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Relationships Between Susceptibility of *Pseudomonas aeruginosa* 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 *Pseudomonas aeruginosa* in hospitalized patients.

Methods. Five years (1997-2001) of North American SENTRY Program data were analyzed. MIC for cefepime (CPM), ciprofloxacin (CIP) and piperacillin/tazobactam (P/T) vs. patient-specific (e.g., age, hospital stay prior to isolate collection (hospital duration), infection source, specimen, primary diagnosis) and hospital-specific (e.g., bed count, geographical region, study year) variables 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 (NS) for isolates (n=487, 93% blood, from 33 hospitals) were: 2, 0.5 to > 16, 14 for CPM; ≤ 0.25, ≤ 0.03 to > 2, 15 for CIP; and 4, ≤ 0.5 to > 64, 26 for P/T. Highly significant variables and interactions between variables identified from multivariable models included hospital duration ($p = 0.008$) and specimen ($p = 0.003$) for CPM; specimen ($p < 0.0001$) for CIP; and hospital duration*primary diagnosis ($p \leq 0.008$) for P/T, with higher MICs resulting from combinations of these and other significant variables. Observed MIC_{50} (% NS) were compared in selected patient cohorts with such combinations (see table). For the patient cohort with at least 2 of the identified characteristics predictive of higher MIC, MIC_{50} remained stable for each agent while % NS increased markedly for P/T.

Independent Variable Combinations	Observed MIC_{50} (% non-susceptible)		
	CPM	CIP	P/T
Entire Population	2 (14)	0.25 (15)	4 (26)
① Duration of Hospital Stay Prior to Pathogen Isolation >10 Days & ②Primary Diagnosis Group: Immunocompromised or Cardiopulmonary	4 (28)	0.25 (20)	8(45)
At least 1 of ① or ② or ③Urinary Tract Infection	2 (15)	0.25 (16)	8 (29)
At least 2 of ① or ② or ③	4 (24)	0.25 (20)	8 (42)

Conclusions. Data such as these may be used to predict variables associated with decreased MICs. Though multivariable models explained a moderate proportion of MIC variability, the higher observed % NS among certain patient cohorts compared to the entire population was clinically relevant. Increased variability in MIC may be further explained by additional factors (e.g., antibiotic use). Collection of these additional data remains an on-going focus of the ARREST Program. Irrespective of this limitation, it appears that in patient cohorts at risk for infection with less susceptible *P. aeruginosa*, CPM and CIP were more active than P/T.

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 *P. aeruginosa* 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 *P. aeruginosa* 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 *P. aeruginosa* 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, 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

- 487 *P. aeruginosa* isolates from 33 hospitals were collected.
  - Between 4 and 7 hospitals were located in each of the Mid-West, Northeast, Southeast, Southwest, and West regions of the U.S., while five were located 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 specimen type, primary diagnosis, and duration of hospital stay prior to pathogen isolation. Higher MICs were associated with urinary isolates, while the nature of other associations was agent-dependent.
- The model R^2 values were moderate among models (18% cefepime, 19% piperacillin/tazobactam, and 22% ciprofloxacin).
- The additional variability explained by inclusion of institution ranged from 7% to 13%. The highest of these improvements (13%) resulted in the highest final R^2 of 32% 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: 26% ciprofloxacin, 47% piperacillin/tazobactam, and 60% cefepime. 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_{50} value predictive of decreased in vitro activity of cefepime and piperacillin/tazobactam was 1 $\log_2$ dilution higher for cohorts having at least 2 of 3 specified model-predictive characteristics vs. the entire population.
- For all three agents, the proportion of non-susceptible isolates in the cohort having at least 2 of 3 specified model-predictive characteristics ranged from 5% to 16% higher than the entire population.

Table 1: Summary Statistics for *P. aeruginosa* Isolates (n=487)

Variable	Category	n	%
Patient Age	≤ 18	57	11.7
	19-40	75	15.4
	41-60	165	33.9
	61-75	113	23.2
	> 75	77	15.8
Study Year	1997	106	21.8
	1998	109	22.4
	1999	162	33.3
	2000	80	16.4
	2001	30	6.2
Primary Diagnosis	Cardiopulm.	83	17.0
	Genitourinary	49	10.1
	GI/Abdom/Liver	34	7.0
	Immunocomp.	101	20.7
	Infection	18	3.7
	Neurologic	14	2.9
	Trauma	33	6.8
	Other	155	31.8
Duration of Hospital Stay Prior to Pathogen Isolation	≤ 1 day	186	38.2
	2-5 days	78	16.0
	6-10 days	69	14.2
	11-20 days	74	15.2
	21-30 days	22	4.5
	> 30 days	58	11.9
Hospital Bed Count	≤ 400	86	17.7
	401-900	314	64.5
	901-1350	85	17.5
	> 1350	2	0.4
Geographic Region	Canada	53	10.9
	Northeast	63	12.9
	Mid-West	144	29.6
	Southeast	91	18.7
	Southwest	98	20.1
	West	38	7.8

Figure 1: MIC Histograms

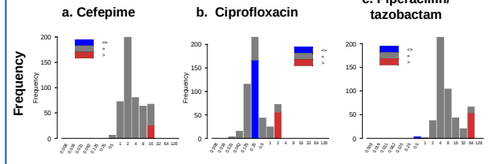

Table 2: Parameter Estimates from the Final Multivariable Models

Variable	Ciprofloxacin		Cefepime		Piperacillin/tazobactam	
	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value
Intercept	-1.7587		1.4377		2.9575	
Study Year		0.055				
1997	0					
1998	0.2206					
1999	-0.7089					
2000	-0.0715					
2001	-0.4100					
Patient sex		0.013				
Male	0					
Female	-0.5497					
Specimen Type		<0.0001		0.003		0.030
Blood	0		0		0	
Urine	1.9649		1.0058		0.8266	
Age						0.074
≤ 18					-0.4804	
19-40					0	
41-60					-0.0957	
61-75					-0.3229	
> 75					-0.4814	
Medical Service				0.072		0.059
Acute Care			-0.6954		-0.6805	
Amb/Output			0.0769		-0.4401	
Medicine			0		0	
Pediatrics			-0.5681		-0.0444	
Surgery			-0.1711		-0.2688	
Other			0.0974		0.4037	
Risk Factor						0.048
Immunocomp.					-1.5506	
Lines					-0.2682	
Renal Failure					-0.0805	
Resp. Failure					0.3868	
Other					0.1097	
None					0	
Primary Diagnosis		0.049		0.064		
Cardiopulm.	-0.1662		0.2079			
Genitourinary	-0.5752		-0.1913			
GI/Abdom/Liver	-0.2907		0.5424			
Immunocomp.	-0.5569		0.0193			
Infection	-0.2049		0.4329			
Neurologic	-0.2480		0.9293			
Trauma	-1.6884		0.0029			
Other	0		0			
Hospital Bed Count				0.027		
≤400			-0.2365			
401-900			0			
901-1350			-0.4865			
>1350			0.5839			
Primary Diagnosis * Duration of Hospital Stay Prior to Pathogen Isolation[1]						0.008
Geographic Region * Hospital Bed Count		0.044				
Duration of Hospital Stay Prior to Pathogen Isolation (days) * Patient Age[1]		0.053				
Clinician-Attributed Source of Infection * Duration of Hospital Stay Prior to Pathogen Isolation (days)[1]				0.053		

[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

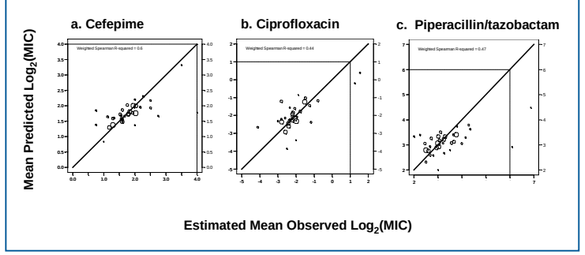

Table 3: Comparison of MIC_{50} and MIC_{90} Values, and Percentage of Non-Susceptible Isolates for the Entire Population vs. Cohorts Defined by Combinations of Independent Variables

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	487	2	16	14	0.25	≥ 4	15	4	≥ 128	26
① Hospital Duration >10 Days & ②Primary Diagnosis Group: Immunocompromised[1] or Cardiopulmonary[2]	64	4	≥ 32	28	0.25	≥ 4	20	8	≥ 128	45
At least 1 of ① or ② or ③ Urinary Tract Infection	289	2	16	15	0.25	≥ 4	16	8	≥ 128	29
At least 2 of ① or ② or ③	83	4	16	24	0.25	≥ 4	20	8	≥ 128	42

[1] Immunocompromised Primary Diagnosis Group included patients with leukemia, cancer, organ transplant, or HIV/AIDS.
[2] Cardiopulmonary Primary Diagnosis Group included patients with congestive heart failure, shortness of breath, cardiovascular, or pulmonary diseases.

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.