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Performance of Prehospital Antibiotic Administration and Blood Culture Collection in a Physician-Staffed Mobile Unit: A Retrospective Cohort Study

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ABSTRACT

Objectives: Prehospital antibiotic administration prior to emergency department (ED) admission could reduce the delay of effective antibiotic treatment and thus mortality of septic patients. Additionally, collecting blood cultures early could improve microbial identification. We assessed the effect of ceftriaxone administration before ED admission on mortality. As our secondary objective, we evaluated the positivity and contamination rate of prehospital blood cultures in a prehospital physician-staffed system.

Methods: The computerized databases of a physician-staffed prehospital unit were screened for patients presenting with suspected sepsis and low systolic blood pressure (< 90 mmHg) between May 2013 and December 2018. The association between prehospital ceftriaxone administration and 28-day mortality, Intensive care unit (ICU) admission and length-of-stay (LOS) was analyzed. The yield of blood cultures and frequency of contamination were calculated.

Results: A total of 165 septic patients matched the inclusion criteria. Prehospital antibiotics were administered in 60.6% (100/165) of cases. Twenty-eight-day mortality was similar between patients receiving and not receiving antibiotics (39.0 % vs 38.5%, $p=1.000$). Hazard ratio of 28-day mortality was 0.87 (95%IC 0.51-1.47). Likewise, no statistically significant impact on 7-day mortality, ICU admission or LOS was found. Blood cultures showed a high positivity rate (35.4%, 23/65) and a low contamination rate (3.1%, 2/65).

Conclusions: In a physician-staffed prehospital system, prehospital blood cultures among critically ill, septic patients showed high positivity and low contamination rates. However, early ceftriaxone administration showed no impact on 28-day mortality, 7-day mortality, ICU admission and ED and ICU LOS.

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Introduction

Sepsis and septic shock remain leading causes of mortality in critically ill patients. Early adequate antibiotic therapy has been shown to decrease mortality in these condition (1, 2). Delayed time-to-antibiotics is reported to increase sepsis mortality (3). For these reasons, broad-spectrum antibiotics should be administered shortly after sepsis recognition (4). In order to further reduce delay of antibiotic administration, efforts have been made to develop and implement sepsis bundles prior to emergency department (ED) admission (5). As with their in-hospital counterparts, many of these prehospital sepsis management approaches include blood culture collection (6). There is conflicting evidence regarding the actual impact of such measures. Several studies suggest that prehospital antibiotic administration may improve survival in septic patients, though evidence from randomized trials is limited, and existing studies often have small sample sizes (7, 8). In contrast, other studies did not demonstrate a benefit regarding survival rate (9, 10).

Nevertheless, the prehospital environment provides a good opportunity to provide care prior to ED admission. We hypothesized that prehospital antibiotic administration could be associated with decreased mortality at 28 days, intensive care unit (ICU) admission and ICU length of stay (LOS). We also calculated the blood culture positivity and contamination rate to assess the performance of prehospital samples.

Methods

Our main objective was to retrospectively analyze medical records from a prehospital, physician-staffed medical mobile unit to determine the performance of prehospital empiric

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antibiotic therapy defined by its effect on 28-day mortality, ICU admission and LOS. We also aimed to describe the performance of prehospital blood cultures defined by their positivity and contamination rates. The study was conducted after approval by the regional ethics committee (Commission Cantonale d'Ethique de la Recherche sur l'être humain, Geneva, Switzerland – project ID 2017-00800).

Study Design and Setting

This was a retrospective cohort study carried out according to the STROBE guidelines (11). The study was conducted in the Geneva canton, at the Geneva University Hospitals (HUG), a Swiss primary and tertiary medical center serving an estimated population of 500'000 (12). It is the only public hospital in the canton of Geneva and the majority of the patients cared for by the local physician-staffed medical mobile unit (SMUR - Service Mobile d'Urgence et de Réanimation) are admitted there.

Thorough descriptions of the SMUR units and of the regional emergency medical system organization have already been published elsewhere (12, 13). Briefly, three levels of prehospital emergency care are available in Geneva. The first level is composed of advanced life support ambulances staffed by two paramedics. Swiss paramedics are trained to an extensive degree of autonomy but still require medical supervision in the most critical cases. They are trained to work using medically delegated protocols and perform most of prehospital care autonomously, including intravenous catheterization, drug administration or electrocardiogram monitoring. Some specific critical tasks are not performed by the paramedics, including but not limited to orotracheal intubation, noninvasive ventilation, continuous infusion of vasoactive drugs and antibiotic administration. The second level is represented by the SMUR medical mobile units, which are only dispatched by the emergency medical call center if a life-threatening condition has been identified by emergency medical dispatchers. The third level is a senior medical supervisor, who is on call around the clock and can provide phone or direct on-site supervision. After each intervention, the prehospital physician fills in a structured, computerized medical file which is reviewed daily by a supervisor for quality control and teaching purposes. At least one standardized prehospital diagnosis must be registered to validate the file.

If sepsis or septic shock is suspected by the prehospital emergency physician, the local protocol recommends the collection of a pair of blood culture bottles (one aerobic vial and one anaerobic vial, BD-Bactec™, 8-10mL) prior to the administration of a broad-spectrum antibiotic (ceftriaxone, 2 g IV). The preliminary diagnosis of sepsis, the subsequent collection of blood cultures and the administration of antibiotics is left to the prehospital physician's discretion. All SMUR paramedics are trained to perform aseptic collection of blood cultures. The collected vials are transported to the ED and processed following standard in-hospital laboratory protocols. Results are considered negative if blood cultures are still sterile after 5 days of incubation. Data collection and analysis were substantially delayed by the Covid-19 pandemic.

Inclusion and Exclusion Criteria

All patients cared for by the SMUR between May 2013 and December 2018 were screened. Patients with a prehospital diagnosis of sepsis and systolic blood pressure lower than 90 mmHg at first contact with the prehospital physician were reviewed for inclusion.

We excluded phone consultations and patients below 18 years of age. We also excluded patients who were not transported to the hospital, who were transported to another hospital than HUG, who were hospitalized in the 24 h preceding the intervention, and those for whom a limitation of care was known and enforced by prehospital staff. Finally, we excluded patients who had received antibiotics prior to prehospital intervention, those with a history of beta lactam allergy and patients for whom the prehospital sepsis diagnosis was not confirmed during hospital stay.

Outcomes

The primary outcome was 28-day mortality, recorded by the cantonal death registry. The secondary outcomes were 7-day mortality, ICU admission and ICU LOS. We also recorded rates of blood culture sampling, positivity and contamination.

Data Description and Collection

Clinical, demographic, biological and microbiological data were obtained through institutional, computerized databases whenever possible. When necessary, further data were retrieved through a manual file review. These data were collected using a REDCap™ case report form hosted at HUG (14, 15).

Descriptive data obtained included age, sex, and variables required to compute the Charleson Comorbidity Index (16). The first vital signs recorded on-site (systolic blood pressure, heart rate, respiratory rate, Glasgow Coma Scale, temperature) were automatically extracted. We recorded if the intervention took place in a medicalized center (defined as 24/7 medical presence), as well as any relevant prehospital procedure performed (intubation, vasoactive drugs administration and antibiotics administration). The National Advisory Committee on Aeronautics score (NACA score) was used to qualify prehospital severity of cases was extracted from the prehospital files (17). The quick Sequential Organ Failure Assessment (qSOFA) was calculated from available clinical data (18).

The initial laboratory results obtained in the ED were also retrieved (hemoglobin, leucocytes count, creatinine, C-reactive protein, procalcitonin and bilirubin). The microbiological data collected included the number of blood cultures collected by SMUR units, reasons for not obtaining cultures if reported, number of blood cultures processed, positive, and contaminated. Contamination was defined as the isolated positivity of one blood culture bottle with known cutaneous germs including *Staphylococcus epidermidis* and other coagulase-negative staphylococci.

Clinical timestamps were extracted to compute the mortality rate at 7 and 28 days, ED LOS, ICU admission rate, time to ICU admission, and ICU LOS. In-hospital medical files were manually reviewed to extract the main diagnoses reported on the discharge reports following the acute care episode.

Statistical Analysis

Categorical variables were expressed as the number of patients or events (n, %) and continuous variables were described as means (± SD). Chi-square tests were performed to compare categorical variables. Normality of distribution was addressed through skewness and kurtosis testing, and either t-tests or Wilcoxon-Mann-Whitney tests were performed accordingly.

We followed a causal inference framework to address confounding by indication, using inverse probability of treatment weighting (IPTW) based on propensity scores (19, 20). We calculated propensity scores for the likelihood of ceftriaxone administration using logistic regression. Covariates included in the propensity score model were those that were associated with both the exposure (ceftriaxone administration) and the outcome (28-day mortality) and were selected a priori based on clinical relevance and included demographics, comorbidities, vital signs at first medical contact, prehospital time intervals, and indicators of illness severity.

Inverse probability of treatment weighting was applied using stabilized weights to estimate the average treatment effect. Balance of covariates after weighting was assessed using standardized mean differences (SMD), with a threshold of <0.1 indicating acceptable balance. Effective sample size was also calculated to assess the impact of weighting on statistical precision.

We estimated the effect of prehospital ceftriaxone on mortality using IPTW-adjusted survival analysis *via* Cox proportional hazards models. Proportional hazards assumptions were assessed graphically and using Schoenfeld residuals. Robust standard errors were used to account for the weighted nature of the sample. As a secondary analysis, we conducted an exploratory analysis using inverse probability weighted Kaplan–Meier survival curves to illustrate mortality over time in the treatment versus control groups.

Concerning blood cultures, the positivity rate was defined as the number of blood cultures showing significant growth during the 5 days of incubation, over the total number of prehospital blood cultures processed through incubation. The contamination rate was defined as the number of contaminated blood cultures over the total number of prehospital blood cultures processed through incubation. True positivity was defined as the positivity rate after exclusion of contaminated samples.

To account for missing data in covariates, we performed multiple imputation using chained equations *via* the mice package (21). Variables included in the imputation model encompassed all those used in the propensity score model and outcome analyses. Predictive mean matching was used for continuous variables, and logistic or polytomous regression was used for categorical variables, as appropriate. We generated 20 imputed datasets and assessed convergence visually. Analyses were conducted separately within each dataset and pooled according to Rubin's rules to obtain final estimates and confidence intervals.

Double-sided p-values lower than 0.05 were considered significant. Statistical analyses were performed using Stata 15 (StataCorp, Texas, USA) and R (version 4.2.0).

Results

Population Description

Of 31'948 patients screened, 300 met our inclusion criteria. Of those 300 identified, we excluded 135 patients after file review. Exclusion criteria are shown in Figure 1. Of the 165 patients included, 100 received ceftriaxone by the SMUR unit and 65 did not. Table 1 describes the patient population, stratified by ceftriaxone administration. Blood cultures were more often collected in the ceftriaxone group. Patients who received ceftriaxone were older and had higher acuity scores compared to those who did not. However, both groups showed similar Charleson Comorbidity Scores. Patients cared for in a medicalized center before emergency service intervention were evenly distributed, as were prehospital intubation and administration of vasoactive drugs. There were no other significant differences regarding clinical features and laboratory findings.

The mean interval between prehospital physician first contact with the patient and ER admission was 47.6 min (SD 16.6). The mean transport interval, defined as the time between leaving the prehospital site and ER admission, was 16.6 min (SD 7.1). Complete data regarding delays and transport time are shown in Supplementary Table 1.

Mortality, Length-of-Stay and ICU Admission

The results showed no statistically significant difference in mortality at 28 days (39.0% vs. 38.5% – Table 2). Mortality at 7 days was also comparable (30.0% vs 29.2%). The time to discharge in the ED and ICU admission were also similar, as were time to ICU admission and LOS. Differences between deceased and surviving patients are shown in Supplementary File Table 2.

The propensity score model adequately balanced covariates between the treated and untreated groups, as reflected by SMDs below 0.1, and exhibited good overlap in propensity score distributions, supporting the appropriateness of the model. The inverse probability-weighted Cox regression estimated a hazard ratio of 0.87 (95%CI 0.51-1.47; $p = 0.592$), with a slight survival benefit after ceftriaxone administration and wide confidence intervals. The inverse probability-weighted survival curves showed a modest non-significant advantage for the treated group up to day 9, but the overall comparison showed no statistically significant difference ($p = 0.86$) in 28-day mortality between both groups (Figure 2).

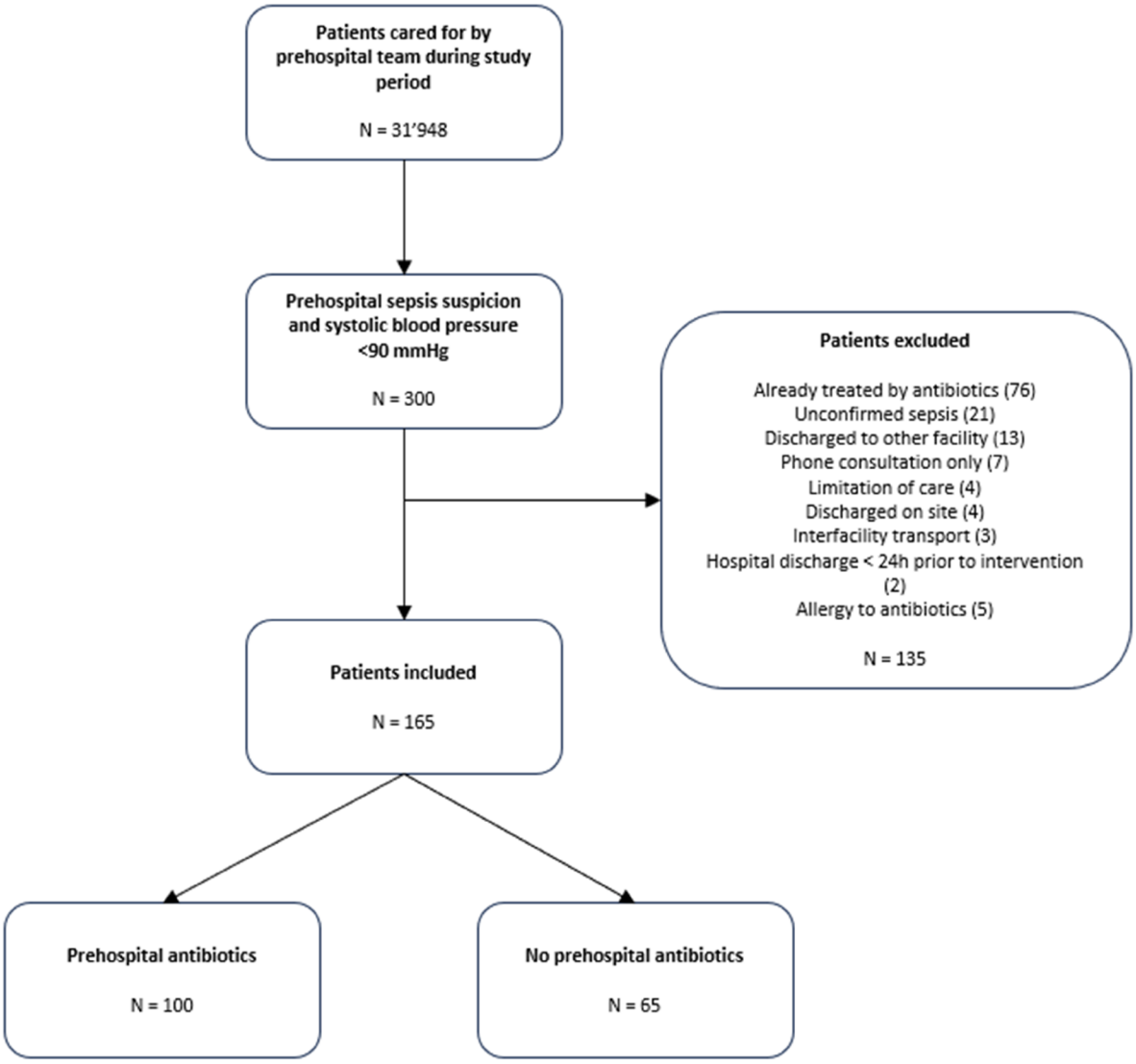

Figure 1. Study flowchart.

Blood Culture Positivity and Contamination Rates

At least one pair of blood cultures was collected in 41.8% of cases (69/165). One pair of prehospital blood cultures was not processed after limitation of care was decided after ED admission and was discarded. The remaining 68 pairs underwent complete incubation and workup. Three blood cultures were lacking proper timestamping and were discarded from the analysis to avoid confusion between prehospital and emergency samples. A total of 65 cultures were finally included in the analysis.

Prehospital blood cultures were positive in 35.4% of cases (23/65). Polymicrobial positivity was recorded in 3 blood cultures. Contamination occurred in 2 cases (2/65, 3.1%). After excluding these contaminated samples, the true positivity was 32.3% (21/65). The overall positivity rate among all blood cultures collected in the HUG ED during the 2015-2018 timeframe was 9.1% (3'189/35'009). Prehospital positivity was thus significantly higher (35.4% vs 9.1%, $p < 0.001$).

Bacterial findings showed a large predominance of Gram-negative bacilli (Table 3). Bacteria with intrinsic resistance to ceftriaxone accounted for 19.2% (5/26) of isolates and were composed of *Pseudomonas aeruginosa* (4/5) and *Enterococcus faecalis* (1/5). One case of *Capnocytophaga canimorsus* showed no bacterial growth in the laboratory; thus, a conventional antibiogram could not be performed. The germ was considered empirically sensitive.

Discussion

This study did not demonstrate a statistically significant effect of prehospital antibiotic administration on 28-day mortality, which was high (39%) as previously reported in similar studies (22, 23). Secondary outcomes regarding mortality at 7 days, ICU admission and ICU length-of-stay were also comparable. However, prehospital blood cultures showed high positivity and low contamination rate and may prove useful for antibiotic administration decision making and prescribing targeted treatment at an earlier stage.

Our findings on prehospital antibiotic administration concur with the only randomized trial conducted in the field to our knowledge, The PHANTASi trial. This study

Table 1. Population demographics and management.

	Ceftriaxone ($n=100$)	No ceftriaxone ($n=65$)	p-value
CHARACTERISTICS			
Age (mean (SD))	77.6 (13.7)	67.1 (19.3)	<0.001
Male sex (n (%))	63 (63.0%)	37 (56.9%)	0.536
CCI (mean (SD))	2.48 (2.21)	2.98 (2.49)	0.186
Intervention in medical center (n (%))	13 (13.0%)	9 (13.8%)	1.000
PREHOSPITAL MANAGEMENT			
qSOFA (mean (SD))	2.31 (0.62)	2.08 (0.71)	0.037
NACA score (mean (SD))	4.74 (0.46)	4.52 (0.56)	0.010
Intubation (n (%))	4 (4.0%)	5 (7.7%)	0.318
Aminergic support (n (%))	31 (31.0%)	17 (26.2%)	0.621
Blood culture obtained (n (%))	66 (66.0%)	3 (4.6%)	<0.001
CLINICAL FEATURES			
First temperature (mean (SD))	38.0 (1.6)	37.4 (2.0)	0.061
Heart rate (mean (SD))	107.7 (21.6)	104.9 (23.1)	0.443
Respiratory rate (mean (SD))	27.0 (8.7)	25.1 (8.2)	0.165
Glasgow Coma Scale (mean (SD))	12.6 (3.1)	12.5 (3.9)	0.760
Systolic Blood Pressure (mean (SD))	80.4 (8.5)	80.2 (7.5)	0.877
LABORATORY RESULTS			
Hemoglobin (g/L; mean (SD))	110.6 (26.7)	115.2 (28.8)	0.306
C-Reactive Protein (mg/L; mean (SD))	125.8 (118.5)	143.7 (133.5)	0.385
Procalcitonin (µg/L: mean (SD))	32.6 (50.6)	30.4 (53.2)	0.496
Creatinine (µmol/L; mean (SD))	171.1 (98.1)	209.8 (164.9)	0.094
Total bilirubin (µmol/L, mean (SD))	20.3 (22.6)	27.7 (33.2)	0.125

Table 2. Outcomes.

	Ceftriaxone ($n=100$)	No ceftriaxone ($n=65$)	p-value
7-day mortality (n (%))	30 (30.0%)	19 (29.2%)	1.000
28-day mortality (n (%))	39 (39.0%)	25 (38.5%)	1.000
ED time to discharge[a] (mean (SD))	7.8 (6.6)	8.4 (6.8)	0.571
ICU admission (n (%))	33 (33.0%)	22 (33.8%)	1.000
Time to ICU admission[a] (mean (SD))	4.4 (2.0)	4.5 (2.2)	0.867
ICU length of stay (LOS)[b] (mean (SD))	4.6 (4.5)	3.9 (4.7)	0.476

[a]In hours.
[b]In days.

found no evidence of a protective effect of prehospital antibiotics administered by paramedical emergency teams, though in a population probably less severely ill than our sample, given an overall 90-day mortality rate of 12%, roughly 3-fold lower than our population (9). On the other hand, our results do not correlate with the retrospective data published by Jouffroy *et al.* which showed a decrease in 30-day mortality after using a prehospital sepsis bundle including prehospital antibiotic under physician supervision in a population fairly similar to our sample (23).

We need to consider our findings regarding several specific factors. Firstly, our geographical setting in an urban and highly medicalized area involves short travel time to the hospital. This probably diminishes the time gained through prehospital antibiotics administration in our setting compared to more remote locations with long travel times. We could not strictly quantify the gain in terms of time-to-antibiotics, due to unavailable data. We did consider the total transportation time to be an acceptable surrogate marker of the magnitude of the delay involved, which proved to be short with an average of 16.6 min. Thus, we consider that our patients likely benefited from a reduction of the time-to-antibiotic but of a limited magnitude, possibly leading to a less significant effect on mortality. Secondly, we suspect the two-level structure of our prehospital services structurally screens the patients, given the physician-staffed team is only called for the most severe cases, showing significant hypotension or other clinical signs of shock. This assumption is corroborated by the high mortality rate in our cohort. For this reason, we suspect our population only reflects the most severe cases of sepsis and septic shock which are burdened with the highest mortality and possibly beyond the reach of the beneficial effect of early empiric antibiotic therapy. Thirdly, it is inaccurate to conclude that the mortality rates rely solely on antibiotic administration when it is performed with a complete supportive care bundle. Given that the attitude of care was similar in our control population in terms of vasopressor agents and aggressive volemic expansion, these measures could have prevented an increase of mortality, even in absence of antibiotic administration.

Concerning blood culture collection, we showed high overall positivity (35.4%) which was comparable to similar studies showing a range between 24% to 42% in smaller samples (6, 24, 25). The contamination rate was low (3.1%). Based on a usual in-hospital target of contamination rate of < 3%, we consider the samples to be of good quality and reliable for clinical use (26). These results confirm that trained prehospital teams can collect valuable microbiological samples before the initiation of antibiotic therapy, allowing ED physicians to administer broader spectrum or additional antibiotics if required without the delay of blood culture collection upon ED arrival. We further hypothesize that the potential early targeting of germs found in prehospital blood culture could enhance antibiotic stewardship (27).

Our study presents several strengths. First, as the evidence regarding medical-led prehospital sepsis management is still scarce, this cohort adds to the few published articles on this matter (23, 24). Second, the HUG has high standards of sepsis care based on strict institutional guidelines; thus, it is unlikely that in-hospital management could have biased the observed findings (28, 29). Third, our trial used robust statistical methods to mitigate bias and provide reliable evidence. Moreover, we studied patients cared for by physician-staffed medical units, which provides findings comparable to the practice of several European countries working with similar emergency services. Finally, our thorough microbiology description permits better understanding of local sepsis etiologies and the adequacy of antimicrobial therapy in our local environment.

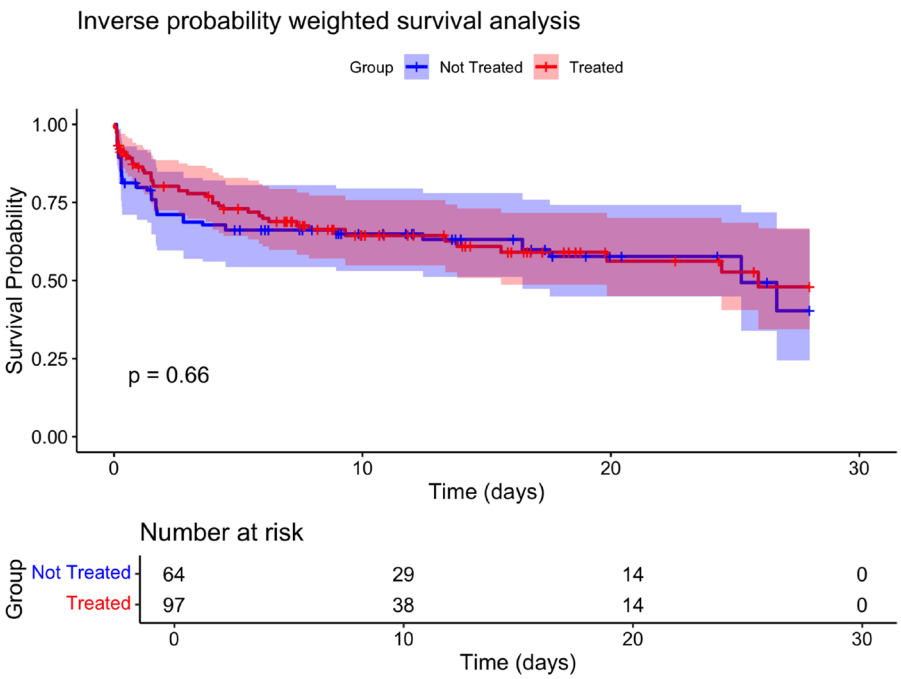

Figure 2. Kaplan-Meier survival analysis.

Table 3. Prehospital microbiological results.

Germ identification	Observation	Considered contaminant	Ceftriaxone suceptibility
Escherichia coli	5	0	S
Klebsiella pneumoniae	4	0	S
Pseudomonas aeruginosa	4	0	R
Streptococcus agalactiae	2	0	S
Streptococcus pyogenes	1	0	S
Staphylococcus epidermidis	1	1	N/A
Staphylococcus hominis	1	1	N/A
Streptococcus mitis	1	0	S
Actinotignum schaali	1	0	S
Bifidobacterium breve	1	0	S
Capnocytophaga canimorsus	1	0	S*
Enterococcus faecalis	1	0	R
Morganella morganii	1	0	S
Proteus mirabilis	1	0	S
Streptococcus anginosus	1	0	S
TOTAL	26	2	

*No antibiogram available, empirically considered susceptible. S: Susceptible; R: Resistant.

Limitations

Our study has several limitations. First, the retrospective and observational design subjects the study to a confounding by indication bias as the decision to perform the sepsis bundle is at the physician's discretion. However, despite its retrospective design, population characteristics are similar in both intervention and control groups. Although our causal inference approach strongly mitigated this, we cannot exclude the possibility of any residual confounding. If residual bias was nonetheless present, it is plausible that the physician could have preferentially administered antibiotics to patients showing signs of frailty or worrying condition. Such bias could have led to decreased survival chances in the antibiotic group. Second, this study is limited in terms of generalizability by the specific local emergency service structure and the urban and highly medicalized environment which is not always translatable internationally. Third, the sample size was limited leading to wide confidence intervals of the effect estimates; therefore, our study could have been underpowered to detect a small, but statistically significant effect. Finally, the impossibility of conducting time-to-antibiotics comparisons prevents us from making a precise quantitative comparison of the gain in terms of delay.

The realization of a randomized trial in a physician-staffed prehospital system regarding the impact of early antibiotic administration on mortality could further address the question, with significant reduction of bias and ensuring proper data availability, including time-to-antibiotics.

Conclusions

In an urban setting with short transport times, prehospital antibiotic administration under physician supervision did not show any significant effect on 28-day and 7-day mortality, ICU admission, ED and ICU LOS. These findings call for the realization of new studies on the subject, and more specifically randomized studies including different environments and emergency services systems to further explore the effect of prehospital antibiotic administration. In contrast, prehospital culture collection had adequate diagnostic performance with high positivity and low contamination rates and could prove useful for better antibiotic targeting and antibiotic stewardship opportunities.

Acknowledgments

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Authorship Statement

R.B., M.A. and L.S. conceived the study. R.B. collected computerized and manual data. A.F. provided microbiological data. R.B. and M.A. conducted statistical analysis. R.B. wrote the first draft. All authors made substantial contributions to the manuscript and were involved in final correction of the draft. All authors have read and agreed to the published version of the manuscript.

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 authors 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

Original data are available upon reasonable request to the corresponding author.

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