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Relationships Between Susceptibility of *Enterobacter* spp. and Hospital- and Patient-Specific Variables: Report from the Antimicrobial Resistance Rate Epidemiology Study Team (ARREST Program)

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ABSTRACT

Introduction. Identification of patients with infection associated with antibiotic-resistant pathogens remains a serious challenge for the study of drug regimens to treat such infections. The ARREST Program was established as a multidisciplinary, collaborative effort to use surveillance data and analytic techniques to better understand factors associated with antimicrobial resistance. The analyses presented herein were conducted to identify factors predictive of decreased susceptibility of *Enterobacter* spp. in hospitalized patients.

Methods. Five years (1997-2001) of North American SENTRY Program data were analyzed. MICs for cefepime (CPM), ciprofloxacin (CIP) and piperacillin/tazobactam (P/T) versus patient-specific variables (e.g., age, duration of hospital stay prior to isolate collection, infection source, infection risk factors) and hospital-specific variables (e.g., bed count, geographical region, study year) were analyzed using multivariable general linear modeling for censored data with backwards stepwise elimination (at $p > 0.1$).

Results. MIC_{50}, MIC range, and % non-susceptible for isolates (n=356, 96% blood, from 30 hospitals) were: ≤ 0.12, ≤ 0.12 to >16, 0.6 for CPM; ≤ 0.25, ≤ 0.015 to > 2, 4.8 for CIP; and 2, ≤ 0.5 to > 64, 22 for P/T. Highly significant variables identified from the multivariable models included bed count ($p \leq 0.001$) and hospital duration ($p \leq 0.008$). The proportion of explained MIC variability ranged from 20-33%. This range increased to 33-43% when hospital was included as a variable in these models. Higher predicted MICs resulted from combinations of these and other significant variables in the models. Observed MIC_{50} (% non-susceptible) for each agent was compared in selected patient cohorts possessing combinations of variables identified through these models (see table).

Independent Variable Combinations	Observed MIC_{50} (% non-susceptible)		
	CPM	CIP	P/T
Entire Population	≤ 0.12 (0.6)	≤ 0.25 (4.8)	2 (22)
① Duration of Hospital Stay Prior to Pathogen Isolation >10 Days & ② Hospital Bed Count < 400	1 (0)	≤ 0.25 (19)	64 (61)
① & ③ Patient Aged 41-60 Years	1 (0)	≤ 0.25 (17)	32 (60)
① & ④ Primary Diagnosis Group: Immunocompromised or Neurological	1 (12)	≤ 0.25 (18)	32 (53)
At least 2 of ①, ②, ③, or ④	0.25 (2.1)	≤ 0.25 (11)	8 (40)
At least 3 of ①, ②, ③, or ④	2 (0)	≤ 0.25 (32)	64 (68)

Conclusions. Surveillance data such as these may be used to predict factors likely associated with decreased susceptibility. Though multivariable models explained a modest proportion of MIC variability, the higher observed MIC_{50} values among patient cohorts compared to the entire population is clinically relevant. Increased variability in MIC may be further explained by consideration of additional hospital- and patient-specific factors not presently collected through this program. Finally, in patients with higher predicted MICs, CPM, in contrast to CIP or P/T, may be a more appropriate empiric choice for therapy when *Enterobacter* spp. are suspected.

INTRODUCTION

- Antimicrobial resistance is a problem of global significance and affects most human pathogens.
- Long-standing national and global antimicrobial surveillance systems represent vastly underutilized databases from which useful information can be extracted.
- The Antimicrobial Resistance Rate Epidemiology Study Team (ARREST) represents a collaborative effort among microbiologists, clinicians, statisticians, and others in order to use surveillance data and analytic techniques to better understand factors predictive of antimicrobial resistance.
- The objective of these analyses was to identify patient- and institution-specific factors predictive of reduced susceptibility of *Enterobacter* spp. to cefepime, ciprofloxacin, and piperacillin/tazobactam using five years of North American surveillance data.

METHODS

Data Collection

- Patient- and institution-specific and susceptibility data for *Enterobacter* spp. isolates (one per patient) collected from North American hospitals participating in the SENTRY Antimicrobial Surveillance Program (1997-2001) were queried for analysis.

Primary Outcome

- The primary outcome variable was the in vitro activity of cefepime, ciprofloxacin, and piperacillin/tazobactam against *Enterobacter* spp. which was measured by the minimum inhibitory concentration (MIC).
- Observed values of MIC included left- and right-censored values, examples of which are ≤ 0.5 and > 4, respectively.
- A $\log_2$ transformation of MIC was used to achieve approximate normal error distributions.
- MIC values were classified as susceptible, intermediate, and resistant using NCCLS interpretive criteria.

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).

Tree-Based Modeling

- Using S-Plus 6.0.1 for UNIX, tree-based modeling was carried out to identify subgroups with 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 for Censored Data

- Using SAS 8.2, general linear modeling (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.
- Models for each of the three antimicrobial agents were constructed using backward stepwise elimination ($p > 0.1$).
- The proportion of error variance explained by the model (denoted as R^2) was used to measure model precision.
- A Spearman correlation measure (R_S) 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.

Cohort Identification and Comparisons

- For each final model for a given agent, independent variables identified through GLM were evaluated to identify cohorts of patients with average MIC values substantially higher or lower than the overall average MIC.

RESULTS

- 356 *Enterobacter* spp. isolates from 30 hospitals were collected.
  - Six hospitals were located in each of the Mid-West, Northeast, and West regions of the U.S., while 4 were located in each of the Southeast and Southwest regions, as well as in Canada.
  - Summary statistics for counts and proportions of isolates across a subset of the independent variables are provided in Table 1.
  - The variability in observed MIC for each agent can be seen in Figure 1.

GLM Results

- The final multivariable model for each agent is presented in Table 2.
- Significant independent variables common to all three models (either individually or as part of a two-way interaction) included duration of hospital stay prior to pathogen isolation and hospital bed count. Higher MICs were associated with longer hospital durations and with hospital bed counts outside a central range of 401-900 beds.
- The model R^2 values were moderate among models (20% cefepime, 25% ciprofloxacin, and 33% piperacillin/tazobactam).
- The additional variability explained by inclusion of institution ranged from 10% to 24%. The highest of these improvements (24%) resulted in the highest final R^2 of 43% for ciprofloxacin.
- The institution R_S^2, which assessed model fit of overall institutional MIC averages across all study years, was moderate to high among the models: 19% ciprofloxacin, 36% cefepime, and 59% piperacillin/tazobactam. Among these models, lower total censoring of MICs corresponded with higher R_S^2 (Figure 2).

Cohort Comparisons

- Tables 3 summarizes comparisons of MIC_{50}, MIC_{90}, and percent non-susceptible for the entire population vs. cohorts defined by combinations of independent variables.
- The MIC_{90} value for cefepime predictive of decreased in vitro activity was generally 1 $\log_2$ dilution higher across the cohorts vs. the entire population. The proportion of non-susceptible isolates in these same groups ranged from 0 to 12% vs. 0.6% for the entire population.
- For ciprofloxacin, the MIC_{90} was generally more than 16-fold higher with percent non-susceptible 2- to 6-fold higher across most cohorts compared to the whole population (11-32% vs. 4.8%).
- For piperacillin/tazobactam, the MIC_{90} differed by at least two-fold, with percent non-susceptible greater than 60% in 4 of 7 cohorts compared to 22% in the entire population.

Table 1: Summary Statistics for *Enterobacter* Isolates (n=356)

Variable	Category	n	%
Patient Age	≤ 18	65	18.3
	19-40	71	19.9
	41-60	103	28.9
	61-75	79	22.2
	> 75	38	10.7
Study Year	1997	87	24.4
	1998	79	22.2
	1999	112	31.5
	2000	51	14.3
	2001	27	7.6
Primary Diagnosis	Cardiopulm.	54	15.2
	Genitourinary	30	8.4
	GI/Abdom/Liver	39	11.0
	Immunocomp.	59	16.6
	Infection	27	7.6
	Neurologic	4	1.1
	Trauma	44	12.4
	Other	99	27.8
Duration of Hospital Stay Prior to Pathogen Isolation	≤ 1 day	128	36.0
	2-5 days	61	17.1
	6-10 days	52	14.6
	11-20 days	47	13.2
	21-30 days	22	6.2
	> 30 days	46	12.9
Hospital Bed Count	≤ 400	80	22.5
	401-900	223	62.6
	901-1350	50	14.0
	> 1350	3	0.8
Geographic Region	Canada	46	12.9
	Northeast	67	18.8
	Mid-West	87	24.4
	Southeast	58	16.3
	Southwest	75	21.1
	West	23	6.5

Figure 1: MIC Histograms

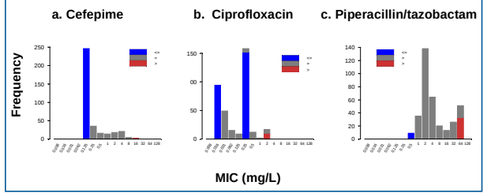

Table 2: Parameter Estimates from the Final Multivariable Models

Variable	Ciprofloxacin Estimate	Ciprofloxacin P-Value	Cefepime Estimate	Cefepime P-Value	Piperacillin/tazobactam Estimate	Piperacillin/tazobactam P-Value
Intercept	-7.0692		-5.5102		0.6464	
Age						0.006
≤ 18					0.7923	
19-40					0	
41-60					1.2488	
61-75					0.6712	
> 75					0.5770	
Medical Service		0.0006				
Acute Care	-1.0030					
Medicine	0					
Pediatrics	-2.9031					
Surgery	-0.1855					
Other	1.2750					
Risk Factor						0.034
Immunocomp.					0.9378	
Lines					-0.2432	
Renal Failure					-1.3347	
Resp. Failure					3.1175	
Other					-0.3202	
None					0	
Primary Diagnosis		0.031				0.49[1]
Cardiopulm.	-1.4503					
Genitourinary	0.3245					
GI/Abdom/Liver	-0.3580					
Immunocomp.	1.1430					
Infection	-0.0489					
Neurologic	2.3227					
Trauma	-1.1501					
Other	0					
Duration of Hospital Stay Prior to Pathogen Isolation		0.0002		< 0.0001		0.0008[1]
≤ 1 day	0		0			
2-5 days	0.5980		0.0312			
6-10 days	-0.4097		-0.6247			
11-20 days	1.6323		1.9519			
21-30 days	2.3511		1.8728			
> 30 days	2.6299		2.9693			
Hospital Bed Count		0.001		0.0009		0.0001
≤ 400	2.0956		2.1727		1.1313	
401-900	0		0		0	
901-1350	0.8617		0.3531		0.9996	
> 1350	1.0536		1.6410		2.2878	
Geographic Region						0.063
Canada					-0.4945	
Northeast					0	
Mid-West					0.4672	
Southeast					-0.0646	
Southwest					-0.1939	
West					1.1318	
Primary Diagnosis * Duration of Hospital Stay Prior to Pathogen Isolation[1]						0.018

[1] For any two-way interactions, P-values are reported, but the large quantity of parameter estimates are omitted.

Figure 2: Mean Model-Predicted MIC vs Mean Observed MIC at the Institution Level

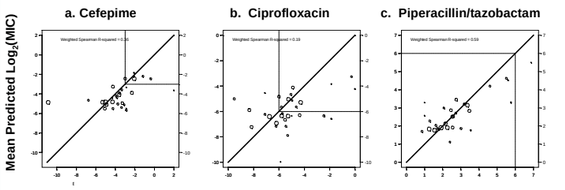

Table 3: Comparison of MIC_{50} and MIC_{90} Values, and Percentage of Non-Susceptible Isolates for the Entire Population vs. Cohorts Defined by Combinations of Independent Variables

Independent Variable Combinations	n	Observed MIC_{50}, MIC_{90}, and % Non-Susceptible (NS)								
		Cefepime			Ciprofloxacin			Piperacillin/tazobactam		
		MIC_{50}	MIC_{90}	%NS	MIC_{50}	MIC_{90}	%NS	MIC_{50}	MIC_{90}	%NS
Entire Population	356	≤ 0.12	2	0.6	≤ 0.25	0.25	4.8	2	64	22
① Hospital Duration >10 Days & ② Hospital Bed Count < 400	31	1	4	0	≤ 0.25	≥ 4	19	64	≥ 128	61
① & ③ Patient Aged 41-60 Years	30	1	4	0	≤ 0.25	≥ 4	17	32	≥ 128	60
① & ④ Primary Diagnosis Group: Immunocompromised[1] or Neurological[2]	17	1	≥ 32	12	≤ 0.25	≥ 4	18	32	≥ 128	53
② & ③	26	0.25	4	0	≤ 0.25	≥ 4	15	16	≥ 128	42
① & ② & ③	11	≤ 0.12	4	0	≤ 0.25	≥ 4	27	64	≥ 128	73
At least 2 of ①, ②, ③, or ④	96	0.25	4	2.1	≤ 0.25	2	11	8	≥ 128	40
At least 3 of ①, ②, ③, or ④	19	2	4	0	≤ 0.25	≥ 4	32	64	≥ 128	68

[1] Immunocompromised Primary Diagnosis Group included patients with leukemia, cancer, organ transplant, or HIV/AIDS.
[2] Neurological Disorder Primary Diagnosis Group included patients with stroke or symptoms of motor dysfunction including consciousness alterations, loss of balance, pain, or weakness.

CONCLUSIONS

- This approach may be useful in identifying institution characteristics and profiles of patients likely to be infected with pathogens with decreased susceptibility.
- Significant independent variables common to all three models included duration of hospital stay prior to pathogen isolation and hospital size.
- Additional data, MIC values beyond the upper and lower bounds of susceptibility testing, an increased proportion of non-susceptible isolates, and additional patient- and institution-specific information such as drug usage, will likely improve the amount of variability that could be explained by each of the multivariable models.
- Patient- or institution-specific variables associated with increased or decreased susceptibility should merit careful consideration when assessing hospital formulary practices or designing clinical trials directed toward the study of drug regimens against resistant pathogens.