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Arriving by Emergency Medical Services Improves Time to Treatment Endpoints for Patients With Severe Sepsis or Septic Shock

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Abstract

Objectives: The objective was to evaluate the effect of arrival to the emergency department (ED) by emergency medical services (EMS) on time to initiation of antibiotics, time to initiation of intravenous fluids (IVF), and in-hospital mortality in patients with severe sepsis and septic shock.

Methods: The authors performed an evaluation of prospectively collected registry data of patients with a diagnosis of severe sepsis or septic shock who presented to an urban academic ED during a 2-year period from January 1, 2005, to December 31, 2006. Descriptive and multivariate analytic methods were used to analyze the data. Using unadjusted and adjusted models, out-of-hospital patients who presented to the ED by ambulance (EMS) were compared to control patients who arrived by alternative means (non-EMS). Primary outcomes measured were ED time to initiation of antibiotics, ED time to initiation of IVF, and in-hospital mortality.

Results: A total of 963 severe sepsis patients were enrolled in the registry. Median time to antibiotics was 116 minutes for EMS (interquartile range [IQR] = 66 to 199) vs. 152 minutes for non-EMS (IQR = 92 to 252, $p \leq 0.001$). Median time to initiation of IVF was 34 minutes for EMS (IQR = 10 to 88) and 68 minutes for non-EMS (IQR = 25 to 121, $p \leq 0.001$). After adjustment for the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, age, and initial serum lactate level, no significant differences in hospital mortality were seen (adjusted relative risk [aRR] for EMS vs. non EMS = 1.24, 95% confidence interval [CI] = 0.92 to 1.66, p = 0.16). The Cox proportional hazard ratio (HR) comparing EMS to non-EMS care after similar adjustment was HR = 1.27 for IVF (95% CI = 1.10 to 1.47, p = 0.004) and HR = 1.25 for antibiotics (95% CI = 1.08 to 1.44, p = 0.003).

Conclusions: Out-of-hospital care was associated with improved in-hospital processes for the care of critically ill patients. Despite shortened ED treatment times for septic patients who arrive by EMS, a mortality benefit could not be demonstrated.

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More than two-thirds of the nearly 750,000 annual cases of severe sepsis in the United States are initially seen in the emergency department (ED).[1] Additionally, the number of cases of severe sepsis has been increasing each year for the past decade.[2,3] Sepsis mortality is estimated to be between 25 and 50%, depending on the characteristics of the study population.[4,5] As with other time-sensitive, high-mortality disease states, the early recognition and treatment of severe sepsis and septic shock have been shown to reduce morbidity and mortality.[4,6–8] Two important and time-sensitive interventions for patients with severe sepsis are early antibiotic administration, and early delivery of intravenous fluids (IVF).[8]

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The Surviving Sepsis Campaign's "International Guidelines for the Management of Severe Sepsis and Septic Shock" recommend that fluid resuscitation and appropriate antimicrobial therapy be administered within 1 hour of recognition of septic shock.[9] Studies have demonstrated that delays in treatment result in significant increases in mortality for patients with other infectious disease processes.[10,11] Similarly, there is evidence to support the benefit of early treatment for life-threatening infections.[4,9,10,12,13] Although definitive associations between time to treatment and mortality are yet to be firmly established, there is mounting evidence that mortality increases with delays in early treatment of severe sepsis and septic shock.[14–16] Therefore, the Surviving Sepsis consensus guidelines explicitly state that the "the resuscitation of a patient in severe sepsis … should begin as soon as the syndrome is recognized and should not be delayed."[9]

To the best of our knowledge, the role of emergency medical services (EMS) in the early management of patients with sepsis has not been explored extensively. Previous studies have demonstrated that arrival by EMS reduces treatment delays for time-sensitive conditions like stroke and acute myocardial infarction (AMI).[17,18] Early treatment has also been directly linked to improved outcomes. For example, improved survival of acute stroke or AMI patients has been correlated with reduced elapsed time prior to definitive care.[19,20] Therefore, there may exist significant, untapped opportunity for early recognition and treatment of critical illness within the EMS patient population.[21,22]

Given the competing demands for resources that exist in many EDs, the timely recognition and rapid treatment of severe sepsis or septic shock can be a difficult task. Ambulance arrival can shorten the time to physician evaluation in the ED,[23] and theoretically reduce time to treatment for severe sepsis and septic shock. Yet this assumption can be challenged by a theoretical counterfactual: out-of-hospital treatments could delay ED diagnosis and treatment for sepsis by temporizing vital sign abnormalities and masking other symptoms of sepsis. Despite this open question, the specific effect of EMS arrival on the ED treatment and overall outcomes of patients with severe sepsis and septic shock has not yet been explored in depth.

Our goal was to evaluate the effect of arrival to the ED by EMS on time to initiation of antibiotics, time to initiation of IVF, and in-hospital mortality in patients with severe sepsis and septic shock. We hypothesized that arrival by EMS would be associated with improved care processes and outcomes for patients with these conditions, when compared to arrival by all other modalities.

METHODS

Study Design

This study was a secondary analysis of prospectively collected registry data. We performed a cohort study of adult patients diagnosed with severe sepsis or septic shock who presented to the ED and were admitted to our hospital over a 2-year period from January 1, 2005, to December 31, 2006. University of Pennsylvania Institutional Review Board approval was obtained for this study and they granted a waiver of informed consent.

Study Setting and Population

Data were collected for patients who presented to the Hospital of the University of Pennsylvania's (HUP) ED during the enrollment period. HUP is an urban, tertiary care, academic medical center with an annual census of greater than 60,000 adult patients per year during the study period and is one of approximately 30 receiving hospitals within the city of Philadelphia.

Philadelphia is the sixth largest city in the country, with a population just under 1.5 million. Annually, there are nearly 250,000 9-1-1 calls for emergency service, and all are answered by the Philadelphia Fire Department (PFD) EMS ambulances that are part of the multitiered service provided by the PFD. During the study period, there were between 40 and 50 ambulances operating in the city. Most of the ambulances are staffed by crews that consist of either two paramedics or one paramedic and a firefighter/emergency medical technician (EMT). During our study period, a small percentage of basic life support ambulances were added to the response structure to augment existing service.

All adult (age > 18 years) subjects admitted to the hospital from the ED were screened for inclusion if serum lactate was measured or a physician documented one of the following indicators of severe sepsis in the ED electronic medical record: sepsis, severe sepsis, septic shock, cryptic septic shock, or use of early goal-directed therapy (EGDT). Subjects who had one or more of these screening criteria underwent detailed medical record review for the presence of severe sepsis and septic shock. After these patients were enrolled into the sepsis registry, they were stratified according to mode of arrival (EMS vs. non-EMS) to the ED. Regarding the sepsis registry, pertinent demographic, comorbidity, laboratory, physiologic, and treatment data were abstracted from the hospital record by five trained investigators using a uniform abstraction form. Completeness and accuracy of data abstraction was verified by one of the other investigators, with adjudication, if necessary, performed by the investigator who maintains the database (DFG).[21] Also included were all patients who were identified as having severe sepsis or septic shock as defined by HUP's severe sepsis pathway, available in the online Data Supplement S1. Subjects were excluded if they left against medical advice, were transferred to another institution, or were initially evaluated by the trauma service as trauma patients.

Study Protocol

A priori rules were developed for determining triage time, time of initial antibiotic administration, and time of initial IVF administration. For analysis of time from triage to antibiotic administration, time zero was considered either triage time or room time, whichever time was earlier, and time of antibiotic administration was considered the time the first antibiotic was started. Likewise, the time from arrival to IVF is the time elapsed from time zero (as defined above) to the time that IVF administration was initiated. In-hospital mortality was determined from review of in-patient records and discharge summaries.

The investigators engaged in a multistep procedure to maximize the proper classification of mode of arrival. For patients arriving via EMS, mode of arrival was confirmed by obtaining the EMS record from a separate database managed by the PFD. These records are uploaded to a secure password-protected website and may be downloaded by the hospital and become an official part of the hospital medical record. If the EMS record was identified, the patient was confirmed as arriving via EMS patient. If the patient was noted, in the triage, nursing, or physician note, to specifically have arrived by a private ambulance company, he or she was considered a private ambulance arrival. If the ED record indicated ambulance/EMS arrival, but there were no corresponding electronic prehospital records from the PFD nor a specific type of EMS service listed, the patient was classified as a provisional EMS patient. To account for possible misclassification, provisional EMS patients were coded separately from confirmed EMS patients and used in a sensitivity analysis for testing the outcomes of interest.

Non-EMS patients were defined as any other arrival method, including walk-in, public transportation, or private vehicle. Severity of illness was calculated using an Acute Physiology and Chronic Health Evaluation II (APACHE II) score.[14] Age and initial serum lactate value were used as additional measures of severity.

Chart abstraction methods followed established standards.[24] To assess reproducibility of data abstraction, 10% of the charts were randomly selected and reabstracted by two investigators (RAB, ZFM), with 100% agreement on the outcome variables of interest and primary independent variable (mode of arrival). Data were recorded using standard database software (Access, Excel, Microsoft Corp., Redmond, WA).

Data Analysis

To evaluate baseline differences in demographics and disease severity between the EMS and non-EMS groups, chi-square or Fisher's exact test was used for categorical data and Student's t-test was used for continuous data. For nonnormally distributed data, such as age, APACHE II score, and serum lactate, the Wilcoxon rank-sum test was used to compare median values. Based on our available sample size, this study was powered to detect an 8% difference in mortality (primary outcome) with a power of 80% and alpha set at 0.05. To assess differences in time from triage to IVF or antibiotic administration (secondary outcomes) between modes of arrival, the Wilcoxon rank-sum test was performed. Kaplan-Meier survival curves, using the cumulative incidence proportion (1 – survival), were created to demonstrate the proportions of study patients receiving the outcome measures at various points of elapsed time.[25] To adjust for differences in patient disease severity (as measured by age, APACHE II score, and initial serum lactate value), a Cox proportional hazards model was performed after confirmation of the proportional hazards assumption. Because the primary outcome was known to have an incidence greater than 10% in this study, regression risk analysis was used to approximate risk.[26] To calculate relative risk (RR) of death by mode of arrival while controlling for age, APACHE II score, and initial serum lactate, a generalized linear model with a log link, Gaussian error, and robust estimates of the standard errors of the model coefficients was used.[27]

We also tested triage level in these models as a possible way to additionally account for baseline disease severity; however, this variable was removed from the final models because it was not statistically significant and also because of the assumption that triage classification may lay along the causal pathway between mode of arrival and process outcomes. If, for example, EMS arrival causes higher relative triage assessment, which in turn brings faster treatment and improved outcomes for septic patients, then the outcomes measured would be most robust without adjustment for triage classification in the final models.

Categorical data are presented as frequencies and percentages and continuous data are presented as means with standard deviations (±SD). Time parameters are presented as medians with interquartile ranges (IQRs). Where applicable, data are presented as relative risks[26] (RRs) or hazard ratios (HRs), with 95% confidence intervals (CIs). Data were analyzed using SAS statistical software (Version 9.2, SAS Institute, Cary, NC), and Stata statistical software (Version 10.1, StataCorp, College Station, TX). A p value of <0.05 was considered statistically significant.

RESULTS

During the study period, there were 963 severe sepsis patients who met inclusion criteria. The median age was 57 years (IQR = 45 to 70 years), 47% were female, and the median APACHE II score was 18 (IQR = 14 to 22). Of the 963 patients in the total cohort, 397 (41%) were classified as EMS, and 566 (59%), as non-EMS. Of the patients who arrived by EMS, 229 arrived by confirmed municipal EMS, 98 by private ambulance service, and 70 were provisional. Patients in the two groups (EMS vs. non-EMS) were similar with respect to sex, but they differed with respect to age, race, APACHE II score, and serum lactate (Table 1).

Overall, 883 patients received IVF in the ED, and 898 patients received at least one dose of antibiotics in the ED. EMS patients has similar rates of IVF administration in the ED compared to non-EMS patients (90.9% vs. 92.3%, $p = 0.47$). EMS patients also received antibiotics in the ED at similar rates compared to those who did not arrive by EMS (93.0% vs. 93.5%, $p = 0.75$). The median times to antibiotics were 116 minutes for EMS (IQR = 66 to 199 minutes) and 152 minutes for non-EMS (IQR = 92 to 252 minutes; $p \leq 0.001$). The median times to initiation of IVF were 34 minutes for EMS (IQR = 12 to 96 minutes) and 68 minutes for non-EMS (IQR = 28 to 134 minutes; $p < 0.001$). The Kaplan-Meier survival curves (using failure function to demonstrate cumulative incidence)[25] representing the proportion of patients receiving IVF and antibiotics by mode of arrival at varying elapsed time intervals are demonstrated in Figures 1 and 2. After adjustment for APACHE II score, initial serum lactate, and age, the Cox proportional HR for

Table 1
Baseline Characteristics of Patients by Mode of Arrival

Patient Characteristics	EMS (*n* = 397)	Non-EMS (*n* = 566)	p-value
Median age, yr (±SD)	65 (±17)	54 (±17)	<0.0001
Female sex, *n* (%)	194 (49)	255 (45)	0.23
Race, *n* (%)			<0.0001
White	111 (28)	304 (54)	
Black or African American	250 (63)	209 (37)	
Other	34 (8)	47 (8)	
Unknown	2 (1)	4 (1)	
Median (range) serum lactate, mmol/L	3.2 (0.7–26.5)	2.7 (0.4–19.6)	0.0002
Median (range) APACHE II	19.0 (2–40)	17.0 (0–34)	<0.0001

APACHE II = Acute Physiology And Chronic Health Evaluation.

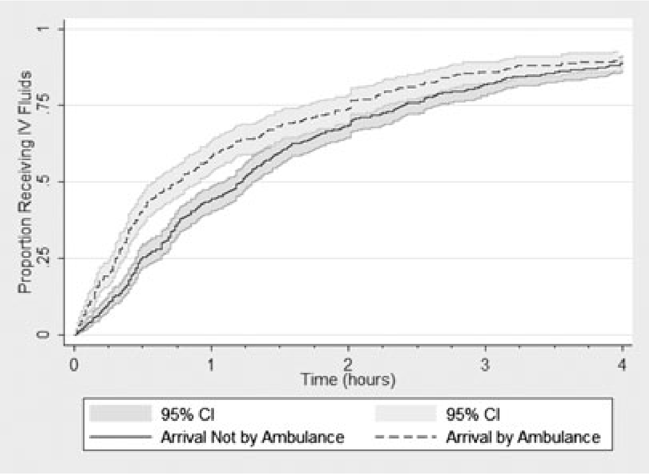

Figure 1. Survival curves for cumulative incidence proportion for initiation of IVF by mode of arrival. IVF = intravenous fluids.

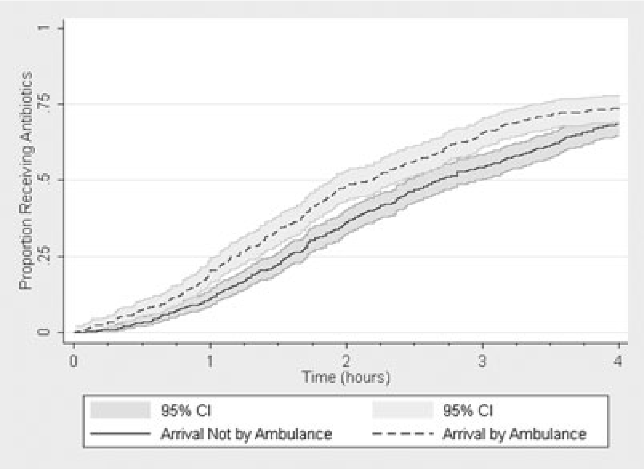

Figure 2. Survival curves for cumulative incidence proportion for initiation of antibiotics by mode of arrival.

Table 2
aRR for Hospital Mortality by EMS Arrival and Covariates

Covariates*	aRR	95% CI	p-value
EMS arrival	1.24†	0.92 to 1.66	0.17
APACHE II	1.05	1.03 to 1.07	<0.001
Serum lactate	1.06	1.04 to 1.09	<0.001
Age	1.01	1.00 to 1.02	0.01

APACHE = Acute Physiology And Chronic Health Evaluation; aRR = adjusted relative risk.
*aRR for covariates represents relative risk of death for increase of 1 point (APACHE II), 1 mmol/L (lactate), and 1 year (age), respectively, after adjustment for all other covariates.
†Reference group is non-EMS.

EMS arrival compared to non-EMS patients was significantly elevated for patients receiving both treatment endpoints (IVF HR 1.27, 95% CI = 1.10 to 1.27; antibiotics HR 1.25, 95% CI = 1.08 to 1.44).

Unadjusted in-hospital mortality was 26.0% for EMS compared to 14.0% for non-EMS patients (p < 0.001). However, after adjustment for APACHE II score, initial serum lactate, and age, the RR for in-hospital mortality among septic patients who arrived by EMS was not statistically different from that of non-EMS patients (RR 1.24, 95% CI = 0.92 to 1.66, p = 0.16). The severity measures and age did not demonstrate colinearity in this model. The adjusted relative risk (aRR) for mortality by mode of arrival and other covariates are in Table 2.

Within the subgroup of patients who arrived by ambulance, patients who arrived by municipal ambulance did not differ significantly from patients who arrived by private ambulance with regard to median time to antibiotics (115 minutes vs. 118 minutes, p = 0.20, respectively), IVF (32 minutes vs. 38 minutes, p = 0.37, respectively) or adjusted mortality (aRR 0.79, 95% CI = 0.56 to 1.11, p = 0.19). All provisionally classified EMS patients (*n* = 70) were reclassified as non-EMS for the sensitivity analysis: results were robust to the original findings, specifically that hospital mortality did not vary significantly by mode of arrival (aRR for EMS = 1.32, 95% CI = 0.99 to 1.76, p = 0.06).

DISCUSSION

This study used sepsis registry data to compare ED processes and outcomes for patients who arrive by EMS to those who arrived by alternate means. We had hypothesized that the effect of EMS care on patients with severe sepsis would be, in part, explained by expedited ED processes for patients who arrived by EMS. We demonstrated that arrival by EMS was associated with significantly shortened time to initiation of IVF and antibiotics. After adjustment for clinical factors, the HRs for use of IVF and antibiotics remained significantly greater for EMS patients. However, we found no significant difference in severity adjusted in-hospital mortality between EMS and non-EMS patients. While some of these differences may have been explained by unmeasured differences in the underlying severity of the patients' conditions, the analysis of relative delays in care for any of these patients, all of whom have severe illness, is instructive.

We know of one other study that has examined the role of EMS care on patients with sepsis. Studnek et al.[28] compared and examined the relationship between mode of arrival and process measures in ED sepsis care, finding shorter time to initiation of antibiotics and EGDT for EMS patients. Our study differs in that we explored mortality as a primary outcome; however, our findings on time to treatment processes are consistent with those of Studnek and colleagues.

There are multiple possible reasons underlying these findings. First, arrival by EMS often bypasses the waiting room and may reduce the chance of critically ill patients being undertriaged in the ED waiting room. Second, EMS patients may, by the very nature of their arrival through the ambulance doors, trigger greater medical attention in the ED. Last, EMS arrival may have led to improved downstream care because the diagnoses of the patients' conditions were made in the field. This, in turn, may have lead to communication of the nature of the problem at the EMS-to-ED handoff or to the automatic continuation of out-of-hospital treatments (such as IVF) in the ED.

Despite the improved process measures for EMS patients, we found that once severity is accounted for, there do not appear to be significant in-hospital mortality differences between EMS and non-EMS care. One possible explanation for this finding is that unmeasured differences in clinical severity between the groups nullified the positive benefit of improved ED processes for EMS patients. Another possible explanation is that reduced time to IVF or antibiotics, when it is on the order of minutes, does not affect the average mortality rate in this heterogeneous patient population with a median APACHE II score of 18. By comparison, Kumar et al.[29] demonstrated a significant effect of time to antibiotics in a patient population with a median APACHE II score of 26.

The implications of these results speak to multiple levels of emergency care. Taken at face value, we might see that in this study population, patients who arrived by EMS receive needed care more rapidly than those who arrived by another mode of transportation. On a higher level, however, these findings address a potentially important aspect of out-of-hospital care that is not commonly considered in patients with sepsis: the ability of EMS care to influence downstream care of life-threatening infections. As ED crowding leads to inevitable delays in diagnosis and treatment of patients with sometimes subtle but serious conditions,[30–32] EMS may represent an effective part of efforts to rapidly diagnose and treat ED patients with critical, time-sensitive illnesses.

LIMITATIONS

These results may not be generalizable to other institutions with different prehospital, triage, and treatment systems than ours. During the study period, ED protocols designed to promote the early detection and treatment of severe sepsis were in place and the results may have less external validity to other hospitals where similar protocols have not been initiated.

Another limitation was the potential for bias due to misclassification of EMS and non-EMS patients. Because we were unable to always reliably confirm the method of arrival for patients who arrived by nonmunicipal EMS transport, we determined that the most conservative approach would be to classify as EMS only those patients who could be confirmed as such using the prehospital records. To address the possibility of misclassification bias, a sensitivity analysis was performed on these data. Our findings were robust to this analysis. Other potential sources of misclassification were the time to treatment outcome measures, which were abstracted from time-stamped medical charting and pharmacy records. At our institution, these charting processes do not differ by mode of arrival, nor does the way in which staff use these systems change depending on whether a patient arrives by private car or ambulance. Last, the chart abstraction methods used included rigorous published methods to minimize classification bias.[24]

The possibility that initiation of IVF in the field artificially delayed the initiation of IVF in the ED exists. If saline was infused by the out-of-hospital providers, the ED team might wait until the field fluid was completed before initiating and recording ED IVF, even if the patient was actually receiving the recommended therapy. While this limitation may have affected the measurement of time to IVF, it should not affect the other process measures (e.g., antibiotics) used in this study. Also, this limitation would, if present, most likely bias the results toward the null hypothesis that EMS arrival does not improve time to ED IVF. There is the possibility that prehospital use of IVF may have also modified the effect of EMS care on sepsis outcomes. However, our group examined the role of prehospital IVF on a smaller cohort of patients arriving by advanced life support units, finding that prehospital fluid does not significantly improve the achievement of goal mean arterial pressure during EGDT.[33] Ideally, a subgroup or interaction analysis of EMS patients comparing patients who did and did not receive prehospital fluids could demonstrate this effect. Nevertheless, in this study, we were unable to determine with accuracy or reliability of the quantity of prehospital fluid provided. In the real world, some patients with severe sepsis will receive prehospital IV fluids and others will not, and this study was designed to reflect this variation.

Additional limitations of this study include the fact that this study did not possess enough statistical power to show a difference in outcomes within types of ambulance transport. However, our primary goals were to demonstrate variations in care between ambulance and alternative modes of arrival. Also, this study did not measure time to other EGDT process measures beyond IVF and antibiotics. Because ideal sepsis care includes a complex series of interventions, it is possible that the earlier use of IVF and antibiotics were alone not able to contribute to mortality differences for these patients. Finally, although APACHE II scores are not validated as a measure of illness severity outside of the ICU, APACHE II is currently the best available marker of severity by which we can make comparisons between critically ill populations of patients in the ED.[14,16]

CONCLUSIONS

Transport of critically ill patients to the ED by municipal EMS was not associated with adjusted differences in hospital mortality. However, out-of-hospital care was associated with improved in-hospital processes for the care of critically ill patients by shortening the elapsed time to initiation of antibiotics and intravenous fluids for patients with severe sepsis or septic shock.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. The Hospital of the University of Pennsylvania's Severe Sepsis Pathway.

The document is in DOC format.
