The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

A Critical Analysis of the Literature on Time-to-Antibiotics in Suspected Sepsis

Jeremy Weinberger,[1,2] Chanu Rhee,[1,2] and Michael Klompas[1,2]

[1]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA, [2]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

The Surviving Sepsis Campaign recommends immediate antibiotics for all patients with suspected sepsis and septic shock, ideally within 1 hour of recognition. Immediate antibiotic treatment is lifesaving for some patients, but a substantial fraction of patients initially diagnosed with sepsis have noninfectious conditions. Aggressive time-to-antibiotic targets risk promoting antibiotic overuse and antibiotic-associated harms for this subset of the population. An accurate understanding of the precise relationship between time-to-antibiotics and mortality for patients with possible sepsis is therefore critical to finding the best balance between assuring immediate antibiotics for those patients who truly need them versus allowing clinicians some time for rapid investigation to minimize the risk of overtreatment and antibiotic-associated harms for patients who are not infected. More than 30 papers have been published assessing the relationship between time-to-antibiotics and outcomes, almost all of which are observational cohort studies. Most report significant associations but all have important limitations. Key limitations include focusing just on the sickest subset of patients (only patients requiring intensive care and/or patients with septic shock), blending together mortality estimates from patients with very long intervals until antibiotics with patients with shorter intervals and reporting a single blended (and thus inflated) estimate for the average increase in mortality associated with each hour until antibiotics, and failure to control for large potential confounders including patients' presenting signs and symptoms and granular measures of comorbidities and severity of illness. In this study, we elaborate on these potential sources of bias and try to distill a better understanding of what the true relationship between time-to-antibiotics and mortality may be for patients with suspected sepsis or septic shock.

Keywords. antibiotics; sepsis; time-to-antibiotics; quality improvement.

The Surviving Sepsis Campaign recommends immediate antibiotics for all patients with suspected sepsis and septic shock, ideally within 1 hour of recognition [1]. Likewise, the Centers for Medicare and Medicaid Services (CMS) SEP-1 measure includes a mandate for broad-spectrum antimicrobials within 3 hours of the first clinical signs of sepsis [2]. These recommendations have sparked considerable controversy. On the one hand, many studies have reported strong associations between delays in antibiotics and higher mortality rates in patients with sepsis. As such, immediate antibiotic treatment may be lifesaving to some patients. On the other hand, up to 40% of patients admitted to intensive care units with a working diagnosis of sepsis turn out to have a low post hoc probability of infection [3, 4]. These patients are exposed to the potential risks of antibiotics without any potential benefits. The risks associated with unnecessary antibiotics in critically ill patients may not be trivial. Several studies have reported that aggressive antibiotic management may be associated with higher mortality rates compared with more conservative strategies [5–10]. As such, judicious antibiotic management may also save lives.

Aggressive time-to-antibiotic targets have potentially far-reaching implications for both hospital systems and patients. If overly tight time-to-treatment targets are set, clinicians can be pressured into taking shortcuts in their evaluation and err on the side of giving antibiotics even when the evidence for infection is equivocal [11]. In addition to exposing uninfected patients to possible harm from antibiotics, early diagnostic closure may also lead to delays in identifying and treating noninfectious sources of instability (such as pulmonary emboli, fluid overload, toxin exposures, drug adverse effects, malignancies, bleeding, mechanical complications of surgery, obstructed organs, etc) that could further harm patients [12].

The tension between the potential benefits versus risks of aggressive antibiotic time-to-treatment targets compels us to understand the strengths and limitations of the literature on time-to-antibiotics as clearly as possible. More than 30 studies have been published on the association between time-to-antibiotics and mortality in sepsis. These studies differ widely in their results. One meta-analysis reported no association between time-to-antibiotics and mortality, whereas another reported strong associations [13, 14]. However, the vast majority of investigations to date are observational studies that vary in populations, sepsis syndromes, study methodology,

Correspondence: Michael Klompas, MD, MPH, Department of Population Medicine, 401 Park Drive, Suite 401 East, Boston, MA 02215 (mklompas@bwh.harvard.edu).

The Journal of Infectious Diseases® 2020;222(S2):S110–8

DOI: 10.1093/infdis/jiaa146

and rigor. In this study, we will review the potential sources of bias in studies of the association between time-to-antibiotics and mortality and try to distill a clearer understanding of this critical issue.

SOURCES OF POTENTIAL BIAS IN STUDIES OF THE ASSOCIATION BETWEEN TIME-TO-ANTIBIOTICS AND MORTALITY

There are 4 major sources of variability that may account for some of the differences between studies of the association between time-to-antibiotics and mortality (Table 1).

Illness Severity: Sepsis Versus Septic Shock

Sepsis as currently defined includes a wide spectrum of illness severity. Up to 20% of patients who ostensibly meet operational criteria for Sepsis-3 (suspected infection and acute organ dysfunction) are well enough to be discharged home from the emergency department [15, 16]. In contrast, patients on the other end of the spectrum—those with septic shock—are at imminent risk of dying. Even with state-of-the-art care, patients with septic shock can face mortality rates of up to 50% [17]. It stands to reason that the urgency of antibiotics may vary across the spectrum of severity of illness seen in patients with sepsis. This has been affirmed in the handful of studies that have differentiated between patients with sepsis alone versus those with septic shock. For example, Seymour et al [18] analyzed approximately 50 000 patients treated for sepsis in New York State. They found a strong association between time-to-antibiotics and mortality overall. However, when they stratified by patients who required vasopressors versus those who did not, there were important differences. In patients who required vasopressors, each hour until antibiotics was associated with a 7% increase in the odds of death (95% confidence interval [CI], 1.05–1.09). In patients who did not require vasopressors, there was no association between time-to-antibiotics and death (odds ratio [OR] = 1.01; 95% CI, 0.99–1.04). A comparable analysis of 35 000 patients in Northern California reported similar results [19]. Each hour until antibiotics was associated with a 1.8% absolute increase in mortality (95% CI, 0.8%–3.0%) for patients with septic shock versus a 0.4% increase (95% CI, 0.1%–0.8%) for patients with severe sepsis. It is notable that all except 1 of the studies cited by the 2016 Surviving Sepsis Campaign Guidelines to justify their recommendation to treat all patients with sepsis within 1 hour of presentation were either focused exclusively on patients with septic shock or were limited to critically ill patients in intensive care units, most of whom had septic shock [20–27]. Given these important differences in the association between time-to-antibiotics and outcomes for patients with septic shock versus sepsis without shock, it is important to be attentive to the precise population included in time-to-antibiotic analyses and to avoid extrapolating findings from patients with very high severity of illness to patients with less severe illness.

Linearizing a Nonlinear Outcome

The prevailing mantra in sepsis has been that each hour until antimicrobial administration is associated with increased mortality. That is to say, "each hour counts," and each hour until antibiotics counts the same. However, close examination of studies that provide hour-by-hour mortality rates suggests a more nuanced pattern. In most studies, hour-by-hour mortality rates tend to be flat for the first 3–5 hours and only thereafter rise clearly and persistently. Mortality rates tend to be substantially higher for patients with major delays (6–24 hours) until antibiotics compared to those who receive antibiotics within the first few hours [14, 20, 24, 28]. Applying statistical models to generate a single blended estimate for the association between each hour until antibiotics and mortality effectively averages the substantial increase in mortality seen with very long delays with the much smaller (or absent) changes in mortality with shorter delays. This gives the false impression that every hour until antibiotics has an equal and measurable impact on mortality. The problem is particularly egregious among studies that include patients with a wide range of intervals until antibiotics.

A precise understanding of the distinct effect of each hour until antibiotics is critical. If it is true that some patients with sepsis without shock can tolerate intervals of a few hours until antibiotics, then this creates an opportunity for clinicians managing patients with equivocal evidence for infection to pursue rapid diagnostics (such as imaging studies, respiratory viral testing, urinalyses, biomarkers, and/or polymerase chain reaction-based blood and sputum studies as appropriate) and to treat for acute noninfectious conditions (such as volume depletion, congestive heart failure, drug overdose, pain, arrhythmia, bronchoconstriction, etc) that collectively could substantially increase certainty for or against bacterial infection. Ideally, then, we need studies that provide distinct adjusted estimates for the association between each hourly interval until antibiotics rather than blended estimates across very broad intervals. In practice, very few studies provide this level of detail.

Controlling for Confounding

In real-world practice, the interval from clinical presentation until antibiotics are administered is not random. There are often clear and understandable reasons why some patients with sepsis get antibiotics immediately, whereas others only receive antibiotics many hours after presentation despite being managed within the same institution. In many cases, the differences in treatment occur because of the different ways patients present [29]. On one hand, clinicians and emergency departments are optimized to rapidly recognize and treat patients with obvious severe illness (eg, hypotension, respiratory failure, impaired consciousness). Early antibiotic administration in this very sick population may lead to bias estimates of the impact of time-to-antibiotics toward the null. On the other hand, clinicians are also more likely to rapidly start antibiotics in patients with

Table 1. Overview of Bias and Confounding in Time-to-Antibiotics Studies

Issue	Sepsis vs Septic Shock	Linearizing Outcomes	Confounding	Time-Zero
Overview	■ There is a physiologic basis for the urgency of antibiotics varying by the severity of sepsis. ■ Despite the marked difference in illness acuity and prognosis between those with and without shock, most studies do not analyze these groups separately.	■ Most time-to-antibiotics studies provide a linearized, blended estimate across multiple hours. ■ This leads to a misleading impression that each hour interval until antibiotics has the same effect on mortality. ■ The solution is to generate independent estimates for each hourly interval	■ Time-to-antibiotic administration is not random. Patients who are more acutely ill or who have obvious signs of infection (eg, fever, meningismus) are more likely to receive early antibiotic therapy. ■ Older patients with multiple comorbidities are more likely to present with vague symptoms and have longer time-to-antibiotics.	■ The definition of time zero before antibiotic administration serves as an important benchmark in bundled sepsis care. ■ Multiple definitions have been used including prehospital contact with EMS, ED triage, time when certain physiologic criteria were met, and time of sepsis recognition.
Examples of Studies that Address these Potential Sources of Bias	Five studies analyze sepsis and septic shock separately: Abe et al [44], Alam et al [39], Ferrer et al [22], Garnacho-Montero et al [43], Liu et al [19] Several other studies include only patients with septic shock: Ko et al [41], Kumar et al [24], Larché et al [38], Puskarich et al [45], Ryoo et al [46]	Selected studies provide hour-by-hour data including the following: Ko et al [41], hourly data to 3 hours; Liu et al [19], hourly data to 5 hours; Peltan et al [15], hourly data to 6 hours; Seymour et al [18], hourly data to 12 hours	An example of a large, well controlled study is Peltan et al [15]. The multivariable model includes adjustment for age, race, sex, Charlson comorbidity index, and SOFA score. There is no adjustment for presenting symptoms.	Examples of different time zero definitions in selected studies include the following: Seymour et al [47], prehospital EMS contact; Peltan et al [15], time from ED triage; Bloos et al [48], physiologic criteria, with the onset of organ dysfunction
Impact	■ Among studies that differentiate between those with and without septic shock, there is a stronger association between longer intervals until antibiotics and mortality in those with septic shock compared to those without shock.	■ In studies that provide hour-by-hour data, mortality rates tend to be flat for the first 3–5 hours for sepsis without shock followed by a sharp increase in mortality thereafter. ■ If it is safe to withhold antibiotics for a few hours in patients with equivocal evidence for infection, this could allow time to obtain additional diagnostics to help clarify whether antibiotics are needed.	■ Controlling for all potential confounders can blunt or eliminate associations between time-to-antibiotics and mortality. ■ Studies that do not control for all potential confounders may provide biased results. Very few time-to-antibiotic studies adjust for presenting symptoms, a potentially important confounder.	■ There is inconsistency in the time zero definition among studies. ■ Differences in duration of illness and time to presentation may be independently associated with mortality and are inherently difficult to control for and capture.

Abbreviations: ED, emergency department; EMS, emergency medical services; SOFA, Sequential Organ Failure Assessment.

classic signs of infection (eg, high fever, meningismus, shortness of breath and purulent sputum, necrotizing soft tissue infections, etc), and these patients tend to be younger and have fewer comorbid conditions than patients who present with vague signs and symptoms [30, 31]. Older and more frail patients with comorbid conditions who present with vague signs and symptoms that are not immediately recognizable as infectious will often require the clinician to sort through a range of possible diagnoses before settling on infection [3]. For example, an elderly patient with heart failure and cancer presenting with fatigue and shortness of breath could have several possible diagnoses including multiple serious but noninfectious conditions (eg, pulmonary embolism, heart failure exacerbation, progression of cancer, new anemia, pulmonary hemorrhage, vasculitis, hypersensitivity pneumonitis due to a medication, etc) as well as a range of possible infections (eg, respiratory viruses, bacterial pneumonia, empyema, endocarditis, herpes virus family-associated syndromes, etc). Sorting through these possibilities takes time, and thus it is not surprising that the interval until antibiotics may be substantially longer in such patients compared with patients with fewer comorbidities and more obvious presentations. It is notable, however, that the same factors that predispose to indistinct presentations (advanced age and multiple comorbidities) are also independent predictors of higher mortality rates [3, 30–32]. Therefore, it is critical to rigorously assess the breadth, completeness, and

Table 2. Summary of Reviewed Time-to-Antibiotics Studies

Study	Sample Size	Does the Paper Differentiate Between Sepsis and Septic Shock?	Does Paper Provide Distinct Effect Estimates for Each Hour-to-Antibiotics?	Does the Paper Adjust for Basic Demographics (Age/Race/Sex)?	Does the Paper Provide Adjustment for Burden of Comorbid Illness?	Does the Paper Provide Adjustment for Illness Severity?	Does the Paper Adjust for Presenting Symptomatology?	What Definition of "Time Zero" Is Used in the Paper?
Abe et al [44]	1124	Yes	Yes—hourly up to 6 hours	Age Sex	Charlson	SOFA	No	Clinical recognition
Alam et al [39] (RCT)	2698	Yes	Yes—hourly up to 4 hours	Age	No	NEWS, qSOFA	Fever or hypothermia required	Prehospital EMS contact
Barie et al [20]	335	No	No	Age Sex	No	APACHE III	Fever required	Physiologic criteria
Bias et al [42]	133	No	No	No	No	No	No	Time from positive blood culture
Bloos et al [48]	1011	No	Yes—0–1 hour, 1–3 hours, 3–6 hours, >6 hours	Age	No	SOFA	No	Physiologic criteria
Bloos et al [40] (RCT)	4183	No	No	Age	No	SAPS II	No	Clinical recognition
Ferrer et al [28]	2796	No	Yes—0–1 hour, 1–3 hours, 3–6 hours, >6 hours	Age Sex	No	APACHE II	No	Physiologic criteria
Ferrer et al [22]	17 990	Yes	Yes—hourly up to 6 hours	No	No	Severity Sepsis Score	No	ED triage or clinical recognition
Ferrer et al [49]	2628	No	No	Age Sex	Charlson	APACHE II SOFA	No	ED triage or clinical recognition
Gaieski et al [23]	261	No	Yes—hourly up to 5 hours	No	No	APACHE II	No	ED triage, bundle initiation
Garnacho-Montero et al [43]	224	Yes	No	Age Sex	Yes—individual organ insufficiencies	SOFA APACHE II	No	Clinical recognition, ED triage
Groot et al [33]	1168	No	Yes—<1 hour, 1–3 hours, >3 hours	No	No	PIRO	No	ED triage
Jalili et al [50]	145	No	Yes—hourly up to 2 hours	No	No	APACHE II	No	ED triage
Joo et al [51]	591	No	No	Age	Yes—individual organ insufficiencies	APACHE II	No	ED triage
Ko et al [41]	2229	Only septic shock	Yes—hourly up to 3 hours	Age Sex	Yes—by individual disease	SOFA	No	ED triage
Kumar et al [24]	2731	Only septic shock	Yes—hourly to 6 hours and then intervals to >36	No	No	APACHE II	No	Physiologic criteria
Larché et al [38]	88	Only septic shock	No	No	All with malignancy	LOD	No	Time of ICU admission
Liu et al [19]	35 000	Yes	Yes—30 minute intervals up to 6 hours	Age Sex	COPS2	LAPS2 ESI	No	ED triage
Peltan et al [15]	10 811	No	Yes—hourly to 6 hours	Age Race Sex	Elixhauser	MEDS SOFA	No	ED triage
Pruinelli et al [52]	5072	No	No	Age Race Sex	Charlson and Comorbidity Severity Scores	No	No	Physiologic criteria
Puskarich et al [45]	291	Only septic shock	Yes—hourly to 6 hours	Age Race	No	SOFA	No	ED triage, clinical recognition
Ryoo et al [46]	426	Only septic shock	Yes—hourly to 5 hours	No	No	SOFA	No	Clinical recognition
Seymour et al [47]	2683	No	No	Age Race Sex	Charlson	Prehospital vitals and interventions	No	Prehospital EMS contact
Seymour et al [18]	49 331	No	Yes—to 12 hours	Age Race	ESRD, chronic respiratory failure, CHF	Discrete measures of illness severity	No	Bundle initiation
Whiles et al [36]	3929	No	Yes—hourly up to 6 hours, intervals up to 24 hours	Age Sex	Charlson	Discrete measures of illness severity	No	ED triage
Wisdom et al [53]	220	No	Yes: <1, 1–3, 3–6. >6 hours	Age Sex	No	Sepsis vs severe sepsis	No	ED triage
Zhang et al [27]	1058	No	Yes—in 6-hour intervals to 24 hours	Age Sex Race	Charlson	APACHE II	No	Blood culture collection

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CHF, congestive heart failure; COPS2, Comorbidity Point Score, Version 2; ED, emergency department; EMS, emergency medical services; ESI, Emergency Severity Index; ESRD, end-stage renal disease; LAPS2, Laboratory Acute Physiology Score; LOD, Logistic Organ Dysfunction; MEDS, Mortality in Emergency Department Sepsis; NEWS, National Early Warning Score; PIRO, Predisposition, Infection/Injury Type, Response and Organ dysfunction; qSOFA, quick Sequential Organ Failure Assessment; RCT, randomized control trial; SOFA, Sequential Organ Failure Assessment.

granularity of covariates included in time-to-antibiotics studies to determine whether they have adequately accounted for these potential confounders. Most studies include adjustment for age, sex, and a limited number of comorbidities. Fewer adjust for race [24, 33], the full breadth of potential confounders, and very granular measures of severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] scores, number and types of vasopressors, PaO_2/FiO_2 ratios, detailed vital signs, etc) [18, 34–36]. Almost none of the time-to-antibiotic studies published thus far have adjusted for patients' presenting signs and symptoms.

Other Potential Sources of Error

There is variability between studies in what is defined as "time zero" before antibiotic administration. Examples include first contact with emergency personnel in the prehospital setting, emergency department triage, the time when specific physiologic criteria were first identified, the time when sepsis was first recognized, and the time when sepsis bundles were initiated. In practice, no time zero is perfect in representing a clinically meaningful time point because patients seek medical care at different points in their illness. These differences may be many hours or even days apart. In the context of bundled care mandates, however, time zero as an important benchmark from which there is an expectation for rapid identification, testing, and treatment [37]. Differences in duration of illness and time to presentation may be independently associated with mortality and are inherently difficult to control for and capture. One method for partially addressing this would be to use only hospital onset septic shock, as was done by Kumar et al [24] in 2006, although this significantly limits generalizing from such studies to patients who present for care already in shock, and it may introduce additional confounding from coexisting illnesses and prior interventions received in the hospital. Sample size in the time-to-antibiotics literature also varies widely, ranging from under 100 patients to almost 50 000 [18, 38]. Given the complex presentations and phenotypes of sepsis, there is an obvious benefit to larger sample size to specifically stratify and subgroup populations while maintaining adequate power.

IDENTIFYING IDEAL STUDIES ASSESSING TIME-TO-ANTIBIOTICS

These major sources of bias effectively undermine the majority of studies of time-to-antibiotics (Table 2). Most studies fail to differentiate between septic shock versus sepsis without shock, report linearized estimates of the association between each hour until antibiotics that blend together very wide intervals until antibiotics, and/or include limited adjustment for comorbidities, severity of illness, and presenting signs and symptoms. To our knowledge, no one single study addresses all of these issues adequately. The studies that come closest to adequately addressing these potential sources of error include 2 randomized trials and a handful of observational studies.

RANDOMIZED TRIALS

There have been just 2 randomized controlled trials addressing time-to-antibiotics and mortality in patients with sepsis. Alam et al [39] investigated the potential benefit of training prehospital emergency personnel to identify patients with signs and symptoms of sepsis and to administer ceftriaxone in the ambulance versus the emergency department. Patients randomized to prehospital antibiotics (n = 1535) received antibiotics a median of 96 minutes earlier than those randomized to receive antibiotics in the emergency department (n = 1137). Despite the difference between arms in time-to-antibiotics, there was no significant difference in 28-day mortality rates (8% in both arms). The majority of patients in this study (more than 96%) had infection or sepsis without shock (those without organ dysfunction would simply be labeled with "infection" under Sepsis-3 criteria) so the findings of this study are only generalizable to less severely ill patients. In addition, the difference in time-to-antibiotics between study arms was only 96 minutes, and thus this study provides good evidence against a 1-hour treatment goal for sepsis without shock but does not speak to the potential benefits of more generous time-to-treatment targets (such as 3 hours or 5 hours).

The second randomized trial of time-to-antibiotics for patients with sepsis was a cluster-randomized study by Bloos et al [40] that implemented a sepsis education and quality intervention in German hospitals and compared this to standard continuing medical education in other hospitals. It is unfortunate that, despite efforts to improve time-to-antibiotics, there was no difference between groups in median time-to-antibiotic delivery (median 1.5 vs 2.0 hours in the intervention vs control group, $P = .41$) and significantly "higher" mortality rates in the intervention group (35.1% vs 26.7%, $P = .01$). However, higher mortality rates were also observed during the preintervention run-in period in the hospitals randomized to the intervention, suggesting that the differences in patient outcomes may have been related to higher disease severity or other hospital-level differences. Given the lack of significant difference in time-to-antibiotics between groups, this study does not add information regarding the optimal time-to-antibiotic target for sepsis, but it does highlight the practical difficulty hospitals face with administering antibiotics within very short intervals, even when specifically focusing on improving this process.

OBSERVATIONAL STUDIES

A 2019 study by Peltan et al [15] was a large (n = 10 811) retrospective cohort study addressing the impact of time from emergency room arrival to antibiotic administration in patients with suspected sepsis. The study included detailed adjustments for age, sex, race, comorbidities (Elixhauser), and illness severity (Mortality in Emergency Department Sepsis [MEDS]

and Sequential Organ Failure Assessment [SOFA] scores) in multivariate analysis. Patients who received antibiotics earlier had more severe organ failure and higher comorbidities, highlighting the importance of adjusting for these potential confounders. The authors reported that each hour delay in antimicrobial administration was associated with increased hospital mortality (OR = 1.16; 95% CI, 1.07–1.26) and 1-year mortality (OR = 1.10; 95% CI, 1.05–1.14). However, these estimates blended the effects of long intervals (>6 hours) with much shorter intervals. To their credit, however, the authors also reported the independent associations between each discrete hourly interval and mortality. There was no clear and consistent association between time-to-antibiotics and mortality until intervals of ≥5 hours for hospital mortality and ≥3 hours for 1-year mortality. The majority of patients in this study did not have septic shock (88%), hence the findings of this analysis are most pertinent for patients with sepsis alone. Limitations of the study include failure to adjust for vague versus explicit presenting signs and symptoms of infection and the inconsistent association between time-to-antibiotics and mortality for hospital mortality versus 1-year mortality. The finding that delays of ≥3 hours may be associated with 1-year mortality but not hospital mortality is intriguing, but it is difficult to discern to what extent the 1-year mortality rates reflect time-to-antibiotics versus patients' underling comorbidities given the discrepancy between short-term versus long-term outcomes.

In a 2017 study, Seymour et al [18] implemented a New York State mandate to protocolize and track sepsis, including a bundle of care to be completed within 3-hours of sepsis identification. Strengths of the study include the large sample size (n = 49 331) and inclusion of data from several hospitals. The authors controlled for age, sex, and race, as well as admission source, insurance type, site of infection, and selected comorbidities. Likewise, crude measures of illness severity such as lactate, mechanical ventilation, platelet count, and vasopressor requirement were included, but a more comprehensive severity index was lacking. There was no adjustment for vague versus explicit presenting signs and symptoms. The authors reported that hourly delays in antibiotics were associated higher mortality rates (OR = 1.04; 95% CI, 1.03–1.06). However, this estimate blended together delays of up to 12 hours with much shorter intervals. The authors only provided crude mortality rates for each hourly interval until antibiotics rather than adjusted estimates. However, crude mortality rates were similar for the first 5 hours until antibiotics and rapidly increased thereafter. The authors did provide subgroup analyses stratified by use of vasopressors. The association between each hour until antibiotics and mortality was significant for patients who required vasopressors (OR = 1.07; 95% CI, 1.05–1.09) but not for those who did not (OR = 1.01; 95% CI, 0.99–1.04).

Liu et al [19] leveraged the electronic medical record in a large California health system to analyze the association of time-to-antibiotics and mortality in patients with sepsis and septic shock. Strengths include a large sample size (n = 35 000) and careful adjustment for comorbidities (Comorbidity Point Score, Version 2 [COPS2] score), age, sex, and severity of illness using the Laboratory Acute Physiology Score 2 (LAPS2) and Emergency Severity Index (ESI) scores. The study did not adjust for race or for explicit versus vague presenting signs and symptoms. The authors found a significant association between time-to-antibiotics counting from emergency department presentation and hospital mortality across all sepsis severity strata (OR = 1.09; 95% CI, 1.05–1.13), but this association was largest for those with septic shock (OR = 1.14; 95% CI, 1.06–1.23). Hour-by-hour associations are provided in a figure for all cases combined but not stratified by sepsis severity. The figure suggests that there was a small but stable increase in mortality with delays of 1–5 hours and a large increase with delays of >5 hours.

Ko et al [41] conducted a propensity-matched analysis in 10 medical centers in Korea to analyze the effect of time-to-antibiotics on mortality in patients with septic shock. They included 2229 patients and adjusted for age, sex, and 9 different comorbidities. The SOFA and APACHE II scores were included to control for illness severity. The authors did not adjust for explicit versus vague presenting signs and symptoms. Hourly data were provided from time of emergency department triage to 3 hours, although this smaller window may have missed differential effects in the 3- to 6-hour range. A significant, and nonlinear, association between time from triage to first antibiotic and mortality was identified. Compared to those that received antibiotics within 1 hour of presentation, there were increasing odds of mortality for those who received antibiotics within 1–2 hours (OR = 1.248; 95% CI, 1.053–1.478), 2–3 hours (OR = 1.186; 95% CI, 0.999–1.408), and greater than 3 hours (OR = 1.419; 95% CI, 1.203–1.675). These findings are germane to septic shock, but no data were provided on sepsis without shock.

It is important when reviewing the literature on time-to-antibiotics to acknowledge that retrospective studies are not able to "step into the shoes" of the clinician making a judgment call on whether sepsis is present. There is significant heterogeneity in sepsis presentation, and many of the signs and symptoms of sepsis overlap with noninfectious related conditions. Any study that retrospectively includes patients based on "confirmed" sepsis removes the uncertainty of diagnosing sepsis in real time. A method that has been used in some studies includes only those with positive blood cultures in the analysis [27, 42, 43]. This ensures that the included patients were truly infected, but it also results in missing a population that may have received unnecessary antimicrobials with associated harms, delays in appropriate care, and diversion of intensive resources.

WHAT IS THE TRUE IMPACT?

At this time, there are no studies that provide a perfect window into the association of time-to-antibiotics with mortality in

patients with sepsis. Such a study would be a large, prospective, randomized controlled trial of immediate versus delayed antibiotics. It is unlikely that such a study will be completed if it is billed as a direct study of time-to-antibiotics, but it might be possible to indirectly get these data from a study randomizing some hospitals to improve their processes for sepsis recognition and immediacy of antibiotics versus usual care. However, the study by Bloos et al [40] underscored the challenge in obtaining meaningful differences in time-to-antibiotics between hospitals using this approach.

We are more likely to get additional data from further observational studies. The ideal observational study is likely one that (1) is very large and thus allows for ample power, (2) provides estimates of the associations between time-to-antibiotics and mortality across distinct strata of illness, including both sepsis and septic shock, (3) includes rigorous adjustment for patients' demographics, comorbidities, granular measures of severity of illness, and vague versus explicit presenting signs and symptoms, and (4) provides independent adjusted associations for each distinct hour from sepsis recognition until antibiotics.

In the interim, while we await further randomized trial data or an optimized cohort study, we are forced to extrapolate from the imperfect studies we have in hand. All told, it appears that there is a reasonably strong relationship between each hour until antibiotics and mortality for septic shock but a less pronounced relationship for sepsis without shock. We have good data that intervals of up to 90 minutes until antibiotics for patients with sepsis without shock make little difference. It appears that the risk for increased mortality in patients with sepsis without shock rises at approximately the 3- to 5-hour mark until antibiotics and thereafter, but data differentiating the precise impact of intervals of 3 versus 5 hours are few and imperfect.

CONCLUSIONS

Antibiotics remain the cornerstone of therapy for bacterial sepsis. Prompt administration is unquestionably important, but what constitutes prompt in the context of diagnostic uncertainty and the potential risks of unnecessary antibiotics remains unclear. Based on the best available data, it appears that there is a strong relationship between each hour until antibiotics and mortality for septic shock but a less pronounced relationship for sepsis without shock. We have good randomized trial data that intervals of up to 90 minutes until antibiotics for patients with sepsis without shock make little difference. In contrast, intervals of ≥5 hours are clearly and consistently associated with higher mortality rates. There are some data that risk might rise after intervals of ≥3 hours, but other studies suggest that risk only rises after intervals of ≥5 hours.

Taken together, we recommend immediate antibiotics for patients with septic shock but thoughtful balancing of risks and benefits of immediate antibiotics for patients with possible sepsis without shock. If the diagnosis of infection is very likely, then there is no reason to delay antibiotics regardless of severity of illness. If there is uncertainty, however, it would appear that a time-limited course of aggressive investigation and treatment of possible noninfectious causes of deterioration is warranted and safe. If these investigations and treatments fail to rule out infection, then antibiotics should be given expeditiously, ideally no later than 3–5 hours after first suspicion of possible sepsis. If rapid investigation establishes a noninfectious cause of disease or treatment of noninfectious conditions quickly leads to substantial improvement, then antibiotics can likely be deferred. This approach merits further investigation and validation.

Notes

Acknowledgments. C. R. was funded in part by the Agency for Healthcare Research and Quality (K08HS025008) during the development of this work. M. K. and C. R. received grant funding from the Centers for Disease Control and Prevention for research on sepsis surveillance unrelated to the current work.

Supplement sponsorship. This supplement is sponsored by bioMérieux, the Gordon and Betty Moore Foundation and Beckman Coulter.

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med **2017**; 45:486–552.
2. QualityNet, Inpatient Hospitals Specifications Manual. Available at: https://www.qualitynet.org. Accessed 14 January 2020.
3. Filbin MR, Lynch J, Gillingham TD, et al. Presenting symptoms independently predict mortality in septic shock: importance of a previously unmeasured confounder. Crit Care Med **2018**; 46:1592–9.
4. Klein Klouwenberg PM, Cremer OL, van Vught LA, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care **2015**; 19:319.
5. Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. Lancet Infect Dis **2012**; 12:774–80.
6. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf **2014**; 5:229–41.
7. Attridge RT, Frei CR, Pugh MJ, et al. Health care-associated pneumonia in the intensive care unit:

guideline-concordant antibiotics and outcomes. J Crit Care **2016**; 36:265–71.
8. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med **2000**; 132:621–30.
9. Kett DH, Cano E, Quartin AA, et al.; Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis **2011**; 11:181–9.
10. Schuetz P, Wirz Y, Sager R, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis **2018**; 18:95–107.
11. Welker JA, Huston M, McCue JD. Antibiotic timing and errors in diagnosing pneumonia. Arch Intern Med **2008**; 168:351–6.
12. Kuye I, Rhee C. Spotlight: Overdiagnosis and Delay: Challenges in Sepsis Diagnosis. Agency for Healthcare Research and Quality Patient Safety Network October, 2018. Available at: https://psnet.ahrq.gov/webmm/case/458/spotlight-overdiagnosis-and-delay-challenges-in-sepsis-diagnosis. Accessed 14 January 2020.
13. Johnston ANB, Park J, Doi SA, et al. Effect of immediate administration of antibiotics in patients with sepsis in tertiary care: a systematic review and meta-analysis. Clin Ther **2017**; 39:190–202.e6.
14. Sterling SA, Miller WR, Pryor J, Puskarich MA, Jones AE. The impact of timing of antibiotics on outcomes in severe sepsis and septic shock: a systematic review and meta-analysis. Crit Care Med **2015**; 43:1907–15.
15. Peltan ID, Brown SM, Bledsoe JR, et al. ED door-to-antibiotic time and long-term mortality in sepsis. Chest **2019**; 155:938–46.
16. Wang HE, Jones AR, Donnelly JP. Revised national estimates of emergency department visits for sepsis in the United States. Crit Care Med **2017**; 45:1443–9.
17. Herrán-Monge R, Muriel-Bombín A, García-García MM, et al. Epidemiology and changes in mortality of sepsis after the implementation of surviving sepsis campaign guidelines. J Intensive Care Med **2019**; 34:740–50.
18. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med **2017**; 376:2235–44.
19. Liu VX, Fielding-Singh V, Greene JD, et al. the timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med **2017**; 196:856–63.
20. Barie PS, Hydo LJ, Shou J, Larone DH, Eachempati SR. Influence of antibiotic therapy on mortality of critical surgical illness caused or complicated by infection. Surg Infect (Larchmt) **2005**; 6:41–54.
21. Barochia AV, Cui X, Vitberg D, et al. Bundled care for septic shock: an analysis of clinical trials. Crit Care Med **2010**; 38:668–78.
22. 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**; 42:1749–55.
23. 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**; 38:1045–53.
24. 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**; 34:1589–96.
25. Bagshaw SM, Lapinsky S, Dial S, et al.; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med **2009**; 35:871–81.
26. Iscimen R, Cartin-Ceba R, Yilmaz M, et al. Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. Crit Care Med **2008**; 36:1518–22.
27. Zhang D, Micek ST, Kollef MH. Time to appropriate antibiotic therapy is an independent determinant of postinfection ICU and hospital lengths of stay in patients with sepsis. Crit Care Med **2015**; 43:2133–40.
28. Ferrer R, Artigas A, Suarez D, et al.; Edusepsis Study Group. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. Am J Respir Crit Care Med **2009**; 180:861–6.
29. Peltan ID, Mitchell KH, Rudd KE, et al. Physician variation in time to antimicrobial treatment for septic patients presenting to the emergency department. Crit Care Med **2017**; 45:1011–8.
30. Henning DJ, Carey JR, Oedorf K, et al. The absence of fever is associated with higher mortality and decreased antibiotic and IV fluid administration in emergency department patients with suspected septic shock. Crit Care Med **2017**; 45:e575–82.
31. Kushimoto S, Abe T, Ogura H, et al.; JAAM Focused Outcome Research on Emergency Care for Acute respiratory distress syndrome, Sepsis and Trauma (FORECAST) Group. Impact of body temperature abnormalities on the implementation of sepsis bundles and outcomes in patients with severe sepsis: a retrospective sub-analysis of the

focused outcome research on emergency care for acute respiratory distress syndrome, sepsis and trauma study. Crit Care Med **2019**; 47:691–9.
32. Yang Y, Yang KS, Hsann YM, Lim V, Ong BC. The effect of comorbidity and age on hospital mortality and length of stay in patients with sepsis. J Crit Care **2010**; 25:398–405.
33. de Groot B, Ansems A, Gerling DH, et al. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. Crit Care **2015**; 19:194.
34. Berkowitz DM, Martin GS. Sepsis and sex: can we look beyond our hormones? Chest **2007**; 132:1725–7.
35. Jones JM, Fingar KR, Miller MA, et al. Racial disparities in sepsis-related in-hospital mortality: using a broad case capture method and multivariate controls for clinical and hospital variables, 2004-2013. Crit Care Med **2017**; 45:e1209–17.
36. Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med **2017**; 45:623–9.
37. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med **2018**; 44:925–8.
38. Larché J, Azoulay E, Fieux F, et al. Improved survival of critically ill cancer patients with septic shock. Intensive Care Med **2003**; 29:1688–95.
39. Alam N, Oskam E, Stassen PM, et al.; PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med **2018**; 6:40–50.
40. Bloos F, Rüddel H, Thomas-Rüddel D, et al.; MEDUSA study group. Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. Intensive Care Med **2017**; 43:1602–12.
41. Ko BS, Choi SH, Kang GH, et al. Time to antibiotics and the outcome of patients with septic shock: a propensity score analysis. Am J Med **2019**. doi:10.1016/j.amjmed.2019.09.012.
42. Bias TE, Vincent WR 3rd, Trustman N, Berkowitz LB, Venugopalan V. Impact of an antimicrobial stewardship initiative on time to administration of empirical antibiotic therapy in hospitalized patients with bacteremia. Am J Health Syst Pharm **2017**; 74:511–9.
43. Garnacho-Montero J, Aldabo-Pallas T, Garnacho-Montero C, et al. Timing of adequate antibiotic therapy is a greater determinant of outcome than are TNF and IL-10 polymorphisms in patients with sepsis. Crit Care **2006**; 10:R111.
44. Abe T, Kushimoto S, Tokuda Y, et al.; JAAM FORECAST group. Implementation of earlier antibiotic administration in patients with severe sepsis and septic shock in Japan: a descriptive analysis of a prospective observational study. Crit Care **2019**; 23:360.
45. 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**; 39:2066–71.
46. Ryoo SM, Kim WY, Sohn CH, et al. Prognostic value of timing of antibiotic administration in patients with septic shock treated with early quantitative resuscitation. Am J Med Sci **2015**; 349:328–33.
47. Seymour CW, Kahn JM, Martin-Gill C, et al. Delays from first medical contact to antibiotic administration for sepsis. Crit Care Med **2017**; 45:759–65.
48. Bloos F, Thomas-Rüddel D, Rüddel H, et al.; MEDUSA Study Group. 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.
49. Ferrer R, Martínez ML, Gomà G, et al.; ABISS-Edusepsis Study group. Improved empirical antibiotic treatment of sepsis after an educational intervention: the ABISS-Edusepsis study. Crit Care **2018**; 22:167.
50. Jalili M, Barzegari H, Pourtabatabaei N, et al. Effect of door-to-antibiotic time on mortality of patients with sepsis in emergency department: a prospective cohort study. Acta Med Iran **2013**; 51:454–60.
51. Joo YM, Chae MK, Hwang SY, et al. Impact of timely antibiotic administration on outcomes in patients with severe sepsis and septic shock in the emergency department. Clin Exp Emerg Med **2014**; 1:35–40.
52. Pruinelli L, Westra BL, Yadav P, et al. Delay within the 3-hour surviving sepsis campaign guideline on mortality for patients with severe sepsis and septic shock. Crit Care Med **2018**; 46:500–5.
53. Wisdom A, Eaton V, Gordon D, Daniel S, Woodman R, Phillips C. INITIAT-E.D.: impact of timing of INITIation of antibiotic therapy on mortality of patients presenting to an emergency department with sepsis. Emerg Med Australas **2015**; 27:196–201.