CHEST Online Supplement

ED Door-to-Antibiotic Time and Long-term Mortality in Sepsis

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e-Appendix 1. Supplemental methods.

Data validation and missing data abstraction

Eligible subjects were identified and clinical and demographic data abstracted from the Intermountain Healthcare Electronic Data Warehouse.[1] This curated and carefully maintained database collects and merges patient-level data from clinical, administrative, billing, and other databases within the Intermountain system. Antibiotic initiation times were verified by manual chart review when the electronic query showed door-to-antibiotic time ≤20 minutes or >12 hours. For members of the study cohort (7.8%) who were included in an independent sepsis registry, we also compared electronically-abstracted data to antibiotic administration times obtained for the registry by manual chart review by trained nurses. This comparison demonstrated perfect agreement for 84.7% of evaluated records, near-perfect agreement (≤6 minute difference) for 1.0%, disagreement in which chart re-review proved the electronic query correct for 13.5%, and 0.8% for which the electronic query appeared incorrect relative to manual chart review.

For data required for the multivariable analysis that was missing in the electronic database or exhibited outlying values (e.g. respiratory rate <4 or ≥55), we performed manual review of patient records. Data missingness ranged from 0.01% (initial systolic blood pressure) to 8.3% (mode of arrival to ED). The only other variable with >1.5% missingness was initial Glasgow Coma Scale (GCS, 6.8%). In addition to the principal investigator (IDP), a team of five abstractors comprised of experienced research coordinators and medical students employed standardized protocols and definitions to verify outlying values and complete missing data. Abstractors were unaware of patients' mortality outcomes or door-to-antibiotic time. Abstractors employed a data abstraction manual which specified element definitions, abstraction criteria, and the priority order of eligible sources from which chart review could obtain each abstracted data element. Standardized data entry was performed using the secure, web-based Research Electronic Data Capture (REDCap) interface, making use of this tool's ability to provide prompts, range checking for numerical entries, and real-time and after-the-fact validation.[2] Each abstractor underwent individualized training lasting approximately 2 hours with the principal investigator. After initial training, the principal investigator reviewed every abstraction by each abstractor until they demonstrated proficiency with no disagreement for an abstraction set of 30-40 charts. Thereafter, the principal investigator reviewed queries generated by the abstractors as well as approximately 5% of non-flagged abstractions to guard against systematic errors and provided feedback to individual abstractors or the group as needed. The entire team also met periodically to discuss data abstraction results and questions.

Among records for which GCS was missing in the electronic database, free text clinical documentation included an explicit GCS value in approximately 15-20% of records. For the remainder, GCS was calculated per the standard GCS point system based on the history and physical exam documented by the ED clinicians. The point system was supplemented by prespecified conversions for

clinical exam findings such as "somnolent." Similarly, where missing, mode of arrival to the ED — ambulance versus "walk in" — was obtained by review of free text physician and nurse documentation. Because both GCS and mode of arrival abstraction required some interpretation of free text data, we performed dual data abstraction for 10% of records that were manually abstracted for these variables. Interrater agreement was "near perfect"[3] for both arrival via ambulance versus walk-in (κ 0.85, 95% CI 0.64-1.00) and for GCS (weighted κ 0.89, 95% CI 0.82-0.96). Of note, there was perfect (100%) interrater agreement for assigning GCS as ≥14 versus ≤13, the format in which GCS was entered into multivariable models in this study.

Exposure & covariates measurement

An initial systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg defined admission hypotension. Receipt of prehospital medical care was indicated by arrival to the ED via ambulance rather than as a walk-in patient. ED acuity was recorded by ED triage nurses using the Canadian Triage Acuity Score, a standardized five-point scale.[4] Since only 9 patients were scored in the lowest acuity category, these patients were combined into the next highest category for analysis. We measured patient comorbidities using a weighted version of the Elixhauser score as derived by von Walraven.[5,6] Mortality risk was calculated using the validated Mortality in ED Sepsis (MEDS) score.[7,8] Baseline SOFA score was calculated using the most recent available data in the window beginning three years prior to the index ED visit and ending 24 hours before ED arrival. Consistent with the Sepsis-3 guidelines,[9] the baseline SOFA score was assumed to be 0 when no applicable data was identified within this time frame. Insurance status was classified as uninsured, Medicaid, Medicare, or private. Patients who were divorced, widowed, or separated from their spouse were classified as not married. Due to its non-normal distribution, GCS was dichotomized as abnormal mentation (≤13) versus normal mentation (≥14) based on the original derivation of the quick SOFA score.[10] For patients presenting prior to October 1, 2015, a discharge diagnosis of sepsis was determined from patients' International Classification of Disease-Clinical Modification version 9 (ICD-9-CM) diagnosis codes using the modified Angus method.[11,12]

Sensitivity analyses

Analysis of the association between door-to-antibiotic time and sepsis mortality is challenged by confounding by indication, which arises here because a major driver of earlier antibiotics (higher illness severity) also influences mortality.[13] In addition to the primary analysis employing multivariable logistic regression to control for confounding, we employed two sensitivity analyses using alternative statistical methods — inverse probability of treatment weighting (IPTW) and matching — to control for confounding by indication.

For the IPTW analysis, we first constructed a propensity score for antibiotic initiation >3 hours after ED arrival.[14,15] Variables included when creating the propensity score were identical to those used for the adjustment in the primary analysis. This propensity score was then used for inverse probability of treatment weighting for robust logistic regression evaluating the association of antibiotic time >3 hours and 1-year mortality analysis. Graphical assessment (Figure E1) demonstrated good predictor balance after IPTW.[16] We report average treatment effect on the treated (ATT), which may be interpreted as the change in odds of mortality due to delayed antibiotics among patients who had door-to-antibiotic time >3 hours.[17]

The matched analysis was conducted using a method based on the similarity/dissimilarity between subjects called the gain-weighted Gower's distance.[18,19] Conceptually, the Gower's distance measures the total dissimilarity for a list of variables; a variation developed by Podani allows incorporation of ordinal variables.[20,21] Gain weighting the Gower's distance allowed prioritizing variables with greater utility ("gain") for predicting whether antibiotics were initiated after three hours when calculating the Gower's distance. Gain — also called variable importance — was computed as the sum of squared improvements over each variable's split points in an ensemble of decision trees generated using extreme gradient boosting (Figure E2).[22-24]

Matching based on the gain-weighted Gower's distance used 1:1 greedy matching with replacement and a caliper radius of half the row-wise average standard deviation. This approach assigned 3,760 unique patients to 2,255 matched pairs exhibiting improved within-pair predictor balance when compared to the unmatched sample (Figure E1). We employed generalized estimating equations with a binomial distribution, logit link, an exchangeable correlation matrix, and robust sandwich estimator to account for the correlation structure of the matched pairs when analyzing the association of door-to-antibiotic time >3 hours and 1-year mortality.[25]

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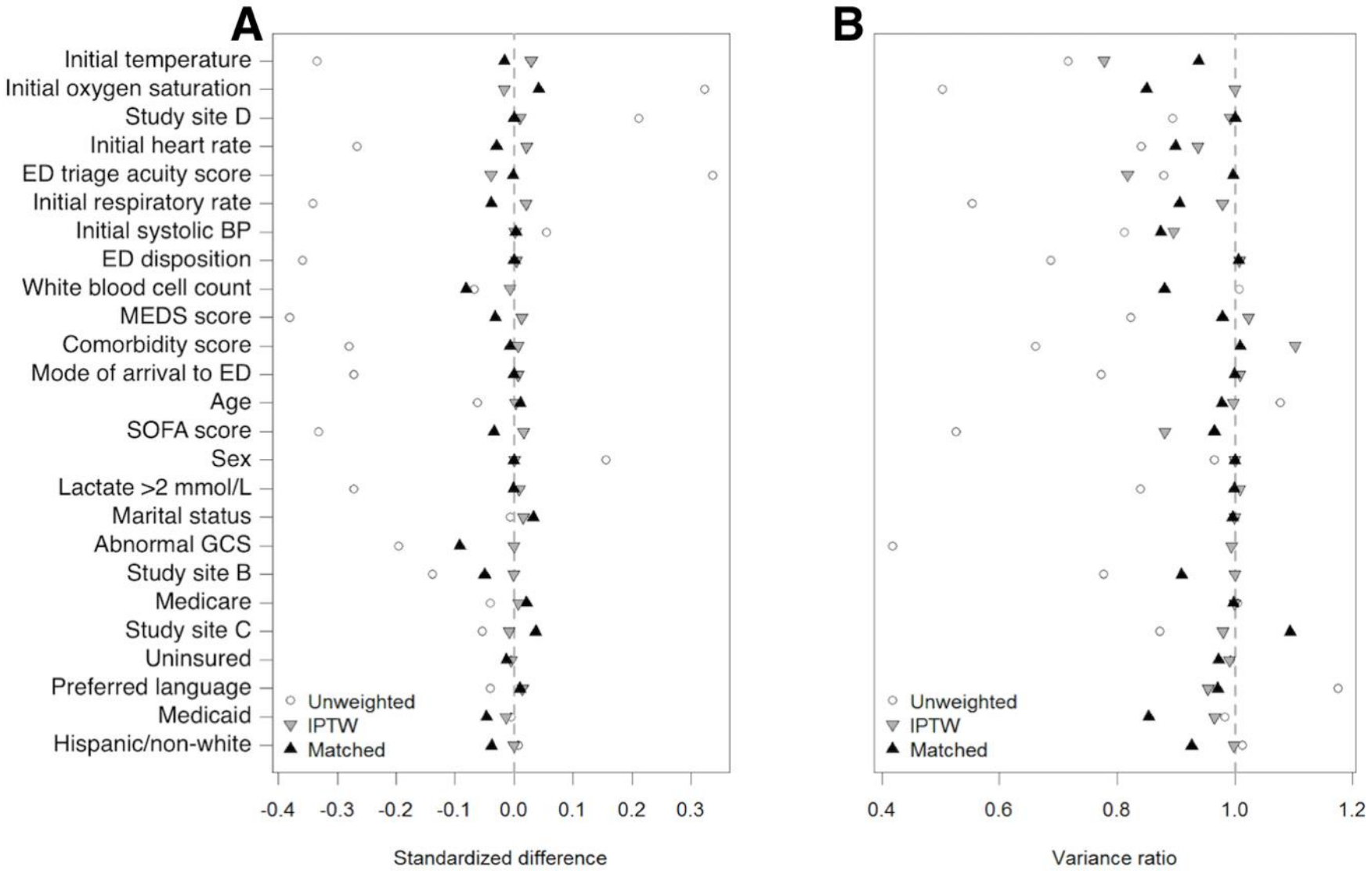
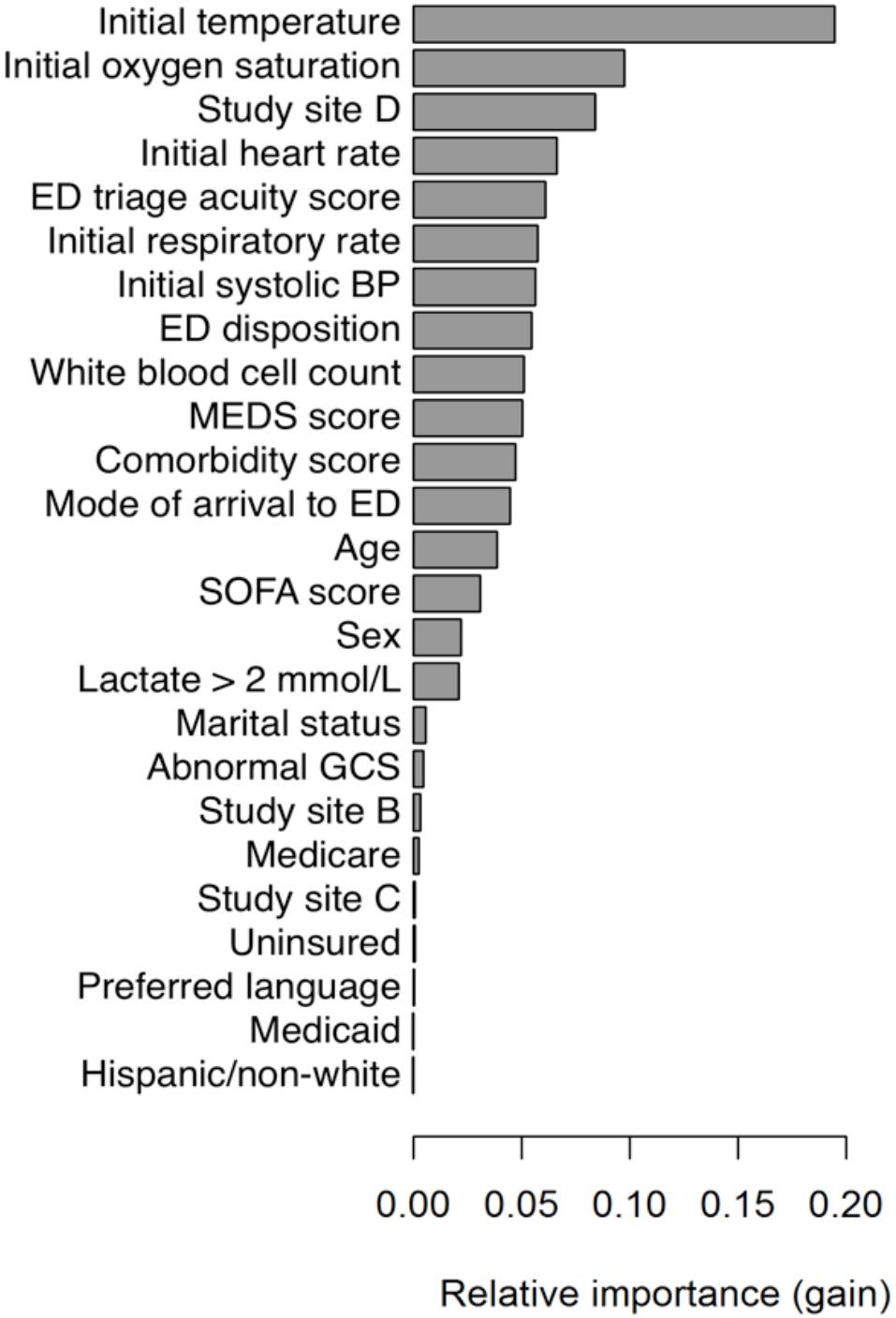
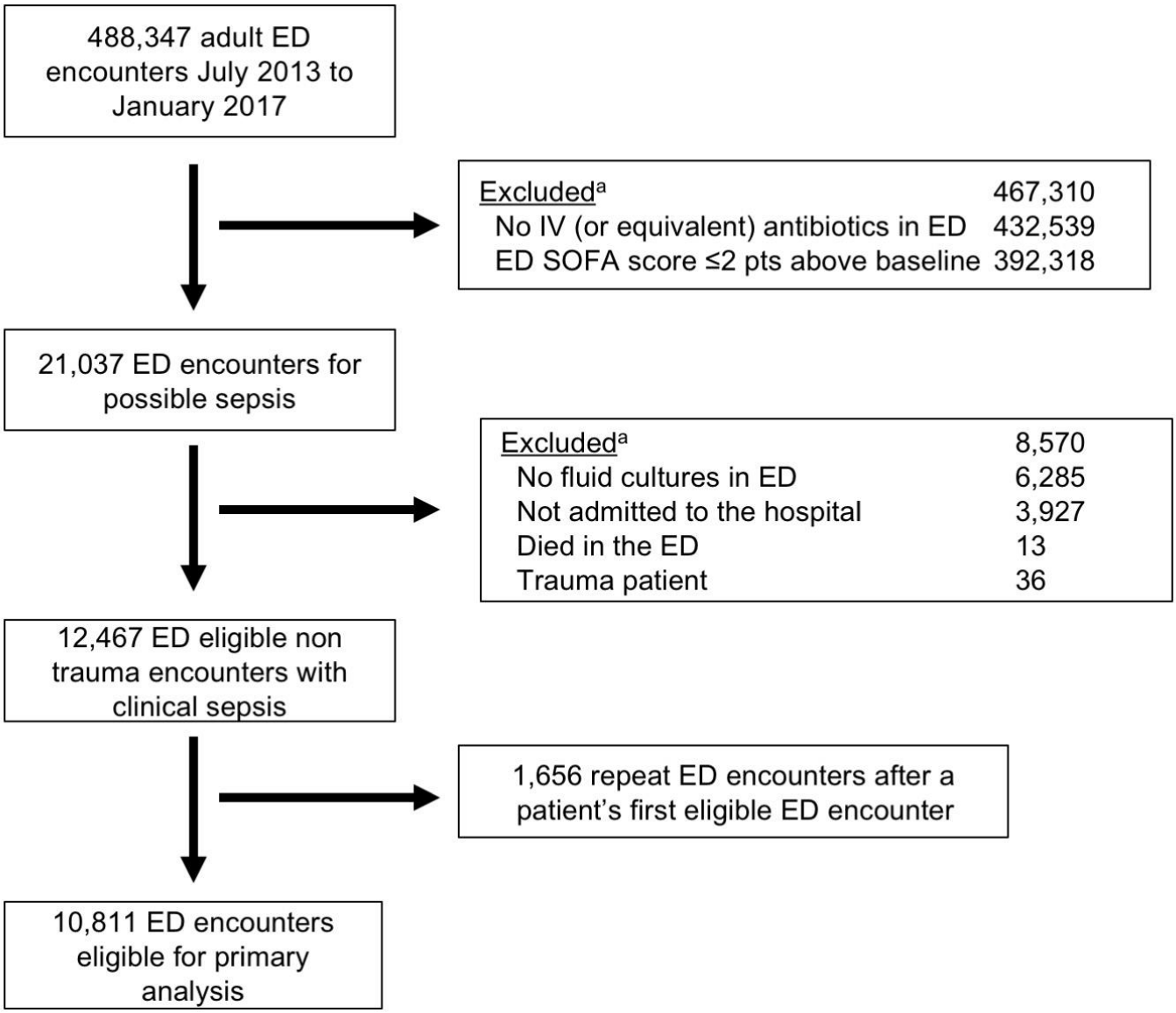


e-Figure 1. Comparison of (A) standardized mean differences and (B) variance ratios for the unweighted sample, after inverse probability of treatment weighting (IPTW) or matching based on gain-weighted Gower's distances. Values closer to 0 for standardized mean differences and values closer to 1 for variance ratio reflect better balance.



e-Figure 2. Variable importance plot for prediction of antibiotic initiation >3 hours from ED arrival based on extreme gradient boosting.



e-Figure 3. Subject inclusion/exclusion flow diagram.
[a] Some patients had >1 reasons for exclusion.

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e-Table 1. Adjusted marginal mortality for ED patients with sepsis based on door-to-antibiotic time

Measure of door-to-antibiotic time	1-year mortality		In-hospital mortality		30-day mortality		90-day mortality	
	Adjusted difference in expected mortality[a] (95% CI)	p value	Adjusted difference in expected mortality[a] (95% CI)	p value	Adjusted difference in expected mortality[a] (95% CI)	p value	Adjusted difference in expected mortality[a] (95% CI)	p value
Per hour from ED arrival	1.1% (0.7-1.6%)	<0.001	0.5% (0.2-0.8%)	<0.001	0.7% (0.3-1.0%)	<0.001	0.7% (0.4-1.1%)	<0.001
>1 hour versus ≤1 hour	2.7% (-0.1-0.6%)	0.057	0.8% (-0.2-2.0%)	0.11	0.7% (-1.1-2.4%)	0.44	1.8% (0.4-3.9%)	0.11
>3 hours versus ≤3 hours	2.9% (0.15-4.4%)	<0.001	1.2% (0.4-2.1%)	0.004	1.5% (0.5-2.6%)	0.005	2.4% (1.1-3.6%)	<0.001
Door-to-antibiotic time interval								
≤1 hr	Reference		Reference		Reference		Reference	
>1 to ≤2 hrs	2.0% (-0.1-4.9%)	0.19	0.8% (-0.4-1.9%)	0.19	-0.2% (-1.9-1.6%)	0.86	1.2% (-1.0-3.4%)	0.30
>2 to ≤3 hrs	2.0% (-0.1-4.9%)	0.17	0.5% (-0.6-1.7%)	0.37	1.0% (-0.8-2.8%)	0.28	1.2% (-1.0-3.4%)	0.29
>3 to ≤4 hrs	3.9% (0.1-7.0%)	0.013	1.5% (0.2-2.9%)	0.028	1.5% (-0.5-3.5%)	0.15	3.1% (0.7-5.5%)	0.012
>4 to ≤5 hrs	4.0% (0.6-7.5%)	0.021	1.0% (-0.6-2.7%)	0.23	1.4% (-0.9-3.8%)	0.22	2.8% (0.1-5.6%)	0.043
>5 to ≤6 hrs	7.5% (3.4-11.6%)	<0.001	3.0% (0.6-5.3%)	0.013	4.1% (1.1-7.1%)	0.007	5.6% (2.1-9.0%)	0.001
>6 hrs	8.8% (4.2-13.5%)	<0.001	5.1% (1.9-8.4%)	0.002	4.9% (1.3-8.5%)	0.008	4.7% (7.6-8.7%)	0.020

Abbreviations: CI, confidence interval; ED, emergency department

[a] Adjusted for pooled triage acuity score; receipt of prehospital medical care; Mortality in ED Sepsis score, Sequential Organ Failure Assessment score; initial vital signs (systolic blood pressure, abnormal Glasgow Coma Scale, heart rate, temperature, respiratory rate, oxygen saturation); ED disposition (intensive care vs ward); comorbidity score; marital status; insurance type; age; sex; Hispanic ethnicity or non-white race; hospital; non-English preferred language, and initial white blood count and initial lactate tested and >2 mmol/L

e-Table 2. Sensitivity analyses of the adjusted association of door-to-antibiotic time and 1-year mortality in ED patients with sepsis

Sensitivity analysis	Adjusted OR for 1-year mortality per 1 hour increase in door-to-antibiotic time (95% CI)	p value
Patients with ICD-9-CM hospital discharge diagnosis consistent with sepsis[a]	1.17 (1.09-1.25)	<0.001
Patients with door-to-antibiotic time ≤6 hours[a]	1.09 (1.04-1.15)	<0.001
Simplified set of adjustment variables[b]	1.12 (1.08-1.16)	<0.001

Abbreviations: CI, confidence interval; ED, emergency department; OR, odds ratio

[a] Adjusted for pooled triage acuity score; receipt of prehospital medical care; Mortality in ED Sepsis score, Sequential Organ Failure Assessment score; initial vital signs (systolic blood pressure, abnormal Glasgow Coma Scale, heart rate, temperature, respiratory rate, oxygen saturation); ED disposition (intensive care vs ward); comorbidity score; marital status; insurance type; age; sex; Hispanic ethnicity or non-white race; hospital; non-English preferred language, and initial white blood count and initial lactate tested and >2 mmol/L

[b] Adjusted for pooled triage acuity score; Mortality in ED Sepsis score, Sequential Organ Failure Assessment score; initial vital signs (systolic blood pressure, abnormal Glasgow Coma Scale); comorbidity score; age; hospital; and initial lactate tested and >2 mmol/L

e-Table 3. Sensitivity analyses employing alternative analysis methods to measure risk of 1-year mortality associated with door-to-antibiotic time >3 hours

Analysis method	OR for 1-year mortality when door-to-antibiotic time is >3 hours (95% CI)	p value
Logistic regression[a]	1.27 (1.13-1.43)	<0.001
Propensity-based inverse probability of treatment weighting[b]	1.28 (1.13-1.44)	<0.001
Matched pairs based on gain-weighted Gower's distance[c]	1.27 (1.06-1.53)	0.01

Abbreviations: CI, confidence interval; OR, odds ratio

[a] Adjusted for pooled triage acuity score; receipt of prehospital medical care; Mortality in ED Sepsis score, Sequential Organ Failure Assessment score; initial vital signs (systolic blood pressure, abnormal Glasgow Coma Scale, heart rate, temperature, respiratory rate, oxygen saturation); ED disposition (intensive care vs ward); comorbidity score; marital status; insurance type; age; sex; Hispanic ethnicity or non-white race; hospital; non-English preferred language, and initial white blood count and initial lactate tested and >2 mmol/L

[b] Average treatment effect among the treated (subjects receiving antibiotics beyond 3 hours)

[c] Includes 2255 matched pairs and 3760 unique patients

e-Table 4. Prior studies examining the association between time-to-antibiotics and long-term mortality in sepsis.

Author (year)	Population		Antibiotic window & delay units		N	Outcome	Adjusted risk per unit of antibiotic delay (95% CI)[a]
	Age group	Population	Antibiotic window start point	Analysis units			
Larché 2003[1]	Adults	Cancer patients admitted to ICU with septic shock	ICU arrival	>2 hr[b]	88	30-day mortality	7.05 (1.17-42.21)
Bloos 2014[2]	Adults	ICU patients with sepsis & septic shock	Organ failure	>1 hr[b]	725	28-day mortality	0.81 (0.54-1.23)
de Groot 2015[3]	Adults	ED patients with suspected infection & ED triage score ≥3/5	ED arrival	>3 hr vs <1 hr[b]	1168	28-day mortality —PIRO score 1-7 (N=413) —PIRO score 8-14 (N=532) —PIRO score >14 (N=223)	 5.31 (0.43-68.2) 0.86 (0.28-2.63) 1.11 (0.40-3.08)
Ryoo 2015[4]	Adults	Septic shock	Shock onset	Hours	426	28-day mortality	1.15 (0.87-1.52)
Han 2017[5]	Children (≤21 yrs)	Pediatric ICU patients with sepsis or septic shock	Sepsis recognition	>3 hr[b]	160	1-year mortality	1.66 (0.85-3.23)

Abbreviations: ED, emergency department; hr, hour; ICU, intensive care unit; OR, odds ratio; PIRO score, Predisposition, Infection, Response, and Organ Failure score

[a] For consistency, published results were inverted as needed to compare longer versus short antibiotic times.

[b] Dichotomous exposure

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