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In Response to: Meta-Analysis of time to antimicrobial therapy in sepsis: Confounding as well as bias

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To the Editor

We read with interest the letter to the editor from Dr. Brent and appreciate his insights (1). Dr. Brent rightfully points out the importance of confounders and their effects on observed associations. Additionally, he notes that in our systematic review and meta-analysis evaluating the impact of the timing of antibiotics on outcomes in severe sepsis and septic shock, we did not control for confounders, which could have affected our results. (2) Dr. Brent is correct in his assertion that we did not control for factors such as severity of illness; however, it was not for a lack of appreciation in the importance of this, but simply a result of the limitation of the available data in the published literature.

While many of the studies included in the meta-analysis did control for severity of illness, the granularity of this data was not available. Therefore, while severity of illness and/or organ dysfunction was often controlled for and reported, patient level data regarding which patients received antibiotics during particular time frames and their associated markers of illness severity in conjunction with mortality were not available. Additionally, all studies included in the meta-analysis did not evaluate severity of illness similarly. These factors made accurate evaluation of the effect of confounders difficult to assess in a meta-analysis, as Dr. Brent points out often the case in this study design.

As mentioned in our original manuscript, the intent of our study was to inform the discussion on the importance of data-driven quality metrics, not to imply that antibiotic administration is not important to patient care and outcomes in severe sepsis and septic shock (2). As the quality metrics advocated by the National Quality Forum and Centers for Medicare and Medicaid Services make no attempt to adjust for severity of illness, and our meta-analysis was intended to critically evaluate the evidence behind this metric as written, we made no attempt to make such an adjustment. Therefore, given the available published

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data at the time, this meta-analysis does not support the use of time to antibiotics as defined by the specific cutoffs studied in our analysis as a marker of quality of care in severe sepsis or septic shock.

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