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Letter to the Editor

Evaluation of a ceiling effect on the association of new resistance development to antipseudomonal beta-lactam exposure in the critically ill

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To the Editor—The growing rate of pathogens developing antibiotic resistance is one of the leading problems facing healthcare around the world.[1,2] Among patients with severe sepsis or septic shock, antipseudomonal β-lactams are valuable first-line treatments and are among the most widely used antibiotics in the critically ill population.[3] Recently, each additional day of cumulative exposure to antipseudomonal β-lactams (specifically cefepime, meropenem, and piperacillin-tazobactam) was associated with increased risk of new resistance emergence in the critically ill.[4] The objective of the current study was to evaluate whether the relationship of that association was linear with each additional day or whether there was a "ceiling effect" in which the associated increase in the risk of new resistance plateaus after a certain duration of exposure.

Methods

The methods used to create this database have been described previously.[4] Briefly, this study 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, between January 1, 2010, and December 31, 2015. Data for this study were obtained from the BJH electronic medical record (EMR) system. 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 1 dose of cefepime, meropenem, or piperacillin-tazobactam during their hospitalization were included.

Cohort entry was defined as the initiation date of any of the 3 antipseudomonal β-lactams listed in the inclusion criteria. Exposure was defined as the cumulative days of antipseudomonal β-lactam exposure following cohort entry stratified in 3 antipseudomonal exposure-day increments. Exposure to antipseudomonal β-lactams were calculated using start and stop orders from the EMR. Development of new resistance was defined as the detection of resistance to any of the antipseudomonal β-lactams that was not identified in the 180 days prior to cohort entry using clinical cultures from any site in the body, with the exception of stool cultures. Patients were censored at 60 days after cohort entry, time of in-hospital mortality, or end of study period.

The primary outcome was development of new resistance to any antipseudomonal β-lactam >3 days after cohort entry. The risk for incident resistance after cohort entry was assessed with cumulative antipseudomonal exposure days comparing 1–3 days (reference) with 4–6 days, 7–9 days, 10–12 days, 13–15 days, 16–18 days, 19–21 days, and ≥22 days. The influence of antipseudomonal β-lactam exposure, as a time-varying exposure, on the development of new resistance until 60 days following cohort entry was analyzed using a Cox proportional hazards model. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

The demographic and clinical characteristics of this cohort have been described previously.[4] Briefly, 7,118 patients met the criteria for inclusion into the cohort. The median age was 61 years old (interquartile range [IQR], 51–71 years old). Most were male (56.5%) and white (67.2%). The median Charlson comorbidity index score was 6 (IQR, 4–8), and admission to the intensive care unit on or prior to cohort entry occurred in 53.5% of the patients. Furthermore, the median cumulative days of exposure to antipseudomonal β-lactams was 7 days (IQR, 3–12 days). Overall, 444 patients developed new resistance with a median time to resistance of 17 days (IQR, 9–29 days).

When comparing the stratified cumulative antipseudomonal exposure days with the reference of 1–3 days, an increased risk of new resistance development was seen starting at 7–9 days (hazard ratio [HR], 1.85; 95% confidence interval [CI], 1.69–2.02) (Table 1). The increase in risk of new resistance continued to grow in magnitude compared to the reference with each subsequent stratified cumulative antipseudomonal exposure days (Table 1).

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Table 1. Cumulative Days of Antipseudomonal β-Lactam Antibiotic Exposure and New Resistance Development

Cumulative Days of Antipseudomonal Exposure	No. of Patients	New Resistance Events, No. (%)	Hazard Ratio (95% Confidence Interval)
1–3	1,816	38 (2.09)	1.00 (reference)
4–6	1,632	85 (5.21)	1.01 (0.93–1.10)
7–9	1,249	98 (7.85)	1.85 (1.69–2.02)
10–12	709	66 (9.31)	2.93 (2.66–3.24)
13–15	474	44 (9.28)	3.94 (3.54–4.39)
16–18	326	30 (9.20)	6.29 (5.62–7.04)
19–21	234	27 (11.5)	7.05 (6.19–8.02)
≥22	678	56 (8.3)	8.52 (7.62–9.53)

Discussion

Our retrospective cohort study showed the associated rise in the risk of new resistance emergence with increasing duration of antipseudomonal β-lactam antibiotic exposure in the critically ill does not appear to exhibit a "ceiling effect" as the cumulative duration of exposure increases. This finding is important because it suggests that the risk of new resistance will continue to increase as the duration of exposure increases, regardless of how long the patient has been on antimicrobial therapy.

Recent estimates showing antibiotic resistances accounting for >2.8 million infections and >35,000 death per year in the United States highlight the need to understand and prevent resistance development.[2] Minimizing durations of antimicrobial therapy is becoming a pillar of antimicrobial stewardship; however, studies evaluating optimal durations are lacking, and many guideline recommendations for duration of therapy continue to rely on expert opinion which may result in longer than necessary exposures.[5–7] Our study further highlights the need for further studies evaluating optimal durations for various types of infections as well as studies regarding strategies to limit antimicrobial exposure to the shortest effective duration.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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Silent clonal spread of vancomycin-resistant *Enterococcus faecalis* ST6 and ST525 colonizing patients at hospital admission in Natal, Brazil

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To the Editor—Infections and gut colonization with vancomycin-resistant enterococci (VRE) have been increasingly reported in hospitalized patients from different regions of Brazil, where difficulties in controlling VRE colonization have been noted.[1-4] Patient colonization with VRE is a major risk factor for developing subsequent infections with these strains.[1,5] The first VRE description dates from 2011 (M. Celeste Melo, personnel data), and VRE infections among hospitalized patients from Natal city (northeastern Brazil) remain low, contrasting with the high rates of VRE infection and colonization of the patients in the southern and southeastern regions, where they have occurred since 1998.[1-3] For early recognition of silent interhospital VRE transmission through colonized patients as in other parts of Brazil, we aimed to search and characterize VRE colonization strains from patients known to have a previously history of hospitalization.

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