

Outcomes of adult patients in the intensive care unit with *Pseudomonas aeruginosa* pneumonia who received an active anti-pseudomonal β -lactam: Does “S” equal success in the presence of resistance to other anti-pseudomonal β -lactams?

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Abstract

Study Objectives: The most commonly prescribed antibiotics for patients with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) due to *Pseudomonas aeruginosa* are the conventional anti-pseudomonal β -lactams (APBLs) (ie, ceftazidime, cefepime, meropenem, or piperacillin-tazobactam). Similar resistance mechanisms in *P. aeruginosa* affect the APBLs, and it is unclear if resistance to one APBL can affect the effectiveness of other APBLs. This exploratory, hypothesis-generating analysis evaluates the impact of APBL resistance among patients in the intensive care unit (ICU) with *P. aeruginosa* HABP/VABP who initially receive a microbiologically active APBL.

Design: A retrospective cohort [GJ1] [LT2] study.

Setting: Kaiser Permanente Southern California members (01/01/2011-12/31/2017).

Patients: The study included adult patients admitted to the ICU with a monomicrobial *P. aeruginosa* HABP/VABP who received a microbiologically active APBL within 2 days of index *P. aeruginosa* respiratory culture.

Intervention: Patients were stratified by presence of resistance to APBL on index *P. aeruginosa* (0 vs. ≥ 1 resistant APBL).

Measurements: Primary outcomes were 30-day mortality and discharge to home.

Main Results: Overall, 553 patients were included. Thirty-day mortality was 28%, and 32% of patients were discharged home. Eighty-eight patients (16%) had a *P. aeruginosa* HABP/VABP that was resistant to ≥ 1 APBL (other than active empiric treatment). Relative to patients with no APBL resistance, patients with resistance to ≥ 1 APBL had a higher 30-day mortality (adjusted odds ratio (aOR) [95% confidence interval (CI)]: 1.65 [1.02–2.66]) and were less likely to be discharged home (adjusted hazard ratio (aHR) [95% CI]: 0.50 [0.29–0.85]).

Conclusion: Further study is needed, but this exploratory analysis suggests that the full APBL susceptibility profile should be considered when selecting therapy for patients with *P. aeruginosa* HABP/VABP.

KEYWORDS

antibiotics, beta-lactams, epidemiology, outcomes, pseudomonas, resistance, treatment

1 | INTRODUCTION

Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) are two of the most common healthcare-associated infections and are most prevalent in intensive care units (ICUs).¹ Although a wide spectrum of bacterial pathogens can cause HABP/VABP, *Pseudomonas aeruginosa* is one of the most frequent causative pathogens.² In most cases, clinicians will treat a HABP/VABP due to *P. aeruginosa* with a conventional anti-pseudomonal β -lactam (APBL) (ie, ceftazidime, cefepime, meropenem, or piperacillin-tazobactam) whether one agent is susceptible, even whether it is resistant to one of the other APBLs.³⁻⁵ The most well-characterized mechanisms of resistance to APBL in *P. aeruginosa* include membrane porin alterations, upregulated efflux pumps, depression of *AmpC* β -lactamases, production of other β -lactamases, and penicillin-binding proteins mutations. Certain APBLs resistance mechanisms have a greater effect on some APBL relative to others (eg, OprD has a greater effect on imipenem relative to meropenem). However, the APBLs are substrates for most of these resistance mechanisms, resulting in less susceptible *P. aeruginosa* isolates, especially when multiple resistance mechanisms are expressed simultaneously.⁶⁻⁹ Although the overlapping resistance mechanisms to APBLs in *P. aeruginosa* are well-characterized,⁶⁻⁹ scant treatment outcomes data are available on the outcomes of patients who were treated with a “susceptible” conventional APBLs when the *P. aeruginosa* was resistant to other APBLs. Given this gap in the literature, this exploratory, hypothesis-screening study evaluated the effect of the presence or absence of APBL resistance on the outcomes of patients with HABP/VABP due to *P. aeruginosa* who initially received therapy with an APBL to which the *P. aeruginosa* was susceptible. The outcomes assessed in this study included in-hospital death or discharge to hospice, 30-day mortality post-index culture, and discharge to home versus non-home.

2 | METHODS

2.1 | Setting

Kaiser Permanente Southern California (KPSC) is an integrated healthcare organization with over 4.8 million members who are representative of the socioeconomic and racial/ethnic diversity of the area's population.¹⁰ KPSC uses electronic health records (EHRs) to integrate medical information including diagnostic, medication, and procedure codes, as well as laboratory results from outpatient, emergency department, and hospital settings. The study protocol was reviewed and approved by the KPSC institutional review board, which waived requirement for informed consent.

2.2 | Study design and population

We conducted a retrospective cohort study among adult (≥ 18 years) KPSC members who had a pneumonia diagnosis (Table S1) with admission and discharge dates from 01/01/2011 to 12/31/2017. Patients were required to have a positive monomicrobial respiratory or blood culture for *P. aeruginosa*, reside in an ICU at index *P. aeruginosa* culture collection, and receive a microbiologically active APBL (ie, ceftazidime, cefepime, meropenem, or piperacillin-tazobactam) within 2 days of index *P. aeruginosa* collection date. Microbiologically active was defined as receipt of a beta-lactam with a corresponding susceptibility test for that treatment documented as “susceptible.” Patients were also required to have drug benefit coverage and 6 months of continuous KPSC enrollment prior to the index date, allowing for 45-day enrollment gaps. We excluded the following patients: (1) those with a diagnosis of cystic fibrosis (ICD-9 codes 277.01, 277.02, 277.03, 277.09 and ICD-10 codes E84.0, E84.11, E84.19, E84.8, E84.9) at any point in their medical history, and (2) death within 2 days from the index *P. aeruginosa* culture collection. For patients with multiple *P. aeruginosa* HABP/VABP, only the first episode was included. Patients were stratified by presence of resistance to APBL (ceftazidime, cefepime, meropenem, or piperacillin-tazobactam) on index *P. aeruginosa* (0 vs. ≥ 1 resistant APBL). Intermediate and resistant were both considered non-susceptible and classified as resistant. During the second year of the study period, the Clinical Laboratory Standards Institute (CLSI) susceptibility breakpoints for *P. aeruginosa* were lowered for the carbapenems (4 mg/L to 2 mg/L) and piperacillin/tazobactam (64/4 mg/L to 16/4 mg/L), and the newly updated breakpoints were adopted at Kaiser immediately thereafter.¹¹

2.3 | Data elements

Demographics, clinical characteristics, comorbidities, antibiotic history, laboratory results, and microbiological data from EHR documentation of inpatient and outpatient care up to 6 months prior to index *P. aeruginosa* culture date were collected. Baseline demographic characteristics of interest included age at index culture date (18–64, 65+ years), sex (male, female), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other). We examined comorbidities and prior healthcare exposure (ie, hospitalization, ICU admission) in the 6 months prior to index *P. aeruginosa* culture date. Antibiotic exposures and prior *P. aeruginosa* clinical cultures were collected in the 30 days prior to index date. Characteristics of the index admission included as follows: source of infection (present at hospital admission- vs hospital-onset), transfer from a skilled nursing

facility (SNF), invasive devices and procedures (endotracheal tube, tracheostomy, gastric or jejunal feeding tube, indwelling urinary catheter, central venous or Port or peripherally inserted central catheter, and prior surgery), and length of stay (LOS) from admission to index culture date. The microbiologically active APBL(s) (ie, ceftazidime, cefepime, meropenem, or piperacillin-tazobactam) received within 2 days of index *P. aeruginosa* collection date were documented. Laboratory data (white blood cell count, estimated glomerular filtration rate) closest to index date (within -2 to +1 day) were also collected. A severity risk score (comorbidity point score version 2 [COPS2¹²]), which is a longitudinal score (assigned monthly to all members) based on 12 months of patient data and estimates mortality risk due to comorbid illness, was included. For this study, COPS2 scores were calculated for the 6 months prior to index date and grouped into quartiles.

2.4 | Outcomes

Outcomes of interest included (1) the composite outcome of in-hospital death or discharge to hospice, (2) 30-day mortality post-index culture, and (3) discharge to home versus non-home (ie, hospice, SNF, acute care facility).

2.5 | Statistical analyses

Descriptive statistics for patients by presence of resistance to APBL on index *P. aeruginosa* (0 vs. ≥ 1 resistant APBL) were performed. Continuous variables were evaluated via means with standard deviation or via median and interquartile range for non-normally distributed data using Student's *t*-test or the nonparametric Mann-Whitney *U*-test. Categorical data were summarized as number and percentage using chi-square test or Fisher's exact test. Quartiles were used as cutoff points to categorize continuous variables (eg, COPS2 and laboratory values) with non-normally distributed data. Kaplan-Meier survival curves were used to visually present the time to discharge home by APBL-resistance status.

Multivariable logistic regression models with inverse probability of treatment weighting (IPTW) were used to evaluate the association between presence of APBL resistance and the composite outcome of in-hospital death/discharge to hospice and 30-day mortality post-index culture. To evaluate the association of APBL resistance and discharge to home, we developed an IPTW Cox proportional hazard regression model, with post-index LOS as the time variable. Odds ratios (OR) or hazard ratios (HR) and 95% confidence intervals (CI) were calculated from the logistic regression and Cox proportional hazards regression, respectively.

For each multivariate regression analysis, IPTW was used to obtain a balanced distribution of characteristics between treated and untreated subjects. The probability of exposure (propensity score) was estimated for each patient using a multivariable logistic regression model, in which resistance status (0 vs. ≥ 1 resistant APBL) was

regressed on observed baseline characteristics. We included baseline covariates in the propensity score model if they were associated with presence of APBL resistance, associated with the outcomes of interest, or based on prior knowledge. Variables included age, sex, race/ethnicity, invasive devices and procedure (endotracheal tube, tracheostomy, gastric or jejunal feeding tube, indwelling urinary catheter, central venous or Port or peripherally inserted central catheter, and prior surgery), source of infection, transfer from SNF, prior 6-month healthcare exposure (hospitalization, ICU admission), exposure to *Pseudomonas* 30 days prior to index culture, LOS from admission to index culture, selected comorbidity (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, diabetes with complications, cancer, and other immune condition), COPS2, prior 30-day antibiotic use, prior use of antibiotics with *P. aeruginosa* activity, and laboratory data (white blood cell count, estimated glomerular filtration rate) closest to index date (within -2 to +1 day).

Second, the weight for each subject was calculated as the inverse of the predicted probability of APBL resistance. The weight was then normalized by dividing the mean weight of each exposure group to avoid extreme large values and resize the weighted population to the original sample size for each group. The variables in the model were assessed for collinearity and were maintained whether the variance inflation factor was < 2.5 , or correlation coefficient was < 0.5 . When two or more variables were found to be collinear, the one with the highest magnitude estimate and/or the most clinically important variable was selected. Standardized difference scores were used to assess whether balance of covariates was achieved between the comparison groups. Standardized difference measurement is a unified approach to quantify the magnitude of difference between groups regardless of sample size, where an absolute value < 0.1 is considered a negligible difference, and < 0.2 is considered adequate balance. For the final IPTW model, the positivity assumption that all subjects have a non-zero probability of receiving each treatment was assessed using the mean, standard deviation, minimum, and maximum of the stabilized weights.

Lastly, the variables that were not fully balanced in the IPTW were tested as independent variables in the final IPTW multivariate models, and variables were included whether their inclusion resulted in a $\geq 10\%$ change in the main exposure estimate. As an additional measure to assess for confounding on the relative scale, a series of stratified analyses based on receipt of combination therapy with aminoglycosides or fluoroquinolones, COPS2 score (> 138 vs. ≤ 138), and pre- and post-implementation of breakpoint changes (2011–2012 vs. 2013–2017) were performed. We used SAS 9.4/SAS Enterprise Guide 7.15 (SAS Institute Inc.) for all analyses.

3 | RESULTS

Following application of age, KPSC membership, and drug benefit criteria, the sample included 12,148 patients (Figure S1). Removal of patients with cystic fibrosis and applying the initial HABP/VABP

TABLE 1 Baseline characteristics by presence of anti-pseudomonal β-lactam (APBL) resistance

	Beta lactam classes			p-Value
	No resistance (n = 465)	Resistance (n = 88)	Total (n = 553)	
Demographics				
Sex				
Female	193 (41.51%)	33 (37.50%)	226 (40.87%)	0.483
Male	272 (58.49%)	55 (62.50%)	327 (59.13%)	
Age on the laboratory collection date, year				
18–64	131 (28.17%)	23 (26.14%)	154 (27.85%)	0.696
65+	334 (71.83%)	65 (73.86%)	399 (72.15%)	
Race/Ethnicity				
Non-Hispanic White (ref)	216 (46.45%)	44 (50.00%)	260 (47.02%)	0.519
Non-Hispanic Black	84 (18.06%)	15 (17.05%)	99 (17.90%)	
Hispanic	109 (23.44%)	23 (26.14%)	132 (23.87%)	
Other	56 (12.04%)	6 (6.82%)	62 (11.21%)	
Index Admission				
Source of infection (culture date ≤48 h of admission)				
Hospital-onset	225 (48.39%)	41 (46.59%)	266 (48.10%)	0.757
Present at hospital admission	240 (51.61%)	47 (53.41%)	287 (51.90%)	
Skilled nursing or long-term care facility transfer	34 (7.31%)	9 (10.23%)	43 (7.78%)	0.349
Invasive devices and procedures (admission to culture date)				
Endotracheal Tube	225 (48.39%)	43 (48.86%)	268 (48.46%)	0.935
Tracheostomy	109 (23.44%)	35 (39.77%)	144 (26.04%)	0.001
Gastric or jejunal feeding tube	186 (40.00%)	45 (51.14%)	231 (41.77%)	0.052
Indwelling urinary catheter	341 (73.33%)	67 (76.14%)	408 (73.78%)	0.584
CVC or Port or PICC	163 (35.05%)	36 (40.91%)	199 (35.99%)	0.294
Surgery prior to index date	69 (14.84%)	14 (15.91%)	83 (15.01%)	0.797
LOS from admission to index culture, days				
1–3	261 (56.13%)	49 (55.68%)	310 (56.06%)	0.501
4–10	120 (25.81%)	19 (21.59%)	139 (25.14%)	
11+	84 (18.06%)	20 (22.73%)	104 (18.81%)	
Hospitalization in 6 months prior to index date				
No	172 (36.99%)	18 (20.45%)	190 (34.36%)	0.003
Yes	293 (63.01%)	70 (79.55%)	363 (65.64%)	
ICU admission in 6 months prior to index date				
No	307 (66.02%)	47 (53.41%)	354 (64.01%)	0.024
Yes	158 (33.98%)	41 (46.59%)	199 (35.99%)	
Exposure to Pseudomonas 30 days prior to index culture				
No Prior Pseudomonas	413 (88.82%)	72 (81.82%)	485 (87.7%)	0.183
Carbapenem-Susceptible Pseudomonas	40 (8.60%)	12 (13.64%)	52 (9.40%)	
Carbapenem-Resistant Pseudomonas	12 (2.58%)	4 (4.55%)	16 (2.89%)	
Comorbidities documented 6 months prior to index date				
Myocardial infarction	89 (19.14%)	15 (17.05%)	104 (18.81%)	0.645
Congestive heart failure	167 (35.91%)	37 (42.05%)	204 (36.89%)	0.274
Peripheral vascular disease	254 (54.62%)	56 (63.64%)	310 (56.06%)	0.118
Cerebrovascular disease	117 (25.16%)	28 (31.82%)	145 (26.22%)	0.193

(Continues)

TABLE 1 (Continued)

	Beta lactam classes			p-Value
	No resistance (n = 465)	Resistance (n = 88)	Total (n = 553)	
Chronic pulmonary disease	234 (50.32%)	47 (53.41%)	281 (50.81%)	0.595
Diabetes with complications	126 (27.10%)	24 (27.27%)	150 (27.12%)	0.973
Cancer	86 (18.49%)	14 (15.91%)	100 (18.08%)	0.563
Other immune condition	83 (17.85%)	30 (34.09%)	113 (20.43%)	0.001
Severity risk score (COPS2; 6 months prior to index date), quartile				
≤90	122 (26.24%)	17 (19.32%)	139 (25.14%)	0.003
91-137	126 (27.10%)	15 (17.05%)	141 (25.50%)	
138-174	116 (24.95%)	21 (23.86%)	137 (24.77%)	
>174	101 (21.72%)	35 (39.77%)	136 (24.59%)	
Prior 30-day antibiotic use				
No	33 (7.10%)	10 (11.36%)	43 (7.78%)	0.171
Yes	432 (92.90%)	78 (88.64%)	510 (92.22%)	
Prior 30-day antibiotics with <i>P. aeruginosa</i> activity				
No	159 (34.19%)	20 (22.73%)	179 (32.37%)	0.035
Yes	306 (65.81%)	68 (77.27%)	374 (67.63%)	
Laboratories closest to index culture (-2 to +1 days from index date)				
WBC, quartile				
≤8.8	123 (26.45%)	16 (18.18%)	139 (25.14%)	0.204
8.9-12.4	123 (26.45%)	20 (22.73%)	143 (25.86%)	
12.5-16.6	108 (23.23%)	26 (29.55%)	134 (24.23%)	
>16.6	111 (23.87%)	26 (29.55%)	137 (24.77%)	
eGFR, quartile ^a				
≤36	116 (24.95%)	23 (26.44%)	139 (25.18%)	0.691
37-71	120 (25.81%)	18 (20.69%)	138 (25.00%)	
72-90	215 (46.24%)	42 (48.28%)	257 (46.56%)	
>90	14 (3.01%)	4 (4.60%)	18 (3.26%)	

Note: Values are presented as no. (%), or indicated in the table.

Abbreviations: COPS2, comorbidity point score version 2; CVC, central venous catheter; eGFR, estimated glomerular filtration rate; PICC, peripherally inserted central catheter; WBC, white blood cell.

^aOne patient missing eGFR value.

criteria further reduced the study sample by 403 and 7970 patients, respectively, to 3775 patients. Next, the population was restricted to patients with a monomicrobial *P. aeruginosa* respiratory or blood culture who resided in the ICU at index *P. aeruginosa* culture collection, survived ≥2 days following index date, and received a microbiologically active APBL (including ceftazidime, cefepime, meropenem, or piperacillin-tazobactam). This resulted in a final sample size of 553 patients.

Overall, the mean (standard deviation) age was 70.5 (14.3) years, 59% were male, and most had many comorbidities. Thirty-day mortality was 28%, 30% of patients died in the hospital or were discharged to hospice, and 32% were discharged home. Of the 553 patients who received a microbiologically active APBL, we observed that 16% (n = 88) of patients were resistant to at least one APBL class (1 (n = 56) or 2 (n = 32) resistant APBL classes). Sputum and endotracheal aspirates were the most common sources of respiratory cultures in each

APBL-resistant class classification (Table S2). The microbiologically active APBL(s) (ie, ceftazidime, cefepime, meropenem, or piperacillin-tazobactam) received within 2 days of index *P. aeruginosa* collection date was cefepime, ceftazidime, piperacillin/tazobactam, and meropenem in 19.0%, 38.9%, 37.8%, and 12.3% of patients, respectively (Table S3). Twenty-nine patients received >1 microbiologically active APBL. Compared with patients without APBL resistance, those with APBL resistance were more likely to have invasive devices between admission and index culture date, been hospitalized or admitted to the ICU in the 6 months prior to index date, have a higher COPS2, and have received prior antibiotics with *P. aeruginosa* activity prior to index date (Table 1).

Results of the unadjusted and adjusted multivariate analyses are shown in Table 2. In the bivariate analyses, numerical differences in 30-day mortality (33.0% vs. 26.7%, respectively, p-value = 0.23), in-hospital mortality/discharge to hospice (35.2% vs. 29.3%,

TABLE 2 Crude and adjusted associations between presence of anti-pseudomonal β-lactam (APBL) resistance (reference = no APBL resistance) and outcomes

	No resistance (n = 465)	≥1 APBL resistant (n = 88)	Crude OR (95% CI) ^a	Adjusted OR (95% CI), IPTW ^b
In-hospital death or discharged to hospice	136 (29.3%)	31 (35.2%)	1.32 (0.81–2.13)	1.42 (0.89–2.29)
30-day mortality	124 (26.7%)	29 (33.0%)	1.35 (0.83–2.21)	1.65 (1.02–2.66)
			Crude HR (95% CI) ^c	Adjusted HR (95% CI), IPTW ^d
Discharged home ^e	162 (34.8%)	15 (17.1%)	0.44 (0.25–0.75)	0.50 (0.29–0.85)

Abbreviations: CI, confidence interval; COPS2, comorbidity point score version 2; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IPTW, inverse probability treatment weighting; LOS, length of stay; OR, odds ratio; SNF, skilled nursing facility; WBC, white blood cell.

^aOR (95% CI) calculated by logistic regression.

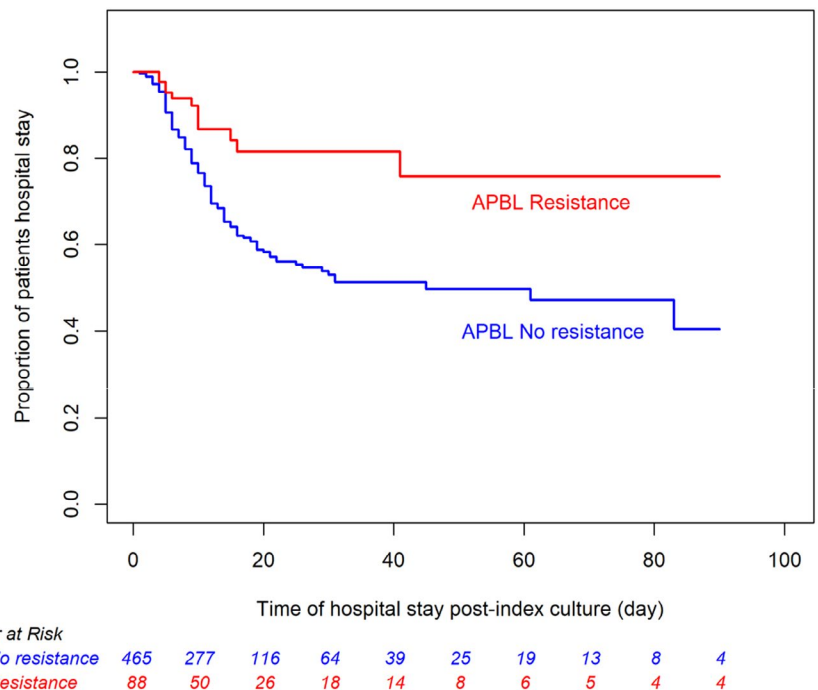
^bOR (95% CI) calculated by logistic regression with IPTW, adjusting for age, sex, race/ethnicity, infection source, SNF transfer, invasive devices and procedures, exposure to Pseudomonas 30 days prior to index culture, prior 6-month healthcare exposure (hospitalization, ICU admission), LOS from admission to index culture, select comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, diabetes with complications, cancer, and other immune condition), COPS2, prior 30-day antibiotics, prior use of antibiotics with *P. aeruginosa* activity, WBC, eGFR.

^cHR (95% CI) calculated using proportional hazard Cox regression.

^dHR (95% CI) calculated using proportional hazard Cox regression with IPTW, adjusting for age, sex, race/ethnicity, infection source, SNF transfer, invasive devices and procedures, exposure to Pseudomonas 30 days prior to index culture, prior 6-month healthcare exposure (hospitalization, ICU admission), LOS from admission to index culture, select comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, diabetes with complications, cancer, and other immune condition), COPS2, prior 30-day antibiotic use, prior use of antibiotics with *P. aeruginosa* activity, WBC, eGFR.

^eReference = Discharged to other including in-hospital death.

FIGURE 1 Kaplan–Meier curve demonstrating time to discharge to home by presence of anti-Pseudomonal β-lactam (APBL) resistance



respectively, *p*-value = 0.26), and discharged to home (17.1% vs. 34.8%, respectively, *p*-value < 0.01) were noted between patients with resistance to ≥1 APBL relative to patients with no APBL resistance. Results of Kaplan–Meier analyses for time to discharge home by APBL resistance status are shown in Figure 1. Results of the IPTW are shown in Figure 2. Following IPTW, the standardized difference for all variables between the two groups was ≤0.2, which

was considered to be balanced with the exception of COP2 (0.22). The mean of the stabilized weights was not far from one, and there were no very extreme values, which was indicative of positivity and that the propensity score model was not mis-specified. In the multivariate analyses with IPTW (Table 2) and baseline covariates that were not fully balanced in the propensity score modeling and resulted in a ≥10% change in the main exposure estimates, patients

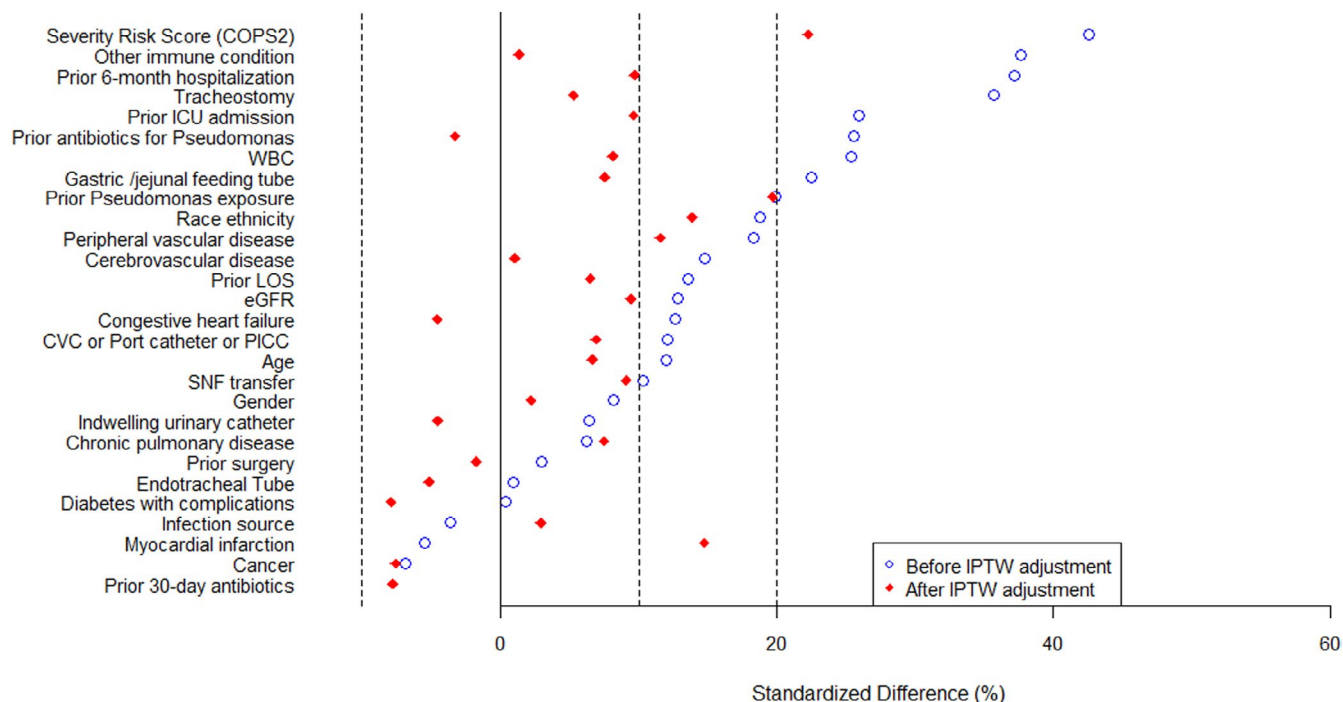


FIGURE 2 Comparison of standardized differences before and after inverse probability of treatment weighting (IPTW). COPS2, comorbidity point score version 2; CVC, central venous catheter; eGFR, estimated glomerular filtration rate; LOS, length of stay; PICC, peripherally inserted central catheter; SNF, skilled nursing facility; WBC, white blood cell

with resistance to ≥ 1 APBL had (1) higher adjusted odds of 30-day mortality (Aor [95% CI]: 1.65 [1.02–2.66]), (2) higher adjusted odds of in-hospital mortality/discharge to hospice (Aor [95% CI]: 1.42 [0.89–2.29]), and (3) lower risk of being discharged to home (Ahr [95% CI]: 0.50 [0.29–0.85]). Results of the exposure-outcome analyses stratified by receipt of combination therapy (fluoroquinolones or aminoglycosides, COPS >138 vs. ≤ 138 , and pre- vs. post-implementation of CLSI breakpoint changes) are shown in Figure 3. The results of the stratified analyses were largely consistent with the overall findings. Caution should be exercised in interpreting the results of the stratified analyses given the small sample size of resulting stratum.

4 | DISCUSSION

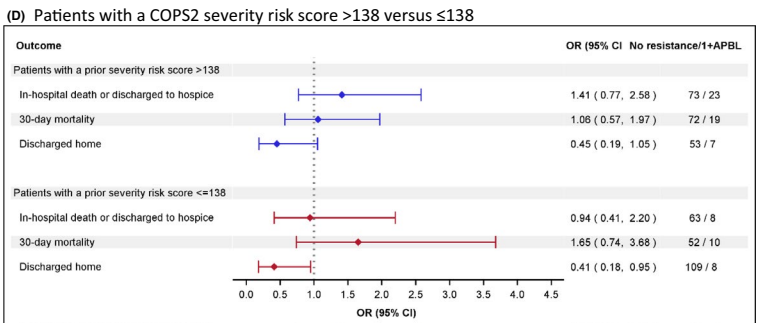
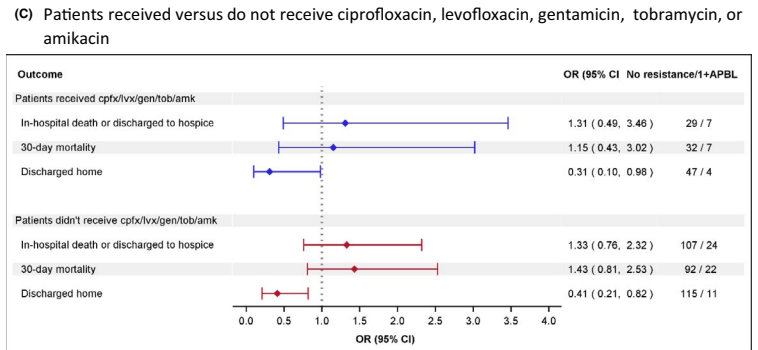
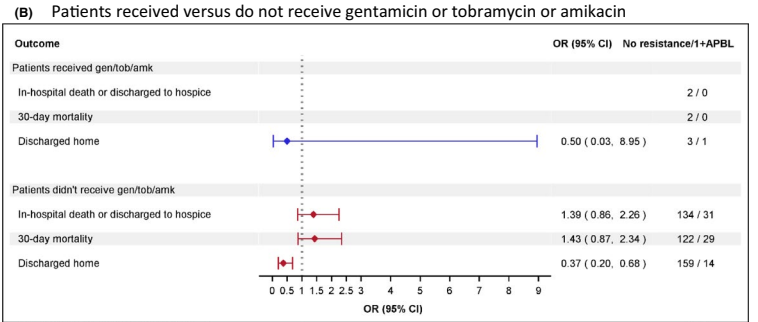
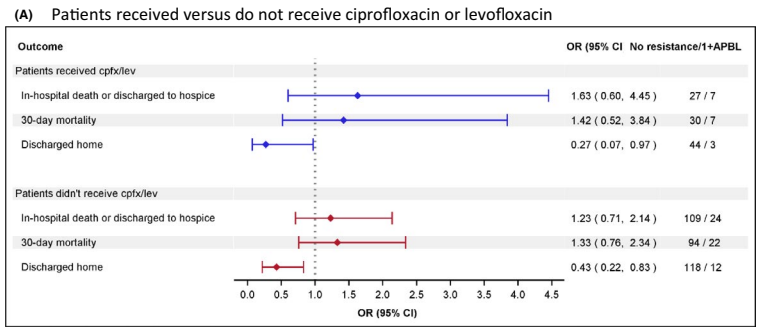
Optimal treatment for patients in the ICU with HABP/VABP due to *P. aeruginosa* remains undefined. There are limited comparator clinical data to define best practices for patients with HABP/VABP due to *P. aeruginosa* and treatment decisions are largely driven by local epidemiology and patient-specific risk factors.^{2,3,5,6} Most often, clinicians will use a conventional APBL to treat patients with HABP/VABP due to *P. aeruginosa* if one is listed as susceptible on culture and susceptibility report,^{3–5} regardless of the presence of resistance to other agents, including other APBLs. Although this is consistent with best antimicrobial stewardship practices, it is estimated that ~15%–20% of all *P. aeruginosa* are susceptible to one of the conventional APBL but are resistant to ≥ 1 other APBLs.^{13–15} Given the overlapping resistance mechanisms in APBL,^{7–9} we conducted this

exploratory, hypothesis-generating study to assess whether clinicians should consider the full APBL susceptibility profile when selecting therapy for patients with HABP/VABP due to *P. aeruginosa*.

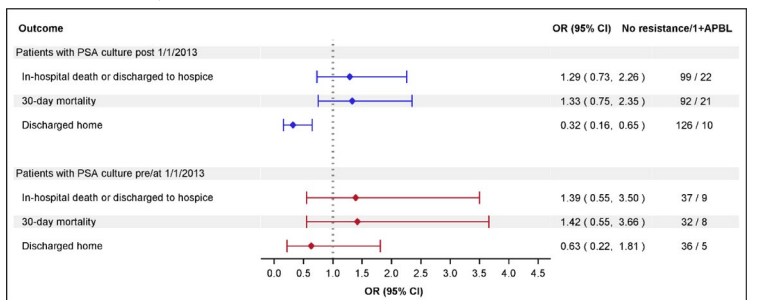
Despite receiving a microbiologically active APBL within 2 days of their *P. aeruginosa* HABP/VABP, patients with *P. aeruginosa* that were resistant to ≥ 1 APBL had worse outcomes relative to those that had no APBL resistance. There was an increased risk of 30-day mortality and an elevated—albeit non-significant—risk estimate for the composite endpoint of in-hospital mortality/discharge to hospice for those with resistance. We believe these are notable findings as a substantial benefit or deleterious effect with a given treatment is needed to reflect a difference in death among adult, hospitalized patients with HABP/VABP due to *P. aeruginosa*.¹⁶ Furthermore, the mortality outcomes assessed in this study align with the all-cause mortality primary end point used by the US Food and Drug Administration in non-inferiority studies of antibacterial agents for HABP/VABP.¹⁷ The presence of resistance to ≥ 1 APBL also resulted in a lower likelihood of being discharged home and a higher probability of continuing care at another healthcare facility. This is also a clinically important finding as it is a surrogate of a patient's functional status and continued healthcare requirements at the time of hospital discharge.¹⁸ Further study is clearly needed, but this exploratory study suggest that the full APBL susceptibility profile should be potentially considered when selecting therapy for patients with HABP/VABP due to *P. aeruginosa*.

Extreme caution needs to be exercised when interpreting the results. It is well established that patients with more resistant infections tend to be sicker and have a worse prognosis independent of the treatment received. Although study design restrictions, stratified analyses,

FIGURE 3 Association between Presence of Anti-Pseudomonal β -lactam (APBL) resistance and Outcomes Stratified by (A-C) Combination Therapy with Aminoglycosides or Fluoroquinolones, (D) Comorbidity Point Score Version 2 (COPS2) score (>138 vs. ≤ 138), and (E) Pre- and Post-Implementation of Clinical Laboratory Standards Institute (CLSI) Susceptibility Breakpoint Changes (2011–2012 vs. 2013–2017). (A) Patients received versus do not receive ciprofloxacin or levofloxacin. (B) Patients received versus do not receive gentamicin or tobramycin or amikacin. (C) Patients received versus do not receive ciprofloxacin, levofloxacin, gentamicin, tobramycin, or amikacin. (D) Patients with a COPS2 severity risk score >138 versus ≤ 138 . (E) Pre- and post-implementation of CLSI *Pseudomonas aeruginosa* breakpoint changes (2011–2012 vs. 2013–2017). APBL, Anti-Pseudomonal β -lactam; CI, confidence interval; CLSI, Clinical Laboratory Standards Institute; COPS2, comorbidity point score version 2; OR, odds ratio



(E) Pre- and post-implementation of CLSI *Pseudomonas aeruginosa* breakpoint changes (2011–2012 versus 2013–2017)



and multivariate regression with IPTW were used to minimize the influence of potential systematic errors, the observed differences in outcomes may have been, in part, a function of unmeasured baseline differences versus presence of resistance to ≥ 1 APBLs. While the contribution of systematic biases needs to be considered, the findings are biologically plausible. Although genomics data on the *P. aeruginosa* isolates were not available to determine the resistance mechanisms expressed, resistance to ≥ 1 APBLs indicates, in most cases, that efflux pump(s) are upregulated, porin(s) are downregulated or deleted, and/or class C AmpC β -lactamases are hyperproduced. All of these mechanisms affect the conventional APBLs included in this analysis with few exceptions, and the extent of their expression determines the degree of resistance to each of the conventional APBLs.³⁻⁵ It is important to note that susceptibility testing is performed at an inoculum size of 1×10^5 to 5×10^5 colony forming units (cfu)/ml^{11,19} and data indicate that the bacterial burden in patients with VABP is $7.5 \log_{10}$ cfu/ml.^{3,20} Due to the sizeable differences in inoculum sizes, the resistance mechanisms are likely to be expressed to a greater extent in the epithelial lining fluid of the lung versus that observed in susceptibility testing, and this augmented expression of resistance could compromise the activity of APBL reported to be susceptible.²¹ Furthermore, the antibiotic concentrations achieved in the epithelial lining fluid of the lung are only a fraction of what is observed in the bloodstream,^{22,23} and this lower exposure profile could compromise the activity of APBL reported to be susceptible in HABP/VABP patients when a common APBL resistance mechanism is expressed.

Several limitations should be noted when interpreting the findings of this study. First, this study is subject to the limitation inherent to the retrospective cohort study design, including study selection bias, confounding, and confounding by indication. Study design restrictions, stratified analyses, and multivariate regression with IPTW were used to minimize the influence of these potential systematic biases.²⁴ However, it is well established that these techniques will not fully account for unmeasured differences between groups. As stated above, this is a key consideration in this study as patients with more resistant infections tend to be sicker and have a worse prognosis independent of the treatment received. Therefore, the results may have been due, in part, to unmeasured baseline differences versus presence of resistance to ≥ 1 APBLs. We also purposefully limited the definition of failure to include only objective measures to minimize any subjective biases that may result from assessing and interpreting observational clinical data.²⁵

This was a study of adult, ICU patients with monomicrobial *P. aeruginosa* HABP/VABP. We required all patients to receive an active agent within 2 days of *P. aeruginosa* index respiratory culture to minimize biases introduced by varying times of receipt of an active agent across resistance groups.²⁶ We selected this restricted population to maximize internal validity and minimize potential biases introduced by delays in therapy and polymicrobial infections. As such, it is unknown whether the observed findings are applicable to other populations, including those with polymicrobial HABP/VABP and other infection sites. We relied on diagnosis codes, microbiologic culture, and treatment data to define HABP/VABP due to *P. aeruginosa*. Reliance on these data to define HABP/VABP due to *P. aeruginosa* may have

resulted in missed cases of HABP/VABP during the study period as pneumonia is often under-coded in hospitalized ICU patients.²⁷⁻²⁹

Consistent with the treatment practices at most US healthcare institutions,³⁻⁵ the active APBL received in $>90\%$ of patients was either cefepime, ceftazidime, or piperacillin/tazobactam. Although this speaks to the generalizability of the findings, there were too few patients in each resultant APBL resistance groups (Table S3) to consider the active APBL received or the adequacy of its dosing in the analyses. Minimum inhibitory concentration (MIC) data for the APBLs were not available. Susceptibility breakpoints for carbapenems and piperacillin/tazobactam were lowered during the second year of the study period (2012), and these revised breakpoints were adopted at Kaiser immediately thereafter.¹¹ This may have resulted in some non-susceptible cases being classified as susceptible. However, we expect this impact to be minimal as it involved only isolates in the first two years of the study, and the results were numerically similar in 2011-2012 versus 2013-2017. Any misclassification of resistant cases as susceptible would have biased the results toward the null, and thus, our results should be viewed in a conservative fashion. We were unable to assess whether any of the newly approved antibiotics with enhanced *P. aeruginosa* microbiologic activity were associated with improved outcomes relative to the conventional APBLs as very few patients (<5) who received one of the newer agents during the study period met the study criteria. The goal of this exploratory study was to simply evaluate whether the presence of APBL resistance modified the outcomes of patients with *P. aeruginosa* HABP/VABP who received an active APBL. Future treatment outcomes studies of patients with *P. aeruginosa* HABP/VABP should include pharmacokinetic/pharmacokinetic assessments to determine whether the APBL selected, its MIC value, and dosing modified the outcomes observed in this analysis.

In conclusion, the current treatment paradigm for *P. aeruginosa* HABP/VABP is to ensure the patients to receive a microbiologically active APBL early in the course of therapy.^{2,3,5,6} Currently, most clinicians will treat with an APBL whether at least one is susceptible, without consideration of the susceptibilities of other APBLs. However, similar resistance mechanisms in *P. aeruginosa* affect the conventional APBLs,⁷⁻⁹ and the results of this exploratory study suggest that patients with *P. aeruginosa* who received an active APBL had worse outcomes whether the *P. aeruginosa* respiratory isolate was resistant to ≥ 1 APBL versus no resistant APBLs. Although extreme caution should be exercised when interpreting the findings as they may be due, in part, to unmeasured baseline differences versus presence of resistance to ≥ 1 APBLs, the results suggest that the full APBL susceptibility profile should be potentially considered when selecting therapy for patients with HABP/VABP due to *P. aeruginosa*. More importantly, this study highlights the critical need to determine whether more intensive APBL dosing, combination therapy, or newer agents with anti-pseudomonal activity are needed to maximize the outcomes of patients with HABP/VABP due to *P. aeruginosa* when there is resistance ≥ 1 APBLs.

CONFLICT OF INTEREST

TPL reports the following disclosures: Merck & Co: consultant, grant recipient, and scientific advisor. Shionogi: consultant, scientific advisor,

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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