395 | 340/374 | 310/326 | 325/358 | 279/310 | 280/279 | 319/280 |
|                              | %               | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    | 99    |
| Escherichia coli Isolates    | 85/86           | 1,065/1,098 | 960/990 | 857/912 | 846/920 | 774/879 | 438/547 | 887/1,249 | 649/941 | 739/1,055 | 816/1,149 | 707/1,055 | 752/1,157 | 1,054/1,683 | 1,054/1,647 | 1,499/1,473 | 1,550/1,395 |
|                              | %               | 99    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    | 97    |
| Klebsiella pneumoniae Isolates| 33/35          | 546/575 | 502/490 | 446/485 | 456/510 | 459/550 | 298/440 | 465/655 | 465/613 | 614/655 | 549/637 | 625/934 | 755/797 | 673/693 | 797/770 |
|                              | %               | 94    | 95    | 93    | 91    | 94    | 90    | 85    | 80    | 89    | 92    | 89    | 92    | 89    | 92    | 90    | 88    | 89    | 90    |
| Pseudomonas aeruginosa Isolates| 66/92         | 666/888 | 495/678 | 406/580 | 362/549 | 399/665 | 276/758 | 379/444 | 379/444 | 592/977 | 580/892 | 590/908 | 527/798 | 774/1,172 | 733/1,110 | 619/897 | 712/1,062 | 692/975 |
|                              | %               | 94    | 95    | 93    | 91    | 94    | 90    | 85    | 80    | 89    | 92    | 89    | 92    | 89    | 92    | 90    | 88    | 89    | 90    |
| Total isolates               | 319            | 3,054  | 2,627  | 2,362  | 2,446  | 2,479  | 1,962  | 3,381  | 2,564  | 3,244  | 3,338  | 3,033  | 3,506  | 3,850  | 4,415  | 4,006  | 3,577  | 3,947  | 3,585  |

Note: Numerator represents the number of isolates susceptible to fluoroquinolones; denominator represents total number of isolates tested yearly.
susceptibility may be due to the use of FQ in the community; thus, to achieve a sustained increase in FQ susceptibility among *E. coli* isolates, community prescribing practices must be targeted. Similar studies have demonstrated that hospital *E. coli* resistance correlates to community FQ use and not to hospital FQ use.\(^{14–17}\) In a study of 9 hospitals and several long-term care facilities, an FQ restriction program was associated with a decline in FQ prescriptions at their facilities, a decrease in the FQ resistance rate in *E. coli* urinary isolates, and a concomitant decrease in FQ use in the community.\(^{18}\) Other stewardship programs that only restricted FQ use in hospitals have failed to demonstrate any improvement in *E. coli* FQ resistance.\(^{19–21}\) Thus, community FQ use, as opposed to hospital use, appears to be driving the development of *E. coli* resistance and its persistence, and stewardship efforts focusing on community restriction are essential.

In terms of the classic healthcare-associated pathogens, there are data demonstrating limited success in improving *P. aeruginosa* susceptibility in the context of FQ restriction, but susceptibility data pertaining to *E. cloacae*, *Acinetobacter* spp. and *K. pneumoniae* susceptibility have not shown significant improvement with similar restriction programs.\(^{20,21,26,27}\) Interestingly, a 1997 study showed that while *E. cloacae*, *Acinetobacter* spp. and *K. pneumoniae* did not improve their susceptibility rates to ciprofloxacin with restricted use, susceptibility rates for non-restricted antibiotics, including β-lactams, demonstrated improvement.\(^{28}\) Other studies have shown similar improvements in susceptibility to other antibiotic classes, including decreasing rates of extended spectrum β-lactamases (ESBL)–producing urinary isolates with FQ restriction.\(^{16}\) Fluoroquinolones, β-lactams, and aminoglycosides are known to co-select for resistance, even with chemically unrelated drug exposure due to multiple plasmid-mediated mechanisms that carry resistance genes to multiple drug classes, such as the *E. coli* ST131 clone.\(^{26}\) Fluoroquinolone exposure is a risk factor for development of ESBL *E. coli* urinary tract infections, and globally, 35%–65% of ESBL-producing *Enterobacteriaceae* are also FQ resistant.\(^{29}\) ESBL-producing bacteria continue to be an escalating problem, especially in the southeastern United States,\(^{30}\) and adoption of FQ restriction in stewardship programs is a useful tool available to fight this trend. Despite the continued decrease in FQ susceptibility in *E. coli* in our study, our overall ESBL rates are low for all isolates, which indicates less likely clonal expansion of multidrug-resistant bacteria in our institution.

Table 2. Rate Ratios\(^*\) (RRs) and Associated 95% Confidence Intervals (CIs) to Compare Annual Trends in Fluoroquinolone Susceptibility Rates Before (1998–2005) and After (2006–2016) the Implementation of an Antimicrobial Stewardship Program Requiring Preauthorization for Fluoroquinolone Use

| Organism               | 1998–2005 RR (95% CI)       | 2006–2016 RR (95% CI)       | \(P\) Value\(^a\) |
|------------------------|-----------------------------|-----------------------------|-------------------|
| Overall                | 0.935 (0.918–0.954)         | 1.000 (0.990–1.009)         | <.0001            |
| *Acinetobacter* spp.   | 0.871 (0.833–0.912)         | 1.038 (1.005–1.072)         | <.0001            |
| *Enterobacter* cloacae | 0.898 (0.870–0.926)         | 1.028 (1.013–1.044)         | <.0001            |
| *Escherichia coli*     | 0.952 (0.941–0.964)         | 0.981 (0.975–0.987)         | <.0001            |
| *Klebsiella pneumoniae*| 0.976 (0.964–0.989)         | 1.002 (0.996–1.008)         | .0002             |
| *Pseudomonas aeruginosa*| 0.937 (0.923–0.951)         | 1.013 (1.006–1.020)         | <.0001            |

\(^*\)Estimated from Poisson regression.

\(^a\)\(P\) value for the comparison of annual trends between periods.

streamlining the choices of FQs through a restricted formulary, we cannot definitively conclude which aspect had the largest effect on our observed susceptibility results. Interestingly, some in vitro data show that gram-negative resistance to levofloxacin occurs faster and reaches higher MICs than for ciprofloxacin.\(^{30}\) Not surprisingly, a survey of US hospital data found that increasing levofloxacin and ofloxacin expenditures were correlated with decreasing *P. aeruginosa* susceptibility to ciprofloxacin.\(^{31}\) In contrast, increased ciprofloxacin use has not been associated with FQ resistance, suggesting that levofloxacin is playing a more significant role in driving FQ class resistance. Thus, the removal of levofloxacin from our formulary may have had a significant impact on our susceptibility profile.

Our study had several limitations. Our data were compiled from a single academic medical center. The stewardship initiative was broadly applied; thus, no control units or hospitals were available for comparison. We did not collect data on the indications for FQ use to evaluate the quality of our restricted use policy; instead, they used FQ DOT per 1,000 patient days as a surrogate measure. Based on this measure alone, our program was highly successful. We witnessed a 60% decline in use between the pre- and postimplementation data. Furthermore, these data focus on clinical isolates gathered in the microbiology laboratory; thus, they do not distinguish between colonizing isolates versus true pathogens. More detailed data on the influence of restricted-use policies on prescribing practices may help elucidate areas of focus for programmatic improvement and may better explain the lack of susceptibility improvement in certain species. For example, it is not clear to us why *Acinetobacter* spp. FQ susceptibility initially improved, then plateaued, and has started to decline over the last few years despite continued low FQ use. This may be the result of cluster outbreaks of *Acinetobacter*, but this trend will require further study. This study occurred over a long period; thus, infection prevention efforts may have also played a role in improving FQ susceptibility. Finally, our data demonstrate the feasibility and the critical importance of long-term tracking to re-evaluate the influence of stewardship programs.

As hospitals and health systems attempt to combat growing resistance rates to antibacterial agents, FQ resistance in gram-negative organisms remains a serious challenge. Our data demonstrate that decreasing overall FQ use, possibly through limiting routine access to levofloxacin specifically, can result in improvement overall in susceptibility of several gram-negative bacteria. For certain organisms, such as *E. coli*, decreasing hospital use alone appears to be insufficient to reverse the FQ resistance
trend, whereas efforts focused on appropriate community FQ use are likely of major importance. Larger, multicenter longitudinal studies focusing on the influence of active ASPs and restricted use of particular agents are critically important to better understanding how these interventions influence antimicrobial resistance patterns and how these policies can be applied for optimal effect.

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