

CORRESPONDENCE



# Another trial for the TARGET trial. Author's reply

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We would like to thank for the opportunity to respond to the points raised in the commentary by Mohammad H. Alshaer and Charles A. Peloquin and we thank the colleagues for the critical reading of the study [1]. First, they recommend to include the day-to-day differences in Sequential Organ Failure Assessment (SOFA) scores as a repeated-measure outcome in the analysis. Progression of the mean SOFA scores in both groups from randomization to day 10 is illustrated in eFigure1 [2]. Unfortunately, the illustration was missing in the Supplementary file 1, but has now been added. Second, concerning the percentage of patients on renal replacement therapy (RRT), in total 16.2% of patients received RRT at any time during therapy with piperacillin/tazobactam (therapeutic drug monitoring (TDM) group 14.3% vs. 18.1% control group). At randomization, 7.1% of patients with TDM received a RRT, compared to 6.3% in patients without TDM. We agree with the colleagues that the increase in mortality observed among patients with higher piperacillin concentrations is most likely a consequence of pronounced sepsis-associated organ dysfunction—most importantly, loss of renal function—which leads to a decreased piperacillin clearance and hence piperacillin accumulation. Third, to assess the effect of piperacillin concentration on the primary outcome mean total SOFA score we also included the mean piperacillin concentration in the linear mixed model, other fixed effects are treatment and renal insufficiency/expected renal replacement, study site was modelled as a random effect. However, we found no evidence that the difference in concentration is affecting the ability to detect the treatment effect. The treatment

effect is even slightly lower than in the model without adjustment ( $\Delta\text{SOFA}=0.1$ , 95% CI  $-0.6$  to  $0.9$ ,  $p=0.71$  with piperacillin adjustment compared to  $\Delta\text{SOFA}=0.3$ , 95% CI  $-0.4$  to  $1.0$ ,  $p=0.39$  without adjustment). Fourth, we agree that patients with an augmented renal clearance (ARC) are at risk for underdosing. In our trial, all patients with an  $\text{eGFR} \geq 20$  ml/min received a daily dose of 13.5 g piperacillin/tazobactam, based on the dosing recommendations of the medicinal product information and also due to the fact that the ultimate aim of the study was to ascertain the benefit of TDM-guided dosing. Giving each patient a higher than recommended dose right from the start would have made the study with its aim to show a benefit for personalized dosing superfluous. Concerning the raised issue that the TDM-based dose adjustment was suboptimal and less than 40% of patients in the TDM arm were within the target range on most of the days of therapy, it must be noted that in our study target attainment was achieved when the piperacillin concentration was within a target range, defined by a lower and upper threshold of piperacillin concentration. This is in contrast to previous studies where target attainment was achieved if the concentration was above a certain threshold and, therefore, apparently higher. Finally, the question about the activity of piperacillin against other than Gram-negative isolates was raised. Looking at the Gram-positive pathogens cultured during the study, overall rate of methicillin resistant *S. aureus* (MRSA) and overall number of *E. faecium*, both non-susceptible to piperacillin/tazobactam, were low. Thus, the influence of an inadequate empiric therapy of non-susceptible Gram-positive pathogens on the overall result should have been rather small.

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### Conflicts of interest

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