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DURATION OF EXPOSURE TO ANTIPSEUDOMONAL ANTIBIOTICS IN THE CRITICALLY ILL AND DEVELOPMENT OF NEW RESISTANCE

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Abstract

Introduction: Minimizing the duration of broad-spectrum antimicrobial exposure in the critically ill is a commonly used strategy aimed at preventing resistance.

Objective: To correlate the duration of exposure to antipseudomonal beta-lactam antibiotics with the development of new resistance in critically ill patients.

Methods: This was a single-center retrospective cohort study. Adult patients with a discharge diagnosis for severe sepsis or septic shock who received at least one dose of cefepime, meropenem, or piperacillin/tazobactam during their hospitalization between 2010 and 2015 were included. Cohort entry was defined as the first day of any antipseudomonal beta-lactam and exposure was defined as the cumulative days of any antipseudomonal beta-lactam exposure during the 60-day follow-up period. The primary outcome was the development of new resistance to any antipseudomonal beta-lactam, three or more days after cohort entry. New resistance was defined as detection of resistance to any antipseudomonal beta-lactam not identified within 180 days before cohort entry. Patients without an outcome or death by day 60 were censored. Cox proportional hazards models were performed to assess the risk of development of new resistance to any

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antipseudomonal beta-lactam with each additional day of exposure. Secondary analyses assessed each individual antipseudomonal beta-lactam.

Results: A total of 7,118 adults were included. Each additional day of exposure to any antipseudomonal beta-lactam resulted in an adjusted hazard ratio (aHR) of 1.04 (95% confidence interval [CI], 1.04–1.05) for new resistance development. The risk of developing new resistance to cefepime, meropenem, and piperacillin/tazobactam for each additional day of exposure resulted in an aHR 1.08 (95% CI 1.07 – 1.09), aHR 1.02 (95% CI 1.01 – 1.03), and aHR 1.08 (95% CI 1.06 – 1.09), respectively.

Conclusions: Among critically ill patients who receive antipseudomonal beta-lactam antibiotics, each additional day of exposure to cefepime, meropenem, and piperacillin/tazobactam is associated with an increased risk of new resistance development.

Keywords

Antipseudomonal beta-lactams; Exposure; Resistance; New resistance development; Severe sepsis; Septic shock

INTRODUCTION

The increasing rate of antibiotic resistance poses a significant threat to the healthcare system around the world. Antibiotic resistance has been linked to increased hospitalizations, length-of-stay, healthcare costs, and mortality (1). In patients with severe sepsis or septic shock, antipseudomonal beta-lactams, most commonly cefepime, meropenem, and piperacillin/tazobactam, are valuable first-line treatment options; the development of resistance to these antibiotics is an important issue that requires the utilization of numerous preventative measures. Minimizing the duration of broad-spectrum antimicrobial exposure is one of the most commonly used practices of antibiotic stewardship which aims to prevent the emergence of new antibiotic resistance (2, 3).

Despite widespread implementation of this strategy, data evaluating the relationship between the duration of antibiotic exposures and subsequent resistance development are limited. The few studies conducted in the critically ill population were derived from small populations, limited follow-up durations of usually less than twenty-eight days, and did not take into consideration infections that occurred prior to study inclusion to assess if the observed resistance is new or preexisting (4–8). Given the importance and widespread adoption of this strategy, data from a large cohort evaluating the association of antipseudomonal beta-lactam exposure and the development of new resistance could provide valuable insights on this issue for practicing clinicians. Therefore, we carried out a retrospective cohort study with the primary goal of determining whether increasing antipseudomonal beta-lactam exposure is associated with a higher likelihood for the development of new antibiotic resistance.

MATERIALS AND METHODS

Study Design and Patient Population

This was a retrospective cohort study of patients with severe sepsis or septic shock conducted at Barnes-Jewish Hospital (BJH), an academic hospital in St. Louis, Missouri (1,300 beds), between 1 January 2010 and 31 December 2015. Data for this study were obtained from the BJH electronic medical record (EMR) system which includes administrative, clinical, laboratory, and pharmacy data repositories. The study protocol was approved by the Washington University and St. Louis College of Pharmacy Institutional Review Boards.

All patients ≥18 years of age with a discharge diagnosis for severe sepsis or septic shock (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 995.92 and 785.52) who received at least one dose of cefepime, meropenem, or piperacillin/tazobactam during their hospitalization were included.

Definitions and Follow-Up

Cohort entry was defined as the initiation date of any antipseudomonal beta-lactam, which was defined as the first day of either cefepime, meropenem, or piperacillin/tazobactam. For secondary analyses of each individual antipseudomonal beta-lactam, cohort entry was defined as the initiation date of only the specific antipseudomonal beta-lactam being assessed. Exposure was defined as the cumulative days of any antipseudomonal beta-lactam exposure following cohort entry and thus treated as a time-varying exposure prior to outcome or censoring. Antipseudomonal beta-lactam exposures were calculated using start and stop orders on the EMR. The initial antipseudomonal beta-lactam dosages employed for treatment of bacterial infections at BJH were as follows: cefepime, 1 to 2g every 8hours; meropenem, 1 to 2g every 8hours; and piperacillin/tazobactam, 4.5g every 6hours. For this study, exposure was derived based on daily exposure and daily doses of the antibiotics were not factored in the analysis. The cumulative days of exposure for each antipseudomonal beta-lactam were assessed in aggregate and separately from cohort entry to censor date. Cumulative days were used instead of stratified cut-points (i.e., <7 days, 7–10 days, ≥10 days) as antibiotic stewardship dictates a reevaluation of antibiotic use on a daily basis to assess for improved symptoms so that broad-spectrum antibiotics can be de-escalated earlier (3). For example, a patient who receives cefepime for five days, then no antipseudomonal beta-lactam for three days, followed by four days of meropenem and no other antipseudomonal beta-lactam during the follow-up period will be counted as having nine days of cumulative antipseudomonal beta-lactam exposure, but only five days of cefepime and four days of meropenem exposure in secondary analyses. Continuing with the previous example, cohort entry was day one of cefepime in the primary antipseudomonal beta-lactam and secondary cefepime analyses, while cohort entry was day nine overall (or day one of meropenem) for the secondary meropenem analysis. For patients who received more than one antipseudomonal beta-lactam on a given day, the antipseudomonal beta-lactam exposure was counted as only one for that day.

The outcome of interest was the development of new antipseudomonal beta-lactam resistance among patients without documented resistance to the antipseudomonal beta-lactam antibiotic prescribed in the 180 days prior to cohort entry. The previous 180 days was chosen to better ensure that any resistance identified during follow-up had not been previously found. New resistance was evaluated with respect to the specific antipseudomonal beta-lactam and not the individual pathogens. For example, if a patient grew a gram-negative pathogen that was pan-sensitive in the previous 180 days, then another gram-negative pathogen was identified during follow-up that was resistant to cefepime, that was considered new resistance even if it was the first time the second pathogen was isolated. Patients with resistance identified within the first three days of cohort entry were censored, as resistance was likely not associated with an antipseudomonal beta-lactam exposure from this hospitalization. Patients were also censored at 60 days following cohort entry, time of in-hospital mortality, or end of study period (whichever occurred first). The primary study outcome was defined as the incidence of new resistance development to any antipseudomonal beta-lactam more than three days after cohort entry. Analyses of each individual antipseudomonal beta-lactam were evaluated as secondary outcomes.

Antimicrobial Susceptibility Testing

Clinical cultures from any site in the body, with the exception of stool cultures and surveillance cultures used to assess for colonization, were evaluated. The microbiology laboratory performed antimicrobial susceptibility of the bacterial isolates using the disk diffusion method according to guidelines and breakpoints established by the Clinical Laboratory and Standards Institute and published during the inclusive years of the study (9). All classifications of antibiotic resistance were based on *in vitro* susceptibility testing using these established breakpoints. For this study, cultures identified as intermediately susceptible were classified as resistant.

Covariates

Covariates collected at cohort entry included patient demographics, comorbidities, Charlson Comorbidity Index score (10), length of hospital stay prior to cohort entry, and intensive care unit (ICU) admission on or prior to cohort entry. Additionally, the cumulative days of exposure following cohort entry for ICU admission, use of mechanical ventilation, use of central vein catheterization, and use of urinary catheterization were also collected and modeled as time-varying exposures.

Statistical Analysis

Descriptive analyses were used to summarize patient demographics and clinical variables. Resistant pathogens were described using proportions for each antipseudomonal beta-lactam. Univariate analyses were performed to assess the influence of antipseudomonal beta-lactam exposure (any and individual antipseudomonal beta-lactams) and covariates on the development of new resistance until 60 days following cohort entry using Cox proportional hazards models. The Charlson Comorbidity Index score covariate was excluded from the models because individual comorbidities where already included. The covariates were tested for collinearity and none were collinear using a variance inflation factor threshold of >10. The proportional hazards assumption was tested using Schoenfeld residuals. Covariates that

did not meet the proportional hazards assumption were assessed as an interaction with time and the change in risk over time was reported. Covariates with a p-value of <0.2 in the univariate model were included in the multivariate Cox proportional hazards models evaluating any antipseudomonal beta-lactam, as well as each individual antipseudomonal beta-lactam separately. Antipseudomonal beta-lactam exposure was entered into each model regardless of significance and covariates were removed using backward selection. The risk for incident antipseudomonal beta-lactam resistance was assessed at each day following cohort entry in relation to the cumulative antipseudomonal beta-lactam exposure on each specified day. The outcome was reported as the association of each additional day of antipseudomonal beta-lactam exposure on the risk for incident antipseudomonal beta-lactam resistance.

We also explored *a priori* sensitivity analyses. To limit the potential for surveillance bias due to different rates of follow-up cultures between patients with resistance and those who were censored (i.e., did not develop resistance), the cumulative number of follow-up cultures collected more than three days after cohort entry was treated as a time-varying exposure for the study outcome using Cox proportional hazards models. The minimum number of follow-up cultures was incrementally increased until there were no significant differences in the number of follow-up cultures between patients with resistance and those who were censored; at the point when there was no significant difference, the influence of increasing antipseudomonal beta-lactam exposure and resistance was evaluated. Additionally, in order to attenuate for unmeasured resistance to antipseudomonal beta-lactam from patients without any culture data prior to cohort entry on the study outcome, we performed analyses requiring patients to have at least one negative culture for antipseudomonal beta-lactam resistance in the 60 days prior to cohort entry. This was done to increase confidence that the resistance observed was new resistance.

All analyses were performed using SAS software version 9.4 (Cary, NC).

RESULTS

A total of 7,118 patients, who received at least one dose of an antipseudomonal beta-lactam during the study period, were included. Demographic and clinical characteristics of the any antipseudomonal beta-lactam cohort as well as the three individual antipseudomonal beta-lactam groups are described in Tables 1 and 2. The majority of patients had at least one dose of cefepime (n = 5,274), followed by meropenem (n = 3,625) and piperacillin/tazobactam (n = 2,463), respectively. The median age for all of the groups was between 60 and 62 years old. The majority of all patients were male (56.0% to 57.6%) and Caucasian (66.2% to 71.1%). Those with meropenem exposure had increased days of hospital stay before cohort entry, rates of ICU exposure on or prior to cohort entry, days of overall antipseudomonal beta-lactam exposure, and days of exposure to central lines compared to the other antipseudomonal beta-lactams (Table 2). Among the three antipseudomonal beta-lactams, piperacillin/tazobactam had the most patients with resistant isolates identified from 180 days prior to cohort entry and within the first three days (92 and 83 patients, respectively) that were censored. There were 76 and 63 patients with resistant isolates from 180 days prior to cohort entry that were censored in the cefepime and meropenem groups, respectively.

Additionally, 37 and 33 patients with resistant isolates within the first three days of cohort entry were censored in the cefepime and meropenem groups, respectively.

Univariate analyses on the influence of antipseudomonal beta-lactam exposure (any and individual antipseudomonal beta-lactams) and covariates on the development of new resistance are described in Appendix 1. Among those with any antipseudomonal beta-lactam exposure, 444 patients developed new resistance to any antipseudomonal beta-lactam, with a median time to resistance of 17 days (interquartile range [IQR], 9–29 days) yielding an incidence rate of 0.16 (95% confidence interval [CI], 0.15–0.17) per 100 patient days. There was a 4% increased risk of new resistance for each additional day of any antipseudomonal beta-lactam exposure (adjusted hazard ratio [aHR] 1.04; 95% CI, 1.04–1.05) (Table 3). When evaluating the cefepime group, 61 patients developed new resistance, with a median time to resistance of 17 days (IQR, 10–24 days) yielding an incidence rate of 0.03 (95% CI, 0.02–0.04) per 100 patient days. There was an 8% increased risk of new resistance for each additional day of cefepime exposure (aHR 1.08; 95% CI, 1.07–1.09). There were 103 patients in the meropenem group that developed new resistance, with a median time to resistance of 14 days (IQR, 8–27 days) yielding an incidence rate of 0.07 (95% CI, 0.06–0.09) per 100 patient days. There was a 2% increased risk of new resistance for each additional day of meropenem exposure (aHR 1.02; 95% CI, 1.01–1.03). Furthermore, 108 patients in the piperacillin/tazobactam group developed new resistance, with a median time to resistance of 13.5 days (IQR, 8–24.5 days) yielding an incidence rate of 0.11 (95% CI, 0.09–0.13) per 100 patient days. There was an 8% increased risk of new resistance for each additional day of piperacillin/tazobactam exposure (aHR 1.08; 95% CI, 1.06–1.09). The results of the sensitivity analyses were consistent with the primary analysis, with the exception of the meropenem group falling out of significance among patients with three or more follow-up cultures (Table 3 and Appendix 2).

A summary of the distribution of bacterial pathogens that developed new resistance among the individual antipseudomonal beta-lactam groups is listed in Table 4. *Pseudomonas aeruginosa* was the most common pathogen to develop new resistance in the meropenem group (65.0%) and the second most common in the cefepime group (18.0%). *Enterobacter* species was the most common resistant pathogen in the piperacillin/tazobactam group (42.7%) and *Acinetobacter baumannii* was the most common resistant pathogen in the cefepime group (19.7%).

DISCUSSION

Antibiotic resistance is a global issue that requires more understanding and interventions from clinicians in order to reduce the development of new resistance. Our study suggests that each additional day of exposure to any antipseudomonal beta-lactam, as well as each individual antipseudomonal beta-lactam evaluated, is associated with an increased risk of developing new resistance within 60 days of initiation. It is important to note that this increase in risk is relative and should be described by comparing different durations of antibiotic exposures. For example, we found each additional day of cefepime results in an 8% (aHR 1.08) increased risk of new resistance; therefore, when comparing a 7-day course to a 10-day course of therapy, the 10-day course is associated with a 24% increased risk of

new resistance compared to the 7-day course of cefepime (8% increase in risk for each additional day for a total of three extra days). Our results confirm the current standard strategy of minimizing antibiotic exposure to the shortest effective duration (11). They also highlight the importance of more frequent evaluation of the appropriateness of antibiotics in the effort to de-escalate or discontinue them, rather than waiting until a 7 or 10-day course is up. Increasing clinician awareness to the potential risks of each additional day of antibiotic exposure can hopefully lead to increased implementation of strategies to reduce inappropriate antibiotic durations (i.e., procalcitonin). These findings provide antibiotic stewards with another tool in their continued efforts to reduce the emergence of resistance.

To our knowledge, this is the largest population-based retrospective study evaluating the association of antipseudomonal beta-lactam exposure with the development of new resistance in the critically ill population. This study is also unique in that antibiotic exposures were not defined in a binary fashion, but rather as a time-dependent variable; a concept highlighted by Munoz-Prince et al (12). The duration of antibiotic exposures varies greatly in the critically ill population and should, therefore, be evaluated as a time-dependent variable when assessing its association on new resistance development.

Our findings build on two prospective studies that evaluated outcomes in critically ill patients with pneumonia. Singh and colleagues found a significantly higher rate of antibiotic resistance and/or incidence of a superinfection in a group of patients that had a mean duration of antibiotic exposure of 10 days compared to a group with a mean of three days of antibiotic exposure (35% versus 15%, P=0.0017) (4). Furthermore, Chastre and colleagues performed a randomized controlled trial evaluating 8-day versus 15-day antibiotic courses for patients with ventilator-associated pneumonia (7). Among patients with recurrent pulmonary infections, the group randomized to receive a 15-day antibiotic course had significantly higher rates of multi-drug resistant pathogens isolated compared to the 8-day group (62.0% versus 42.1%, P=0.04). Unlike our study, neither of the studies took steps to only identify new resistance development, instead, both used broad definitions of resistance and assessed it as secondary outcomes using smaller sub-groups.

Our study only used clinical cultures and not surveillance cultures for colonization. This made our study more closely emulate real-world situations in which clinicians may not readily have access to routine surveillance cultures. Despite the difference in methods, our results were analogous to a prospective cohort study evaluating antibiotic exposures and resistance in critically ill patients who were colonized with gram-negative pathogens (13). Among those colonized with *P. aeruginosa*, exposure to meropenem was found to be independently associated with an increased risk of resistance development. More recently, Yusuf and colleagues conducted a cohort study in critically ill patients using clinical cultures for *P. aeruginosa* that were initially susceptible to the antibiotics studied (14). Their findings were similar to ours in that meropenem was associated with an increased risk of resistance development at 8 to 15 days and >15 days exposure compared to 0 to 7 days of exposure. Unlike our study, neither of these studies evaluated cefepime exposure for resistance development, and piperacillin/tazobactam was not significant in both studies. The lack of significance among the piperacillin/tazobactam groups in both studies could be attributed to

low sample size as both studies included <200 patients, compared to the 2,463 patients in the piperacillin/tazobactam group in our study.

Our study has several important limitations. First, our study was conducted using a database from a single-center which may decrease generalizability to other institutions. However, our findings on the potential impact of antibiotic exposure on resistance have been supported by several studies, and our robust sample size helps increase generalizability. Second, our dataset did not include any possible antibiotic exposures or any relevant clinical data from outside hospitals the patients may have encountered during the study period. We believe this limitation is a roadblock that is commonly faced by clinicians who have to provide care for their patients without having access to outside hospital records (15). The sensitivity analysis among patients with at least one negative culture for antipseudomonal beta-lactam resistance in the 60 days prior to cohort entry confirmed our initial results which help increase the degree of confidence in our primary analysis. Third, our focus was on resistance development to the antipseudomonal beta-lactams evaluated, and not the specific pathogens or their molecular mechanisms that allowed for resistance emergence. Lastly, our reliance on ICD-9-CM codes and the retrospective nature of our design may lead to possible misclassification bias and confounding.

CONCLUSIONS

Among patients with severe sepsis or septic shock, each additional day of exposure to an antipseudomonal beta-lactam was associated with an increased risk of new resistance (aHR 1.04; 95% CI, 1.04–1.05). Furthermore, each additional day of exposure to cefepime (aHR 1.08; 95% CI, 1.07–1.09), meropenem (aHR 1.02; 95% CI, 1.01–1.03), and piperacillin/tazobactam (aHR 1.08; 95% CI, 1.06–1.09) was also associated with increased risk of new resistance. Clinicians should be vigilant in their efforts to limit exposure to antipseudomonal beta-lactams to the shortest effective duration to curb resistance emergence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Description of baseline characteristics at cohort entry

	Any AP (n=7118)	Cefepime (n=5274)	Meropenem (n=3625)	Piperacillin-tazobactam (n=2463)
Patient age (years), median (IQR)	61 (51–71)	62 (52–71)	60 (50–69)	61 (51–70)
Male, n (%)	4021 (56.5)	3037 (57.6)	2078 (57.3)	1380 (56.0)
Race, n (%)				
Caucasian	4782 (67.2)	3492 (66.2)	2579 (71.1)	1648 (66.9)
African American	1860 (26.1)	1417 (26.9)	804 (22.2)	661 (26.8)
Other	476 (6.7)	365 (6.9)	242 (6.7)	154 (6.3)
Charlson Comorbidity Index score, median (IQR)	6 (4–8)	6 (4–9)	6 (4–8)	6 (4–8)
Comorbid conditions, n (%)				
Dementia	198 (2.8)	159 (3.0)	75 (2.1)	69 (2.8)
Congestive heart failure	2648 (37.2)	2108 (40.0)	1395 (38.5)	835 (33.9)
Chronic obstructive pulmonary disease	2849 (40.0)	2161 (41.0)	1485 (41.0)	936 (38.0)
Liver disease	2104 (29.6)	1529 (29.0)	1226 (33.8)	742 (30.1)
Renal disease	2506 (35.2)	1968 (37.3)	1315 (36.3)	815 (33.1)
Diabetes	2900 (40.8)	2146 (40.7)	1485 (41.0)	1012 (41.1)
Neoplastic disease	2413 (33.9)	1876 (35.6)	1316 (36.1)	815 (33.1)
HIV/AIDS	107 (1.5)	86 (1.6)	58 (1.6)	31 (1.3)
Cohort entry date relative to admission date (days), median (IQR)	0 (0–2)	1 (0–4)	4 (0–11)	1 (0–4)
Admission to ICU on or prior to cohort entry	3806 (53.5)	2864 (54.3)	2241 (61.8)	1469 (59.6)

AP: antipseudomonal beta-lactam; IQR: interquartile range; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome; ICU: intensive care unit

Table 2.

Description of cumulative variables after cohort entry

	Any AP (n=7118)	Cefepime (n=5274)	Meropenem (n=3625)	Piperacillin-tazobactam (n=2463)
Overall AP exposure (days), median (IQR)	7 (3–12)	5 (3–9)	7 (3–12)	4 (2–7)
Overall hospital days, median (IQR)	13 (7–24)	12 (6–23)	13 (6–25)	11 (6–21)
Days in ICU, median (IQR)	2 (0–8)	2 (0–8)	2 (0–9)	3 (0–7)
Mechanical ventilation days, median (IQR)	2 (0–7)	2 (0–8)	3 (0–9)	2 (0–7)
Central line days, median (IQR)	7 (1–17)	8 (2–19)	10 (3–21)	8 (2–16)
Urinary catheter days, median (IQR)	5 (0–12)	5 (0–13)	6 (1–14)	5 (1–12)

AP: antipseudomonal beta-lactam; IQR: interquartile range; ICU: intensive care unit

Table 3:

Hazard ratios for new resistance development with each additional day of exposure grouped by AP

	Adjusted hazard ratio (95% confidence interval)			
	Any AP	**Cefepime**	**Meropenem**	**Piperacillin-tazobactam**
Each additional day of exposure	1.04 (1.04–1.05)[a]	1.08 (1.07–1.09)[b]	1.02 (1.01–1.03)[c]	1.08 (1.06–1.09)[d]
Sensitivity analyses (each additional day of exposure)[e]				
Among patients with multiple follow-up cultures[f]	1.01 (1.01–1.02)[g]	1.07 (1.06–1.08)[h]	1.00 (0.99–1.01)[i]	1.05 (1.04–1.06)[i]
Among patients with ≥ 1 negative culture for AP resistance 60 days prior to cohort entry	1.01 (1.00–1.02)	1.22 (1.14–1.31)	1.02 (1.01–1.04)	1.10 (1.08–1.12)

AP: antipseudomonal beta-lactam

[a]Adjusted for race, dementia, congestive heart failure, chronic obstructive pulmonary disease, cohort entry date relative to admission date (days), days in intensive care unit, mechanical ventilation days, central line days, and urinary catheter days

[b]Adjusted for congestive heart failure, chronic obstructive pulmonary disease, days in intensive care unit, mechanical ventilation days, central line days, and urinary catheter days

[c]Adjusted for age, chronic obstructive pulmonary disease, renal disease, cohort entry date relative to admission date (days), days in intensive care unit, mechanical ventilation days, and central line days

[d]Adjusted for race, liver disease, diabetes, days in intensive care unit, mechanical ventilation days, central line days, and urinary catheter days

[e]Details regarding variables included in the multivariable models for the sensitivity analyses are listed in Appendix 2

[f]Sensitivity analysis accounting for possible surveillance bias by treating number of follow-up cultures as a time-varying exposure, then increasing the number until no significant difference existed between those with resistance and those censored

[g]Among patients with ≥ 6 follow-up cultures

[h]Among patients with ≥ 8 follow-up cultures

[i]Among patients with ≥ 3 follow-up cultures

Table 4.

Bacterial pathogens that developed new resistance distribution

	New resistance		
	Cefepime (n=61)	**Meropenem (n=103)**	**Piperacillin- tazobactam (n=108)**
Pathogens, n (%)			
Achromobacter species	6 (9.8)	2 (1.9)	1 (1)
Acinetobacter baumannii	12 (19.7)	11 (10.7)	5 (4.9)
Burkholderia cepacia	0 (0)	2 (1.9)	0 (0)
Citrobacter species	3 (4.9)	0 (0)	8 (7.8)
Enterobacter species	8 (13.1)	9 (8.7)	44 (42.7)
Escherichia coli	14 (23.0)	2 (1.9)	10 (9.7)
Klebsiella oxytoca	2 (3.3)	0 (0)	4 (3.9)
Klebsiella pneumoniae	3 (4.9)	4 (3.9)	14 (13.6)
Morganella morganii	0 (0)	0 (0)	0 (0)
Proteus mirabilis	1 (1.6)	1 (1.0)	0 (0)
Providencia species	0 (0)	1 (1.0)	0 (0)
Pseudomonas aeruginosa	11 (18.0)	67 (65.0)	13 (12.6)
Serratia species	0 (0)	0 (0)	8 (7.8)
Stenotrophomonas maltophilia	1 (1.6)	3 (2.9)	0 (0)
Other rare gram-negative pathogen	0 (0)	0 (0)	1 (1.0)
Source of isolation, n (%)[a]			
Blood	27 (23.1)	20 (11.4)	41 (16.9)
Respiratory specimen	50 (42.7)	88 (50.3)	90 (37.0)
Urine	27 (23.1)	34 (19.4)	41 (16.9)
Other	13 (11.1)	33 (18.9)	71 (29.2)

[a]Different totals are due to some resistant pathogen being isolated from multiple culture sites in the same patient