Title

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Journal

Journal of the American College of Emergency Physicians Open, 5(2)

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Publication Date

2024-04-01

DOI

10.1002/emp2.13149

Peer reviewed

Received: 6 November 2023 | Revised: 23 February 2024 | Accepted: 4 March 2024

DOI: 10.1002/emp2.13149

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
WILEY

ORIGINAL ARTICLE

Infectious Disease

Timing of antibiotic treatment identifies distinct clinical presentations among patients presenting with suspected septic shock

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Funding information
National Heart, Lung, and Blood Institute, Grant/Award Numbers: K24HL141354, U01HL123004; National Diabetes and Digestive and Kidney Diseases, Grant/Award Number: K24DK113381

Abstract

Objective: Recent clinical guidelines for sepsis management emphasize immediate antibiotic initiation for suspected septic shock. Though hypotension is a high-risk marker of sepsis severity, prior studies have not considered the precise timing of hypotension in relation to antibiotic initiation and how clinical characteristics and outcomes may differ. Our objective was to evaluate antibiotic initiation in relation to hypotension to characterize differences in sepsis presentation and outcomes in patients with suspected septic shock.

Methods: Adults presenting to the emergency department (ED) June 2012–December 2018 diagnosed with sepsis (Sepsis-III electronic health record [EHR] criteria) and hypotension (non-resolving for ≥30 min, systolic blood pressure <90 mmHg) within 24 h. We categorized patients who received antibiotics before hypotension ("early"), 0–60 min after ("immediate"), and >60 min after ("late") treatment.

Results: Among 2219 patients, 55% received early treatment, 13% immediate, and 32% late. The late subgroup often presented to the ED with hypotension (median 0 min) but received antibiotics a median of 191 min post-ED presentation. Clinical characteristics notable for this subgroup included higher prevalence of heart failure and liver disease ($p < 0.05$) and later onset of systemic inflammatory response syndrome (SIRS) criteria compared to early/immediate treatment subgroups (median 87 vs. 35 vs. 20 min, $p < 0.0001$). After adjustment, there was no difference in clinical outcomes among treatment subgroups.

Conclusions: There was significant heterogeneity in presentation and timing of antibiotic initiation for suspected septic shock. Patients with later treatment commonly had hypotension on presentation, had more hypotension-associated comorbidities, and

Supervising Editor: Faheem Guirgis, MD

developed overt markers of infection (eg, SIRS) later. While these factors likely contribute to delays in clinician recognition of suspected septic shock, it may not impact sepsis outcomes.

KEYWORDS
critical care, electronic health records, emergency medicine, organ dysfunction scores, sepsis, systemic inflammatory response syndrome

1 | INTRODUCTION

1.1 | Background

Appropriate recognition and treatment timing in sepsis has been a focus of multiple studies, guideline development, and quality improvement measures. In sepsis, delays in antibiotic administration are associated with increased mortality, particularly after the development of hypotension.[1] Every hour delay in antibiotics after onset of hypotension is associated with an estimated 4%–7% increase in mortality.[1–4] Thus, current guidelines recommend clinicians administer antibiotics within 1 h[5] of shock and/or recognition of sepsis.[6,7]

1.2 | Importance

Although studies have explored the relationship between treatment timing and outcomes in patients with sepsis and septic shock,[2,3,6,8–10] less is known about differences in clinical presentation between patients receiving later versus early antibiotic treatment. A study of patients with septic shock in the emergency department (ED) found that those with less overt signs of infection on triage were more likely to receive later administration in antibiotics and increased mortality,[3,11] yet it is unknown what other clinical characteristics are associated with later treatment.[12]

1.3 | Goals of this investigation

The objective of our analysis was to consider antibiotic initiation in relation to initial hypotension to characterize differences in sepsis presentation and outcomes among patients who presented to the ED with suspected septic shock.

2 | METHODS

2.1 | Study design and setting

We conducted a retrospective cohort study of adults presenting to the University of California, San Francisco (UCSF) Helen Diller Medical Center at Parnassus Heights ED with suspected septic shock within 24 h of ED presentation between June 1, 2012, and December 31, 2018. The study site is a 600-bed urban, academic teaching hospital with ~30,000 ED encounters and 9000 inpatient admissions per year. The study was approved with waiver of informed consent by the UCSF Human Research Protection Program (IRB #16-20956). Since 2012, our institution has used an Epic-based electronic health record (EHR) platform (Epic Systems Corporation). All data elements were extracted from Clarity, the relational database that stores Epic's inpatient data, using structured query language.

2.2 | Selection of participants

We included adults (≥18 years old) with suspected infection, defined as having blood cultures ordered, receiving parenteral antibiotics, and meeting EHR-based Sepsis-III criteria (Sequential Organ Failure Assessment [SOFA] score ≥ 2) within 24 h of ED presentation.[13] Additionally, patients met EHR-sepsis criteria with (1) at least 4 days of sequential antibiotic therapy (or death or discharge to hospice before 4 days of antibiotic therapy) or (2) a sepsis discharge billing code,[14] a method previously developed and validated by Rhee and colleagues.[14] The study was limited to patients with "suspected septic shock," defined as a systolic blood pressure (SBP) less than 90 mmHg within 24 h of ED presentation, similar to a recently published article by Pak et al.[4] We excluded those with resolution of hypotension within 30 min of its start to eliminate spurious hypotension. Repeat encounters were treated independently.

To validate our EHR-based sepsis diagnosis, we reviewed 50 randomly selected charts of patients without a sepsis discharge code (10 early, 10 immediate, and 30 late subgroups) to determine whether patients had true sepsis and found that 68% of patients were confirmed sepsis ($n = 34$) and 22% were likely sepsis ($n = 11$). Among patients ultimately determined not to be sepsis on review ($n = 5$, 10%), treatment with empiric antibiotics at presentation was almost always determined to be appropriate (Table S1).

2.3 | Measurements

We collected components of SOFA and systemic inflammatory response syndrome (SIRS) criteria with timestamps to assess timing of multiple infectious and organ dysfunction measures.[15] Missing components of SOFA/SIRS did not contribute to the final score as per convention.[13] To calculate both SOFA and SIRS, all relevant clinical

values were extracted along with their EHR chart timestamp. We sorted the components values sequentially by timestamp, assigned SIRS and/or SOFA points to each value, and then added points. Criteria were met at the timestamp at which the SOFA or SIRS score equaled ≥2. We considered meeting SOFA, SIRS, or our institution's EHR sepsis alert[16] as timestamps at which physicians may suspect sepsis ("sepsis recognition criteria"). Timestamps of vasopressor and antibiotic administration were obtained along with blood culture results.

Patient demographics were extracted including age, sex, ethnicity, primary language, need for interpreter, insurance status, and pre-admission housing location. All International Classification of Diseases (ICD)-9/10 admission and discharge diagnosis codes were extracted. We used comorbidity groupings of ICD-9/10 codes present on admission to identify pre-existing comorbidities and underlying organ dysfunction using the Elixhauser risk of mortality score.[17] ED and admission triage level were collected to assess severity of illness.

2.4 | Outcomes

We calculated time from ED presentation to the following: meeting sepsis recognition criteria (SIRS/SOFA/EHR Sepsis Alert), first elevated lactate, first episode of hypotension, first IV antibiotic order, and first IV antibiotic administration. Key outcomes extracted included need for mechanical ventilation, need for vasopressors, incidence of bacteremia based on discharge coding and/or presence of a positive blood culture, length of stay (LOS), and discharge disposition.

2.5 | Analysis

While traditionally "time zero" for sepsis is the time of ED presentation, we used the time of initial hypotensive episode as "time zero" a priori to define our antibiotic treatment subgroups. Categories of treatment timing were motivated by the Surviving Sepsis Campaign guidelines and included (1) "early treatment"—antibiotics administered prior to hypotension, (2) "immediate treatment"—antibiotics administered within 60 min of hypotension, and (3) "late treatment"—antibiotics administered more than 60 min after hypotension onset. Demographic and clinical characteristics were compared between the treatment subgroups.

To determine the relationship between sepsis treatment subgroup and in-hospital mortality, in-hospital mortality or transfer to hospice, and LOS for survivors, we performed a matched propensity score analysis using variables known to be associated with treatment and in-hospital mortality. We used optimal full matching on propensity score, implemented using the "MatchIt" and "optmatch" R packages[18,19] and implemented the propensity score that achieved the best balance as measured by the standardized mean differences (SMD) (Figures S1–S4). To estimate the average treatment effect in the treated (ATT), we fit logistic and quasi-Poisson regression models that included treatment subgroup, covariates with an SMD > 0.1, covariates thought to be highly predictive of the outcome, the interaction of treatment and these covariates, and matching weights. We performed g-computation using the "marginaleffects" R package to estimate the ATT, expressed as a rate ratio for the binary outcomes and a difference of mean days for LOS[20] including cluster-robust standard errors. Associations were considered statistically significant at $p < 0.05$ level. Analyses were conducted using Stata 12.0 (StataCorp) and R 4.1.2 (R Core Team). As a sensitivity analysis, we developed multivariable models for each outcome using simple adjustment and also modeled time between antibiotics and hypotension as a continuous variable.

The Bottom Line

Among 2,219 patients with sepsis and hypotension, antibiotic timing relative to hypotension was not associated with differences in clinical outcomes; however, patients with antibiotic administration >60 minutes after hypotension had more chronic comorbidities and developed systemic inflammatory response syndrome (SIRS) criteria later.

3 | RESULTS

3.1 | Characteristics of study subjects

A total of 2219 patients were included (Figure 1). Overall, patients received antibiotics a median of 2.2 h after ED admission (interquartile range [IQR] 1.2–4.2 h) and developed hypotension at a median of 3.9 h (IQR, 0.09–10.6 h). The median time from antibiotic receipt to hypotension was −0.7 h (IQR: −6.9–1.5 h) (Figure S5). There were 1222 patients who received antibiotics before the onset of hypotension (55%, early treatment subgroup), 284 who received antibiotics 0–60 min after onset of hypotension (13%, immediate treatment subgroup), and 713 who received antibiotics more than 60 min after the onset of hypotension (32%, late treatment subgroup). Compared to the early treatment subgroup, the late treatment subgroup had a higher prevalence of pre-existing comorbidities, including chronic renal failure, chronic liver disease, congestive heart failure, and cancer (p-values < 0.05).

4 | MAIN RESULTS

4.1 | Presenting clinical data

There were significant differences in demographic and presenting clinical characteristics between the groups (Table 1). The late treatment subgroup was much less likely to present with SIRS. Fever on ED triage was more prevalent in the early treatment (9.3% vs 23.9%, $p < 0.001$) and immediate treatment subgroups (17.6%, $p < 0.001$). Similarly, the late treatment subgroup was less likely to present with tachycardia

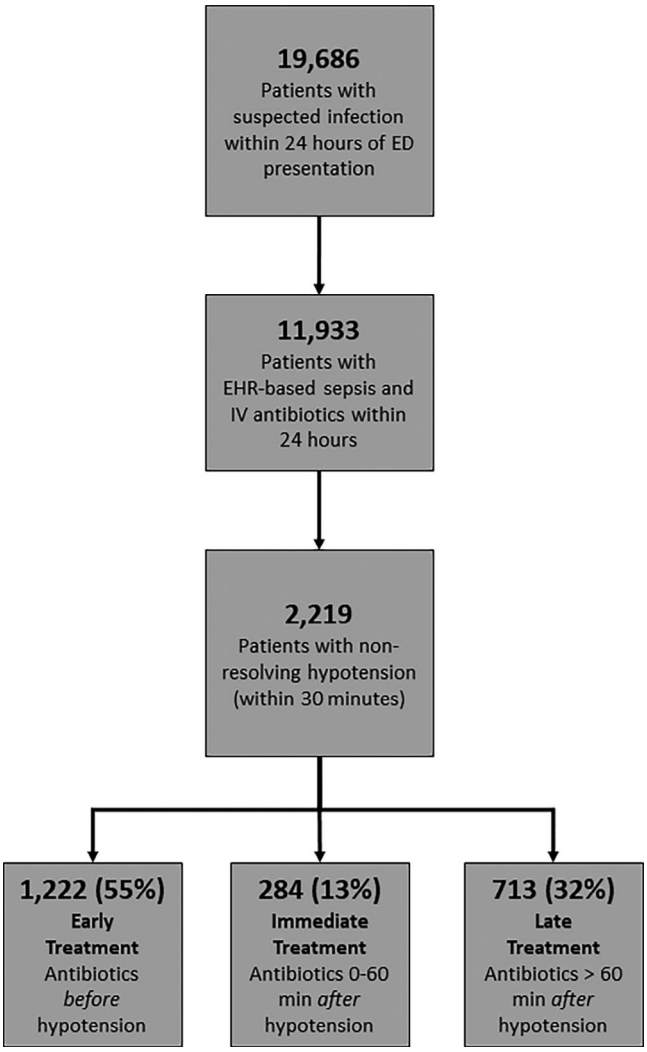

FIGURE 1 Identification of the study population. All individuals ≥18 years of age who presented to the University of California San Francisco Emergency Department (ED) between June 1, 2012, and December 31, 2018, were included in the source population. We excluded those who were not identified as sepsis by the Sequential Organ Failure Assessment (SOFA) score, those who did not receive IV antibiotics, and those who did not experience hypotension within 24 h of ED presentation. Our final analytic cohort included 2219 patients who had suspected septic shock.

(heart rate > 90 beats/min) (57.6% vs 71.8% [early], $p < 0.001$; vs 66.5% [immediate], $p = 0.010$) and tachypnea (respiratory rate > 20 breaths/min) (19.5% vs 32.7%, [early], $p < 0.001$; vs 38.4% [late], $p < 0.001$). In contrast, the late treatment subgroup was much more likely to have hypotension on ED presentation (SBP < 90 mmHg) compared to both the early treatment (60.2% vs 0.1%, $p < 0.001$) and immediate treatment subgroups (vs 49.6%, $p = 0.002$).

4.2 | Time to sepsis recognition and treatment from ED presentation

Patterns and timing of sepsis recognition criteria varied based on the treatment subgroup (Figure 2). The early treatment subgroup met SIRS (median 35 min, IQR 0–154 min), SOFA (median 111 min, IQR 43–268 min), and received an EHR sepsis alert (median 83 min, IQR 36–287 min) relatively early during the ED admission (Table 2) but did not develop hypotension until several hours later (median 558 min, IQR 304–912 min). In comparison, the immediate treatment subgroup met SIRS (median 20 min, IQR 0–90 min), SOFA (median 52 min, IQR 10–98 min), and received an EHR sepsis alert (median 42 min, IQR 19–91) more rapidly after ED admission, developed hypotension soon after ED admission (median 7 min, IQR 0–73 min), and received antibiotics quickly after initial ED presentation (median 51 min, IQR 37–102 min). Finally, the late treatment subgroup developed hypotension very close to ED presentation (median 0 min, IQR 0–64 min) but met SIRS (median 87 min, IQR 16–277 min), SOFA (median 87 min, IQR 37–173 min), and received an EHR sepsis alert (median 81 min, IQR 38–192 min) later in the ED course. The median time to antibiotic administration following ED presentation in the late treatment subgroup was 191 min (IQR 103–381 min), and median time from hypotension to antibiotic administration was 152 min (IQR 93–273 min).

4.3 | Hospital course and outcomes

There were several differences in hospital course and outcomes across the three treatment subgroups (Table 2). Compared to the late treatment subgroup, the early treatment subgroup was less likely to receive vasopressors and more likely to receive mechanical ventilation (vasopressors: 33.4% vs. 28.1%, $p = 0.014$; mechanical ventilation: 15.6% vs. 19.9%, $p = 0.018$), whereas the immediate treatment subgroup had increased vasopressor requirement (46.8%, $p < 0.001$). The late treatment subgroup was less likely to have a positive blood culture or sepsis discharge code compared to the immediate treatment group (p values < 0.05) but not significantly different from the early treatment subgroup. There were no significant differences in LOS or inpatient mortality across treatment subgroups.

4.4 | Multivariable analysis

When comparing the early treatment subgroup to the late treatment subgroup, there was no significant difference in ATT for in-hospital mortality (ATT 1.25, 95% confidence interval [CI] 0.86–1.83), in-hospital mortality or transfer to hospice (ATT 1.18, 95% CI 0.83–1.67), or LOS among the survivors (ATT 1.75, 95% CI −0.45 to 3.94) (Figure 3). When comparing the immediate treatment subgroup to the late treatment subgroup, there was no significant difference in ATT for in-hospital mortality (ATT 1.00, 95% CI 0.79–1.27), in-hospital mortality or transfer to hospice (ATT 1.08, 95% CI 0.88–1.34), or LOS among survivors (ATT 1.75, 95% CI −0.87 to 2.07). There was no difference in the results when we used simple adjustment methods (Table S2). In addition, we found no difference in results when modeling time from antibiotics to hypotension as a continuous variable (data not shown).

TABLE 1 Baseline characteristics of 2219 patients with suspected septic shock, stratified by timing of hypotension in relation to antibiotic administration.

Factor	Antibiotics before hypotension Early Treatment ($n = 1222$)	Antibiotics 0–60 min after hypotension Immediate treatment ($n = 284$)	Antibiotics >60 min after hypotension Late treatment ($n = 713$)	Early vs late *p*-Value	Immediate vs. late *p*-value
Patient demographics					
Age at ED admission (years), mean (SD)	64.0 (18.4)	66.1 (16.3)	61.8 (16.5)	**0.007**	<**0.001**
Female	596 (48.8%)	125 (44.0%)	345 (48.4%)	0.870	0.210
White	513 (42.0%)	108 (38.0%)	344 (48.2%)	**0.007**	**0.003**
Limited English proficiency	269 (22.0%)	62 (21.8%)	110 (15.4%)	<**0.001**	**0.016**
Medi-Cal payer	310 (25.4%)	58 (20.4%)	176 (24.7%)	0.740	0.150
Admission from skilled nursing facility	102 (8.3%)	48 (16.9%)	64 (9.0%)	0.630	<**0.001**
Elixhauser risk of mortality score, mean (SD)	14.2 (12.0)	16.5 (12.8)	17.0 (12.5)	<**0.001**	0.520
Chronic renal failure	270 (22.1%)	68 (23.9%)	208 (29.2%)	<**0.001**	0.096
Chronic liver disease	201 (16.4%)	66 (23.2%)	183 (25.7%)	<**0.001**	0.420
Congestive heart failure	248 (20.3%)	45 (15.8%)	154 (21.6%)	0.500	**0.040**
Cancer	292 (23.9%)	68 (23.9%)	199 (27.9%)	0.050	0.200
Year of admission				0.512	**0.001**
2012	29 (3.3%)	16 (6.8%)	23 (4.5%)		
2013	100 (11.5%)	47 (19.9%)	54 (10.6%)		
2014	122 (14.1%)	29 (12.3%)	78 (15.3%)		
2015	141 (16.3%)	44 (18.6%)	70 (13.7%)		
2016	161 (18.6%)	31 (13.1%)	83 (16.2%)		
2017	150 (17.3%)	41 (17.4%)	100 (19.6%)		
2018	164 (18.9%)	28 (11.9%)	103 (20.2%)		
Presenting clinical data					
First qualifying SOFA within the first 24 h, mean (SD)	6.9 (3.5)	8.2 (3.7)	7.4 (3.5)	**0.001**	**0.002**
First temperature ≥38.3°C	292 (23.9%)	50 (17.6%)	66 (9.3%)	<**0.001**	<**0.001**
First temperature ≤36.0°C	63 (5.2%)	46 (16.2%)	48 (6.7%)	0.150	<**0.001**
First systolic blood pressure < 90 mmHg	1 (0.1%)	141 (49.6%)	429 (60.2%)	<**0.001**	**0.002**
First heart rate > 90 beats per minute	878 (71.8%)	189 (66.5%)	411 (57.6%)	<**0.001**	**0.010**
First respiratory rate > 20 breaths per minute	400 (32.7%)	109 (38.4%)	139 (19.5%)	<**0.001**	<**0.001**
First WBC count > 12,000 or < 4000 per microliter	682 (55.8%)	167 (58.8%)	407 (57.1%)	0.590	0.620
First lactate > 2 mg/dL	713 (58.3%)	204 (71.8%)	410 (57.5%)	0.720	<**0.001**
≥2 SIRS criteria within the first 24 h	1186 (97.1%)	276 (97.2%)	671 (94.1%)	**0.003**	**0.045**
≥2 SIRS criteria on triage	509 (41.7%)	129 (45.4%)	159 (22.3%)	<**0.001**	<**0.001**
EHR sepsis alert triggered in ED	945 (77.3%)	251 (88.4%)	556 (78.0%)	0.740	<**0.001**

Abbreviations: ED, emergency department; EHR, electronic health record; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

P-Values that achieved statistical significance (p<0.05) appear in bold font.

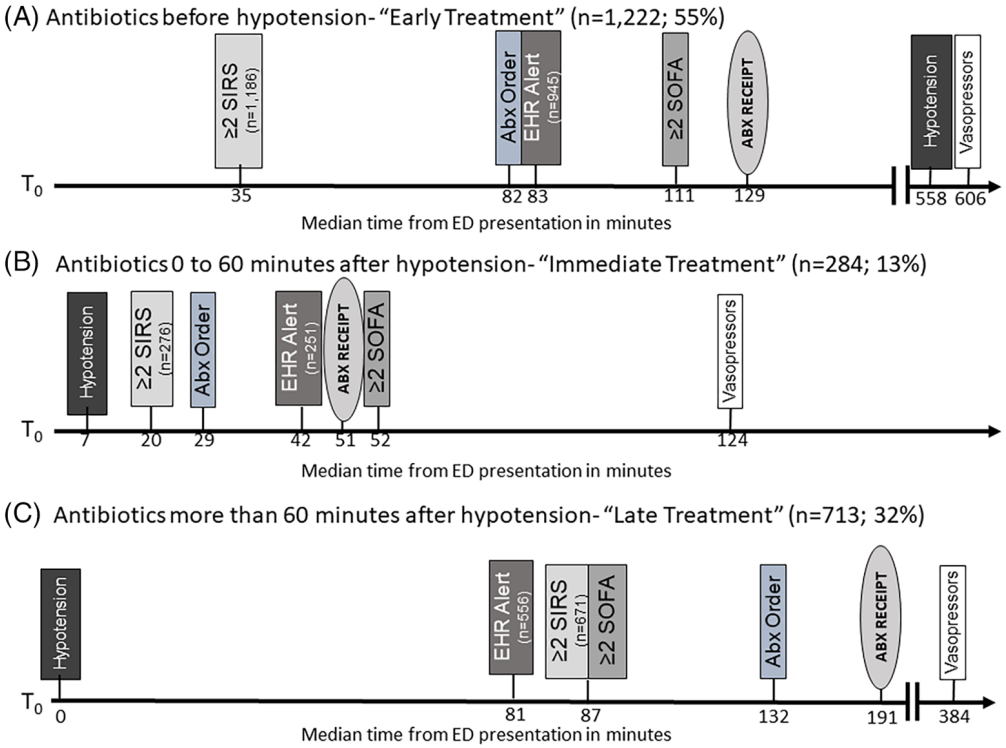

FIGURE 2 Timeline of hypotension, sepsis presentation, and treatment for each category of sepsis treatment timing. Frequency of each timepoint being met can be found in Tables 1 and 2; median time to each event is displayed in this figure and median and interquartile range can also be found in Table 2. Abbreviations: ED, emergency department; EHR, electronic health record; Abx, antibiotics; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

5 | LIMITATIONS

This was a single-center retrospective study of EHR data; however, EHR data can reveal moment-to-moment timestamps for treatment administration and vital signs observation, which are critical for timely sepsis identification. While EHR-based sepsis identification may never reach the "gold standard" of chart review or prospective identification and our study may have been impacted by misclassification, it is increasingly utilized as the measure of sepsis outcomes for quality, safety, and multicenter research studies.[21] We conducted manual chart review on 50 patients without a sepsis discharge code and found that a large majority had confirmed sepsis on presentation or received antibiotics appropriately. These findings reflect the inevitable diagnostic uncertainty that clinicians commonly face early during critical and acute illness.[22] It also highlights the necessary minority of patients requiring sepsis "overtreatment," particularly among those at high risk of mortality. It is possible that our definition of hypotension as "time zero" for when antibiotics should be administered for patients with suspected septic shock could be flawed and that there are other more appropriate triggers for antibiotic treatment; however, finding those triggers may be difficult if they are not charted in the EHR. Finally, our multivariable analysis did not control for time-varying covariates, which could have impacted our outcome analysis.

6 | DISCUSSION

In this study of patients who presented to the ED with suspected septic shock, we found that most patients received antibiotics before (55%) or within 60 min (13%) of incident hypotension but receipt of antibiotics more than 60 min after hypotension was common (32%). Our study exposed important differences in sepsis presentation, treatment timing, and evolution of illness within these three distinct antibiotic treatment subgroups. Patients in the early and immediate treatment subgroups both had SIRS criteria and EHR alert triggers for treatment shortly after ED presentation. The late treatment subgroup frequently had hypotension early in presentation, often before other inflammatory measures of sepsis, and was more likely to have comorbidities that may have confounded clinician interpretation of hypotension. Finally, while we employed rigorous propensity score matching methods, we found no significant difference in outcomes when comparing the late treatment subgroup to either the early or immediate treatment subgroup.

Our study highlights that sepsis presentation is not "one size fits all" and not all patients follow a classic sepsis trajectory from infection to multi-system organ failure. In our cohort, a significant number of patients had hypotension as their only presenting symptom of sepsis, which is most frequently anticipated later in the sepsis trajectory. By only focusing on the most common sepsis presentations, we may

TABLE 2 Hospital course of 2219 patients with suspected septic shock, stratified by timing of hypotension in relation to antibiotic administration.

Factor	Antibiotics before hypotension Early ($n = 1222$)	Antibiotics 0–60 min after hypotension Immediate ($n = 284$)	Antibiotics > 60 min after hypotension Late ($n = 713$)	Early vs. late *p*-Value	Immediate vs. late *p*-Value
Emergency department course and treatments					
Time in minutes from ED admission to[a]					
SIRS ≥ 2[b]	35 (0, 154)	20 (0, 90)	87 (16, 277)	<**0.001**	<**0.001**
SOFA ≥ 2[b]	111 (43, 286)	52 (10, 98)	87 (37, 173)	<**0.001**	<**0.001**
EHR sepsis alert[b]	83 (36, 287)	42 (19, 91)	81 (38, 192)	0.18	<**0.001**
First episode of hypotension	558 (304, 912)	7 (−3, 73)	0 (0, 64)	<**0.001**	<**0.001**
Fluid administration[c]	90 (46, 214)	36 (18, 89)	68 (36, 165)	<**0.001**	<**0.001**
Blood culture order	38 (13, 123)	19 (9, 53)	44 (17, 177)	**0.005**	<**0.001**
Antibiotic order	82 (37, 163)	29 (16, 63)	132 (58, 305)	<**0.001**	<**0.001**
Antibiotics administered	129 (75, 223)	51 (37, 102)	191 (103, 381)	<**0.001**	<**0.001**
Vasopressors administered[d]	606 (286, 1092)	124 (60, 356)	384 (135, 755)	<**0.001**	<**0.001**
Hospital course and outcomes					
ICU admission	412 (33.7%)	158 (55.6%)	242 (33.9%)	0.92	<**0.001**
Vasopressor administration	343 (28.1%)	133 (46.8%)	238 (33.4%)	**0.014**	<**0.001**
Mechanical ventilation in first 72 h	243 (19.9%)	57 (20.1%)	111 (15.6%)	**0.018**	0.086
Blood culture positive	210 (17.2%)	56 (19.7%)	102 (14.3%)	0.097	**0.035**
Inpatient mortality	192 (15.7%)	60 (21.1%)	125 (17.5%)	0.30	0.19
Hospital length of stay in days among survivors[a]	6.0 (4.0, 10.0)	6.1 (3.8, 10.1)	6.0 (3.8, 10.8)	0.93	0.96
Sepsis discharge code	867 (70.9%)	236 (83.1%)	511 (71.7%)	0.74	<**0.001**

[a]Time in minutes data summarized using median and interquartile range.
[b]A total of 2133 patients met SIRS criteria, all patients met SOFA criteria, and 1711 patients had an electronic health record (EHR) sepsis alert triggered in the emergency department (ED).
[c]A total of 1810 patients received IV fluids.
[d]A total of 714 patients received vasopressors.
P-Values that achieved statistical significance ($p<0.05$) appear in bold font.

miss important subgroups of patients who are just as clinically ill, who experience similar outcomes, and who could benefit from the same swift sepsis treatment offered to those with more classic sepsis presentations.[23–26] Our results also suggest that the late treatment subgroup is more likely to have comorbidities that may confound the diagnosis of sepsis. For patients who present with lone hypotension, along with a history of heart failure or liver disease, physicians may not recognize the presence of sepsis, even though these conditions warrant an elevated level of clinical suspicion given increased risk of poor outcomes.[27,28] In addition, it is well recognized that patients receiving cancer treatment are more likely to have a blunted immune response to sepsis and may not present with SIRS physiology.[29,30] While clinical trials often exclude these patients, real-world data like those presented in our study are critical for determining treatment and management strategies.

By using hypotension as sepsis "time zero" for treatment groups, we were able to identify different sepsis presentation patterns. Among those in the late treatment subgroup, 60% had hypotension on triage, compared to <1% among those who were in the early treatment subgroup. A high proportion of patients already had hypotension on ED presentation, ruling out the possibility that more expedient treatment in the early treatment subgroup was the sole reason for later hypotension onset. In contrast, the immediate treatment subgroup presented with hypotension shortly after ED arrival, but also met SIRS and SOFA criteria soon after ED arrival. Given that the immediate subgroup received timely antibiotics less than 60 min after incident hypotension, this may offer further evidence that frontline clinicians are heavily reliant on these sepsis recognition criteria to identify sepsis.

Antibiotic treatment timing was not associated with mortality in our cohort of patients with suspected septic shock, even after propensity score adjustment. The Immediate treatment subgroup was enriched for patients who were most acutely ill and overtly sick on presentation. These patients were most likely to present to the ED from a skilled nursing facility. Though clinicians treated sepsis readily in relation to both ED presentation and hypotension (within 60 min of hypotension), this group was most likely to require ICU level care and

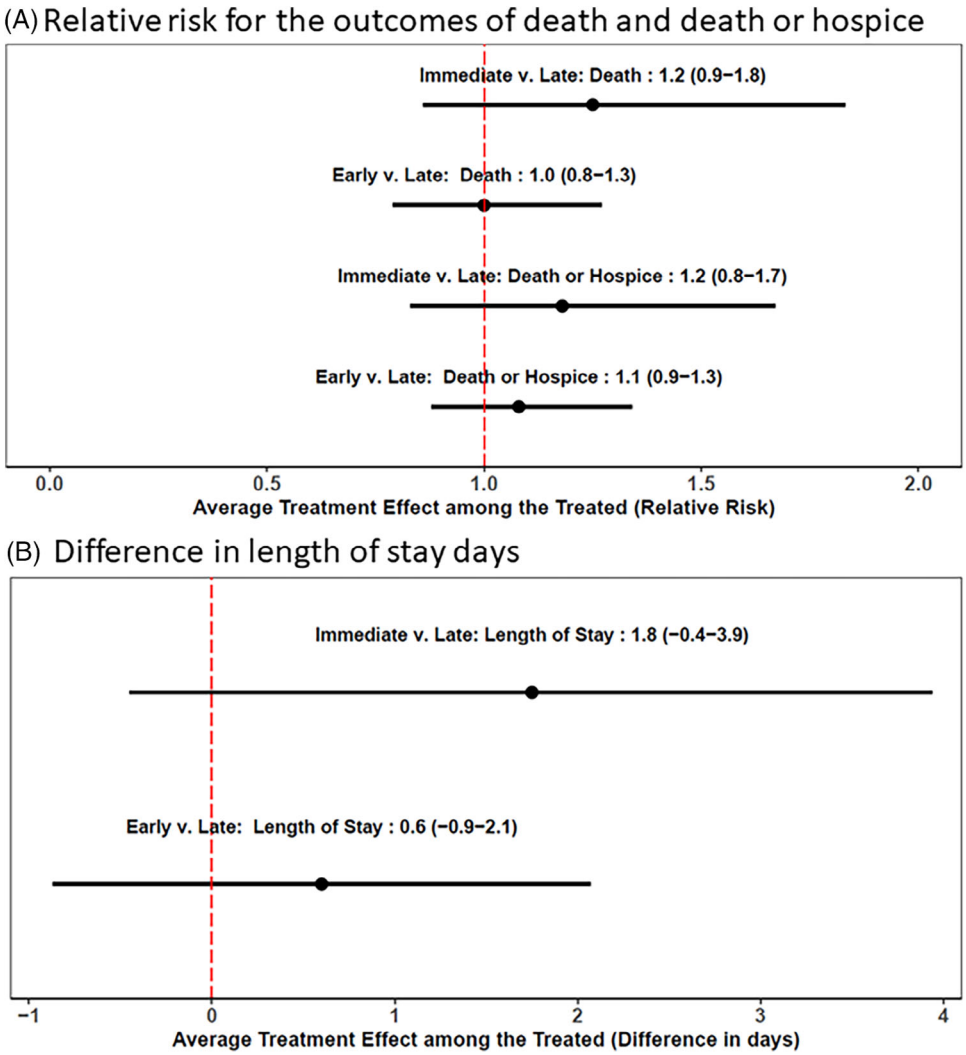

FIGURE 3 Average treatment effect in the treated (ATT) for the outcomes of death (A), death or hospice (A), and length of stay (B). The ATT was calculated comparing those in the immediate versus late treatment subgroups and comparing those in the early versus late treatment subgroups.

had the worst clinical outcomes, although these differences were fully attenuated on adjusted analyses. While antibiotic delays have been associated with worse clinical outcomes in sepsis in prior studies, particularly among patients with hypotension and shock,[4] our findings are similar to those presented by Filbin et al.,[11] where those presenting without fever and with delays in antibiotic administration had several other underlying factors that explained increased mortality. Another block-randomized controlled trial assessing the impact of pre-hospital antibiotic administration in patients that met SIRS criteria was unable to show a difference in outcomes based on antibiotic timing. In addition, when conducting observational studies using clinical data, the association between antibiotic timing and outcomes can be significantly impacted by time windows, variables, and definitions used to model the relationship, as a recent study by Pak et al. has shown.[4]

Our study demonstrated that, by evaluating suspected septic shock based on antibiotic timing in relation to hypotension onset (instead of ED presentation time), there was significant heterogeneity in sepsis presentation and treatment timing. Patients commonly received antibiotics more than 60 min after initial hypotension (32%), which is beyond the current Surviving Sepsis Campaign recommendation for patients with suspected shock. These patients notably presented with less overt signs of classic sepsis (e.g., SIRS) and more comorbid conditions that could impair clinician recognition of hypotension (e.g., heart failure, liver disease, and cancer diagnosis) as a harbinger of sepsis. However, while these findings suggest that lone hypotension may be an early warning sign of sepsis in the ED, larger prospective studies are needed to determine if earlier treatment for these patients could improve clinical outcomes.

AUTHOR CONTRIBUTIONS

Priya A. Prasad, Armond M. Esmaili, Katie E. Raffel, Margaret C. Fang, and Kirsten N. Kangelaris conceived the research project and study design. Priya A. Prasad, Armond M. Esmaili, Sandra Oreper, Alexander J. Beagle, and Colin Hubbard designed and conducted the data cleaning

and statistical analysis. Priya A. Prasad, Armond M. Esmaili, Sandra Oreper, and Kirsten N. Kangelaris drafted the manuscript. Priya A. Prasad, Margaret C. Fang, and Sandra Oreper provided interpretation of the findings. All authors contributed substantially to interpretation of findings, revising the manuscript, and providing final approval of the submitted manuscript. Priya A. Prasad takes responsibility for the paper as a whole.

ACKNOWLEDGMENTS

Dr. Fang's institution received funding from the National Heart, Lung, and Blood Institute K24HL141354 and Patient-Centered Outcomes Research Institute. Dr. Liu's institution received funding from the National Diabetes and Digestive and Kidney Diseases K24DK113381. Dr. Matthay's institution received funding from the National Heart Lung and Blood Institute NHLBI U01HL123004.

CONFLICT OF INTEREST STATEMENT

Dr Prasad and Ms. Oreper report personal fees from EpiExcellence, LLC, outside the submitted work. The other authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

This study includes identified protected health information. Parties interested in using the data included in our study may contact Dr. Prasad to discuss collaboration and data sharing, after appropriate human subjects review and data use agreements have been executed.

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REFERENCES

1. 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(6):1589-1596. doi:10.1097/01.CCM.0000217961.75225.E9
2. 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(23):2235-2244. doi:10.1056/NEJMoa1703058
3. 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(7):856-863. doi:10.1164/rccm.201609-1848OC
4. Pak TR, Young J, McKenna CS, et al. Risk of misleading conclusions in observational studies of time-to-antibiotics and mortality in suspected sepsis. *Clin Infect Dis*. 2023;77(11):1534-1543. doi:10.1093/cid/ciad450
5. SCCM | Surviving Sepsis Campaign Guidelines 2021. Society of Critical Care Medicine (SCCM). Accessed February 2, 2022. https://sccm.org/Clinical-Resources/Guidelines/Guidelines/Surviving-Sepsis-Guidelines-2021
6. Sterling SA, Miller R, 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 HHS public access. *Crit Care Med*. 2015;43(9):1907-1915. doi:10.1097/CCM.0000000000001142
7. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143. https://journals.lww.com/ccmjournal/fulltext/2021/11000/surviving_sepsis_campaign__international.21.aspx
8. 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 HHS public access. *Crit Care Med*. 2018;46(4):500-505. doi:10.1097/CCM.0000000000002949
9. Sivayoham N, Blake LA, Tharimoopantavida SE, Chughtai S, Hussain AN, Rhodes A. Treatment variables associated with outcome in emergency department patients with suspected sepsis. *Ann Intensive Care*. 2020;10(1):136. doi:10.1186/s13613-020-00747-8
10. Lee CC, Yang CY, Su BA, et al. The hypotension period after initiation of appropriate antimicrobial administration is crucial for survival of bacteremia patients initially experiencing severe sepsis and septic shock. *J Clin Med*. 2020;9(8):2617. doi:10.3390/jcm9082617
11. 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(10):1592-1599. doi:10.1097/CCM.0000000000003260
12. Husabø G, Nilsen RM, Flaatten H, et al. Early diagnosis of sepsis in emergency departments, time to treatment, and association with mortality: an observational study. *PLoS One*. 2020;15(1):e0227652. doi:10.1371/journal.pone.0227652
13. Singer M, Deutschman CS, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA—J Am Med Assoc*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287
14. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. *JAMA—J Am Med Assoc*. 2017;318(13):1241-1249. doi:10.1001/jama.2017.13836
15. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992; 101(6):1644-55. doi:10.1378/chest.101.6.1644 https://reader.elsevier.com/reader/sd/pii/S001236921638415X?token=E3526CB961D26530F78D6A224C14252D6C784A3BFEC36B3C26458D91AF86AB9816B7EBB8368EE7B2C0B9B22B062B0A8E
16. Narayanan N, Gross AK, Pintens M, Fee C, MacDougall C. Effect of an electronic medical record alert for severe sepsis among ED patients. *Am J Emerg Med*. 2016;34(2):185-188. doi:10.1016/j.ajem.2015.10.005
17. Elixhauser A. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8-27.
18. Ho DE, Imai K, King G, Stuart EA. MatchIt : nonparametric preprocessing for parametric causal inference. *J Stat Softw*. 2011;42(8). doi:10.18637/jss.v042.i08
19. Hansen BB, Klopfer SO. Optimal full matching and related designs via network flows. *J Comput Graph Stat*. 2006;15(3):609-627. doi:10.1198/106186006x137047
20. Arel-Bundock [aut V, cre, cph, Diniz MA, Greifer N, Bacher E. marginaleffects: predictions, comparisons, slopes, marginal means, and hypothesis tests. Accessed August 17, 2023. https://cran.r-project.org/web/packages/marginaleffects/index.html
21. Seymour CW, Kennedy JN, Wang S, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA*. 2019;321(20):2003. doi:10.1001/jama.2019.5791
22. Prescott HC, Iwashyna TJ. Improving sepsis treatment by embracing diagnostic uncertainty. *Ann Am Thorac Soc*. 2019;16(4):426-429. doi:10.1513/AnnalsATS.201809-646PS
23. Canet E, Taylor DM, Khor R, Krishnan V, Bellomo R. qSOFA as predictor of mortality and prolonged ICU admission in emergency department patients with suspected infection. *J Crit Care*. 2018;48:118-123. doi:10.1016/j.jcrc.2018.08.022
24. Anand V, Zhang Z, Kadri SS, Klompas M, Rhee C. Epidemiology of quick sequential organ failure assessment criteria in undifferentiated patients and association with suspected infection and sepsis. *Chest*. 2019;156(2):289-297. doi:10.1016/j.chest.2019.03.032

25. Abdullah SMOB, Sørensen RH, Dessau RBC, Sattar SMRU, Wiese L, Nielsen FE. Prognostic accuracy of qSOFA in predicting 28-day mortality among infected patients in an emergency department: a prospective validation study. *Emerg Med J*. 2019;36(12):722-728. doi:10.1136/emermed-2019-208456
26. Mellhammar L, Linder A, Tverring J, et al. NEWS2 is superior to qSOFA in detecting sepsis with organ dysfunction in the emergency department. *J Clin Med*. 2019;8(8):1128. doi:10.3390/jcm8081128
27. Martin G. Disparities in sepsis. *Shock*. 2006;25(1):4. 10.1097/00024382-200606001-00011
28. Sinapidis D, Kosmas V, Vittoros V, et al. Progression into sepsis: an individualized process varying by the interaction of comorbidities with the underlying infection. *BMC Infect Dis*. 2018;18(1):242. doi:10.1186/s12879-018-3156-z
29. Silva MMM, de Oliveira-Figueiredo DST, Cavalcanti ADC. Prevalence and factors associated with sepsis and septic shock in oncological patients in intensive therapy. *Rev Bras Enferm*. 2022;75(1):e20201338. doi:10.1590/0034-7167-2020-1338
30. Danai PA, Moss M, Mannino DM, Martin GS. The epidemiology of sepsis in patients with malignancy. *Chest*. 2006;129(6):1432-1440. doi:10.1378/chest.129.6.1432

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Prasad PA, Esmaili AM, Oreper S, et al. Timing of antibiotic treatment identifies distinct clinical presentations among patients presenting with suspected septic shock. *JACEP Open*. 2024;5:e13149. https://doi.org/10.1002/emp2.13149

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