Antimicrobial Delay and Outcome in Severe Sepsis

To the Editor:

I read with great interest the article by Ferrer et al (1) that shows the results of their retrospective analysis of a severe sepsis/septic shock dataset collected in conjunction with the work of the Surviving Sepsis Campaign. The authors should be lauded for their confirmation that time to antimicrobial therapy is a critical determinant of survival in septic shock, a finding that reflects our own published observations several years past (2, 3). However, the authors suggest that their data show that severe sepsis (absent septic shock) also shows a substantial antimicrobial delay-dependent mortality risk.

This proposition appears questionable based on the presented data. Table 1 presented by Ferrer et al (1) shows that septic shock accounts for approximately 64.2–70.7% of cases in the dataset depending on whether the total number of cases labeled septic shock or total shock (inclusive of elevated lactate, vasopressor use, or both) are used. Further, I understand that the authors classified those patients who did not present with shock as severe sepsis. Based on our own Co-operative Antimicrobial Therapy of Septic Shock Database (4), as many as 15–20% of patients presenting with severe sepsis may progress to septic shock despite appropriate antimicrobials. If those are included in the total, then the total fraction of cases with septic shock within the Surviving Sepsis Campaign dataset used in this study may be 80–90%. This value is congruent with the approximate 90% frequency of cardiovascular dysfunction (which is not defined) noted as an organ failure in the study (1).

Regrettably, the study authors do not show any separate data on the relationship of delays in antimicrobial therapy to outcome of severe sepsis without septic shock. Given the powerful relationship between delays in antimicrobial and outcome of septic shock shown by both the study authors and ourselves, it is very likely that the relationship in the full dataset may be driven by the septic shock subgroup. There are theoretical reasons why a relationship to outcome might not be expected to exist with delays in antimicrobial therapy of sepsis without shock (5). A similar comment could be made for a variety of other well-known retrospective studies examining antimicrobial delays in severe infections (6).

There is a significant impetus to validate the Surviving Sepsis guidelines that recommend antimicrobial initiation within an hour of recognition of both septic shock and severe sepsis without septic shock (7). However, given the adverse impact of excessive antimicrobial use on the emergence of resistance, such guidelines should be supported by the most rigorous possible analysis of available data. An analysis of severe sepsis cases that do not progress to septic shock would be well advised.

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REFERENCES

1. Ferrer R, Martin-Loeches I, Phillips G, et al: Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program. *Crit Care Med* 2014; 42:1749–1755
2. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
3. Kumar A, Haery C, Paladugu B, et al: The duration of hypotension before the initiation of antibiotic treatment is a critical determinant of survival in a murine model of *Escherichia coli* septic shock: Association with serum lactate and inflammatory cytokine levels. *J Infect Dis* 2006; 193:251–258
4. Kumar A, Zarychanski R, Light B, et al; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group: Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis. *Crit Care Med* 2010; 38:1773–1785
5. Kumar A: An alternate pathophysiologic paradigm of sepsis and septic shock: Implications for optimizing antimicrobial therapy. *Virulence* 2014; 5:80–97
6. Meehan TP, Fine MJ, Krumholz HM, et al: Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997; 278:2080–2084
7. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637

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The authors reply:

We thank Dr. Kumar (1) for his thoughtful letter and the opportunity to present some further data that will hopefully clarify his questions as well as provide further information for the readership. Dr. Kumar (1) raises the question of whether our study shows a substantial antimicrobial delay-dependent mortality risk in patients with severe sepsis (absent septic shock). The authors appreciate the opportunity to address this question since; due to space limitations, we could not show the data on the analysis of patients with severe sepsis alone, although we allude to this population in the article. It is true that septic shock accounted for 65–70% of patients in the database. It is also true that we did not continuously monitor patients for progression to sepsis throughout their ICU/hospital stay. However, if emergency department (ED) patients progressed to septic shock and were on vasopressors by the time they arrived in the ICU, they were classified as septic shock. All patients entered into the database had to be admitted to the ICU. Then the data collector screened the charts for severe sepsis and septic shock.

We captured patients who were admitted to the ICU, and then entered origin of admission and time of presentation (To = ED triage time). If their diagnosis on arrival to the ICU was septic shock on vasopressors, then that was how they were entered into