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In Response to: Systematic Bias in Meta-analyses of Time to Antimicrobial in Sepsis Studies

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Sepsis; septic shock; antibiotics; time to antibiotics

To the Editor

We read with great interest the letter to the editor from Dr. Kumar (1). Dr. Kumar lists several weaknesses present in the existing published literature assessing the effect of time to antibiotics on outcomes in severe sepsis and septic shock as presented in our recent systematic review and meta-analysis.(2) These limitations were addressed in our original report, most notably the lack of evaluation on appropriateness of antibiotics on outcomes.(2) However, we feel further clarification is warranted.

The intent of our study was not to evaluate the impact of the time to effective antibiotics on outcomes in severe sepsis and septic shock. Rather, our goal was to evaluate the impact of incremental time to antibiotics as markers of quality of care in severe sepsis or septic shock. Given the recent Center for Medicare and Medicaid Services requirement for mandatory reporting on adherence to National Quality Forum Measure 0500 - Severe Sepsis and Shock Management Bundle, we thought it necessary to evaluate the evidence base driving this particular component of the metrics (broad spectrum antibiotic administration within three hours of triage time or one hour from shock onset) and determine if there is an actual meaningful effect on patient outcomes.(3)

Dr. Kumar astutely recognizes that treatment with ineffective antimicrobial agents could be viewed by some as being equivalent to not receiving an antimicrobial agent at all. However, again from a quantitative metric of the quality of care provided, it is an unreasonable expectation that clinicians be held to a standard of administration of effective or “appropriate” antibiotics in the earliest hours of resuscitations given that the data needed to confirm this standard (organism, sensitivity, etc.) is typically not available for many hours or even days after the initial antimicrobial decision. Further, appropriateness would be impossible to determine in cases where sepsis is expected to be culture negative, which

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represents a significant portion of sepsis cases. (4) Additionally, if time to antibiotics is used as a marker of quality of care in sepsis management but does not actually impact outcomes, as our analysis suggests, this could encourage unthoughtful use of broad-spectrum antibiotics simply to attain compliance with the metrics, with potential detrimental effects on antibiotic stewardship and side effects to patients, but without reasonable benefit.

Finally, Dr. Kumar raises a concern that most of the studies included in our report originated from emergency department (ED) patient cohorts and cites this as a potential source of bias. This was a necessary component of our criteria as our goal was to assess the evidence base driving recommended metrics, and the ED is where the majority of sepsis patients initially are evaluated.(5) He states that approximately half of the patients who present to the ED will have pre-existing hypotension upon ED arrival (based on unpublished data from the CATSS database), suggesting that not knowing with any certainty when hypotension began in the prehospital setting biases the data towards the null. The included figure in his letter suggesting a 70% mortality rate when antibiotics are delayed between 2–6 hours is not consistent with previously published data in contemporaneous ED cohorts and does not inform the discussion in any meaningful way. (6, 7) Nevertheless, at this current time, the time of hypotension onset prior to ED arrival and time to treatment and interventions are not part of the consensus recommendations nor quality metrics, which served as the basis for this analysis. (3)

We are appreciative to Dr. Kumar for his work in this area and his insights and suggestions about our report. We look forward to further studies from him and others that will no doubt continue to shed light on the impact of the time to antibiotics on outcomes in severe sepsis and septic shock. Although Dr. Kumar is skeptical, we stand firmly behind our reported analysis of the current literature that suggests no mortality benefit with the administration of antibiotics as recommended by the current guidelines, suggesting the current evidence does not support the use of these antibiotic timing metrics as markers of quality of care.

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Reference List

1. Kumar A. Systematic Bias in Meta-analyses of Time to Antimicrobial in Sepsis Studies. *Crit Care Med.* 2016 in press.
2. Sterling SA, Miller WR, Pryor J, et al. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Med.* 2015; 43:1907–1915. [PubMed: 26121073]
3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013; 41:580–637. [PubMed: 23353941]
4. Heffner AC, Horton JM, Marchick MR, Jones AE. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. *Clin Infect Dis.* 2010; 50:814–820. [PubMed: 20144044]
5. Wang HE, Shapiro NI, Angus DC, Yealy DM. National estimates of severe sepsis in United States emergency departments. *Crit Care Med.* 2007; 35:1928–1936. [PubMed: 17581480]

6. Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014; 370:1683–1693. [PubMed: 24635773]
7. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010; 303:739–746. [PubMed: 20179283]

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