9-1-2017

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Recommended Citation

Cheng, L., Nelson, B., Mehta, M., Shi, Q., Gomez-Simmonds, A., & Uhlemann, A. (2017). Reply to Aitken et al., "Should Piperacillin-Tazobactam Be Used as Definitive Therapy Against Enterobacteriaceae Harboring Inducible AmpC β-Lactamases?". *Antimicrobial Agents and Chemotherapy, 61* (9), e01163-17. https://doi.org/10.1128/AAC.01163-17

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AUTHOR REPLY

Reply to Aitken et al., "Should Piperacillin-Tazobactam Be Used as Definitive Therapy against *Enterobacteriaceae* Harboring Inducible AmpC β-Lactamases?"

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We appreciate Aitken et al.'s careful review (1) of our recent paper assessing the use of piperacillin-tazobactam for the treatment of bloodstream infections caused by *Enterobacteriaceae* harboring AmpC β-lactamases (2). We respectfully disagree with their assertion that the numerical increase in mortality seen with the use of piperacillin-tazobactam compared to the mortalities of patients on carbapenems and/or cefepime in our and other studies suggests that inferior outcomes are to be expected with piperacillin-tazobactam.

Aitken et al. are correct to point out that the odds ratio (OR) for the 30-day survival, not mortality, of patients receiving piperacillin-tazobactam versus that of patients receiving cefepime or meropenem was 0.5 in the propensity-matched data set. Therefore, the OR for 30-day mortality was 2.0 (95% confidence interval, 0.5 to 7.7), representing 3 additional deaths in the piperacillin-tazobactam group. This result was not statistically significant ($P = 0.33$), indicating that we were unable to detect an association between the treatment regimen and the occurrence of mortality in this study. It is worth noting that the large confidence intervals reported here suggest a low level of the precision of the OR. Thus, it is inappropriate to draw a firm conclusion about the relative odds of mortality based on its numerical value alone. As we pointed out in our publication, propensity score matching lowered our ability to detect differences in outcomes. In the overall cohort, the OR for 30-day survival was 1.16, as reported, and the OR for 30-day mortality was 0.86 (95% confidence interval, 0.3 to 2.3; $P = 0.8$). It is worth noting that in creating the propensity score-matched cohort, fewer deaths were excluded from the piperacillin-tazobactam group (3/9) than from the carbapenem/cefepime group (6/9).

Aitken et al. also suggested that using multivariable logistic regression is preferred to propensity score matching for some data sets. We opted for propensity score matching to minimize differences between baseline characteristics of treatment groups. In addition, a low number of outcome events in our data set made it difficult to perform multivariate models. Multivariable analyses of the overall cohort were attempted by incorporating variables that were significantly different between treatment groups, but these models demonstrated poor fit. However, they also showed no association between treatment groups and mortality, supporting our findings from the propensity score-matched analysis.

The commenters further mention a paper by Harris and colleagues from 2017 with similar results (i.e., a numerically higher rate of recurrence of *Enterobacter* spp. bacteremia without a statistically significant difference) and a small patient population (3).

Citation Cheng L, Nelson BC, Mehta M, Shi Q, Gomez-Simmonds A, Uhlemann A-C. 2017. Reply to Aitken et al., "Should piperacillin-tazobactam be used as definitive therapy against *Enterobacteriaceae* harboring inducible AmpC β-lactamases?" Antimicrob Agents Chemother 61:e01163-17. https://doi.org/10.1128/AAC.01163-17.

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This is a response to a letter by Aitken et al. (https://doi.org/10.1128/AAC.01160-17).

We direct them to a much larger meta-analysis also conducted by Harris et al. in 2016 that included 11 studies and revealed no strong evidence to suggest the superiority of carbapenems to other treatment regimens, including β-lactamase/β-lactamase inhibitors, in patients with bloodstream infections due to *Enterobacteriaceae* with AmpC β-lactamases (4). We welcome future studies of the efficacy of non-carbapenem-containing regimens, such as piperacillin-tazobactam, for the treatment of AmpC-harboring *Enterobacteriaceae*. As we discussed in our original paper, prospective studies and meta-analyses are needed to further delineate patient populations that might benefit from this treatment approach and to identify specific risk factors warranting the use of carbapenem or cefepime.

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