Impact of Prehospital Ceftriaxone in Patients with Sepsis

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Disclosures

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Jack Cederberg, PharmD: nothing to disclose

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Objectives

1. Understand the role of antibiotics when treating patients with sepsis or septic shock
2. Review literature evaluating antibiotics in the prehospital setting for presumed sepsis
3. Evaluate local data and outcomes of prehospital ceftriaxone administration by prehospital providers using a standardized sepsis protocol

Background

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Thinking beyond

Background

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection

In the United States, there are approximately 350,000 deaths each year because of sepsis and septic shock

The Surviving Sepsis Campaign provides recommendations for sepsis and septic shock management, including antibiotic utilization

The early administration of antibiotics is among the most important interventions to improve mortality in patients with sepsis

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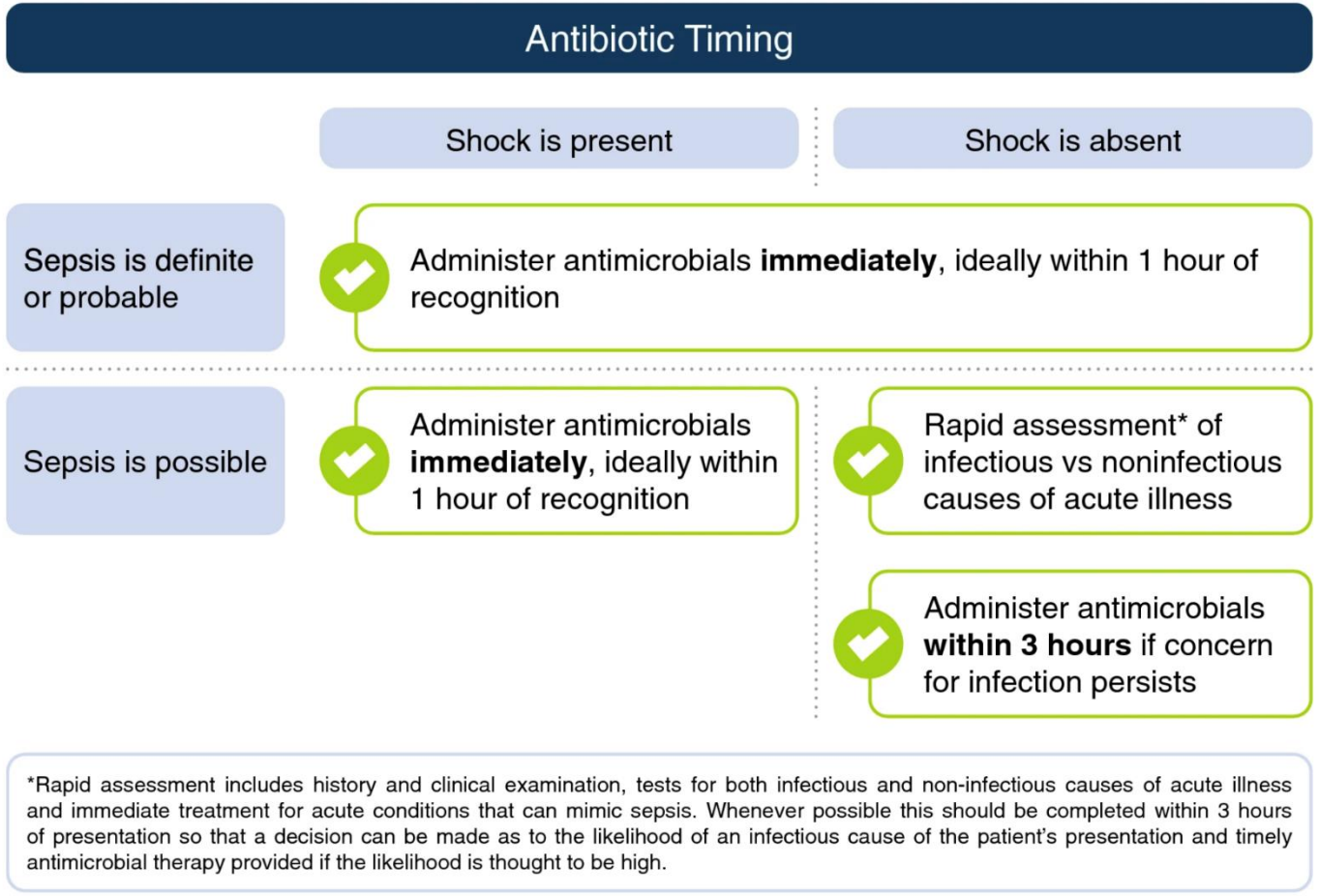
JAMA 2016;315(8):801-810| *Eur Heart J Open* 2021;1(1):1-4| *Intensive Care Med* 2021;47:1181-1247 | *Am J Respir Crit Care Med* 2017;196(7):856-869

Antibiotics in Sepsis



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Intensive Care Med 2021;47:1181-1247

Prehospital Sepsis Alert - Criteria

Suspected infection

AND

At least two of the following:

Altered mentation
RR ≥20 breaths/min
HR >90 bpm
Systolic BP ≤100 mmHg

AND

End tidal CO_2 ≤30 mmHg

RR: respiratory rate, HR: heart rate, bpm: beats per minute, BP: blood pressure, mmHg: millimeters of mercury

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Prehospital Sepsis Alert - Interventions

Interventions

- Ceftriaxone 2 grams IV/IO, mixed in 100 mL NS and dripped *or* slow IV/IO push **AND**
- Normal saline 500 mL IV/IO bolus

If systolic BP ≤90 mmHg or other signs/symptoms of shock, give vasopressor to maintain systolic BP >90 mmHg or improve signs/symptoms of shock

- Epinephrine push dose (1:100,000) 10-20 mcg IV/IO every 2-3 minutes as needed (max total 100 mcg) **OR**
- Epinephrine drip (1 mg/250 mL) 0.05 to 5 mcg/kg/min, titrate to effect

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Peer-Reviewed Literature

Study	Population and Treatment	Results (Antibiotics vs None)	Conclusion
Alam N, et al. 2018 RCT	2698 patients in the Netherlands treated with prehospital antibiotics due to sepsis Ceftriaxone 2 gm: n=1535 Standard of care: n=1137	28-day mortality: 8% vs. 8% (p=NS) Time to antibiotics, min: 26 vs. 70 (p=0.14) 28-day readmission: 7% vs. 10% **(p<0.01)**	Prehospital ceftriaxone did not improve mortality outcomes among sepsis patients
Varney J, et al. 2022 SR/MA	Systematic review of 19 studies involving prehospital administration of antibiotics in sepsis Prehospital antibiotics: n=1779 No prehospital antibiotics: n=1744	28-day mortality: 10.7% vs. 16.7% **(p=0.02)** Hospital LOS: MD 0.11 (95% CI -1.85 to 2.07) ICU LOS: MD 4.50 (95% CI -3.34 to 12.33)	Prehospital antibiotics reduced 28-day mortality but did not shorten hospital and ICU LOS
Kotnarin R, et al. 2023 CS	194 patients in Thailand meeting pre-arrival sepsis criteria by EMS Antibiotic group: n=90 Non-antibiotic group: n=90	In-hospital mortality: 32.2% vs. 47.8% **(p=0.03)** Hospital LOS, days: 9.5 vs. 8.0 (p=NS) ICU admission: 7.8% vs. 6.% (p=NS) ICU LOS, days: 7.0 vs. 13.5 (p=NS)	Administering antibiotics in prehospital settings can reduce in-hospital mortality

RCT: randomized controlled trial, SR/MA: systematic review and meta-analysis, CS: cohort study, EMS: emergency medical services, gm: gram, NS: not significant, LOS: length of stay, ICU: intensive care unit

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Lancet Respir Med 2018;6(1):40-50 | *Health Sci Rep* 2022;5(3):582 | *Open Access Emerg Med* 2023;15:199-206

Methods

Study Purpose

Evaluate the impact of prehospital ceftriaxone on initial culture yields, the development of antimicrobial resistance, and overall safety

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Study Design

Single-center, retrospective cohort study

UT Health San Antonio Institutional Review Board approved

From August 1, 2022 to August 1, 2024

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Population

Inclusion Criteria	Exclusion Criteria
• Presented to University Health emergency department • Met prehospital sepsis alert criteria per San Antonio Fire Department protocol	• Age < 18 years • Pregnant • Transferred from outside hospital • Trauma • Required emergency surgery • Cardiac arrest • On antimicrobials at home • Incarcerated • Allergy to ceftriaxone • Incomplete documentation of EMS vital signs

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Outcome Measures

Primary Outcome

In-hospital mortality

Secondary Outcomes

30-day mortality

Hospital admission requirements, length of stay (hours)

ICU admission requirements, length of stay (hours)

Time to first antibiotic administration (minutes)

Initial culture yields

Development of ceftriaxone resistance

Incidence of *Clostridium difficile* infection

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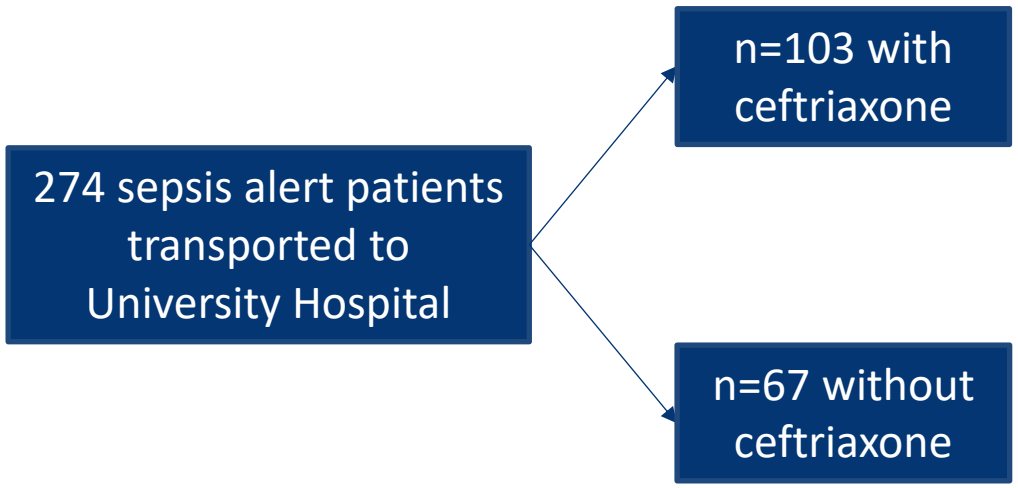
Recruitment



Exclusion Criteria (with CRO)	No.
Trauma	2
Required emergency surgery	3
Out-of-hospital cardiac arrest	1
Antimicrobials at home	10
Incomplete vital signs documentation	51

Exclusion Criteria (without CRO)	No.
Required emergency surgery	1
Antimicrobials at home	5
Incarceration	1
Allergy to ceftriaxone	1
Incomplete vital signs documentation	29

CRO: ceftriaxone

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Statistical Analysis

Variable	Statistical Methods
Categorical comparisons with count less than five	Fisher's Exact Test
Categorical comparisons with count greater than five	Pearson Chi-Square
Medians of non-parametric continuous variables	Mann Whitney U test

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Results

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Patient Demographics

Demographics	Ceftriaxone (n=103)	No Ceftriaxone (n=67)	*p* value
Age (yrs), median (IQR)	68 (56-76)	63 (53-74)	0.13
Male, no. (%)	58 (56.3)	36 (53.7)	0.74
Weight (kg), median (IQR)	72.6 (59-85)	81.6 (63-91.2)	**0.02**
BMI (kg/m²), median (IQR)	25 (20.6-30.1)	27.1 (22-33.5)	**0.02**
Race/Ethnicity, no. (%)			0.88
non-Hispanic Black	9 (8.7)	5 (7.5)	
non-Hispanic White	33 (32)	25 (37.3)	
Hispanic/Latino	56 (54.5)	35 (52.2)	
Other Race/Multiracial*	5 (4.9)	2 (3)	

*Includes Asian (N=3), American Indian/Alaskan Native (N=1), Unknown or not reported (N=3)

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Baseline Characteristics

Characteristics	Ceftriaxone (n=103)	No Ceftriaxone (n=67)	*p* value
Initial vital signs, median (IQR)			
Systolic BP (mmHg)	101 (87-127)	114 (93-136)	**0.04**
Diastolic BP (mmHg)	62 (54-76)	65 (55-78)	0.46
MAP (mmHg)	74.7 (64.7-93)	82 (69.7-99.7)	0.13
Reparatory rate (breaths/min)	20 (16-28)	24 (16-34)	0.05
Heart rate (beats/min)	109 (95-123)	110 (91-132)	0.35
Initial GCS, median (IQR)	15 (13-15)	14 (13-15)	0.83
Initial WBC (K/mcl), median (IQR)	12.4 (8.3-18.2)	13.3 (8.2-17.5)	0.82
Lactic acid (mmol/L), median (IQR)			
Baseline	2.5 (1.8-4.4)	2.5 (1.8-4.2)	0.72
Repeat	2.4 (1.6-3.3)	2.3 (1.4-3.8)	0.67

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Infectious Etiology

Etiology, no. (%)	**Ceftriaxone (n=103)**	**No Ceftriaxone (n=67)**	***p* value**
Neurological	1 (1)	0	1
Respiratory	20 (19.4)	12 (17.9)	0.81
Gastrointestinal/Abdominal	11 (10.7)	12 (17.9)	0.18
Genitourinary	33 (32)	13 (19.4)	0.07
Musculoskeletal	0	2 (3)	0.15
Endovascular	1 (1)	1 (1.5)	1
Skin/Soft Tissue	19 (18.4)	7 (10.4)	0.16
Other/Unknown	25 (24.3)	20 (29.9)	0.42

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Pre-Hospital Data and Interventions

Data Points	Ceftriaxone (n=103)	No Ceftriaxone (n=67)	*p* value
EMS time-to-hospital (min), median (IQR)	37.5 (30.6-44.4)	36.6 (28.3-45.4)	0.67
Antibiotics			
Time to first dose (min), median (IQR)	19.5 (14.6-24.9)	79 (55-152)	**<0.01**
Antibiotic on admission, no. (%)	88 (85.4)	59 (88.1)	0.63
CRO ordered on admission, no. (%)	32 (31.1)	27 (40.3)	0.22
Intravenous fluids			
Received prehospital, no. (%)	74 (71.8)	21 (31.3)	**<0.01**
Received in hospital, no. (%)	94 (91.3)	60 (89.6)	0.71
Total volume (mL/kg IBW), median (IQR)	28.3 (14.6-36.6)	26.5 (14.6-33.6)	0.62

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Clinical Outcomes

Characteristics	Ceftriaxone (n=103)	No Ceftriaxone (n=67)	*p* value
In-hospital mortality, no. (%)	14 (13.6)	9 (13.4)	0.98
30-day mortality, no. (%)	18 (17.5)	13 (19.4)	0.75
Admission requirements			
Hospital admission, no. (%)	99 (96.1)	66 (98.5)	0.65
Hospital LOS (hours), median (IQR)	186.8 (99.2-290.7)	189.5 (114.5-322.4)	0.84
ICU admission, no. (%)	38 (36.9)	34 (50.7)	0.07
ICU LOS (hours), median (IQR)	76.2 (18-205.9)	57.8 (40.3-112.2)	0.84
Vasopressors			
Required, no. (%)	27 (26.2)	22 (32.8)	0.35
Duration (hours), median (IQR)	63.4 (16-161.5)	36.9 (15.8-96.6)	0.53

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Diagnostic Outcomes

Characteristics	Ceftriaxone (n=103)	No Ceftriaxone (n=67)	*p* value
Initial blood cultures, no. (%)			
Positive	19 (18.4)	24 (35.6)	**0.01**
CRO susceptible	5 (26.3)	12 (50)	0.12
Other initial cultures, no. (%)			
Urine	28 (27.2)	18 (26.9)	0.96
Respiratory	7 (6.8)	9 (13.4)	0.15
Stool	0	3 (4.5)	0.06
Abscess/Exudate	7 (6.8)	7 (10.4)	0.4
Other	3 (2.9)	2 (3)	1
CRO susceptible	4 (35)	15 (42.9)	0.49

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Safety Outcomes

Safety Measure	Ceftriaxone (n=103)	No Ceftriaxone (n=67)	*p* value
30-day rate of CRO resistance, no. (%)	10 (9.7)	7 (10.4)	0.88
90-day rate of C *diff* infection, no. (%)	4 (3.9)	3 (4.5)	1

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Discussion

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Thinking beyond

Discussion

- Differences in sepsis/septic shock definitions
- Comparison of baseline characteristics
- Risks and benefits of impacting initial blood culture diagnostics

Limitations

- Sample size limited to single-center approach
- Emergent nature of prehospital documentation
- Intention-to-treat style analysis
- Sample is not reflective of the totality of our local prehospital sepsis resuscitation

Conclusion

Prehospital ceftriaxone:

- Reduced time to initial antibiotics
- Did not impact in-hospital or 90-day mortality
- Reduced initial blood culture yields
- Did not reduce admission requirements or impact disposition
- Did not result in adverse safety outcomes

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