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Antibiotic Timing and Progression to Septic Shock Among Patients in the ED With Suspected Infection

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BACKGROUND: Recent medical society opinions have questioned the use of early antimicrobials in patients with sepsis, but without septic shock.

RESEARCH QUESTION: Is time from ED presentation to administration of antibiotics associated with progression to septic shock among patients with suspected infection?

STUDY DESIGN AND METHODS: This was a retrospective cohort study from March 2007 through March 2020. All adults with suspected infection and first antimicrobial administered within 24 h of triage were included. Patients with shock on presentation were excluded. We performed univariate and multivariate logistic regression analyses predicting progression to septic shock.

RESULTS: Seventy-four thousand one hundred fourteen patient encounters were included in the study. Five thousand five hundred ten patients (7.4%) progressed to septic shock. Of the patients who progressed to septic shock, 88% had received antimicrobials within the first 5 h from triage. In the multivariate logistic model, time (in hours) to first antimicrobial administration showed an OR of 1.03 (95% CI, 1.02-1.04; $P < .001$) for progression to septic shock and 1.02 (95% CI, 0.99-1.04; $P = .121$) for in-hospital mortality. When adjusted for severity of illness, each hour delayed until initial antimicrobial administration was associated with a 4.0% increase in progression to septic shock for every 1 h up to 24 h from triage. Patients with positive quick Sequential Organ Failure Assessment (qSOFA) results were given antibiotics at an earlier time point than patients with positive systemic inflammatory response syndrome (SIRS) score (0.82 h vs 1.2 h; $P < .05$). However, median time to septic shock was significantly shorter ($P < .05$) for patients with positive qSOFA results at triage (11.2 h) compared with patients with positive SIRS score at triage (26 h).

INTERPRETATION: Delays in first antimicrobial administration in patients with suspected infection are associated with rapid increases in likelihood of progression to septic shock. Additionally, qSOFA score has higher specificity than SIRS score for predicting septic shock, but is associated with a worse outcome, even when patients receive early antibiotics.

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KEY WORDS: antibiotics; qSOFA; septic shock; SIRS; suspected infection

ABBREVIATIONS: GCS = Glasgow Coma Scale; qSOFA = quick Sequential Organ Failure Assessment; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment

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Take-home Points

Study Question: Is time from ED presentation to administration of antibiotics associated with progression to septic shock among patients presenting with suspected infection?

Results: Our retrospective, observational study evaluated > 74,000 patients in the ED with suspected infection, of whom > 5,500 progressed to septic shock. Time to antibiotic administration was associated significantly with progression to septic shock in a multivariate logistic regression model that included several confounders, with an OR of 1.03 per 1 h of antibiotic delay. The median time to receive antibiotics was 1.8 h for all patients, and the antibiotic timing effect was most important within the first 5 h of ED arrival. The patients who were sicker at presentation were more likely to progress to shock, but even among those who seemed less sick at presentation, a minority did demonstrate shock and earlier antibiotics were associated with less progression to shock. Antibiotic timing also significantly affected in-hospital mortality.

Interpretation: Early receipt of antibiotics among patients treated in the ED with suspected infection is associated with reduced progression to septic shock and death, and antibiotic administration to prevent progression is most effective in the first hours after presentation to the ED.

Since the advent of early goal-directed therapy and subsequently the Surviving Sepsis Campaign, a tenet of appropriate sepsis care has been that treatment should be undertaken as soon as possible and with specific, measurable goals.[1,2] One such goal is rapid administration of antibiotics for patients with suspected sepsis. The Surviving Sepsis Campaign guidelines recommend that antibiotics be given within 1 h of sepsis recognition for patients with either sepsis or septic shock. The earliest data supporting such a notion were from a study of 17 North American ICUs in which the time of onset of septic shock could be observed. In this study, mortality increased by 7.4% for every 1 h elapsed between shock onset and antibiotic administration.[3] Subsequent large analyses in nonshock sepsis demonstrated that time from presentation to receipt of antibiotics is associated with mortality in patients treated in the ED.[4,5] One study demonstrated an association of time to antibiotics with progression from severe sepsis to septic shock.[6]

The CMS Sep-1 core measures were established in 2015, Q6 based on the previously described findings and the Surviving Sepsis Campaign recommendations. However, recent medical society positions have suggested that Sep-1 core measures should be modified to remove sepsis without shock.[7,8] With regard to timing of antibiotic administration, authors assert that the data for rapid administration of antibiotics in septic shock are stronger than the data for rapid administration of antibiotics in other levels of sepsis. These authors also state that flaws in the existing data demonstrating a relationship between delayed antibiotic administration and poorer outcomes include the studies being retrospective, not accounting for differences in severity of illness, and linearizing data that they view as nonlinear. Taking these critiques into account, we evaluated a large cohort of patients to determine the relationship between time from presentation to administration of antibiotics and progression to septic shock among all patients who sought treatment at the ED with suspected infection.

Methods

This was a retrospective cohort study performed at The University of Kansas Hospital in Kansas City, Kansas. The protocol was approved by the institutional review board (Identifier: 00001753). De-identified data were obtained from the electronic medical record using the Healthcare Enterprise Repository for Ontological Narration, an i2b2 data repository.[9]

All adults (≥ 18 years of age) who sought treatment at the ED with suspected infection from March 2007 through March 2020 were included in the study. Suspected infection was defined as patients having blood or body fluid cultures obtained and antimicrobials initiated within 4 h of one another. Because the study was based in the ED, no requirement was made for continuation of antibiotics. Patients were excluded from the study if no reasonable ED triage time or time of first antimicrobial administration were recorded (ie, antimicrobial administration time before triage time). Patients also were excluded if they had septic shock on presentation, which we defined as vasopressor infusion (epinephrine, norepinephrine, vasopressin, phenylephrine, or dopamine) initiated within 3 h of ED triage time, excluding bolus vasopressor. We further excluded patients who received their initial antimicrobial more than 24 h after admission, characterizing these patients as whose in whom infection developed after hospital admission.

The time of first antimicrobial and first broad-spectrum antimicrobial administration, as specified by the CMS Sep-1 core measure, were recorded for each patient.[1] The difference in hours between ED triage time and recorded time of first antimicrobial administration was used to determine duration of time to antimicrobial

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administration. Progression to septic shock was defined as vasopressor administration initiated more than 3 h after ED triage time.

Patient vital signs for the first 3 h from ED triage and Sequential Organ Failure Assessment (SOFA) variables were collected. We also collected hospital length of stay, discharge destination, and in-hospital mortality. International Classification of Diseases, Ninth and Tenth Revisions, diagnosis codes were collected to determine the source of infection and Elixhauser Comorbidity Index was determined. Systemic inflammatory response syndrome (SIRS) and quick SOFA (qSOFA) scores were calculated using triage vital signs. SOFA score was calculated using available values within the first 3 h of triage.

Statistical analysis was completed using Stata version 15.0 software (StataCorp). Mann-Whitney *U* tests and χ^2 tests were used to compare patients who progressed to septic shock with those who did not. Univariate logistic regressions were completed to determine variables associated with antibiotic administration within 1, 3, and 5 h. Variables that were statistically significant in the univariate analyses were included in a multivariate logistic regression model. We completed separate univariate logistic regressions for determining variables associated with progression to septic shock and for in-hospital mortality based on the Sepsis 2 and Sepsis 3 diagnosis criteria for severe sepsis and sepsis, respectively.[10,11] Statistically significant variables from these univariate regressions were combined into multivariate logistic regression models predicting septic shock and in-hospital mortality. Goodness of fit was tested using a linear regression of observed and predicted decile means. Hosmer-Lemeshow goodness of fit was not used because of the large sample size.[12] To stratify patients based on severity of illness, we calculated a propensity score for receipt of antibiotics within 1 h of presentation using qSOFA score, SIRS score, and presence of severe sepsis on presentation. For this propensity score, the qSOFA and SIRS scores were calculated using triage vital signs, and severe sepsis on presentation was defined as having a positive SIRS score and presence of at least one Sepsis 2-defined organ dysfunction, including increased lactate level, and with both findings present within 3 h of triage.[10]

Results

Seventy-eight thousand four hundred thirty-eight patient encounters met the inclusion criteria. For final analysis, 74,114 encounters were included (Fig 1). Characteristics of patients who did and did not progress to septic shock are in Table 1. Sources of infection are in Table 2. Of the 74,114 patients, 5,510 patients (7.4%) progressed to septic shock based on the Sepsis 2 definition, and 4,092 patients (5.5%) progressed to septic shock based on the Sepsis 3 definition. Patients who progressed to septic shock showed increased hospital length of stay (12.3 ± 12.3 days vs 3.69 ± 5.0 days; $P < .001$) and increased in-hospital mortality (10.7% vs 0.60%; $P < .001$) when compared with patients who did not progress to septic shock. Of the patients who progressed to septic shock, a higher proportion had a SIRS score of ≥ 2 at triage (43.1% vs 28.1%; $P < .001$), a qSOFA score of ≥ 2 (8.78% vs 2.59%; $P < .001$), and severe sepsis on presentation (16.2% vs 5.96%; $P < .001$).

The median time to initial antimicrobial administration was 1.85 h for all patients and did not change on an annualized basis over the study period. Piperacillin plus tazobactam or ceftriaxone represented > 90% of broad-spectrum antibiotics administered. For patients who progressed to septic shock based on the Sepsis 2 definition, median time to first antimicrobial administration was 1.67 h (interquartile range, 0.66-3.88 h), whereas it was 1.86 h (interquartile range, 0.80-3.80 h) for patients who did not progress to septic shock ($P < .05$). Figure 2 displays the cumulative percentage of patients who progressed to septic shock (Sepsis 2) with

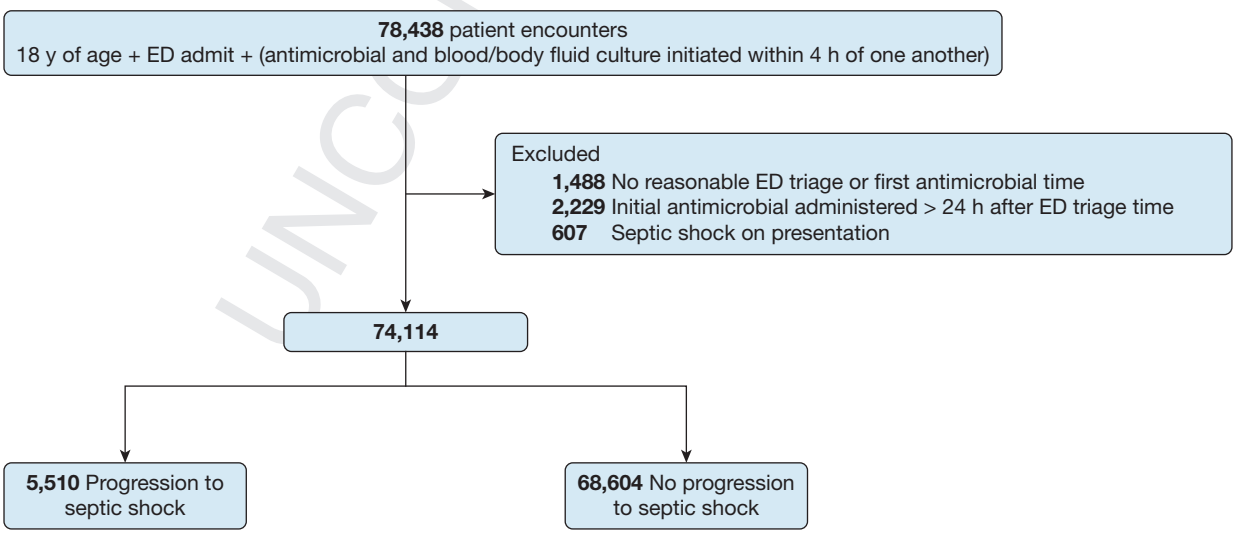

Figure 1 – *Patient selection flowchart.*

TABLE 1] Patient Characteristics

Characteristic	All Patients	Patients With Progression to Septic Shock (Sepsis 2)	Patients Without Progression to Septic Shock (Sepsis 2)	*P* Value[a]
No. of patients	74,114 (100)	5510 (7.4)	68,604 (92.6)	...
Age, y	53.4 ± 18.6	59.2 ± 16.3	52.9 ± 18.7	< .001
Sex				< .001
Male	31, 522 (42.5)	2,945 (53.4)	28,577 (41.7)	
Female	42,592 (57.5)	2,565 (46.6)	40,027 (58.3)	
Race				< .001
White	45,510 (61.4)	3,744 (68.0)	41,766 (60.9)	
Black	18,665 (25.2)	1,120 (20.3)	17,545 (25.6)	
Other	9,939 (13.4)	646 (11.7)	9,293 (13.5)	
SOFA score	3.36 ± 3.0	6.30 ± 3.7	3.12 ± 2.8	< .001
SIRS score ≥ 2	21,625 (29.2)	2,377 (43.1)	19,248 (28.1)	< .001
qSOFA score ≥ 2	2,261 (3.05)	484 (8.78)	1,777 (2.59)	< .001
Severe sepsis on presentation	4,978 (6.7)	891 (16.2)	4,087 (5.96)	< .001
Weighted Elixhauser score	6.84 ± 9.0	11.1 ± 10.1	6.50 ± 8.8	< .001
Initial ED results				
Systolic BP	135 ± 26	128 ± 28	136 ± 25	< .001
GCS score ≤ 13	2,597	436 (7.9)	2,161 (3.1)	< .001
Lactate > 2 mM	8,562 (11.6)	1,625 (29.5)	6,937 (10.1)	< .001
WBC count	10.5 ± 6.8	12.2 ± 7.8	10.3 ± 6.7	< .001
In-hospital mortality	1,004 (1.35)	592 (10.74)	412 (0.60)	< .001
Total no. of unique infection ICD codes	2.45 ± 1.5	2.86 ± 1.8	2.42 ± 1.5	< .001
Hospital LOS	4.32 ± 6.3	12.6 ± 15.0	3.67 ± 6.0	< .001

Data are presented as No. (%) or mean ± SD, unless otherwise indicated. GCS = Glasgow Coma Scale; ICD = International Classification of Diseases; LOS = length of stay; qSOFA = quick Sequential Organ Failure Assessment; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment.

[a]Calculated using χ^2 or Mann-Whitney *U* tests comparing the patients who progressed to septic shock vs those who did not.

each passing hour until antimicrobial administration. The points were calculated by dividing the total number of patients who progressed to septic shock having received antimicrobials within the given interval from triage by the total number of patients for the respective propensity category. Figure 2A displays all patients. Figure 2B breaks the population into propensity score groups, with group 1 being the least ill and group 3 being the most ill. Figure 2C displays the same type of graph, with the denominator being the total number of all patients who progressed to shock having received antimicrobials within 10 h of ED triage. These graphs illustrate that the greatest increase in percentage of patients progressing to septic shock occurs with antimicrobials administered in the first 5 h. After the first 5 h, the rate of increase slows. Of the patients who progressed to septic shock, 88% had received antimicrobials within the first 5 h from triage. Figure 2B shows the highest rate of increase within the first 5 h occurs with the group 3 propensity score, the most ill patient population. For this group 3 propensity score curve, 6.5% of those who received antimicrobials within the first hour of presentation progressed to septic shock.

TABLE 2] Sources of Infection

Source	No. of Patients (%)
Urinary tract infection	25,136 (34)
Respiratory and lung	28,117 (37.9)
Cellulitis	13,812 (18.6)
Intraabdominal	6,855 (9.3)

The univariate logistic regressions predicting progression to septic shock are displayed in e-Table 1. Triage to first antimicrobial administration time (OR, 1.014; 95% CI, 1.008-1.021; $P < .001$), Elixhauser

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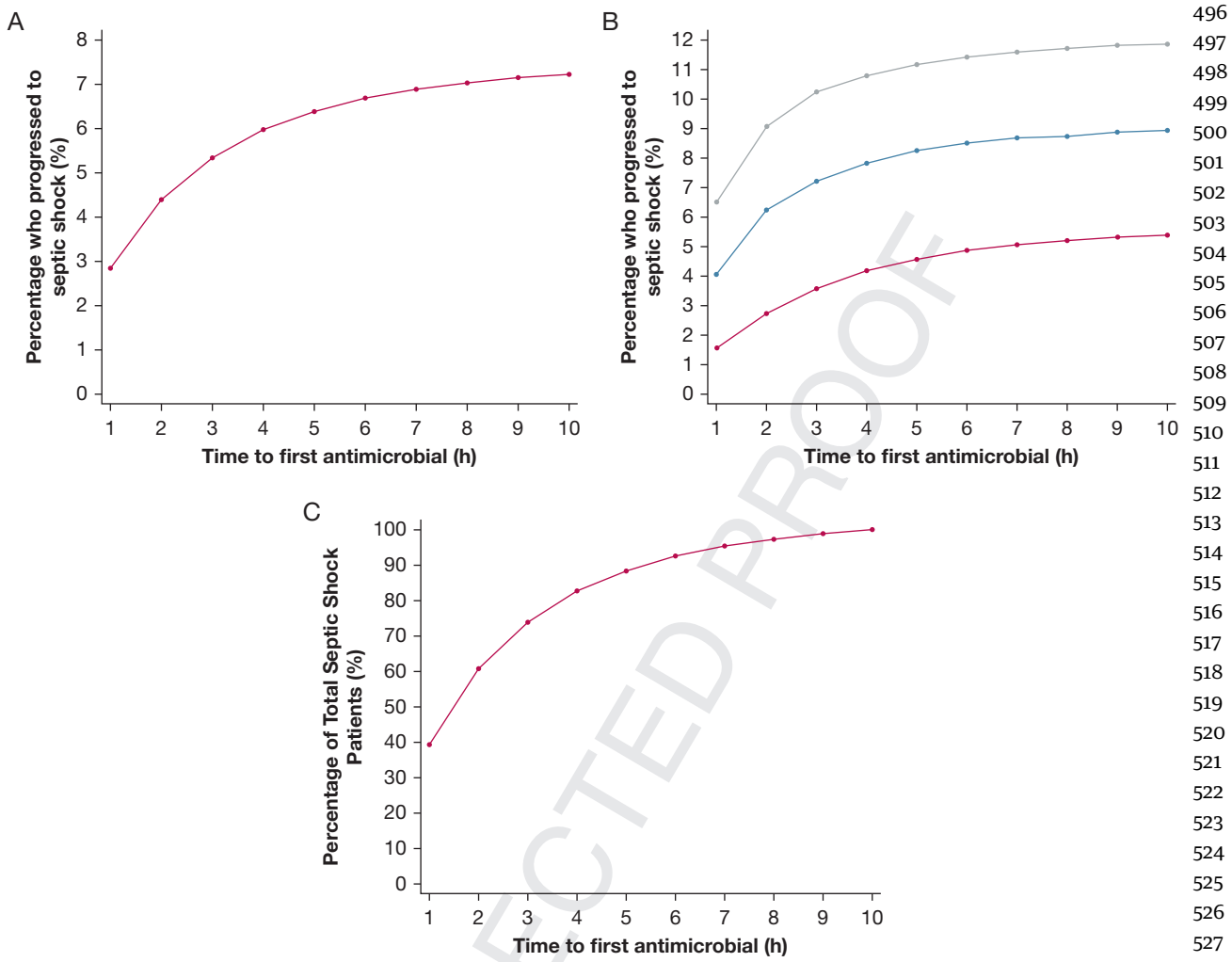

Figure 2 – *A-C, Line graphs showing the cumulative percentages of patients who progressed to septic shock with each passing hour until antimicrobial administration. Septic shock was defined as vasopressor administration. The points were calculated by dividing the total number of patients who progressed to septic shock having received antimicrobials by that interval from triage by the total number of patients for the respective propensity category. A, All patients. B, Population divided into three groups based on propensity score, with group 1 being the least severely ill and group 3 being the most severely ill (blue = group 1; red = group 2; and green = group 3). C, Same type of graph, with the denominator being the total number of all patients who progressed to shock within 10 h of ED triage.*

comorbidity index, SOFA score, SIRS score, qSOFA score, male sex, White race, sources of infection, and initial serum lactate level were associated with progression to septic shock. In the multivariate logistic regression analysis (Table 3), SOFA score was most associated with progression to septic shock and mortality. qSOFA score was removed from the multivariate logistic regression model because it was correlated highly with other variables and did not affect the model prediction. In the multivariate logistic model, time to first antibiotic administration showed an OR of 1.03 (95% CI, 1.02-1.04; $P < .001$) for progression to septic shock (Sepsis 2) and 1.02 (95% CI, 0.99-1.04; $P = .121$) for in-hospital mortality. To assess the overall fit of the model, we completed a linear regression of observed and predicted decile means; the P values for the slope being equal to 1 and the y intercept being equal to 0 were > 0.35, indicating the model was a good fit. If triage to antibiotics time was > 3 h, the OR for progression to septic shock (Sepsis 2) was 1.17 (95% CI, 1.07-1.29; $P = .001$). The propensity score groups were statistically different from one another when they were used in a logistic regression to predict progression to septic shock (e-Table 2). When adjusting for the propensity score, time to first antimicrobial administration showed an OR of 1.04 (95% CI, 1.03-1.04; $P < .001$) for progression to Sepsis 2 septic shock and 1.02 (95% CI, 1.006-1.04; $P = .007$) for in-hospital mortality.

TABLE 3] Multivariate Logistic Regressions Predicting Progression to Septic Shock and Mortality

Variable	Sepsis 2 Septic Shock (n = 5,510)			Sepsis 3 Septic Shock (n = 4,092)			In-Hospital Mortality (n = 1,004)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
SOFA score	1.45	1.43-1.47	< .001	1.40	1.37-1.41	< .001	1.25	1.23-1.28	< .001
SIRS score	1.19	1.15-1.24	< .001	1.20	1.15-1.25	< .001	1.31	1.22-1.41	< .001
Lactate	1.12	1.09-1.14	< .001	1.09	1.06-1.11	< .001	1.20	1.17-1.24	< .001
White race	1.09	1.00-1.18	.058	1.11	1.008-1.22	.034	1.32	1.19-1.55	.001
GCS	1.06	1.03-1.09	< .001	1.04	1.01-1.06	.006	1.01	0.98-1.05	.441
Time to antibiotics	1.03	1.02-1.04	< .001	1.02	1.008-1.03	.001	1.02	0.98-1.04	.090
Elixhauser Comorbidity Index	1.02	1.01-1.02	< .001	1.01	1.009-1.02	< .001	1.05	1.05-1.06	< .001
Diastolic BP	1.008	1.005-1.01	< .001	1.008	1.005-1.01	< .001	1.00	0.99-1.001	.536
Age	1.007	1.004-1.009	< .001	1.006	1.003-1.009	< .001	1.03	1.02-1.03	< .001
Systolic BP	0.99	0.99-0.99	< .001	0.99	0.99-0.99	< .001	0.99	0.99-0.99	< .001
Source of infection									
Respiratory	1.07	0.99-1.17	.091	1.08	0.99-1.18	.103	1.33	1.15-1.55	< .001
Urinary Tract	0.95	0.87-1.03	.213	0.91	0.82-0.99	.043	0.85	0.63-0.93	.046
Skin	1.42	1.29-1.56	< .001	1.42	1.28-1.58	< .001	0.76	0.63-0.93	.007
Intra-abdominal	1.29	1.14-1.45	< .001	1.23	1.08-1.40	.002	0.89	0.72-1.11	.292

GCS = Glasgow Coma Scale; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment.

Table 4 displays median time to septic shock (Sepsis 2) and median time to first antimicrobial administration for patients who showed positive SIRS score, qSOFA score, both, or neither at presentation. Median time to septic shock (44.9 h) and antimicrobial administration (2.33 h) were highest for patients without positive SIRS or qSOFA scores at presentation, whereas they were lowest for patients with both at triage. Patients with positive qSOFA scores were given antibiotics at an earlier time point than patients with positive SIRS scores (0.82 h vs 1.2 h; $P < .05$). However, median time to septic shock was significantly lower ($P < .05$) for patients with positive qSOFA score at triage (11.2 h) compared with patients with positive SIRS score at triage (26 h). Sensitivities and specificities of SIRS and qSOFA scores for septic shock and mortality (e-Table 3) were commensurate with previous analyses.[13-15]

The univariate logistic regressions predicting antibiotics with 1-h, 3-h, and 5-hintervals from triage are displayed in e-Table 4. SIRS score, qSOFA score, and severe sepsis on presentation were most associated with receiving antimicrobials within the first hour of triage. Within the

TABLE 4] qSOFA and SIRS Score Septic Shock and Antimicrobial Timing Comparison

Variable	Median Time to Sepsis 2 Septic Shock (h)	Median Time to First Antimicrobial Administration (h)
Negative qSOFA and SIRS scores	44.9 (19.2-111.7)	2.33 (1.1-4.4)
Positive qSOFA score (n = 2,261)[a]	11.2 (5.5-49.7)	0.82 (0.35-2.15)
Positive SIRS score (n = 21,625)[b]	26 (8.4-92.6)	1.2 (0.52-2.69)
Positive qSOFA and SIRS scores (n = 1,607)	9.8 (5.3-39.4)	0.7 (0.32-1.73)

qSOFA = quick Sequential Organ Failure Assessment; SIRS = systemic inflammatory response syndrome.
[a]qSOFA score ≥ 2.
[b]SIRS score ≥ 2.

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SIRS and qSOFA scores, temperature and respiratory rate were most associated with early antibiotics.

Discussion

To our knowledge, this is the first study to examine the relationship of antibiotic timing and progression to septic shock in a broad population of patients with suspected infection treated in the ED. We found that for each passing hour from ED triage time to antimicrobial administration, risk of progression to septic shock increased by 4.0% for every 1 h up to 24 h from triage while adjusting for severity of illness. Our findings further emphasize that the first few hours from ED triage time are the most critical for antibiotic administration to prevent illness progression in patients with a variety of infections.

The Infectious Diseases Society of America and the American College of Emergency Physicians propose that recommendations for administering antibiotics within 1 h are overly aggressive and that more time should be taken to be certain of infection before administering antibiotics.[7,8] They base their critiques on specific weaknesses of previous retrospective analyses that the current study was designed to address. Specifically, we accounted for disease severity at presentation and included time to antibiotics as only one feature in the multivariate logistic regression analysis of factors associated with development of shock. For patients with septic shock, delay of antibiotic administration is associated with increased mortality.[16] Our data demonstrated that antibiotic timing also is associated with increased risk of progression to septic shock in a broad population of patients with suspected infection seeking treatment at the ED. Additionally, our data showed that the odds of progression to septic shock are highest during the first 5 h in the ED. Delays in antibiotic administration for each passing 1 h from ED triage time are associated significantly with increased progression to septic shock, emphasizing the importance of early antibiotics for patients with suspected infection.

Our initial analyses indicated that receiving antibiotics within the first hour after triage is associated with increased progression to septic shock. Adjustment for qSOFA and SIRS scores demonstrated that patients with overt signs of sepsis at presentation both were more likely to progress to shock and were more likely to receive early antibiotics. In essence, these patients both seemed more ill and literally were sicker at presentation. Our data underscored that patients with clear signs of sepsis at presentation are those most likely to progress to septic shock with delays in antibiotic administration. A similar relationship has been demonstrated with the outcome of 30-day mortality.[4] A substantial proportion of patients in our study demonstrated shock despite receiving antibiotics within 1 h, suggesting that some patients have entered a trajectory to shock before entering the ED. We suspect that the duration of sepsis before presentation to the ED is a key factor, but this cannot be analyzed in our data set. Interestingly, the mortality rate from shock in our study is lower than expected at 10.7%. We believe that mortality could be lower because patients received their antibiotics by the time shock criteria were met, compared with studies in which septic shock was diagnosed before antibiotics were administered.

Even in the least ill patients by propensity score, delays in antibiotic administration were associated significantly with progression to septic shock, especially during the first 4 h from triage. One critique of previous similar studies is that the rate of progression to shock or mortality may not increase until as much as 5 h have passed from ED triage.[7] However, as the present data illustrate, it is important to understand the distinction between rate, which is appropriately expressed as number or proportion per hour (or per some unit of time), and odds ratio for progression with increasing time. The latter expresses that the likelihood of progressing to shock, given exposure to an additional 1 h without antibiotics, is greater than the likelihood of progressing to shock without that 1-h delay. In the patient population, the rate of progression to shock did not increase on an hourly basis, but the odds of shock developing did. In fact, our data suggested that if all infected patients received antibiotics within the first hour, progression to septic shock might be eliminated in 60% of such patients. An additional critique of previous studies is that logistic regression linearizes a relationship that may be nonlinear. The implication of the critique is that regression coefficients overestimate the effect of time delay by incorporating high rates of progression or mortality that occurred with prolonged delays. However, the present data indicated that linearizing actually could underestimate the effect of delaying antibiotics very early in the patient's course.

Patients with vague symptoms experience delayed administration of antibiotics and a higher risk of mortality.[17] Because the patients with low propensity scores were not severely ill at ED triage and may have demonstrated vague symptoms, antibiotic administration may have been delayed. Nevertheless,

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our data revealed that antibiotic delays are also associated with progression to septic shock in this patient subgroup.

We also examined how SIRS and qSOFA scores compare regarding severity of illness and progression of the condition. In our study, qSOFA score showed a higher specificity, but lower sensitivity, for predicting progression to septic shock. Patients with positive qSOFA scores at triage were given the first antibiotics at an earlier time than patients with positive SIRS scores, but they also progressed to septic shock at an earlier time and showed a higher likelihood of doing so. We believe this to be because patients with positive qSOFA scores at triage arrive at a more advanced stage of their illness than patients with only positive SIRS scores, and this could also explain qSOFA's tighter association with mortality. Although antibiotics were initiated earlier in the patients with positive qSOFA scores, we posit that they had a baseline higher risk of progression to septic shock, given their advanced state at presentation. Patients with positive SIRS scores at triage showed a risk of progression to shock that was intermediate between those patients who evidently had more vague symptoms and those with positive qSOFA scores. Our data demonstrated that both the Sepsis 2 and Sepsis 3 criteria are indicative of sepsis, but the patients with positive Sepsis 3 criteria have a higher association with progression to septic shock.

Our findings corroborate other studies that demonstrated a relationship between early antibiotic administration and decreased risk of septic shock or mortality.[4-6,18,19] However, our study is novel in that we evaluated all patients suspected of infection, instead of only patients with sepsis present at triage. Although the progression to shock was lower among patients without overt sepsis at presentation, a principle of quickly administering antibiotics as soon as infection is recognized seems to be appropriate. This finding underscores the need for more sophisticated means of detecting infection early, such as via machine learning and artificial intelligence, especially among patients who seek care with less overt signs or symptoms of sepsis.

A limitation in this retrospective study is that we were not able to determine reasons for delays in antibiotic administration, such as late recognition by providers. Our data set includes signs of infection and sepsis, but not symptoms; having access to symptom data could illuminate further the possibility that some patients with vague symptoms of infection, sepsis, or both already are at risk of progression to shock. We also were not able to account for antimicrobials that could have been administered before the patient sought treatment at the ED. Additionally, we could not assess the appropriateness of the chosen antimicrobial, and the well-known insensitivity of body fluid cultures for infection makes it impossible to discern which patients with suspected infection actually are infected. Serum lactate presented a gray area for our analysis. According to Sepsis 2 criteria, a lactate level of > 4 mM could define shock in the absence of hypotension, whereas according to Sepsis 3 criteria, shock requires the presence of both increased lactate and hypotension. Because refractory hypotension is the feature common to these criteria, we chose not to characterize patients as having septic shock on the basis of lactate. We defined septic shock as time of vasopressor administration. Hypotension unresponsive to fluid resuscitation is the true defining feature of septic shock, but this time point cannot be determined from our data. We did not collect data on fluid timing or amounts, because previous studies showed no effect of fluid timing on sepsis mortality.[20] However, fluid timing likely is associated with timing of vasopressor initiation. Finally, we did not collect data on duration of vasopressors or vasopressor-free days.

Interpretation

Delays in first antimicrobial administration in patients with suspected infection are associated with rapid increases in likelihood of progression to septic shock. Additionally, qSOFA score has higher specificity than SIRS score for predicting septic shock, but is associated with a worse outcome even when patients receive early antibiotics.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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