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MAJOR ARTICLE

A Nonrestrictive Approach to Fluoroquinolone Stewardship at Two Community Hospitals

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Background. Fluoroquinolones are one of the most prescribed antimicrobials in the United States and have been increasingly used in inpatient and outpatient settings to treat various infectious diseases syndromes. Due to the unwanted collateral effects on antibiotic resistance, poor susceptibility rates among Gram-negative pathogens, and adverse effects, fluoroquinolones are often targeted by hospital antimicrobial stewardship programs to prevent overutilization. This study describes the association of nonrestrictive antimicrobial stewardship interventions at 2 nonacademic community hospitals on levofloxacin utilization, prescribing patterns on alternative antibiotics, and *Pseudomonas aeruginosa* nonsusceptibility rates to levofloxacin.

Methods. Nonrestrictive antimicrobial stewardship interventions included monitoring and reporting of fluoroquinolone susceptibility trends to physician groups, performing medication use evaluations of levofloxacin accompanied with prescriber detailing, daily prospective audit and feedback, implementation of beta-lactam-based institutional guidelines for empiric therapy in various infectious disease syndromes, review and adjustment of electronic medical record order sets containing fluoroquinolones, and intensive prescriber education. No preauthorization of levofloxacin was used during this study period. Antibiotic utilization data were collected for the time periods of August 2015 through January 2021. Correlation between levofloxacin and other broad-spectrum antibiotc use was investigated as well as the impact on *Pseudomonas aeruginosa* levofloxacin nonsusceptibility rates.

Results. Both hospitals showed an overall downward trend in the prescribing of levofloxacin during the time period of August 2015 to January 2021. There was a significant negative correlation between monthly ceftriaxone and levofloxacin days of therapy for both hospitals ($P < .0001$). There was a positive correlation between levofloxacin days of therapy and *P aeruginosa* nonsusceptibility ($P < .02$ at both hospitals).

Conclusions. Our results demonstrate that a nonrestrictive approach to fluoroquinolone stewardship interventions had a significant impact on reducing levofloxacin utilization, increasing ceftriaxone utilization, and improving *P aeruginosa* levofloxacin susceptibility.

Keywords. fluoroquinolone stewardship; antibiotic stewardship; antimicrobial stewardship program; antimicrobial resistance; levofloxacin.

Fluoroquinolones (FQ) are broad-spectrum antibiotics that have been increasingly used in both the inpatient and outpatient settings over the last 2 decades [1, 2]. Levofloxacin (LVX) specifically is one of the most commonly used antimicrobials in the United States [3]. Its high bioavailability, once-daily dosing, and broad activity against enteric and respiratory pathogens, including *Pseudomonas aeruginosa*, make it an appealing anti-infective in various treatment settings. These attributes coupled with its availability as an oral formulation has led to overutilization in both the inpatient and outpatient settings [4]. This has resulted in diminished effectiveness as an empiric therapy for urinary tract and intra-abdominal infections due to the increasing emergence of resistance among pathogens commonly causing these infections. To date, hospital and community resistance rates of *Escherichia coli* and *P aeruginosa* to FQ have been increasing [2, 5, 6]. Currently, per the US Food and Drug Administration (FDA) and various national treatment guidelines, alternative agents are recommended in urinary tract and upper respiratory tract infections due to increased pathogen resistance and associated adverse drug reactions [7]. Fluoroquinolones as a class are associated with several toxicities, with a spectrum of reactions including cardiotoxic effects, central nervous system effects, photosensitivity, tendinopathies, and glycemic disturbances [8, 9]. Due to these concerns, in 2016 the FDA issued a warning

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stating that FQ should only be used if no alternative agents are appropriate for the treatment of acute bronchitis, uncomplicated urinary tract infection, and acute sinusitis, due to the potential risks outweighing the benefits of FQ use for these indications. In addition, FQ have been found to have direct and "collateral" effects on resistance, including development of resistance to other classes of antibiotics such as carbapenems [10]. Furthermore, their usage has been associated with *Clostridioides difficile* and methicillin-resistant *Staphylococcus aureus* infections [11–13].

Based on the high FQ resistance among common organisms, their association with *C difficile* infection, and documented adverse drug reactions, we developed strategies to curb the excessive use of LVX in our institutions that did not involve LVX preauthorization. A restrictive intervention involving antibiotic preauthorization has been shown to significantly decrease antibiotic usage, but this has important disadvantages [14–18]. These disadvantages include loss of prescriber autonomy, real-time resource intensive, and potential for manipulation of the restricted antibiotic approval system to gain prescription access [19]. On the contrary, nonrestrictive approaches to reduce inappropriate antibiotic use have been described in the literature, but these methods are relatively scarce in comparison to restriction methods. The nonrestrictive strategies described have included prospective audit and feedback to decrease total antibiotic use with sustained reduction over the period of years as well as modifications of local clinical guidelines and intensive prescriber education [20, 21]. Specific nonrestrictive interventions that we used included the following: monitoring and reporting FQ susceptibility trends to physician groups, performing medication use evaluations of LVX accompanied with prescriber detailing, daily prospective audit and feedback, implementation of beta-lactam-based institutional guidelines for empiric therapy in various infectious disease syndromes, review and adjustment of electronic medical record (EMR) order sets containing FQ, and intensive prescriber education. No preauthorization of LVX was used during this study period.

In this study, we describe the impact of nonrestrictive antimicrobial stewardship interventions targeting LVX use in 2 nonacademic community hospitals, specifically its effect on LVX prescribing patterns, alternative antibiotic utilization, and inpatient collected *P aeruginosa* nonsusceptibility rates.

METHODS

This study took place at Hoag Hospital (HH) and Providence St. Joseph Hospital of Orange (PSJH) from August 2015 to January 2021 and was approved by each respective institutional review boards. Both institutions are nonacademic community hospitals each consisting of more than 450 beds in the greater Los Angeles metropolitan area of Southern California.

Antimicrobial Stewardship Interventions

In January 2017, both institutions formally initiated a nonrestrictive approach to antimicrobial stewardship with the goal of decreasing LVX use. The bundle of interventions was based on certain action elements of the 2019 Centers for Disease Control and Prevention Core Elements of Hospital Antibiotic Stewardship Programs. The primary method consisted of prescriber education at both institutions provided by antimicrobial stewardship program personnel through various physician group meetings. Education in the form of in-person presentations included the risks associated with FQ use and providing FQ-sparing recommendations for infections where FQs were known to be frequently used. This included the substitution of (1) LVX plus metronidazole with ceftriaxone (CRO) plus metronidazole as empiric therapy for most intra-abdominal infections and (2) CRO plus azithromycin instead of LVX for community-acquired pneumonia. Fluoroquinolone susceptibility trends were regularly monitored and reported to various physician groups. Medication use evaluations were conducted to determine for which infectious disease syndromes LVX was mostly prescribed and the distribution of LVX prescribing among different provider specialties. Anonymous peer comparison reports of LVX prescribing were shared with providers to enable individualized feedback. Changes to institutional treatment guidelines and sepsis order sets were conducted to remove or place LVX lower in the antibiotic selection list. In situations in which there was a concern and a need for double coverage of *P aeruginosa* due to low susceptibilities of select beta-lactams, aminoglycosides were recommended in place of LVX due to its lower resistance rates among *P aeruginosa*. Both institutions conducted daily prospective audit and feedback of LVX use by infectious diseases and clinical pharmacists. No preauthorization of LVX was used during this study period; thus, any provider was able to prescribe LVX at each respective hospital. For PSJH, education provided to physician groups occurred biannually from 2017 to 2018. Reporting of provider peer comparison of LVX prescribing occurred in 2017 and 2019. Electronic medical record order sets and treatment guidelines were updated in 2019. Routine prospective audit and feedback was performed since January 2017 and throughout the study period. At HH, educational quarterly meetings occurred from 2017 to 2019 at hospitalist, intensivist, and antimicrobial stewardship committee meetings. These meetings also provided peer comparisons of prescribers' LVX use. Order-set and institutional guideline changes occurred from September 2016 to March 2017. Prospective audit and feedback was performed from 2017 and throughout the study period.

Antibiotic Use and Resistance Rates

Antibiotic utilization data were collected for the time periods of August 2015 through January 2021 using monthly days of therapy (DOT) per 1000 patient-days (PD) as the metric. Data for

monthly use of LVX and CRO were obtained from the same sources at both institutions in an effort to minimize deviations in reported patient-days or antibiotic use. Utilizing hospital EMR surveillance systems, antibiogram data including susceptibility rates of *P aeruginosa* were collected for the time period of August 2015 through January 2019. Nonsusceptibility to LVX was calculated based on the number of *P aeruginosa* isolates collected from inpatient locations that were either resistant or intermediate to LVX. Susceptibility results were specific for organisms isolated from inpatient hospital locations, with emergency department collected strains excluded. All susceptibility data at both institutions were collected before implementation of the recommended Clinical and Laboratory Standards Institute (CLSI) LVX minimum inhibitory concentration breakpoint update publicized in February 2019 [22]. Due to changes in the CLSI minimum inhibitory concentration breakpoints for LVX, which were implemented by both hospitals, and additional changes in cascading practices by one of the hospital's microbiology laboratories, consistent data on LVX susceptibility was only available through January 2019.

Statistical Analysis

Statistical analysis was performed using GraphPad version 6.0 and R statistical computing software version 3.6.1. Correlation analysis was performed by Spearman correlation test. An interrupted time-series analysis was used to examine the pattern in the utilization of LVX [23, 24]. Data from both hospitals were assessed and adjusted for seasonality. The interrupted time-series regression included both times, the intervention, and the interaction of time and intervention as independent variables. This analysis assesses whether there was an overall trend, whether mean levels of LVX were the same before and after the intervention, and whether there was a change in trend at the point of intervention indicated by a significant slope change. Finally, Pettitt's test was used to determine whether the data supported a statistically significant trend change point

RESULTS

Both HH and PSJH showed an overall downward trend in the prescribing of LVX during the time period of August 2015 to January 2021. In August 2015, HH used 62 DOT/1000 PD of LVX, and by January 2021 the reported DOT/1000 PD was 8. In August 2015, PSJH used 100 DOT/1000 PD of LVX, and by January 2021 use was at 20 DOT/1000 PD. Overall unadjusted LVX and other broad-spectrum antibiotic use for each hospital over the study period are depicted in Figure 1*A* and *B*. Of note, ciprofloxacin and ceftazidime are nonformulary at HH and PSJH, respectively. The seasonally adjusted monthly use is depicted in Figure 1*C* and *D* for each hospital.

The interrupted time-series regression with seasonally adjusted data was significant for time (months) for both HH and PSJH ($P < .0001$ and $P < .01$, respectively), indicating that both hospitals showed an overall downward trend in the rate of use. Average LVX usage was less after the intervention for both hospitals ($P < .0001$ and $P < .01$, respectively). The interaction of time and intervention was significant only for HH where there was a slope change at the intervention point of January 2017, in which the slope before intervention was −1.99 and −0.49 after (Figure 1*E*). Thus, for HH, there was a more dramatic decrease in LVX use before the formal commencement of the LVX stewardship initiative, compared with the timeframe thereafter. No statistically significant change in slope was identified for PSJH because the slope showed a continuous decline over the timeframe (Figure 1*F*). Pettitt's test revealed significant trend changes for both HH and PSJH ($P < .0001$ and $P < .0001$, respectively); however, these points were after the intervention point of January 2017. The test indicated a trend change at the time point of March 2018 for HH and at the time point of May 2018 for PSJH. Both points were after the intervention point, which indicated that the downward trend continued until finding a stable utilization rate.

As mentioned above, both hospitals observed an overall decrease in FQ use over the August 2015 to January 2021 timeframe. Reviewing DOT/1000 PD data graphically along with other broad-spectrum antibiotics, we noted that CRO use tracked in the opposite direction of LVX. Therefore, LVX and CRO DOT data were tested for correlation using Spearman correlation analysis for HH, because the data was not normally distributed, and Pearson correlation analysis for PSJH. There was a significant negative correlation between monthly CRO and LVX DOT for both hospitals; as LVX DOT decreased, CRO DOT increased ($P < .0001$). This correlation was consistent when performing an analysis of 3-month and 6-month data of CRO and LVX DOT for HH and PSJH ($P < .0001$) (Figure 2). Correlation analysis of LVX and other broad-spectrum antibiotics depicted in Figure 1*A* and *B* was also performed, and it was demonstrated that CRO was the antibiotic with the strongest correlation with LVX (Table 1).

There was a positive correlation between LVX DOT and *P aeruginosa* nonsusceptibility to LVX in which the percentage of nonsusceptible isolates over a 6-month timeframe decreased as LVX DOT decreased at each hospital ($P = .0161$ and $P = .0068$, for HH and PSJH, respectively). Furthermore, after analyzing the nonsusceptibility and DOT data on a 3-month basis, we noted there was also a significant positive correlation during this timeframe for each hospital ($P = .0067$ and $P = .0132$, for HH and PSJH, respectively) (Figure 3).

DISCUSSION

In this study, 2 separate community hospitals implemented the same goal and approaches to reducing LVX use. The initial drive for establishing an antimicrobial stewardship goal of

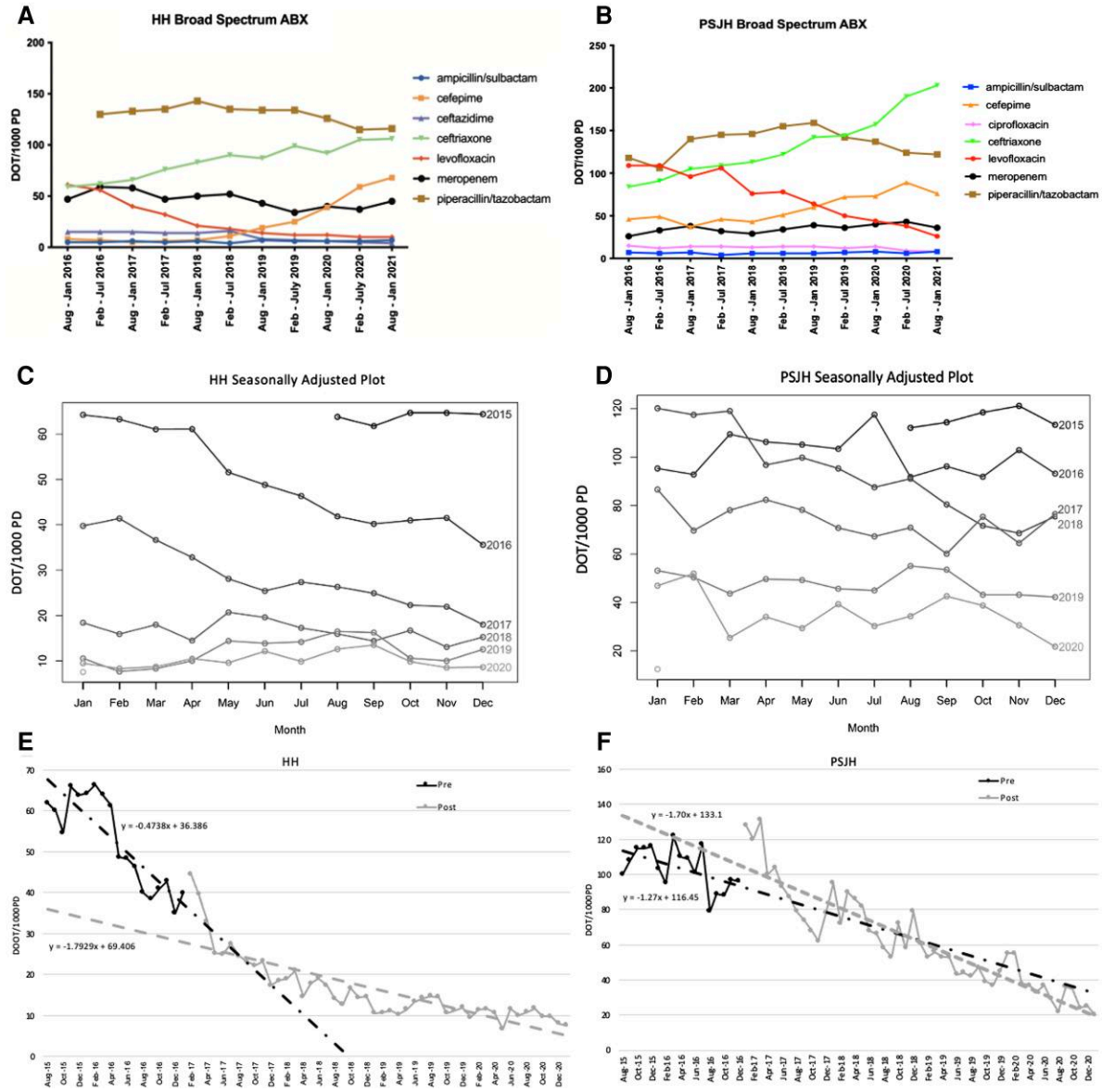

Figure 1. Broad-spectrum antibiotic (ABX) days of therapy (DOT)/1000 patient-days (PD) by every 6 months: (*A*) Hoag Hospital (HH); (*B*) Providence St. Joseph Hospital of Orange (PSJH). Seasonally adjusted levofloxacin (LVX) DOT/1000 PD by month and year: (*C*) HH; (*D*) PSJH. LVX DOT/1000 PD with trend lines are depicted in (*E*) and (*F*) for HH and PSJH, respectively.

reducing LVX use at each institution was due to the high LVX resistance rates among *Enterobacterales* and *P aeruginosa*, which made them poor empiric therapeutic choices for Gram-negative infections, and the risk of FQ-associated toxicities. Both institutions were successful in decreasing LVX use as indicated by the time-series regression demonstrating an overall downward trend and the average LVX usage being less after the intervention. The decrease in LVX use was sustained over a 4-year period and continues to this day (data not shown). This was achieved through nonrestrictive approaches targeting prescribing behaviors primarily through prescriber education, prospective audit and feedback, and modifications to institutional antibiotic recommendations, among other various interventions. Although both institutions formally initiated the goal of decreasing LVX use in 2017, HH's LVX use had already began to decline in the summer of 2016, likely due to the issued FDA warning regarding FQ use in May 2016. This resulted in 2 different slopes that were significantly different in which the first slope had a steeper decrease compared to the second slope, which was less steep and essentially flat, indicating that LVX prescribing had plateaued (Figure 1*E*). Providence St. Joseph Hospital of Orange had 1 slope that demonstrated a continuous decrease over the timeframe (Figure 1*F*).

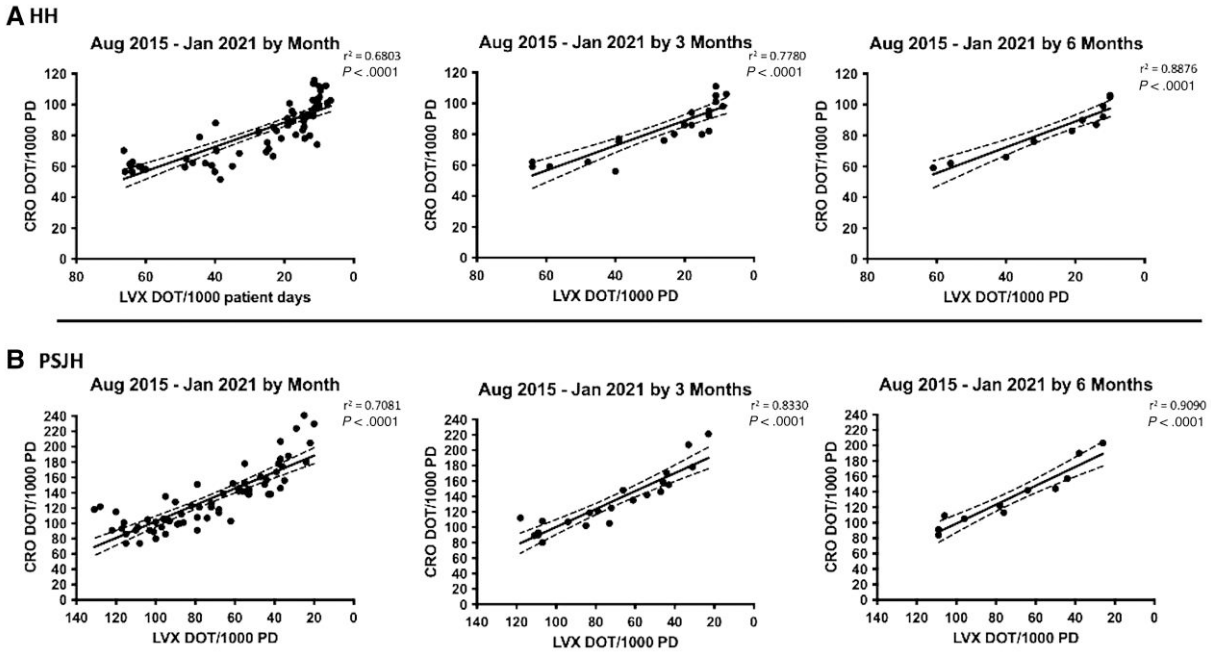

Figure 2. Correlation analysis of levofloxacin (LVX) and ceftriaxone (CRO) days of therapy (DOT)/1000 patient-days (PD) by months, 3 months, and 6 months at (*A*) Hoag Hospital (HH); (*B*) Providence St. Joseph Hospital of Orange (PSJH).

Furthermore, as LVX use decreased, we found a significant correlation with increased use of CRO (Figure 2). This was expected because many of our institutional guidelines and order sets replaced LVX with CRO due to its higher susceptibility rates among *Enterobacterales*. Prescriber education on utilizing beta-lactam antibiotic alternatives further shifted provider prescribing behavior away from LVX. This phenomenon has been referred to in the literature as "squeezing the balloon"—noteworthy because both LVX and CRO are known to add selective pressure for extended-spectrum beta-lactamase (ESBL)-producing organisms [25–27]. Nevertheless, FQs as a class have been implicated in serious and sometimes debilitating adverse drug reactions not seen with beta-lactam antibiotics. Based on the superior susceptibility profile of CRO compared with LVX among the *Enterobacterales* organisms, empiric treatment with CRO when these organisms are suspected is crucial for optimizing patient outcomes.

The nonrestrictive approach used by our institutions has been described for various antibiotic classes, including FQ; however, the available published literature on this approach is relatively scarce in comparison to restriction methods [20, 21, 28]. Numerous studies have previously described successful reduction in FQ prescribing through preauthorization in which FQ were restricted to qualified prescribers, certain diseases states, or required approval from antimicrobial stewardship personnel [14–17, 29]. Antimicrobial stewardship programs utilizing this restriction approach have been largely successful in decreasing FQ utilization and have had significant positive impacts on associated outcomes such as *C difficile* infection rates, FQ resistance rates, and burden of ESBL-producing organisms [13, 14, 30, 31]. The restrictive approach to decreasing targeted antimicrobial use can be more rapid compared to nonrestrictive approaches; however, due to the perceived negative connotation with this approach, our institutional antimicrobial stewardship programs chose alternative interventions to change prescribing behavior with less of a perceived negative connotation among prescribers. Although nonrestrictive approaches are thought to be more labor intensive and time consuming particularly before an impact is observed, we saw decreases in LVX prescribing in the months after the formal implementation of this antimicrobial stewardship initiative.

At each of our institutions, LVX susceptibility among *E coli* and *P aeruginosa* were approximately 70%. There have been a number of studies that demonstrated correlation between FQ use and FQ nonsusceptibility among *P aeruginosa* and *E coli*, in which decreases of FQ use within the hospital and community settings resulted in decreases in FQ nonsusceptibility in these organisms [6, 14, 30, 32]. Likewise, in our study, we found a positive correlation between LVX use and LVX nonsusceptibility in *P aeruginosa*, where decreases in LVX correlated with a decrease in nonsusceptible *P aeruginosa* organism isolation. We cannot say that this correlation was solely due to decreases in inpatient LVX use, because it is possible that decreases in FQ use within the community setting could have also contributed.

Table 1. Correlation Analysis of LVX Versus Other Broad-Spectrum Antibiotics[a]

Hospital	Broad-Spectrum Antibiotics					
HH	SAM	FEP	CAZ/CIP*	CRO	MEM	TZP
r	−0.6135	−0.865	0.8453	−0.9863	0.7506	0.5123
r^2	0.376	0.748	0.715	0.973	0.563	0.263
P Value	.484	.0011	.0018	<.0001	.01	.1318
PSJH	SAM	FEP	CIP	CRO	MEM	TZP
r	−0.5247	−0.8753	0.6692	−0.9534	−0.6525	−0.1032
r^2	0.275	0.7662	0.4478	0.9090	0.4257	0.0107
P Value	.0975	.0004	.0243	<.0001	.0295	.7626

Abbreviations: CAZ, ceftazidime; CIP, ciprofloxacin; CRO, ceftriaxone; FEP, cefepime; HH, Hoag Hospital; LVX, levofloxacin; MEM, meropenem; PSJH, Providence St. Joseph Hospital of Orange; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam.

[a]Spearman correlation was used for HH data, and Pearson was used for PSJH. *CIP is formulary only at PSJH, and CAZ is formulary only at HH.

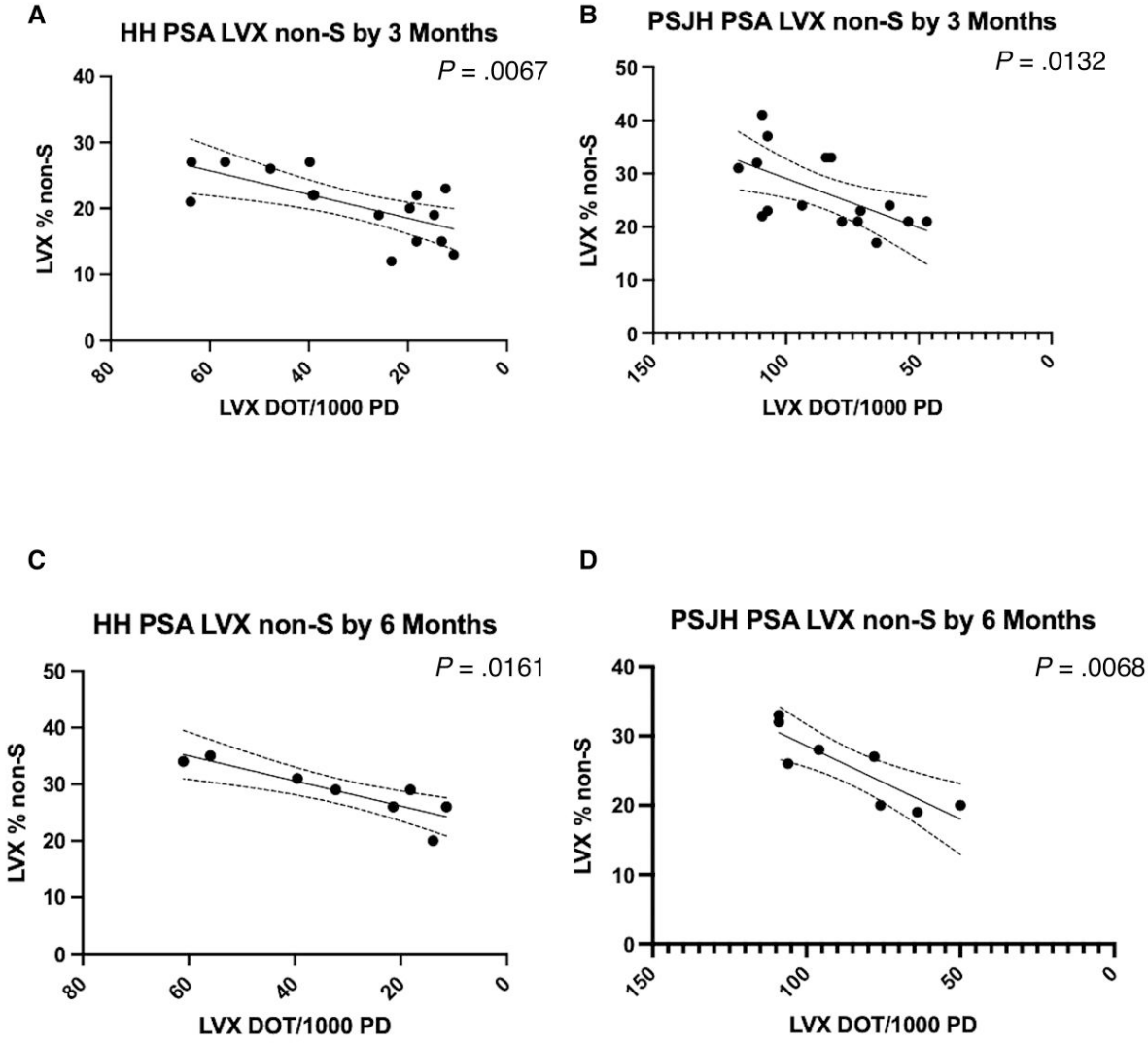

Figure 3. Correlation analysis of *Pseudomonas aeruginosa* (PSA) levofloxacin (LVX) nonsusceptibility (non-S) and LVX days of therapy (DOT)/1000 patient-days (PD) data on a 3-month basis for (*A*) Hoag Hospital (HH) and (*B*) Providence St. Joseph Hospital of Orange (PSJH) and on a 6-months basis for (*C*) HH and (*D*) PSJH.

Recent reports show that community FQ prescribing has decreased after previous FDA warnings on FQ use [33, 34]. Although we tried to minimize this potential impact by including organisms isolated from inpatient locations only and excluded outpatient and emergency department locations, it is still possible that community FQ prescribing may have contributed.

Furthermore, antibiogram susceptibility data were used to determine *P aeruginosa* resistance to LVX, which has potential limitations [35]. The antibiogram evaluated at each hospital may underestimate the true nonsusceptibility rates; because antibiogram susceptibility data are developed from the CLSI M39 standard of including only the first isolate from a patient within a calendar year, susceptibility data from subsequent isolates in each patient may have demonstrated nonsusceptibility to LVX within a designated time period [36]. Despite that the hospital-wide antibiogram included isolates from inpatient cultures only, a portion of isolates collected close to the time of hospital admission may have resistance phenotypes beyond the influence of our inpatient stewardship interventions [35, 37]. However, antibiogram evaluation was the method used for gauging antibiotic susceptibility rates in both of our respective hospitals and was used for selecting empiric antibiotic regimens. Moreover, the effect of our stewardship efforts on *E coli* and *Klebsiella pneumoniae* susceptibility rates to LVX was not assessed due to FQ susceptibility result suppression rules applied at HH for enteric Gram-negative isolates. Fluoroquinolone susceptibility results were not reported in the EMR if the isolate proved to be susceptible, and results were only displayed if the organism was resistant to LVX, preventing accurate analysis of susceptibility rates because suppressed results could not be calculated in the overall rate. Use of ciprofloxacin was not analyzed because its use was not targeted due to its exclusion from HH's drug formulary and low baseline use at PSJH. Of note, ciprofloxacin DOT/1000 patient-days remained consistent throughout the study time period at PSJH (Figure 1*B*). Hospital-onset *C difficile* rates decreased at both hospitals during the postintervention period; however, analyses were not conducted for this study due to multiple confounders potentially contributing to the decreased *C difficile* rates. These potential confounders included changes in testing methodology, routine probiotic use in patients on broad spectrum antibiotics, and increase in infection prevention measures and outreach.

CONCLUSIONS

We demonstrated that a nonrestrictive antimicrobial stewardship approach to decreasing LVX use resulted in increased CRO utilization and a decrease in LVX nonsusceptible *P aeruginosa* organisms. We speculate the decrease in LVX may result in less adverse drug reactions, along with a higher likelihood of achieving active empiric antimicrobial therapy due in part to CRO's superior susceptibility rates among the *Enterobacterales* organisms, coupled with a demonstrated improvement in LVX susceptibility among inpatient *P aeruginosa* isolates. This was accomplished by targeting prescribing behaviors and the provision of provider feedback and education, which may have less of a negative connotation compared to restrictive approaches.

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