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In Response to: Timing of Antibiotic Administration in Sepsis and Septic Shock: The Impact That a Meta-Analysis Does Not Depict

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To the Editor

We read with interest the letter from Drs. Shirakura and Kuriyama.¹ Their letter to the editor enumerates several concerns with our previously published systematic review and meta-analysis which evaluated the effect of time to antibiotics on outcomes in severe sepsis and septic shock.² Though some of these limitations were addressed in the manuscript, we feel additional clarification is warranted. The comments offered by Dr. Shirakura et al relate to differences between the aim of our meta analysis, which was to assess the evidence behind a proposed quality metric that has recently been implemented by the United States Center for Medicare and Medicaid Services (CMS) based on the most recent Surviving Sepsis Campaign Guidelines, versus broader questions regarding the optimal treatment of well-defined patients.

The authors point out that there is a broad range of sepsis syndromes and they opine that pooling these patient for evaluation may not be appropriate. The authors note the variance in the clinical presentations of sepsis and the wide variability in patient reserve, response to treatment, and rates of progression. This complexity formed the precise rationale for further evaluation of the proposed quality metric which fails to even acknowledge these critical confounders. As there are no randomized clinical trials evaluating delay in time to antibiotic administration, nor would any be expected due to ethical concerns, we submit that a meta-analysis of the available data us the most reasonable approach to answer our a priori question. As expected and noted in the manuscript, there is significant clinical heterogeneity among included populations. Given the overall size of the combined studies, however, we are confident that our results are largely representative of the general population that visit emergency departments (ED). In clinical practice such heterogeneity is unavoidable and the proposed quality metric makes no attempt to normalize for such differences between patients; our study made no attempt to control for this factor. However, an ideal metric would, in our opinion, consider the severity of illness and clinical confounders when attempt to assess the quality of a resuscitation. While the authors note there has been a reported

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inflection point for survival in murine models of sepsis, a well-controlled model with minimal heterogeneity, there is no current method of identifying the exact point prior to hospital arrival the patient may or may not have reached such an inflection point, making this observation moot in actual clinical practice.

The authors also address the use of “less than one hour” from time to antibiotics from shock recognition as the reference group. They point out concerns with the utilization of this reference point especially in the case of Ferrer et al⁵, the largest contributor of patients in our analysis, citing higher mortality and higher severity scores in the “less than one hour” group in that study. Given that the current guideline recommendations suggest antibiotics within less than one hour of shock recognition, this was the only reasonable reference group as that time point is the proposed standard.

Finally, the authors regret our exclusion of studies evaluating only neutropenic or immunocompromised patients. These patients were excluded as our goal was to evaluate the impact of time to antibiotics in severe sepsis and septic shock in the typical patient, and inclusion of such studies would have introduced unnecessary selection bias into our study as studies of these patients represents a proportionally larger component of the literature than in clinical practice. However, we agree with the authors that these patients represent a particularly vulnerable population and thus we believe should be evaluated in separate analyses.

In summary, based on the available literature, we found patients failing to meet the Surviving Sepsis Campaign and CMS quality metric for timing of antibiotics did not demonstrate significantly increased mortality compared to patients meeting the measure in undifferentiated ED patients with severe sepsis. We appreciate the authors’ response and thoughtful insights and agree that the Surviving Sepsis Campaign has increased recognition, overall care, and outcomes of patients with sepsis. However, based on our analysis the current literature evidence does not support the current recommended time frames regarding time to antibiotics as a marker of the overall quality of care in severe sepsis and septic shock.

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