Relationship between Various Definitions of Prior Antibiotic Exposure and Piperacillin-Tazobactam Resistance among Patients with Respiratory Tract Infections Caused by *Pseudomonas aeruginosa*[▽]

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Contemporary literature lacks a definition of prior antibiotic exposure which captures all patients at risk of developing piperacillin-tazobactam-resistant *Pseudomonas aeruginosa* (PTR-PA). The results indicated that individual antibiotics that are associated with PTR-PA differ depending on the definition of prior antibiotic exposure utilized. When the specific antibiotic used was replaced by the number of prior exposures, the number of exposures was the only variable associated with an increased risk of antibiotic resistance at each time threshold.

Several studies have shown that previous antibiotic use increases the risk of a *Pseudomonas aeruginosa* infection that is resistant to many commonly used antimicrobials (8–11, 15). Contemporary literature lacks a definition of prior antibiotic exposure which captures all patients at risk of developing piperacillin-tazobactam (PT)-resistant *P. aeruginosa* (PTR-PA). Some studies include those receiving at least one dose of antibiotics within the 30 days prior to pathogen identification, while others required various durations of administration ranging from 24 h to 72 h of antibiotic exposure (1, 2, 4, 6, 9, 12, 14, 16). The literature also does not describe the significance of multiple antecedent antibiotic exposures.

A retrospective cross-sectional study was performed at Albany Medical Center Hospital (Albany, NY) to evaluate existing definitions of prior antibiotic exposure as well as the impact of multiple antecedent exposures associated with PTR-PA. A data set from a previously published paper on risk factors for multidrug-resistant *P. aeruginosa* was used to address the study aims (11).

Two sets of analyses were performed. In the first set, duration of prior antibiotic exposure for each drug class was categorized into four thresholds of antecedent exposure. The first threshold included those who had received at least 24 h of prior antibiotics and those who had not. The same process was applied to categorize patients who had received at least 48 h and 72 h of prior antibiotics, respectively. Finally, the classification and regression tree (CART) technique was used to identify the critical threshold duration of antibiotic exposure for each drug class associated with a higher proportion of PTR-PA; the CART methodology has been employed in several previous publications to determine the prior antibiotic exposure most predictive of antibiotic resistance (3, 7, 10, 11,

18). Each definition of prior antibiotic exposure was examined in a separate analysis. In the second set of analyses, the process was repeated according to the cumulative number of prior drug exposures within each of the aforementioned prior antibiotic exposure duration thresholds: patients were categorized as having received zero, one, two, or more than three prior antibiotics within each duration threshold and analyzed separately.

Due to the large proportion of PTR-PA, backwards stepwise Poisson regression was employed to determine variables independently associated with PTR-PA for each prior antibiotic exposure analysis (13, 17). All variables associated with PTR-PA in the bivariate analysis ($P < 0.2$) were considered for inclusion in the regression model for each analysis. Prevalence ratios were computed for variables in the final model (13, 17). Prevalence ratios reflect the increased risk of PTR-PA in the exposed patients relative to the unexposed patients.

Among the 351 patients who met eligibility criteria between January 2002 and April 2004, PTR-PA was cultured from 139 (39.6%) patients. The bivariate analysis demonstrating the relationship between the clinical features and PTR-PA is shown in Table 1. Prior receipt of all antipseudomonal agents examined was significantly associated with PTR-PA at each time threshold of prior exposure (including CART-derived breakpoints), with the exception of cefepime for ≥ 24 h ($P = 0.092$). The number of prior antibiotic exposures within each of the time thresholds was also significantly associated with PTR-PA. As the number of prior antibiotics increased, the percentage of patients with PTR-PA increased proportionally at each prior antibiotic time threshold.

Variables independently associated with PTR-PA in the backwards stepwise Poisson regression analyses for each of the prior antibiotic exposure thresholds studied are shown in Table 2. Prior PT was associated with PTR-PA at each time threshold evaluated in the multivariate analyses. Of the other prior antibiotic exposures examined, prior antibiotic exposures associated with PTR-PA varied for each of the prior antibiotic exposure thresholds studied.

To assess the effect on multiple antecedent exposures, the

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TABLE 1. Bivariate analysis of the relationship between clinical features and PTR-PA

Covariate ^a	No. (%) of patients		P
	PTR-PA (n = 139)	No PTR-PA (n = 212)	
Demographic or medical history characteristic			
Age of ≥ 64 yr*	55 (39.6)	37 (17.5)	<0.001
Sex (male)	90 (64.7)	125 (59)	0.3
Admission of ≥ 72 h in duration within 6 mo prior to culture	63 (45.3)	91 (42.9)	0.87
LOS of ≥ 33 days prior to collection*	69 (49.6)	56 (26.4)	<0.001
ICU at onset	118 (84.9)	169 (79.7)	0.2
ICU LOS of ≥ 27 days prior to culture*	53 (38.1)	21 (9.9)	<0.001
Mechanical ventilation at culture	120 (86.3)	161 (75.9)	0.02
Mechanical ventilation of ≥ 26 days*	58 (41.7)	21 (9.9)	<0.001
Diabetes mellitus	52 (37.4)	46 (21.7)	0.001
Chronic obstructive pulmonary disease	53 (38.1)	65 (30.7)	0.147
Dialysis	29 (20.9)	15 (7.1)	<0.001
Decubitus ulcers	39 (28.1)	33 (15.6)	0.005
Prior exposure to antibiotic			
Aminoglycoside			
≥ 24 h	76 (54.7)	83 (39.2)	0.004
≥ 48 h	59 (42.4)	66 (31.1)	0.03
≥ 72 h	51 (36.7)	50 (23.6)	0.008
≥ 5 days*	43 (30.9)	32 (15.1)	<0.001
Carbapenem			
≥ 24 h	25 (18.0)	11 (5.2)	<0.001
≥ 48 h	25 (18.0)	10 (4.7)	<0.001
≥ 72 h*	22 (15.8)	10 (4.7)	<0.001
Cefepime			
≥ 24 h	39 (28.1)	43 (20.3)	0.092
≥ 48 h	35 (25.2)	35 (16.5)	0.05
≥ 72 h	34 (24.5)	27 (12.7)	0.005
≥ 9 days*	20 (14.4)	10 (4.7)	0.002
Fluoroquinolone			
≥ 24 h	53 (38.1)	44 (20.8)	<0.001
≥ 48 h	46 (33.1)	38 (17.9)	0.001
≥ 72 h	42 (30.2)	32 (15.1)	0.001
≥ 4 days*	38 (27.3)	25 (11.8)	<0.001
PT			
≥ 24 h	56 (40.3)	42 (19.8)	<0.001
≥ 48 h	53 (38.1)	38 (17.9)	<0.001
≥ 72 h	51 (36.7)	34 (16.0)	<0.001
≥ 11 days*	32 (23.0)	16 (7.5)	<0.001
No. of antibiotic exposures			
≥ 24 h			
0	31 (22.3)	78 (36.8)	
1	36 (25.9)	74 (34.9)	
2	28 (20.1)	39 (18.4)	
≥ 3	44 (31.7)	21 (9.9)	<0.001
≥ 48 h			
0	42 (30.2)	96 (45.3)	
1	34 (24.5)	68 (32.1)	
2	27 (19.4)	31 (14.6)	
≥ 3	36 (25.9)	17 (8.0)	<0.001
≥ 72 h			
0	47 (33.8)	111 (70.3)	
1	34 (24.5)	64 (30.2)	
2	26 (18.7)	26 (12.3)	
≥ 3	32 (23.0)	11 (5.2)	<0.001
CART exposures [†]			
0	58 (41.7)	138 (65.1)	
1	38 (27.3)	59 (27.8)	
2	20 (14.4)	12 (5.7)	
≥ 3	23 (16.5)	3 (1.4)	<0.001

^a ICU, intensive care unit; LOS, length of stay; PT, piperacillin-tazobactam; *, CART-derived breakpoint; †, CART exposures: receipt of aminoglycoside for ≥ 5 days, carbapenem for ≥ 3 days, cefepime for ≥ 9 days, fluoroquinolone for ≥ 4 days, or PT for ≥ 11 days.

TABLE 2. Independent predictors of PTR-PA: results of the Poisson regression analyses for each of the prior antibiotic exposure thresholds studied

Covariate ^a	Prevalence ratio	95% Confidence interval	P
≥24 h			
Aminoglycoside	1.32	1.02–1.72	0.04
Carbapenem	1.35	1.00–1.83	0.05
PT	1.43	1.05–1.94	0.02
≥48 h			
Carbapenem	1.42	1.04–1.93	0.03
PT	1.48	1.09–2.01	0.01
≥72 h			
Fluoroquinolone	1.31	1.00–1.72	0.05
PT	1.46	1.10–1.95	0.001
CART breakpoints			
AG within ≥5 days	1.36	1.04–1.77	0.02
FQ within ≥4 days	1.42	1.08–1.85	0.01
Cefepime within ≥9 days	1.53	1.13–2.06	0.006
PT within ≥11 days	1.42	1.08–1.88	0.01

^a AG, aminoglycosides; FQ, fluoroquinolones; PT, piperacillin-tazobactam.

individual antibiotic exposures were removed from the model and were replaced with the number of prior antibiotic exposures that the patient had for each time threshold (Table 3). At each time threshold, the quantity of previous antibiotic exposures was the only variable associated with an increased risk of PTR-PA.

Our study quantified the relationship between prior antibiotic exposure and the risk of PTR-PA according to various contemporary definitions of exposure duration. We are aware of only one other paper that compares different thresholds of antecedent antibiotic exposure and the risk of antimicrobial resistance (5). This study demonstrated that exposure thresholds of greater intensity resulted in a stronger association between antimicrobial exposure and risk of antibiotic-resistant *Pseudomonas aeruginosa*.

In this analysis, prior exposure to PT was consistently associated with PTR-PA at each time threshold evaluated. The risk of PTR-PA associated with prior use of aminoglycosides, carbapenems, and fluoroquinolones fluctuated per time threshold, and the strength of association became more pronounced in the bivariate analyses as the duration of prior exposure increased. Interestingly, our CART-derived breakpoints captured the greatest number of antibiotics associated with PTR-PA in both the bivariate and the multivariate analyses. In addition, the ability to discriminate between PTR-PA and PT-susceptible *Pseudomonas aeruginosa* isolates increased as the prior exposure definition reached the CART breakpoints. Carbapenems had the shortest duration of prior antibiotic exposure associated with PTR-PA (3 days), followed by fluoroquinolones (4 days). The longest duration was noted for cefepime (9 days) and PT (11 days). These findings suggest that there may be differences in the duration of prior antibiotic exposure associated with selection of resistance for different antibiotic classes. However, further study is needed to elucidate this before definitive conclusions can be drawn.

An additional feature of our analysis is examination of the

TABLE 3. Results of the Poisson regression analyses of the cumulative number of prior antibiotic exposures within each of the prior antibiotic exposure thresholds studied

Covariate	Result for cumulative no. of prior exposures		
	Prevalence ratio	95% Confidence interval	P value
≥24 h			
No. of prior exposures	1.26	1.20–1.50	<0.001
≥48 h			
No. of prior exposures	1.31	1.18–1.46	<0.001
≥72 h			
No. of prior exposures	1.36	1.22–1.50	<0.001
CART breakpoints			
No. of prior exposures	1.45	1.32–1.59	<0.001

association between PTR-PA and the number of cumulative prior drug exposures within each time threshold studied. We hypothesize that the specific antibiotic administered is not as important as the number of antibiotic exposures. This hypothesis was confirmed when the model was adjusted to replace individual antibiotics with the number of prior antibiotic exposures at each exposure threshold studied. We observed a linear relationship between the number of prior antibiotic exposures and PTR-PA, and the number of exposures was the only significant variable associated with PTR-PA at each time threshold examined.

A few limitations should be noted. First, the time thresholds and number of antecedent exposures that we found to be associated with PTR-PA were specific for *Pseudomonas aeruginosa* respiratory tract infections. The same relationship may not exist for other body sites where *Pseudomonas aeruginosa* may be recovered or for other pathogens. Second, prescribing practices and institutional antibiotic susceptibility patterns vary. In addition, formulary differences may exist and account for the results. For example, ceftazidime was not available for use during the study period. For this reason, the observed results may be unique to our institution.

In conclusion, our results indicate that individual antibiotics that are associated with PTR-PA at our institution differ depending on the definition of prior antibiotic exposure utilized. Furthermore, we demonstrated that multiple prior antibiotic exposures were more important and had a greater strength of association with PTR-PA than individual prior exposures. In light of the results, future studies should evaluate the association between the cumulative number of prior antibiotic exposures and antibiotic resistance when assessing variables most predictive of drug-resistant pathogens. Future studies should also evaluate individual antibiotic pharmacodynamic exposure profiles (e.g., area under the concentration-time curve, ratio of area under the concentration-time curve to MIC, peak concentration, trough concentration, time that the concentration exceeds the MIC, etc.) to differentiate the degree of prior exposure associated with antibiotic resistance.

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