P1036

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

SM Bhavnani,[1,2] JP Hammel,[1] PG Ambrose,[1,2] A Forrest,[2] RN Jones[3]

Cognigen Corporation, NY;[1] Buffalo Pharmacometrics Group, SUNY at Buffalo, NY;[2] The Jones Group, North Liberty, IA[3]

For more information, please contact:
Sujata M. Bhavnani, Pharm.D., M.S.
Cognigen Corporation
395 Youngs Road, Buffalo, NY, 14221
sujata.bhavnani@cognigencorp.com
716-633-3463, ext. 273

ABSTRACT

Introduction. *S. pneumoniae* remains a leading cause of morbidity and mortality worldwide. 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 pneumococci in hospitalized patients.

Methods. Five years (1997-2001) of North American SENTRY Program data were analyzed. MICs for amoxicillin-clavulanate (A-C), azithromycin (AZM), cefepime (CPM), ceftazidime (CTZ), ceftriaxone (CTX), clarithromycin (CLAR), erythromycin (ERY), and levofloxacin (LEV) versus patient-specific variables (e.g., age, specimen type) and hospital-specific variables (e.g., bed count, geographical region, study year) were analyzed using multivariable general linear modeling (GLM) for censored data with backwards stepwise elimination (at p > 0.1), yielding 1 model for each of these 8 agents.

Results. Of the 483 blood isolates from 29 hospitals, a range of 41-100% of MIC values were available for individual agents. Significant and frequently-identified factors included geographical region (6/8 models) and age (4/8 models). High predicted MICs resulted from combinations of these and other variables identified. Based on the model for CPM, factors predictive of high MICs were the following: geographical region = Southwest or Southeast, age ≤ 18 years, and specimen type = lower respiratory. The observed % non-susceptible (NS) and MIC_{90} are compared for all agents for cohorts of patients with 2 to 3 versus those patients with 0 to1 of these variables (see table). The %NS was at least three times higher for patients with 2 to 3 versus 0 to 1 variables for 6/8 models.

	Observed % Non-Susceptible MIC_{90}							
	CPM	A-C	AZM	CTZ	CTX	CLAR	ERY	LEV
All Isolates	1.9 (0.5)	3.7 (2)	11 (1)	19 (8)	3.5 (0.5)	9.9 (≤ 0.25)	13 (2)	0.5 (1)
2 or 3 Variables	9.8 (1)	19 (4)	26 (4)	50 (16)	13 (2)	26 (2)	36 (4)	0 (2)
0 or 1 Variables	1.1 (0.5)	2.3 (2)	9.5 (≤ 0.12)	15 (4)	2.3 (0.5)	8.7 (≤ 0.25)	11 (1)	0.6 (1)

Conclusions. This approach may be used to predict factors associated with decreased susceptibility. GLM models explained a moderate proportion of MIC variability, and the higher observed %NS among certain patient cohorts compared to the entire population of isolates is clinically relevant. Further explanation of the variability in MIC will require identification of additional variables (including antibiotic use). Collection of these additional data remains an on-going focus of the ARREST Program. Finally, in patients with higher predicted MICs, CPM, CTX, and LEV, in contrast to other agents studied, may be more appropriate empiric choices when pneumococci is suspected.

INTRODUCTION

- Antimicrobial resistance is a problem of global significance and affects most human pathogens.
- Studies identifying risk factors associated with increased resistance continue to be an important endeavor.
- 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 were to identify patient- and institution-specific factors predictive of reduced susceptibility of *S. pneumoniae* to cefepime (CPM), amoxicillin-clavulanate (A-C), azithromycin (AZM), ceftazidime (CTZ), ceftriaxone (CTX), clarithromycin (CLAR), erythromycin (ERY), and levofloxacin (LEV) using five years of North American surveillance data.

METHODS

Data Collection

- Patient- and institution-specific and susceptibility data for *S. pneumoniae* 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 A-C, AZM, CPM, CTZ, CTX, CLAR, ERY, and LEV against *S. pneumoniae* 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, and formulary demographics).

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 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.
- Models for each of the 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.
- Only those cohorts with an adequate sample size (10 or more observations) were compared.
- Within each cohort, the MIC_{90} and percent non-susceptible were computed and compared between agents.

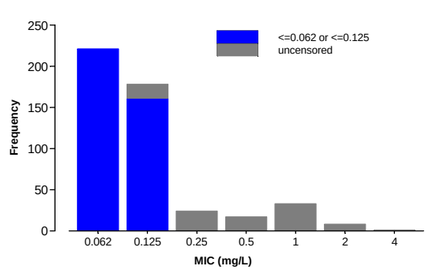
RESULTS

- 483 *S. pneumoniae* isolates from 29 hospitals were collected.
  - Summary statistics for counts and proportions of isolates across a subset of the independent variables are provided in Table 1.
  - Seven hospitals were located in the Mid-Western U.S., while 5 were located in each of the Northeast and West regions of the U.S., and 4 were located in each of the Southeast and Southwest regions. Four were located in Canada.
  - The variability in observed MIC for each agent was visually assessed using histograms. Such a histogram is shown for cefepime (Figure 1).
- Left-censoring of MIC values exceeded 79% for 6/8 agents. For ceftazidime and levofloxacin, the proportion of left-censoring was only 43% and 17%, respectively.

Table 1: Summary Statistics for *S. pneumoniae* Isolates (N = 483)

Variable	Category	N	%
Patient Age	≤ 18	89	18.4
	19-40	112	23.2
	41-60	133	27.5
	61-75	87	18.0
	> 75	62	12.8
Study Year	1997	148	30.6
	1998	135	28.0
	1999	100	20.7
	2000	77	15.9
	2001	23	4.8
Patient Sex	Male	266	55.1
	Female	217	44.9
ICU	Yes	80	16.6
	No	403	83.4
Clinician-Attributed Source of Infection	Abdominal	3	0.6
	Blood	1	0.2
	Lines	2	0.4
	Lower Resp.	158	32.7
	Tissue/bone	2	0.4
	Upper Resp.	2	0.4
	Other	315	65.2
Medical Service	Acute Care	49	10.1
	Medicine	245	50.7
	Pediatrics	48	9.9
	Surgery	35	7.2
	Other	106	21.9
Primary Diagnosis	Cardiopulm.	230	47.6
	Genitourinary	10	2.1
	GI/Abdom/Liver	15	3.1
	Immunocomp.	39	8.1
	Infection	30	6.2
	Neurologic	20	4.1
	Trauma	7	1.4
	Other	132	27.3
Risk Factor for Infection	Immunocomp.	2	0.4
	Lines	29	6.0
	Renal Failure	2	0.4
	Resp. Failure	5	1.0
	Other	15	3.1
	None	430	89.0
Duration of Hospital Stay Prior to Pathogen Isolation	≤ 1 day	403	83.4
	2-5 days	59	12.2
	6-10 days	9	1.9
	11-20 days	7	1.4
	21-30 days	2	0.4
	> 30 days	3	0.6
Nosocomial Infection	Yes	33	6.8
	No	450	93.2
Hospital Bed Count	≤ 400	145	30.0
	401-900	263	54.5
	901-1350	69	14.3
	> 1350	6	1.2
Geographic Region	Canada	83	17.2
	Northeast	123	25.5
	Mid-West	116	24.0
	Southeast	55	11.4
	Southwest	59	12.2
	West	47	9.7

Figure 1: MIC Histogram for Cefepime



Overview of GLM Model Results

- The statistical significance of patient- and institution-specific factors in the final multivariable model for each agent is presented in Table 2.
- Significant independent variables most frequent among the models (either alone or as part of a two-way interaction) included geographic region (6/8 models) and patient age (4/8 models).
- The model R^2 values were low to moderate among models, ranging from 0% for ceftriaxone to 42% for levofloxacin.
- The additional variability explained by inclusion of institution ranged from 7.7% to 24%. The highest resulting final R^2 of 47% was obtained for levofloxacin.
- The institution $R_S{}^2$, which assessed model fit of overall institutional MIC averages across all study years, ranged from 0% for ceftriaxone to 84% for levofloxacin. The agents with the least amount of MIC censoring, levofloxacin (18%) and ceftazidime (45%), also exhibited the highest $R_S{}^2$ values of 84% and 46%, respectively.

Table 2: P-Values for Independent Variables in Final Multivariable Models

Independent Variables	CPM	A-C	AZM	CTZ	CTX	CLAR	ERY	LEV
① Patient Age	0.012	0.036		0.051				0.26[c]
② Patient Sex			0.022					
③ Site of Infection[a]								
④ Clinician-attributed Source of Infection[b]	0.007	0.005						
⑤ Medical Service	0.048							0.003
⑥ Primary Diagnosis				0.002				0.49[c]
⑦ Risk Factor for Infection								
⑧ Duration of Hospital Stay Prior to Pathogen Isolation				0.078				0.004[c]
⑨ Hospital Bed Count								0.095[c]
⑩ Geographic Region	0.005	0.006		0.033		0.098	0.044	< 0.0001
⑪ ICU								
⑫ Study Year		0.088		0.070				
Independent Variable Interactions								
① & ⑥								0.007
⑧ & ⑨								0.059

[a] Site of infection was either blood or urine
[b] Attributed source of infection represents clinician-identified source of blood or urine infection
[c] Independent variable involved in an interaction with another independent variable and the statistical significance determined by interaction P-value

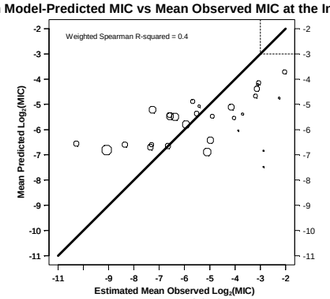
Cefepime GLM Results

- The final multivariable model for cefepime is presented in greater detail in Table 3.
- The values of independent variables most predictive of high MICs were the following: geographical region = Southwest or Southeast, age ≤ 18 years, and specimen type = lower respiratory.
- The model R^2 value was 14%. The additional variability explained by the inclusion of institution was 7.7%. The institution $R_S{}^2$ was 40% (Figure 2).

Table 3: Parameter Estimates from the Final Multivariable Model for Cefepime

Variable	Estimate	Standard Error	P-Value
Intercept	-7.4016	0.7989	
Age			0.012
≤ 18	1.9477	0.7591	
19-40	0		
41-60	-0.6360	0.6147	
61-75	0.5790	0.6628	
> 75	0.9826	0.7140	
Medical Service			0.048
Acute Care	1.0314	0.7320	
Medicine	0		
Pediatrics	-1.1462	0.9096	
Surgery	0.6471	0.8162	
Other	1.1799	0.5514	
Geographic Region			0.005
Canada	-0.6665	0.7381	
Northeast	0		
Mid-West	0.0939	0.6348	
Southeast	1.9745	0.7385	
Southwest	1.6082	0.7467	
West	0.5613	0.7828	
Clinically-Attributed Source of Infection			0.007
Lower Respiratory	1.4441	0.5313	
Other Sources	0		

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



Cohort Comparisons

- Table 4 summarizes comparisons of MIC_{90} and percent non-susceptible for the entire population versus cohorts defined by combinations of significant independent variables identified from the final multivariable model for cefepime.
- Given the large degree of left-censoring for most of the agents, specific MIC_{50} values were not available.
- The proportion of non-susceptible isolates was at least 3 times higher for patients with 2 or 3 of the predictive factors in comparison to patients with none or only one of the factors for 6 of the 8 agents.
- In comparison to patients with none or only one of the predictive factors from the cefepime model, patients with 2 or 3 of the factors had MIC_{90} values at least 1 $\log_2$ dilution higher for all 8 agents. For 5 of the 8 agents, the MIC_{90} was at least 2 $\log_2$ dilutions higher.

Table 4: Comparison of Percentage of Non-Susceptible Isolates, and MIC_{90} Values for the Entire Population vs Cohorts Defined by Combinations of Independent Variables

Independent Variable Combinations	Observed % Non-Susceptible MIC_{90}							
	CPM	A-C	AZM	CTZ	CTX	CLAR	ERY	LEV
Entire Population	1.9 (0.5)	3.7 (2)	11 (1)	19 (8)	3.5 (0.5)	9.9 (≤ 0.25)	13 (2)	0.5 (1)
① Geographical Region: Southwest or Southeast	2.7 (1)	7 (2)	19 (2)	27 (16)	63 (2)	20 (2)	22 (2)	0 (2)
② Age ≤ 18	5.6 (1)	9 (2)	13 (2)	36 (8)	10 (0.5)	14 (2)	18 (2)	0 (1)
③ Specimen Type: Lower Respiratory	2.5 (1)	5.7 (≤ 2)	8.7 (≤ .12)	22 (8)	3.2 (1)	7.3 (≤ .25)	13 (2)	0.7 (2)
2 or 3 of ①, ②, or ③	9.8 (1)	19 (4)	26 (4)	50 (16)	13 (2)	26 (2)	36 (4)	0 (2)
0 or 1 of ①, ②, or ③	1.1 (0.5)	2.3 (2)	9.5 (≤ 0.12)	15 (4)	2.3 (0.5)	8.7 (≤ 0.25)	11 (1)	0.6 (1)

CONCLUSIONS

- This approach may be useful in identifying institution characteristics and profiles of patients likely to be infected with pathogens with decreased susceptibility.
- 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 GLM 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.