

Risk factors and outcome in extended spectrum beta-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia

To the Editor

Given our interest in the epidemiology of nosocomial infection, and the impact of multidrug resistance, I read with great interest the study by Dr. Memon et al¹ regarding risk factors and mortality associated with bacteremia caused by extended-spectrum β -lactamase producing (ESBL) *Escherichia coli* and *Klebsiella pneumoniae*. In this study, the only variable identified as a significant risk factor for ESBL involvement was nosocomial infection. Because hospitals are recognized as epicenters of antibiotic consumption this finding is in line with the expectations. In univariate analysis, no difference in mortality was found between patients with bacteremia caused by ESBL or non-ESBL pathogens. Indeed, on the condition of early initiation of appropriate antimicrobial therapy, the involvement of multidrug resistance does not necessarily worsen the prognosis of patients with *Enterobacteriaceae* bacteremia.²⁻⁵ However, I have some concerns on the results obtained by the multivariable regression model, performed to identify independent risk factors for death. Based on this analysis, the variable 'nosocomial infection' was identified as a risk factor for mortality, whereas ESBL involvement was not. Given the strong relationship between nosocomial infection and ESBL involvement, it seems like there exists an important collinearity, which potentially confounds the results of the multivariable regression analysis. It is unlikely that 'nosocomial infection' as such would increase the risk of death, but ESBL involvement clearly is a risk factor for inappropriate antimicrobial therapy, and as a consequence may cause bad outcome. Therefore, I wonder how the regression model would turn out if the variable 'nosocomial infection' would be replaced by the (closely related) variable 'ESBL-producing pathogen'. It would also be worthwhile to explore the impact of early initiated appropriate therapy in the logistic regression model of this specific cohort. Furthermore, I assume there might as well exist a substantial collinearity between the variables 'septic shock' and 'intensive care unit care', which are both recognized as independent risk factors for mortality. I would greatly appreciate if the authors could elaborate on these comments and suggestions.

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Reply from the Author

We thank Prof. Blot for his letter, and his interest in our study.¹ Prof. Blot has raised a valid point that the way the multivariate analysis is carried out in our paper generally includes the problem of collinearity.⁶ We agree with Prof. Blot's comments that "given the strong relationship between nosocomial infection and ESBL involvement, it seems like there exists an important collinearity, which potentially confounds the results of the multivariable regression analysis." We checked the collinearity among these 2 variables initially by performing correlations.⁷ The correlation coefficient matrix demonstrates correlations of 0.20, which do not indicate collinearity. We then looked for tolerance and the variance inflation factor (VIF) to identify collinearity. The tolerance was high and VIF was between 1 and 2, which again do not indicate collinearity in the model.⁷ We also agree with Prof. Blot on the importance of exploring the impact of early initiated appropriate therapy in the logistic regression model, and mentioned this as one of the limitations of our study. We do not agree with Prof. Blot's assumption of substantial collinearity between the variables 'septic shock' and 'intensive care unit care', which are both recognized as independent risk factors for mortality. The calculation of the variance inflation factor revealed numbers ranging between 1 and 2, far below the value of 10 that indicates collinearity. As suggested by Prof. Blot, when we replaced variable 'nosocomial infection' by 'ESBL-producing pathogen,' the new variable did not come out to be a statistically significant independent risk factor for mortality. In conclusion, the authors appreciate the comments from Prof. Blot and fully agree with him in principle. A recalculation of the statistical analysis led to the same conclusions as the previous statistical analysis had revealed.

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