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Clinical Prediction Tool To Identify Patients with *Pseudomonas aeruginosa* Respiratory Tract Infections at Greatest Risk for Multidrug Resistance▽

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Despite the increasing prevalence of multiple-drug-resistant (MDR) *Pseudomonas aeruginosa*, the factors predictive of MDR have not been extensively explored. We sought to examine factors predictive of MDR among patients with *P. aeruginosa* respiratory tract infections and to develop a tool to estimate the probability of MDR among such high-risk patients. This was a single-site, case-control study of patients with *P. aeruginosa* respiratory tract infections. Multiple-drug resistance was defined as resistance to four or more antipseudomonal antimicrobial classes. Clinical data on demographics, antibiotic history, and microbiology were collected. Classification and regression tree analysis (CART) was used to identify the duration of antibiotic exposure associated with MDR *P. aeruginosa*. Log-binomial regression was used to model the probability of MDR *P. aeruginosa*. Among 351 *P. aeruginosa*-infected patients, the proportion of MDR *P. aeruginosa* was 35%. A significant relationship between prior antibiotic exposure and MDR *P. aeruginosa* was found for all of the antipseudomonal antibiotics studied, but the duration of prior exposure associated with MDR varied between antibiotic classes; the shortest prior exposure duration was observed for carbapenems and fluoroquinolones, and the longest duration was noted for cefepime and piperacillin-tazobactam. Within the final model, the predicted MDR *P. aeruginosa* likelihood was most dependent upon length of hospital stay, prior culture sample collection, and number of CART-derived prior antibiotic exposures. A history of a prolonged hospital stay and exposure to antipseudomonal antibiotics predicts multidrug resistance among patients with *P. aeruginosa* respiratory tract infections at our institution. Identifying these risk factors enabled us to develop a prediction tool to assess the risk of resistance and thus guide empirical antibiotic therapy.

The prevalence of multiple-drug-resistant (MDR) *Pseudomonas aeruginosa* has increased over the past decade and has become a major concern among hospitalized patients (2, 11, 14, 18, 20, 24, 30). The United States Intensive Care Unit Surveillance Study demonstrated a significant rise in MDR *P. aeruginosa* isolates from 4% in 1993 to 14% in 2002 (30). Among non-intensive care unit (ICU) patients, the Surveillance Network reported an increase in the proportion of MDR *P. aeruginosa* infections from 5.5% to 7.0% between 1998 and 2001 (20). These examples are consistent with other large-scale multisite surveillance studies (11, 18, 24).

The presence of multiple-drug resistance within *P. aeruginosa* infections further diminishes the treatment options for an organism inherently resistant to many antimicrobials. Often, therapy for MDR *P. aeruginosa* is limited to colistin, an antimicrobial with a low toxicity threshold (24). Patients with MDR *P. aeruginosa* are at an increased risk for inappropriate empirical antimicrobial therapy, and studies have demonstrated that delays in appropriate antimicrobial treatment may be detrimental to patient outcomes (17, 19, 22, 23, 26, 27).

Despite the increasing prevalence of MDR *P. aeruginosa*, risk factors have not been extensively explored and quantitative evaluations of the relationship between prior antimicrobial exposure and multiple-drug resistance among patients with *P. aeruginosa* respiratory tract infections have not been performed (1, 3, 4, 14, 31, 32, 35). Furthermore, no study has quantified the probability of multiple-drug resistance in a given patient with a *P. aeruginosa* infection when one or more risk factors are present. Information regarding prior exposure to antibiotics associated with an increased probability of MDR *P. aeruginosa* is vital; this knowledge can be used in the initial antibiotic selection process to increase the likelihood of appropriate empirical antibiotic therapy prior to the availability of antibiotic susceptibility results and thus potentially minimize the harm caused by delayed treatment (19, 22, 23, 25, 26). This study examined the risk factors for multiple-drug resistance among patients with *P. aeruginosa* infections and developed an institution-specific tool to estimate the likelihood of multiple-drug resistance among such patients.

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MATERIALS AND METHODS

Study population. To accomplish the study objectives, a retrospective case-control study was performed at Albany Medical Center Hospital, a tertiary-care academic hospital located in Albany, N.Y. All patients with a positive respiratory *P. aeruginosa* clinical culture between January 2002 and April 2004 were eligible. The study included patients at least 18 years of age who had a *P. aeruginosa* clinical respiratory culture (e.g., sputum, bronchial aspirate, bronchoalveolar lavage) meeting the Centers for Disease Control and Prevention criteria for infection (12) and who did not have a diagnosis of cystic fibrosis. Only unique isolates were considered in the analysis. If a patient had both a non-MDR and an MDR *P. aeruginosa* isolate recovered at the same time, we selected the most resistant organism because treatment would be based on it. If a patient developed multidrug resistance during therapy, both cultures would be considered in the analysis. This study was approved (expedited) by the Albany Medical Center Hospital institutional review board.

Patient data. Trained reviewers used a structured data collection instrument to abstract the following information from medical records: age, sex, comorbid conditions, health care contact within 180 days of admission, length of hospitalization prior to collection of a *P. aeruginosa* culture sample (total and ICU), hospital unit at collection of *P. aeruginosa* culture sample (ICU versus non-ICU), number of consecutive ICU days prior to culture sample collection, mechanical ventilation at culture sample collection, severity of illness at sample collection (calculated by using the Acute Physiological and Chronic Health Evaluation [APACHE-II] score [21]), antibiotic therapy history during hospitalization, and microbiologic data.

The presence of the following comorbid conditions was documented: diabetes mellitus, heart failure (New York Heart Association classes II to IV [7]), chronic obstructive pulmonary disease, hepatic dysfunction (Child-Pugh class C) (33), renal failure (as indicated by the necessity for dialysis), and presence of decubitus ulcers (stages II to IV) (28).

Prior health care exposure was defined as health care institution admission (hospital, nursing home, long-term care facility, etc.) for at least 72 h in the 6 months prior to admission. The APACHE-II score was calculated from the worst physiological score within the first 24 h prior to *P. aeruginosa* culture sample collection. Prior antibiotic use was defined as administration of antibiotics within 30 days preceding the collection of a *P. aeruginosa* culture sample. Treatment data included all antibiotics (date, time, dose, route, and duration) administered prior to *P. aeruginosa* culture sample collection at the index hospital. Data regarding prior antibiotic use at outside hospitals or in an outpatient setting were not collected because of the difficulty in recovering accurate data.

Microbiologic data. Microbiologic data included all positive *P. aeruginosa* clinical cultures, including the date and time the *P. aeruginosa* culture result was recorded. Microbiologic data on other organisms present at the same *P. aeruginosa* culture sample site or causing an infection at a distal site were also documented. Antibiotic susceptibilities and MICs reported by the microbiology laboratory were recorded. Susceptibility testing was performed by the Kirby-Bauer method and interpreted according to Clinical and Laboratory Standards Institute guidelines (6). The agents tested included piperacillin-tazobactam, cefepime, ciprofloxacin, imipenem, meropenem, tobramycin, amikacin, and aztreonam. Intermediate results were considered resistant.

Multidrug resistance was defined as resistance to at least four classes of antipseudomonal agents. For this analysis, each of the following represents a "unique" drug class: piperacillin-tazobactam, cefepime, imipenem-meropenem, ciprofloxacin, gentamicin-tobramycin, and amikacin. It should be noted that several formulary changes occurred during the study period. For example, meropenem was replaced with imipenem-cilastatin in February 2004 and switched back to meropenem when the drug supply stabilized in February 2005. Susceptibility was based on the formulary agent from each respective class at the time of *P. aeruginosa* culture sample collection.

Data analysis. Categorical variables were compared by the Pearson χ^2 or Fisher exact test, and continuous variables were compared by the Student *t* or Mann-Whitney U test. Breakpoints in the distribution of continuous variables were determined by classification and regression tree (CART) analysis, a useful analytical tool to identify breakpoints within a continuous variable where the outcome of interest is distinctly different between the resulting groups (36). The CART technique was used to identify the duration of antibiotic exposure for each drug class associated with a higher proportion of MDR *P. aeruginosa*. It was also used to identify breakpoints for age and length-of-stay (LOS) variables.

Because of the large proportion of multidrug resistance, log-binomial regression was used to directly estimate the predicted probability of MDR *P. aeruginosa* (29, 34). A clinical prediction tool was devised in a manner similar to a previously published prediction rule for methicillin-resistant *Staphylococcus aureus* (25). All variables associated with multidrug resistance in the bivariate analysis ($P < 0.2$) were considered for inclusion in the explanatory log-binomial regression model. A stepwise approach was used to derive a parsimonious model, and variables remained in the final model if the associated *P* value was <0.05. Because of the study design, prevalence ratios (PR) were computed for variables in the final model (29, 34). To assess if the final PR was confounded, all potential confounders were put back into the model to assess their impact. All calculations were computed with SAS version 9.0 (SAS, Cary, NC), SPSS version 11.5 (SPSS, Chicago, IL), and CART software (Salford Systems, San Diego, CA).

TABLE 1. Descriptive statistics for the MDR *P. aeruginosa* retrospective study sample

Characteristic	Value[a]
Mean age, yr (SD)	60.5 (18.9)
Sex (male)	215 (61.2)
Resided in a health care institution for >72 h in 6 mo prior to admission	154 (43.9)
Median LOS prior to onset, days (range)	24 (0–178)
ICU at onset	287 (81.8)
Median ICU LOS prior to onset, days (range)	16 (0–177)
Mechanical ventilation at onset	281 (80.1)
APACHE-II score at culture collection (SD)	15.3 (7.1)
Congestive heart failure	73 (20.8)
Diabetes mellitus	98 (27.9)
Chronic obstructive pulmonary disease	118 (33.6)
Hepatic dysfunction	20 (5.7)
Dialysis	44 (12.5)
Decubitus ulcers	72 (20.5)

[a] All data are presented as number (percentage) unless otherwise indicated.

RESULTS

During the study period, 351 patients met the eligibility criteria and were included; baseline data on characteristics are presented in Table 1. The mean age was 60.5 ± 18.9 years, and the majority of patients were male (61%). The median hospital LOS prior to *P. aeruginosa* culture sample collection was 24 days, and 82% of the patients were in the ICU at culture sample collection. The *P. aeruginosa* culture sample was collected 48 h after admission in the majority of patients (93%). Of the 26 patients with culture sample collection within 48 h of admission, 19 had a documented health care exposure in the 6 months prior to admission; there were seven community-acquired cases, and all of these cases involved non-multidrug resistant organisms. The hospital mortality rate 30 days post culture sample collection was 9%. Overall antibiotic susceptibility and antibiotic susceptibility stratified by MDR *P. aeruginosa* (resistance to at least four classes) are displayed in Table 2. The overall prevalence of MDR *P. aeruginosa* was 36%, with the highest susceptibility observed for amikacin and cefepime (82% and 53%, respectively), followed by tobramycin at 37%; susceptibilities were lower than 20% for the other agents examined. For the non-MDR *P. aeruginosa* isolates, susceptibility was ≥90% for only amikacin, cefepime, and piperacillin-tazobactam.

The bivariate analyses of the relationship between clinical features and MDR *P. aeruginosa* are shown in Table 3. There was a significantly higher percentage of MDR *P. aeruginosa* among patients with the following clinical features: age of >60 years, LOS prior to culture sample collection of ≥33 days,

TABLE 2. Overall and stratified *P. aeruginosa* antibiotic susceptibility by resistance to at least four drug classes[a]

Antibiotic	Overall (n = 351)	MDR *P. aeruginosa* (n = 122)	Non-MDR *P. aeruginosa* (n = 229)
Amikacin	319 (90.9)	100 (82.0)	219 (95.6)
Aztreonam	204 (58.1)	23 (18.9)	181 (79.0)
Cefepime	287 (81.8)	64 (52.5)	223 (97.4)
Ciprofloxacin	149 (42.5)	4 (3.3)	145 (63.3)
Meropenem	197 (56.1)	21 (17.2)	176 (76.9)
Piperacillin-tazobactam	212 (60.4)	6 (4.9)	206 (90.0)
Tobramycin	237 (67.5)	45 (36.9)	192 (83.8)

[a] All data are presented as number (percentage) unless otherwise indicated.

residence in an ICU at culture sample collection, an ICU LOS prior to culture sample collection of ≥27 days, mechanical ventilation at culture sample collection, diabetes mellitus, dialysis, and presence of decubitus ulcers. The relationship between prior antibiotic exposure and MDR *P. aeruginosa* is also shown in Table 3. A significant relationship between prior antibiotic exposure and MDR *P. aeruginosa* was found for all of the antipseudomonal antibiotics studied. The association between duration of antibiotic exposure prior to culture sample collection and MDR *P. aeruginosa* derived by CART, however, was different for each antibiotic class. The shortest duration of prior antibiotic exposure associated with MDR *P. aeruginosa* was observed for the carbapenems and fluoroquinolones; the longest duration was noted for cefepime and piperacillin-tazobactam.

TABLE 3. Bivariate analysis of the relationship between clinical features and MDR *P. aeruginosa*[a]

Clinical feature	MDR *P. aeruginosa* (n = 122)	No MDR *P. aeruginosa* (n = 229)	P value
Age of ≥61 yr[b]	93 (66.9)	104 (49.1)	0.001
Sex (male)	82 (67.2)	133 (58.1)	0.09
Admission for ≥72 h within 6-mo prior to culture	54 (44.3)	100 (43.7)	0.9
LOS prior to collection of ≥33 days[b]	73 (59.8)	58 (25.1)	<0.001
ICU at onset	107 (87.7)	180 (78.6)	0.04
ICU LOS of ≥27 days prior to culture[b]	73 (59.8)	55 (24.0)	<0.001
Mechanical ventilation at culture	109 (89.3)	172 (75.1)	0.001
Congestive heart failure	27 (22.1)	46 (20.1)	0.65
Diabetes mellitus	47 (38.5)	51 (22.3)	0.001
Chronic obstructive pulmonary disease	46 (37.7)	72 (31.4)	0.2
Hepatic dysfunction	5 (4.1)	15 (6.6)	0.35
Dialysis	26 (21.3)	18 (7.9)	<0.001
Decubitus ulcers	35 (28.7)	37 (16.2)	0.006
Prior antibiotic exposure			
Carbapenem, ≥3 days[b]	33 (27.0)	31 (13.4)	0.002
Fluoroquinolone, ≥4 days[b]	33 (27.0)	30 (13.0)	0.001
Aminoglycoside, ≥5 days[b]	39 (32.0)	36 (15.9)	<0.001
Cefepime, ≥9 days[b]	19 (15.6)	11 (4.8)	0.001
Piperacillin-tazobactam, ≥12 days[b]	41 (33.6)	37 (16.9)	<0.001

[a] Resistance to at least four drug classes. All data are presented as number (percentage) unless otherwise indicated.
[b] CART-derived breakpoint.

TABLE 4. Relationship between number of antipseudomonal antibiotic exposures and MDR *P. aeruginosa* (n = 351)[a]

No. of antibiotic exposures[b]	MDR *P. aeruginosa* (n = 122)	No MDR *P. aeruginosa* (n = 229)	% MDR *P. aeruginosa* (n = 351)
0	34 (27.9)	122 (53.3)	21.8
1	39 (32.0)	74 (32.3)	34.5
2	28 (23.0)	29 (12.1)	49.1
3	16 (13.1)	3 (1.3)	84.2
4	3 (2.5)	1 (0.4)	75
5	2 (1.6)	0 (0)	100

[a] All data are presented as number (percentage) unless otherwise indicated.
[b] Note that carbapenem exposure for ≥3 days, fluoroquinolone exposure for ≥4 days, aminoglycoside exposure for ≥5 days, cefepime exposure for ≥9 days, and piperacillin-tazobactam exposure for ≥12 days were defined as antibiotic exposures prior to culture collection.

The relationship between the number of prior antibiotic exposures and MDR *P. aeruginosa* is shown in Table 4. A statistically significant relationship between the number of CART-derived prior antibiotic exposures and MDR *P. aeruginosa* was noted. The proportion of MDR *P. aeruginosa* rose with increased numbers of prior antibiotic exposures. A subset analysis of the relationship between an individual antibiotic exposure(s) and MDR *P. aeruginosa* was performed; no individual prior antibiotic exposures biased the relationship between the number of exposures and the observed MDR *P. aeruginosa* proportion, and all contributed equally to the observed association (data not shown).

All of the variables associated with MDR *P. aeruginosa* in the bivariate analysis ($P < 0.2$) were included in the log-binomial regression at model entry. For this analysis, the number of prior antibiotic exposures was consolidated into an ordinal variable with the following four rank-ordered categories: zero, one, two, and three or more prior antibiotic exposures. The two variables retained in the final log-binomial regression model were the number of prior antibiotic exposures (PR for a 1-U increase = 1.3; 95% confidence interval, 1.2 to 1.5; $P < 0.001$) and an LOS prior to culture sample collection of ≥33 days (PR = 1.9; 95% confidence interval, 1.3 to 2.6; $P < 0.001$). Interaction terms were explored, but none were identified. Furthermore, the ordering of prior antibiotic exposures was also considered but was not associated with MDR *P. aeruginosa*.

The interpretation of the final prediction model is presented in Table 5. The predicted likelihood of MDR *P. aeruginosa* was

TABLE 5. Predicted likelihood of MDR *P. aeruginosa* in a patient with a *P. aeruginosa* respiratory culture (n = 351)

LOS (days)	Predicted, actual MDR *P. aeruginosa* frequency, % (n), after following no. of prior antibiotic exposures:			
	0	1	2	≥3
<33	19.0, 20.0 (135)	25.2, 22.6 (62)	33.4, 34.8 (23)	NA,[a] 0 (0)
≥33	35.4, 33.3 (21)	47.0, 49.0 (51)	62.3, 58.8 (34)	82.7, 84.0 (25)

[a] NA, not applicable. The predicted MDR *P. aeruginosa* likelihood is not provided here because no patient in our sample had an LOS of ≥33 days prior to collection and three or more prior antibiotic exposures.

TABLE 6. Comparison of prior antipseudomonal antibiotic exposure and MDR *P. aeruginosa* among the 135 patients with a hospital LOS of <33 days prior to culture sample collection and no prior CART-derived antibiotic exposure[a]

Prior antibiotic exposure[b]	MDR *P. aeruginosa* (n = 27)	No MDR *P. aeruginosa* (n = 108)	P value
Carbapenem, 1–3 days	1 (3.7)	12 (11.1)	0.2
Fluoroquinolone, 1–4 days	4 (14.8)	12 (11.1)	0.6
Aminoglycoside, 1–5 days	8 (29.6)	32 (29.6)	1.0
Cefepime, 1–9 days	1 (3.7)	17 (15.7)	0.1
Piperacillin-tazobactam, 1–12 days	18 (66.7)	55 (50.9)	0.1
No. of prior antibiotic exposures:			
0	5 (18.5)	23 (21.3)	
1	13 (48.1)	46 (42.6)	
2	8 (29.6)	35 (32.4)	
3	1 (3.7)	4 (3.7)	0.9

[a] All data are presented as number (percentage) unless otherwise indicated.
[b] Carbapenem exposure for 1 to 3 days, fluoroquinolone exposure for 1 to 4 days, aminoglycoside exposure for 1 to 5 days, cefepime exposure for 1 to 9 days, and piperacillin-tazobactam exposure for 1 to 12 days were defined as antibiotic exposures prior to culture sample collection.

most dependent upon an LOS prior to culture sample collection of ≥33 days, and the probability of MDR *P. aeruginosa* increased in a log-linear manner within the two LOS strata based on the frequency of prior antibiotic exposure. The predicted likelihood of MDR *P. aeruginosa* was not provided when the LOS prior to collection was ≥33 days and there were at least three prior antibiotic exposures because no patients met this criterion within the actual distribution. The clinical features included in the model could not explain every episode of MDR *P. aeruginosa* among *P. aeruginosa* respiratory culture samples, and there was an estimated MDR *P. aeruginosa* rate of 19.0% in the absence of these characteristics.

Table 5 also shows the predicted likelihood of having MDR *P. aeruginosa* versus the actual probability of having MDR *P. aeruginosa* among the strata identified in the log-binomial regression analysis. Overall, the model accurately estimated the likelihood of MDR *P. aeruginosa* in this study population, and the predicted likelihood was within 5% for all resulting cells. Of the 135 *P. aeruginosa* respiratory culture samples recovered from patients with an LOS of <33 days and no CART-derived prior antibiotic exposures, 27 (20%) contained MDR *P. aeruginosa*. Further evaluation of these 135 episodes revealed that there was a higher proportion of diabetes mellitus (37% versus 16.7%; $P < 0.05$) and a longer median LOS prior to culture (13 days versus 8 days; $P < 0.05$) among MDR *P. aeruginosa* versus non-MDR *P. aeruginosa* patients, respectively. There were no other significant differences in clinical features noted between groups. The relationship between exposure to antipseudomonal antibiotics for a duration shorter than the CART-derived breakpoint and MDR *P. aeruginosa* is shown in Table 6. No significant differences in prior antibiotic exposures were observed between groups, and the number of prior antibiotic exposures less than the CART-derived breakpoints was not associated with MDR *P. aeruginosa*.

DISCUSSION

Consistent with large-scale surveillance studies (2, 11, 18, 20, 30), a high prevalence of MDR *P. aeruginosa* was observed at our institution (34.5%). Empirical therapy options for suspected MDR *P. aeruginosa* respiratory infections within our institution are limited to amikacin (although the role of aminoglycoside monotherapy for respiratory tract infections is highly debated) and alternative *P. aeruginosa* therapy options like colistin; we currently advocate colistin for patients with MDR *P. aeruginosa* infections. Given the importance of rapid, appropriate treatment (17, 19, 22, 23, 26, 27), we developed an institution-specific clinical tool to identify patients with *P. aeruginosa* respiratory tract infections at greatest risk for multidrug resistance. Our thought was that knowledge of the probability of multidrug resistance in a given patient with a *P. aeruginosa* respiratory tract infection would facilitate empirical antibiotic selection, identify situations where colistin should be used empirically, and minimize delays in appropriate therapy.

The first step in the clinical prediction rule development was identification of institution-specific risk factors for MDR *P. aeruginosa*. The MDR *P. aeruginosa* risk factors identified in our study are largely consistent with those previously reported (1, 3, 4, 5, 8–10, 13, 31, 32, 35). Populations found to be most vulnerable to MDR *P. aeruginosa* in the bivariate analysis included patients at least 61 years of age, patients with prolonged hospital stays, patients in the ICU on mechanical ventilation, and patients with comorbid conditions including diabetes, end stage renal disease requiring dialysis, and decubitus ulcers. We also found a strong association between prior exposure to antibiotics with antipseudomonal activity and MDR *P. aeruginosa*, which is consistent with prior studies (1, 3, 4, 5, 8–10, 13, 31, 32, 35). Our study, however, was unique in that it sought to quantify the duration of antibiotic exposure for each antipseudomonal agent or class that was associated with the highest probability of multidrug resistance among patients with *P. aeruginosa* infections. Specifically, CART was used to identify the relationship between duration of exposure and multidrug resistance risk.

Contrary to previous reports that have typically found only one or two antibiotic classes to be predictive of MDR *P. aeruginosa* (1, 3, 4, 5, 8–10, 13, 31, 32, 35), we found that all antipseudomonal agents were associated with MDR *P. aeruginosa* in the bivariate analysis. The duration of prior antibiotic exposure associated with MDR *P. aeruginosa* derived by CART, however, varied among the antipseudomonal classes studied. The shortest duration of prior antibiotic exposure associated with MDR *P. aeruginosa* was observed for the carbapenems and fluoroquinolones; the longest duration was noted for cefepime and piperacillin-tazobactam. These findings highlight the importance of performing quantitative evaluations of the association between prior antibiotic exposure and antibiotic resistance. Specifically, this study demonstrates that significant associations between prior antibiotic exposure and resistance may only exist once the threshold exposure duration is exceeded; this risk factor would otherwise be missed if not quantitatively assessed (data not shown).

While individual antipseudomonal class exposures were found to be important predictors in the bivariate analysis, the number of CART-derived prior antibiotic exposures proved to

be the only significant prior antibiotic exposure variable in the final binomial model. There was a log-linear relationship between the number of CART-derived prior antibiotic exposures and the probability of MDR *P. aeruginosa*. As the number of prior exposures increased, there was a commensurate increase in the probability of MDR *P. aeruginosa*. This relationship has been noted in other MDR *P. aeruginosa* risk factor studies, and the frequency of exposures should be considered when assessing the relationship between prior antibiotic exposure and resistance (1).

By identifying institution-specific MDR *P. aeruginosa* risk factors and using stepwise log-binomial regression modeling techniques, we were able to derive an institution-specific clinical prediction tool. In contrast to standardized prediction rules used in clinical practice, this clinical prediction tool was intended to assist clinicians in their empirical decision-making process by helping to quantify the risk of MDR *P. aeruginosa* in a given patient with *P. aeruginosa* respiratory infection. Log-binomial regression identifies the best linear combination of predictors that maximize the likelihood of obtaining the observed MDR *P. aeruginosa* rates. The major advantage of log-binomial regression, however, is the utility of the final model, a mathematical equation that can be used to predict the probability of multidrug resistance on the basis of the combination of risk factors present in a given individual with a *P. aeruginosa* infection. Understanding the probability of MDR *P. aeruginosa* enhances the ability of clinicians to make more-informed treatment decisions and potentially maximize clinical outcomes by increasing the likelihood of appropriate antimicrobial therapy (25). We believe that by ensuring appropriate empirical therapy, the clinical prediction tool will significantly decrease treatment delays. Clinicians will typically know if they are treating *P. aeruginosa* once the results of the Gram stain are available. Culture results are usually available 24 h after the Gram stain, and antibiotic susceptibility results follow in another 24 h. Once the antibiotic susceptibility results are available, it takes an additional 12 to 24 h for the medical team to write a new antibiotic order, the pharmacy to dispense and deliver the medication, and nursing to administer it. With the clinical prediction rule, this delay in therapy will be minimized and outcomes may be improved by ensuring prompt delivery of appropriate therapy.

The clinical prediction tool was derived from the final log-binomial model, which included a hospital LOS of at least 33 days prior to culture sample collection and the number of CART-derived antibiotic exposures. Given that LOS was assessed as a binary variable and was the strongest predictor in the model, the derived clinical prediction tool was first partitioned by an LOS of ≥33 days (LOS of ≥33 days and LOS of <33 days) and the probability of MDR *P. aeruginosa* within the two LOS strata was based on the number of prior antibiotic exposures. In order to estimate the likelihood of multidrug resistance in a given patient with a clinical respiratory *P. aeruginosa* culture, one must first ascertain if the hospital LOS is ≥33 days and then determine the number of prior CART-derived antipseudomonal drug exposures in a given patient. For example, if the patient's prior LOS was <33 days and the patient received an aminoglycoside for at least 5 days and piperacillin-tazobactam at least 12 days prior to *P. aeruginosa* culture sample collection (during two prior exposures), the model estimates that the probability of MDR *P. aeruginosa* is 33%. In clinical practice, it is important to note that we would consider ≥1 month prior *P. aeruginosa* culture sample collection equivalent to ≥33 days prior to facilitate ease of use by a clinician.

While the LOS breakpoint of 33 days was the most optimal cut point identified in the CART analysis and provided the best model fit, we did several post-hoc analyses to determine if the other LOS breakpoints provided different estimates of multidrug resistance. The second most optimal breakpoint identified in CART was 13 days. We performed an exploratory analysis, and the predicted and actual proportions of multidrug resistance stratified by the number of exposures were similar between patients with an LOS of <13 days and patients with an LOS of <33 days; it was not until ≥33 days when we observed a significant increase in the actual proportion of multidrug resistance. We also examined an LOS breakpoint of 7 days, and the actual proportion of multidrug resistance was relatively similar between LOS breakpoints of 7 and 33. The <7-day LOS strata, however, were too small when 7 days was used, especially for an increasing number of exposures, to draw any meaningful conclusions. Our goal was to be as straightforward as possible, and given that patients had similar proportions of multidrug resistance, we did not think it was necessary to expand the model to include more LOS strata. It was only after patients were in the hospital for >33 days that we observed an increase in multidrug resistance in the various drug exposure categories.

Limitations to the present study exist and should be noted. First, this study only explored respiratory culture data from a single site. Institutional differences in prescribing patterns, antibiotic formularies, and patient populations may affect the applicability of these results to other institutions. Second, the control group we selected differs from current recommendations for standard risk factor studies (15, 16). Specifically, it is recommended that studies evaluating the role of antimicrobials as risk factors for the isolation of resistant organisms among hospitalized patients use a control group that is sampled from the same base population, including those not infected with *P. aeruginosa*. However, because the primary aim of this study was to identify factors predictive of multidrug resistance among patients known to be culture positive for *P. aeruginosa*, we felt that patients with non-MDR *P. aeruginosa* were the appropriate control to properly answer this research question. As previously stated, the primary objective of this study was to develop an institution-specific mechanism to direct antibiotic selection for patients with *P. aeruginosa* respiratory tract infections. To appropriately address the study hypothesis, we used a control group that was infected with *P. aeruginosa* without multidrug resistance in order to estimate the likelihood of multidrug resistance in patients with *P. aeruginosa*. Lastly, we cannot exclude the possibility of patient-to-patient transmission of MDR *P. aeruginosa* strains. However, MDR *P. aeruginosa* was usually identified in patients with a long ICU stay and multiple antibiotic exposures. If patient-to-patient transmission did occur, this may have weakened the association between MDR *P. aeruginosa* acquisition and receipt of antibiotics.

In conclusion, our data support the major role of a prolonged hospital stay and exposure to antipseudomonal antibi-

otics as predictors of the presence of MDR *P. aeruginosa* among patients with *P. aeruginosa* respiratory tract infections. Although previous exposure to all antipseudomonal antibiotics significantly increased the risk of MDR *P. aeruginosa*, the length of the exposure time necessary for this effect differed between antibiotic classes. Furthermore, there was a log-linear relationship between the number of CART-derived prior antibiotic exposures and the probability of MDR *P. aeruginosa* proportion. Identification of institution-specific risk factors can be used to develop a mechanism to identify patients at greatest risk for multidrug resistance and thus guide empirical antibiotic therapy for patients with *P. aeruginosa* respiratory tract infections. Institution-specific clinical tools of this nature should be considered when making empirical antimicrobial therapy selection decisions for patients with infections likely to have high rates of antimicrobial resistance. Furthermore, clinical prediction tools developed at an external institution should be validated prior to implementation.

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