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Antibiotics for Sepsis: Does Each Hour Really Count, or Is It Incestuous Amplification?

> Incestuous amplification—the (extreme) reinforcement of ideas and/or beliefs that occurs when like-minded people communicate with each other (1).

"Each hour's delay in initiating antibiotics costs lives" is a doctrine that has attained quasireligious status. Like most (quasi) religions, this is founded more on faith and hope than hard fact. With the failure of other beliefs previously touted as incontrovertible, such as the 24-hour sepsis management bundles (2) and, more recently, a specific early goal-directed therapy strategy (3), we need to believe we are offering some benefit to our acutely ill patients. A blind faith in the primacy of early antibiotics suits this purpose, yet I confess to being decidedly agnostic and fearful. The increasing level of antimicrobial resistance is rightly viewed as a global crisis (4). The indiscriminate and inappropriate use of antibiotics will only serve to accelerate this problem. Furthermore, antibiotics themselves also cause harm—for example, organ injury, mitochondrial dysfunction, the impact on the microbiome, and overgrowth by fungi and *Clostridium difficile* (5–8).

The "each hour delay" mantra is, however, being drummed into healthcare providers, hospital administrators, funders, and governmental bodies. Quality-improvement programs are being driven by financial penalty. In the United Kingdom, the National Institute for Health and Care Excellence is proposing a quality standard, required by healthcare commissioners, that impels antibiotics within an hour of identifying "suspected sepsis" (9). Fear of retribution and litigation will coerce the clinician—especially the junior clinician—to treat everyone "just in case." A core quality measure requiring a reduction in time to first antibiotic dose for community-acquired pneumonia from 8 to 4 hours was achieved at the expense of a significant decrease in diagnostic accuracy (10). What impact will a 1-hour time limit have? Will clinician paranoia result in antibiotics being given for every hospitalized exacerbation of chronic obstructive pulmonary disease and each child with tracheobronchitis? Will clinicians still complete a full course of antibiotics "just in case," notwithstanding confident early exclusion of bacterial infection (11)?

The strength of evidence for "each hour delay" is not particularly compelling. To my knowledge, every theistic study supporting this dogma is based solely on retrospective analyses of databases usually collected for administrative or other reasons. Crucial items of data are usually lacking, such as confirmation of infection and adequacy of antibiotic choice, antibiotic dosing, and source control. Noninfectious mimics accounted for 18% of patients initially diagnosed and treated as septic in a U.S. emergency department (ED) (12), whereas 13% of 2,579 patients admitted to two Dutch intensive care units (ICUs) with a presumptive diagnosis of sepsis had a *post hoc* infection likelihood of "none" and an additional 30% of only "possible" (13). Inadequate early source control increased 28-day mortality from 26.7 to 42.9%, regardless of the appropriateness of empiric antibiotic therapy (14). Using *in vitro* sensitivities, empiric antibiotic regimens were ineffective in up to a third of cases with proven gram-negative bacteremia (15). These major confounders are not addressed yet surely must impact on outcomes.

Second, the raw data are heavily adjusted statistically to deliver the evangelical message. An analysis performed on 17,990 patients within the Surviving Sepsis Campaign database saw no relationship between actual mortality and antibiotic commencement for up to a 5-hour delay, yet adjustment by "[hospital] location where sepsis was suspected, geographic location [of the hospital], infection source, various organ failures, hypotension (resolved and unresolved), mechanical ventilation, and other clinical characteristics (unpublished

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observations)" enabled demonstration of a 7.5% "linear increase in the risk of mortality for each hour of delay in antibiotic administration" (16). A further 457 patients entered into the database received no antibiotics, but their outcomes were unreported.

Clearly, some adjustment is necessary. Septic patients presenting as moribund are obviously much more likely to die, yet such patients are (it is hoped) more likely to be recognized and treated promptly, and not just with antibiotics. How does the speed and quality of resuscitation impact? Conversely, the gray, indeterminate case that evolves in a downhill manner from a relatively mild initial presentation, and whose underlying sepsis belatedly declares itself, will be managed in a very different manner and may also be compromised by delays in nonantibiotic treatment. There are inherent dangers to both under- or overadjustment of data.

Large population-based adjustments can never hope to accurately capture the intricacies and nuances of these factors. How confident can we be in the validity of the adjustments? My own faith is usually undermined by issues with biological plausibility. Time Zero (either from when the infection starts or organ dysfunction actually begins) and time to presentation/recognition of sepsis is largely unknown but will vary from hours to several days. An excessive delay could be arguably injurious. However, expecting an hour-by-hour linear relationship between mortality risk and delay in antibiotic commencement from presentation/recognition lacks credibility. Kumar and colleagues were the first to draw such a striking straight-line relationship in 2,154 ICU patients using delay in commencing antibiotics after the onset of hypotension (17). Yet, they did not consider the impact of sedation related to mechanical ventilation as a confounding factor in causing hypotension. Notwithstanding the absence of "plausible bacterial pathogen isolated or definitive radiologic, surgical, autopsy, or biopsy evidence of infection" in 22.1% of their population, each hour of delay in initiating effective (proven or adjudicated) antimicrobial therapy was associated with a 7.6% decrease in survival. The authors excluded 558 patients in whom appropriate antibiotics were commenced prehypotension. Paradoxically, survival in this subset (52.2%) was lower than in those receiving treatment within the first 5 hours posthypotension.

Kumar and colleagues also reported that failure to give an effective antibiotic within 36 hours was virtually a death sentence (17). Yet, antibiotic sensitivities are rarely reported before 36 hours and, in my experience, large numbers of these undertreated patients do survive. Indeed, nearly half of 51 reviewed studies failed to show an association between inappropriate empiric antibiotic choice and increased mortality in patients with proven bacteremia (18). A recent prospective study of 679 adults with gram-negative bacteremia in 10 English hospitals identified initial empiric therapy as inappropriate in 34%, yet 30-day mortality was identical (15%). The authors concluded that "outcome is determined primarily by patient and disease factors" (15).

Third, and perhaps most crucially, there is a striking disconnect between these and other "positive" adjusted retrospective analyses and every prospective study I am aware of that has specifically examined the impact of antibiotic delay, some also stratifying by illness severity (14, 15, 19–23). Each of these prospective studies has failed to show a relationship between delay in antibiotic administration within 5 to 6 hours of patient presentation and mortality. They comprise sample sizes from hundreds to thousands and populations from EDs, general wards, and ICUs. A before–after study, ethically approved and National Institutes of Health funded, conducted on 484 patients in the surgical ICU of the University of Virginia, assessed outcomes in the year before and after implementation of a policy of withholding antibiotics until objective microbiological confirmation of infection (23). Case mix and patient management were similar across the epochs. Remarkably, a median 10-hour overall delay in initiating antibiotics was associated with a halving in mortality rate (13 vs. 27%). Even in those patients with significant hypotension, a median 16-hour delay in starting antibiotics in the conservatively managed group was associated with a 26% mortality compared with 66% in those aggressively managed ($P = 0.0004$).

In view of this healthy (or perhaps unhealthy) skepticism, the *Journal* kindly invited me to peer review the article by Liu and colleagues (pp. 856–863) in this issue (24). The authors mined a large administrative database from 21 Northern California hospitals and randomly selected 35,000 patients treated for presumed infection in EDs and subsequently hospitalized. They performed a complex adjustment for patient and hospital factors to generate a risk-adjusted odds ratio for hospital mortality of 1.09 (95% confidence interval, 1.05–1.13) for each elapsed hour between ED registration and antibiotic administration. No data were forthcoming on confirmation of infection; empiric antibiotic sensitivities: adequacy of nonantibiotic management, including source control; or the speed/efficacy of resuscitation.

Clearly, the authors are expert and highly respected in the field of critical care epidemiology, and I would not pretend to fully understand their sophisticated adjustments of the raw data. Although their headline finding sits neatly with the prevailing credo, the results of their adjustments unfortunately also fail my biological plausibility test. For example, compared with patients given antibiotics within the first hour, those treated at any time starting between Hours 2 and 5 had a similar 25 to 30% increase in the adjusted odds risk of mortality. The risk was doubled if treatment was delayed until Hours 5 to 6. So why should the first hour from ED registration be so crucial, especially when Time Zero is unknown? And why should each subsequent hour's delay until hour 5 then not show an effect, followed by a big late rise? Of note, nearly 30% of the total cohort of patients (and 33% of total deaths) received antibiotics within Hour 0 to 1, but only 2.5% (and 2.5% of deaths) of the cohort had antibiotics started between Hours 5 and 6. Other oddities include a big increase in adjusted mortality risk for noninvasive ventilation but no difference for mechanical ventilation or heart rate and a protective effect for altered mental status. Yet this same database was also used for the validation of the Quick Sequential Organ Failure Assessment score, in which altered mental status was a major prognosticator for mortality (25).

I certainly do not advocate that antibiotics be unnecessarily delayed or withheld, especially when faced with a critically ill patient (26). Any sick patient, regardless of etiology, should be seen promptly with due consideration given to possible antibiotic prescription. However, a blanket policy of throwing antibiotics at every patient on "suspicion" of sepsis (however vague) will carry unintended and potentially far more harmful consequences. The alternative option of a world of highly virulent, pan–drug-resistant microorganisms is far less palatable. I am yet to be convinced that each hour does matter, or by the *prima facie*

argument that antibiotics make a huge difference to outcomes. Watchful waiting with removal of any potentially infected plastic tubing may be all that is needed in many patients. The practice of medicine should be about appropriate risk management rather than operating within a climate of fear and penalization. We should accept there will always be a chance of getting it wrong and try hard to minimize this risk. A more circumspect yet still time-critical approach to determine if infection is indeed present, to identify the site and likely cause of infection, to discuss optimal treatment with seniors and specialists, and to gauge any deterioration may prove superior. Epidemiology studies should generate hypotheses but not dictate healthcare policy. We should not suspend belief completely but should certainly challenge it with constructive agnosticism and good science. Would the equipoise exist for prospective randomized studies of immediate versus considered antibiotic therapy? ■

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ORIGINAL ARTICLE

The Timing of Early Antibiotics and Hospital Mortality in Sepsis

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Abstract

Rationale: Prior sepsis studies evaluating antibiotic timing have shown mixed results.

Objectives: To evaluate the association between antibiotic timing and mortality among patients with sepsis receiving antibiotics within 6 hours of emergency department registration.

Methods: Retrospective study of 35,000 randomly selected inpatients with sepsis treated at 21 emergency departments between 2010 and 2013 in Northern California. The primary exposure was antibiotics given within 6 hours of emergency department registration. The primary outcome was adjusted in-hospital mortality. We used detailed physiologic data to quantify severity of illness within 1 hour of registration and logistic regression to estimate the odds of hospital mortality based on antibiotic timing and patient factors.

Measurements and Main Results: The median time to antibiotic administration was 2.1 hours (interquartile range, 1.4–3.1 h). The adjusted odds ratio for hospital mortality based on each hour of delay in antibiotics after registration was 1.09 (95% confidence interval [CI], 1.05–1.13) for each elapsed hour between registration and antibiotic administration. The increase in absolute mortality associated with an hour's delay in antibiotic administration was 0.3% (95% CI, 0.01–0.6%; $P = 0.04$) for sepsis, 0.4% (95% CI, 0.1–0.8%; $P = 0.02$) for severe sepsis, and 1.8% (95% CI, 0.8–3.0%; $P = 0.001$) for shock.

Conclusions: In a large, contemporary, and multicenter sample of patients with sepsis in the emergency department, hourly delays in antibiotic administration were associated with increased odds of hospital mortality even among patients who received antibiotics within 6 hours. The odds increased within each sepsis severity strata, and the increased odds of mortality were greatest in septic shock.

Keywords: sepsis; septic shock; antibacterial agents

At a Glance Commentary

Scientific Knowledge on the Subject: Prior work evaluating antibiotic timing in sepsis has shown mixed results and focused on more severely ill patients, often including patients with long delays in antibiotic administration. This has resulted in clinical equipoise regarding timing thresholds for antibiotic administration in sepsis.

What This Study Adds to the Field: We evaluated 35,000 patients treated within a contemporary multicenter sepsis quality improvement program using granular data including vital signs, laboratory values, and severity of illness indices. Although increased time to antibiotics after emergency department presentation was associated with increased mortality in all sepsis severity groups, the increase in the odds of mortality was greatest in septic shock.

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It is widely accepted and biologically plausible that giving antibiotics as early as possible to patients with sepsis should improve their outcomes (1, 2). This has motivated international guidelines and quality benchmarks in sepsis care (1, 3, 4). It is further motivating several planned clinical trials of administering antibiotics to suspected patients with sepsis even in prehospital settings and before full hospital evaluation (5–7).

However, the desire to shorten the time to antibiotic administration may also incur potential harms and costs (8–10). Such harms might arise from a greater proportion of patients receiving antibiotics unnecessarily because less time is available for clinicians to evaluate alternate etiologies for the patient's presentation (9). Unnecessary antibiotics can result in adverse patient-specific and community-level consequences (11, 12). Within resource-constrained settings like the emergency department (ED), the focus on antibiotic timing could also result in decreased attention to, and investment in, other time-sensitive patient needs (13). Prior efforts to mandate and report antibiotic timing in pneumonia were challenged for several reasons, including antibiotic overuse, and subsequently withdrawn (8–10).

In the absence of a randomized clinical trial to evaluate the benefits of early antibiotic administration, the current evidence remains mixed (14–32). Although no one disputes the need for prompt antibiotic therapy in patients with sepsis, additional study is necessary. Specifically, the availability of granular data from the electronic medical record now permits asking whether administering antibiotics within 1 hour provides more benefit than antibiotics given at 2 or 3 hours. Differences in outcomes related to decision-making in these very early intervals of care could have an important impact on clinical practice, care guidelines, and reporting metrics. We sought to examine data drawn from a multicenter setting to quantify the association between antibiotic timing and mortality among patients with sepsis of all severity levels. Some of the results of these studies have been previously reported in the form of an abstract at the American Thoracic Society International Conference in 2016 (33).

Methods

This study was approved by the Kaiser Permanente Northern California Institutional Review Board.

Subjects

We conducted a retrospective study of patients with sepsis aged greater than or equal to 18 years hospitalized through the ED at the 21 hospitals in the Kaiser Permanente Northern California integrated healthcare delivery system between July 1, 2010, and December 31, 2013. We based our sepsis definitions on prior international consensus definitions of sepsis because they were in clinical use during the period in which this study was conducted (34). We included patients with sepsis based on previously described methods including the presence of inpatient *International Classification of Disease Clinical Modification* ninth edition diagnosis codes of 038 and subtypes 995.91, 995.92, and/or 785.52 (35–37); and their receipt of antibiotics (i.e., antibacterial agents) within 6 hours of ED registration time. We randomly selected 5,000 patients hospitalized in 2010 and 10,000 patients hospitalized in each year between 2011 and 2013; we selected fewer cases from late 2010 because a regional sepsis quality improvement program was completing implementation.

Hospitalization Data

We linked patients with sepsis with corresponding electronic databases based on methods described in prior studies using electronic medical record flowsheet, laboratory, diagnosis, and treatment data (38–41), incorporating composite comorbid disease burden (Comorbidity Point Score 2) and acute severity of illness (Laboratory Acute Physiology Score 2 [LAPS2]) scores. We determined predicted hospital mortality with an automated hospital risk prediction model that demonstrated good discrimination in this population (C statistic, 0.80). We assessed intensive care unit admission from the ED using bed history records and determined patients' resuscitation care order status at hospital admission as "full code" versus "not full code" (42). We ascertained hospital mortality from inpatient records (38–41).

ED Data

To minimize confounding and to optimize risk-adjustment of patients at the very beginning of their treatment course, we characterized patients' ED clinical status based on detailed patient data from their first hour after registration. By including vital signs and treatment patterns within the first hour, we sought to digitally recapitulate, and adjust for, the clinical context that motivated decisions about antibiotic timing by emergency providers. In the first hour, we quantified the total number of vital signs recorded (heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, temperature) and the number of instances with patients' respiratory rate greater than or equal to 22 breaths per minute, systolic blood pressure less than or equal to 90 mm Hg, and heart rate greater than or equal to 100 beats per minute. We then calculated the mean systolic blood pressure, heart rate, and respiratory rate values in the first hour. We also determined whether patients required invasive or noninvasive ventilation and counted the number of intravenous vasopressors required at 1 and 6 hours. Finally, we used illness acuity ratings assigned at the time of ED presentation based on the Emergency Severity Index (including resuscitative, emergent, urgent, less urgent, or nonurgent categories).

To further quantify sepsis-related organ dysfunction, we evaluated patient laboratory data within their first 6 hours after ED registration within binary categories, including band forms greater than or equal to 10%, platelets less than or equal to 100,000/μl, serum creatinine greater than or equal to 2 mg/dl, total bilirubin greater than or equal to 2 mg/dl, and international normalized ratio greater than or equal to two; missing values (ranging from 1.9% for creatinine to 71.2% for band forms) were imputed as normal. We used each patient's first serum lactate value if collected within 6 hours; missing lactate values (n = 1,144; 3.3%) were imputed to the median based on severity strata. Finally, we determined abnormal mentation based on prior methods for evaluating ED Glasgow Coma Scores and/or nursing flowsheet entries (41).

Sepsis Severity Strata

We grouped patients into three levels of sepsis severity based on prevalent definitions in 2013: (*1*) septic shock, (*2*) severe sepsis, and (*3*) sepsis. We classified patients as having septic shock if they required vasopressors or had a first serum lactate value greater than or equal to 4 mmol/L. In the remaining sample, we classified patients as having severe sepsis if they had a lactate value greater than or equal to 2 mmol/L, had greater than or equal to one instance of hypotension, required invasive or noninvasive mechanical ventilation, or had laboratory-determined organ dysfunction (as described previously). We classified the remaining patients as having sepsis. We selected all variables describing clinical, organ failure, and severity strata characteristics *a priori*.

Antibiotic Administration

We calculated the time from ED registration to the administration of the first intravenous or enteral antibiotic in hours. We also determined the number of unique antibiotics administered within the first 6 hours. For multivariable regression analyses, we grouped patients' antibiotic administration times within 30-minute increments from 0–6 hours after ED registration. For the purposes of graphical demonstration, we grouped antibiotic administration within hourly increments over the 6-hour interval.

Statistical Analysis

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as number (%). We compared characteristics between patients based on sepsis severity strata with analysis of variance or chi-square tests. We displayed time to antibiotic administration using kernel density plots and compared time to antibiotics between sepsis severity strata with the Kruskal-Wallis rank test.

We estimated the impact of antibiotic timing on risk-adjusted hospital mortality using logistic regression based on the clinical variables described previously. We assessed for collinearity between variables and removed those with a correlation coefficient greater than or equal to 0.6 (predicted hospital mortality and vital sign counts). Our fully adjusted model included patient characteristics and severity of illness (age, sex, LAPS2, Comorbidity Point Score 2, Emergency Severity Index category, code status), treatments (vasopressors, invasive ventilation, or noninvasive ventilation at 1 h), mean vital sign values, sepsis severity strata, the presence of abnormal laboratory values, and hospital facility. To assess how the association between the timing of antibiotics and mortality differed across sepsis severity groups, we assessed the fully adjusted model within each severity strata subgroup separately. To evaluate how potential antibiotic appropriateness impacted outcomes, we conducted a *post hoc* subgroup analysis of two cohorts determined based on the administration of a broad versus a narrow first antibiotic (*see* Table E1 in the online supplement). We conducted analyses using STATA/SE version 13.1 (StataCorp, College Station, TX) and considered a P value less than or equal to 0.05 to be significant.

Results

Of the 35,000 patients in our sample, 13.3% (n = 4,668) met criteria for septic shock and 52.0% (n = 18,210) met criteria for severe sepsis (Table 1). Observed mortality was 3.9%, 8.8%, and 26.0% in patients with sepsis, severe sepsis, and septic shock, respectively. Including only full code patients, mortality was 2.4%, 8.5%, and 21.6%, respectively. All comparisons between groups were highly significant. For example, the frequency of elevated band forms was 10.1% (n = 1,229) in sepsis compared with 31.4% (n = 1,466) in septic shock. The time to the first lactate value was shortest in septic shock (0.8 [0.5–1.7] h); shock patients also had the highest mean lactate value (4.6 [4.0–5.9] mmol/L). Among patients with septic shock, 2.4% and 43.4% had vasopressors initiated within 1 and 6 hours, respectively. Among patients with septic shock who were full code at admission, 81.3% were admitted directly to the intensive care unit.

Antibiotic Timing and Use

Overall, the median time to antibiotic administration was 2.1 hours (interquartile range, 1.4–3.1 h) (Figure 1); this timing did not differ across years. The median time to antibiotics was shortest in patients with septic shock (1.7 h) and longest in patients with sepsis (2.3 h; $P < 0.001$). Patients receiving earlier antibiotics had greater severity of illness compared with those receiving later antibiotics based on acuity level, acute severity of illness (LAPS2), vital signs, and laboratory values (*see* Table E1). They also had the highest unadjusted mortality (11.4% and 9.5% for Hour 1 and Hour 2 patients, respectively). In total, 42.2% of patients received one antibiotic and 42.5% received two antibiotics (Table 2). The frequency of receiving two or more antibiotics increased as sepsis severity increased (52.0% in sepsis vs. 71.7% in septic shock; $P < 0.01$). The most common antibiotic used in all groups was ceftriaxone, and the second most common antibiotic varied among azithromycin (sepsis), vancomycin (severe sepsis), and pipercillin-tazobactam (septic shock).

Hospital Mortality

The fully adjusted odds ratio for hospital mortality based on antibiotic timing was 1.09 (95% confidence interval [CI], 1.05–1.13) per elapsed hour after ED presentation (Table 3). The odds ratios were similar in patients with sepsis (1.09; 95% CI, 1.00–1.19; $P = 0.046$) and severe sepsis (1.07; 95% CI, 1.01–1.24; $P = 0.014$), whereas they were increased in septic shock (1.14; 95% CI, 1.06–1.23; $P = 0.001$). The absolute increase in mortality associated with an hour's delay in antibiotic administration was 0.3% (95% CI, 0.01–0.6%; $P = 0.04$) for sepsis, 0.4% (95% CI, 0.1–0.8%; $P = 0.02$) for severe sepsis, and 1.8% (95% CI, 0.8–3.0%; $P = 0.001$) for shock. Figure 2 displays the adjusted odds ratios based on hourly increments of antibiotic administration time each compared with the reference value of less than 1 hour. In subgroup analysis, delays in broad antibiotic administration were associated with an increased effect size (1.08; 95% CI, 1.01–1.16; $P = 0.02$) compared with delays in narrow antibiotic administration (odds ratio, 1.05; 95% CI, 1.01–1.10; $P = 0.03$).

Discussion

In this study, we used a large, multicenter, and contemporary sample of patients with

Table 1. Clinical Characteristics, Stratified by Sepsis Severity Level

	Overall (*n* = 35,000)	Sepsis Severity Strata		
		Sepsis (*n* = 12,122)	Severe Sepsis (*n* = 18,210)	Septic Shock (*n* = 4,668)
Age, yr	73 (60–83)	72 (56–83)	74 (62–83)	73 (61–83)
Male	16,961 (48.5)	5,235 (43.2)	9,322 (51.2)	2,404 (51.5)
Full code (42)	25,671 (73.4)	9,133 (75.3)	13,130 (72.1)	3,408 (73.0)
LAPS2 value	100 (74–129)	80 (59–104)	104 (81–129)	149 (122–177)
COPS2 value	56.9 ± 51.1	46.3 ± 45.5	63.5 ± 52.9	58.8 ± 53.3
Predicted mortality, %	9.0 ± 12.3	4.4 ± 6.3	8.6 ± 10.6	22.2 ± 19.2
ED acuity level				
Resuscitative	1,086 (3.1)	84 (0.7)	478 (2.6)	524 (11.2)
Emergent	14,248 (40.7)	3,766 (31.1)	7,743 (42.5)	2,739 (58.7)
No. of instances in 1 h				
Vital signs recorded	15 (9–19)	11 (9–17)	15 (9–20)	18 (12–28)
SBP <90 mm Hg	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)
RR ⩾22 breaths/min	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–2)
HR ⩾90 beats/min	1 (0–2)	1 (0–2)	1 (0–2)	2 (1–3)
Mechanical ventilation	495 (1.4)	0 (0.0)	195 (1.1)	300 (6.4)
Noninvasive ventilation	1,208 (3.5)	0 (0.0)	858 (4.7)	350 (7.5)
Vasopressor use	110 (0.3)	0 (0.0)	0 (0.0)	110 (2.4)
Mean values in first hour				
SBP, mm Hg	127.3 ± 25.5	133.3 ± 21.4	127.0 ± 25.9	113.4 ± 27.7
HR, beats/min	101.8 ± 21.0	101.5 ± 19.1	100.9 ± 21.1	106.4 ± 24.5
RR, breaths/min	21.4 ± 5.1	20.6 ± 4.3	21.5 ± 5.1	23.4 ± 6.3
Laboratory abnormalities				
Bands ⩾10%	5,550 (15.9)	1,229 (10.1)	2,855 (15.7)	1,466 (31.4)
Creatinine ⩾2.0 mg/dl	5,593 (16.0)	0 (0.0)	4,181 (23.0)	1,412 (30.3)
INR ⩾1.5	4,757 (13.6)	0 (0.0)	3,690 (20.3)	1,067 (22.9)
Platelets ⩽100,000	2,661 (7.6)	0 (0.0)	2,006 (11.0)	655 (14.0)
Bilirubin ⩾2.0 g/dl	1,974 (5.6)	0 (0.0)	1,394 (7.7)	580 (12.4)
First lactate value, mmol/L	1.8 (1.2–2.7)	1.3 (1.0–1.5)	2.2 (1.5–2.7)	4.6 (4.0–5.9)
Time to first lactate, h	1.0 (0.6–2.1)	1.1 (0.6–2.6)	0.9 (0.6–2.0)	0.8 (0.5–1.7)
First non-ED hospital unit				
Intensive care	7,221 (20.6)	760 (6.3)	3,112 (17.1)	3,349 (71.7)
Hospital mortality	3,285 (9.4)	474 (3.9)	1,596 (8.8)	1,215 (26.0)

Definition of abbreviations: COPS2 = Comorbidity Point Score, version 2; ED = emergency department; HR = heart rate; INR = international normalized ratio; LAPS2 = Laboratory and Acute Physiology Score, version 2; RR = respiratory rate; SBP = systolic blood pressure.
Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as number (%). All comparisons between sepsis severity strata were significant to a $P < 0.001$. ED acuity level is based on the Emergency Severity Index.

sepsis to evaluate the association between early antibiotic timing and hospital mortality. We found that each elapsed hour between ED registration and antibiotic administration was associated with a 9% increase in the odds of mortality. This relative effect was similar for patients with sepsis and severe sepsis, whereas it was largest for patients with septic shock.

Although no one recommends delaying antibiotics for patients with sepsis, the existing evidence supporting the mortality benefits of earlier antibiotic administration is mixed (14–30, 32). In a frequently cited study, Kumar and coworkers (19) retrospectively evaluated 2,154 critically ill patients with septic shock between 1989 and 2004. After controlling for measures of illness severity and management decisions, they found that increasing time intervals between the first episode of persistent hypotension and the administration of effective antibiotics was associated with increased mortality. Notably, however, the median time from hypotension to antibiotic administration was 6 hours after the recognition of shock and the overall mortality rate was 56.2%, likely representing the much less aggressive approach to sepsis care from a prior era and heavy selection criteria to enter the cohort.

More recently, Ferrer and coworkers (20) conducted a retrospective analysis of Surviving Sepsis Campaign data including 17,990 patients from 165 intensive care units between 2005 and 2010. The adjusted odds of hospital mortality increased as the time from patient triage or sepsis identification to antibiotics increased. This international study also captured a more contemporary approach to sepsis care, with only 12% of patients receiving antibiotics greater than 6 hours after presentation and a 29.7% overall mortality rate. Although one of the study's strengths was that it considered patients with sepsis identified in a variety of different hospital settings, it was nonetheless limited to patients eventually admitted to the intensive care unit. As a result, the study only addresses antibiotic timing in the most severely ill patients with sepsis, who make up a modest fraction of all sepsis inpatients (35).

In a recently published metaanalysis of 11 studies by Sterling and coworkers (15), the authors found no significant association between early antibiotics and improved mortality. Including data drawn from more than 16,000 patients in six studies, the authors found that the odds ratio for mortality among patients receiving antibiotics more than 3 hours after triage time was 1.16 ($P = 0.21$) compared with patients receiving antibiotics in less than 3 hours. However, the lack of patient-level

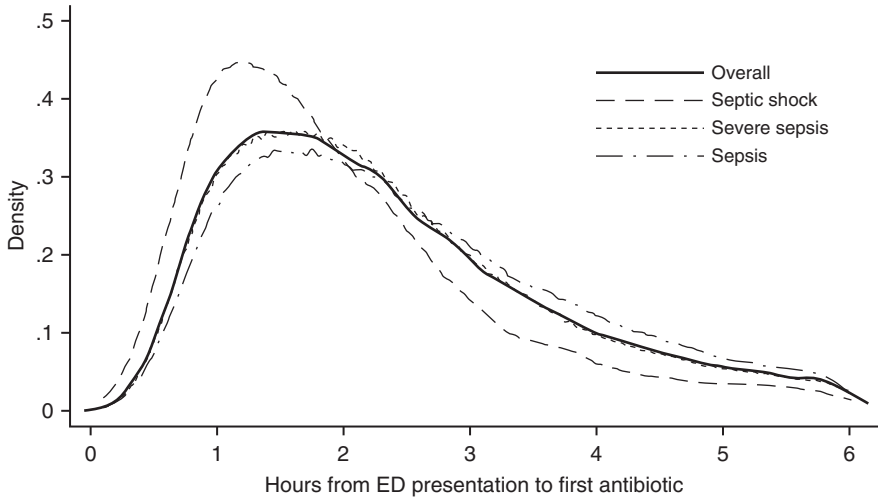

Figure 1. Kernel density plot showing time to first antibiotic administration from emergency department registration. Distribution in the overall cohort is shown with a *solid line*, the septic shock cohort is shown in a *dashed line*, the severe sepsis cohort with a *dotted line*, and the sepsis cohort with a *dashed-dotted line*. ED = emergency department.

data, heterogeneity in the eligible studies, and a smaller sample size may have limited the power to detect statistical significance for the point estimates, which favored earlier antibiotics and could still be associated with meaningful absolute population-level mortality benefits given sepsis' high prevalence. Other smaller studies have reported similar findings (14, 17, 18, 28, 29, 31, 32, 43).

The current study seeks to address the limitations of prior studies. First, we evaluated a multicenter sample of patients treated within the contemporary framework of a sepsis quality improvement program. We sought to evaluate whether antibiotic timing continued to show an association with improved outcomes in the modern era of care, especially because some earlier elements of sepsis care no longer seem to impact patient outcomes (44). We further chose to limit our evaluation to patients who received antibiotics within 6 hours because, in the context of aggressive screening and treatment, patients who receive antibiotics later than 6 hours are likely to have demonstrated diagnostic uncertainty or received potentially delayed care (1). Even in the setting where the median time to antibiotics was 2.1 hours from ED registration, early antibiotics were significantly associated with improved survival.

Second, we evaluated patients presenting with variable sepsis severity, most of who were not treated in critical care settings. Although critically ill patients with sepsis have high mortality, they comprise a relatively small proportion of all patients with sepsis based on 2001 consensus definitions (34). We sought to demonstrate whether the biologically plausible principle of early infection control with antibiotics would show consistent benefits for all infected patients with systemic inflammation. We found that early antibiotics were associated with improved survival among all patients with sepsis, a finding that has broad implications for a large cohort of inpatients whom together comprise as many as half of all hospital deaths in the United States (35). However, the increasing odds of mortality associated with later antibiotics were most prominent among patients with septic shock for whom each hourly delay was associated with a 1.8% increase in hospital mortality.

Finally, we addressed prior limitations by using inpatient data characterized by breadth (drawn from a large population sample of 35,000 hospitalizations) and depth (including detailed physiologic and treatment measures). We also included a wide variety of predictors that would be clinically relevant for emergency providers in the midst of early decision-making about antibiotic administration. Our findings demonstrate the benefits of leveraging already available electronic medical record data from narrow time intervals to address confounding and reliably evaluate highly time-sensitive outcomes.

Our findings support currently held beliefs that administering early antibiotics to infected patients with systemic inflammation is beneficial for reducing mortality. Our study also helps address prior conflicting evidence and redefines what constitutes equipoise about the exact timing thresholds that are necessary to ensure optimal care. This is especially relevant

Table 2. Antibiotic Usage (Number and Percentage) in the Cohort Stratified by Sepsis Severity level

		Sepsis Severity		
	Overall (*n* = 35,000)	**Sepsis (*n* = 12,122)**	**Severe Sepsis (*n* = 18,210)**	**Septic Shock (*n* = 4,668)**
Unique antibiotics administered within 6 h, n (%)				
One	14,767 (42.2)	5,815 (48.0)	7,632 (41.9)	1,320 (28.3)
Two	14,869 (42.5)	5,053 (41.7)	7,796 (42.8)	2,020 (43.3)
Three or more	5,364 (15.3)	1,254 (10.3)	2,782 (15.3)	1,328 (28.5)
Most common antibiotics (n; %)				
First	Ceftriaxone (16,796; 48.0)	Ceftriaxone (5,846; 48.2)	Ceftriaxone (8,754; 48.1)	Ceftriaxone (2,196; 47.0)
Second	Vancomycin (8,840; 25.3)	Azithromycin (2,370; 19.6)	Vancomycin (4,721; 25.9)	Pip/Tazo (1,819; 39.0)
Third	Pip/Tazo (8,131; 23.2)	Vancomycin (2,348; 19.4)	Pip/Tazo (4,264; 23.4)	Vancomycin (1,771; 37.9)
Fourth	Azithromycin (6,706; 19.2)	Pip/Tazo (2,048; 16.9)	Azithromycin (3,438; 18.9)	Azithromycin (898; 19.2)
Fifth	Ciprofloxacin (5,435; 15.5)	Ciprofloxacin (1,961; 16.2)	Ciprofloxacin (2,753; 15.1)	Ciprofloxacin (721; 15.4)

Definition of abbreviation: Pip/Tazo = pipercillin-tazobactam.

Table 3. Odds Ratios for Hospital Mortality Based on the Time of Antibiotic Administration in Unadjusted and Adjusted Logistic Regression Models

Model	Odds Ratio for Hospital Mortality, per Elapsed Hour until Antibiotic Administration	95% CI	*P* Value
Unadjusted	0.89	0.86–0.91	<0.001
+ Sepsis severity strata	0.96	0.93–0.99	0.013
+ Severity of illness	1.08	1.04–1.12	<0.001
+ Demographics	1.09	1.05–1.13	<0.001
Fully adjusted model, in each subgroup			
Sepsis only	1.09	1.00–1.19	0.046
Severe sepsis only	1.07	1.01–1.24	0.014
Septic shock only	1.14	1.06–1.23	0.001

Definition of abbreviation: CI = confidence interval.
Beyond the unadjusted model, each subsequent model includes an additional set of covariates, including sepsis severity strata (categorized as sepsis, severe sepsis, or septic shock), severity of illness (Laboratory and Acute Physiology Score, version 2; Emergency Severity Index; mean vital sign values; presence of altered mental status; laboratory data; need for direct intensive care unit transfer; number of vasopressors given within the first h; and number of antibiotics given within 6 h), and demographics (age; sex; code status; Comorbidity Point Score, version 2; and facility). The results of the fully adjusted model within each sepsis severity subgroup are shown at the bottom of the table.

because a clinical trial that randomizes patients with sepsis to delayed antibiotics is unlikely to be deemed ethical, at least while the harms of indiscriminate antibiotics remain incompletely characterized.

The current study does not resolve all questions about antibiotic timing (e.g., are antibiotics given at 2 h more beneficial than those given at 3 or 4 h) because the odds ratio confidence limits we observed between 2 and 5 hours are overlapping. These data could suggest that among patients with clear evidence of septic shock, earliest antibiotics confer the greatest mortality benefits.

However, among patients with less diagnostic certainty for sepsis, modest delays in antibiotics may not substantially increase mortality. This finding has important implications for antibiotic timing when it is placed within the larger context of competing ED priorities and resource needs. Clinical trials that examine antibiotic timing intervals when sepsis is uncertain and/or cost-effectiveness studies evaluating the costs and benefits of accelerated antibiotic pathways may prove highly useful.

Our study was limited in several important ways. First, we evaluated a sample of patients treated at a network of hospitals with an existing sepsis performance improvement program. The mortality among full code patients with septic shock (21.6%) was similar to that reported in recent clinical trials (44–47). Thus, our results may be less generalizable to hospitals where sepsis care occurs outside of focused sepsis improvement programs. Second, we were not able to adjust for concomitant sepsis treatments administered to patients along with antibiotics. For example, patients receiving earlier antibiotics may have also received other treatments, such as fluid resuscitation, earlier, such that early antibiotics are only a marker of an overall higher quality of sepsis care. We were also not able to adjust for patients who received preexisting antibiotics. Third, we did not specifically evaluate the adequacy of antibiotics based on microbiologic results and specific susceptibility patterns. Fourth, we limited our evaluation to patients who received antibiotics within 6 hours of ED presentation because this represents a contemporary and guideline-concordant standard of sepsis care. Fifth, we identified patients with sepsis with diagnostic codes that may lack sensitivity for certain patient subgroups (e.g., low-risk patients with sepsis). Finally, we did not evaluate the impact of antibiotic timing outside of the ED because the recognition and treatment of sepsis in other hospital settings is highly variable and less amenable to robust analysis.

In summary, in a large, contemporary, multicenter sample of patients with sepsis admitted through the ED, we found that each elapsed hour between presentation and antibiotic administration was associated with a 9% increase in the odds of mortality in patients with sepsis of all severity strata. Although antibiotics given within the first hour of registration were associated with the greatest benefit, antibiotics given between hours 2 and 5 were associated with similar odds of mortality. Earlier antibiotics conferred the greatest absolute benefit in patients with septic shock. ■

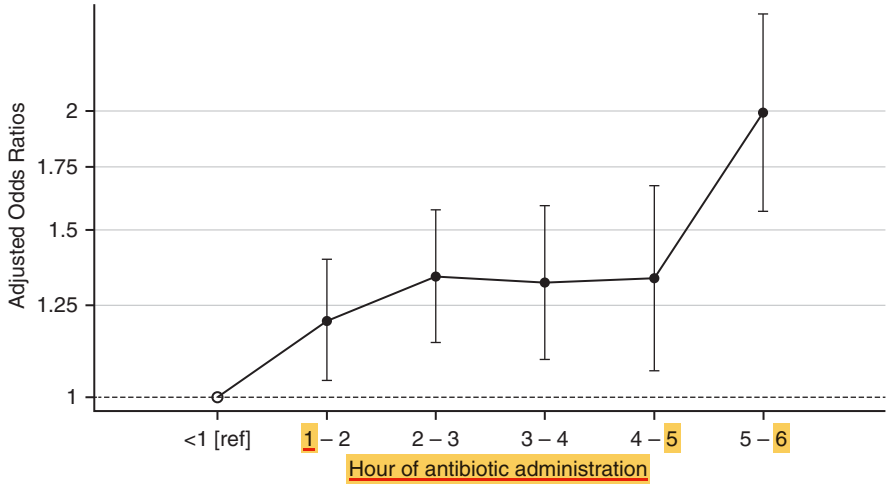

Figure 2. Adjusted odds ratios for hospital mortality comparing patients within each hourly antibiotic administration group with the reference group of patients given antibiotics in <1 hour. The *y-axis* is on logarithmic scale and the *error bars* represent 95% confidence intervals.

Author disclosures are available with the text of this article at www.atsjournals.org.

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The Timing of Early Antibiotics and Hospital Mortality in Sepsis: Playing Devil's Advocate

To the Editor:

In this issue of the *Journal*, Liu and colleagues have reported that hourly delays in antibiotic administration were associated with increased odds of hospital mortality even among patients receiving antibiotics within 6 hours (1) [pp. 856–863]. The overarching theme and implication of these findings is that clinicians should strive to deliver antibiotics to patients presenting to the emergency department (ED) with presumed sepsis as expeditiously as possible to improve survival (1). We applaud the authors' intentions of providing additional evidence that prompt administration of appropriate antimicrobial therapy in sepsis is lifesaving, but making this conclusion without following the outcomes of those patients without sepsis who received prompt, but unnecessary, antimicrobial therapy, leads to potentially skewed and biased assumptions (1–5). In fact, the authors make mention of this in their introduction when they list the potential harms of timely antibiotic administration (i.e., receipt of antibiotics unnecessarily culminating in adverse patient and community consequences, decreased attention to other diseases and patient-specific needs), but overlook this important fact when discussing their results and conclusions (1). The intent of this letter is to highlight the ramifications that neglecting to include those nonseptic patients who needlessly received antibiotics conceivably had on the researchers' results, while urging the investigators to reevaluate their findings in light of this potential bias.

The authors discuss their approach, which led to the 35,000 patients with sepsis who were included in their retrospective analysis, which included incorporating patients admitted with sepsis-specific *International Classification of Diseases* codes who received antibiotics within 6 hours of ED registration time (1). However, the authors neglect to include, and fail to mention, the exclusion of those patients who received prompt antibiotics who were later found not to be septic (i.e., presumably those with systemic inflammatory response syndrome resulting from noninfectious causes or viral infections) (1). It is these patients who received antibiotics unnecessarily, and their direct and indirect downstream health consequences of receiving unneeded antibiotics, that have significant potential to bias the authors' conclusion that prompt antibiotic administration improves survival in patients with sepsis. A more accurate conclusion given the study's methodology might be: for those patients presenting to the ED who received antibiotics within 6 hours and were admitted with a sepsis-specific diagnosis, rapid administration of antibiotics was associated with less odds of mortality.

It is safe to assume that a significant fraction of those nonseptic patients who received antibiotics unnecessarily had poorer outcomes and possibly higher mortality than if they never received antibiotics in the first place (6, 7). To list the potential ways inappropriate and unnecessary antibiotic administration can cause harm is beyond the scope of this letter, but suffice it to say there are many (6, 7).

Overall, we commend the authors for aspiring to demonstrate that antibiotics administered as quickly as possible in patients presenting to the ED with a systemic inflammatory response may improve sepsis survival, but making this conclusion without incorporating the potential harms of delivering unneeded antibiotics to nonseptic patients can lead to potentially inaccurate interpretations. Thus, despite these most recent findings, it remains imperative that clinicians weigh the benefits of prompt antibiotic administration with antibiotic stewardship. ■

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Reply

From the Authors:

Economists have long recognized the importance of externalities: the "spillover" benefits and harms that result from specific actions that are unaccounted for in the cost of the activity itself. In 1920, Arthur Pigou described an example of a negative externality as the sparks emanating from a train traversing railway tracks that ignite surrounding fields and forests (1). When unaccounted for in the train ticket price, the resulting loss of crops or timber, "innocent bystanders" of train travel, become costs borne solely by the landowner. To redress this problem, Ronald Coase suggested that an efficient solution could be achieved through bargaining if the affected parties had access to perfect information about the benefits and harms of the activity (2). With this information, they could agree on appropriate compensation. Short of this, governing bodies could enact Pigovian taxes (named after Pigou) to properly remunerate each party. In either case, the key criterion for a solution is the availability of information about an activity's benefits and harms. Unfortunately, this criterion is rarely met in real-world economics.

Similarly, when it comes to modern antibiotic prescribing practice, we lack adequate information. Even in the relatively narrow question of antibiotic timing among patients hospitalized for acute infection, numerous studies have shown mixed results regarding the importance of earlier antibiotics, resulting in controversy (3). We thus restricted our current study to address this question using highly granular data in a large and contemporary cohort (4) [this issue, pp. 856–863]. However, we did this acknowledging that many other important questions, particularly about the negative externalities of antibiotic timing and use, remain.

For example, as we suggested in our study and Dr. Chertoff and Dr. Ataya have reiterated, what are the innocent bystander costs of prioritizing early antibiotics, either for patients who ultimately do not have infection or even for other patients being treated by the same teams? Recent data highlight the bystander risks associated with being in proximity to another patient requiring urgent intervention (5). On a larger scale, how do we best reconcile outpatient recommendations, which increasingly focus on limiting the use of inappropriate antibiotics, with inpatient recommendations, which increasingly focus on earlier identification and treatment? Further, how do we understand the effect of health system–level antibiotic usage patterns against the background of rising antibiotic resistance threats resulting from medical, agricultural, and husbandry practices (6)?

We urgently need additional studies that inform our decisions about best antibiotic prescribing practices, particularly by allowing us to balance the individual and societal costs and benefits of differing practices. In addition to traditional outcomes studies, we will need ecological studies that look beyond the hospital setting, as well as cost-benefit analyses that enable a longer-term and societal perspective. Randomized clinical trials may play a role when patients present with uncertain diagnoses and less severe organ dysfunction. Novel diagnostic tools allowing us to distinguish bacterial and viral infections may offer even more efficient solutions for tailoring antibiotic use. Over time, these approaches will contribute the critical information we need to answer antibiotic use questions focused less on "who?" and "when?" and increasingly on "for what gain?" and "at what cost?" ■

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