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MAJOR ARTICLE

Quantifying Gram-Negative Resistance to Empiric Treatment After Repeat ExpoSure To AntimicRobial Therapy (RESTART)

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Background. Antibiotic exposure is a primary predictor of subsequent antibiotic resistance; however, development of cross-resistance between antibiotic classes is also observed. The impact of changing to a different antibiotic from that of previous exposure is not established.

Methods. This was a retrospective, single-center cohort study of hospitalized adult patients previously exposed to an antipseudomonal β-lactam (APBL) for at least 48 hours in the 90 days prior to the index infection with a gram-negative bloodstream or respiratory infection. Susceptibility rates to empiric therapy were compared between patients receiving the same (repeat group) versus a different antibiotic from prior exposure (change group).

Results. A total of 197 patients were included (n = 94 [repeat group] and n = 103 [change group]). Pathogen susceptibility to empiric therapy was higher in the repeat group compared to the change group (76.6% vs 60.2%; $P = .014$). After multivariable logistic regression, repeat APBL was associated with an increased likelihood of pathogen susceptibility (adjusted odds ratio, 2.513; $P = .012$). In contrast, there was no difference in susceptibility rates between the repeat group and the subgroup of change patients who received an empiric APBL (76.6% vs 78.5%; $P = .900$). Longer APBL exposure duration ($P = .012$) and chronic kidney disease ($P = .002$) were associated with higher nonsusceptibility to the exposure APBL. In-hospital mortality was not significantly different between the repeat and change groups (18.1% vs 23.3%; $P = .368$).

Conclusions. The common practice of changing to a different APBL from that of recent exposure may not be warranted.

Keywords. antimicrobial stewardship; bloodstream infection; cefepime; gram-negative infection; gram-negative resistance; meropenem; piperacillin-tazobactam; pneumonia.

Antimicrobials are among the most commonly prescribed drugs; however, approximately 50% of antimicrobial utilization is inappropriate [1, 2]. Misuse has contributed to an antimicrobial resistance global health emergency estimated to be responsible for 700 000 deaths per year worldwide [3].

Increasing resistance to commonly utilized antibiotics has devastating effects. For example, infections due to multidrug-resistant pathogens are associated with worse clinical outcomes compared to those caused by more susceptible pathogens [4]. Moreover, inadequate early therapy is associated with increased mortality for severe gram-negative infections [5–11]. In cases of severe illness caused by a presumed bacterial infection, many clinicians rely on broad-spectrum antibiotics to cover the majority of likely pathogens. Frequently, patients are treated with broad-spectrum antibiotics although there appears to be a substantial difference between perceived risk and actual detection of resistant pathogens [12, 13]. Additionally, this practice perpetuates the cycle of resistance as broader antibiotics are utilized to combat growing resistance, subsequently contributing to further increasing resistance. A balance between optimizing empiric therapy to improve clinical outcomes without "overtreating" large populations is needed.

Previous antibiotic exposure is consistently recognized as a primary predictor of subsequent antibiotic-resistant pathogen colonization and/or infections [1, 3, 10, 11, 14, 15]. Exposure to an antibiotic class increases the likelihood of resistance to that same class; however, development of cross-resistance to other classes is also observed and adds complexity to optimizing empiric antibiotic decision making [16, 17]. Guidance for empiric treatment of resistant gram-negative infections suggests considering antibiotic exposure in the past 30 days with endorsement of a gram-negative agent from a different class

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that offers a comparable spectrum of activity to that of the previous exposure [18]. The Infectious Diseases Society of America guidelines for pneumonia do not specify using the same versus a different agent as the empiric treatment choice in instances of previous exposure to an antipseudomonal agent [19, 20]. Although it is clear that antibiotic exposure increases the likelihood of infection with a subsequent resistant pathogen, it is not clear whether changing to another antibiotic will improve susceptibility rates or clinical outcomes. We sought to determine whether empiric therapy with the same antipseudomonal β-lactam (APBL) versus a different APBL or other antibiotic from prior exposure impacts the likelihood of susceptibility in serious gram-negative infections.

METHODS

Setting and Participants

This retrospective, single-center cohort study was conducted at Methodist Dallas Medical Center, a 580-bed urban community teaching hospital. All hospitalized adult (≥18 years) patients with a gram-negative pathogen identified on blood and/or respiratory cultures (index infection) between 1 April 2017 and 31 March 2022 were eligible for inclusion. To be included, patients additionally needed to have been treated with a study APBL (cefepime, piperacillin-tazobactam, or meropenem) for at least 48 hours in the 90 days prior to the index infection. Patients were excluded if they had a history of a bacterial isolate resistant to any of the study APBLs in the previous 6 months, any antibiotic exposure within 5 days of the index infection, or previous exposure to >1 APBL (Figure 1). Antibiotic exposure and resistant bacterial pathogens were determined for any hospitalization occurring within the 6 hospitals of Methodist Health System. Data were collected from the hospital's electronic medical record (EMR) with a query that included age, sex, hospital length of stay (LOS), intensive care unit (ICU) LOS, Charlson Comorbidity Index score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score (using the worst physiological parameters within 24 hours of index infection), microbiology laboratory results (pathogen identification, specimen type and source), and antibiotic exposures. Manual chart review was performed to collect data on the infection source (for bacteremia), pathogen susceptibility testing results, and timing/duration of prior antibiotic exposure. Source of infection was determined based on concomitant positivity of blood cultures with other sterile cultures (eg, cerebrospinal fluid, tissue, or urinary) plus the descriptive diagnosis documented in the EMR. When these criteria were not met, an "unknown source of infection" was assigned.

The primary outcome of this study included rates of susceptibility in patients receiving empiric therapy with the same APBL from prior exposure (repeat group) compared to rates of susceptibility in patients receiving an antibiotic different from the prior exposure (change group). A priori subgroup comparisons were planned between groups with pathogens "susceptible" compared to "nonsusceptible" to the initial exposure APBL and between groups stratified by the initial APBL received. Post hoc analysis of the subgroup of patients that received an APBL as treatment in the change group was also conducted. Secondary outcomes included ICU LOS, hospital LOS, and in-hospital all-cause mortality.

Microbiology Methods

Pathogen identification and antimicrobial susceptibility testing was standardized and was determined using a MicroScan Walkaway system (Beckman Coulter) until June 2021 when matrix-assisted laser desorption/ionization–time of flight began being utilized for pathogen identification. The minimum inhibitory concentration (MIC) breakpoints and interpretative criteria utilized were up to date and concordant with the Clinical and Laboratory Standards Institute M100 document (Supplementary Table 1). All classifications of antibiotic susceptibility were based on in vitro susceptibility testing using these established breakpoints. The presence of an extended-spectrum β-lactamase (ESBL) was determined by testing ceftazidime and cefotaxime with and without the presence of clavulanate. A ≥3 2-fold concentration decrease in and MIC for either agent in combination with clavulanate versus the MIC of the agent alone was considered to confirm the presence of an ESBL. Additionally, any isolates testing intermediate to a study antibiotic were classified as nonsusceptible for analyses purposes.

Statistical Methods

The sample size was based off the primary outcome (ie, rates of susceptibility) and assumed that the use of the same empiric antibiotic from previous exposure led to a 30% incidence of nonsusceptibility and the use of a different empiric antibiotic from previous exposure led to a 13% incidence of nonsusceptibility for gram-negative pathogens identified [11]. A sample size of 180 (90 patients in each arm) was estimated to meet 80% power and the study timeframe was established to capture the necessary cohort based on incidence rates of gram-negative infections at our hospital. Descriptive analysis was performed for all continuous variables. Mean and standard deviation were presented for normally distributed data and median and interquartile range (IQR) were presented for nonparametric data. Count and proportions are presented for all categorical variables. Categorical data were analyzed using Pearson χ^2 or Fisher exact test where appropriate, and continuous data were analyzed using Student t test where appropriate. Risk factors for nonsusceptibility to the treatment antibiotic and to the exposure APBL were evaluated utilizing both univariate and multivariable analyses. Repeat APBL exposure, along with all variables associated with the outcome of interest at a P value <.2 on bivariate analyses and biologic plausibility,

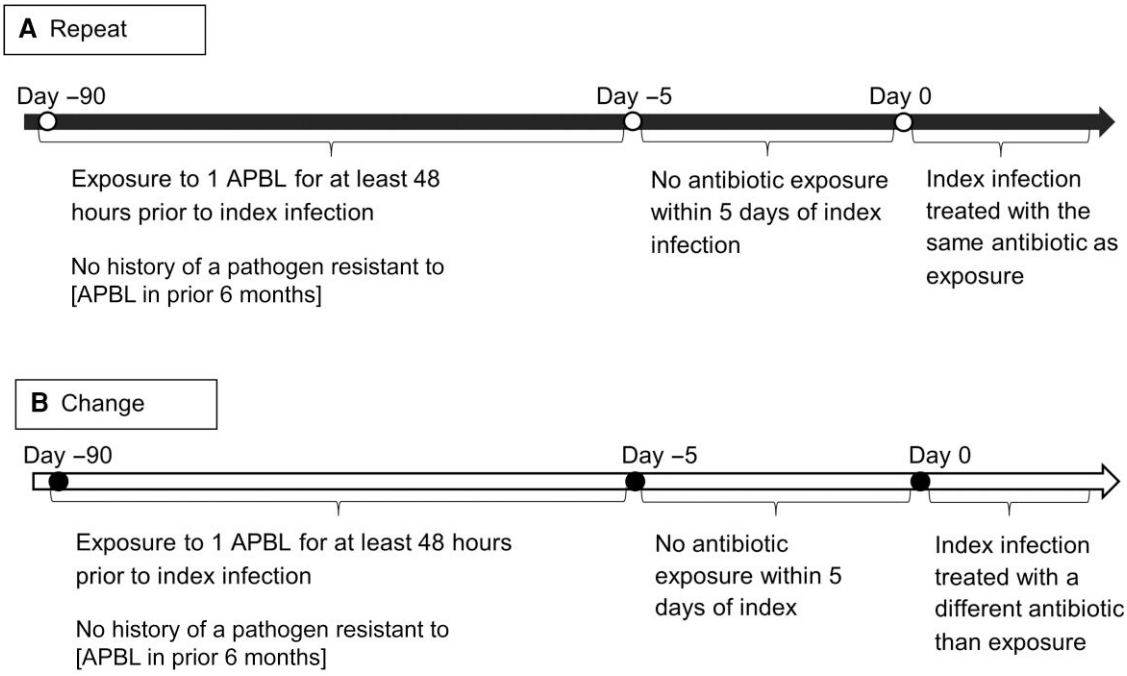

Figure 1. Eligibility for study cohort. All included patients received at least 48 hours of 1 antipseudomonal β-lactam (APBL) between day –90 and day –5 prior to the index gram-negative infection. Patients treated with the same APBL were in the repeat group (*A*) and those treated with a different antibiotic were in the change group (*B*).

were entered into conditional logistic regression models simultaneously. The variables were then removed in a backward, stepwise fashion, being retained in the logistic regression model if the *P* value for the likelihood ratio test for their removal was <.1. Repeat APBL was forced to remain in the final step of the regression models even if no statistical association was observed. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test; models with a nonsignificant result were considered adequate. Multicollinearity was assessed via the variance inflation factor, with values between 1 and 5 considered acceptable. A *P* value <.05 was considered statistically significant. All statistical analyses were performed using SPSS software (IBM SPSS Statistics, version 22.0).

Patient Consent Statement

This retrospective review of the EMR was approved and informed consent requirements were waived by the Methodist Health System Institutional Review Board (Dallas, Texas).

RESULTS

Cohort Description

A total of 605 patients were evaluated for eligibility with 197 included: 94 patients in the repeat group and 103 in the change group (Supplementary Figure 1). Baseline patient characteristics, infection microbiology, exposure and treatment antibiotics, and clinical outcomes between the 2 groups are described in Table 1. The majority of overall patients were male (61.4%), with a lower rate observed in the repeat group (56.4%) compared to the change group (66.0%). There were fewer patients with pneumonia in the repeat group (41.5%) compared to the change group (52.4%). ICU admission (68.1% vs 69.9%), vasopressor support (46.8% vs 40.8%), and mechanical ventilation (42.6% vs 50.5%) were frequent in both the repeat and change groups. The treatment antibiotic was more commonly piperacillin-tazobactam (53.2% vs 28.2%; $P < .001$) and less likely meropenem (2.1% vs 12.6%; $P = .006$) in the repeat group compared to the change group. Total hospital LOS (median, 12 [IQR, 5–28] vs 15 [IQR, 7–26] days; $P = .404$), ICU LOS (median, 7 [IQR, 3–16] vs 12 [IQR, 3–20] days; $P = .331$), and in-hospital mortality (18.1% vs 23.3%; $P = .369$) were comparable between the repeat and change groups (Table 1).

Microbiology

A total of 58 (29.4%) patients had a previously identified gram-negative infection during the APBL exposure time frame of which 30 (51.7%) were the same pathogen as the cause of the index infection (Supplementary Table 2). The most commonly identified pathogens causing the index infection overall were *Klebsiella* spp (27.9%), *Escherichia coli* (24.4%), and *Pseudomonas* spp (17.8%). *Klebsiella* spp were more common in the repeat group than in the change group (35.1% vs 21.4%). In contrast, *Pseudomonas* spp were less frequently identified in the repeat group compared to the change group (14.9% vs 20.4%). An ESBL phenotype was determined in 10.2% of

Table 1. Patient Characteristics and Outcomes

Variable	Repeat (n = 94)	Change (n = 103)	*P* Value
Age, y, mean ± SD	59.4 ± 13.1	61.0 ± 13.9	.395
Male sex	53 (56.4)	68 (66.0)	.165
Charlson Comorbidity Index, median (IQR)	5 (3–8)	5 (3–8)	.721
Chronic heart failure	26 (27.7)	24 (23.3)	.483
Chronic kidney disease	31 (33.0)	33 (32.0)	.888
COPD	25 (26.6)	21 (20.4)	.304
Connective tissue disease	2 (2.1)	3 (2.9)	.989
Cerebrovascular accident	13 (13.8)	16 (15.5)	.736
Dementia	8 (8.5)	6 (5.8)	.464
Diabetes mellitus	45 (47.9)	54 (52.4)	.523
Hemiplegia	4 (4.3)	7 (6.8)	.542
HIV	0 (0)	4 (3.9)	.123
Leukemia	4 (4.3)	1 (1.0)	.194
Lymphoma	5 (5.3)	1 (1.0)	.105
Myocardial infarction	7 (7.4)	16 (15.5)	.077
Liver disease	24 (25.5)	20 (19.3)	.303
Peptic ulcer disease	5 (5.3)	1 (1.0)	.105
Peripheral vascular disease	8 (8.5)	13 (12.6)	.35
Solid tumor without metastases	8 (8.5)	11 (10.7)	.606
Solid tumor with metastases	5 (5.3)	5 (4.9)	.882
Solid organ transplant	11 (11.7)	16 (15.5)	.435
Type of index infection			
Pneumonia	39 (41.5)	54 (52.4)	.142
Community-acquired	9 (9.6)	11 (10.7)	.622
Hospital-acquired	11 (11.7)	14 (13.6)	.506
Ventilator-associated	19 (20.2)	29 (28.2)	.092
Bacteremia	55 (58.5)	50 (48.5)	.133
Pathogen of index infection			
Achromobacter xylosidans	2 (2.1)	1 (1.0)	.261
Burkholderia cepacia	0 (0)	1 (1.0)	
Citrobacter freundii	0 (0)	1 (1.0)	
Citrobacter koseri	1 (1.1)	3 (2.9)	
Enterobacter cloacae	10 (10.6)	6 (5.8)	
Escherichia coli	21 (22.3)	27 (26.2)	
Klebsiella aerogenes	3 (3.2)	3 (2.9)	
Other *Klebsiella* spp	30 (31.9)	19 (18.4)	
Morganella morganii	1 (1.1)	0 (0)	
Proteus mirabilis	4 (4.3)	8 (7.8)	
Providencia spp	3 (3.2)	1 (1.0)	
Pseudomonas spp	14 (14.9)	21 (20.4)	
Serratia spp	4 (4.3)	8 (7.8)	
Stenotrophomonas maltophilia	1 (1.1)	4 (3.9)	
FEP/TZP-R	10 (10.6)	10 (9.7)	.829
Severity			
APACHE II, median (IQR)	16.5 (5.8–36.4)	18.7 (6.7–38.9)	.425
ICU stay	64 (68.1)	72 (69.9)	.783
Mechanical ventilation	40 (42.6)	52 (50.5)	.265
Vasopressors	44 (46.8)	42 (40.8)	.394
Exposure antibiotic			
Cefepime	43 (45.7)	41 (39.8)	.4
Meropenem	2 (2.1)	5 (4.9)	.448
Piperacillin-tazobactam	49 (52.1)	57 (55.3)	.651
Fluoroquinolone exposure	5 (5.3)	8 (7.8)	.573
Treatment antibiotic			
Cefepime	42 (44.7)	39 (37.9)	.331
Meropenem	2 (2.1)	13 (12.6)	.087

Table 1. Continued

Variable	Repeat (n = 94)	Change (n = 103)	*P* Value
Piperacillin-tazobactam	50 (53.2)	29 (28.2)	<.001
Double coverage	4 (4.3)	2 (1.9)	.428
Non-APBL	0 (0)	24 (23.3)	<.001
Hospital LOS, d, median (IQR)	12 (5–28)	15 (7–26)	.404
ICU LOS, d, median (IQR)	7 (3–16)	12 (3–20)	.331
In-hospital mortality	17 (18.1)	24 (23.3)	.369

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; APBL, antipseudomonal β-lactam; COPD, chronic obstructive pulmonary disease; FEP/TZP-R, cefepime/piperacillin-tazobactam resistant; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SD, standard deviation.

pathogens and did not differ between groups. Most pathogens with an ESBL phenotype were *Klebsiella* spp (50%) or *E coli* (45%) isolates along with 1 *Proteus mirabilis* isolate (5.0%).

Antibiotic Susceptibility

Pathogen susceptibility to the empiric antibiotic given for the index infection was higher in the repeat group compared to the change group (76.6% vs 60.2%; $P = .014$; Figure 2). It is important to note that after accounting for patients in the change group who received an antibiotic other than an APBL (23.3%), the susceptibility rate increased to 78.5%. Susceptibility rates to the exposure APBL were not different between the repeat and change group (76.6% vs 74.8%; $P = .767$; Figure 2). A total of 39 pathogens nonsusceptible to the empiric APBL utilized were identified with most either having an ESBL phenotype (n = 15 [38.5%]), or being *Pseudomonas aeruginosa* (n = 8 [20.5%]) or *Stenotrophomonas maltophilia* (n = 5 [12.8%]). In multivariable logistic regression, the repeat group was associated with increased likelihood of pathogen susceptibility to treatment (adjusted odds ratio [aOR], 2.513 [95% confidence interval {CI}, 1.227–5.146]; $P = .012$; Table 2). Bacteremia (aOR, 2.080 [95% CI, 1.125–3.847]; $P = .020$) and ICU admission (aOR, 2.293 [95% CI, 1.337–3.933]; $P = .003$) were associated with increased likelihood of susceptibility to empiric therapy, whereas cefepime/piperacillin-tazobactam resistance (FEP/TZP-R) (aOR, 0.041 [95% CI, .010–.160]; $P < .001$) and chronic obstructive pulmonary disease (COPD) (aOR, 0.332 [95% CI, .148–.741]; $P = .007$) were associated with a decreased likelihood of susceptibility. An additional multivariable logistic regression model was created including only patients who received an APBL as treatment in the change group (n = 79; Table 3). The repeat group did not exhibit a difference in susceptibility to treatment in this model (aOR, 0.936 [95% CI, .433–2.021]; $P = .865$). COPD (aOR, 0.323 [95% CI, .141–.739]; $P = .007$) and dementia (aOR, 0.289 [95% CI, .086–.964]; $P = .043$) were the only variables significantly associated with a decrease in likelihood of susceptibility to treatment.

In the subgroup of patients with a previously identified pathogen (n = 80), the median duration of APBL exposure in the 90 days preceding the index infection was similar (3 [IQR, 2–6] vs 4 [IQR, 2–6] days; $P = .381$) to those without a previously identified pathogen. Similar results were observed comparing patients with a previous gram-negative infection to those without. Moreover, the time between the exposure and index infection was shorter for patients with a previously identified pathogen than those without (29 [IQR, 10–65] vs 21 [IQR, 9–47] days; $P = .063$). Similar results were observed comparing patients with a previous gram-negative infection to those without (median time from APBL exposure to infection: 41 [IQR, 14–68] vs 21 [IQR, 8–45] days; $P = .009$).

Susceptibility rates were highest for meropenem overall (94.9%) and across all groups when stratified by initial APBL exposure (Supplementary Table 3). Susceptibility rates were similar for both cefepime (77.2%) and piperacillin-tazobactam (75.1%) overall and for all exposure subgroups with minimal increases in susceptibility observed in changing from cefepime (exposure) to piperacillin-tazobactam (treatment) or vice versa.

Patients with a pathogen nonsusceptible to exposure APBL (n = 49) were compared to those with a susceptible pathogen (n = 148) (Supplementary Table 4). The nonsusceptible pathogen group was more likely to have pneumonia (61.2% vs 42.8%; $P = .026$), COPD (38.8% vs 18.1%; $P = .003$), and an infection caused by a FEP/TZP-R pathogen (36.7% vs 1.4%; $P < .001$) compared to the susceptible group. The median duration of APBL exposure in the 90 days preceding the index infection was longer (5 [IQR, 2–7] vs 3 [IQR, 2–5] days; $P = .019$) and the median time between the exposure and index infection was shorter (17 [IQR, 7–39] vs 27 [IQR, 11–57] days; $P = .022$) among patients with an APBL-nonsusceptible pathogen (Supplementary Figure 2). In multivariable logistic regression, exposure duration (aOR, 1.099 [95% CI, 1.021–1.184]; $P = .012$) and chronic kidney disease (aOR, 2.2025 [95% CI, 1.968–4.234]; $P = .002$) were associated with increased likelihood of nonsusceptibility to the exposure APBL (Supplementary Table 5). When forced into exploratory multivariable models, prior infections were not significantly associated with nonsusceptibility; hence, it was excluded from the final model.

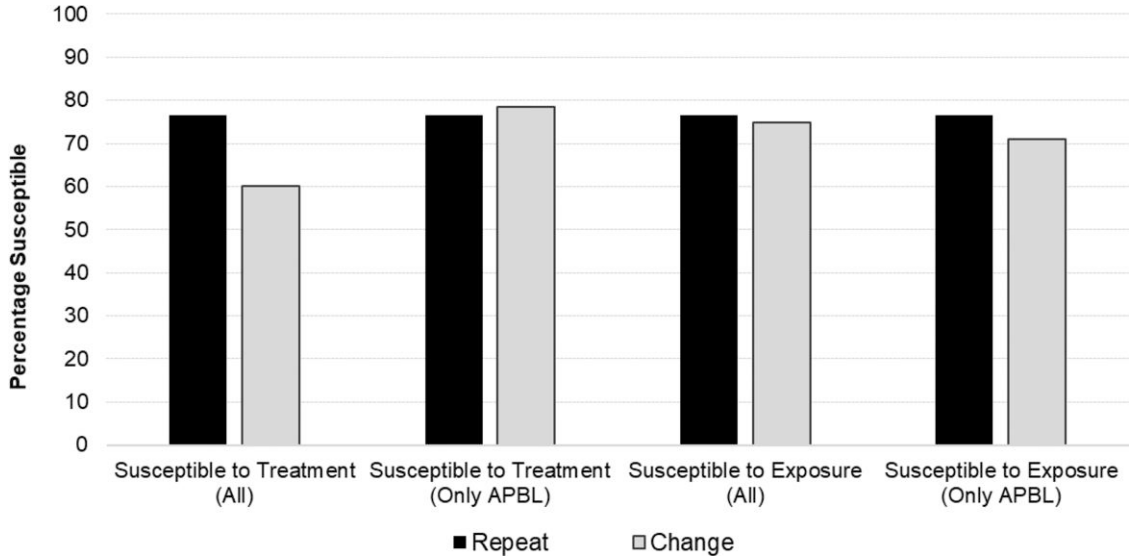

Figure 2. Susceptibility to treatment and exposure antibiotic between the repeat and change groups. Abbreviation: APBL, antipseudomonal β-lactam.

Table 2. Predictors of Susceptibility to Treatment Antibiotic

Predictor	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Repeat group	2.164 (1.165–4.021)	.015	2.513 (1.227–5.146)	.012
FEP/TZP-R	0.062 (.017–.221)	<.001	0.041 (.010–.160)	<.001
Bacteremia	1.962 (1.067–3.607)	.030	2.080 (1.125–3.847)	.020
ICU	1.613 (.856–3.041)	.139	2.293 (1.337–3.933)	.003
COPD	0.459 (.232–.906)	.025	.332 (.148–.741)	.007
SOT	2.279 (.820–6.328)	.114	2.726 (.794–9.360)	.111

Hosmer-Lemeshow goodness-of-fit = 0.434; area under the receiver operating characteristic curve = 0.796.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEP/TZP-R, cefepime/piperacillin-tazobactam resistant; ICU, intensive care unit; OR, odds ratio; SOT, solid organ transplant.

DISCUSSION

Repeated exposure to the same APBL was associated with a significantly higher likelihood of treatment susceptibility to gram-negative pneumonia or bloodstream infections in this cohort. Conversely, when the evaluation was limited to only APBL treatment, no difference in likelihood for susceptibility was found between the repeat and change groups. An empiric APBL for serious gram-negative infections is clearly favorable over non-APBLs (eg, ceftriaxone) in the setting of recent antibiotic exposure; however, changing to a different APBL from that of the recent exposure may not be warranted. Moreover, the magnitude and timing of the exposure appear to be important considerations. Both longer and more recent exposures were associated with decreased likelihood of susceptibility to the exposure APBL.

Frequently, clinicians may choose an APBL based on a patient's recent treatment history (eg, utilize cefepime in a patient recently treated with piperacillin-tazobactam). Although this logic is well meaning, it is not currently well established based on robust evidence. Our study found the likelihood of gram-negative pathogen susceptibility to be comparable between the repeat group and the change group when evaluating cefepime and piperacillin-tazobactam. In contrast, meropenem demonstrated higher rates of susceptibility across all subgroups of APBL exposure although actual empiric utilization of this agent was limited.

Our results suggest that the majority of patients with a suspected gram-negative infection at our institution would have the greatest benefit if treated with a carbapenem; however, we do not know what the clinical (or epidemiologic) impact of such a strategy would be. Carbapenems remain a "last line" class of antibiotics and are protected through judicious utilization at many hospitals such as our own. Our study only evaluated patients with an identified gram-negative infection. We know that many patients present with an infectious process (including sepsis and septic shock) that has no identified pathogen. Moreover, many patients are treated with antibiotics even though they do not have a bacterial infection. Taking these discrepancies into consideration, routine use of carbapenems to improve the likelihood of in vitro activity among patients with recent APBL exposure must be balanced against the potential harms, most notably further exacerbation of antimicrobial resistance. Thus, further evaluations of the interplay between prior antibiotic exposure and empiric utilization are needed to define the optimal strategy.

Table 3. Predictors of Susceptibility to Treatment Antibiotic in Subgroup of Antipseudomonal β-Lactam Treatment Only

Predictor	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Repeat group	0.897 (.438–1.840)	.768	.936 (.433–2.021)	.865
FEP/TZP-R	0.037 (.010–.136)	<.001	…	
Bacteremia	2.355 (1.131–4.903)	.022	2.580 (.943–7.057)	.065
COPD	0.330 (.152–.714)	.005	0.323 (.141–.739)	.007
SOT	2.357 (.667–8.338)	.183	1.944 (.515–7.336)	.326
Mechanical ventilation	0.627 (.305–1.285)	.200	1.344 (.489–3.695)	.567
Dementia	0.349 (.113–1.076)	.067	0.289 (.086–.964)	.043

Hosmer-Lemeshow goodness-of-fit = 0.983; area under the receiver operating characteristic curve = 0.690.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEP/TZP-R, cefepime/piperacillin-tazobactam resistant; OR, odds ratio; SOT, solid organ transplant.

Johnson et al evaluated prior antibiotic exposure in a cohort of patients with gram-negative bloodstream infections complicated by sepsis or septic shock [11]. Prior antibiotic exposure and inappropriate initial therapy were associated with higher rates of in-hospital mortality in the overall cohort. In contrast, the rates of inappropriate initial antimicrobial therapy and in-hospital mortality were similar in a subgroup analysis comparing patients receiving the same antibiotics to those with prior antibiotic exposure who did not have antibiotic reuse. We similarly found no difference in susceptibility rates between repeat utilization of an APBL compared to changing to an alternative for treatment of serious gram-negative infections. Although similarities between likelihood of susceptibility are present between studies, we should recognize the disparity in overall rates of susceptibility to the repeat APBL identified in the Johnson et al cohort (55%) compared to the current study (70.9% to 76.6%). This comparison reflects the need for epidemiologic guidance on a local level to optimize antibiotic use in critical populations.

Empiric antimicrobial decision making can be difficult to optimize due to the lack of robust data available to guide treatment. Current guidance recommends considering past culture data within the last 6 months as well as any exposure to antimicrobials within the prior 30 days when determining empiric therapy for gram-negative infections [18]. Although prior studies have attempted to design models and tools to predict resistance patterns and improve empiric antibiotic decision making, inappropriate empiric prescribing practices are an ongoing issue [21–23]. We observed 23 instances in the current cohort where a patient received an antibiotic considered too "narrow" based on recent APBL exposure. Of those cases, 91% of the patients could have been effectively treated by utilizing the same exposure APBL. Micek et al developed a real-time alert for patients prescribed the same antibiotic (cefepime, meropenem, or piperacillin-tazobactam) to which they had exposure or isolation of an antibiotic-resistant pathogen in the previous 6 months [24]. The automated alert was able to identify >40% of critically ill patients who were prescribed inappropriate antibiotics. Sanden et al evaluated antibiotic exposures among patients with consecutive gram-negative infections at a single hospital and found varying degrees of increased resistance to most antibiotic classes following exposure [17]. Moreover, cross-resistance was observed for a majority of antibiotic classes where exposure to 1 class was associated with increased resistance in another. In the current study, change from cefepime or piperacillin-tazobactam to the other APBL was not associated with increased likelihood of pathogen susceptibility. Cross-resistance between classes may add complexity to decision making as simply switching to another APBL was not beneficial. Moreover, timing and duration of exposures may be important considerations for predictive analytics. Patel et al demonstrated that the threshold for an exposure predictive of resistance among *P aeruginosa* respiratory infections is different for various antibiotics but increases with the duration of exposure for all agents evaluated [25]. Additionally, each additional day of APBL exposure has been demonstrated to increase the likelihood of subsequent resistance [26]. We set a threshold of 48 hours for APBL exposure but similarly found that patients with pathogens nonsusceptible to the exposure APBL had longer and more recent exposures compared to those with susceptible isolates. Further evaluations of how to optimize real-time prediction of resistance in serious gram-negative infections are needed.

This study has several limitations. First, this cohort represents the experience at a single large community teaching hospital in an urban setting and may not be representative of other clinical settings or hospitals. Although the pathogens identified in the cohort are seemingly representative of the most common gram-negative pathogens identified among patients with serious infections, differences in geography, practice setting, and patient populations should not be ignored. Second, data collection for exposures or microbiological history was limited to the EMR utilized at our hospital, limiting the acquisition of data on additional exposures or prior history of resistant pathogens that occurred at other facilities. Third, piperacillin-tazobactam and cefepime were classified as nonsusceptible for pathogens with an ESBL phenotype, which decreased the likelihood of pathogen susceptibility reported in this study although it may not have been reflective of the determined MIC. Although this subject remains somewhat controversial, current

recommendations favor carbapenems for serious infections caused by ESBL-producing Enterobacterales [18]. Fourth, meropenem exposure was underrepresented and was evaluated in combination with the other 2 APBLs in the current cohort. Rates of meropenem susceptibility were higher following exposure than those observed for the other APBLs, but the limited sample makes it difficult to draw definitive conclusions. Further exploration of carbapenem utilization and subsequent carbapenem resistance are warranted. Additionally, analysis was limited to the commonly utilized APBLs: cefepime, meropenem, and piperacillin-tazobactam. Newer antibiotics were not evaluated in the current study but could be used in patients with recent exposure to APBLs, and evaluation on a local level is warranted. Last, exposures of 48 hours or more within 90 days prior to the index infection were treated the same regardless of the extent or timing of the exposures. Comparisons between patients with an infection due to a pathogen susceptible and those nonsusceptible to the exposure APBL demonstrated that the magnitude and timing of exposure impact the likelihood of susceptibility. Development of specific cutoffs for both may assist in further delineating this relationship, although sensitivity analyses of patients with an exposure within 30 days did not alter the observed results (data not shown).

Clinicians should recognize the threat of rising antimicrobial resistance rates. Due to poor outcomes observed among patients who receive inadequate early antimicrobial therapy, our study aimed to evaluate the impact of the common practice of utilizing a different antibiotic than that of recent exposure. Prior resistance to an antibiotic in the previous 6 months can assist in guiding empiric treatment, so our study excluded such patients to focus on whether exposure led to the development of new resistance. Although pathogen resistance is not influenced by one particular variable, we chose to focus on a risk factor that is relatively easy to identify (and account for). When faced with the choice of repeating treatment with an APBL that was administered in the past versus a different APBL, our study suggests that changing to a different APBL does not confer a significant increase in susceptibility rates against gram-negative pathogens universally. Such results may not be consistent in other practice settings. Determining and integrating information regarding previous resistance and antibiotic exposure at the time of empiric prescribing is vital to improve care for patients with serious gram-negative infections. Refining this approach on a local level is a vital antimicrobial stewardship objective.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis **2009**; 48: 1–12.
2. Magill SS, O'Leary E, Ray SM, et al. Assessment of the appropriateness of antimicrobial use in US hospitals. JAMA Netw Open **2021**; 4:e212007.
3. Baekkeskov E, Rubin O, Munkholm L, Zaman W. Antimicrobial resistance as a global health crisis. Vol. 1. Oxford encyclopedia of crisis analysis. Oxford, UK: Oxford University Press; **2020**.
4. Barrasa-Villar JI, Aibar-Remón C, Prieto-Andrés P, Mareca-Doñate R, Moliner-Lahoz J. Impact on morbidity, mortality, and length of stay of hospital-acquired infections by resistant microorganisms. Clin Infect Dis **2017**; 65:644–52.
5. Lodise TP, Zhao Q, Fahrbach K, Gillard PJ, Martin A. A systematic review of the association between delayed appropriate therapy and mortality among patients hospitalized with infections due to *Klebsiella pneumoniae* or *Escherichia coli*: how long is too long? BMC Infect Dis **2018**; 18:625.
6. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in *Enterobacteriaceae* bacteraemia: a systematic review and meta-analysis. J Antimicrob Chemother **2007**; 60:913–20.
7. Peralta G, Sánchez MB, Garrido JC, et al. Impact of antibiotic resistance and of adequate empirical antibiotic treatment in the prognosis of patients with *Escherichia coli* bacteraemia. J Antimicrob Chemother **2007**; 60:855–63.
8. Lodise TP J, Patel N, Kwa A, et al. Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother **2007**; 51:3510–5.
9. Russotto V, Cortegiani A, Graziano G, et al. Bloodstream infections in intensive care unit patients: distribution and antibiotic resistance of bacteria. Infect Drug Resist **2015**; 8:287–96.
10. Kang CI, Kim SH, Park WB, et al. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother **2005**; 49:760–6.
11. Johnson MT, Reichley R, Hoppe-Bauer J, Dunne WM, Micek S, Kollef M. Impact of previous antibiotic therapy on outcome of gram-negative severe sepsis. Crit Care Med **2011**; 39:1859–65.
12. Webb BJ, Sorensen J, Jephson A, Mecham I, Dean NC. Broad-spectrum antibiotic use and poor outcomes in community-onset pneumonia: a cohort study. Eur Respir J **2019**; 54:1900057.
13. Rhee C, Kadri SS, Dekker JP, et al. Prevalence of antibiotic-resistant pathogens in culture-proven sepsis and outcomes associated with inadequate and broad-spectrum empiric antibiotic use. JAMA Netw Open **2020**; 3:e202899.
14. Hyle EP, Bilker WB, Gasink LB, Lautenbach E. Impact of different methods for describing the extent of prior antibiotic exposure on the association between antibiotic use and antibiotic-resistant infection. Infect Control Hosp Epidemiol **2007**; 28:647–54.
15. Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States, 2019. Atlanta, GA: CDC; **2019**.
16. Leibovici L, Berger R, Gruenewald T, et al. Departmental consumption of antibiotic drugs and subsequent resistance: a quantitative link. J Antimicrob Chemother **2001**; 48:535–40.
17. Sanden L, Paul M, Leibovici L, Andreassen S. Quantifying the associations between antibiotic exposure and resistance—a step towards personalised antibiograms. Eur J Clin Microbiol Infect Dis **2016**; 35:1989–96.
18. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of extended-spectrum

β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). Clin Infect Dis **2021**; 72:e169–83.
19. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med **2019**; 200:e45–67.
20. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis **2016**; 63:e61–111.
21. Vasudevan A, Mukhopadhyay A, Li J, Yuen EG, Tambyah PA. A prediction tool for nosocomial multi-drug resistant gram-negative bacilli infections in critically ill patients—prospective observational study. BMC Infect Dis **2014**; 14:615.
22. MacFadden DR, Coburn B, Shah N, et al. Decision-support models for empiric antibiotic selection in gram-negative bloodstream infections. Clin Microbiol Infect **2019**; 25:108.e1–7.
23. Lodise TP, Bonine NG, Ye JM, Folse HJ, Gillard P. Development of a bedside tool to predict the probability of drug-resistant pathogens among hospitalized adult patients with gram-negative infections. BMC Infect Dis **2019**; 19:718.
24. Micek ST, Heard KM, Gowan M, Kollef MH. Identifying critically ill patients at risk for inappropriate antibiotic therapy: a pilot study of a point-of-care decision support alert. Crit Care Med **2014**; 42:1832–8.
25. Patel N, McNutt LA, Lodise TP. Relationship between various definitions of prior antibiotic exposure and piperacillin-tazobactam resistance among patients with respiratory tract infections caused by *Pseudomonas aeruginosa*. Antimicrob Agents Chemother **2008**; 52:2933–6.
26. Teshome BF, Vouri SM, Hampton N, Kollef MH, Micek ST. Duration of exposure to antipseudomonal β-lactam antibiotics in the critically ill and development of new resistance. Pharmacotherapy **2019**; 39:261–70.