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In Response to: Time Matters: Antibiotic timing in Sepsis and Septic Shock

Sarah A. Sterling, MD, Michael A. Puskarich, MD, William R. Miller, MD, and Alan E. Jones, MD¹

¹Department of Emergency Medicine, University of Mississippi Medical Center School of Medicine, 2500 N State St., Jackson, MS 39216, USA

Dear Editor

We read with great interest the letter to the editor from Youke et al.(1) We appreciate their critical appraisal of our previously published paper,(2) and thank the authors for identifying aspects of our methodological approach that require clarification and to address potential discrepancies. We believe the major difference in Youke and colleagues findings and ours is the inclusion of patients for the evaluation of triage time from the Ferrer study.(3) To evaluate the time to antibiotics from triage time, we only included patients with sepsis identified in the emergency department in the analysis and did not include patients when sepsis was identified on the wards or in the intensive care unit (ICU). We would suggest these two groups of patients represent clinically distinct cohorts, as the relative timing of the onset sepsis and hemodynamic instability can be estimated with some degree of accuracy in the inpatient setting, yet is unknowable in the prehospital setting. Due to this significant distinction, we do not believe these data from the inpatient setting can be generalized to the emergency department, and accounts for the major difference in the analyses. Further, the authors of the Ferrer study stated that times to antibiotic administration for those identified in the floor or ICU were measured from the recognition of severe sepsis or shock, whereas those in identified in the ED were measured from triage. On reanalysis of our data, we found that due to a transposition error, our initially reported total number of patients receiving antibiotics in the greater than three hours from triage group was indeed reported incorrectly for the Ferrer and Puskarich studies (no other time points and other studies were impacted) representing a misallocation error.(3;4) This accounts for the 17 additional patients identified by Youke et al in the Puskarich study; however, we could not reproduce the unaccounted 3334 patients presented by Youke et al related to the Ferrer study. In their letter, Youke et al report a total of 17993 patients from the Ferrer study, which in original published form only included 17990 patients in total. It is possible they solicited additional input from the author which altered their numbers and prevents our replication.(1;3) We included only the published numbers from the Ferrer study in our meta-analysis, as per our protocol, we did

Contact Information: Alan E. Jones, MD, Chairman, Department of Emergency Medicine, University of Mississippi Medical Center, 2500 N State Street, Jackson, MS 39216, Tel: +1601-984-5572, Fax: +1601-984-5583, aejones@umc.edu.

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not require additional input from the author since all data was available in published form.
(2)

Taking all of these issues into consideration, and after excluding patients not admitted via the emergency department (consistent with our a priori protocol and analysis plan), our results did not change after re-analysis of the data (Odds Ratio 1.18, 95% CI 0.99–1.39). Consistent with our initial analysis, we found no statistically significant difference in mortality for patients receiving antibiotics in more or less than three hours from emergency department triage time. Though we feel antibiotics are and will remain a vital component of the treatment of sepsis and septic shock, our analysis of the available published literature suggests there is no mortality benefit in antibiotic administration in less than three hours from emergency department triage. We affirm our findings which suggest the current evidence does not support the use of antibiotic timing metrics as markers of quality of care in severe sepsis and septic shock.

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