The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis

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Objectives: We sought to systematically review and meta-analyze the available data on the association between timing of antibiotic administration and mortality in severe sepsis and septic shock.

Data Sources: A comprehensive search criteria was performed using a predefined protocol.

Study Selection: Inclusion criteria: adult patients with severe sepsis or septic shock, reported time to antibiotic administration in relation to emergency department triage and/or shock recognition, and mortality. Exclusion criteria: immunosuppressed populations, review article, editorial, or nonhuman studies.

Data Extraction: Two reviewers screened abstracts with a third reviewer arbitrating. The effect of time to antibiotic administration on mortality was based on current guideline recommendations: 1) administration within 3 hours of emergency department triage and 2) administration within 1 hour of severe sepsis/septic shock recognition. Odds ratios were calculated using a random effect model. The primary outcome was mortality.

Data Synthesis: A total of 1,123 publications were identified and 11 were included in the analysis. Among the 11 included studies, 16,178 patients were evaluable for antibiotic administration from emergency department triage. Patients who received antibiotics more than 3 hours after emergency department triage (< 3 hr reference) had a pooled odds ratio for mortality of 1.16 (0.92–1.46; $p = 0.21$). A total of 11,017 patients were evaluable for antibiotic administration from severe sepsis/septic shock recognition. Patients who received antibiotics more than 1 hour after severe sepsis/shock recognition (< 1 hr reference) had a pooled odds ratio for mortality of 1.46 (0.89–2.40; $p = 0.13$). There was no increased mortality in the pooled odds ratios for each hourly delay from less than 1 to more than 5 hours in antibiotic administration from severe sepsis/shock recognition.

Conclusion: Using the available pooled data, we found no significant mortality benefit of administering antibiotics within 3 hours of emergency department triage or within 1 hour of shock recognition in severe sepsis and septic shock. These results suggest that currently recommended timing metrics as measures of quality of care are not supported by the available evidence. (*Crit Care Med* 2015; XX:00–00)

Key Words: antibacterial agents; antibiotics; septic shock; severe sepsis; shock recognition; timing of antibiotics

Severe sepsis and septic shock remain a major cause of emergency department (ED) visits and ICU admissions and are associated with significant morbidity, mortality, and healthcare costs (1, 2). Previous studies have suggested improved outcomes with the implementation of a structured resuscitation, focusing largely on IV fluid resuscitation, timely broad-spectrum antibiotics, and vasopressor therapy (3–7). Although some authors have suggested the primacy of timely antibiotics administration for improved mortality in severe sepsis and septic shock (8, 9), previously published research evaluating the association of the time to antibiotic administration on outcomes has produced disparate results.

In 2006, Kumar et al (10) reported a 7.6% increase in mortality in patients with sepsis for each hourly delay after the onset of shock. Although subsequent studies have failed to demonstrate such substantial results, several studies have reported increased mortality associated with delays in antibiotic administration either from shock recognition or time from ED triage (8–10). Other studies have not demonstrated any increase in mortality with delay of antibiotic administration based on triage time (11, 12).

The most recent Surviving Sepsis Campaign (SSC) guidelines include specific recommendations regarding the timing

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TABLE 1. Scoring Criteria for Included Articles in Systematic Review

Score	Study Design	Identification of Patients With Sepsis	Population Sampling	Data on Timing of Antibiotics
2	Implementation	Standard, consensus definition	Consecutive or random	Prospectively entered
1	Prospective	Nonstandard criteria	Convenience	Described record extraction
0	Retrospective	Not defined or unknown	Not specified or unknown	Not described or unknown

Maximum score of 8: 0–3 low quality, 4–6 moderate quality, and > 6 high quality.

of antibiotics: "The administration of effective IV antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) should be the goal of therapy" (13). Additionally, the SSC recommends a "sepsis bundle," which requires administration of broad-spectrum antibiotics within 3 hours from ED triage. The authors of the SSC guidelines note that achieving these goals may not be operationally feasible in some cases and acknowledge that previous research has shown that compliance with guidelines regarding antibiotic administration frequently is not achieved (12–14). Despite these limitations, time to antibiotics administration has gained increasing focus as a potential metric for the quality of care of patients with severe sepsis and septic shock (15).

To our knowledge, no previous study has pooled the available data to evaluate the impact of time to antibiotics on sepsis outcomes. Our objective was to perform a systematic review of the published literature and to meta-analyze the available data on the association between the timing of antibiotics and mortality in severe sepsis and septic shock.

METHODS

We developed and followed a comprehensive protocol and data collection instrument that followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (16) recommendations prior to the start of the study. As this was not a study of human subjects but rather a synthesis of the previously published literature, it was exempt from institutional review board approval.

Search Strategy

A comprehensive literature search was performed using a predefined, written protocol of The Cochrane Database, CINAHL, PubMed, and Scopus databases with no start date to January 2015. The search criteria, developed with the help of a medical librarian, used the following Medical Subject Headings terms:

1. Septic shock OR Severe sepsis OR Sepsis AND
2. Antibacterial agents OR Antibiotics

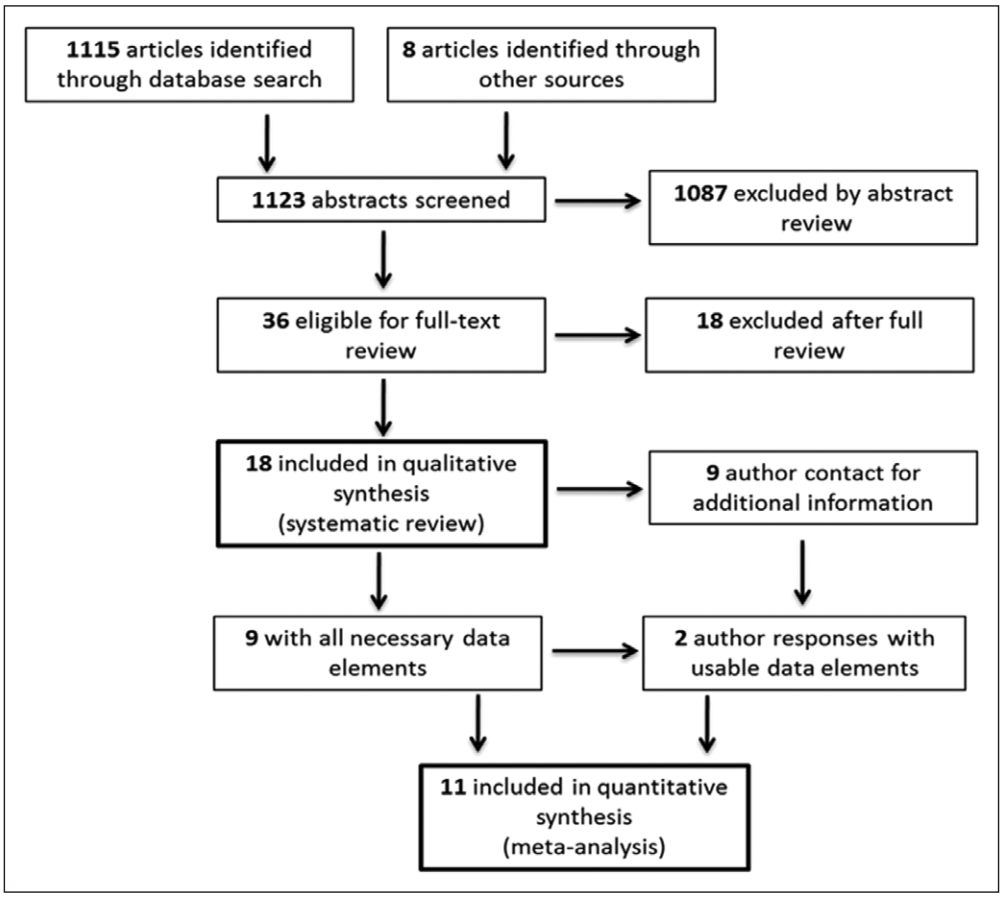

Figure 1. Flowchart for inclusion in systematic review and meta-analysis.

Inclusion and Exclusion Criteria and Outcomes

Articles were eligible for inclusion if they evaluated human patients with severe sepsis or septic shock, reported timing of antibiotic administration from ED triage and/or septic shock/severe sepsis recognition, and reported mortality data. Studies involving nonhumans, those involving patients less 18 years old, and those focused solely on neutropenic or immunocompromised subjects were excluded. Review articles, editorials, case studies, and letters to the editor were excluded, although bibliographies were

evaluated for relevant articles. Given an anticipated limited availability of high-quality clinical trials evaluating our stated objective, all study types, except those previously mentioned, were eligible for inclusion. If the time to antibiotics or mortality was not explicitly reported, the study was potentially eligible for inclusion pending author contact. The primary outcome was mortality.

Study Selection

Two authors (S.A.S., J.P.) independently reviewed abstracts of all relevant studies yielded from the initial search. In cases of disagreement, a review of the full article was conducted and inclusion determined by a third reviewer (A.E.J.). The full article of each study passing the relevance screen was independently reviewed for eligibility by two authors (S.A.S., W.R.M.). In cases of disagreement, a third reviewer (A.E.J.) determined inclusion. Data abstraction was performed using a standard data collection form for each study identified for final inclusion. For articles that did not include complete data for inclusion in the meta-analysis portion, corresponding authors were contacted for additional information.

Quality Assessment

Though there is limited validity of scoring nonrandomized control trials for quality (17), we elected to utilize a scoring system to determine study quality, given the anticipated inclusion of multiple study types. Therefore, we developed predetermined a scoring system for all included studies based on commonly excepted measures of quality, with four categories were scored between 0 and 2 (**Table 1**).

Timing of Antibiotic Administration and Statistical Analysis

The effect of time to antibiotic administration on mortality was assessed in two ways based on the SSC guideline recommendations (13): 1) antibiotic administration within 3 hours of hospital presentation/ED triage and 2) antibiotic administration within 1 hour of severe sepsis/septic shock recognition.

To assess the association between mortality and the time to antibiotics from triage, the antibiotic timing was categorized as within 3 hours of triage or 3 hours and longer from triage with the former used as the reference group. To evaluate association between mortality and the time from septic shock/severe sepsis recognition to antibiotic administration, the antibiotic timing was categorized as within 1 hour or more than 1 hour from shock/severe sepsis recognition. We also performed a sensitivity analysis of the effect of time to antibiotics from severe sepsis/shock recognition in hourly increments (1–2, 2–3, 3–4, 4–5, > 5 hr) using less than 1 hour as the reference group. Odds ratios (OR) and 95% CIs were calculated using a random effect model (18). Publication bias was assessed using funnel and L'Abbe plots. Heterogeneity was assessed using Cochran Q test.

RESULTS

Study Inclusion

Our comprehensive literature search yielded 1,123 publications for possible inclusion. Of these, 36 were deemed relevant and eligible for full review with good interrater agreement (98.5%) in those identified. After full review and adjudication, 18 articles were deemed potentially eligible for inclusion. Of these, nine contained data for meta-analysis and nine required author contact for clarification of the data. After author contact, two articles provided additional data, leaving 11 articles for the full meta-analysis (**Fig. 1**). A summary of reasons for exclusion at each stage of the analysis is shown in **Table 2**. Of the 11 included articles, three contained only data for timing from triage, five contained only data for timing from severe sepsis/septic shock recognition, and three contained data for both time points. All of the studies included in the meta-analysis were considered moderate-to-high quality (> 4 points) by our quality score (**Table 3**).

TABLE 2. Summary of Reasons for Exclusion at Each Stage of Search

Reason for Exclusion	No. of Reports
After relevance screen	
No antibiotic timing	131
Mortality data	10
Wrong focus/wrong group	608
Editorial, Letter, Conference articles	104
Neutropenic/immunocompromised	64
Nonhuman study	73
Pediatrics	10
Non-English	4
Antibiotic prophylaxis	83
Total	1,087
After article review	
Wrong focus/wrong group	9
Review/abstract	3
Mortality data	5
Non-English	1
Total	18
After author contact	
Failed author contact	5
Positive author response but unable to use data	2
Total	7

Study Descriptions and Analyses

A list of 18 studies potentially eligible for inclusion were systematically reviewed and summarized in tabular format for the study characteristics, main findings, justification for inclusion/exclusion in meta-analysis, and quality assessment and listed in Table 3.

Six of the 11 included studies contained the necessary data on 16,178 patients for inclusion in the analysis of the effect of time to antibiotic administration from triage on mortality.

TABLE 3. Summary of Included Studies

Authors	Patient Location	Primary Outcome	Study Sites	Years Conducted
Bloos et al (29)	ICU	28-d mortality	Multicenter, German	2010–2011
Bruce et al (30)	ED	3 hr Surviving Sepsis Campaign targets, in-hospital mortality	Single center, United States	2011–2012
Cullen et al (31)	ICU	TTA	Single center, Australia	2005–2008
Ferrer et al (34)	ICU	In-hospital mortality	Multicenter, Europe	2005–2007
Ferrer et al (8)	ED/ICU	In-hospital mortality	Multicenter United States, Europe, South America	2005–2010
Gaieski et al (9)	ED	In-hospital mortality	Single center, United States	2005–2006
Gurnani et al (32)	ICU	TTA and appropriate fluid resuscitation	Single center, United States	2006–2007
Hitti et al (33)	ED	TTA from order	Single center, United States	February 2008 to May 2008
Hutchison et al (19)	Not specified	Discharge status, hospital/ICU LOS, TTA, cost	Single center, United States	2008–2009
Joo et al (35)	ED	In-hospital mortality	Single center, Korea	2008–2012
Kumar et al (10)	ED/ward/ICU	In-hospital mortality	Multicenter, United States, Canada	1989–2004
Mok et al (36)	Ward/ICU	TTA	Single center, Canadian	2009–2010
Puskarich et al (11)	ED	In-hospital mortality	Multicenter, United States	2007–2009
Ryoo et al (37)	ED	28-d mortality	Single center, United States	2010–2012
Tipler et al (38)	ED/ICU	TTA from physician order	Single center, United States	2008–2010
Venkatesh et al (12)	ED	Time to septic shock recognition	Single center, United States	2006–2008
Vilella and Seifert (14)	ED	TTA, appropriate antibiotics	Single center, United States	2010–2011
Yokota et al (39)	ICU	Bundle compliance, appropriate antibiotics	Single center, Brazil	2005–2012

ED = emergency department, TTA = time to antibiotic, LOS = length of stay.

A total of 10,208 patients receiving antibiotics within 3 hours of triage of whom 2,574 died and 5,970 patients receiving antibiotics in 3 or more hours after triage of whom 1,793 died. As seen in **Figure 2**, the pooled OR for patients who received antibiotics 3 or more hours after triage was 1.16 (95% CI, 0.92–1.46; $p = 0.21$) as compared to those that received antibiotics within 3 hours of triage. No statistical heterogeneity ($p = 0.09$) or publication bias was observed.

Eight of the 11 studies contained the necessary data on 11,017 patients for inclusion in analysis of the effect of time to antibiotics administration from severe sepsis/septic shock recognition. A total of 3,335 patients were included in the within

No. of Patients	Timing of Antibiotics	Quality Scoring (Maximum = 8)	Reason for Exclusion	Primary Finding
1,011	Sepsis recognition	6	Included	No significant association between TTA and survival
195	Triage	4	Included	Protocol implementation reduced TTA but did not significantly improve mortality
89	Sepsis recognition	4	Mortality data	Median TTA and time to appropriate antibiotics exceeded 1 hr
2,796	Sepsis recognition	8	Included	Early antibiotic treatment was associated with improved mortality
17,990	Sepsis recognition and triage	5	Included	Delay in antibiotic associated with no increased mortality in unadjusted analysis but increased mortality in adjusted analysis
261	Sepsis recognition and triage	5	Included	No significant association from triage TTA and mortality. Significant association with mortality and appropriate antibiotics in < 1 hr
118	Sepsis recognition	8	Mortality data	A sepsis protocol emphasizing early antibiotics and adequate fluids improved clinical outcomes
110	Triage	5	Mortality data	Storing antibiotics in the ED reduces TTA
119	Triage	6	Mortality data	Significant reduction in TTA, but no difference in mortality
591	Triage	4	Included	Antibiotics within 3 hr of ED arrival associated with improved mortality
2,731	Sepsis recognition	5	Included	Antibiotics in 1st hr of hypotension increased survival
100	Sepsis recognition	5	Mortality data	Median TTA exceeded 1 hr time frame
291	Sepsis recognition and triage	7	Included	No increase in mortality with hourly delays from triage or sepsis recognition
426	Sepsis recognition	4	Included	Mortality did not increase with hourly delays to antibiotics
209	Sepsis recognition	5	Mortality data	A sepsis protocol improved TTA, but TTA still > 1 hr time frame
267	Sepsis recognition and triage	5	Mortality data	TTA from triage would misclassify performance on a large number of pts
184	Triage	5	Included	Times to 1st and last antibiotics were not associated with survival
1,279	Sepsis recognition	5	Included	Appropriate antibiotics improved mortality

1 hour of recognition group of whom 1,174 died and 7,682 patients received antibiotics in 1 or more hours after severe sepsis/shock recognition of whom 3,581 deaths. The pooled OR for patients who received antibiotics in more than 1 hour of severe sepsis/shock recognition was 1.46 (95% CI, 0.89–2.40; $p = 0.13$) compared with those who received antibiotics within 1 hour of severe sepsis/septic shock recognition (Fig. 2). Although we did find statistical heterogeneity ($p < 0.001$), there was evidence of no publication bias. The total number of included patients from each study is listed in **Table 4**.

In the sensitivity analysis, four of the 11 studies contained complete data at every time point between less than 1 hour

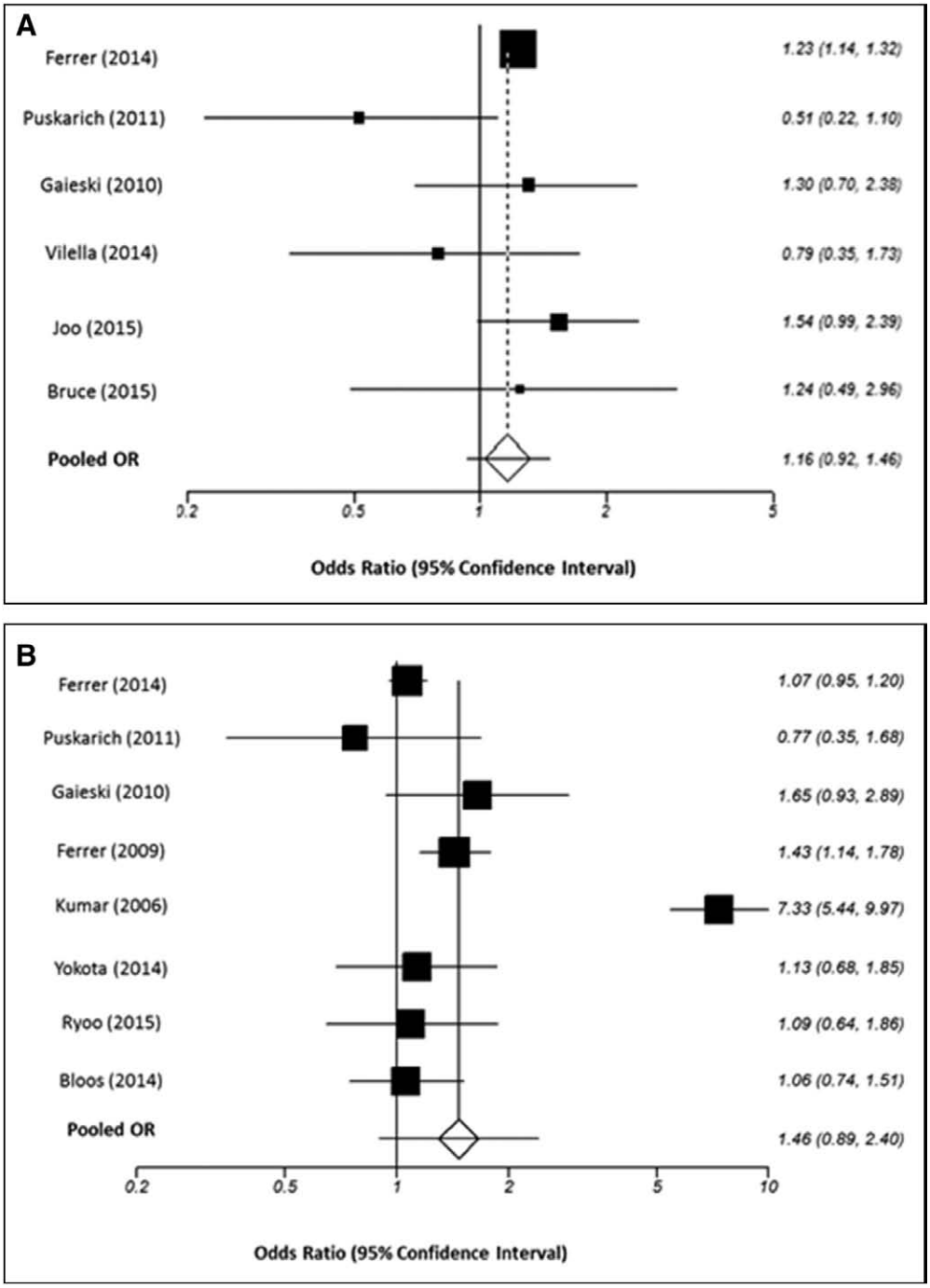

Figure 2. Summary of forest plots. **A**, Pooled odds ratios for mortality and time to antibiotics in less than or more than 3 hr from triage time. **B**, Pooled odds ratios for mortality and time to antibiotics in less than or more than 1 hr from severe sepsis/shock recognition.

and more than 5 hours for further assessment of the effect of hourly delays to antibiotic administration from severe sepsis/shock recognition. The groups contained 848 deaths of 2,318 patients in the less than 1-hour group, 471 deaths of 1,298 patients in the 1- to 2-hour group, 323 deaths of 853 patients in the 2- to 3-hour group, 245 deaths of 615 patients in the 3- to 4-hour group, 193 deaths of 453 patients in the 4- to 5-hour group, and 1,537 deaths of 2,386 patients in the more than 5-hour group. We observed no statistical significant increased mortality in the pooled ORs for each hourly incremental delay in antibiotic administration from severe sepsis/shock recognition (**Table 5**).

DISCUSSION

The SSC international guidelines for the management of severe sepsis and septic shock recommend administering antibiotics within 1 hour of recognition and within 3 hours of ED triage (13). Using the available published data, our results indicate that in patients with severe sepsis and septic shock, antibiotic administration within 3 hours of ED triage and/or within 1 hour of shock recognition is not associated with significant improvement in mortality. Our findings do not support the SSC guideline recommendations on timing of antibiotic administration and raise concern about the use of time to antibiotic administration as currently recommended as a specific metric of treatment quality in sepsis care (13).

The recognition and treatment of severe sepsis and septic shock remain a complex and challenging burden for clinicians with a persistently high mortality rate (1, 2, 12). In the past 15 years, research has suggested that an early structured approach to recognition and treatment of sepsis improves outcomes likely due to a combination of factors including heightened recognition or awareness, early reversal of microcirculatory or endothelial dysfunction, reversal of hypoperfusion, and/or eradication of infectious nidus (3–5, 7). However, the results of studies focusing on the impact of timing of antibiotic administration have been inconsistent (8, 9, 11, 14, 19).

While it is recognized that failure to administer effective antimicrobial therapy will at some time point be detrimental to patient outcomes, the exact time frame when this shift begins to occur remains unknown. Furthermore, no randomized clinical trials examine the impact of the timing of antibiotics on

TABLE 4. Total Number of Patients Included in Meta-Analysis From Each Study

Author	No. of Patients
Meta-analysis based on triage time	
Ferrer et al (8)	14,639
Puskarich et al (11)	308
Gaieski et al (9)	261
Vilella and Seifert (14)	184
Joo et al (35)	591
Bruce et al (29)	195
Meta-analysis based on severe sepsis/shock recognition	
Ferrer et al (8)	5,062
Puskarich et al (11)	172
Gaieski et al (9)	261
Ferrer et al (34)	1,737
Kumar et al (10)	2,174
Yokota et al (39)	358
Ryoo et al (37)	426
Bloose et al (29)	827

outcomes directly (20), and for obvious reasons, it is unlikely any direct experimental investigation will be planned in the near future given current guideline recommendations and ethical concerns regarding patient safety of such a design (13). Thus, our results represent the most comprehensive and robust analysis of the differentiation and true impact of timing of antibiotic administration on outcome during the earliest phases of sepsis care.

There are multiple potential explanations for our findings of no mortality benefit when antibiotics are given within 3 hours of triage or 1 hour of severe sepsis/septic shock recognition. First, given the complexity of the pathophysiologic insult of sepsis and resulting organ dysfunction, it is unlikely that a limited single point in time intervention, such as administration of a single dose of antibiotics, would have a profound and singular impact on survival. In fact, no other therapeutic agent has ever been shown to provide this effect despite many decades of research. As recently found in the Protocolized Care for Early Septic Shock trial, many of the aggressive interventions targeted over the last several years may not be as impactful as initially reported (21). Second, it is plausible that in some patients, the initiation of resuscitation prior to the administration of antibiotics provides the most ideal circumstance for the host to have a sustained and robust hemodynamic response to the propagation of the inflammatory cascade and resultant insult that can be instigated by release of components during bacterial lysis (22–25).

Time to antibiotic administration is a logical and tempting metric to target when considering the quality of sepsis care. Venkatesh et al (12) examined whether using the SSC recommendation metric of 3 hours from ED triage to antibiotic administration could adequately characterize what is realized in practice. In this study, the triage-based metric performed poorly, misclassifying 23.4% of patients, likely due to the variable progression and clinical course in severe sepsis and septic shock. Furthermore, Villar et al (26) found that 15% of patients with documented severe sepsis and septic shock do not meet diagnostic criteria until more than 3 hours after hospital arrival. Both studies concluded that a triage-based metric was inadequate to evaluate ED performance in severe sepsis and septic shock and suggested that time to antibiotics from triage is not a reliable quality metric (12, 26). Our results provide quantitative data to support these conclusions in that we found no mortality benefit when antibiotics were administered within 3 hours of triage or 1 hour of severe sepsis/septic shock recognition.

We believe that an incorrect interpretation of this report would be that early administration of antibiotics is not of substantial importance. Antimicrobial administration is largely considered the cornerstone therapy for bacterial infections and a mandatory component of the management of severe sepsis and septic shock. Rather, our results should serve to highlight the importance of data-driven and evidence-based metrics for measuring quality in the care of acute critical conditions, such as sepsis, rather than empiric, arbitrary, or nonevidence-based metrics that do not have patient-oriented outcome benefit, are not operationally feasible, and/or cannot be practically achieved in a comprehensive individual and systems change approach.

As a systematic review and meta-analysis of previously published literature, our results are limited by the inherent flaws

TABLE 5. Odds Ratios for Mortality From With Each Hourly Incremental Delay in Antibiotic Administration From Severe Sepsis/Septic Shock Recognition

Author	< 1 Hr	1–2 Hr	2–3 Hr	3–4 Hr	4–5 Hr	> 5 Hr
Ferrer et al (8)	Reference value	0.94 (0.80, 1.12)	0.89 (0.73, 1.08)	0.92 (0.73, 1.15)	0.97 (0.75, 1.25)	1.38 (1.18, 1.61)
Gaieski et al (9)	Reference value	1.65 (0.84, 3.20)	1.38 (0.44, 3.96)	1.72 (0.42, 6.36)	4.13 (0.45, 50.6)	0.92 (0.02, 11.82)
Kumar et al (10)	Reference value	1.67 (1.10, 2.53)	2.59 (1.67, 4.01)	3.01 (1.94, 4.67)	3.98 (2.45, 6.47)	15.23 (11.1, 21.1)
Ryoo et al (37)	Reference value	0.91 (0.47, 1.75)	1.31 (0.62, 2.71)	1.17 (0.39, 3.14)	1.10 (0.30, 3.39)	1.30 (0.34, 4.13)
Pooled odds ratio (95% CI)	Reference value	1.21 (0.84, 1.72)	1.42 (0.76, 2.67)	1.53 (0.72, 3.28)	1.90 (0.72, 5.01)	2.47 (0.46, 13.36)

and shortcomings of the included parent studies. Also, no randomized clinical trials have directly examined the effect of time to antibiotic administration on outcomes; our data were derived from cohort studies and different patient populations. While a randomized trial of immediate versus delay antibiotic administration would be difficult to design and implement, given the current variability of associative data, such a trial would be a substantial contribution to the current evidence base. Third, there was evidence of statistical heterogeneity among the included studies evaluating time to antibiotic administration from severe sepsis/shock recognition. While this is a limitation, given the large sample size in this study, the findings appear to be robust and maintain validity.

Several publications appeared to have patient populations that had the potential to be included in our analysis but did not contain data that would allow for inclusion and analysis. We attempted author contact in these cases on three different occasions. We received responses in half of these requests and no response, either positive or negative, in half of requests. Although we followed recommended methodology for making valiant attempts to obtain all potential data for inclusion, it remains possible that their inclusion could have altered the results of this study and the lack of their inclusion heightens the possibility of information bias in our report.

Finally, we did not limit our study to appropriate or effective antibiotics (defined as an identified organism with in vitro sensitivity to an administered antibiotic). This was an a priori decision and viewed by the authors as the most clinically relevant and valid approach. Our rational for this decision were as follows: 1) our primary aims were to evaluate the antibiotic recommendations of the SSC guidelines, which recommend that broad-spectrum antibiotics that are likely effective based on patient history and local antibiogram-resistant patterns, but do not specify that the antibiotics should be "appropriate" (i.e., sensitive to the subsequently cultured microbe); 2) including appropriateness of antibiotic choice into a meta-analysis would introduce irreconcilable clinical heterogeneity because undoubtedly the standard definition of appropriateness would vary greatly between articles, including deciding on which cultures to include, what constitutes a positive culture, and how to handle conditions in which cultures are expected to be negative (such as cellulitis); 3) half or more of sepsis cases are culture negative and information on the offending organism and sensitivities are almost never available to treating clinicians at the time of antibiotic choice and administration, often taking between 12 and 120 hours for bacterial speciation and sensitivities using traditional blood culture techniques (27, 28). In a post hoc review of the studies included in the meta-analysis, several studies mentioned appropriate antibiotics, but only one contained usable population-level data on the effect of appropriate or effective antibiotics on mortality. Among the studies that mentioned appropriate antibiotic therapy, there were vast differences in definitions for appropriate or effective antibiotics, highlighting the clinical heterogeneity with this definition. Following are the some examples of the various definitions: a) One study included culture-negative shock, but guideline-adherent broad-spectrum antibiotics and for culture-positive patients, in vitro activity against causative organism. This article only evaluates those with appropriate antibiotics administered within 6 hours of first antibiotic treatment; b) one study reported only culture-positive patients, with appropriateness of antibiotics determined within 24 hours of diagnosis, not the initial dose of antibiotics; c) one study discussed but never defined appropriate antibiotics; d) one study defined local institutional antibiotic guideline adherence as appropriate regardless of culture results. Although we recognize that the impact of appropriate or effective antibiotics in the early resuscitation of severe sepsis and septic shock remains an important question, there do not appear to be data available for meta-analysis of this subgroup, and we suggest that future investigations should address this question with standard definitions and approaches.

CONCLUSION

In this comprehensive analysis of pooled data from the available literature in patients with severe sepsis and septic shock, administration of antibiotics within 3 hours of ED triage or within 1 hour of recognition of severe sepsis/septic shock did not confer mortality benefit. These results suggest that currently recommended specific timing metrics in international guidelines are not supported by the currently available evidence. Future stakeholders should consider these data when developing metrics to measure quality of care in severe sepsis and septic shock.

REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
2. Wang HE, Shapiro NI, Angus DC, et al: National estimates of severe sepsis in United States emergency departments. *Crit Care Med* 2007; 35:1928–1936
3. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
4. Jones AE, Focht A, Horton JM, et al: Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. *Chest* 2007; 132:425–432
5. Jones AE, Brown MD, Trzeciak S, et al; Emergency Medicine Shock Research Network Investigators: The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis. *Crit Care Med* 2008; 36:2734–2739
6. Nguyen HB, Corbett SW, Steele R, et al: Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007; 35:1105–1112
7. Puskarich MA, Marchick MR, Kline JA, et al: One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: A before and after study. *Crit Care* 2009; 13:R167
8. 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
9. Gaieski DF, Mikkelsen ME, Band RA, et al: Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom

early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010; 38:1045–1053

10. 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
11. Puskarich MA, Trzeciak S, Shapiro NI, et al; Emergency Medicine Shock Research Network (EMSHOCKNET): Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit Care Med* 2011; 39:2066–2071
12. Venkatesh AK, Avula U, Bartimus H, et al: Time to antibiotics for septic shock: Evaluating a proposed performance measure. *Am J Emerg Med* 2013; 31:680–683
13. 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
14. Vilella AL, Seifert CF: Timing and appropriateness of initial antibiotic therapy in newly presenting septic patients. *Am J Emerg Med* 2014; 32:7–13
15. Institute for Healthcare Improvement: Sepsis resuscitation bundle: Timing of antibiotics. May 13, 2013. Available at: http://www.ihi.org/resources/Pages/Measures/TimingofAntibiotics.aspx. Accessed June 5, 2015
16. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol* 2009; 62:1006–1012
17. Reeves BC, Deeks JJ, Higgins JPT, et al: Chapter 13: Including non-randomized studies. *In*: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Higgins JPT, Green S (Eds). The Cochrane Collaboration, 2011. Available at: http://www.cochrane-handbook.org. Accessed June 5, 2015
18. Borenstein M, Hedges LV, Higgines JPT, et al: Fixed-Effect Versus Random-Effects Models. Introduction to Meta-Analysis. John Wiley & Sons, 2009
19. Hutchison RW, Govathoti DA, Fehlis K, et al: Improving severe sepsis outcomes: Cost and time to first antibiotic dose. *Dimens Crit Care Nurs* 2011; 30:277–282
20. Siddiqui S, Razzak J: Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults. *Cochrane Database Syst Rev* 2010; 10:CD007081
21. 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
22. Shenep JL, Mogan KA: Kinetics of endotoxin release during antibiotic therapy for experimental gram-negative bacterial sepsis. *J Infect Dis* 1984; 150:380–388
23. Peng ZY, Wang HZ, Srisawat N, et al: Bactericidal antibiotics temporarily increase inflammation and worsen acute kidney injury in experimental sepsis. *Crit Care Med* 2012; 40:538–543
24. Lepper PM, Held TK, Schneider EM, et al: Clinical implications of antibiotic-induced endotoxin release in septic shock. *Intensive Care Med* 2002; 28:824–833
25. Mignon F, Piagnerelli M, Van Nuffelen M, et al: Effect of empiric antibiotic treatment on plasma endotoxin activity in septic patients. *Infection* 2014; 42:521–528
26. Villar J, Clement JP, Stotts J, et al: Many emergency department patients with severe sepsis and septic shock do not meet diagnostic criteria within 3 hours of arrival. *Ann Emerg Med* 2014; 64:48–54
27. Kirn TJ, Weinstein MP: Update on blood cultures: How to obtain, process, report, and interpret. *Clin Microbiol Infect* 2013; 19:513–520
28. Kerremans JJ, Verboom P, Stijnen T, et al: Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. *J Antimicrob Chemother* 2008; 61:428–435
29. Bloos F, Thomas-Ruddel D, Ruddel H, et al: Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: A prospective observational multi-center study. *Crit Care* 2014; 18:R42
30. Bruce HR, Maiden J, Fedullo PF, et al: Impact of nurse-initiated ED sepsis protocol on compliance with sepsis bundles, time to initial antibiotic administration, and in-hospital mortality. *J Emerg Nurs* 2015; 41:130–137
31. Cullen M, Fogg T, Delaney A: Timing of appropriate antibiotics in patients with septic shock: A retrospective cohort study. *Emerg Med Australas* 2013; 25:308–315
32. Gurnani PK, Patel GP, Crank CW, et al: Impact of the implementation of a sepsis protocol for the management of fluid-refractory septic shock: A single-center, before-and-after study. *Clin Ther* 2010; 32:1285–1293
33. Hitti EA, Lewin JJ III, Lopez J, et al: Improving door-to-antibiotic time in severely septic emergency department patients. *J Emerg Med* 2012; 42:462–469
34. Ferrer R, Artigas A, Suarez D, et al: Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009; 180:861–866
35. Joo Y, Chae M, Hwang S, et al: Impact of timely antibioitc administration on outcomes in patients with severe sepsis and septic shock in the emergency department. *Clin Exp Emerg Med* 2014; 1:35–40
36. Mok K, Christian MD, Nelson S, et al: Time to administration of antibiotics among inpatients with severe sepsis or septic shock. *Can J Hosp Pharm* 2014; 67:213–219
37. Ryoo S, Kim W, Sohn C, et al: Prognostic value of timing of antibiotic administration in patients with septic shock treated with early quantitative resuscitation in emergency department patients. *Am J Med Sci* 2015; 349:328–333
38. Tipler PS, Pamplin J, Mysliwiec V, et al: Use of a protocolized approach to the management of sepsis can improve time to first dose of antibiotics. *J Crit Care* 2013; 28:148–151
39. Yokota PK, Marra AR, Martino MD, et al: Impact of appropriate antimicrobial therapy for patients with severe sepsis and septic shock–A quality improvement study. *PLoS One* 2014; 9:e104475

3. Aiken LH, Cimiotti JP, Sloane DM, et al: Effects of nurse staffing and nurse education on patient deaths in hospitals with different nurse work environments. *Med Care* 2011; 49:1047–1053
4. Waldman JD, Kelly F, Arora S, et al: The shocking cost of turnover in health care. *Health Care Manage Rev* 2004; 29:2–7
5. Suzuki E, Itomine I, Kanoya Y, et al: Factors affecting rapid turnover of novice nurses in university hospitals. *J Occup Health* 2006; 48:49–61

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The authors reply:

Ms. Knight (1) asserts that our findings recommend achieving a ratio of 2.5 patients per nurse and 14 patients per physician to decrease mortality in the ICU. Instead of a "recommended ratio," we have proposed a maximum threshold, above which insufficient staffing may endanger patient safety (2). Hence, we argue that the optimal patient-to-caregiver ratio would be less than this upper threshold, which was rarely exceeded during time shifts in our study. Although the usual standard of care in a French ICU is probably closer to Australian guidelines than such a maximum threshold, we agree that there is a significant variability in ICU staffing patterns around the world. Certainly, larger studies involving different countries will be needed to validate these findings.

Patient-to-caregiver ratio is a proxy that reflects indirectly the combination of individual and collective phenomenon. As suggested by Ou and Hua (3), detailed investigations in the specific context of each ICU would be helpful to determine how human factors can modulate this ratio. Beyond optimal ratio, how ICU teams are structured may be critical in emergency situations. Achieving a better understanding of what drives the dynamics of an ICU team will allow for the development of solutions to maintain performance even in case of suboptimal patient-to-caregiver ratios. For example, team continuity based on turnover rate of healthcare staff and the accumulation of duty hours in the past between nurses and intensivists could significantly affect patient care. The accumulation of team experience has been found to improve outcomes in operating rooms (4) or outside the healthcare realm (5). Furthermore, several characteristics of healthcare workers may affect the generalizability of a predefined ratio, including individual background and skills, previous experience, and length of service in the ICU. The physical and mental conditions on a given day are also essential, and a sudden or more insidious fatigue related to excessive workloads could reduce personnel's vigilance and increase the risk of errors. Better identification of factors contributing to the relationship between patient-to-caregiver ratio and ICU team performance is key to adjusting staffing with workload. Finally, it should be mentioned that observational data only show the association between covariates and outcome that does not imply causal relationships between these.

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REFERENCES

1. Knight LD: Staffing Ratios and Patient Outcomes: Looking Beyond Nurses, Doctors, and Survival at ICU Discharge. *Crit Care Med* 2016; 44:e107–e108
2. Neuraz A, Guérin C, Payet C, et al: Patient mortality is associated with staff resources and workload in the ICU: A multicenter observational study. *Crit Care Med* 2015; 43:1587–1594
3. Ou X, Hua Y: Patient Mortality Is Associated With Staff Resources and Workload in the ICU. *Crit Care Med* 2016; 44:e108–e109
4. Xu R, Carty MJ, Orgill DP, et al: The teaming curve: A longitudinal study of the influence of surgical team familiarity on operative time. *Ann Surg* 2013; 258:953–957
5. Huckman RS, Staats BR, Upton DM: Team familiarity, role experience, and performance: Evidence from Indian software services. *Manag Sci* 2009; 55:85–100

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Timing of Appropriate Antibiotics in Sepsis: How Much Does Each Hour Matter?

To the Editor:

In a recent issue of *Critical Care Medicine*, we read with interest the report by Sterling et al (1), who performed a meta-analysis on the effect of antimicrobial timing on mortality outcomes in severe sepsis and septic shock. Sterling et al (1) acknowledge the heterogeneity of data currently available in the literature, but found in their analyses that time to antimicrobial therapy did not correlate with mortality. They uphold early appropriate antimicrobial therapy as a tenet of sepsis care, while cogitating about the inflection point of mortality with respect to antimicrobial timing. Their findings are contradictory to the most recent guidelines for management of sepsis (2).

We have recently published a retrospective analysis of *Enterobacteriaceae* sepsis, severe sepsis, and septic shock among patients who all received appropriate antibiotic therapy within 12 hours of the time that a positive blood culture was collected. In that cohort, we found no correlation between 30-day mortality and timing of antibiotic therapy (3). The strengths of our study include the homogeneous pathogen population and the elimination of inappropriate therapy as a confounding variable for mortality. We have taken data from our prior study and analyzed mortality within each sepsis classification with respect to timing of appropriate therapy. As seen in Figure 1, there was no difference in time to appropriate antimicrobial therapy between survivors and nonsurvivors among sepsis