The identification of patients infected with antibiotic-resistant strains of bacteria for inclusion in clinical trials remains a serious challenge for the future development of agents for use against such infections. To identify patient- and institution-specific factors predictive of reduced susceptibility of Enterobacter species, Pseudomonas aeruginosa, and Klebsiella pneumoniae to cefepime, ciprofloxacin, and piperacillin-tazobactam, 5 years (1997–2001) of North American surveillance data were analyzed. The relationship between minimum inhibitory concentration (MIC) values for each organism-agent pair and patient- and institution-specific variables was analyzed using multivariable general linear modeling. The variables most commonly associated with decreases in susceptibility were duration of hospital stay before pathogen isolation, hospital size, primary diagnosis, and medical service. Combinations of these variables were associated with increases in observed MIC₉₀ values of as much as 16–32-fold. Our findings demonstrate a relationship between MIC and certain patient- and institution-specific variables. Such data should be considered in the design of clinical trials directed at the study of resistant pathogens.

Resistance to antimicrobial agents is a problem of global significance and affects most human pathogens. Recently, the pharmaceutical industry has shifted resources away from the development of antibiotics, especially those for the treatment of patients infected with antibiotic-resistant bacteria [1]. In February 2002, the US Food and Drug Administration convened an advisory committee meeting (composed of representatives from the US Food and Drug Administration Anti-Infective Advisory Board, Pharmaceuticals Research and Manufacturers of America, and the Infectious Diseases Society of America) to discuss these issues and strategies for maintaining high standards for the clinical study of new antimicrobial agents [2]. A major element of these discussions focused on the challenges of developing antibiotics for the treatment of infections caused by resistant strains of bacteria. It has become clear to all parties that more-complete information is needed to identify patients who have serious infections associated with antibiotic-resistant organisms [3].

Long-standing national and global antimicrobial surveillance systems, which traditionally have been used for studies of MIC₅₀ and MIC₉₀ values, represent vastly underused databases from which useful information can be extracted [4]. General linear modeling (GLM) and tree-based analysis methods can be used to delineate important interrelationships between measures of microbiologic activity and patient- and/or institution-specific variables. Sets of characteristics that serve to identify institutional profiles and patient populations in which organisms with elevated MIC values are found may then...
be used as a guide to define patient cohorts of interest for further study.

Using data collected from the SENTRY Antimicrobial Surveillance Program, the Antimicrobial Resistance Rate Epidemiology Study Team (ARREST) was established as a collaborative effort to use surveillance data and analytic techniques to better understand factors predictive of antimicrobial resistance. In the present article, we provide an overview of the ARREST program, the methods used, and the results derived from analyses conducted. We also discuss the utility of these analytical techniques, when they are combined with comprehensive microbiology-based surveillance data, for specifically identifying both profiles of institutions at which infections with strains with decreased susceptibility occur and patients infected with such strains. Moreover, we draw attention to how this information could be used to optimize clinical trial design.

METHODS

Data and descriptive statistics. All relevant susceptibility and patient- and institution-specific data for Enterobacter species, Pseudomonas aeruginosa, and Klebsiella pneumoniae isolates collected from North American hospitals participating in the SENTRY Antimicrobial Surveillance Program (1997–2001) were gathered for analysis. All isolates of each species were collected consecutively from unique patients during pathogen prevalence studies of bloodstream, pneumonia, skin and soft-tissue, and urinary tract infections. All strains were processed as they appeared in a defined time period as consecutive occurrences, without preselection bias.

Organisms were processed locally and then referred to a reference laboratory for confirmation of organism identification and testing by reference quantitative susceptibility methods, as described elsewhere [5, 6]. Twenty-seven agents were tested, but only 2 broad-spectrum β-lactams and ciprofloxacin were included in the analyses described in the present article.

Nine organism–antimicrobial agent pairs resulting from combinations of the 3 organisms described above and 3 agents (cefepime, ciprofloxacin, and piperacillin-tazobactam) were the focus of this study. The primary outcome variable (or dependent variable) of interest for each organism-agent pair was susceptibility, as measured by the quantitative MIC of each organism to each agent. To obtain an integer value and an approximately normal distribution for MIC values, a base 2 logarithmic (log2) transformation was applied to this measure. The MIC50 (median) and MIC90 were used to further describe each independent variable was evaluated for each of the 9 organism-agent pairs. Independent variables examined included age of patient, sex of patient, duration of hospital stay before isolation of a pathogen, residence in the intensive care unit, primary diagnosis group, primary risk factor for infection, source of infection, and medical service type. Institution-specific characteristics included bed size, type of institution, geographic region, and study year.

Using S-Plus, version 6.0.1 for Unix (Insightful), tree-based modeling was performed as a means of describing potentially complex relationships between the independent variables and MIC values. The resulting tree models were used to identify possible interactions between independent variables to be considered for inclusion in the multivariable regression models and to identify important breakpoints within continuous independent variables.

Using the LIFEREG procedure of SAS, version 8.2 (SAS Institute), multivariable GLM tailored to accommodate data for a dependent variable with right- and left-censoring was performed. For the purposes of these analyses, right- and left-censored data were MIC values greater than the upper or less than the lower margin of the MIC range tested. For example, an MIC observation of ≤0.25 mg/mL is left-censored at a censoring value of 0.25 mg/mL, and an MIC observation of >4 mg/mL is right-censored at a censoring value of 4 mg/mL. General linear models were constructed using backward stepwise elimination (at P > .1) of the above-described independent variables for each of the 9 organism-agent pairs. Backwards elimination with initial models that included all independent variables and selected interactions was chosen over other stepwise procedures to best satisfy the normality assumption of residual errors. Continuous independent variables were entered into the analysis as such or were categorized into subgroups (using breakpoints to define interpretable subgroups of sufficient size) to account for potential nonlinear relationships. The principal measure of association between MIC value and each independent variable of interest was a corresponding parameter estimate (with 95% CI), which describes the estimated difference in the MIC value associated with varying levels of a categorical independent variable or with a 1-unit change in a continuous independent variable.

Assessment of model precision. The proportion of variability explained by the independent variables in a regression model, the estimate of which is expressed as “R2,” could not be estimated using a sum-of-squares method in the presence of censored data. Instead, the maximum likelihood estimate of the model error variance was used to estimate this proportion. Because this measure estimates the same underlying proportion as does the sum-of-squares method, we referred to the maximum likelihood estimate as “R2.” The models were refit, adding institution as an independent variable. If there was marked
improvement in $R^2$, we would consider this a suggestion that there were other important institution-specific independent variables not being considered in our current analysis.

Using the final model derived for each of the 9 organism-agent pairs, the average predicted log MIC value within institutions, across all study years and for specific study years, was computed. Spearman’s correlation measures, the square value of which was denoted as “$R^2$,” were used to assess the strength of association between predicted and observed institutional means of the MIC.

**Cohort identification and comparisons.** For each final model for a given organism-agent pair, independent variables identified through GLM were evaluated to identify cohorts of patients with average MIC values that were substantially higher or lower than the overall average MIC. Only those cohorts with an adequate sample size (≥10 observations) were compared. Within each cohort, the observed MIC$_{90}$ and MIC$_{95}$ and the percentage of nonsusceptible isolates were computed (on the basis of NCCLS interpretive criteria) and compared among agents [5, 6].

**RESULTS**

During 1997–2001, groups of 30–33 hospitals participating in the SENTRY Antimicrobial Surveillance Program contributed 487 *P. aeruginosa*, 626 *K. pneumoniae*, and 356 *Enterobacter* species isolates with complete institution- and patient-specific information. Of these, ∼95% were blood isolates. Approximately two-thirds of the isolates came from hospitals ranging in size from 401 to 900 beds, and the remaining isolates were similarly distributed among hospitals with >900 or ≤400 beds. Approximately 11% of isolates were obtained from Canadian hospitals, and the remaining 89% of isolates were from regions within the United States. These distributions were consistent with selection criteria for SENTRY hospitals, which included geographic representation and previous study experience demonstrating compliance on the part of the site. With respect to the latter criterion, distribution of hospitals tended to be skewed towards institutions with more beds, because these institutions tested larger volumes of isolates. Institutions generally were tertiary care or teaching hospitals.

The proportion of MIC values that were censored (i.e., values greater than the upper or less than the lower margin of the MIC range tested) was >51% for both cefepime and ciprofloxacin against *Enterobacter* species and *K. pneumoniae*; the proportion of censored data was markedly less for the other 5 organism-agent pairs (range, 4%–46%). Overall, the lowest proportions of censored MIC values were observed for piperacillin-tazobactam against *Enterobacter* species, *K. pneumoniae*, and *P. aeruginosa* (12%, 4%, and 12%, respectively). The proportion of right-censored MIC values was generally low and was >10% only for 2 individual organism-agent pairs. The proportion of MIC values that were left-censored, however, was impressive for certain pairs, and as many as 89% of values were left-censored for cefepime against *K. pneumoniae*.

The final multivariable model for each organism-agent pair resulting from the inclusion of independent variables and interactions between these variables is summarized in table 1. There were certain consistent patterns of significance either across or within organisms. Among the models for the 9 pairs, the most common independent variables were duration of hospital stay before isolation of a pathogen (9 pairs), hospital size (6), primary diagnosis (6), and medical service (4). With respect to duration of hospital stay before isolation of a pathogen (described by categorical levels for ranges of days), differences in MIC$_{90}$ values were >4-fold between at least 2 categorical levels for 8 of the 9 models. Differences of ≥4-fold were observed between subgroups for both primary diagnosis and hospital size categories in 4 and 3 of the models, respectively. A 2-log$_2$ dilution difference in MIC$_{90}$ between subgroups was attributed to age, source of infection, medical service type, geographic region, and category of risk factor for infection for at least 1 of the 9 models.

The final models for *P. aeruginosa* tended to contain a larger set of independent variables and interactions than did those for the other microorganisms. Associations between MIC values and hospital size showed greater statistical significance for *Enterobacter* species than for the other organisms. Few interactions that had been considered on the basis of the results of tree-based modeling remained in the final multivariable models. Only 1 of the 9 models summarized in table 1, the model for ciprofloxacin against *P. aeruginosa*, contained as many as 2 interactions.

The model $R^2$ values (expressed as percentage of variability explained) were low to moderate among all models, ranging from 14% to 33% (median, 19%). The additional variability explained by inclusion of institution ranged from 5% to 24%. The greatest of these improvements (24%) resulted in the highest final $R^2$, of 43%. The institution $R^2$ values, which assessed model fit of overall institutional MIC averages across all study years, ranged from 6% to 74% (median, 44%), although the 3 smallest $R^2$ values occurred for models for which ≥70% of MIC values were censored. The remaining institution $R^2$ values were ≥44%.

Cohorts of patients predicted to have isolates with higher MIC values were identified using independent variables that were both significantly associated with MIC and for which at least a 1-tube (i.e., 1-log$_2$) dilution difference in median MIC between categorical levels (consisting of isolates from at least 10 patients) was seen. Duration of hospital stay before isolation of a pathogen was chosen to define cohorts across all organisms.
Table 1. *P* values for independent variables remaining in multivariable general linear models of susceptibility of *Enterobacter* species, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* isolates to various antibiotics.

<table>
<thead>
<tr>
<th>Independent variable (variable no.) or interaction (variable nos.)</th>
<th>Enterobacter species</th>
<th>K. pneumoniae</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>Ciprofloxacin</td>
<td>Pip-taz</td>
<td>Cefepime</td>
</tr>
<tr>
<td>Independent variable*</td>
<td>Association between variable and MIC for organism-agent pair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient age (1)</td>
<td>.006</td>
<td>.039</td>
<td>.074</td>
</tr>
<tr>
<td>Patient sex (2)</td>
<td>.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of infection* (3)</td>
<td>.003</td>
<td>&lt;.0001</td>
<td>.030</td>
</tr>
<tr>
<td>Clinician-identified source of infection* (4)</td>
<td>.32*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical service (5)</td>
<td>.0096</td>
<td>.011</td>
<td>.072</td>
</tr>
<tr>
<td>Primary diagnosis (6)</td>
<td>.031</td>
<td>.49*</td>
<td>.005</td>
</tr>
<tr>
<td>Risk factor for infection (7)</td>
<td>.0064</td>
<td>.049</td>
<td>.016</td>
</tr>
<tr>
<td>Duration of hospital stay before isolation of pathogen (8)</td>
<td>&lt;.0001</td>
<td>.0002</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hospital size (9)</td>
<td>.0009</td>
<td>.001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Geographic region (10)</td>
<td>.063</td>
<td>.030</td>
<td>.54*</td>
</tr>
<tr>
<td>Study year (11)</td>
<td>&lt;.0001</td>
<td>.008</td>
<td>.034</td>
</tr>
<tr>
<td>Interactions between independent variables*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and 2</td>
<td>.053</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and 6</td>
<td>.018</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 and 8</td>
<td>.060</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 and 8</td>
<td>.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 and 10</td>
<td>.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 and 11</td>
<td>.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Independent variables remaining in the multivariable general linear models were those for which *P*<.1. Pip-taz, piperacillin-tazobactam.

* P values are not shown for associations that were not significant.

* Site of infection was either blood or urine.

* Clinician-identified source was blood or urine infection.

* For this variable, statistical significance was achieved in its interaction with another independent variable.

* P values are not shown for associations that were not significant or were not evaluated.

Primary diagnosis was important for cohorts describing 2 of the 3 organisms (*Enterobacter* species and *P. aeruginosa*), with immunocompromised patients common to both sets of cohorts.

Tables 2–4 summarize comparisons of MIC<sub>50</sub> values, MIC<sub>90</sub> values, and percentages of nonsusceptible isolates for the entire population with those for cohorts defined by combinations of independent variables. As shown in table 2, the MIC<sub>90</sub> for cefepime against *Enterobacter* species was generally 1-log, dilution greater across the cohorts, relative to that of the entire population. The proportion of nonsusceptible isolates in these same groups ranged from 0.0% to 12%, compared with 0.6% for the entire population. In contrast, for ciprofloxacin against *Enterobacter* species, the MIC<sub>90</sub> was generally >16-fold higher, and the percentage of nonsusceptible isolates was 2–6-fold higher across cohorts, compared with the whole population (11%–32% vs. 4.8%). Similarly, for piperacillin-tazobactam against *Enterobacter* species, the MIC<sub>90</sub> differed by >2-fold, and the percentage of nonsusceptible isolates was >60% in 4 of 7 cohorts, compared with 22% in the entire population.

**DISCUSSION**

An evaluation of clinical response to therapy in patients infected with bacterial strains with elevated MIC values is highly desirable for predicting clinical efficacy. Historically, however, it has proven difficult in ethical clinical trials to collect a statistically meaningful number of patient cases with true infection caused by such strains. This difficulty arises, in part, from existing practices in clinical trial design, in which patients from whom a strain considered to be nonsusceptible was isolated tend to be excluded [7]. Even when investigators have sought out patients with infection involving strains with elevated MIC values, it has proven difficult to find such strains, despite considerable commitment from investigators and expenditure of resources. Indeed, most data in the literature describing studies of patients infected with resistant organisms are from small case series, are poorly described, and/or are from retrospective cohort examinations [8–10].

Thus, one of the challenges in improving clinical trial design will be to expand the current collective base of knowledge about...
the epidemiology of patients with resistant infections. The AR-
REST program, which was assembled to investigate factors that
predict antimicrobial resistance, represents a collaboration be-
tween microbiologists, clinicians, statisticians, and other inter-
ested parties. This sharing of expertise across a number of
disciplines has led to the application of modeling techniques
to censored data collected through large surveillance programs.

The ultimate goal of the analyses undertaken was to identify
important relationships that could be used to better characterize
cohorts of patients infected with bacterial strains with decreased
susceptibility. A common and impressive finding across all 9
organism-agent pair models was the relationship between in-
creased duration of hospital stay before isolation of a pathogen
and higher MIC. Although this factor alone intuitively would
be expected to be associated with increased MIC, the ability to
predict the magnitude of impact of this variable on MIC, either
alone or as part of an interaction with another variable, rep-
resents a valuable step forward from classic surveillance ana-
alytical practices. As might also be expected, primary diagnosis
and patient age of 41–60 years were also important variables associated
with elevated MIC values across various organism-agent pairs.

**Table 2. Comparison of MIC<sub>50</sub> values, MIC<sub>90</sub> values, and percentages of nonsusceptible (NS) isolates for the entire population with those for cohorts defined by combinations of independent variables predictive of decreased in vitro activity of cefepime, ciprofloxacin, and piperacillin-tazobactam against *Enterobacter* species.**

<table>
<thead>
<tr>
<th>Independent variables (variable nos.)</th>
<th>No. of isolates</th>
<th>Cefepime</th>
<th>Ciprofloxacin</th>
<th>Piperacillin-tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>356</td>
<td>≤0.12</td>
<td>≤0.25</td>
<td>2</td>
</tr>
<tr>
<td>Hospital stay of &gt;10 days before</td>
<td>31</td>
<td>0.25</td>
<td>≥4</td>
<td>&gt;128</td>
</tr>
<tr>
<td>isolation of pathogen (1) and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital size of &lt;400 beds (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and patient age of 41–60 years</td>
<td>30</td>
<td>≤0.25</td>
<td>≥4</td>
<td>17.0</td>
</tr>
<tr>
<td>1 and immunocompromised&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or neurological&lt;sup&gt;b&lt;/sup&gt; diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group (4)</td>
<td>17</td>
<td>0.25</td>
<td>≥4</td>
<td>16.0</td>
</tr>
<tr>
<td>2 and 3</td>
<td>26</td>
<td>0.25</td>
<td>≥4</td>
<td>17.0</td>
</tr>
<tr>
<td>1, 2, and 3</td>
<td>11</td>
<td>≤0.12</td>
<td>≥4</td>
<td>17.0</td>
</tr>
<tr>
<td>At least 1 of the following: 1, 2, 3</td>
<td>96</td>
<td>0.25</td>
<td>≤0.25</td>
<td>17.0</td>
</tr>
<tr>
<td>and 4</td>
<td></td>
<td></td>
<td>≥4</td>
<td>17.0</td>
</tr>
<tr>
<td>At least 2 of the following: 1, 2, 3</td>
<td>19</td>
<td>2</td>
<td>≤0.25</td>
<td>17.0</td>
</tr>
<tr>
<td>and 4</td>
<td></td>
<td>0.25</td>
<td>≥4</td>
<td>17.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients with leukemia, cancer, organ transplant, or HIV infection/AIDS.

<sup>b</sup> Patients with stroke or symptoms of motor dysfunction, including consciousness alterations, loss of balance, pain, and weakness.

Despite the extensive amount of censored data seen, model
performance was similar for each agent within and across the
pathogens monitored. As expected, the agents with the most
intense microbiologic activity were also the agents with the
greatest proportion of left-censored MIC values. Correspond-
ingly, the percentage of nonsusceptible isolates within cohorts
and for all patients was lowest for these organism-agent pairs.

The low-to-moderate $R^2$ values for multivariable models indi-
cated that only modest proportions of the variability in MIC
values for individual isolates could be explained by the final
models summarized in table 1. Models for *Enterobacter* species
explained a greater proportion of variability in MIC in isolates
across patients than did models for *K. pneumonia* or *P. aeru-
ginosa*. Models predicting MICs for *K. pneumonia* were the
least impressive, as evidenced by the lower $R^2$ values and the
relatively small number of independent variables identified.
Moreover, only a small proportion of *K. pneumonia* isolates
had high MIC values. With regard to models for cefepime and
piperacillin-tazobactam against *K. pneumoniae*, the small size
of the group of isolates with reduced susceptibility was in large
part the result of the low prevalence of extended-spectrum $\beta$-
lactamase–producing isolates within the population studied.
Assuming the same degree of model fit in extended-spectrum
$\beta$-lactamase–enriched populations, it is likely that the magni-
tude of change in percentage of nonsusceptible isolates ob-
erved among cohorts of patients would have been more im-
pressive for these 2 models.
Table 3. Comparison of MIC\textsubscript{50} values, MIC\textsubscript{90} values, and percentages of nonsusceptible (NS) isolates for the entire population with those for cohorts defined by combinations of independent variables predictive of decreased in vitro activity of cefepime, ciprofloxacin, and piperacillin-tazobactam against Klebsiella pneumoniae.

<table>
<thead>
<tr>
<th>Independent variables (variable nos.)</th>
<th>No. of isolates</th>
<th>Susceptibility of K. pneumoniae to indicated antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefepime</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>MIC\textsubscript{50}, mg/L</td>
<td>MIC\textsubscript{90}, mg/L</td>
</tr>
<tr>
<td>All patients</td>
<td>626</td>
<td>&lt;0.12</td>
</tr>
<tr>
<td>Hospital stay of &gt;5 days before isolation of pathogen (1) and patient on a medical or surgical service (2)</td>
<td>109</td>
<td>&lt;0.12</td>
</tr>
<tr>
<td>Either 1 or 2 (3)</td>
<td>490</td>
<td>&lt;0.12</td>
</tr>
<tr>
<td>Neither 1 nor 2 (4)</td>
<td>136</td>
<td>&lt;0.12</td>
</tr>
<tr>
<td>3 or 4</td>
<td>252</td>
<td>&lt;0.12</td>
</tr>
</tbody>
</table>

Generally, however, superior model performance was apparent across models for all organism-agent pairs when the strength of association between predicted and observed institutional mean MIC values were assessed. Thus, given the independent variables evaluated, a relatively large proportion of variability in MIC across institutions could be explained for isolates averaged within institutions, as opposed to isolates from individual patients. This is perhaps not unexpected, because more-detailed information about individual patients likely would be needed to explain the remaining variability in MIC values. The modest improvement in model precision achieved by the inclusion of institution as an independent variable indicated that a great deal of the unexplained variability in MIC values rests at the level of the individual.

Thus, the combination of certain factors (censoring patterns observed for certain organism-agent pairs, lower proportion of nonsusceptible isolates, and the lack of additional patient- and institution-specific information) likely limited the amount of variability that could be explained by the models presented here. Despite these limitations, information gained from these analyses may be useful as points to consider in the design of clinical trials studying organisms with decreased in vitro susceptibility, namely:

1. Most independent variables do not have an impact on MIC in a like manner across organism-agent combinations.
2. Interactions between independent variables are associated with decreased susceptibility more often for some organisms than for others.
3. The independent variables most frequently associated with increased MIC values include (in decreasing order of occurrence) duration of hospital stay before isolation of a pathogen, primary diagnosis group, hospital size, medical service, patient age, and geographic region.

Although some of these points are intuitive, the models described provide insight into the magnitude of the impact on variability that could be explained by the models presented here.
susceptibility of combinations of independent variables in specific cohorts. In addition, important similarities and differences in patterns of susceptibility between organisms and antimicrobial agents also were identified. Perhaps the most obvious data that can be used to improve the models are measures of previous antimicrobial exposure in both the patient and the institution. This remains an important issue and a focus of our continuing investigational efforts.

In a recent publication, McGowan et al. [11] postulated that factors driving resistance rates for specific organism-agent pairs in a given hospital may also influence resistance rates for other pairs. Because these investigators found significant correlations among pairs of third-generation cephalosporins and *Enterobacter* species, *K. pneumoniae*, and *P. aeruginosa*, we examined the model results for the MIC of cefepime against these same organisms and found at least 1 independent variable significantly related to MIC common to each of these 3 pairs. The hypothesis of McGowan et al. [11] is intuitive and may prove to be true; our results do not confirm the hypothesis but are not inconsistent with it.

Through these analyses, a novel approach to GLM, together with tree-based modeling, was used to delineate important relationships between microbiologic activity and patient- and institution-specific variables. Independent variables most predictive of decreased MIC across most models for *Enterobacter* species, *P. aeruginosa*, and *K. pneumoniae* included the duration of hospital stay before isolation of a pathogen, primary diagnosis group, hospital size, medical service, patient age, and geographic region. As assessed by examination of cohorts of patients, higher MIC90 values were seen among patients with combinations of these variables (in some instances, >16–32-fold higher than the overall MIC90 for the entire population).

In conclusion, we feel that the use of such data will allow the identification of patient and institution profiles likely to be associated with infection with pathogens with decreased susceptibility. Furthermore, these variables warrant careful consideration in the design of clinical trials directed at the study of drug regimens likely to be successful against resistant pathogens.

**Acknowledgments**

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**References**