ORIGINAL ARTICLE

Ability of an Antibiogram to Predict *Pseudomonas aeruginosa* Susceptibility to Targeted Antimicrobials Based on Hospital Day of Isolation

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OBJECTIVE. To determine the utility of an antibiogram in predicting the susceptibility of *Pseudomonas aeruginosa* isolates to targeted antimicrobial agents based on the day of hospitalization the specimen was collected.

DESIGN. Single-center retrospective cohort study.

SETTING. A 750-bed tertiary care medical center.

PATIENTS AND METHODS. Isolates from consecutive patients with at least 1 clinical culture positive for *P. aeruginosa* from January 1, 2000, to June 30, 2007, were included. A study antibiogram was created by determining the overall percentages of *P. aeruginosa* isolates susceptible to amikacin, ceftazidime, ciprofloxacin, gentamicin, imipenem-cilastin, piperacillin-tazobactam, and tobramycin during the study period. Individual logistic regression models were created to determine the day of infection after which the study antibiogram no longer predicted susceptibility to each antibiotic.

RESULTS. A total of 3,393 isolates were included. The antibiogram became unreliable as a predictor of susceptibility to ceftazidime, imipenem-cilastin, piperacillin-tazobactam, and tobramycin after day 10 and ciprofloxacin after day 15 but longer for gentamicin (day 21) and amikacin (day 28). Time to unreliability of the antibiogram varied for antibiotics based on location of isolation. For example, the time to unreliability of the antibiogram for ceftazidime was 5 days (95% confidence interval [CI], <1–8) in the intensive care unit (ICU) and 12 days (95% CI, 7–21) in non-ICU hospital wards ($P = .003$).

CONCLUSIONS. The ability of the antibiogram to predict susceptibility of *P. aeruginosa* decreases as duration of hospitalization increases.

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Pseudomonas aeruginosa is a common and potentially lethal etiology of gram-negative infections.[1,2] In fact, *P. aeruginosa* has become the most common etiology of gram-negative bloodstream infections (BSI) among hospitalized patients and the third most common etiology of BSI in hospitalized and community-dwelling patients.[3,4] Infections due to *P. aeruginosa* are associated with a high rate of crude mortality, ranging from 28% to 48% for non–intensive care unit (ICU) and ICU patients, respectively.[5] Unfortunately, the increasing prevalence of multidrug-resistant *P. aeruginosa* complicates treatment decisions and leads to potential delays in appropriate empiric antimicrobial therapy.[6] Importantly, patients who receive inappropriate empiric antimicrobial therapy for gram-negative sepsis have mortality rates of 14%–38%.[5,7,8]

Clinicians often make empiric treatment decisions regarding initial antimicrobial therapy based on institution-specific antibiograms. These antibiograms frequently provide a summary of in vitro activity of antimicrobials at a specific institution. Most antibiograms are collated and reported annually in order to detect changes and trends in antibiotic resistance in a specific location (eg, a hospital or unit).

Infectious Disease Society of America guidelines regarding antibiotic stewardship recommend using institutional antibiograms in the development of empiric antibiotic therapy guidelines.[9] However, the ability of an antibiogram to predict antimicrobial susceptibility in individual patients (and therefore guide empiric therapy) can be limited by several factors, including sampling bias, inclusion of multiple samples of the same isolate, inclusion of surveillance (ie, nonclinical) isolates, and differences in resistance patterns based on the patient population, infection site, and healthcare location.[10,11]

Antibiograms also do not take into account the timing of the onset of infection. Infections occurring later in the hospital course are more likely to be caused by resistant path-

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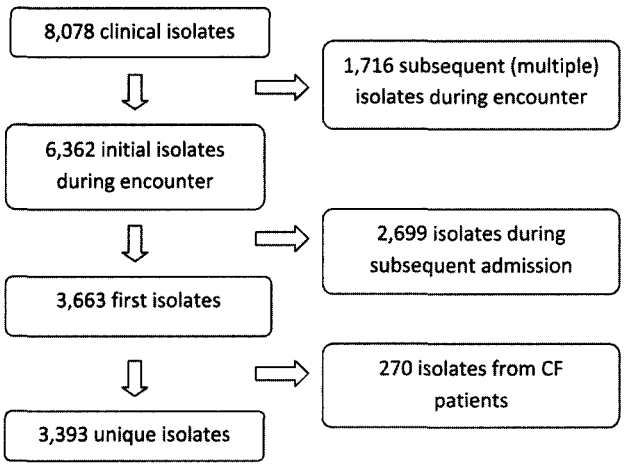

FIGURE 1. Selection of *Pseudomonas aeruginosa* isolates for inclusion in analyses.

ogens than infections diagnosed early in the course of hospitalization,[12-14] but it is not clear how this trend affects the value of the antibiogram as a tool to guide empiric antibiotic choice. Thus, our primary objective was to determine the utility of an antibiogram in predicting the susceptibility of *P. aeruginosa* isolates to anti-pseudomonal antimicrobial agents based on the day of hospitalization the specimen was collected. Our secondary objective was to describe the impact of the location of isolation on the predictive capability of the study antibiogram.

METHODS

This single-center retrospective cohort study was reviewed and approved by the Duke University Hospital (DUH) Institutional Review Board. Potential subjects were identified by querying the DUH Microbiology Laboratory and Duke Health Technology Solutions administrative databases. First, we reviewed all positive clinical cultures for *P. aeruginosa* from January 1, 2000, to June 30, 2007. Cultures obtained in either the outpatient setting or the inpatient setting were included. Second, only the first isolate from each admission or encounter was included to minimize the potential influence of duplicate isolates (independent of number of cultures or source). Patients could be included multiple times in our sample if they had more than 1 independent admission and/or encounter with a pseudomonal infection. Patients with cystic fibrosis were excluded. Data (including age, admission date, culture date, presence/absence of cystic fibrosis, and susceptibility results) were extracted from electronic medical records.

In vitro susceptibility testing was performed on all isolates and interpreted by the Duke University Clinical Microbiology Laboratory according to criteria published by the Clinical Laboratory Standards Institute[15] for the following antibacterials: amikacin, ceftazidime, ciprofloxacin, gentamicin, imipenem-cilastin, meropenem, piperacillin-tazobactam, and tobramycin. Intermediately susceptible and resistant strains were classified as nonsusceptible. A study antibiogram was then produced by determining the overall percentages of *P. aeruginosa* isolates susceptible to each antimicrobial during the entire study period. Due to the high (>99.8%) similarity to imipenem-cilastin data, susceptibility data for meropenem were ultimately not included in our analyses.

For the primary analysis, we identified the day of hospitalization after which the study antibiogram no longer reliably predicted susceptibility to the targeted antibiotics. First, the day of infection was calculated for all isolates based on the day of hospitalization. Isolates obtained on the first day of admission and outpatient isolates were assigned a day of infection of 1. Logistic regression models were then created for each antibiotic, comparing percent susceptible (dependent variable) to day of infection (independent variable). The percent susceptible value for each antibiotic from the study antibiogram was then compared with results from the logistic regression models in order to identify the day of infection after which the study antibiogram no longer reliably predicted susceptibility to the antibiotic (ie, the average percent susceptible to that antibiotic was lower than the value calculated for the study antibiogram). This value is hereafter labeled as "time to unreliability" of the antibiogram. Importantly, this descriptive term is not intended to imply statistical reliability.

Simple logistic regression models were created as reference models for each antibiotic, with day of infection as the independent variable and susceptibility of each isolate as the dependent variable. Quadratic (day of infection^2) and cubic (day of infection^3) variables were created and added to each model in stepwise fashion and included if significant. Ultimately, simple logistic models were created for ceftazidime, imipenem-cilastin, tobramycin, and piperacillin-tazobactam. Logistic models with quadratic terms were created for ciprofloxacin, gentamicin, and amikacin. No models included a cubic term. Susceptibility data from isolates obtained more than 30 days after admission were not included in the models due to sporadic and decreasing numbers of isolates.

TABLE 1. Sources of 3,393 *Pseudomonas aeruginosa* Isolates Obtained at Duke University Hospital from January 1, 2000, to June 30, 2007

Characteristics	*n*, % (N = 3,393)
Source of culture	
Urine	1,161 (34)
Respiratory	747 (22)
Blood	706 (21)
Other	376 (11)
ENT	293 (9)
Eye	60 (2)
Abdominal	50 (2)

NOTE. ENT, ear, nose, and throat.

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TABLE 2. Susceptibility of *Pseudomonas aeruginosa* Isolates Susceptible to Targeted Antibiotics Based on Site of Care (Inpatient vs Outpatient and Inpatient Intensive Care Units [ICUs] vs Non-ICU)

Antibiotic	Study antibiogram, % (n = 3,393)[a]	Inpatient isolates (n = 2,302)[a]	Outpatient isolates (n = 1,091)[a]	P	Isolates from ICUs (n = 644)[b]	Isolates from non-ICU inpatients (n = 1,658)[b]	P
Amikacin	95.0	2,192 (95)	1,023 (94)	.09	617 (96)	1,575 (95)	.55
Ceftazidime	89.3	1,994 (87)	1,034 (95)	<.0001	504 (78)	1,490 (90)	<.0001
Ciprofloxacin	72.8	1,439 (71)	734 (77)	.0004	404 (65)	1,035 (73)	<.0001
Gentamicin	80.4	1,831 (80)	892 (82)	.10	497 (77)	1,334 (81)	.07
Imipenem-cilastin	90.8	2,043 (89)	1,024 (94)	<.0001	525 (82)	1,518 (92)	<.0001
Piperacillin-tazobactam	93.3	2,107 (92)	1,059 (97)	<.0001	561 (87)	1,546 (93)	<.0001
Tobramycin	92.6	2,103 (92)	1,035 (95)	.0002	565 (88)	1,538 (93)	<.0001

NOTE. All data are no. (%) unless otherwise indicated.

[a] Susceptibility data were missing for the following antibiotics: amikacin (n = 7), ceftazidime (n = 1), ciprofloxacin (n = 407), gentamicin (n = 5), imipenem-cilastin (n = 14), and tobramycin (n = 5).

[b] Susceptibility data were missing for the following antibiotics: amikacin (n = 4), ceftazidime (n = 1), ciprofloxacin (n = 269), gentamicin (n = 2), imipenem-cilastin (n = 8), and tobramycin (n = 3).

In order to determine the impact of the location of isolation on the predictive capability of the study antibiogram, we repeated the process described above after first stratifying isolates into outpatient and inpatient locations. For inpatient isolates, we further stratified into ICU and non-ICU ward locations. The χ^2 test was used to compare susceptibilities by location. Differences in time to unreliability of the antibiogram based on location were determined using logistic regression by including a binary variable for location (ICU vs non-ICU) in each of the models created above. Interaction terms (eg, ICU × day) were also evaluated for inclusion. Outpatient specimens were excluded from these models.

Data were maintained in a Microsoft Access database. All statistical analyses were performed using SAS v9.2.

RESULTS

We identified 8,078 *P. aeruginosa* isolates during the study period. After application of our inclusion/exclusion criteria, data from 3,393 isolates were included (Figure 1). The majority of clinical isolates were from respiratory, blood, or urine samples (Table 1). The median patient age was 57 years (range, 0–104).

The study antibiogram is presented in Table 2. Among the targeted antibiotics, amikacin exhibited the highest percent susceptibility (95%), while ciprofloxacin yielded the lowest (73%). In total, 2,302 (68%) isolates were obtained during hospitalization, while 1,091 (32%) were obtained in outpatient settings. Among the 2,302 inpatient isolates, 644 (28%) were from ICUs. Percent susceptibility to antibiotics changed based on location at the time of isolation (Table 2). In general, susceptibilities were lower among inpatient isolates than among outpatient isolates. For example, 1,034 (95%) outpatient isolates were susceptible to ceftazidime, while only 1,994 (87%) inpatient isolates were susceptible to ceftazidime (P < .0001). However, most antibiotic susceptibilities decreased by only 1%–6%. More notable decreases were observed when comparing isolates obtained in ICUs with isolates obtained in non-ICU hospital wards, though the

TABLE 3. Time to Unreliability of the Antibiogram for *Pseudomonas aeruginosa* Isolates Based on Location of Isolation

Antibiotic	Overall day (95% CI)	Non-ICU hospital ward day (95% CI)	ICU day (95% CI)	P[a]
Amikacin	28 (21–>30)	24 (<1–>30)	>30 (<1–>30)	.69
Ceftazidime	10 (8–11)	12 (7–21)	5 (<1–8)	.003
Ciprofloxacin	15 (9–19)	19 (13–22)	10 (<1–18)	.66
Gentamicin	21 (12–27)	21 (12–29)	22 (<1–>30)	.26
Imipenem-cilastin	10 (8–14)	>30 (13–>30)	2 (<1–8)	<.0001
Piperacillin-tazobactam	10 (7–13)	11 (2–>30)	5 (<1–10)	.07
Tobramycin	9 (5–14)	13 (1–>30)	1 (<1–8)	.03

NOTE. CI, confidence interval; ICU, intensive care unit.

[a] Comparison of time to unreliability of the antibiogram for isolates obtained in the ICU vs non-ICU hospital wards.

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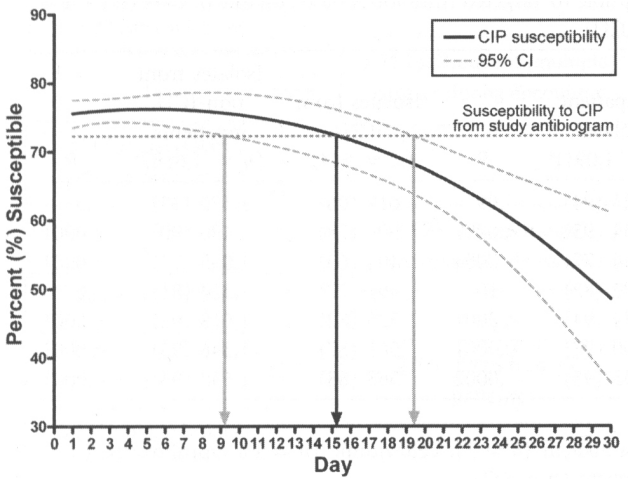

FIGURE 2. Time to unreliability of the antibiogram as a predictor for *Pseudomonas aeruginosa* susceptibility to ciprofloxacin (CIP).

decreases varied by antibiotic. For example, susceptibility to ceftazidime decreased by 12% and imipenem-cilastin decreased by 10%, while susceptibility to amikacin actually increased by 1%.

Time to unreliability of the antibiogram also varied for each antibiotic (Table 3). For example, the antibiogram became unreliable as a predictor of tobramycin on day 9; ceftazidime, imipenem-cilastin, and piperacillin-tazobactam on day 10; and ciprofloxacin on day 15 but remained reliable for gentamicin (day 21) and amikacin (day 28) for longer. Figure 2 demonstrates the output from the quadratic logistic regression model created for ciprofloxacin (time to unreliability, 15 days; 95% confidence interval [CI], 9–19).

As before, time to unreliability of the antibiogram varied for several antibiotics based on location of isolation (Table 3). For example, the time to unreliability of the antibiogram for ceftazidime was 5 days (95% CI, <1–8) in the ICU and 12 days (95% CI, 7–21) in non-ICU hospital wards (P = .003).

DISCUSSION

Our study is the first to demonstrate that the reliability of data presented in the antibiogram decreases as length of hospitalization increases. In general, our study antibiogram became unreliable as a predictor for *P. aeruginosa* susceptibility to ceftazidime, imipenem-cilastin, piperacillin-tazobactam, and tobramycin after approximately 1.5 weeks of hospitalization, to ciprofloxacin after approximately 2 weeks, and to gentamicin and amikacin after 3 or more weeks. The reliability was even shorter for *P. aeruginosa* isolates obtained in ICUs. In contrast, the antibiogram was completely reliable for predicting susceptibility of *P. aeruginosa* isolates obtained in outpatient settings.

Antibiograms are often used by clinicians as an aid in selecting initial empiric antibiotic therapy and for monitoring changes in local antimicrobial-resistant patterns over time.[16-19] The utility of an institution's antibiogram to predict antimicrobial susceptibility in individual patients (and therefore guide empiric antimicrobial therapy), however, can be limited by several factors. Sampling bias may result when clinicians submit samples for patients with more severe infections or longer hospital stays or, conversely, from predominantly outpatient settings.[10] In addition, duplicate isolates may be included if provisions are not in place to identify multiple samples obtained from the same patient. Similarly, provisions must also be in place to avoid reporting of susceptibility testing from isolates obtained as part of infection control surveillance rather than from clinical specimens. The origin of the pathogen (ie, community associated vs healthcare associated), patient age group, prior antimicrobial exposure, infection site, or patient location at the time of isolation (ICU vs intermediate care) are usually not considered.[11]

Based on our findings, it is evident that the utility of the antibiogram decreases as the length of hospital stay increases. Thus, clinicians must be aware of this limitation and seek additional guidance when choosing empiric antimicrobial therapy for a patient with a prolonged hospitalization. There are numerous explanations for why this observation may occur. Of likely primary significance is the interaction between known trends: (1) organisms isolated from patients later in the hospitalization are more likely to represent infections acquired during the hospitalization[20] and (2) infections occurring later in the hospital course are more likely to be caused by resistant pathogens than infections diagnosed early in the course of hospitalization.[12-14]

There are limitations to our retrospective observational study. First, we did not include data on potential patient-specific confounders (such as prior antibiotics, severity of illness, and comorbidities). Thus, we were unable to measure the potential impact of healthcare exposure (eg, nursing home or hemodialysis) in this analysis. While we excluded cystic fibrosis patients in an attempt to minimize the impact of multidrug-resistant *P. aeruginosa* infections, such patients would normally have been included in the antibiogram data. As such, our results are not generalizable to this specific population. Next, we assumed that patients with positive clinical cultures represented infection. Data from clinical specimens, regardless of whether the culture represents infection or colonization, however, are typically included in standard antibiograms. Finally, our results likely require further validation, as we were unable to test our models in an independent sample of patients.

Our results must be interpreted in the context of local epidemiology. While we suspect that the same trends we described are present in other hospitals, our models are specific to our setting, location, and patient population. As such, we encourage other institutions to perform similar analyses to determine time to unreliability of the antibiogram in light of local epidemiology. These data could potentially be used to modify institution-specific guidelines for the empiric treat-

ment of hospital-acquired infections where *Pseudomonas* spp. are likely pathogens.

Clinicians should be aware of methodologies considered in the formulation of the institution's antibiogram. The antibiogram is an important tool to help guide clinicians in choosing appropriate empiric antimicrobial agents for suspected infection. Based on our findings, we believe clinicians should be cautious when using antibiogram data to predict the likelihood of susceptibility of *P. aeruginosa* isolates in patients with prolonged hospitalization.

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