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Out-of-hospital characteristics and care of patients with severe sepsis: a cohort study

Christopher W. Seymour^{1,*}, Roger A. Band, MD FACEP², Colin R. Cooke, MD, MSc¹, Mark E. Mikkelsen, MD MSCE³, Julie Hylton, BS², Tom D. Rea, MD, MSc⁴, Christopher H. Goss, MD, MSc¹, and David F. Gaieski, MD²

Roger A. Band: roger.band@uphs.upenn.edu; Colin R. Cooke: cookecr@umich.edu; Mark E. Mikkelsen: mark.mikkelsen@uphs.upenn.edu; Julie Hylton: julie.hylton@gmail.com; Tom D. Rea: rea123@u.washington.edu; Christopher H. Goss: goss@u.washington.edu; David F. Gaieski: david.gaieski@uphs.upenn.edu

¹ Division of Pulmonary & Critical Care Medicine, University of Washington, Seattle, WA

² Department of Emergency Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

³ Division of Pulmonary & Critical Care Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

⁴ King County Medic One, Division of General Internal Medicine, University of Washington, Seattle, WA

Abstract

Purpose—Early recognition and treatment in severe sepsis improves outcomes. Yet, out-of-hospital patient characteristics and emergency medical services (EMS) care in severe sepsis is understudied. Our goal was to describe out-of-hospital characteristics and EMS care in patients with severe sepsis, and evaluate associations between out-of-hospital characteristics and severity of organ dysfunction in the emergency department (ED).

Materials & Methods—We performed a secondary data analysis of existing data from patients with severe sepsis transported by EMS to an academic medical center. We constructed multivariable linear regression models to determine if out-of-hospital factors are associated with serum lactate and SOFA in the ED.

Results—Two hundred sixteen patients with severe sepsis arrived by EMS. Median serum lactate in the ED was 3.0 mmol/L (IQR:2.0-5.0) and median SOFA score was 4 (IQR:2-6). Sixty-three percent (135) of patients were transported by advanced life support providers and 30% (62) received IV fluid. Lower out-of-hospital Glasgow coma scale (GCS) was independently associated with elevated serum lactate ($p<0.01$). Out-of-hospital hypotension, greater respiratory rate, and lower GCS were associated with greater SOFA ($p<0.01$).

Conclusions—Out-of-hospital fluid resuscitation occurred in less than one-third of patients with severe sepsis, and routinely measured out-of-hospital variables were associated with greater serum lactate and SOFA in the ED.

* Corresponding author and address for reprints: Christopher W. Seymour, MD, Senior Fellow, Division of Pulmonary Critical Care Medicine, University of Washington, Harborview Medical Center, Box 356522, seymoc@u.washington.edu, Phone: 206-731-8482.

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Keywords

emergency medical services; hypotension; out-of-hospital; sepsis; lactic acid; multiple organ failure

Introduction

Severe sepsis is common, with an estimated incidence of 1-3 cases per 1,000 population (>750,000 cases per annum), and a rate that has been increasing over the past two decades. (1,2). Mortality remains high (20-50%), with a significant decrease in measured quality of life in survivors.(3). Hospital costs have been estimated between \$20,000 – 50,000 per case, with a total burden of up to \$17 billion per year.(1,2) Cost and incidence of severe sepsis are expected to increased as the population ages. (2)

Many recent studies have evaluated the time to treatment and its impact on patient survival in sepsis. In particular, delivery of antibiotics,(4) goal-directed volume resuscitation,(5) and lung protective ventilation,(6) are all more effective when provided to patients earlier in their course. These interventions are endorsed by multiple international societies,(7) and when applied collectively, can reduce mortality from sepsis by 5-20% (8,9).

(10) Many investigators have identified clinical and biological strategies that facilitate earlier recognition of severe sepsis cases in the emergency department (ED), medical ward, and the intensive care unit (ICU).(11-13) However, for up to half of patients with severe sepsis, the earliest encounter with healthcare providers occurs in the pre-hospital setting,(14) a phase of care omitted from the aforementioned consensus guidelines and treatment studies. (7) Though the importance of out-of-hospital care has been well-recognized in trauma, stroke, myocardial infarction, and cardiac arrest patients,(15,16) (17,18) the out-of-hospital phase is understudied in patients with severe sepsis. Our recent pilot work suggests that out-of-hospital fluid resuscitation may reduce time to goal clinical endpoints in severe sepsis. (19)

To inform future studies of out-of-hospital recognition, we aimed to 1) describe the out-of-hospital characteristics and care provided to patients hospitalized for severe sepsis after being transported to the ED by emergency medical services (EMS), and 2) to determine out-of-hospital factors associated with an increased serum lactate and SOFA score in the ED.

Methods

Study design

This study was approved by the institutional review boards of the University of Washington and the University of Pennsylvania with waiver of informed consent. We performed a secondary analysis of a retrospective cohort study of subjects who met criteria for severe sepsis during ED care.

Study setting and population

We used a stepwise identification process to screen for subjects at the Hospital of the University of Pennsylvania (Figure 1). We screened all ED subjects who presented between January 2005 and December 2006 of age ≥ 18 years for the following exclusion criteria: (1) discharge from the ED, (2) left against medical advice, (3) transfer to another institution, (4) activation of the trauma alert system. We screened remaining patients for severe sepsis utilizing the following criteria: (1) the measurement of a serum lactate; (2) physician documentation of one of the following indicators of potential severe sepsis in the ED

electronic medical record (EMR): sepsis, severe sepsis, septic shock, cryptic septic shock, or administration of early goal-directed therapy (EGDT). We performed detailed medical record review on subjects who had one or more screening criteria to determine the presence of severe sepsis and septic shock, and transport to the ED by city EMS.

Variable definitions

We defined sepsis as suspected infection in the presence of any two or more systemic inflammatory response syndrome (SIRS) criteria.(20) We defined severe sepsis as sepsis associated with hypoperfusion, hypotension, or organ dysfunction.(5,20,21) We defined hypoperfusion as a serum lactate ≥ 2 mmol/L, and hypotension and acute organ dysfunction according to the 2001 consensus conference criteria.(21) We defined septic shock as hypotension (systolic blood pressure (SBP) <90 mm Hg) despite adequate fluid resuscitation (>1500 ml) or use of vasoactive agents.(7,20,22,23). These methods for cohort construction are previously described.(23)

Variable collection and data quality

We obtained data from three sources for all subjects included in the final cohort: 1) the out-of-hospital EMS record; 2) ED electronic medical record; and 3) in-patient medical records. City paramedics and emergency medical technicians (EMTs) complete out-of-hospital records using a hand-held touch pad, with drop down menus to prompt data entry. These records are considered part of the permanent hospital record for each patient and are available for review 24 hours after hospital arrival. We utilized out-of-hospital vital signs which were the first recorded values in the EMS record, including systolic/diastolic blood pressure (mmHg), respiratory rate (breaths per min), oxygen saturation (%), heart rate (beats per min), and Glasgow coma scale. We abstracted level of transport (advanced life support (ALS) vs. basic life support (BLS)), placement of intravenous access, delivery of intravenous fluid, use of ECG monitoring, delivery of supplemental oxygen, and endotracheal intubation. We also abstracted pertinent demographic, co-morbidity, laboratory, physiologic, and treatment data from the hospital record by five trained investigators using a uniform abstraction form. The lead investigator (DFG) performed adjudication of the completeness and accuracy of data abstraction when needed. We calculated the duration spent in the ED (min) using the following equation: date/time ED discharge – date/time ED triage. We determined vital status (alive or dead) at hospital discharge.

Outcomes

To study out-of-hospital factors associated with worse organ dysfunction in the ED, our *a priori* primary outcome was the initial serum lactate, measured by a serum-based assay catalyzed by lactate oxidase (Vitros, Ortho Clinical Diagnostics, Rochester, NY). This value was present in all patients. Our secondary outcome was maximum sequential organ failure assessment (SOFA) score measured during the ED stay. (24,25) SOFA is a previously validated scoring system used to quantify the degree of organ dysfunction for critically ill patients. Missing values for SOFA score calculation were presumed to be in the normal range, and worst values were utilized for score calculation.(26) Because SOFA score calculation incorporates mean arterial pressure and GCS, we expected an association between systolic blood pressure and GCS measured during the out-of-hospital phase of care and SOFA score measured in the ED. To address this limitation, we studied the association between out-of-hospital factors and the total SOFA score, minus the cardiovascular and neurologic points, in a sensitivity analysis.(27,28)

Data analysis

We described continuous data using means with standard deviation (SD) or medians with interquartile range (IQR) depending on normality as assessed from graphical distributions. We expressed discrete variables as frequencies or percentiles. To illustrate out-of-hospital vital signs and interventions, we categorized subjects by the presence or absence of shock on ED evaluation. We used bivariate linear regression to study associations between elements of out-of-hospital care and both serum lactate and SOFA score. We log transformed serum lactate in regression analyses due to non-normality, and we exponentiated regression coefficients to determine percent change in lactate for one unit increases in covariates. To determine the independent factors associated with lactate and ED SOFA score, we entered candidate out-of-hospital variables in two, distinct multivariable linear regression models. We included only *a priori* covariates thought to be prognosticative of or to confound lactate or SOFA into our model. *A priori* determined out-of-hospital covariates were: initial systolic blood pressure, heart rate, GCS, respiratory rate, oxygen saturation, level of transport (ALS/BLS), use of ECG monitoring, placement of intravenous access, use of supplemental oxygen, and out-of-hospital intubation. To improve parsimony, we collapsed the presence of co-morbidities into a single, dichotomous variable that reflects the presence or absence of any single co-morbidity. We assessed collinearity between candidate variables using the variance inflation factors for the multiple regression model and explored, when present, using Spearman's rank correlation coefficient and bivariate linear regression models. We excluded the delivery of IV fluid in the final model due to collinearity with placement of IV catheter. We performed regression diagnostics of final models to evaluate the influence of each observation on the vector of regression coefficients. We used the Huber-White estimator to generate standard errors for regression coefficients. Our study was powered to evaluate 11-22 covariates in the multivariable regression models.(29,30) To test the importance of missing data, we used normal value substitution for patients with missing out-of-hospital oxygen saturation (Table E1),(31) and performed a sensitivity analysis of our final multivariable models for lactate and SOFA. All tests for statistical significance were unpaired, two tailed ($p < 0.05$), and we conducted all analyses were using STATA version 10.0 (StataCorp, College Station, TX).

Results

Two hundred sixteen patients were transported to the ED by city EMS during the study period (Figure 1). The main reasons for non-inclusion were discharge from the ED (76%) and trauma transport (4.7%). Subjects were primarily male, with a mean (SD) APACHE II score of 16 (7) (Table 1). The source of severe sepsis was most often respiratory (32%), and ten patients (4.6%) were surgical admissions. Early goal-directed therapy was initiated in one third of patients, while over half required admission to the ICU (Table 1). Fifty-one subjects died during hospitalization (24%).

Vital sign abnormalities, including measured systemic inflammatory response syndrome (SIRS) criteria (RR, HR), were common in the out-of-hospital environment, while out-of-hospital SBP ≤ 90 mmHg occurred in $<25\%$ of subjects (Figure 2). Patients were more commonly transported by an ALS certified providers than by BLS certified providers. Out-of-hospital monitoring and interventions were more commonly performed among patients with septic shock on ED arrival (Figure 3). In the entire cohort, out-of-hospital intravenous fluid was delivered to only 62 subjects (30%), and fluid volume was recorded in only 26 subjects, with a median volume delivered of 300 cc (IQR:200-500). Among subjects with septic shock, intravenous fluid was delivered to only 38%. Out-of-hospital providers were unable to place IV catheters in 18 subjects (8%).

Median serum lactate was 3.0 mmol/L [IQR: 2.0-5.0 mmol/L], and 41% (84) of subjects presented with initial lactate ≥ 4.0 mmol/L. In bivariate analyses, lower out-of-hospital oxygen saturation, SBP, and GCS were associated with an increased serum lactate ($p < 0.03$). In Table E1, for example, an increase in oxygen saturation by 10% was associated with a decrease in serum lactate by 13.9% (95% CI: 9.6, 19). In our multivariable linear regression model (Table 2), GCS was the only factor independently associated with serum lactate ($p < 0.01$).

Maximum SOFA score was greater in patients with out-of-hospital tachypnea, lower blood pressure, lower GCS, and lower oxygen saturation (Table E1). Table 2 displays the out-of-hospital factors associated with an increased SOFA score in multivariable linear regression analysis ($p < 0.05$). For example, each 10 mmHg decrease in SBP was associated with an increase in SOFA by 0.19 (β) points. After adjustment for other factors, level of EMS transport, provision of supplemental oxygen, IV catheters, and EKG monitoring were not associated with maximum SOFA score in the ED. Elevated respiratory rate remained independently associated with both non-cardiovascular ($p < 0.01$) and non-neurologic SOFA ($p < 0.01$) in sensitivity analyses. When accounting for missing data in out-of-hospital oxygen saturation using normal value substitution in a sensitivity analysis, our multivariable models for lactate and SOFA were consistent with the results of the complete case analysis (Table E3).

Discussion

In this cohort of patients hospitalized with severe sepsis, 22 percent arrived to the ED after receiving out-of-hospital care by EMS. We observed that out-of-hospital hypotension, hypoxemia, and altered mental status were uncommon, and that variability in the out-of-hospital care delivered to these patients was common. We observed that reduced out-of-hospital neurologic status was independently associated with greater initial serum lactate in the ED, and that hypotension, tachypnea, and reduced neurologic status on initial EMS assessment were associated with a greater ED SOFA score.

To date, investigators have dedicated little attention to the frequency of out-of-hospital interventions delivered during EMS care in severe sepsis. We identified variability in the out-of-hospital procedures performed by EMS. Similar to a prior cohort of out-of-hospital respiratory distress in Canada, we observed that endotracheal intubation was infrequent (performed in $< 2\%$ of subjects).⁽³²⁾ In our previous pilot data, administration of intravenous fluid EMS occurred in 48% of patients who also received EGDT in the ED.⁽¹⁹⁾ In this larger cohort of patients transported by both ALS and BLS, the overall use of intravenous fluid was lower (30%), but still exceeded that seen in large observational studies of pre-hospital trauma (11%) or respiratory distress (1.1%)⁽³²⁻³⁴⁾. Even among patients with septic shock upon ED arrival, EMS providers administered out-of-hospital intravenous fluid in less than 40% of patients. This may reflect brief transport times in our urban catchment area,⁽³⁵⁾ lack of “spill-over” of evidence for early fluid resuscitation in the ED to the out-of-hospital phase, or fear of inducing pulmonary edema during out-of-hospital care.⁽⁵⁾ We did not observe that EMS procedures or transport by ALS were significantly associated with either SOFA or serum lactate in our sample, perhaps due to the smaller proportion of patients transported by basic life support or type I error.

The presence of patient physiologic distress during out-of-hospital care is common in many critical illnesses, including myocardial infarction,⁽³⁶⁾ trauma and traumatic brain injury,⁽³⁷⁾ and acute stroke,⁽³⁸⁾ often portending a worse prognosis. Similarly, we found that alterations in out-of-hospital vital signs in severe sepsis were prognostic of early physiologic derangements in the ED, suggestive of global tissue hypoxia and worse outcome.⁽³⁹⁾

Specifically, out-of-hospital tachypnea was independently associated with maximum SOFA score in the ED, and a majority of subjects exceeded respiratory rates specified by SIRS criteria.(20) This may reflect a greater respiratory compensation for the metabolic acidosis found in severe sepsis(40), the predominance of cases with a pulmonary source of sepsis in our cohort, or an early warning sign of impending respiratory failure.(41)

Compared to patients who are neurologically intact, patients with an alteration in neurologic status in the out-of-hospital phase were more likely to have a higher lactate and SOFA score. This finding may reflect the presence of circulating inflammatory mediators known to alter the blood brain barrier which are found at higher levels in severe sepsis patients not receiving EGDT.(42,43) The association between neurologic status and greater organ dysfunction was not robust to models using non-neurologic SOFA score; yet, our data is consistent with a comparison study of patients with out-of-hospital hypotension in whom a one unit increase in out-of-hospital GCS was associated with a 7% reduction in the hazard ratio for in-hospital mortality.(44)

We observed out-of-hospital hypotension in less than 25% of severe sepsis patients transported by EMS. When present, out-of-hospital hypotension was independently associated with ED SOFA score, although this was not robust to sensitivity analyses excluding the cardiovascular component of SOFA. Other investigators have reported that out-of-hospital hypotension is a surrogate for clinical outcomes among both trauma and non-trauma medical patients; however, these cohorts did not assess early physiologic outcomes such as lactate or SOFA, or specify *a priori* subgroups of patients with sepsis.(45) Out-of-hospital hypotension may also reflect pre-existing cardiovascular disease, a known risk factor for mortality in severe sepsis,(46) or differences in the volume of out-of-hospital fluid delivered, an exposure not routinely captured by out-of-hospital providers in this cohort.

Our findings have important implications. This cohort study builds on our previous pilot data, demonstrating the variability in EMS procedures before hospital arrival, and the uncommon presence of hypotension, hypoxemia, and altered mental status during the initial EMS assessment. The out-of-hospital phase represents the earliest opportunity for patient identification and treatment, similar to patients transported with myocardial infarction and stroke. Future studies of EMS interventions, such as protocolized intravenous fluid resuscitation, may require clinical tools or prediction rules that use clinical characteristics to classify patients with or without severe sepsis. Our finding that out-of-hospital hypotension occurred in <25% of patients, argues that single vital sign derangements may be insufficient for early recognition of severe sepsis by EMS. Identification of out-of-hospital factors prognostic of organ dysfunction, such as tachypnea, hypotension, and reduced GCS, may also facilitate ED triage and early application of EGDT for patients with severe sepsis.(44,47) We used a previously described and comprehensive approach to screen and define severe sepsis using consensus guidelines,(24,25,27) with the source of severe sepsis and hospital mortality rates similar to other cohorts.(8,48) Unlike prior studies of out-of-hospital care which have utilized administrative databases,(14) study information was derived from clinical data review using detailed abstraction from linked out-of-hospital and ED patient records. Data abstracted contained commonly employed clinical measures in the out-of-hospital phase which are used to assess the physiologic status of transported patients,(49) as well as two immediate and reliable physiologic outcomes in the ED, each of which are strongly associated with clinical outcomes in severe sepsis.(23,39,50)

Limitations

We performed a secondary analysis with a fixed sample size which limited the power to detect important differences that may be present during out-of-hospital care. Second, inadequate documentation of out-of-hospital data in less ill patients may introduce

information bias in our descriptive findings. Yet, key physical assessments and interventions were collected with electronic data entry by EMS providers in order to limit transcription error. We hypothesize more accurate data documentation may be present in sicker patients, adding a conservative bias to our results. Third, we utilized a single measurement of out-of-hospital vital signs in our analyses. Variability in vital sign measurement by EMS may introduce error given the known differences in non-invasive blood pressure measurements and standard measurements when used during transport,(51,52) and may arise from environmental factors such as ambulance noise. (53) Further investigations should incorporate analyses of serial vital sign measurements in the out-of-hospital phase and their clinical implications.(45) Fourth, ED clinicians may have provided different treatments to patients prior to lactate measurement. We believe this introduces minimal bias into our models, as a minority of patients received EGDT, and median time to lactate measurement in our cohort was brief (Table 1). Finally, three factors inherent to our study design threaten the external validity of our findings: 1) chart-based criteria for cohort inclusion, 2) data from a single, urban EMS provider, and 3) inclusion of patients with severe sepsis not receiving EGDT. Our case finding procedure has been previously described, and may be insensitive to patients with cryptic sepsis. If so, this likely adds a conservative bias to our results, as even patients with septic shock were infrequently monitored and resuscitated in the pre-hospital setting. Because we included patients meeting criteria for severe sepsis in the ED who did not receive EGDT, summary measures of severity of illness are less compared to other ED cohorts.(26,54) Future studies may incorporate prospective ED screening methods as well as out-of-hospital care in suburban or rural areas with longer transport distances or different EMS response algorithms.(55) Experiences in physician-accompanied ambulances, common in European EMS systems, (56) may provide contrast to this North American experience, as physicians have been shown to secure advanced airways and deliver intravenous fluid resuscitation to trauma patients more commonly than paramedics.(57)

In conclusion, we observed that out-of-hospital hypotension, hypoxemia, and altered mental status were uncommon in a cohort of ALS and BLS patients who were hospitalized with severe sepsis. Out-of-hospital interventions including fluid resuscitation, monitoring, and serial vital signs occurred in less than half of subjects, while routinely-measured, out-of-hospital clinical variables were associated with greater serum lactate and SOFA score upon ED arrival. Future studies are needed to address the role of out-of-hospital interventions in improving clinical outcomes in severe sepsis and recognition strategies for severe sepsis before hospital arrival.

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List of abbreviations

APACHE	acute physiology and chronic health evaluation
ALS	advanced life support
BLS	basic life support
CNS	central nervous system
ECG	electrocardiogram
ED	emergency department
EGDT	early goal directed therapy
EMS	emergency medical services
EMT	emergency medical technician
GCS	Glasgow coma scale
ICU	intensive care unit
IQR	interquartile range
IV	intravenous
SBP	systolic blood pressure

SIRS systemic inflammatory response syndrome
SOFA sequential organ failure assessment

Figure 1.

Subject accrual diagram. *Abbreviations:* AMA = against medical advice, ED = emergency department, EMS = emergency medical services, WBS = without being seen.

Figure 2. Frequency of vital sign alteration on initial out-of-hospital assessment, error bars represent upper bound of 95% confidence interval

Figure 3.
Frequency of EMS interventions during transport, error bars represent upper bound of 95% confidence interval

Table 1Subject characteristics ^a

Variable	Total cohort
N	216
Age, yrs	61 ± 17
Male gender, n (%)	116 (54)
Co-morbidities, n (%)	
COPD	9 (4)
CHF	12 (6)
Chronic renal insufficiency	29 (14)
Chronic liver failure	5 (2)
Immunosuppression	28 (13)
Diabetes mellitus	72 (34)
Sepsis category, n (%)	
Respiratory	67 (32)
Urologic	65 (31)
Bacteremia	32 (15)
Wound / soft tissue	23 (11)
Gastrointestinal	20 (9)
Central nervous system	10 (5)
Catheter-associated	3 (1)
Other	16 (7)
No source	5 (2)
Pre-hospital assessments:	
Systolic blood pressure, mmHg	121 ± 33
Heart rate, bpm	103 ± 25
Respiratory rate, bpm	20 ± 6
Oxygen saturation, %	97 [94 - 98]
Glasgow coma scale	15 [14 - 15]
ED assessments:	
APACHE II score	16 ± 7
Serum lactate, mmol/L	3 [2 - 5]
SOFA score	4 [2 - 6]
Presence of shock, n %	63 (29)
DNR status, n %	17 (9)
ED therapy:	
Received EGD, n %	76 (35)
Placement of central line, n %	81 (41)
Use of vasopressors, n %	24 (12)
Total fluid in first 6 hrs, L	2.4 ± 1.5
Mechanical ventilation, n %	46 (21)
Admission for surgery, n %	10 (5)

Variable	Total cohort
Time from triage to ED discharge, hrs	7 [5-10]
Time from triage to lactate, min	61 [30,169]
<i>Outcome, n %</i>	
ICU admission	136 (65)
Hospital mortality	51 (24)
60-d mortality	68 (32)

^aData shown as N (%), median [IQR], or mean $\pm$ SD

Table 2Final multivariable regression models of prognostic factors for serum lactate and SOFA score^a

Model	Change in outcome per unit increase in covariate (β)	95% confidence interval	P value
Serum lactate ^b			
Glasgow Coma Scale	- 4.9 %	[-7.7, -1.2 %]	<0.01
SOFA score ^c			
Respiratory rate (per 5 bpm)	0.53	[0.22, 0.83]	<0.01
Systolic blood pressure [per 10mmHg]	-0.19	[-0.33, -0.05]	<0.01
Glasgow Coma Scale	-0.25	[-0.37, -0.12]	<0.001
Presence of co-morbidity	0.71	[0.002, 1.4]	0.049

^a Adjusted for all variables shown in Table E1, only significant variables reported herein^b Serum lactate is log-transformed; β coefficient is exponentiated to generate percent change in lactate for one unit increase in covariate ($e^{\beta} - 1$)^c β coefficient represent absolute change in SOFA for one unit increase in covariate

Abbreviations: SOFA = sequential organ failure assessment