

## Original Research

# Prehospital Antibiotics Improve Morbidity and Mortality of Emergency Medical Service Patients with Sepsis

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## Abstract

### Background

Severe sepsis is a major cause of mortality in patients evaluated in the Emergency Department (ED). Early initiation of antibiotic therapy and IV fluids in the ED is associated with improved outcomes. We investigated whether early administration of antibiotics in the prehospital setting improves outcomes in these patients with sepsis.

### Methods

This is a retrospective study comparing outcomes of patients meeting sepsis criteria in the field by EMS, who were treated with IV fluids and antibiotics. Their outcomes were compared with controls where fluids were administered prehospital and antibiotics were initiated in the ED. We compared morbidity and mortality between these groups.

### Results

Early antibiotics and fluids were demonstrated to show significant improvement in outcomes in the patients meeting sepsis criteria treated in the pre-hospital setting. The average age for sepsis patients receiving antibiotics in the prehospital setting was statistically higher than that for patients in the historical control group, 73.23 years and 67.67, respectively ( $p < 0.036$ ), and there was no statistically significant difference of Charlson Comorbidity Index between the groups ( $p$  two-tail = 0.28). Average intensive care unit length of stay was 2.51 days in the in the prehospital group and 5.18 days in the historical controls, and the prehospital group received fewer blood products than the historical controls ( $p = 0.0003$ ).

### Conclusions

Early IV administration of antibiotics in the field significantly improves outcome in EMS patients who meet sepsis criteria based on a modified qSOFA score.

### Keywords

sepsis/diagnosis; sepsis/therapy; Emergency Medical Services; prehospital; antibiotics; anti-biotic prophylaxis; retrospective studies; emergency treatment; time factors

## Introduction

Sepsis is a life-threatening condition that remains the leading cause of death in non-cardiac intensive care units.<sup>1</sup> Early prehospital recognition using sepsis identifying criteria and treatment of sepsis with intravenous broad-spectrum antibiotics and fluid resuscitation has been thought to decrease overall mortality in the septic patient.<sup>1,2</sup> Of note, prehospital

identification protocols have been shown to effectively improve clinical outcomes in this patient setting while improving workflow in Emergency Departments (ED).<sup>2</sup> The following article depicts the benefits of prehospital care more commonly addressed by EMS (Emergency Medical Service) protocols, activating a sepsis alert in a timely manner as a means to improve overall patient care delivery by reduc-

ing in-hospital mortality. Studies have additionally demonstrated that EMS providers can be successfully trained to obtain blood cultures with low contamination rates comparable to thresholds used in the inpatient setting.<sup>3</sup> Previously developed prehospital sepsis screening protocols have been limited by relatively low sensitivity and/or specificity.<sup>4</sup> A 2016 review of prehospital management of sepsis by EMS providers found a lack of studies in the literature exploring treatment and identification of sepsis using objective, high quality criteria.<sup>5</sup>

The revision of sepsis with the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) is arguably the most dramatic change in sepsis identification in the past 25 years. The publication of Sepsis-3 cited prior reliance on the systemic inflammatory response syndrome (SIRS) criteria as inadequate in guiding clinical management, which has sparked much debate.<sup>6,7</sup> Quick sequential (sepsis-related) organ function assessment (qSOFA) is another sepsis screening tool that evaluates for the presence of two or more of the following clinical criteria: altered mentation, respiratory rate  $\geq 22$  breaths per minute and systolic blood pressure (SBP)  $\leq 100$  mmHg. Proponents of qSOFA highlight that utilizing clinical criteria readily available at the bedside facilitates quicker identification of sepsis and should replace all previous screening protocols.<sup>7</sup> In the prehospital setting, qSOFA has the benefit of using information that is immediately available to providers. SIRS, as a previously utilized screening tool in EMS, is limited by its inclusion of laboratory data, such as white blood cell count and lactic acid levels, which are typically not available before hospital arrival. Therefore, qSOFA is a more feasible tool for EMS providers in the field to perform using their own clinical judgment.

There are multiple regulatory challenges in advancing prehospital care. Variation in local EMS protocols and guidelines is one of the most encountered barriers.<sup>8,9</sup> The purpose of this study is to evaluate the effect of early EMS/prehospital recognition and treatment of sepsis using modified qSOFA criteria on assessable items, such as hospital length of stay, ICU stay, mechanical ventilator days, vasopressor utilization, blood product administration and blood culture contamination. Obtaining

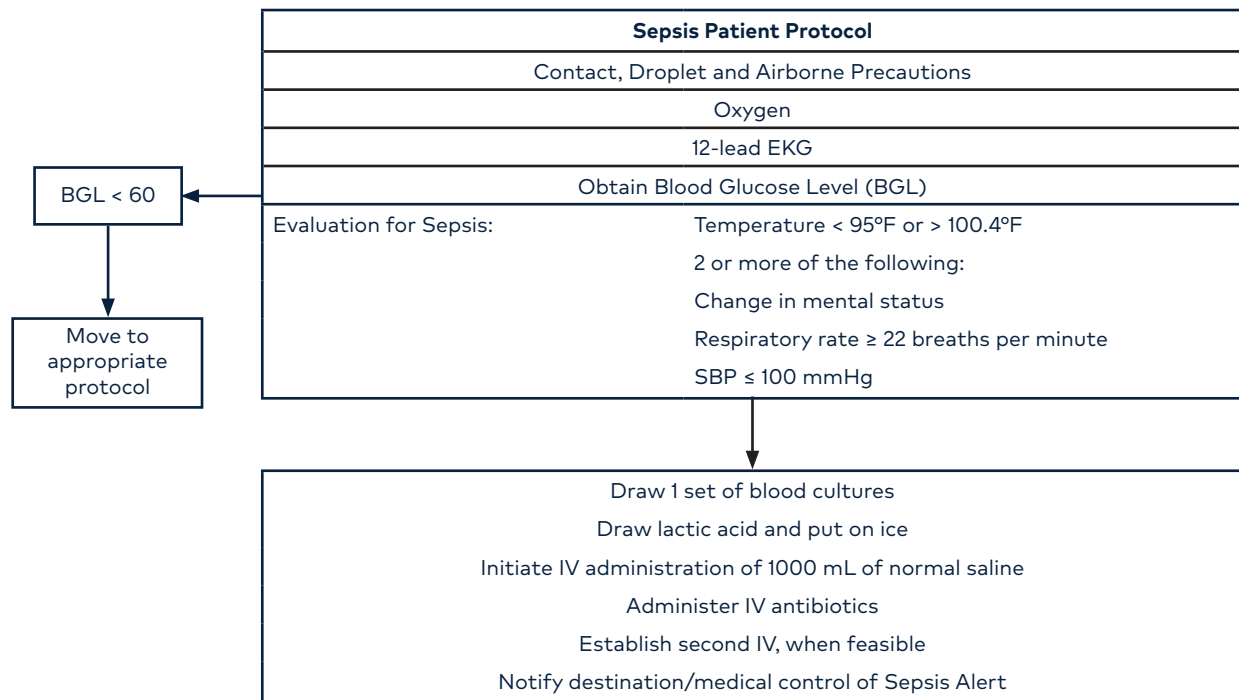
blood cultures at an established rate or low rate of contamination, beginning broad spectrum antibiotic therapy and initiating intravenous fluid treatment in the prehospital setting with high-quality objective screening criteria has the potential to decrease mortality.<sup>10</sup> Previous studies have shown delay in ED antibiotic administration is associated with a 3–7% increase in patient mortality for every 1 hour delay in treatment.<sup>10</sup> In this study, we hypothesized that prehospital antibiotics administered in patients meeting sepsis criteria based on a modified qSOFA score would improve morbidity and mortality in these patients.

## Methods

### Study Population and Setting

We conducted a retrospective study of patients transported to the ED at a busy academic medical center that sees approximately 100,000 patients per year. These patients met sepsis criteria based on a modified qSOFA score or in whom sepsis was clinically suspected prehospital. The modified qSOFA score included hypo- or hyperthermia (temperature  $< 95^{\circ}\text{F}$  or  $> 100.4^{\circ}\text{F}$ , respectively) in addition to at least two of the following: altered mentation, respiratory rate  $\geq 22$  breaths per minute and SBP  $\leq 100$  mmHg. Data were gathered from the electronic health record (EHR) of the participating hospital, as well as from the patient care reports of participating EMS agencies. Patients over the age of 18 years old were included if they were transported by EMS and if their modified qSOFA score was  $\geq 2$  with hypo- or hyperthermia. Patients over the age of 18 years old were excluded if they were not transported by EMS or if EMS providers did not suspect sepsis based on modified qSOFA screening. Additionally, any patient who was pregnant at the time of treatment was excluded from analysis, and patients with repeat enrollment only had their first occurrence included. EMS carried out these protocols between October 2015 and April 2018.

The participating regional medical center assisted local EMS agencies in implementing a sepsis protocol in two phases. Phase 1 included standing orders for the use of intravenous fluid (IVF) prehospital resuscitation with 1 liter of normal saline and took place from October 2015 to September 2016. Phase 2 included standing



**Figure 1.** Sepsis protocol for EMS administration of antibiotics. EKG = electrocardiogram; BGL = blood glucose level; SBP = systolic blood pressure; IV = intravenous; EMS = emergency medicine services

orders for the use of IVF resuscitation, as well as administration of broad spectrum intravenous antibiotics according to suspected source (ceftriaxone, cefepime or vancomycin). A blood draw was obtained for the collection of venous blood cultures and venous lactic acid to be analyzed in the lab of the participating medical center upon arrival to the ED (**Figure 1**). The venous lactic acid blood draw was placed on ice during transport. The first choice of antibiotic for acute mental status change or urinary tract infection was ceftriaxone 2 grams IV. The first-choice of antibiotic for pneumonia, abdominal pain, diarrhea or suspected blood stream or catheter related infection was cefepime 2 grams IV. The first-choice of antibiotic for skin, soft tissue or wound infection was vancomycin 1 gram IV. Phase 2 was implemented starting October 2016 and continued to April 2018. Sepsis patients transported by EMS during the Phase 1 period served as a control for the study.

### Data Collection

This study was approved by the Institutional Review Board (IRB) of Edward Via College of Osteopathic Medicine. Data were collected on each patient group using the hospital EHR

and EMS patient care reports. Parameters of interest were: length of hospital stay, length of intensive care unit (ICU) stay, mortality, number of days spent on a ventilator, number of blood products used, whether vasopressors were used, whether antibiotics were given pre-hospital, time from EMS arrival on scene to antibiotics, the type of antibiotic received, blood culture collection and results, blood culture contamination, venous lactate collection and results, Charlson Comorbidity Index, qSOFA score and discharge diagnosis. This study was approved by the affiliated Institutional Review Board.

### Data Analysis

Once all data were compiled, comparisons were made between the study cohort and control group regarding patient in-hospital mortality using a chi-square test with statistical significance set at  $p < 0.05$ . The hospital length of stay, ICU length of stay, number of ventilator days, number of blood products received, age (with age greater than 90 years old adjusted to 90 years for further de-identification) and Charlson Comorbidity Index were compared using T-tests for two samples assuming un-

equal variance with statistical significance set at  $p < 0.05$ . Chi-square tests were used to determine whether a difference existed in the use of vasopressors between the two groups, as well as to examine whether there was a difference in the use of mechanical ventilation between the groups. A Fisher's exact test was used to determine if a difference existed in rates of contamination of blood cultures between EMS providers and nursing staff of the ED of the participating hospital. Additionally, patients' final diagnoses (sepsis, severe sepsis, septic shock or other diagnosis), alongside their respective qSOFA scores for the study cohort, were observed to determine the rate at which sepsis was detected. It is noteworthy that the participating hospital used SIRS criteria for diagnosis of sepsis rather than the modified qSOFA screening performed by EMS. Therefore, the charts for patients whose final diagnoses did not include sepsis, severe sepsis or septic shock were reviewed to determine if they should have been assigned such a diagnosis based on these criteria. We conducted additional review of a subset of the data limiting inclusion to only subjects of the study cohort with qSOFA  $\geq 2$ .

## Results

### Protocol Compliance

There were 345 total participants, with 47 included in the study cohort and 298 in the historical control. Of the 47 patient encounters included in the study cohort, 43 (91%) received prehospital IV antibiotics. Of those 47 patients, 51% received ceftriaxone, 32% received cefepime and 9% received vancomycin. The remaining 9% did not receive prehospital antibiotics. Average time to antibiotics for the study cohort (regardless of whether antibiotics were received prehospital) was 31.4 minutes (standard deviation = 19.51). The median qSOFA score for those patients receiving antibiotic therapy prehospital was 2, and the median qSOFA score for those 4 patients not receiving

antibiotic therapy prehospital was also 2.

Ninety-three percent of patients receiving prehospital antibiotics also received IVF resuscitation with normal saline. Ninety percent of patients receiving both IV antibiotics and IVF prehospital also had blood cultures and a lactic acid sample drawn by EMS. Of the 4 patients who did not receive prehospital antibiotics, 75% received IVF. None of these 4 patients had blood cultures or lactic acid samples drawn. There were three documented cases of unsuccessful attempts at IV access, which precluded EMS from administering IVF, antibiotics and from obtaining blood samples. There was a single instance of intraosseous (IO) catheterization rather than IV catheterization, and the IO access was not used for lab draws.

### Demographics

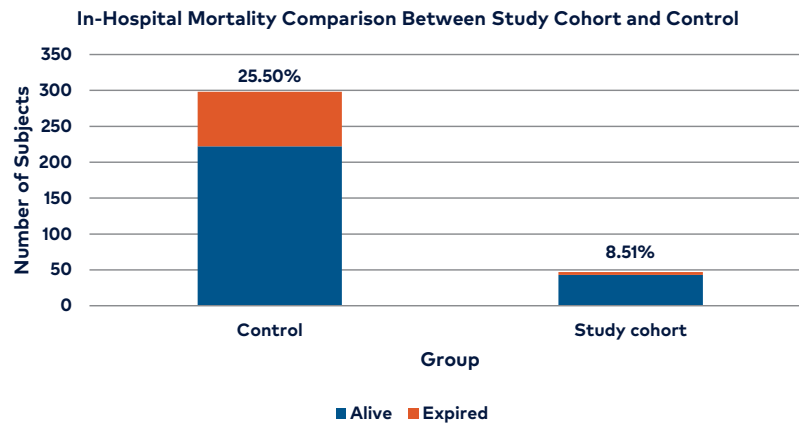
The median age for the control group was 68 years, and there were 158 males and 140 females. The cohort group from the Phase 2 period October 2016 to April 2018 consisted of 25 males and 22 females with a median age of 77.5 years. The patients in the cohort group were transported by a single EMS agency, and the patients in the control group were transported by multiple EMS agencies (**Table 1**). A T-test showed a statistically significant difference in the ages ( $p = 0.04$ ) between the groups with a higher average for the patients in the study cohort versus the control. A comparison of the average Charlson Comorbidity Index, which predicts 10-year survival by taking into account patient comorbidities, was performed between the two groups. This demonstrated 4.64 (95% CI, 3.96–5.32) for the study cohort and 4.24 (95% CI, 3.95–4.50) for the control, revealing no statistically significant difference by T-test analysis ( $p$  two-tail = 0.26).

### Mortality

A difference was found between the two groups' in-hospital mortality rates. Four pa-

**Table 1.** Patient Demographics by Group Including Age, Sex and Charlson Comorbidity Index

	Study cohort (n=47)	Historical control (n=298)
Age (years), median	77.5	68
Males (%)	25 (53.2%)	158 (53%)
Charlson Comorbidity Index	4.64 (95% CI, 3.96–5.32)	4.24 (95% CI, 3.95–4.50)



**Figure 2.** Comparison of in-hospital mortality between the study cohort (n=47) and historical controls (n=298). We found a reduction in mortality among the study cohort (n=4) compared to the historical control (n=76), ( $\chi^2 = 6.582$ ;  $p = 0.01$ ).

tients (8.5%) from the study cohort expired, while 76 (25.5%) patients from the control group expired. This lower mortality in the study cohort was statistically significant ( $\chi^2 = 6.582$ ;  $p = .01$ ) and represented an approximately 66% decrease in in-hospital mortality between the groups (**Figure 2**).

### Hospital Length of Stay

The study cohort had a mean hospital length of stay of 11.85 days (95% CI, 6.47–17.23), and the control group had a mean hospital length of stay of 10.62 days (95% CI, 9.12– 2.12). The two-sample T-test showed there was no significant difference between these two groups' lengths of hospital stay ( $p$  two-tail = 0.66).

### ICU Length of Stay

Patients in the study cohort stayed an average of 2.51 days (95% CI, 0.28–4.74) in the ICU; patients from the control group spent an average of 5.18 days (95% CI, 4.31–6.06) in ICU care. The two-sample T-test showed a statistically significant difference in these two means ( $p$  two-tail = 0.03).

### Ventilator Days

Patients of the study cohort averaged 1.91 days (95% CI, -0.22 – 4.04) on a mechanical ventilator, and patients of the control group spent an average of 2.48 days (95% CI, 1.74–3.22) on a mechanical ventilator. The two-sample T-test showed no statistically significant difference between these two means between the groups ( $p = 0.62$ ). The chi-square test to determine whether a difference existed in the use of

mechanical ventilation between the two groups revealed no significant difference ( $\chi^2 = 2.0369$ ;  $p = 0.15$ ).

### Blood Products

In the study cohort, patients received an average of 0.28 blood products (95% CI, 0.02–0.54) while in the hospital; whereas patients from the control group received an average of 1.10 blood products (95% CI, 0.74–1.46) during their stay. A two-sample T-test showed that there was a statistically significant difference between the mean number of blood products received between the groups ( $p$  two-tail < 0.001).

### Blood Culture Contamination

In the study cohort, EMS providers collected a total of 41 blood cultures with 1 blood culture per patient. Of these, 30 were negative (no growth), and 11 were positive (growth detected after 3 days). Of the 11 positive blood cultures, four were flagged in the EHR as possible instances of contamination. This constitutes a contamination rate of 9.8% of total blood cultures drawn by EMS. Nursing staff in the ED collected a total of 53 blood cultures, including 45 negative cultures and 8 positive cultures. Of these 8 positive cultures, only one was identified as a possible instance of contamination. This resulted in a contamination rate of 1.9% of total blood cultures drawn from these patients. A Fisher's exact test revealed that the difference in rates of contamination between these two groups was not statistically significant (Fisher's exact  $p = 0.16$ ). The sepsis coordinator for the participating hospital—with infectious

disease input—reviewed cases in which the lab technicians recognized blood cultures as possible or probable contaminants and believed none of these were instances of true contamination.

### Vasopressors

The chi-square test to determine whether a difference existed between the two groups regarding the prevalence of vasopressor use in patient resuscitation showed no statistically significant difference ( $\chi^2 = 2.961$ ;  $p = 0.09$ ).

### Modified qSOFA Prediction of Sepsis

In all, 40 patients of 47 from the study cohort had a final diagnosis of sepsis, severe sepsis or septic shock. Of these patients, 35 (89%) were assigned a qSOFA score  $\geq 2$  and were hypo- or hyperthermic. Additionally, 6 patients were assigned a qSOFA score  $\geq 2$  and were hypo- or hyperthermic but did not have a final diagnosis of sepsis, severe sepsis or septic shock.

### Subset Analysis for qSOFA $\geq 2$

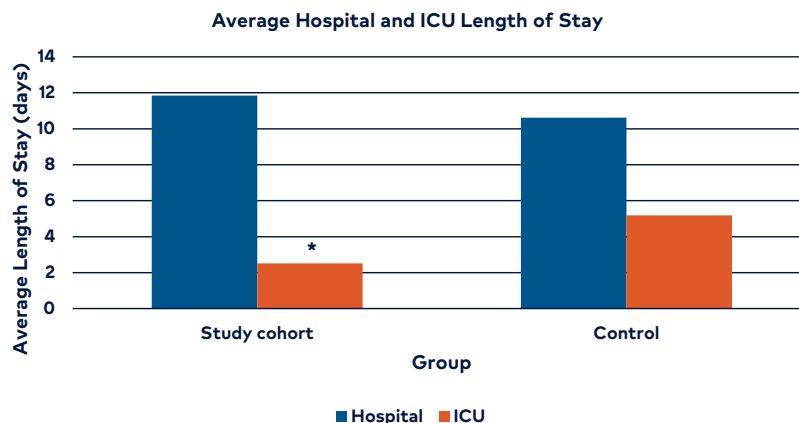
The subset of study cohort patients with qSOFA  $\geq 2$  comprised 41 patients, of whom 35 were assigned a diagnosis of sepsis. Four patients (10%) in this subset expired. Chi-square analysis revealed that this mortality rate was significantly lower than mortality in the control group ( $\chi^2 = 6.0346$ ,  $p = 0.01$ ). Within this subset of the study cohort, average hospital length of stay was 12.85 days (95% CI, 6.74–18.96) compared to 10.62 days (95% CI, 9.12–12.12,  $p$  two tail = 0.48). Mean ICU length of stay for the study cohort of 2.51 days (95% CI, 0–5.02) was shorter than the control group mean of 5.18 days (95% CI, 4.31–6.06,  $p$  two tail = 0.048). The study cohort subset averaged 1.98 ventilator days (95% CI, -0.44–4.39), which was not statistically different from the control average of 2.48 days (95% CI, 1.74–3.22,  $p$  two tail = 0.69). There was no difference in use of mechanical ventilation between the groups on chi-square analysis ( $\chi^2 = 1.4778$ ;  $p = 0.22$ ). The patients of this subset required an average of 0.32 blood products (95% CI, 0.02–0.61), which was statistically fewer than the control requirement of 1.10 blood products (95% CI, 0.74–1.46,  $p$  two tail < 0.001). There was no statistically significant difference in vasopressor use between this subset of the study cohort and the control when analyzed by chi-square test ( $\chi^2 =$

2.3447;  $p = 0.13$ ). Additionally, the average patient age for the study cohort subset was 73.63 years (95% CI, 68.71–78.56), which was statistically greater than the cohort average age of 67.71 years (95% CI, 66.05–69.29,  $p$  two tail = 0.02). The average Charlson Comorbidity Index for the subset was 4.61 (95% CI, 3.88–5.34), and it was not statistically different from the control average of 4.22 (95% CI, 3.95–4.50,  $p$  two tail = 0.33).

### Discussion

The present study demonstrates that when EMS providers initiate sepsis alert protocols including IVF, IV antibiotics and blood collection for patients with suspected sepsis it significantly reduces mortality when compared to suspected sepsis patients transported under protocols allowing for IVF resuscitation only. Previous studies have highlighted the importance of not delaying goal-directed therapy in sepsis patients.<sup>1,2</sup> Though other research studies have addressed the subject of prehospital identification of sepsis and/or prehospital treatment through IVF resuscitation,<sup>3,4,5</sup> we believe that this is the first study to explore the impact of prehospital sepsis protocols that include IVF, IV antibiotics and blood collection on in-hospital mortality for sepsis patients identified using the modified qSOFA screening criteria by EMS personnel.

A study of all non-trauma, non-arrest EMS encounters from 2000 to 2009 transported to a hospital by King County EMS (King County, Washington) showed that 3.3 per 100 EMS encounters were patients with severe sepsis, which represent a higher rate of EMS encounters for acute myocardial infarction or stroke.<sup>11</sup> Other studies suggest that over half of sepsis patients seen in the ED utilize EMS for transport.<sup>12,13</sup> Early recognition and treatment of sepsis in the prehospital scene may produce a positive impact in the care and outcome of these patients. Guerra et al. conducted a study on the implementation of a sepsis alert protocol for EMS providers where the receiving hospital was notified of incoming severe sepsis patients. It was found that these trained EMS providers identified fewer than half (47.8%) of severe sepsis patients they transported, and the mortality of the group in whom severe sepsis was recognized was much lower than those



**Figure 3.** Average hospital and ICU length of stay for study cohort versus historical controls. The study group had a significantly shorter ICU length of stay (2.51 days [95% CI, 0.28 – 4.74] vs 5.18 days [95% CI, 4.31 – 6.06]), two-sample t-test  $p = 0.03^*$ .

in whom sepsis was not recognized.<sup>14</sup> A prospective study of EMS sepsis patients revealed that treatment by EMS with IVF resuscitation was associated with reduced hospital mortality when compared to prehospital treatment with intravenous catheter alone.<sup>15</sup> Furthermore, recognition of sepsis in the prehospital setting has been associated with reduced time to antibiotics administered in the ED for severe sepsis patients,<sup>16,17,18</sup> while delays in antibiotic administration have been associated with increased in-hospital mortality.<sup>19</sup>

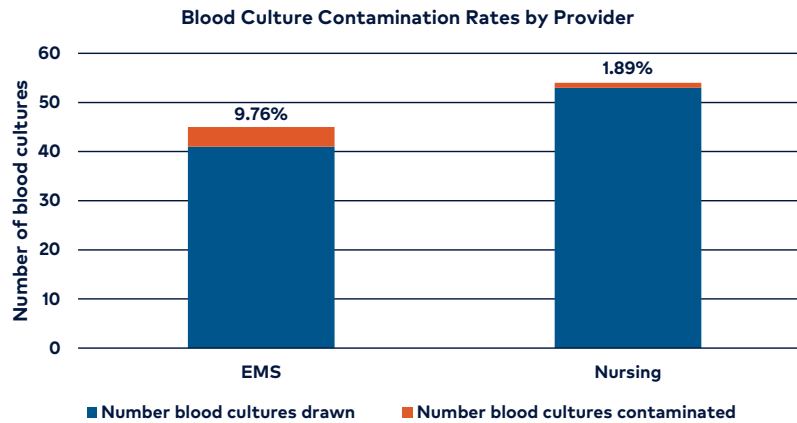
There is a paucity of literature relating prehospital treatment of sepsis and length of hospital or ICU stay. Though Femling et al. reported a shorter time to antibiotic therapy and central line placement for severe sepsis patients, they found no improvement in hospital length of stay. However, they did show that severe sepsis patients receiving high-volume IVF resuscitation experienced shorter hospital stays than those who did not.<sup>17</sup> In one of the few published reports to examine the use of prehospital IV antibiotic therapy for septic shock, Chamberlain demonstrated a reduction in mean ICU length of stay for septic shock patients receiving prehospital antibiotics versus those who received their first antibiotics in the ED.<sup>20</sup> Our results further demonstrate that patients transported by EMS under protocols allowing prehospital IV antibiotic therapy do not experience shorter overall hospital lengths of stay. Yet they do experience shorter ICU lengths of stay compared to patients transported by EMS prior to the establishment of prehospital antibiotic protocols for sepsis (**Figure 3**).

Though the Fisher's exact test comparing nursing and EMS rates of blood culture contamination did not achieve statistical significance (**Figure 4**), the observed rate of nearly 10% contamination by EMS providers is higher than previously reported in the literature.<sup>3</sup> The potential for contamination in the prehospital environment may be higher than in the hospital. This result represents an opportunity for better training in aseptic phlebotomy technique for those EMS providers who will be drawing blood cultures in the field.

When subset analysis was conducted for study cohort subjects with  $qSOFA \geq 2$  only, all results mirrored those of the study cohort (including patients with  $qSOFA < 2$ ). We still observed lower morbidity, mortality, reduced use of blood products and decreased length of ICU stay for these patients versus the historical control. There were no differences between this subset of the study cohort and the control with regards to overall hospital length of stay, average ventilator days or use of vasopressors.

### Limitations

In addition to the limitations inherent to a retrospective study, the primary limitations for this study lie in population selection. Some patients were included with  $qSOFA < 2$  into the study cohort after thorough chart review of the admitting and discharge diagnoses, as well as the clinical course by the hospital sepsis coordinator. The study cohort was a relatively small sample of 47 patients transported by a single EMS agency. A larger sample of patients may



**Figure 4.** Blood culture contamination rates by emergency medical services (EMS) and nursing providers for the study cohort. The number of contaminated blood cultures was derived by hospital lab technicians' charting of possible contamination. There was no statistical difference between the rates of contamination (Fisher's exact test,  $p = 0.16$ ).

have resulted in a higher level of precision for the measured parameters; however, the data obtained in this initial study remains promising. The number of negative blood cultures obtained reflect the difficulty in diagnosing early sepsis, even with established parameters, such as qSOFA criteria. Obtaining blood cultures in the prehospital setting is worthwhile, as it may direct antibiotic selection in admitted patients, in addition to complying with the Surviving Sepsis Guidelines. Initial antibiotic selection in the prehospital setting was driven by suspected source using local EMS protocol. Upon hospital arrival further antibiotic selection was completed by the admitting physician. Meanwhile, the control group included 298 patients transported by multiple EMS agencies under a protocol allowing for IVF resuscitation for suspected sepsis but not IV antibiotics. There could be a difference in population demographics that confound the results, given the wider inclusion of patients for the Phase 1 group. T-test analysis of the ages for the study cohort and the control group showed a statistically significant difference with a higher average age for the study cohort. T-test of the Charlson Comorbidity Index for both groups revealed no significant difference. If the observed differences in mortality and ICU length of stay are not due to the implementation of protocols for prehospital antibiotic administration, then it may be the case that EMS providers have become more adept at recognizing sepsis in the prehospital setting. Additionally use of the Charlson Comorbidity Index to determine illness severity might contribute to selection

bias, although there is no statistical difference between the groups. Average time to antibiotics was not analyzed in the control group due to limitations of data de-identification. Future studies may benefit from these additional points of comparison. Finally, over the past several years we have as a healthcare system put more emphasis on sepsis bundle compliance. Our study may have benefited from the overall improvements in hospital care that have taken place during this time.

## Conclusion

The present study is the first to find an association between prehospital antibiotics and in-hospital morbidity and mortality for sepsis patients identified by using the modified qSOFA. In this study, we demonstrated that prehospital administration of IV antibiotics by EMS personnel for patients suspected of having sepsis improved ICU length of stay and lowered mortality in comparison to historical controls. The same results were found when only patients with qSOFA  $\geq 2$  were taken into account. These results suggest that patients with suspected sepsis should be treated with IV antibiotics in the prehospital setting.

## Conflicts of Interest

The authors declare they have no conflicts of interest.

Drs. Martel, Melmer, Kozlowski, Pangia, Gutovitz and Jehle are and Ms. Kassen are employees of Grand Strand Medical Center, a hospital



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