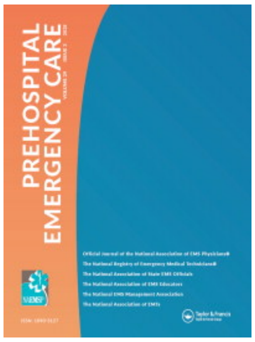

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Prehospital Sepsis Recognition and Antibiotic Administration: A Retrospective Analysis

Peter Antevy[a], Kenneth A. Scheppke[a], Charles Coyle[a], Sophie Tenenbaum[a,b], Grant Aran[a], Julia Leser[a], Nancy Burdett[a], David A. Farcy[a,c] and Tony Zitek[a,d]

[a]Palm Beach County Fire Rescue, West Palm Beach, Florida; [b]School of Medicine and Health Sciences, George Washington University, Washington, District of Columbia; [c]Department of Emergency Medicine, Mount Sinai Medical Center, Miami Beach, Florida; [d]Department of Emergency Medicine, Kaiser Permanente Modesto Medical Center, Modesto, California

ABSTRACT

Objectives: Although earlier antibiotics are known to be beneficial in sepsis, very few emergency medical services (EMS) agencies have protocols for prehospital antibiotics for sepsis. Therefore, we sought to assess how well a large EMS agency that uses prehospital antibiotics for sepsis adheres to its sepsis protocol (when initiated), and to determine how soon antibiotics are typically given.

Methods: We conducted a retrospective chart review of patients identified as "sepsis alerts" by EMS clinicians from a single EMS system in Florida, USA. The prehospital sepsis protocol dictated that EMS clinicians initiate a "sepsis alert" if the patient had a suspected infection and at least 2 of the following 3 criteria based on the sequential (sepsis-related) organ failure assessment (qSOFA) score: altered mental status, respiratory rate > 22 breaths per minute or end-tidal $CO_2 < 25$ mmHg, or systolic blood pressure < 100 mmHg. Per protocol, patients meeting sepsis criteria were supposed to receive intravenous ceftriaxone and intramuscular gentamicin. We reviewed the charts of sepsis alert patients to determine demographic information, clinical characteristics, sepsis protocol compliance, and when patients received antibiotics.

Results: Between June 1, 2023, and June 30, 2024, there were 1308 patients for whom a prehospital sepsis alert was initiated. Median age was 80.0 years (IQR: 72–87.5), and 48.5% had hypotension (systolic blood pressure < 100 mmHg). Of the 1308 sepsis alert patients, review of documentation confirmed that 1301 (99.5%) had a suspected infection with at least 2 sepsis alert criteria. In total, 1264 (96.6%) received at least 1 antibiotic (either ceftriaxone or gentamicin) prior to hospital arrival. The median time from 9-1-1 call to first antibiotic administration was 26 min (IQR: 21–31 min). The first antibiotic was given a median of 11 min (IQR: 7–16 min) prior to hospital arrival.

Conclusions: For patients in whom a sepsis alert was initiated, EMS clinicians adhered to the sepsis protocol and administered antibiotics prior to hospital arrival in 97% of cases. Patients received their first antibiotic a median of approximately 26 min after 9-1-1 call and 11 min prior to hospital arrival.

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Introduction

Sepsis continues to be a leading cause of morbidity and mortality despite extensive efforts to enhance its management (1,2). Notably, previous research indicates that patients with severe sepsis transported by emergency medical services (EMS) agencies have a hospital mortality rate of approximately 20% (3). The critical role of early antibiotic administration for patients with sepsis is well established, as numerous observational studies have demonstrated a clear association between delayed antibiotics and increased mortality (4–8). With that being said, few EMS agencies use antibiotics for patients with suspected sepsis (9).

For years, some experts have advocated for initiating sepsis treatment in the prehospital setting (3), and some prior studies have found that EMS clinicians can effectively identify septic patients (10–12), which can reduce the time to antibiotic administration upon hospital arrival. However, the benefits of prehospital sepsis alerts have been reported as modest in some studies (11,13,14). While 2 small observational studies have suggested a benefit of prehospital antibiotics for sepsis (15,16), a large, randomized trial conducted in the Netherlands found no significant reduction in 28-day mortality from prehospital antibiotics (17). However, only 3.9% of the patients in that trial had septic shock (17), which may have resulted in a cohort of patients not sick enough to demonstrate a benefit of earlier antibiotics. Given the previously published data suggesting a benefit for earlier antibiotics for septic patients (4–8), we suspect that prehospital antibiotics can improve outcomes if given to the right group of patients.

One large EMS system in Florida, United States (U.S.) began to administer prehospital antibiotics for patients with suspected sepsis in 2019. Using data from this system, we

CONTACT Tony Zitek zitek10@gmail.com

performed a retrospective study to determine the percentage of "sepsis alert" patients who met the protocolized criteria for sepsis. We also sought to determine the time from 9-1-1 call to first antibiotic administration and how soon before hospital arrival patients received antibiotics.

Methods

Study Design and Setting

We performed a cross-sectional analysis using retrospective chart review of prehospital "sepsis alert" patients treated by a single fire-based EMS system located in Palm Beach County, Florida, U.S. This EMS system employs approximately 1500 paramedics, operates 55 rescue trucks (ambulances), and uses 2 helicopters. Their legal jurisdiction is 976,900 residents. Additionally, they have mutual and automatic aide agreements with surrounding departments for which their protocols are used. On average, their system transports 229 patients by ground per day and responds to approximately 400 emergency scene aeromedical transports per year.

In crafting this manuscript, we followed the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines. The study was approved by the Pearl Institutional Review Board (IRB ID 2024-0248), which waived the need for informed consent, given the nature of the study. There was no funding for this study.

The Sepsis Protocol

In 2019, the EMS system initiated a protocol to administer antibiotics in the prehospital setting to patients with suspected sepsis. All nonpregnant adult patients with a suspected infection who had at least 2 of the following 3 criteria were classified as a sepsis alert: hypotension (systolic blood pressure (SBP) < 100 mmHg), altered mental status, and tachypnea (respiratory rate > 22 or end-tidal carbon dioxide ($EtCO_2$) < 25 mmHg). These criteria are based on the quick sequential [sepsis-related] organ failure assessment (qSOFA) score (18), which has been shown to have good predictive ability for sepsis in the prehospital setting (19). The sepsis alert criteria used differ from the qSOFA criteria only in that $EtCO_2$ is not considered in the qSOFA score. The EMS medical directors added $EtCO_2$ to the sepsis alert criteria because prior work demonstrated the association of low prehospital $EtCO_2$ with sepsis (20) and because low $EtCO_2$ may be a better predictor of mortality than qSOFA (21). The EMS clinicians are taught to use the "HAT" mnemonic (*H*ypotension, *A*ltered mental status, *T*achypnea) as a tool to remember the criteria for initiating a sepsis alert.

Per protocol, once a patient was deemed to be a "sepsis alert," they were to receive 2 L of intravenous (IV) normal saline (if time permitted prior to hospital arrival) as well as ceftriaxone 2 g IV and gentamicin 80 mg intramuscular (IM). These specific antibiotics were chosen after discussion with an infectious disease physician who preferred ceftriaxone and gentamicin for their broad spectrum, low cost, and easy storage (no refrigeration required).

For patients with persistent hypotension, the sepsis protocol directed EMS clinicians to administer push-dose epinephrine to maintain an SBP ≥ 100 mmHg. Initially, septic pediatric patients were not given prehospital antibiotics, but in 2023, the protocol was amended to include pediatric patients who met protocol Handtevy criteria for age-adjusted hypotension and tachypnea (22). Antibiotic dosing for pediatric patients was 50 mg/kg of IV ceftriaxone and 2.5 mg/kg of IM gentamicin.

Training

Shortly before the sepsis protocol went into effect, all EMS clinicians watched a video presentation by 2 physicians – 1 of the medical directors and an infectious disease physician. This presentation explained the protocol and the rationale for it. Additionally, EMS captains attended an in-person training session focused on identifying sepsis alerts and administering antibiotics correctly. The EMS captains were expected to help educate their teams, which they did, in part, by reviewing every sepsis alert case and providing feedback to the clinicians involved in the case.

Selection of Patients

All patients who were transported from June 1, 2023, until June 30, 2024 as "sepsis alerts" were eligible for inclusion. June 2023 was used as the start date because the electronic medical record system was switched in 2023, making the search for earlier records substantially more difficult. Additionally, preliminary analysis indicated that over 1300 sepsis alert patients were transported between those dates, which (by gestalt) was deemed adequate for the study goals.

Patients with missing data points were excluded from the analyses in which those data points were required. Otherwise, all patients were included for analysis.

Measurements

An investigator with experience in information technology searched the EMS system's medical records (MetroPCR) for "sepsis alert" patients. For each patient, the following variables were automatically abstracted (without manual chart review): date of service, patient age, sex, race/ethnicity, time of 9-1-1 call, time at scene, time at patient, depart scene time, transport complete time, ceftriaxone administration time, gentamicin administration time, amount of IV crystalloid administered, initial blood glucose level, initial heart rate, initial SBP, highest respiratory rate, temperature, and lowest $EtCO_2$. A sample of charts were manually reviewed to confirm accuracy of the data that we obtained through automated abstraction. Additionally, 1 medical student and 2 premedical student research assistants performed manual chart review using a standardized spreadsheet to abstract the following data: reason why antibiotics were not administered (if not administered), whether or not the patient had altered mental status, and whether or not sepsis alert criteria were met.

The 3 abstractors were trained on chart review by 1 of the investigators (PA). Periodic meetings were held to address uncertainties. The abstractors were aware that the study related to prehospital sepsis treatment, but they were unaware of the specific study hypotheses. At the conclusion of the study, data were audited by a different investigator (TZ), and outlier data points were referred back to the study abstractors to confirm accuracy. We did not assess interrater reliability as data points were mostly from automated abstraction and they were generally quite objective. However, we otherwise followed the chart review methods recommended by Gilbert et al. (23).

Outcomes

The primary outcome was the presence of a documented suspected infection with 2 or more sepsis alert criteria. Secondary outcomes included whether or not patients received the protocolized antibiotics, the time from 9-1-1 call to first antibiotic administration, and the time from first antibiotic administration to hospital arrival.

Statistical Analysis

We calculated descriptive statistics for baseline characteristics and for outcomes. For continuous variables, we report the mean (standard deviation (*SD*)) for normal data and the median (interquartile range (IQR)) for non-normal data. We used the Shapiro-Wilk test to assess normality. For categorical variables, we determined the frequencies and percentages. Data were aggregated in Excel version 16.95 (Microsoft, Redmond, Washington) and analyzed in R Studio version 2023.09.0.

In a small number of cases, the documented time of antibiotic administration was after hospital arrival. Since EMS clinicians in this system do not administer medications after hospital arrival, we suspect that the documentation reflected a delayed entry rather than actual time of administration. Since the exact time of antibiotic administration for these cases could not be confirmed, these cases were excluded from the analysis evaluating antibiotic administration times.

Results

Baseline Characteristics

Between June 6, 2023, and June 30, 2024, we identified 1308 consecutive patients for whom a prehospital sepsis alert was initiated. Baseline characteristics are shown in Table 1. Patients ranged in age from 11 to 104 years with median age of 80.0 years (IQR: 72–87.5). Three patients (0.2%) were pediatric (< 18 years old). Patients were 55.0% male and 76.2% non-Hispanic white.

Hypotension (SBP < 100 mmHg) was present in 48.5% of patients, and 12.2% received a push dose vasopressor in the prehospital setting. Mean highest respiratory rate was 32.5 breaths per minute (*SD* 10.4); 85.2% of patients had RR > 22 and 62.4% had an $EtCO_2 < 25$ mmHg.

Table 1. Baseline characteristics of the 1308 prehospital sepsis alert patients.

Characteristic	Value
Median age (IQR), years[a]	80.0 (72–87.5)
Male, *n* (%)	720 (55.0%)
Race, *n* (%)	
Non-Hispanic White	997 (76.2%)
Non-Hispanic Black	150 (11.5%)
Hispanic	114 (8.7%)
Other	47 (3.6%)
Mean initial HR (SD), beats/minute	98.6 (25.5).
Median initial SBP (IQR), mmHg[b]	108 (90–140)
Median initial shock index	0.87 (0.67–1.11)
Mean highest RR (SD), breaths/minute[c]	32.5 (10.4)
Temperature ≥ 100.4 °F, *n* (%)[d]	432 (39.6%)
Temperature < 96.8 °F, *n* (%)[d]	29 (2.6%)
Mean lowest $EtCO_2$ (SD), mmHg[e]	22.2 (9.2)
Median blood glucose (IQR), mg/dL[f]	151 (125–201)

[a]One patient (critically ill) had no age documented.
[b]Systolic blood pressure (SBP) was not recorded for two patients.
[c]Respiratory rate (RR) was not recorded for two patients.
[d]Temperature was not recorded for 218 patients.
[e]End-tidal carbon dioxide ($EtCO_2$) was not recorded for 19 patients.
[f]Blood glucose was not measured 50 patients.

There were 218 patients who did not have a temperature recorded. Of the remaining 1092 patients, 432 (39.6%) had a fever (temperature ≥ 100.4 °F) and 29 (2.6%) had hypothermia (temperature < 96.8 °F).

Patients were transported to 15 different hospitals. Median time from arrival at the scene to arrival at the hospital was 31 min and 10 s (IQR: 26 min and 41 s to 36 min and 37 s).

Missing data are specified above and at the bottom of Table 1. Otherwise, no data points were missing.

Main Results

Regarding the primary outcome, since all included patients were sepsis alerts, all patients should have had a suspected infection plus at least 2 of the 3 sepsis alert criteria. In fact, 1301 (99.5%) of 1308 included patients had a suspected infection with at least 2 sepsis alert criteria. In the remaining 7 patients only 1 of the sepsis alert criteria was noted on review of documentation.

Of the 1308 sepsis alert patients, 1264 (96.6%) received at least 1 antibiotic (either ceftriaxone or gentamicin) prior to hospital arrival (Figure 1). Specifically, 1188 (90.8%) received IV ceftriaxone, 1223 (93.5%) received IM gentamicin, and 1147 (87.7%) received both.

Among the 76 cases in which the patient failed to receive ceftriaxone but received gentamicin, there were 26 cases (34.2%) in which documentation indicated that ceftriaxone was not given because IV access could not be established. In 1 case (1.3%), documentation indicated ceftriaxone was not given because of a cephalosporin allergy.

Of the 41 cases in which the patient received ceftriaxone but not gentamicin, there were 2 cases (4.9%) in which documentation indicated concern for a gentamicin allergy.

In the 44 cases in which the patient did not receive any prehospital antibiotics, there were 4 cases (9.1%) in which the reason documented for not administering antibiotics was insufficient time before hospital arrival. There were 3 cases (6.8%) in which the patient refused antibiotics; and there

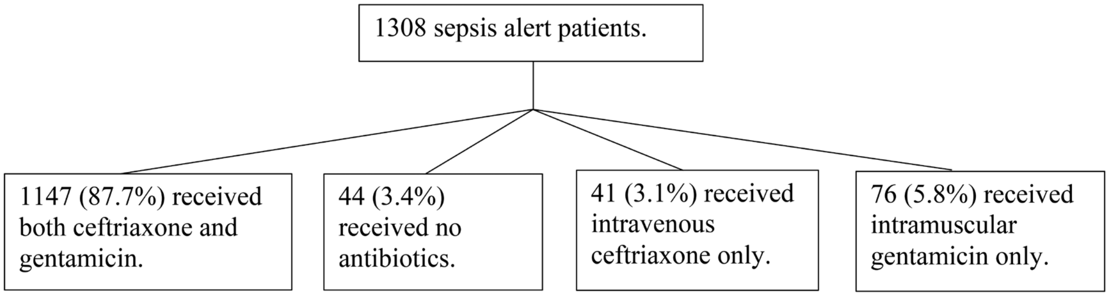

Figure 1. Flow of patients documented as being prehospital sepsis alerts.

were 4 cases (9.1%) in which it was documented that patient was already taking antibiotics. There were 2 cases (4.5%) in which the patient was documented as being allergic to both antibiotics. There was 1 case (2.3%) in which the receiving emergency department requested by radio that the patient not receive antibiotics so that blood cultures could be done first.

Except as stated above, documentation did not specify why antibiotics were not given. However, there was a gentamicin shortage in June and July of 2023, and nine cases in which the patient did not receive antibiotics occurred during these two months.

As per protocol, patients were administered IV crystalloids. The median volume of IV normal saline administered prior to hospital arrival was 700 mL (IQR: 300–1000).

There were 26 patients for whom the antibiotics were documented as being given after hospital arrival (which does not happen and was therefore suspected to indicate erroneous documentation). Excluding these patients, the first antibiotic was given a median of 11 min and 22 s (IQR: 7 min and 14 s to 15 min and 40 s) prior to hospital arrival. The median time from 9-1-1 call to first antibiotic administration was 26 min and 0 s (IQR: 21 min and 24 s to 31 min and 12 s).

Discussion

In this cross-sectional analysis of prehospital patients treated in a single EMS system in Florida, nearly all patients classified as sepsis alerts met the criteria for this designation and the first antibiotic was administered a median of 26 min after the 9-1-1 call and 11 min prior to hospital arrival. To date, this is the largest study conducted in the U.S. about the use of prehospital antibiotics for sepsis. In comparison, the only prior U.S.-based study included just 47 patients who received prehospital antibiotics (15). Additionally, a study from France reported on 98 patients with septic shock were treated with antibiotics in the prehospital setting and found an association between prehospital antibiotics administration and reduced mortality. However, in that study, antibiotic administration was based on physician discretion rather than a standardized protocol (24). Overall, these findings underscore the potential impact of protocolized prehospital antibiotic administration on sepsis outcomes and highlight the need for further research in this area.

Although some prior studies suggest that EMS recognition of sepsis is poor or inconsistent (25–27), our study seems to indicate otherwise. In particular, our data suggest that when patients were determined to be sepsis alerts, they almost always met criteria for that designation. However, given the nature of the study design, it is not clear how often EMS clinicians failed to initiate a sepsis alert on patients who met prehospital criteria for sepsis or who did not meet prehospital criteria but were ultimately diagnosed with sepsis in the hospital. Nonetheless, our data suggest that when patients received antibiotics, there was an indication for them. This should help alleviate fears that prehospital antibiotic protocols result in unnecessary antibiotic administration, although there are some caveats to that. Namely, our study did not assess the percentage of sepsis alert patients who were ultimately diagnosed with sepsis in the hospital, so some patients may have received antibiotics for a sepsis mimic. That being said, previous research demonstrates the positive predictive value of qSOFA scores ≥ 2 for sepsis-related mortality to be high (18,28–30). Moreover, the administration of antibiotics to patients who are ultimately deemed to not be septic occurs with some regularity even in ED-based sepsis treatment (31) and may, to some extent, be an unavoidable consequence of pursuing earlier antibiotic administration.

Compared to the trial conducted by Alam et al. (17), the patients in our study were both older and sicker. In the Alam study, the median age was 73 years, and less than 1/4 of the patients had a qSOFA score < 2. In contrast, in our study, the median age was 80 years and 99.5% had a qSOFA score ≥ 2. The higher severity of illness and increased mortality risk in our cohort should shift the risk-benefit ratio of earlier antibiotics more toward benefit.

Additionally, when considering the risk-benefit ratio of a prehospital sepsis protocol that includes antibiotic administration, it is crucial to consider how much sooner antibiotics are administered if given in the prehospital setting compared to waiting until after hospital arrival. Although the administration of the first antibiotic occurred a median of just 11 min prior to hospital arrival in our study, prior data have shown that even hospitals with very aggressive ED sepsis protocols take a median of approximately 30 min to administer antibiotics to septic patients and fail to administer antibiotics within the first hour after arrival 18.5% of the time (31). Meanwhile, an older study by Seymour et al., found the median time from hospital arrival to antibiotic administration in 9 Pennsylvania hospitals was 3.6 h (32). These findings indicate that prehospital administration likely results in a much greater reduction in time to antibiotics than the

11 min observed in our study, and even greater reductions would be expected in EMS systems with longer transport times.

One concern often raised regarding the sepsis protocol evaluated in this study is the lack of blood culture collection prior to antibiotic administration, which may appear to violate standard sepsis management guidelines (33). Previous research has demonstrated that blood cultures lose sensitivity when obtained after antibiotic administration (34). However, there is no evidence that delaying antibiotics to obtain blood cultures in critically ill patients with sepsis improves outcomes. Moreover, surviving sepsis campaign guidelines specifically state that blood cultures should be obtained before antimicrobials, "if it results in no substantial delay in the start of antimicrobials (i.e., < 45 min)" (33). The available data suggest that deferring antibiotic administration to the hospital will often result in a delay of > 45 min. Thus, we acknowledge the potential benefits of identifying the specific causative organism with blood cultures but contend that the urgency of initiating potentially lifesaving antibiotic therapy outweighs the risk of sterilizing cultures. For those concerned about this issue, it is also worth noting that blood culture media (such as BACTEC PLUS (Becton Dickinson)) can neutralize antibiotics in the blood culture specimen, substantially reducing the likelihood of false negative blood cultures from prior antibiotic exposure (35).

One final point to consider is that prehospital pediatric sepsis alerts are exceedingly rare. Although our study allowed for treatment of pediatric patients with sepsis, only 3 such patients were identified. The rarity of prehospital pediatric sepsis was also demonstrated in a 2019 Cincinnati study, which additionally reported that the median time to antibiotics after arrival in the ED was 76.5 min for pediatric patients with septic shock (36). This highlights the ongoing uncertainty regarding the optimal methods for identifying and managing pediatric sepsis in the prehospital setting. Further research is needed to develop and validate effective prehospital strategies for this vulnerable population.

Limitations

First, the analysis did not include hospital outcomes or a comparison group, leaving the clinical significance of our findings uncertain. We are working on obtaining hospital data for future analyses. Second, while protocol compliance was high for patients in whom a sepsis alert was initiated, the study design did not allow us to determine how often patients who met criteria for a sepsis alert were not identified as such. Next, given the nature of the study design, the accuracy of our data was subject to measurement bias and misclassifications in outcomes may have occurred. We relied on the quality of the documentation by EMS clinicians and we did not assess the inter-rater reliability among data abstractors. In particular, antibiotic administration times should be considered approximations as they were documented during high-stress scenarios where patient care was prioritized over precise timekeeping.

Conclusions

In this retrospective analysis of patients treated by a single EMS system, when EMS clinicians activated a sepsis alert they followed the sepsis protocol and administered antibiotics before hospital arrival in 97% of cases. Patients received their first antibiotic a median of 26 min after 9-1-1 call and 11 min prior to hospital arrival. The clinical significance of these findings cannot be definitively established based on this study alone. Further research with longer term outcomes is needed to evaluate the impact of prehospital antibiotics.

Authors Contributions

PA, KAS, CC, DAF, and TZ conceived the study. PA and TZ designed the study. PA, CC, ST, GA, JL, and NB collected the data. PA, CC and TZ supervised the conduct of the study and data collection. PA, ST, GA, JL, NB and TZ managed the data, including quality control. TZ provided statistical advice on study design. PA, KAS, and TZ analyzed the data. PA and TZ drafted the manuscript, and all authors contributed substantially to its revision. TZ takes responsibility for the paper as a whole.

Declaration of Generative AI in Scientific Writing

The authors did not use a generative artificial intelligence (AI) tool or service to assist with preparation or editing of this work. The author(s) take full responsibility for the content of this publication.

Disclosure Statement

No potential conflict of interest was reported by the author(s).

Data Sharing Statement

Deidentified data are available upon reasonable request of Dr. Zitek (zitek10@gmail.com).

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