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Relationship Between Increased Levofloxacin Use and Decreased Susceptibility of *Streptococcus pneumoniae*: Report From the ARREST Program

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ABSTRACT

Background: Increasing reports describing the emergence of quinolone non-susceptible *Streptococcus pneumoniae* (SP) are of clinical concern. We examined the relationship between outpatient quinolone use and susceptibility of community-acquired SP isolates.

Methods: Using multivariable general linear modeling for censored data with backward stepwise elimination (p>0.1), 6 yrs (1997-2002) of U.S. SENTRY Program and IMS data were analyzed to determine relationships between levofloxacin (LEV) MIC and certain variables among patients with SP infection including: age, duration of hospital stay prior to isolate collection, primary diagnosis group, medical service, hospital bed count, geographical region, and study year. Since 95% of isolates were community-acquired, outpatient quinolone use for the region surrounding each hospital (Rx/100 persons for ciprofloxacin, gatifloxacin, LEV, moxifloxacin, ofloxacin & trovafloxacin) was considered.

Results: LEV MIC_{50}, MIC_{90}, and MIC range were (n=384 from 26 hospitals): 1.0, 1.0, and ≤0.25 to >4.0, respectively. Significant variables associated with changes in the geometric mean of the MIC included: geo region (p<0.0001), medical service (p=0.0002), study year (p=0.0006), bed count (p=0.001), primary diagnosis group (p=0.02), LEV use (p=0.02), duration of hospital stay prior to isolate collection (p=0.07) and 2 interactions, duration of hospital stay prior to isolate collection*bed count (p=0.06) and LEV use*geographical region (p=0.08). MIC increased with LEV use across all geographical regions. Within the Southwest and West, LEV use increases from ≤0.4 to >3 and ≤0.4 to 1.5-3 Rx/100 were associated with MIC increases of 54% and 126%, respectively. The model explained 43% of the MIC variance. Across hospitals, observed vs. fitted within-hospital mean MIC values were highly correlated (weighted Spearman R=0.84).

Conclusions: Increased LEV use, in addition to other variables, was associated with decreased SP susceptibility. Given an environment of increasing SP resistance, these data may be useful in better understanding factors related to quinolone resistance.

INTRODUCTION

- Over the last 6 years, quinolones have emerged as important agents for the treatment of community-acquired respiratory tract infections.
- Increasing reports describing the emergence of quinolone non-susceptible *S. pneumoniae* are of clinical concern.
- The Antimicrobial Resistance Rate Epidemiology Study Team (ARREST Program) was established as a collaborative effort in order to use surveillance data and analytic techniques to better understand factors predictive of antimicrobial resistance.
- This analysis was undertaken to examine the relationships between susceptibility of community-acquired *S. pneumoniae* isolates and risk factors of interest including outpatient quinolone use, and both patient- and institution-specific factors.

METHODS

Data Collection

- Patient- and institution-specific and susceptibility data for *S. pneumoniae* blood isolates (one per patient) collected from North American hospitals participating in the SENTRY Antimicrobial Surveillance Program (1997-2002) were queried for analysis.
- IMS U.S. regional quinolone use data (1997-2002) were matched to the region surrounding each hospital.

Primary Outcome

- The primary outcome variable was the *in vitro* activity of levofloxacin against *S. pneumoniae* as measured by the minimum inhibitory concentration (MIC).
- Observed values of MIC included left- and right-censored values of the form ≤0.5 (or ≤0.25 for 1997) and >4, respectively.
- A $\log_2$ transformation of MIC was used to achieve approximate normal error distributions.
- Using NCCLS interpretive criteria, MIC values were classified as susceptible (≤2), intermediate (4), and resistant (>4).

Independent Variables

- Patient-specific variables included age, sex, specimen type, medical service category, infection risk factors, primary diagnosis, duration of hospital stay prior to pathogen isolation, nosocomial infection, and residence in an ICU.
- Additional independent variables included study year and institution-specific variables (hospital bed count and geographic region).
- Regional ciprofloxacin, gatifloxacin, LEV, moxifloxacin, ofloxacin, and trovafloxacin use data were each considered as independent variables. Data for each agent were normalized by the population for the region surrounding each hospital (by Metropolitan Statistical Area) and expressed as the number of prescriptions/100 persons.

Tree-Based Modeling

- Using S-Plus 6.0.1 for Unix, tree-based modeling was carried out to identify subgroups that manifested impressive differences in MIC using recursive partitioning.
- Potential two-way interactions between independent variables for inclusion in regression modeling were identified.

Multivariable General Linear Modeling (GLM) for Censored Data

- Using SAS® 8.2, GLM for censored data was carried out.
- Continuous independent variables were categorized into subgroups (using breakpoints to define interpretable subgroups of sufficient size) to account for potential nonlinear relationships.
- The model was constructed using backward stepwise elimination (at p>0.1).
- The proportion of error variance explained by the model (denoted as R^2) was used to measure model precision.
- A Spearman correlation measure was used to assess the strength of association between model-predicted and observed MIC means within institutions, across all study years and within study years.

RESULTS

- 384 *S. pneumoniae* blood isolates from 26 hospitals were collected.
  - 8 and 6 hospitals were located in the Midwest and Northeast regions of the U.S, respectively.
  - All other regions had 4 hospitals each.
  - The variability in observed MIC was narrow with an estimated standard deviation of 0.59 on the $\log_2$ scale and a range of observed MIC values from ≤0.25 to >4 (Figure 1).
- There were 71 (18%) left-censored observations (with MIC values of ≤0.25 or ≤0.5) and one right-censored observation. Proportions of isolates by categories of each independent variable are summarized in Table 1.
- Population-adjusted quinolone use trends among all isolates for the study period are shown in Figure 2.
- Mean MIC values were >50% higher for isolates in 2001 vs. 1997.

Figure 1: Distribution of Levofloxacin MIC Against *S. pneumoniae* Isolates (n=384)

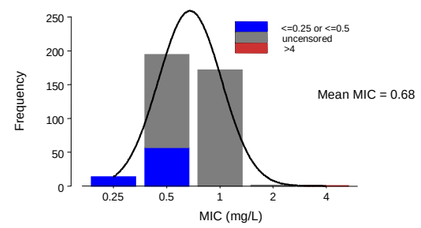
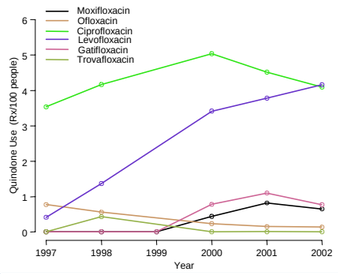


Table 1: Proportion of Isolates by Selected Independent Variables

Variable	Category	n	%
Patient Age			
	≤18	48	12.5
	19-40	99	25.8
	41-60	127	33.1
	61-75	67	17.4
	>75	43	11.2
Medical Service			
	Acute Care	25	6.5
	Medicine	240	62.5
	Pediatrics	27	7.0
	Surgery	29	7.6
	Other	63	16.4
Primary Diagnosis			
	Cardiopulmonary	211	54.9
	Genitourinary	5	1.3
	Gastrointestinal	13	3.4
	Immunocompromised	25	6.5
	Infection	9	2.3
	Neurologic	20	5.2
	Trauma	6	1.6
	Other	95	24.7
Duration of Hospital Stay Prior to Pathogen Isolation	≤1 day	333	86.7
	2-5 days	39	10.2
	6-10 days	6	1.6
	11-20 days	4	1.0
	21-30 days	1	0.3
	>30 days	1	0.3
Hospital Bed Size			
	≤400	116	43.2
	401-900	180	46.9
	901-1350	32	8.3
	>1350	6	1.6
Geographic Region			
	Northeast	135	35.2
	Central	91	23.7
	Southeast	35	9.1
	Southwest	41	10.7
	West	82	21.4

Figure 2: Population-Adjusted Quinolone Use Trends (1997-2002)



GLM Model Results

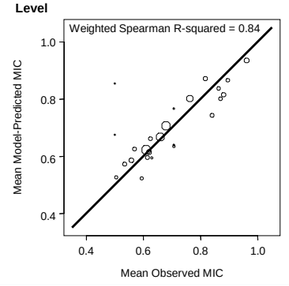
- Parameter estimates for the final model are presented in Table 2.
- Maximal dilution changes between categories of primary diagnosis and medical service represented 57% and 44% higher predicted mean MIC values, respectively.
- The association between LEV use across geographical regions and MIC increase (p=0.076) was highly significant in a GLM model which excluded study year (p< 0.0001). LEV use and time were highly co-linear and the effects of each were difficult to separate.
- The model (fit to data from all the isolates) explained a moderate proportion of the variability in MIC between isolates (R^2 = 44%). However, when fit by institution as shown in Figure 3, model-predicted mean MIC values within hospitals were strongly correlated with observed mean MIC values averaged over all study years (Spearman correlation = 0.84).

Table 2: Parameter Estimates for Final GLM Model

Variable	Category	Estimate	Maximal Dilution Change†	P-Value
Intercept		-0.8994		
Study Year			0.4125	0.0006
	1997	0		
	1998	0.3755		
	2000	0.0469		
	2001	0.1473		
	2002	-0.0370		
Primary Diagnosis			0.6503	0.021
	Cardiopulmonary	-0.0070		
	Gastrointestinal	0.0596		
	Genitourinary	0.0076		
	Immunocompromised	-0.0208		
	Infection	-0.3961		
	Neurologic	-0.2698		
	Trauma	-0.5907		
	Other	0		
Medical Service			0.5223	0.0002
	Acute Care	0.0907		
	Medicine	0		
	Pediatrics	-0.2428		
	Surgery	0.1554		
	Other	0.2795		
Geographic Region * Levofloxacin Use ††				0.080
Prior Duration of Hospital Stay * Bed Count ††				0.056

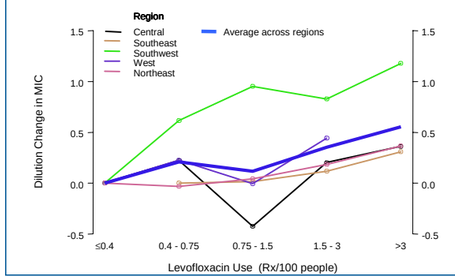
†Represents the maximal change in $\log_2$ MIC value among parameter estimates for a categorical variable.
†† Two-way interactions included duration of hospital stay prior to pathogen isolation*hospital bed count and geographical region*LEV use. P-values for main effects measuring associations within reference categories ranged from <0.0001 to 0.07.

Figure 3: Mean Model-Predicted vs. Mean Observed MIC at the Institution Level



- Figure 4 demonstrates changes in MIC across the levofloxacin use categories for each of the geographic regions.
  - Across all regions, increased LEV use was associated with increased MIC of *S. pneumoniae.*
  - On average, MICs were ~60% higher in locations with high compared with low LEV use.
  - The largest MIC changes were observed in the Southwest (126%) and Western United States (48%).

Figure 4: Change in MIC vs. Levofloxacin Use



CONCLUSIONS

- The use of GLM tailored for censored data allowed for the prediction of MIC and estimation of the likelihood of decreased susceptibility based upon patient, institution, and quinolone consumption factors.
- These data demonstrate a significant increase in the MIC of levofloxacin to *S. pneumoniae* over the study period.
- We were able to detect an association between increasing levofloxacin use and decreased susceptibility of *S. pneumoniae*.
- Identification of risk factors and appropriate intervention may arrest further progression of resistance.