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Prehospital Antibiotics for Patients With Suspected Sepsis
The PITSTOP-Antibiotics Factorial Randomized Clinical Trial

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IMPORTANCE Early treatment with antibiotics is considered an important intervention to reduce mortality for patients with sepsis.

OBJECTIVE To determine the effect of earlier treatment with antibiotics in the ambulance on 90-day mortality compared with usual treatment in the emergency department.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, 2 × 2 factorial randomized, placebo-controlled trial was conducted among 4 paramedic services and their destination hospitals in Ontario, Canada. Participants were adults with suspected sepsis, defined as suspected infection, fever (≥38.0 °C), and hypotension (systolic blood pressure <100 mm Hg). Patients were enrolled between March 23, 2020, and August 20, 2025, with final follow-up in December 2025.

INTERVENTIONS Patients were randomized to receive 1 g of intramuscular ceftriaxone or placebo (and to receive liberal fluids vs usual fluids; reported separately) during prehospital care in the ambulance. All patients could receive open-label antibiotics in the emergency department.

MAIN OUTCOMES AND MEASURES The primary outcome was hospital mortality, defined as death prior to hospital discharge to day 90. There were 17 secondary outcomes, including all-cause mortality at 90 days, hospitalization, intensive care unit admission, use of mechanical ventilation, use of dialysis, positive culture results, and antibiotics within 24 hours of hospital arrival.

RESULTS Among 2091 randomized patients, 2048 were eligible for the primary analysis, with 1026 randomized to receive ceftriaxone and 1022 randomized to receive placebo. The median (IQR) age of patients was 75 (62-85) years and 1162 (56.7%) were males. The mean (SD) time from paramedic arrival at patient to administration of study drug was 37 (36) minutes in the ceftriaxone group and 39 (55) minutes in the placebo group. Most patients (735 of 795 [92.5%] in the ceftriaxone group and 730 of 792 [92.2%] in placebo group) were treated with antibiotics in the hospital after a mean (SD) of 247.3 (207.7) minutes after paramedic arrival among patients in the ceftriaxone group and 252.8 (218.0) minutes among the placebo group. The rate of hospital mortality was 182 of 1009 (18.0%) in the ceftriaxone group and 186 of 1011 (18.4%) in the placebo group (risk ratio, 0.97 [95% CI, 0.81-1.17]; $P = .77$). Of 17 secondary outcomes, all were similar between the groups.

CONCLUSIONS AND RELEVANCE Among patients with suspected sepsis on evaluation by paramedics, earlier treatment with antibiotics in the ambulance did not reduce mortality compared with usual care provided in the emergency department.

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Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1,2] The mortality rate associated with sepsis ranges from 20% to 50%, with increased mortality in patients diagnosed with septic shock.[3,4] Early administration of antibiotics is considered important for reducing mortality in sepsis and septic shock, although this association has not been consistent across all studies.[5-9] However, delays to appropriate antibiotic therapy after presentation to the hospital remain common.[10,11]

Nearly half of patients with sepsis are treated and transported to the hospital by paramedics.[12,13] Prehospital treatment with antibiotics is not routine, but may help reduce delays due to wait times for assessment in emergency departments. The PHANTASi trial evaluated prehospital intravenous ceftriaxone vs usual care in patients with suspected infection, fever, or hypothermia and either tachycardia or tachypnea and found no difference in mortality.[14] Yet, the rate of shock and 28-day mortality were low (4% and 8%, respectively), suggesting that life-threatening organ dysfunction was uncommon. The 2026 Surviving Sepsis Campaign guidelines provide a conditional recommendation suggesting administration of antimicrobial therapy in the ambulance to adults with definite or probable sepsis and hypotension and who have an anticipated time to in-hospital evaluation of more than 60 minutes.[15] However, this recommendation is based on very-low-certainty evidence and no randomized trials.

This multicenter, placebo-controlled, 2 × 2 factorial randomized trial was designed to evaluate whether prehospital treatment with antibiotics provided in the ambulance can reduce 90-day mortality in patients with suspected sepsis, defined as the presence of suspected infection, fever, and hypotension. Patients with intravenous access were also randomized to receive a more liberal fluid resuscitation strategy or usual care (reported separately).

Key Points

Question Does treatment with prehospital antibiotics in the ambulance improve outcomes for patients with suspected sepsis compared with usual treatment in the emergency department?

Findings In this randomized clinical trial including 2048 patients with suspected infection, fever, and hypotension conducted in 4 large paramedic services in Ontario, Canada, the hospital mortality rate was similar among patients who received prehospital ceftriaxone (18.0%) compared with those who received placebo (18.4%).

Meaning Prehospital treatment with antibiotics in the ambulance did not reduce mortality in patients with suspected sepsis.

Methods

Trial Design

The Paramedic Initiated Treatment of Sepsis Targeting Out-of-Hospital Patients With Antibiotics (PITSTOP-Antibiotics) trial was conducted in 4 paramedic services (Halton Region Paramedic Services, Peel Regional Paramedic Services, Toronto Paramedic Services, and York Region Paramedic Services) and their associated destination hospitals in Southern Ontario, Canada (population of approximately 6 million). The trial also evaluated prehospital treatment with liberal intravenous fluids compared with usual fluid resuscitation among those with intravenous access. The protocol and statistical analysis plan were published before the completion of enrollment and unblinding of the database (see Supplement 1 for protocol).[16] Reporting adheres to the Consolidated Standards of Reporting Trials Extension (CONSORT Extension) reporting guideline for factorial randomized clinical trials.[17]

The Centre for Clinical Trial Support at Sunnybrook Research Institute was responsible for trial coordination and oversight. The trial received approval from the research ethics boards of the base hospitals for participating paramedic services and most destination hospitals (see eMethods in Supplement 2 for details). Eligible patients were enrolled under a waiver of consent using established procedures for conducting prehospital research involving patients with severe illness requiring time-sensitive therapies. Prehospital data from all patients were collected using the paramedic electronic patient care records. Where approved by local research ethics boards, in-hospital data were collected by trained abstractors from patients' medical records from destination hospitals. All retrieved data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Sunnybrook Research Institute. The study database was linked using personal health information to the population health databases contained at ICES (formerly known as the Institute for Clinical Evaluative Sciences) to obtain primary outcome data and some secondary outcomes (see eMethods in Supplement 2 for details). ICES is a prescribed entity for the purposes of section 45 of Ontario's Personal Health Information Protection Act and contains multiple administrative health databases.

Two formal interim analyses evaluating mortality during transport and hospital mortality were planned by an independent data and safety monitoring committee at one-third (n = 680) and two-thirds (n = 1360) enrollment. Using the Haybittle-Peto boundary, a conservative significance threshold of $P < .001$ was applied at each analysis, resulting in a negligible penalty on type I error rate.[18] The committee recommended continuing enrollment after the first interim analysis and the trial had already reached its full target sample size by the time the second interim analysis results were available.

Patients

Eligible patients were adults (age ≥18 years) with suspected sepsis, defined as suspected infection (eg, suspected pneumonia, urinary tract infection, skin infection, bone and joint infection, intra-abdominal infection, meningitis), fever (temperature ≥38.0 °C measured by paramedic or measured during the previous 24 hours), and hypotension (systolic blood pressure <100 mm Hg). Patients were excluded if they had alternative obvious causes of hypotension (such as severe bleeding, trauma, or ST-segment elevation myocardial infarction), known allergy to penicillin or cephalosporin, known *Clostridioides difficile* infection within the last 6 weeks, or were known to be receiving oral or subcutaneous anticoagulants (see eMethods in Supplement 2 for full eligibility criteria).

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Randomization and Interventions

Randomization was stratified by paramedic service and used permuted blocks of variable sizes. Patients were assigned in a 1:1 ratio to receive either 1 g of ceftriaxone or a similar volume (2.8 mL) of 0.9% saline administered by intramuscular injection. The vials containing ceftriaxone and placebo were identical to maintain randomization concealment. Patients, paramedics, all clinicians, research staff, and biostatisticians remained blinded to treatment assignment.

All other treatments were provided by paramedics according to medical directives for prehospital care from the time of arrival to the patient, during transport to hospital, and until transfer of care to the emergency department. All in-hospital treatments were at the discretion of treating clinicians in destination hospital emergency departments. The emergency department clinicians were provided with an information sheet explaining the study and recommending that patients be treated per usual care, including with antibiotics if deemed necessary.

Outcomes

The primary outcome was hospital mortality, defined as death prior to hospital discharge to day 90. Secondary outcomes obtained from provincial databases included mortality at 90 days after enrollment, organ dysfunction during the first 24 hours (mechanical ventilation, vasopressor therapy, dialysis) and hospitalization (mechanical ventilation), rates and duration of hospital admission, intensive care unit admission during index hospitalization, and discharge destination (home vs not). Secondary outcomes obtained from hospital medical records included the percentage of patients with positive blood culture results during first 24 hours; microbiological profile including frequency distribution of microorganism species and resistant organisms; percentage of patients receiving additional antibiotics within 24 hours of hospital admission; frequency distribution of first antibiotics (if any) delivered within the first 24 hours of hospital arrival; mean time to antibiotics delivered within first 24 hours of hospital arrival (if any); percentage of patients receiving fluid bolus (>250 mL) within first 24 hours of hospital arrival; total amount of intravenous crystalloid infused during transport and first 24 hours of hospitalization; percentage of patients with blood, urine, and sputum cultures taken during first 24 hours with organisms resistant to ceftriaxone (ie, inappropriate antibiotic therapy); percentage of enrolled patients suspected to have sepsis or infection by emergency department physician; and percentage of patients with any ceftriaxone-resistant organism during the first 24 hours. Safety outcomes included percentages of patients with pulmonary edema documented during transport to hospital and with anaphylaxis or suspected allergic reactions.

Statistical Analysis

We assumed the baseline hospital mortality of patients with suspected sepsis and hypotension who are transported by paramedics to range from 17% to 23%.[19,20] To detect a plausible 5% absolute reduction in hospital mortality,[21] we estimated 1020 patients per group would provide a power of 80%, with α error of 5% and 2-sided testing. This sample size was estimated to also provide sufficient power to detect an interaction effect between antibiotic and fluid interventions in the factorial design of a mortality difference of 10%.

The primary analysis population included patients who met all eligibility criteria and received the study intervention. Patients who were enrolled in the trial but for whom 1 or more exclusion criteria were subsequently identified were included in the primary analysis but excluded from a secondary sensitivity analysis. Baseline characteristics were summarized using descriptive statistics. The primary outcome was analyzed using a log-binomial model and accounted for the stratified randomization and the randomized assignment (2 × 2 factorial) in the PITSTOP-Fluids trial.[22] If no interactions between the treatments evaluated were detected, the terms corresponding to the PITSTOP-Fluids trial were dropped from the model. When the log-binomial model did not converge, a modified Poisson regression was used. Secondary binary outcomes were analyzed and reported using risk ratios (RRs) with 95% CIs and continuous outcomes were analyzed using linear regression and reported as differences in means and 95% CIs. In prespecified sensitivity analyses, hospital mortality was adjusted for important baseline variables (eg, age, sex, comorbidities) using Poisson multivariable regression modeling. Time to death was summarized by Kaplan-Meier curves and compared using Cox proportional hazard models and the treatment effects expressed as hazard ratio (HR) and 95% CI with censoring at 90 days. Subgroup analyses were conducted among patients with outcomes available at ICES and considered whether any of 3 prespecified factors modified the effect of prehospital sepsis treatment on subsequent patient outcomes: sex (male vs female), age (<65 vs ≥65 years), or sepsis hospital volume (high vs low). Post hoc exploratory analyses considered 6 postrandomization subgroups of patients with greater disease severity (systolic blood pressure at hospital arrival [<100 vs ≥100 mm Hg]; elevated lactate after hospital arrival [<2.0 vs ≥2.0 mmol/L; <4.0 vs ≥4.0 mmol/L]; vasopressors after hospital arrival; greater time to transfer of care in emergency department [<60 vs ≥60 minutes]; and any positive culture result [any, blood, urine] in the first 24 hours). We also conducted a post hoc sensitivity analysis of the primary model that retained the treatment group and interaction terms for the PITSTOP-Fluids trial; for this analysis we considered 3 group assignments (liberal intravenous fluids, usual intravenous fluids, no intravenous access). Additional post hoc sensitivity analyses of the primary model were performed by removing all patients with exclusion criteria that were identified after randomization, imputing outcome data using extreme scenarios (ie, assuming all patients receiving ceftriaxone died and all patients receiving placebo lived and vice versa) for patients who were randomized but did not meet inclusion criteria or did not receive the study medication, and restricting to the first enrollment for patients who were enrolled more than once.

A 2-sided P <.05 was considered to indicate statistical significance. Analyses were performed with SAS software version 9.4 (SAS Institute). For multiplicity of testing, the CIs were not adjusted, and should therefore not be used instead of hypothesis testing.

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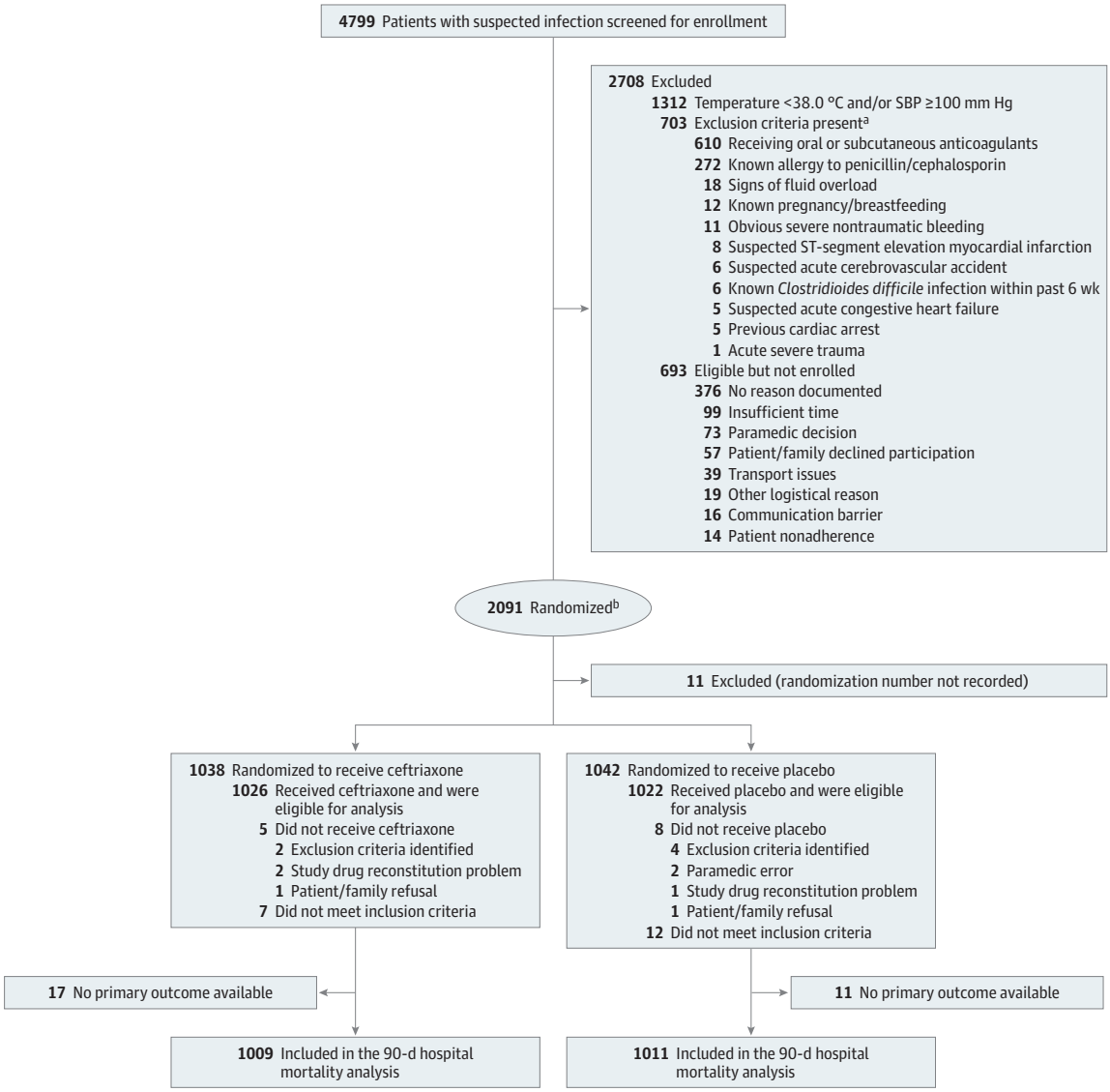
Figure. Flow Diagram of Participants in the PITSTOP-Antibiotics Trial



[a]Patients may have had more than 1 exclusion criteria, so numbers add to more than 703.

[b]Of the 2091 patients randomized, 39 were enrolled twice (accounting for 78 enrollments) and 4 were enrolled 3 times (accounting for 12 enrollments); these were considered unique enrollments in the primary analysis. For 57 patients, 1 or more exclusion criteria were identified after randomization (30 in the ceftriaxone group and 27 in the placebo group); these patients were included in the primary analysis.

PITSTOP-Antibiotics indicates Paramedic Initiated Treatment of Sepsis Targeting Out-of-Hospital Patients With Antibiotics; SBC, systolic blood pressure.

Results

Between March 23, 2020, and August 20, 2025, a total of 4799 patients with suspected infection were screened. Overall, 2091 patients were randomized, of whom 2048 were eligible for analysis (1026 randomized to receive ceftriaxone and 1022 randomized to receive placebo; **Figure**). Primary outcomes were available for 1009 patients (98.3%) in the ceftriaxone group and 1011 (98.9%) in the placebo group.

Baseline characteristics by randomization are provided in **Table 1**. The median (IQR) age of patients was 75 (62-85) years, 1162 (56.7%) were males, and 886 (43.3%) were females. The most common comorbidities were cardiovascular disease (54.6% in the ceftriaxone group; 50.2% in the placebo group), hypertension (48.7% in the ceftriaxone group; 43.7% in the placebo group), and diabetes (30.0% in the ceftriaxone group; 26.5% in the placebo group). The most common sources of infection suspected by paramedics were pneumonia (22.6% in the ceftriaxone group; 22.5% in the placebo group) or urinary tract infections (22.6% in the ceftriaxone group; 22.4% in the placebo group). Overall, there were no important differences between the groups. The mean time from paramedic arrival at patient to administration of study drug was also similar

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Table 1. Baseline Characteristics of the Patients

Variable	Ceftriaxone (n = 1026)	Placebo (n = 1022)
Randomized in PITSTOP-Fluids Trial, No. (%)		
Liberal IV fluids group	425 (41.4)	417 (40.8)
Usual IV fluids group	411 (40.1)	403 (39.4)
No IV access (ineligible)	190 (18.5)	202 (19.8)
Age, median (IQR), y	75 (63-86)	74 (62-84)
Female, No. (%)	454 (44.2)	432 (42.3)
Male, No. (%)	572 (55.8)	590 (57.7)
Time from 911 call to arrival at patient, median (IQR), min	12 (8-18)	11 (8-17)
Paramedic level, No. (%)		
Advance care paramedic	631 (61.5)	614 (60.1)
Primary care paramedic	395 (38.5)	408 (39.9)
Location, No. (%)		
House	491 (47.9)	477 (46.7)
Nursing home	229 (22.3)	222 (21.7)
Apartment	206 (20.1)	218 (21.3)
Other[a]	100 (9.7)	105 (10.3)
Paramedic suspected infection source, No. (%)		
Pneumonia	232 (22.6)	230 (22.5)
Urinary tract infection	232 (22.6)	229 (22.4)
Skin infection, bone, and/or joint infection	64 (6.2)	68 (6.7)
Abdominal	66 (6.4)	78 (7.6)
Other[b]	432 (42.1)	417 (40.8)
Initial vital signs		
Systolic blood pressure, mean (SD), mm Hg	90.4 (18.9)	92.1 (18.8)
Systolic blood pressure <90 mm Hg, No./total No. (%)	502/1022 (49.1)	464/1018 (45.6)
Heart rate ≥ 91/min, No. (%)	816 (79.5)	837 (81.9)
Respiratory rate ≥20/min, No. (%)	774 (75.4)	763 (74.7)
Oxygen saturation <96%, No./total No. (%)	624/1026 (60.8)	623/1019 (61.1)
Temperature, mean (SD), °C	38.7 (0.9)	38.7 (0.9)
GCS score <15, No./total No. (%)[c]	503/1017 (49.5)	505/1019 (49.6)
NEWS2 score ≥5, No./total No. (%)[d]	921/1017 (90.6)	899/1016 (88.5)
NEWS2 score ≥7, No./total No. (%)[d]	791/1017 (77.8)	784/1016 (77.2)
qSOFA score ≥1, No./total No. (%)[e]	1017/1017 (100)	1019/1019 (100)
qSOFA score ≥2, No./total No. (%)[e]	737/1017 (72.5)	742/1019 (72.8)
qSOFA score ≥3, No./total No. (%)[e]	327/1017 (32.2)	347/1019 (34.1)
Neighborhood income quintile, No. (%)[f]	n = 977	n = 971
1 (Lowest income)	245 (25.1)	245 (25.2)
2	218 (22.3)	235 (24.2)
3	193 (19.8)	191 (19.7)
4	159 (16.3)	156 (16.1)
5 (Highest income)	162 (16.6)	144 (14.8)
Comorbidities, No. (%)[f,g]	n = 993	n = 990
Cardiovascular disease	542 (54.6)	497 (50.2)
Hypertension	483 (48.6)	433 (43.7)
Diabetes	298 (30.0)	262 (26.5)
Cancer	204 (20.5)	190 (19.2)
Chronic kidney disease	183 (18.4)	161 (16.3)
Dementia	177 (17.8)	177 (17.9)
Chronic obstructive pulmonary disease	79 (8.0)	79 (8.0)
Dyslipidemia	51 (5.1)	51 (5.2)
Atrial fibrillation	40 (4.0)	51 (5.2)
Cirrhosis	16 (1.6)	18 (1.8)
Charlson-Deyo comorbidity score, median (IQR)[f,g]	0 (0-3)	0 (0-2)
Long-term care resident, No. (%)	172 (17.3)	193 (19.5)
Destination hospital characteristics		
Academic hospital, No. (%)	338 (32.2)	331 (32.4)

Abbreviations: GCS, Glasgow Coma Scale; IV, intravenous; NEWS2, National Early Warning Score 2; qSOFA, Quick Sequential Organ Failure Assessment.

[a] Other location denotes that the incident location did not match any of the standard preset categories.

[b] Other could be selected by paramedics on the patient care record when infection was suspected but source was uncertain.

[c] Glasgow Coma Scale (GCS) score is a clinical scoring system used to assess a person's level of consciousness after brain injury and is scored across the 3 domains of eye opening (1 to 4), verbal response (1 to 5), and motor response (1 to 6), with lower scores indicating more impairment and higher scores indicating normal alertness and functioning.

[d] NEWS2 evaluates 6 physiological parameters plus an additional factor for supplemental oxygen, with scores of 5 to 6 representing medium risk and scores of 7 or greater representing high risk of deterioration.[23]

[e] qSOFA assigns 1 point for abnormal respiratory rate (≥22 breaths per minute), systolic blood pressure (≤100 mm Hg), or altered mental status (GCS score <15), with higher scores representing a higher risk of poor clinical outcomes.

[f] Data on income quintile, comorbidities, and Charlson-Deyo comorbidity score[24] were obtained through linkage to provincial health databases.

[g] A Charlson-Deyo comorbidity score of 0 means no comorbidities, while higher scores (up to 37) indicate a greater burden of disease and a higher risk of mortality.[24]

between the groups (37.1 minutes with ceftriaxone vs 38.9 minutes with placebo; **Table 2**).

Data describing hospital treatments were available for 1595 patients (78.0%) (eTables 1 and 2 in Supplement 3). Sepsis or infection was suspected by emergency department clinicians in most patients (96.8% in the ceftriaxone group and 97.4% in the placebo group; **Table 3**; eTable 4 in Supplement 3). Most patients (92.5% in the ceftriaxone group and 92.2% in the placebo group) received an intravenous antibiotic in hospital, typically more than 3 hours after paramedic arrival at patient (mean of 201.1 minutes in the ceftriaxone group and 207.0 minutes in the placebo group). Hypotension (51.6% in the ceftriaxone group and 51.9% in the placebo group) and lactate elevation greater than 2.0 mmol/L (59.3% in the ceftriaxone group and 52.6% in the placebo group) were common after hospital arrival, and treatment with vasopressors was required in 18.7% of patients in the ceftriaxone group vs 20.5% in the placebo group.

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Table 2. Prehospital Characteristics and Care Processes

Variable	Ceftriaxone (n = 1026)	Placebo (n = 1022)	Difference (95% CI)
Time from arrival at patient to administration of study drug, min			
Mean (SD)	37.1 (35.9)	38.9 (55.3)	−1.8 (−5.8 to 2.2)
Median (IQR)	31 (24 to 39)	31 (23 to 41)	
Time from arrival at patient to hospital arrival, mean (SD), min	45.9 (13.9)	45.4 (13.5)	0.4 (−0.7 to 1.6)
Time from arrival at patient to transfer of care in ED, min			
Mean (SD)	94.7 (50.5)	95.5 (58.4)	−0.7 (−5.5 to 4.0)
Median (IQR)	80 (65 to 106)	80 (64 to 103)	
Supplemental oxygen administered, No. (%)	428 (41.7)	415 (40.6)	1.1 (−3.2 to 5.4)
Length of peripheral IV infusion, mean (SD), min	835 (81.4)	818 (80.0)	1.3 (−2.1 to 4.8)
Fluid bolus (≥250 mL) administered, No. (%)	771 (75.1)	744 (72.8)	2.3 (−1.5 to 6.1)
IV fluid delivered from time of arrival at patient to transfer of care in ED, mL			
Mean (SD)	803.8 (746.4)	790.8 (754.0)	13.0 (−52.0 to 78.1)
Median (IQR)	600 (10 to 1500)	500 (0 to 1500)	
Vasopressors prior to transfer of care in ED, No. (%)	7 (0.7)	8 (0.8)	−0.1 (−0.8 to 0.6)
Final vital signs prior to transfer of care in ED			
Systolic blood pressure, mean (SD), mm Hg	99.6 (19.5)	99.2 (18.4)	0.5 (−1.2 to 2.1)
Heart rate/min, mean (SD)	104.7 (22.6)	104.7 (22.1)	0 (−2 to 1.9)
Final systolic blood pressure <100 mm Hg, No. (%)	541 (52.8)	536 (52.5)	0.3 (−4 to 4.7)
Glasgow Coma Scale score <15, No./total No. (%)	452/1018 (44.4)	444/1018 (43.6)	−0.8 (−5.1 to 3.5)
Survival to ED arrival, No. (%)[a]	1026 (100)	1022 (100.00)	−0.1 (−0.3 to 0.1)
Adverse events related to study drug administration, No. (%)	64 (6.2)	15 (1.5)	4.8 (3.1 to 6.4)

Abbreviations: ED, emergency department; IV, intravenous.

[a] One patient in the placebo group who declined transport to the hospital was classified as survived to admission.

The in-hospital mortality rate was 18.0% (n = 182) in the ceftriaxone group vs 18.4% (n = 75) in the placebo group (RR, 0.97 [95% CI, 0.81-1.17]; *P* = .77; unadjusted risk difference, −0.4% [95% CI −3.7% to 3.0%]). The test of interaction for the 2 interventions studied in the 2 × 2 factorial design was not significant (*P* = .82). Sensitivity analyses testing different modeling assumptions yielded similar results (eTable 4 in Supplement 3) and survival curves were similar (eFigure 1 in Supplement 3). Most patients (n = 1771) were admitted to the hospital and similar percentages of patients were admitted to the intensive care unit or received life-support treatments. Other secondary outcomes were similar between the groups (Tables 2, 3, and 4). Treatment effects were consistent across prespecified and post hoc subgroups (Table 4; eTable 3, eFigure 2 in Supplement 3).

There were fewer patients with positive culture results in the ceftriaxone group (40.1%) compared with the placebo group (52.7%) (eTable 5, eTable 6 in Supplement 3). Only 14.8% of patients in the ceftriaxone group vs 13.1% in the placebo group had cultures that grew microorganisms that were resistant to ceftriaxone. Adverse events were rare in both groups (6.2% in the ceftriaxone group and 1.5% in the placebo group) and were most frequently related to pain at the injection site (eTable 7 in Supplement 3).

Discussion

In this large, multicenter, randomized clinical trial, early administration of ceftriaxone in the ambulance to patients with suspected sepsis, defined as infection, fever, and hypotension, did not reduce hospital mortality compared with placebo and usual care in the emergency department.

Prioritizing treatment with early antibiotics for sepsis represents a long-standing recommendation in international clinical practice guidelines.[15] Previous observational studies have shown an association between earlier antibiotics and decreased mortality, particularly among patients in the emergency department or hospitalized patients with septic shock.[5-7,25-27] Conducting randomized clinical trials of earlier vs later antibiotic administration in the hospital would generally be considered impractical or unethical; the current trial overcame these challenges by providing antibiotics in a setting in which these treatments are generally unavailable—at the point of first contact in the ambulance. In this trial, prehospital antibiotics were given to patients with suspected sepsis and hypotension a mean of 3 hours earlier than when provided as part of usual care in hospital, yet this did not translate into differences in outcomes.

Several possibilities were considered to explain the lack of effect in this trial: that the incorrect antibiotic or route were used, that paramedics using the protocol identified patients who were not sick enough to benefit or were not infected, or that enrollment in the trial helped prompt emergency department teams to provide earlier antibiotics. However, intramuscular and intravenous ceftriaxone have similar pharmacokinetics and very low rates of ceftriaxone resistance were detected[28]; enrolled patients frequently had elevated lactate after hospital arrival and had a high associated mortality, similar to that expected for patients with sepsis[29]; most enrolled patients were diagnosed with infection by emergency department physicians and treated with antibiotics; and, despite

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Table 3. Emergency Department and Hospital Care Processes

Emergency department and first 24 h[a]	Ceftriaxone (n = 800)	Placebo (n = 795)	Difference (95% CI)
Infection documented by ED clinician, No. (%)	774 (96.8)	774 (97.4)	−0.6 (−2.3 to 1.1)
Infection source as documented by ED clinician, No. (%)[b]	n = 774	n = 774	
Respiratory	247 (31.9)	231 (29.8)	2.1 (−2.5 to 6.7)
Blood	195 (25.2)	195 (25.2)	0 (−4.3 to 4.3)
Abdominal	60 (7.8)	52 (6.7)	1.0 (−1.5 to 3.6)
Urinary	160 (20.7)	209 (27)	−6.3 (−10.6 to −2.1)
Skin and joint	37 (4.8)	33 (4.3)	0.5 (−1.6 to 2.6)
Other	75 (9.7)	54 (7.0)	2.7 (0 to 5.5)
Antibiotics administered during first 24 h, No./total No. (%)	735/795 (92.5)	730/792 (92.2)	0.3 (−2.3 to 2.9)
Time from paramedic arrival at patient to first antibiotic dose in ED, min	n = 735	n = 730	
Mean (SD)	247.3 (207.7)	252.8 (218.0)	−5.5 (−27.4 to 16.4)
Median (IQR)	188.5 (123.5 to 297)	182.5 (119 to 309)	
Time from randomization to first antibiotic dose in ED, min	n = 733	n = 726	
Mean (SD)	214.9 (204.6)	219.3 (211.3)	−4.4 (−25.8 to 16.9)
Median (IQR)	154 (93 to 164)	152.5 (91 to 268)	
Time from hospital arrival to first antibiotic dose in ED, min	n = 735	n = 730	
Mean (SD)	201.1 (207.1)	207.0 (217.0)	−6.0 (−27.8 to 15.8)
Median (IQR)	138 (78.5 to 252.5)	135 (73 to 261)	
Time from randomization to first antibiotic dose in ED ≥1 h, No./total No. (%)	669/733 (91.3)	666/726 (91.7)	0.5 (−2.4 to 3.3)
Antibiotic administered in the ED, No. (%)[c]	n = 735	n = 730	
Ceftriaxone	492 (66.9)	492 (67.4)	−0.5 (−5.3 to 4.4)
Piperacillin-tazobactam or amoxicillin	338 (46.0)	318 (43.6)	2.4 (−2.7 to 7.5)
Macrolides	130 (17.7)	113 (15.5)	2.2 (−1.6 to 6.0)
Vancomycin, daptomycin, linezolid	99 (13.5)	97 (13.3)	0.2 (−3.3 to 3.7)
Carbapenems	73 (9.9)	97 (13.3)	−3.4 (−6.6 to −0.1)
Anaerobic agents	61 (8.3)	51 (7.0)	1.3 (−1.4 to 4.0)
Fluroquinolones	19 (2.6)	28 (3.8)	−1.2 (−3.1 to 0.6)
Other cephalosporins	17 (2.3)	20 (2.7)	−0.4 (−2.0 to 1.2)
Other antibiotics (not otherwise listed above)	32/735 (4.2)	31/730 (4.2)	0.1 (−2.0 to 2.2)
Any IV fluids administered within first 24 h of ED arrival, No. (%)	692/789 (87.7)	685/789 (86.8)	0.9 (−2.4 to 4.2)
IV fluids administered during first 24 h after ED arrival, mL	n = 789	n = 785	
Mean (SD)	1821.3 (1548.1)	1723.2 (1572.4)	98 (−56.3 to 252.3)
Median (IQR)	1500 (1000 to 2500)	1400 (960 to 2500)	
Total IV fluids administered pre hospital and during first 24 h after ED arrival, mL	n = 789	n = 784	
Mean (SD)	2639.6 (1677.3)	2497.7 (1719.8)	141.9 (−26.1 to 309.9)
Median (IQR)	2500 (1500 to 3500)	2250 (1250 to 3400)	
First vital signs in ED, No.	798	788	
First systolic blood pressure in ED, mean (SD), mm Hg	100.5 (20.5)	100.1 (19.2)	0.4 (−1.6 to 2.3)
First heart rate/min in ED, mean (SD)	107.0 (21.8)	107.3 (22.3)	−0.3 (−2.4 to 1.9)
First temperature in ED, mean (SD), °C	38.4 (0.8)	38.4 (0.9)	0 (−0.1 to 0.1)
Temperature≥ 38.1 °C, No. (%)	574 (71.9)	552 (70.1)	1.9 (−2.6 to 6.3)
First systolic blood pressure in ED <100 mm Hg, No./total No. (%)	412/798 (51.6)	409/788 (51.9)	−0.3 (−5.2 to 4.6)
First CBC results			
Hemoglobin, mean (SD), g/dL [total No.]	11.3 (2.3) [790]	11.2 (2.3) [793]	0.3 (−2 to 2.5)
Hemoglobin <9.0 g/dL, No. (%) [total No.]	108 (13.7) [790]	130 (16.4) [793]	−2.7 (−6.2 to 0.8)
WBC count, mean (SD), 10^3/μL [total No.]	13 (8.2) [790]	13.1 (13.5) [792]	−0.1 (−1.2 to 1)
Platelet count, mean (SD), 10^3/μL [total No.]	206.5 (107.9) [787]	213.1 (117.4) [791]	−6.6 (−17.7 to 4.6)
Lactate, No./total No. (%)	n = 765	n = 774	
≥2 mmol/L	454/765 (59.3)	407/774 (52.6)	6.8 (1.8 to 11.7)
≥4 mmol/L	177/765 (23.1)	164/774 (21.2)	1.9 (−2.2 to 6.1)

Abbreviations: CBC, complete blood count; IV, intravenous; WBC, whole blood count.

SI conversion factor: To convert lactate to mg/dL, divide values by 0.111.

[a] Data on emergency department (ED) measures were available from medical record review only.

[b] See eTable 3 in Supplement 3 for a complete list of infections suspected by ED physicians.

[c] Patients may have received multiple antibiotics, so percentages do not equal 100.

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Table 4. Primary and Secondary Clinical Outcomes

Outcome	Ceftriaxone (n = 1009)	Placebo (n = 1011)	Risk ratio (95% CI)
Mortality			
Hospital mortality (primary outcome), No./total No. (%)[a]	182/1009 (18.0)	186/1011 (18.4)	0.97 (0.81-1.17)
Restricted to liberal IV fluids group[b]	75/416 (18.0)	74/408 (18.1)	0.99 (0.74-1.33)
Restricted to usual IV fluids group[c]	76/408 (18.6)	70/401 (17.5)	1.04 (0.78-1.39)
Restricted to no IV access group[d]	31/185 (16.8)	42/202 (20.8)	0.82 (0.54-1.24)
Mortality to 90 d, No./total No. (%)	273/1009 (27.1)	255/1011 (25.2)	1.07 (0.93-1.24)
Secondary outcomes, No.[e]	n = 993	n = 990	
Mechanical ventilation during first 24 h, No. (%)	80 (8.1)	79 (8.0)	1.01 (0.75-1.36)
Dialysis during first 24 h, No. (%)	22 (2.2)	17 (1.7)	1.29 (0.69-2.41)
Vasopressors administered during first 24 h, No. (%)[f]	149/796 (18.7)	163/794 (20.5)	0.91 (0.69-1.20)
Hospital admission within 24 h, No. (%)	892 (89.8)	879 (88.8)	1.01 (0.98-1.04)
Hospital admission duration, median (IQR), d	8 (5-15)	8 (5-15)	
ICU admission, No. (%)	188 (18.9)	170 (17.2)	1.12 (0.93-1.3)
ICU duration, median (IQR), d	5 (3-8)	5 (3-10)	
Mechanical ventilation during hospitalization, No. (%)	102 (10.3)	101 (10.2)	1.01 (0.78-1.3)
Acute kidney injury, No. (%)[g]	375 (37.8)	339 (34.2)	1.10 (0.98-1.24)
Dialysis during hospitalization, No. (%)	30 (3.0)	32 (3.2)	0.93 (0.57-1.53)
Discharge destination after hospital admission, No. (%)[h]	n = 892	n = 879	
Home	549 (61.5)	508 (57.8)	
Death	142 (15.9)	149 (17.0)	
Long-term care	117 (13.1)	138 (15.7)	
Other	84 (9.4)	84 (9.6)	

Abbreviations: ICU, intensive care unit; IV, intravenous.

[a] $P = .77$ for comparison of primary outcome.

[b] Analyzed according to randomization to liberal IV fluids group in 2 × 2 factorial trial.

[c] Analyzed according to randomization to usual IV fluids group in 2 × 2 factorial trial.

[d] Analyzed according to randomization to no IV access in 2 × 2 factorial trial.

[e] Data on these secondary outcomes available through linkage to ICES databases, see eMethods in Supplement 2 for details.

[f] Data on vasopressor use were available from medical record review only.

[g] Acute kidney injury identified using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes (see eMethods in Supplement 2 for details).

[h] Discharge destination among patients admitted to the hospital.

awareness of trial enrollment, delays to antibiotics in the emergency department were still observed. It is possible that early administration of antibiotics in previous nonrandomized studies served as a surrogate for other aspects of care that contributed to improved outcomes. It is also possible that there is no benefit to providing antibiotics 3 hours earlier than usual care.

One prior trial evaluated prehospital administration of antibiotics using a randomized design. The PHANTASi trial included patients with lower severity of illness, less shock, and lower control group mortality.[14] The PHANTASi trial studied intravenous ceftriaxone, which requires a longer administration time compared with intramuscular ceftriaxone that was used in the current trial. Patients in the PHANTASi control group received in-hospital antibiotics a median of 70 minutes after hospital arrival, compared with a median of 207 minutes after hospital arrival in the placebo group in the current trial. Despite these differences, both trials showed no mortality benefit when antibiotics were provided in the ambulance prior to hospital arrival.

The current trial also showed no benefit from earlier, prehospital antibiotic administration for patients with greater severity of illness. Despite compelling data from observational studies, there was no treatment by group interaction for those with persistent hypotension at hospital arrival, elevated lactate measured in hospital, or those with greater time to transfer of care in the emergency department.

Limitations

There are several limitations. First, the trial design limited the diagnostic approach by paramedics to using "suspicion of sepsis," defined as suspected infection and presence of fever and hypotension. It is possible that use of a different early warning score, point-of-care test, or assessment of capillary refill time would have improved our ability to diagnose infected patients at high risk of poor outcomes.[7,30-32] However, emergency department physicians suspected infection in most enrolled patients, and more than 90% of patients received empiric antibiotics after hospital arrival. Second, blood cultures were not obtained prior to prehospital drug administration and, as expected, the rate of blood culture result positivity was lower in the ceftriaxone group. Third, the presence of hypotension as an inclusion criterion was assessed prior to fluid administration by paramedics, and some of these patients may have improved and appeared less sick after fluid administration. Nonetheless, the 90-day mortality rate was comparable to other recent sepsis trials.[29] Fourth, the trial did not collect information about antibiotic prescribing or symptoms of infection prior to study enrolment, so disease trajectory before paramedic involvement cannot be described. Fifth, the trial enrolled more than 2000 patients but was underpowered to detect small but potentially clinically important differences in mortality.[33]

Conclusions

Among patients with suspected sepsis, earlier treatment with antibiotics in the ambulance did not reduce mortality compared with usual care provided in the emergency department.

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REFERENCES

1. Nguyen HB, Rivers EP, Abrahamian FM, et al; Emergency Department Sepsis Education Program and Strategies to Improve Survival (ED-SEPSIS) Working Group. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. *Ann Emerg Med*. 2006; 48(1):28-54. doi:10.1016/j.annemergmed.2006.02.015

2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315 (8):801-810. doi:10.1001/jama.2016.0287

3. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310. doi:10.1097/00003246-200107000-00002

4. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16): 1546-1554. doi:10.1056/NEJMoa022139

5. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596. doi:10.1097/01.CCM.0000217961.75225.E9

6. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42(8): 1749-1755. doi:10.1097/CCM.0000000000000330

7. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med*. 2017;376 (23):2235-2244. doi:10.1056/NEJMoa1703058

8. Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. *Lancet Infect Dis*. 2012;12(10):774-780. doi:10.1016/S1473-3099(12)70151-2

9. Im Y, Kang D, Ko RE, et al; Korean Sepsis Alliance (KSA) investigators. Time-to-antibiotics and clinical outcomes in patients with sepsis and septic shock: a prospective nationwide multicenter cohort study. *Crit Care*. 2022;26(1):19. doi:10.1186/s13054-021-03883-0

10. Nguyen HB, Corbett SW, Steele R, et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med*. 2007;35(4):1105-1112. doi:10.1097/01.CCM.0000259463.33848.3D

11. Funk D, Sebat F, Kumar A. A systems approach to the early recognition and rapid administration of best practice therapy in sepsis and septic shock. *Curr Opin Crit Care*. 2009;15(4):301-307. doi:10.1097/MCC.0b013e32832e3825

12. Strehlow MC, Emond SD, Shapiro NI, Pelletier AJ, Camargo CA Jr. National study of emergency department visits for sepsis, 1992 to 2001. *Ann*

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Emerg Med. 2006;48(3):326-331.e3313. doi:10.1016/j.annemergmed.2006.05.003

13. Studnek JR, Artho MR, Garner CL Jr, Jones AE. The impact of emergency medical services on the ED care of severe sepsis. *Am J Emerg Med*. 2012;30(1):51-56. doi:10.1016/j.ajem.2010.09.015

14. Alam N, Oskam E, Stassen PM, et al; PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. *Lancet Respir Med*. 2018;6(1):40-50. doi:10.1016/S2213-2600(17)30469-1

15. Prescott HC, Antonelli M, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2026. *Intensive Care Med*. 2026;52(5):863-936. doi:10.1007/s00134-026-08361-1

16. Scales DC, Rogowsky A, Burry L, et al. Prehospital antibiotics and intravenous fluids for patients with sepsis: protocol for a 2×2 factorial randomised controlled trial. *BMJ Open*. 2025;15(5):e104257. doi:10.1136/bmjopen-2025-104257

17. Kahan BC, Hall SS, Beller EM, et al. Reporting of factorial randomized Trials: extension of the CONSORT 2010 Statement. *JAMA*. 2023;330(21):2106-2114. doi:10.1001/jama.2023.19793

18. Lai TL, Shih MC, Zhu G. Modified Haybittle-Peto group sequential designs for testing superiority and non-inferiority hypotheses in clinical trials. *Stat Med*. 2006;25(7):1149-1167. doi:10.1002/sim.2357

19. Seymour CW, Band RA, Cooke CR, et al. Out-of-hospital characteristics and care of patients with severe sepsis: a cohort study. *J Crit Care*. 2010;25(4):553-562. doi:10.1016/j.jcrc.2010.02.010

20. Seymour CW, Rea TD, Kahn JM, Walkey AJ, Yealy DM, Angus DC. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. *Am J Respir Crit Care Med*. 2012;186(12):1264-1271. doi:10.1164/rccm.201204-0713OC

21. Bernard GR, Vincent JL, Laterre PF, et al; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344(10):699-709. doi:10.1056/NEJM200103083441001

22. Scales DC, Rogowsky A, Seymour CW, et al; PITSTOP Investigators. Prehospital fluid resuscitation for patients with suspected sepsis: the PITSTOP-Fluids factorial randomized clinical trial. *JAMA*. Published online November 24, 2026 doi:10.1001/jama.2026.25614

23. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation*. 2013;84(4):465-470. doi:10.1016/j.resuscitation.2012.12.016

24. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619. doi:10.1016/0895-4356(92)90133-8

25. Suttapanit K, Deeiad P, Damdin S, Scales DC, Supatanakij P. Association between early prehospital administration antibiotic and 28-day mortality in sepsis. *Prehosp Emerg Care*. Published online September 26, 2026. doi:10.1080/10903127.2026.2733964

26. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med*. 2017;196(7):856-863. doi:10.1164/rccm.201609-1848OC

27. Peltan ID, Brown SM, Bledsoe JR, et al. ED door-to-antibiotic time and long-term mortality in sepsis. *Chest*. 2019;155(5):938-946. doi:10.1016/j.chest.2019.02.008

28. Scully BE, Fu KP, Neu HC. Pharmacokinetics of ceftriaxone after intravenous infusion and intramuscular injection. *Am J Med*. 1984;77(4C):112-116.

29. Shapiro NI, Douglas IS, Brower RG, et al; National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network. Early restrictive or liberal fluid management for sepsis-induced hypotension. *N Engl J Med*. 2023;388(6):499-510. doi:10.1056/NEJMoa2212663

30. Neyra JA, Legrand M, Tidswell MA, et al. Polymyxin B haemoadsorption in endotoxic septic shock (Tigris): a multicentre, open-label, Bayesian, randomised, controlled, phase 3 trial. *Lancet Respir Med*. 2026;14(5):443-452. doi:10.1016/S2213-2600(26)00047-0

31. Lane DJ, Wunsch H, Saskin R, et al. Screening strategies to identify sepsis in the prehospital setting: a validation study. *CMAJ*. 2020;192(10):E230-E239. doi:10.1503/cmaj.190966

32. ANDROMEDA-SHOCK-2 Investigators for the ANDROMEDA Research Network, Spanish Society of Anesthesiology, Reanimation and Pain Therapy (SEDAR), and Latin American Intensive Care Network (LIVEN), Hernandez G, Ospina-Tascón GA, et al. Personalized hemodynamic resuscitation targeting capillary refill time in early septic shock: the ANDROMEDA-SHOCK-2 randomized clinical trial. *JAMA*. 2025;334(22):1988-1999. doi:10.1001/jama.2025.20402

33. Cuthbertson BH, Scales DC. "Paying the piper": the downstream implications of manipulating sample size assumptions for critical care randomized control trials. *Crit Care Med*. 2020;48(12):1885-1886. doi:10.1097/CCM.0000000000004664

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