

## **DATA SUPPLEMENT**

### **PREHOSPITAL CARE AND EMERGENCY DEPARTMENT DOOR-TO- ANTIBIOTIC TIME IN SEPSIS**

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**Supplemental methods.**

**Table E1.** Terms or phrases in emergency department chief complaints indicative of suspicion or diagnosis of sepsis or infection at ED triage

ED chief complaint	Number of subjects*
Sepsis or septic shock	50
Fever	37
Rigors or chills	10
Cough	13
Dysuria	1
Named specific source of infection	41
Total subjects with ED chief complaints indicative of sepsis	117/361

\* Some subjects had >1 triage chief complaint component consistent with suspicion or diagnosis of sepsis or infection

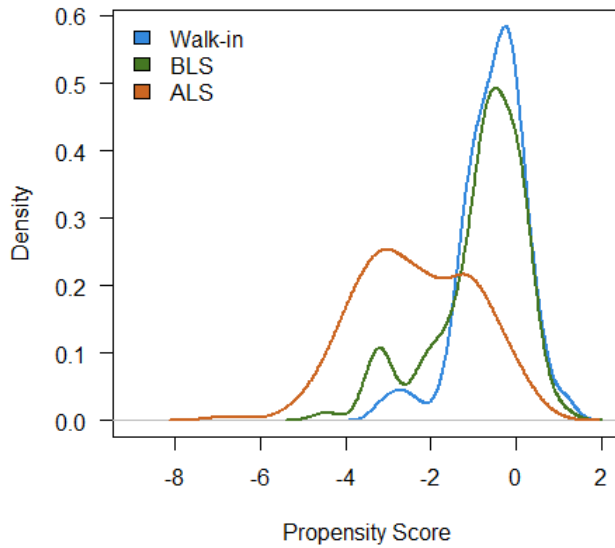
Propensity score analysis

Propensity scores provide the probability of treatment assignment based on known baseline characteristics, offering a useful if still imperfect method to mitigate the risk of confounding by indication in an observational analysis of different treatment strategies or processes (1-3). We conducted two propensity score-based sensitivity analyses. Since walk-in, BLS, and ALS care provide an ordered sequence of prehospital care intensity, propensity scores for prehospital care level (walk-in, BLS, or ALS) were fit using a proportional odds logistic regression model for the 361 community-dwelling patients in the primary analysis (4,5). Predictor variables included in the model were source of infection (pneumonia, intraabdominal/gastrointestinal, skin or soft tissue, urinary tract, unknown/other/no source); nighttime ED arrival; Hispanic ethnicity or non-white race; age; Charlson comorbidity index; and first-available GCS; systolic blood pressure; and respiratory rate. The prehospital care level propensity score for each study subject was calculated as the logit of the first fitted values of the proportional odds logistic regression model. Since this model is constrained to have the odds be proportional between each level, all necessary information is contained in the first fitted value. The distribution of generated propensity scores is shown in Table E2 and Figure E1.

**Table E2.** Summary statistics of generated propensity scores

EMS level	N (%)	Mean	St.Dev	Min	Max
Walk-in	101 (28%)	-0.5	0.8	-3.2	1.2
Basic Life Support	111 (30.7%)	-0.8	1.1	-4.5	1.1
Advanced Life Support	149 (41.3%)	-2.3	1.4	-6.8	0.6
Total	361 (100%)	-1.4	1.4	-6.8	1.2

**Figure E1.** Distribution of propensity scores by actual level of prehospital care.



The propensity scores were used in two analyses . First, we repeated the primary analysis using stabilized inverse probability of treatment weighting (IPTW) based on a propensity score (28,29). Standardized between-group differences for model covariates before and after stabilized IPTW are shown in Table E3 and demonstrates good improvement in standardized differences after IPTW. The IPTW model, which included the MEDS score as an independent covariate, assigned each subject a regression weight inverse to that subject’s probability of receiving each level of care, thereby balancing covariate distributions across prehospital treatment levels. Stabilization of weights was achieved by using the mean treatment level probability (rather than unity) as the numerator for regression weight calculation.

**Table E3.** Standardized differences in model covariates before and after inverse probability of treatment weighting

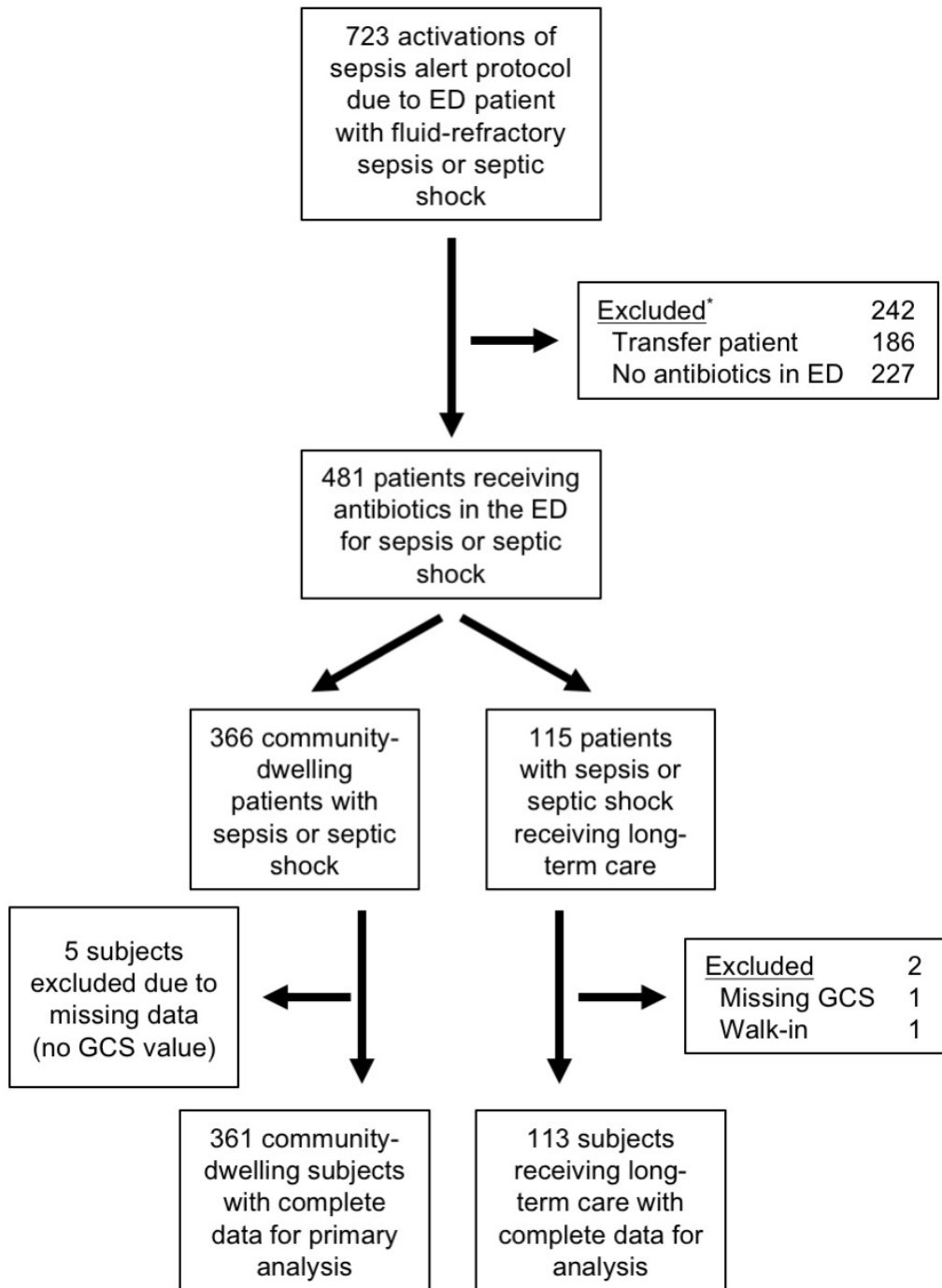
Variable	Standardized differences					
	Walk-in vs BLS		Walk-in versus BLS		BLS versus ALS	
	Simple	IPTW	Simple	IPTW	Simple	IPTW
Charlson index	0.079	0.082	0.078	0.008	0.003	0.091
Age	0.442	0.267	0.266	0.093	0.169	0.361
First systolic blood pressure	0.063	0.040	0.374	0.099	0.423	0.126
First respiratory rate	0.079	0.021	0.334	0.246	0.361	0.204
Nighttime ED arrival	0.299	0.327	0.325	0.155	0.025	0.170
Female sex	0.130	0.244	0.137	0.082	0.268	0.327
Non-white race or Hispanic	0.131	0.087	0.289	0.040	0.156	0.046
GCS $\leq$ 13	0.258	0.003	1.17	0.092	0.891	0.089
Infection source-Pneumonia	0.435	0.550	0.334	0.387	0.687	0.546

For the linear regression model with propensity score adjustment sensitivity analysis, the propensity score and MEDS score were employed as the adjustment variables for the prehospital level of care exposure of interest (6).

## REFERENCES

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**Figure E2.** Subject inclusion flow diagram



\* Some subjects met both exclusion criteria

**Table E4.** Demographic and clinical characteristics by level of prehospital care for sepsis patients sent from long-term care facilities

	Basic life support (N=44)	Advanced life support (N=69)
Age	61.8 (17.8)	63.3 (14.3)
Female sex	18 (40.9%)	22 (31.9%)
Non-white race or Hispanic	20 (45.5%)	26 (37.7%)
Prehospital care		
Prehospital IV access	0 (0%)	53 (76.8%)
Prehospital shock	15 (34.1%)	36 (52.2%)
EMS scene to ED arrival (mins)	34.3 (18.3)	39.5 (13.9)
Infection source		
Pneumonia	13 (29.6%)	26 (37.7%)
Soft tissue infection	7 (15.9%)	8 (11.6%)
Intraabdominal infection	3 (6.8%)	3 (4.3%)
Urinary tract infection	18 (40.9%)	22 (31.9%)
Other/unknown	3 (6.8%)	10 (14.5%)
ED admission data		
Hypotension by ED arrival*	21 (47.7%)	43 (62.3%)
First Glasgow Coma Score*	14 (8.5-15)	8 (4-13)
Lactate (mmol/L)	3 (1.9-4.95)	4.5 (2.9-7.3)
White blood count (1000/dL)	14.7 (7.9)	13.9 (8.3)
SOFA score	3 (1-4.5)	6 (4-8)
ED management data		
Total IV fluid (L)*	4.0 (3.0-5.0)	4.0 (3.0-5.0)
Vasopressors*	9 (20.5%)	27 (39.1%)
Minutes to antibiotic initiation	160 (122)	99 (72)
Antibiotic initiation $\leq$ 3 hours	31 (70.5%)	62 (89.9%)
MEDS score	8.0 (3.5)	10.5 (3.3)
Charlson comorbidity index	2.5 (2.0)	3.0 (2.4)
Death before discharge	9 (20.5%)	15 (21.7%)
ED length of stay (mins)	411 (293-527)	270 (203-333)
Hospital length of stay (days)	6.4 (4.0-13.4)	6.8 (3.5-11.8)

Values reported as mean (SD), N (%) or median (IQR).

\* Includes all care in both ED and prehospital setting

Abbreviations: ED, emergency department; EMS, emergency medical services; IV, intravenous; MEDS score, Mortality in Emergency Department Sepsis score; mins, minutes; SOFA, Sequential Organ Failure Assessment

**Table E5.** Sensitivity analysis using stabilized inverse probability of treatment weighting based on propensity score to assess association of prehospital care with door-to-antibiotic time in community-dwelling sepsis patients

Variable	Adjusted regression coefficient* (95% CI)	p value
Level of prehospital care		<0.001 <sup>†</sup>
Basic life support vs no prehospital care	15.3 (-18.4, 51.0)	0.51 <sup>‡</sup>
Advanced life support vs no prehospital care	-37.7 (-71.0, -4.3)	0.022 <sup>‡</sup>
Advanced life support vs basic life support	-54.0 (-85.6, -22.3)	<0.001 <sup>‡</sup>
MEDS score	-9.0 (-12.1, -6.0)	<0.001

Abbreviations: CI, confidence interval; MEDS score, Mortality in Emergency Department Sepsis score

\* Expected change in door-to-antimicrobial time for a one unit change in exposure variable.

<sup>†</sup> Result of F-test to assess overall significant effect of prehospital level of care on door-to-antibiotic time.

<sup>‡</sup> Confidence intervals and p values adjusted for multiple comparisons using Tukey's multiple comparisons correction.

**Table E6.** Sensitivity analysis using propensity score adjustment to assess association of prehospital care with door-to-antibiotic time in community-dwelling sepsis patients

Variable	Adjusted regression coefficient* (95% CI)	p value
Level of prehospital care		0.007 <sup>†</sup>
Basic life support vs no prehospital care	4.6 (-31.5, 40.7)	0.95 <sup>‡</sup>
Advanced life support vs no prehospital care	-43.2 (-83.3, -3.0)	0.032 <sup>‡</sup>
Advanced life support vs basic life support	-47.8 (-84.9, -10.6)	0.008 <sup>‡</sup>
MEDS score	-6.3 (-9.9, -2.7)	<0.001
Propensity score	10.6 (-0.26, 21.4)	0.056

Abbreviations: CI, confidence interval; MEDS score, Mortality in Emergency Department Sepsis score

\* Expected change in door-to-antimicrobial time for a one unit change in exposure variable.

<sup>†</sup> Result of F-test to assess overall significant effect of prehospital level of care on door-to-antibiotic time.

<sup>‡</sup> Confidence intervals and p values adjusted for multiple comparisons using Tukey's multiple comparisons correction.



**Table E7.** Adjusted association of prehospital care with door-to-antibiotic time in community-dwelling sepsis patients without hypotension by ED arrival

Variable	Adjusted difference in door-to-antibiotic time* (95% CI)	p value
Overall comparison		0.24 <sup>†</sup>
Basic life support vs no prehospital care	-10.4 (-63.6, 42.8)	0.89 <sup>‡</sup>
Advanced life support vs no prehospital care	-45.6 (-110.1, 19.0)	0.22 <sup>‡</sup>
Advanced life support vs basic life support	-35.2 (-99.0, 28.7)	0.40 <sup>‡</sup>

Abbreviation: CI, confidence interval

\* Adjusted for nighttime emergency department arrival, Mortality in ED Sepsis score, source of infection, Hispanic ethnicity or non-white race, age, Charlson comorbidity index, first-available Glasgow Coma Score, and first-available respiratory rate.

<sup>†</sup> Result of F-test to assess overall significant effect of prehospital level of care on door-to-antibiotic time.

<sup>‡</sup> Confidence intervals and p values adjusted for multiple comparisons using Tukey's multiple comparisons correction.

**Table E8.** Adjusted association of prehospital care with door-to-antibiotic time in community-dwelling sepsis patients with hypotension by ED arrival

Variable	Adjusted difference in door-to-antibiotic time* (95% CI)	p value
Overall comparison		0.032 <sup>†</sup>
Basic life support vs no prehospital care	42.3 (-3.0, 87.5)	0.073 <sup>‡</sup>
Advanced life support vs no prehospital care	4.4 (-38.9, 47.8)	0.97 <sup>‡</sup>
Advanced life support vs basic life support	-37.8 (-76.1, 0.4)	0.053 <sup>‡</sup>

Abbreviation: CI, confidence interval

\* Adjusted for nighttime emergency department arrival, Mortality in ED Sepsis score, source of infection, Hispanic ethnicity or non-white race, age, Charlson comorbidity index, first-available Glasgow Coma Score, and first-available respiratory rate.

<sup>†</sup> Result of F-test to assess overall significant effect of prehospital level of care on door-to-antibiotic time.

<sup>‡</sup> Confidence intervals and p values adjusted for multiple comparisons using Tukey's multiple comparisons correction.

**Table E9.** Interaction between hypotension by ED arrival and prehospital care with door-to-antibiotic time in community-dwelling sepsis patients

Variable	Adjusted difference in door-to-antibiotic time* (95% CI)	p value
Interaction of prehospital care and hypotension		0.033 <sup>†</sup>
With versus without hypotension by ED arrival		
No prehospital care	-95.2 (-151.5, -38.8)	<0.001 <sup>‡</sup>
Basic life support	-47.7 (-92.3, -2.3)	0.038 <sup>‡</sup>
Advanced life support	-9.0 (-52.4, 34.4)	0.69 <sup>‡</sup>
No hypotension by ED arrival		
Basic life support vs no prehospital care	-8.9 (-51.9, 34.2)	0.88 <sup>‡</sup>
Advanced life support vs no prehospital care	-61.4 (-110.1, -12.6)	0.009 <sup>‡</sup>
Advanced life support vs basic life support	-52.5 (-101.3, -4.7)	0.032 <sup>‡</sup>
Hypotension by ED arrival		
Basic life support vs no prehospital care	38.9 (-32.8, 110.6)	0.41 <sup>‡</sup>
Advanced life support vs no prehospital care	24.9 (-42.5, 92.2)	0.66 <sup>‡</sup>
Advanced life support vs basic life support	-14 (-70.0, 40.9)	0.82 <sup>‡</sup>

Abbreviation: CI, confidence interval; ED, emergency department

\* Adjusted for nighttime emergency department arrival, Mortality in ED Sepsis score, source of infection, Hispanic ethnicity or non-white race, age, Charlson comorbidity index, hypotension by ED arrival, first-available Glasgow Coma Score, and first-available respiratory rate.

<sup>†</sup> Result of F-test to assess overall significant effect of interaction term between prehospital level of care and hypotension by ED arrival.

<sup>‡</sup> Confidence intervals and p values adjusted for multiple comparisons using Tukey's multiple comparisons correction.