Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department

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Objective: **To study the association between time to antibiotic administration and survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department.**

Design: **Single-center cohort study.**

Setting: **The emergency department of an academic tertiary care center from 2005 through 2006.**

Patients: **Two hundred sixty-one patients undergoing early goal-directed therapy.**

Interventions: **None.**

Measurements and Main Results: **Effects of different time cutoffs from triage to antibiotic administration, qualification for early goal-directed therapy to antibiotic administration, triage to appropriate antibiotic administration, and qualification for early goal-directed therapy to appropriate antibiotic administration on in-hospital mortality were examined. The mean age of the 261 patients was 59 ± 16 yrs; 41% were female. In-hospital mortality was 31%. Median time from triage to antibiotics was 119 mins (interquartile range = 76–192 mins) and from qualification to antibiotics was 42 mins (interquartile range = 0–93 mins). There was no significant association between time from triage or time from qualification for early goal-directed therapy to antibiotics and mortality when assessed at different hourly cutoffs. When analyzed for time from triage to appropriate antibiotics, there was a significant association at the ≤1 hr (mortality 19.5 vs. 33.2%; odds ratio = 0.30 [95% confidence interval = 0.11–0.83]; *p* = .02) time cutoff; similarly, for time from qualification for early goal-directed therapy to appropriate antibiotics, a significant association was seen at the ≤1 hr (mortality 25.0 vs. 38.5%; odds ratio = 0.50 [95% confidence interval = 0.27–0.92]; *p* = .03) time cutoff.**

Conclusions: **Elapsed times from triage and qualification for early goal-directed therapy to administration of appropriate antimicrobials are primary determinants of mortality in patients with severe sepsis and septic shock treated with early goal-directed therapy. (Crit Care Med 2010; 38:000–000)**

KEY WORDS: TO COME

It has been estimated that one patient presents to an emergency department (ED) in the United States with severe sepsis or septic shock every minute, and mortality ranges from 25% to 50% (1, 2). Until recently, treatment options were limited. Antibiotic therapy has long been one of the mainstays of treatment. New therapies have emerged in the past decade, including early goal-directed therapy (EGDT), which uses an algorithmic resuscitation strategy, systematically measuring and correcting central venous pressure (central venous pressure), mean arterial pressure, and central venous oxygen saturation ($ScvO_2$) at the most proximal phase of critical infection (3). In a randomized, single-center trial, EGDT produced a 16% absolute reduction in in-hospital mortality. In patients with hemodynamic instability, the initial steps of care, including establishing vascular access and fluid resuscitation, may take precedence over early antibiotic administration (4). It is notable that in the original EGDT trial, 13.7% of the patients in the EGDT group and 7.6% of the patients in the standard therapy group did not receive antibiotics during the first 6 hrs of their ED stay (3). However, in a study by Kumar et al (5), examining the duration of hypotension until the administration of appropriate antimicrobials in patients with septic shock, each hour's delay to antibiotic administration was associated with, on average, a 7.6% increase in mortality. Therefore, what priority early antibiotic administration should be given in an algorithmic resuscitation strategy remains unclear.

The Surviving Sepsis Campaign's 2008 "International guidelines for the management of severe sepsis and septic shock" recommend that appropriate antimicrobial therapy be administered within 1 hr of recognition of severe sepsis or septic shock (4). The recommendation was primarily based on the study by Kumar et al (5) and on one other retrospective study (6). Given the competing demands that exist in many EDs, administration of antimicrobial

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The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e3181cc4824

therapy within this 1-hr time frame can be a difficult task to accomplish unless specific protocols are implemented to streamline ordering and delivery of antibiotics. The 2006 Emergency Department Management Guidelines (7) created by the ED-SEPSIS Working Group state, "Although there are insufficient data to conclude that delays on the order of hours are deleterious, administration of antibiotics within the time of ED care and as soon as possible once there is a reasonable suspicion of severe sepsis/septic shock will likely increase the chance of favorable outcome compared with later administration."

We studied the impact of antibiotic timing on survival in patients receiving a standardized resuscitation algorithm (EGDT) for severe sepsis or septic shock in our ED. We hypothesized that earlier administration of antimicrobial therapy in patients receiving EGDT (within the time frame recommended by the Surviving Sepsis Campaign) would be associated with improved survival.

MATERIALS AND METHODS

Study Design and Setting. After obtaining approval from our Institutional Review Board, we conducted a retrospective analysis of a cohort of patients with severe sepsis and septic shock treated with EGDT in the Hospital of the University of Pennsylvania's ED between January 5, 2005, and December 31, 2006. The Hospital of the University of Pennsylvania is an urban, tertiary care medical center with an annual ED volume of approximately 55,000 adult patients.

Inclusion Criteria. Inclusion criteria included 1) inclusion in the severe sepsis and septic shock database; 2) initiation of EGDT (defined as algorithmic volume resuscitation, placement of central venous catheter, and measurement of central venous pressure, mean arterial pressure, and $ScvO_2$) during the patient's ED stay.

Data Collection. The data used in this study were part of a prospective quality improvement initiative to evaluate the impact of an EGDT program on survival in patients with severe sepsis and septic shock in the Hospital of the University of Pennsylvania ED (see Appendix A for EGDT protocol). Generally accepted definitions of severe sepsis and septic shock were used (Appendix B) (8). Patients qualified for EGDT if they had: 1) cryptic septic shock, defined as severe sepsis with a lactate ≥4 mmol/L as a marker of significant tissue hypoperfusion; or 2) septic shock as defined in Appendix B (3). The EGDT program started actively treating patients in January 2005, and two authors (DFG, MG) were contacted by pager or e-mail about all of the patients included in the present study. More than 150 data points were collected per patient. Severity of illness was calculated using an ED Acute Physiology and Chronic Health Evaluation II score (3, 9, 10). There were no specific recommendations in the EGDT protocol regarding antibiotic timing or type; however, an ED-based severe sepsis antibiogram (Appendix B) was available for guidance in antibiotic choice if desired. Data were recorded using standard database software (Access; Microsoft Corporation, Redmond, WA). The retrospective study was completed in accordance with established standards for chart reviews in emergency medicine (11, 12). Data entry on standardized forms was done by five data entry personnel (one emergency medicine attending; one critical care fellow; two emergency medicine residents; and one medical student), including four authors (DFG, RM, FFF, MEM), who were trained before the start of the study. Each person entered a minimum of 30 charts, using *a priori*-determined rules, available in a standardized glossary, for data entry in each category, including triage time, time of qualification for EGDT, time of initial antibiotic administration, appropriateness of antibiotic selection, and time of appropriate antibiotic administration (Appendix C). One author (DFG) met regularly (at least once a month) with each data abstractor to review data entry and to resolve conflicts about data coding and timing intervals. The research hypothesis was generated after data entry was completed and, therefore, the data abstractors were blinded to the hypothesis of this study. Kappa value of interrater reliability comparing one investigator's (DFG's) assignment of time from triage to antibiotics with those of the other data entry personnel was calculated using Cohen's kappa calculation.

Data Analysis. Descriptive data are presented as mean (SD) for continuous data, medians with interquartile ranges (IQRs) for time variables, and frequencies and percents for categorical data. We compared in-hospital mortality in patients receiving antibiotics at different time cutoffs, using Fisher's exact test. We examined time to antibiotics in four ways: elapsed time from triage to antibiotic administration; from qualification for EGDT to antibiotic administration; from triage to appropriate antibiotic administration; and from qualification for EGDT to appropriate antibiotic administration. Timing cutoffs included: ≤1 hr vs. >1 hr; ≤2 hrs vs. >2 hrs; ≤3 hrs vs. >3 hrs; ≤4 hrs vs. >4 hrs; and ≤5 hrs vs. >5 hrs.

Multivariable logistic regression was used to adjust for potential confounding in the association between time to antibiotics and in-hospital mortality. We considered age, Acute Physiology and Chronic Health Evaluation II score, initial lactate, initial systolic blood pressure, initial temperature, and amount of intravenous fluid given during the first 6 hrs and over the total ED stay as potential confounders. Potential confounders were determined *a priori* and were forced into the final model. We present the adjusted odds ratio for in-hospital mortality and 95% confidence interval. Statistical sig-

Table 1. Baseline characteristics of patients (n = 261)

Variable	Value	SD or IQR	Range
Age, yrs	59	16.1	22–101
Female gender, %	41		
Race			
Black, %	48		
White, %	43		
Other, %	9		
APACHE II score	17.9	6.4	
Qualified for EGDT at presentation to ED, %	47		
SIRS criteria			
Temperature, °F	99.2	2.7	91.7–107.0
Heart rate, beats/min	115.2	25.9	30–182
Respiratory rate, breaths/min	22.1	7.3	6–64
Partial pressure of CO_2, mm Hg	34.5	11.4	12–95
White blood count, per mm^3	14.7	10.9	0.1–90.5
Early goal-directed therapy criteria			
Systolic blood pressure, mm Hg	107.8	27.2	32–173
Lactate, mmol/L	5.6	3.6	0.8–26.5
Baseline laboratory values			
Hemoglobin, mg/dL	11.8	2.9	2.8–19.8
Platelets, per mm^3	233.0	156.0	5–1098
CO_2, mg/dL	20.6	6.5	1–56
International normalized ratio	1.46	0.59	1–>50
Total bilirubin, mg/dL	2.5	4.0	0.1–26.6

APACHE, Acute Physiology and Chronic Health Evaluation; EGDT, early goal-directed therapy; ED, emergency department; SIRS, systemic inflammatory response syndrome.

nificance was defined as a p value $<.05$. To calculate the probability of death, we used a marginal standardization approach wherein we used the estimates from the multivariable logistic regression to determine the average predicted probability of death for a given group (13). Statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC) and STATA (version 10; StataCorp, College Station, TX) statistical software.

RESULTS

The average age of the 261 patients receiving EGDT studied was 59 ± 16 yrs; 41% were female; 48% were black, and 43% were white. Forty-seven percent (n = 123) of the patients qualified for EGDT at triage; 53% (n = 138) qualified later during their ED stay. Cryptic shock was the qualifying diagnostic category for 48% (n = 126) of the patients; septic shock was the qualifying diagnostic category for the remaining 52% (n = 135). Mean Acute Physiology and Chronic Health Evaluation II score was 17.9 ± 6.4 (Table 1).

All patients received antibiotics during their ED course. The median length of time from triage to antibiotics was 119 mins (IQR, 76–192 mins); from qualification for EGDT to antibiotics was 42 mins (IQR, 0–93 mins); from triage to appropriate antibiotics was 127 mins (IQR, 79–224 mins); and from qualification for EGDT to appropriate antibiotics was 47 mins (IQR, 0–108 mins). Kappa value of interrater reliability for time to antibiotics = 0.91. The most common sources of infection were: respiratory (30.6%), genitourinary (22.8%), gastrointestinal (19.7%), and primary bacteremia (14.9%) (Table 2). Cultures were positive in 148 (56.7%) patients. Our ED antibiogram was followed in all of the culture-negative cases (Appendix B); 126 (85.1%) of the culture-positive cases received appropriate initial antibiotic coverage during their ED stay; 22 (14.9%) of the culture-positive cases were initially given inappropriate antibiotics. Two patients who initially received inappropriate antibiotics were subsequently given appropriate antibiotics before transfer from the ED.

In-hospital mortality was 31.0% for the cohort as a whole; it was 35.1% for culture-positive patients vs. 25.7% (p = .11) for culture-negative patients (Table 3). Mortality for culture-positive patients who received appropriate initial antibiotics in the ED was 32.5%; mortality for culture-positive patients who did not receive appropriate initial antibiotics in the ED was 50.0% (p = .15).

Table 2. Source of infection

Source	Percent
Respiratory	30.6
Genitourinary	22.8
Gastrointestinal	19.7
Primary bacteremia	14.9
Skin/soft tissue	7.5
Central venous catheter	5.9
Central nervous system	2.4
Surgical site	2.0
Endocarditis	1.6
Other	5.8
Total	306 sites

Forty-three patients had two or more primary sources.

We found no relationship between time from triage to administration of antibiotics and mortality outcome after adjusting for potential confounders. The lack of relationship between time of antibiotic administration and mortality outcome extended to >5 hrs from triage to antibiotic administration. Similarly, we found no relationship between time from qualification for EGDT to antibiotic administration and mortality. In the analysis examining time from triage to appropriate antibiotic administration, mortality was significantly decreased when antibiotics were given in ≤1 hr vs. >1 hr. Finally, in the analysis examining time from qualification for EGDT to appropriate antibiotics, mortality was significantly decreased when antibiotics were given in ≤1 hr vs. >1 hr (Tables 4,–7; Figures

Table 3. Culture results

	Number	Percent
Total patients	261	
Culture-negative patients	113	43.3
Culture-positive patients	148	56.7
Urine	71	27.2
Blood	83	31.8
Other	50	19.2
Polymicrobial	25	9.6
Multiple sources	42	16.1
Total positive cultures	204	N/A
Gram-positive organisms	67	25.7
Enterococcus	18	6.9
Streptococcus pneumoniae	14	5.4
MSSA	14	5.4
MRSA	8	3.1
Group B *Streptococcus*	5	2.0
Streptococcus viridans	4	1.5
Other staphylococci (hominis, lugdunensis)	3	1.2
Group A *Streptococcus*	1	0.4
Gram-negative organisms	96	36.6
Escherichia coli	30	11.5
Klebsiella	21	8.0
Pseudomonas species	15	5.7
Citrobacter	6	2.3
Acinetobacter	5	1.9
Enterobacter species	5	1.9
Proteus mirabilis	4	1.5
Haemophilus influenzae	2	0.8
Serratia	2	0.8
Stenotrophomonas	1	0.4
Morganella	1	0.4
Other gram-negative organisms	4	1.5
Anaerobic organisms	9	3.4
Clostridium difficile	4	1.5
Bacteroides fragilis	3	1.2
Other *Clostridia*	1	0.4
Fungi	6	2.3
Candida albicans	5	1.9
Candid glabrata	1	0.4
Legionella species	1	0.4

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; N/A, not applicable.

Table 4. In-hospital mortality: Triage to ED antibiotics

Cutoffs	Number	Mortality, %	Difference, %	Adjusted OR	Adjusted 95% CI	Adjusted p Value	Probability of Death
≤1 hr	46	26.1	6.0	0.51	0.21–1.22	.13	.20 vs. .28
>1 hr	215	32.1					
≤2 hrs	136	30.9	0.3	0.72	0.38–1.37	.30	.25 vs. .28
>2 hrs	125	31.2					
≤3 hrs	187	29.4	5.7	0.64	0.32–1.29	.21	.25 vs. .31
>3 hrs	74	35.1					
≤4 hrs	217	30.0	6.4	0.80	0.35–1.84	.59	.27 vs. .29
>4 hrs	44	36.4					
≤5 hrs	237	32.1	−11.2	0.86	0.56–6.15	.31	.28 vs. .16
>5 hrs	24	20.8					

ED, emergency department; OR, odds ratio; CI, confidence interval.

Table 5. In-hospital mortality: Qualified for EGDT to ED antibiotics

Cutoffs	Number	Mortality, %	Difference, %	Adjusted OR	Adjusted 95% CI	Adjusted p Value	Probability of Death
≤1 hr	154	26.6	10.8	0.58	0.31–1.08	.09	.22 vs. .34
>1 hr	107	37.4					
≤2 hrs	218	29.8	7.4	0.77	0.34–1.70	.51	.26 vs. .34
>2 hrs	43	37.2					
≤3 hrs	239	30.1	10.8	0.62	0.23–1.69	.36	.26 vs. .39
>3 hrs	22	40.9					
≤4 hrs	252	30.6	13.9	0.77	0.17–3.59	.74	.27 vs. .37
>4 hrs	9	44.4					
≤5 hrs	257	31.1	−6.1	1.33	0.12–14.20	.82	.27 vs. .24
>5 hrs	4	25.0					

EGDT, early goal-directed therapy; ED, emergency department; OR, odds ratio; CI, confidence interval.

Table 6. In-hospital mortality: Time from triage to appropriate antibiotics

Cutoffs	Number	Mortality, %	Difference, %	Adjusted OR	Adjusted 95% CI	Adjusted p Value	Probability of Death
≤1 hr	41	19.5	13.7	0.30	0.11–0.83	.02	.13 vs. .29
>1 hr	220	33.2					
≤2 hrs	124	28.2	5.4	0.54	0.29–1.03	.06	.22 vs. .31
>2 hrs	137	33.6					
≤3 hrs	172	27.9	9.2	0.53	0.27–1.01	.05	.23 vs. .34
>3 hrs	89	37.1					
≤4 hrs	200	28.5	10.8	0.62	0.31–1.24	.18	.25 vs. .34
>4 hrs	61	39.3					
≤5 hrs	218	30.7	1.8	0.82	0.37–1.79	.62	.27 vs. .29
>5 hrs	43	32.6					

OR, odds ratio; CI, confidence interval.

1,–4). These findings were supported by the sensitivity analyses at other time cutoffs. Similar results were seen when the patients were divided into two categories (patients with cryptic shock and patients with septic shock), which were subsequently analyzed as described previously (not shown in tables).

DISCUSSION

Severe sepsis and septic shock are vexing healthcare problems in the United States and around the world. There is a large burden of disease and high mortality; outcomes have, until recently, remained relatively static, and the incidence is increasing. The optimal treatment strategy is constantly evolving and includes initial resuscitation, rapid diagnosis, timely administration of appropriate antibiotics, source identification and control, and meticulous ED and intensive care unit (ICU) management. The question of how antibiotic administration should be prioritized in the initial resuscitation sequence of patients with severe sepsis and septic shock has been unanswered. We hypothesized that earlier antibiotic administration would be associated with lower in-hospital mortality in patients treated with a uniform resuscitation strategy (EGDT). We examined time from triage to antibiotic administration (a commonly tracked performance measure) and time from qualification for EGDT to antibiotic administration, which is much more in keeping with the Surviving Sepsis Campaign's recommendation of rapid antibiotic administration after recognition of severe sepsis or septic shock. The results of our study identify three important factors in the relationship between mortality and timing of antibiotic administration in severe sepsis and septic shock: 1) the time the patient qualified for EGDT; 2) the length of time from triage to administration of appropriate antibiotics; and 3) the length of time from qualification for EGDT to administration of appropriate antibiotics. Based on the results of this study, we recommend that practitioners administer appropriate antibiotics as rapidly as possible once there is a reasonable suspicion of severe sepsis and septic shock and place a high priority on developing systems to streamline their timely administration. Appropriate antibiotics should be given within 1 hr of qualification for EGDT. Of note, in our study, there were only five patients (four of whom died) who received inappropriate antibiotics within 1 hr of triage and only 10 patients (five of whom died) who received inappropriate antibiotics within 1 hr of qualification for EGDT. Given this, the mortality benefit of timely antibiotics is likely driven by the timely administration of appropriate antibiotics.

Our findings support the recommendations on timeliness of antibiotic administration published by the Surviving Sepsis Campaign. Their recommendations are based primarily on expert opinion and the results of two retro-

Table 7. In-hospital mortality: Time from qualification for EGDT to appropriate antibiotics

Cutoffs	Number	Mortality, %	Difference, %	Adjusted OR	Adjusted 95% CI	Adjusted p Value	Probability of Death
≤1 hr	144	25.0	13.5	0.50	0.27–0.92	0.03	.20 vs. .35
>1 hr	117	38.5					
≤2 hrs	201	28.4	11.6	0.57	0.27–1.15	0.12	.24 vs. .38
>2 hrs	60	40.0					
≤3 hrs	220	28.6	15.3	0.47	0.22–1.01	0.05	.24 vs. .43
>3 hrs	41	43.9					
≤4 hrs	232	29.3	15.5	0.49	0.20–1.18	0.11	.25 vs. .42
>4 hrs	29	44.8					
≤5 hrs	238	29.8	13.7	0.48	0.18–1.25	0.13	.25 vs. .43
>5 hrs	23	43.5					

EGDT, early goal-directed therapy; OR, odds ratio; CI, confidence interval.

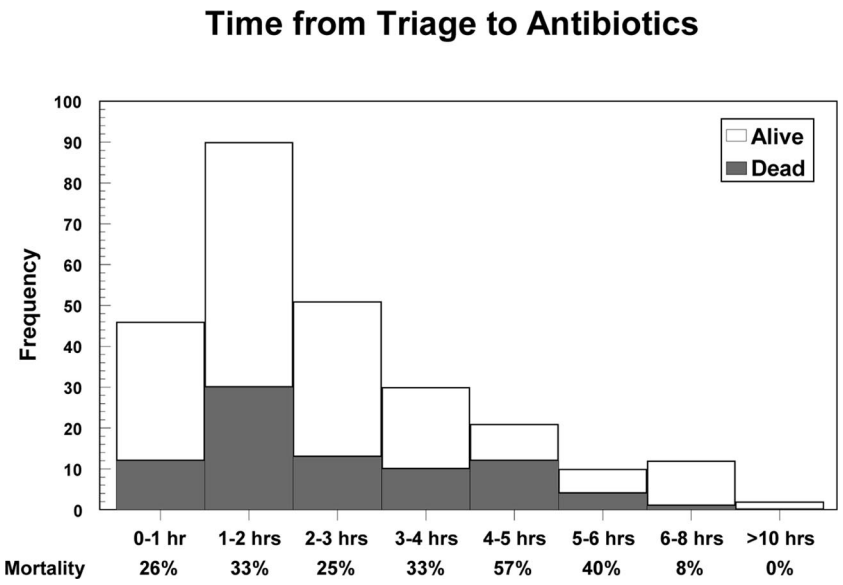

Figure 1. Number of patients and mortality at hourly intervals based upon time from triage to antibiotics.

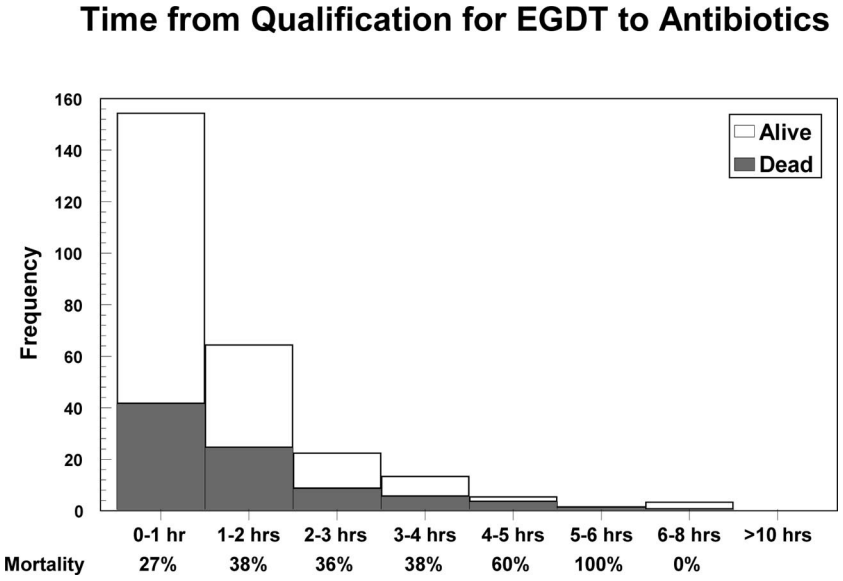

Figure 2. Number of patients and mortality at hourly intervals based upon time from qualification for EGDT to antibiotics.

spective studies (5, 6). The first study demonstrated a logarithmic relationship between the duration of hypotension before administration of appropriate antimicrobials and mortality in patients admitted to the ICU with septic shock. Direct admissions from the ED accounted for 44.4% of the patients included. In this study, each hour's delay from the onset of hypotension to administration of appropriate antibiotics was associated with an average increase in in-hospital mortality of 7.6% (5). The second study found that delaying antifungal therapy for >12 hrs after the initial positive fungal culture was drawn was an independent predictor of hospital mortality (6).

How early is early enough for antibiotic administration in severe sepsis and septic shock? A handful of recent studies have attempted to answer this question. For example, a retrospective analysis of patients with severe pneumonia resulting from *Legionella pneumophilia,* found that delays to antibiotic administration >8 hrs from ICU admission were associated with increased mortality (14). Another retrospective study examining predictors of 30-day mortality in critically ill patients with cancer with septic shock found that mortality was increased when time from ICU admission to first antibiotic administration was >2 hrs (15). Finally, the Finnsepsis Study Group (16) examined how early treatment guidelines, including early antibiotic administration and early hemodynamic optimization, were being adopted in the treatment of septic shock in Finland. They examined 92 patients with septic shock admitted from the ED to the ICU, dividing them into patients receiving antibiotics in <3 hrs vs. >3 hrs from ED admission. They found that a "delayed start of antibiotics was the most significant individual early treatment variable resulting in increased mortality." However, compliance with EGDT screening and resuscitation end points was unsatisfactory in their cohort: lactate measurement occurred during the first 6 hrs in 58%; antibiotics were given in <3 hrs in 53%; central venous pressure was measured during the first 6 hrs in 37%; mean arterial pressure >65 mm Hg was achieved in 74%; and $ScvO_2$ was measured within 6 hrs in 19.6%. This variability of care makes it hard to generalize from the patients with septic shock in their cohort to a

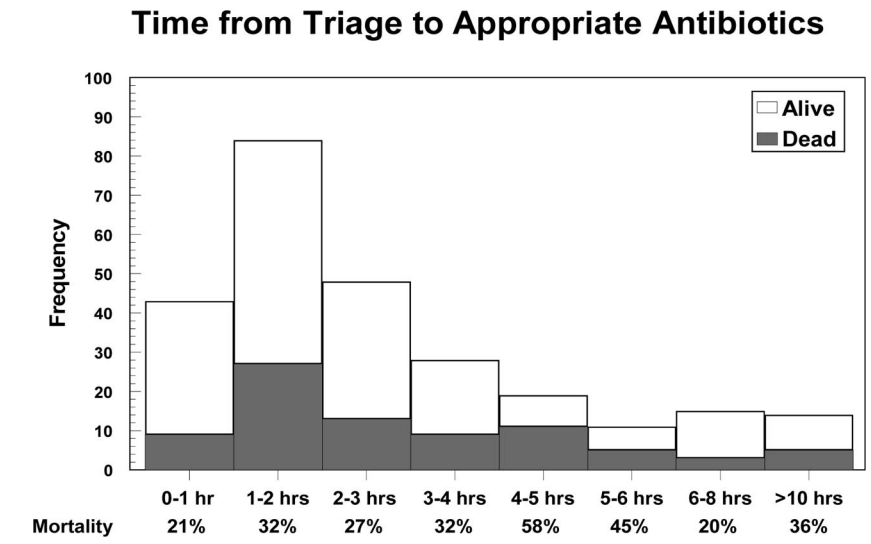

Figure 3. Number of patients and mortality at hourly intervals based upon time from triage to appropriate antibiotics.

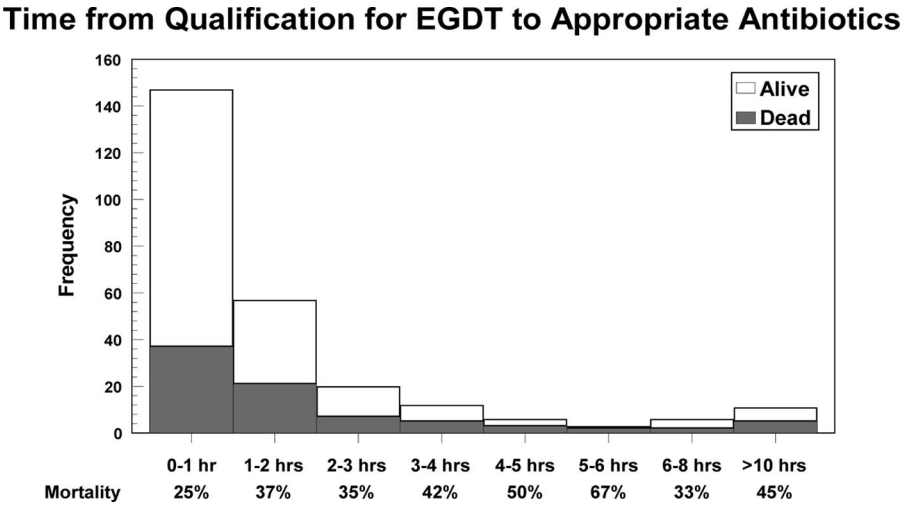

Figure 4. Number of patients and mortality at hourly intervals based upon time from qualification for EGDT to appropriate antibiotics.

group of patients managed with a more uniform resuscitation strategy.

How do our findings diverge from those of prior studies investigating the relationship between time to antibiotics and mortality in patients with septic shock? All 261 patients in our cohort underwent hemodynamic optimization during the first 6 hrs of their hospital presentation. This included assessment of serum lactate, early volume resuscitation, and invasive monitoring for central venous pressure, mean arterial pressure, and $ScvO_2$. Despite variations in presentation, the median time from triage to antibiotics was 119 mins, 97.6% received antibiotics within 6 hrs of triage, and all of the patients received antibiotics before transfer from the ED to the ICU. Within this aggressive, uniform resuscitation strategy at the most proximal point of critical infection, time from qualification for EGDT to appropriate antibiotic administration had a significant effect on in-hospital mortality outcome. This effect was not present when time from triage to antibiotic administration was analyzed; this suggests that the commonly used performance measure of time from triage to antibiotics in diseases such as pneumonia needs to be modified to take into account the appropriateness of the antibiotics that were given and the pathophysiological implications of the time of onset of hemodynamic instability. We did not find the logarithmic changes in mortality seen in the study of Kumar et al, and we hypothesize that the reason for this is threefold: 1) in the study of Kumar et al, the median time to appropriate antibiotics was 6 hrs (IQR = 2–15 hrs), whereas in our study, it was just over 2 hrs (127 mins [IQR, 79–224 mins]); 2) resuscitation strategies were heterogeneous over time and location in the study of Kumar et al, whereas a single, algorithmic hemodynamic optimization strategy initiated in the ED was used in all patients in our study; and 3) the study of Kumar et al benefited from a much larger sample size.

Results of animal studies using an intra-abdominal sepsis model suggest a critical inflection point between 12 and 15 hrs after induction of septic shock; this inflection point coincides with the onset of persistent hypotension and the development of significant lactic acidosis. When antibiotic administration is delayed beyond this point, mortality increases dramatically (17). Our data are consistent with this finding and suggest that a similar inflection point exists in patients presenting to the ED with severe infections, who qualify for goal-directed hemodynamic optimization strategies. This inflection point may coincide with triage (47% of our patients qualified for EGDT at triage) or may develop during the initial hours of evaluation and treatment in the ED (53% of our patients qualified at some point after triage). When appropriate antibiotics are administered before or coincident with this inflection point, mortality is significantly lower than when appropriate antibiotic administration is delayed beyond that point. Our findings support the Surviving Sepsis Campaign's recommendation of antibiotic administration within 1 hr of recognition of septic shock and suggest that the recommendations from the ED-SEPSIS Working Group that "administration of antibiotics within the time of ED care and as soon as possible once there is a reasonable suspicion of severe sepsis/septic shock will likely increase the chance of favorable outcome compared with later administration" are not rigorous enough given our current understanding of the role of appropriate antibiotics in the treatment of life-threatening severe sepsis.

This study has several limitations. It was performed at a single center using a uniform, algorithmic resuscitation strategy, and caution should be taken in

generalizing these results to the treatment of patients with severe sepsis and septic shock in institutions with different resources or that use other management strategies. Despite analyzing our data from multiple perspectives, we cannot rule out that sicker patients received antibiotics sooner and that the results are confounded by these patients being at higher risk of death; however, this confounding should bias toward the null. It is possible that differences in times to EGDT end points not considered in this analysis played a role in mortality outcome. In addition, it is possible that the fact that one author met with the other data abstractors on a regular basis to address questions about data entry injected bias instead of accuracy into time calculations and classification assignments. Because of overall sample size, we may have been unable to demonstrate an hour-to-hour increase that would be present in a larger cohort.

CONCLUSIONS

Our study demonstrates that time from qualification for EGDT to administration of appropriate antibiotics is an important determinant of outcome in patients with severe sepsis and septic shock who qualify for hemodynamic optimization strategies. Administration of appropriate antibiotics is one of many early resuscitation interventions that must be performed as soon as possible in patients with critical infections. Appropriate antibiotics should be administered within 1 hr of qualification for EGDT. However, the exact timing of the antibiotic administration must be tailored to the resuscitation of the specific patient and will depend on the priority of interventions in the individual patient including airway management, volume resuscitation, vasopressor administration, correction of myocardial dysfunction, and source control. In general, the delivery of antibiotics needs to be moved toward the beginning of this resuscitation algorithm, and protocols and systems must be developed to ensure the timely administration of potentially life-saving antibiotics. These include identifying antibiotics that can be given rapidly by intravenous push vs. those that require infusion over an extended time frame. Also, the central antibiotics in an institution's severe sepsis and septic shock antibiogram must be immediately available in the ED and ICUs, eliminating delays to order, prepare, and deliver medications from centralized pharmacies.

ACKNOWLEDGMENTS

The investigators recognize the invaluable contributions of Andrea Miltiades, BA, to data abstraction and data entry for this study.

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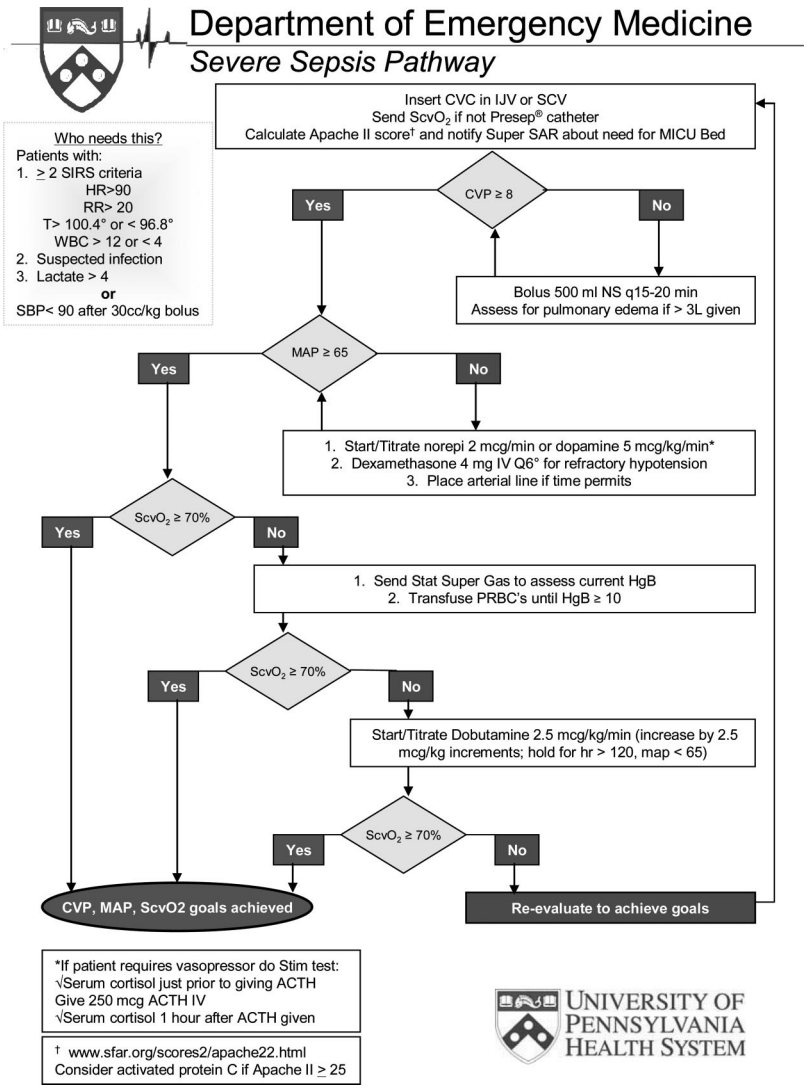
APPENDIX A: THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA'S SEVERE SEPSIS PATHWAY



APPENDIX B: *A PRIORI* RULES FOR DEFINING SEPTIC SHOCK, CRYPTIC SHOCK, AND QUALIFICATION FOR EARLY GOAL-DIRECTED THERAPY, ASSIGNING TIMES TO QUALIFICATION FOR EARLY GOAL-DIRECTED THERAPY AND ANTIBIOTIC ADMINISTRATION, AND ASSESSING APPROPRIATENESS OF ANTIBIOTIC ADMINISTRATION

Definitions of Septic Shock and Cryptic Shock. Generally accepted definitions of severe sepsis and septic shock were used: 1) severe sepsis was defined as two or more systemic inflammatory response syndrome criteria: temperature <96°F or >100.4°F; heart rate >90 beats/min; respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg; and white blood cell count <4000/mm^3, >12,000/mm^3, or >10% bands; a presumed or documented source of infection; and at least one organ dysfunction, including change in mental status, acute renal dysfunction, platelets <100/mm^3, lactate >3 mmol/L, and total bilirubin >4 mg/dL among others; septic shock was defined as two or more systemic inflammatory response syndrome criteria, a presumed or documented source of infection, and a systolic blood pressure (SBP) ≤90 mm Hg after a fluid challenge of 20 to 30 mL/kg over 30 mins; a patient was also considered to be in septic shock if their SBP remained at least 40 mm Hg below a well-documented baseline SBP after 20- to 30-mL/kg fluid challenge over 30 mins (8); conversely, if a patient had a well-documented baseline low SBP (between 75 and 90 mm Hg), then they were not considered to be in septic shock if their blood pressure was in this range. Cryptic shock was defined as severe sepsis with a lactate ≥4 mmol/L as a marker of significant tissue hypoperfusion (3).

Definition of Qualified at Triage. Patients were classified as "qualifying for EGDT at triage" if they were hypotensive in triage and remained so during their initial intravenous fluid resuscitation in the ED (20–30 mL/kg); if they became hypotensive during the first 60 mins after triage and that hypotensive reading occurred after adequate initial fluid resuscitation (20–30 mL/kg); or if they had an elevated serum lactate (≥4 mmol/L as a marker of significant tissue hypoperfusion) result available on the ED electronic medical record within 1 hr of triage. If these criteria were not met and the patient qualified at a later point, they were classified as "not qualifying for EGDT at triage."

Time From Triage to Antibiotic Administration. For analysis of time from triage to antibiotic administration, time zero was considered triage time or room time, whichever time was earlier, and time of antibiotic administration was considered the time the first antibiotic was started by the nurse caring for the patient.

For analysis of time from qualification for EGDT to antibiotic administration, time zero for cryptic shock was considered the time the lactate value ≥4 mmol/L was received on the ED electronic medical record and for septic shock was the time of the first hypotensive reading (SBP ≤90 mm Hg or >40 mm Hg below baseline) after adequate volume resuscitation (20–30 mL/kg) or the time of onset of hypotension if the SBP was always ≤90 mm Hg or >40 mm Hg below baseline during the initial resuscitation. For these patients, time of antibiotic administration was considered the time the first antibiotic was started by the nurse caring for the patient. Time from triage to appropriate antibiotic administration and time from qualification for EGDT to appropriate

antibiotic administration were defined using the same time zero points given previously, and defining time of appropriate antibiotic administration as the time the antibiotic covering the causative organism was started, up to 36 hrs after triage or qualification; if the time of administration of appropriate antibiotics was >36 hrs from time zero, the time to administration was considered 36 hrs.

Appropriate Antibiotics. Appropriate antibiotics were defined as: 1) antibiotics for which the causative pathogens were sensitive *in vitro*; 2) in cases of polymicrobial infection, all pathogens felt to be contributing to severe sepsis or septic shock had to be covered by antibiotics for which the organisms were sensitive *in vitro*; and 3) in cases of culture-negative severe sepsis or septic shock, broad-spectrum antibiotics appropriate for the presumed site of infection.

APPENDIX C: EMERGENCY DEPARTMENT SEVERE SEPSIS ANTIBIOGRAM