The Impact of Early Antibacterial Therapy on ICU Patient Outcomes for Sepsis: A Causal Analysis

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INTRODUCTION

Setting

- **eICU Collaborative Research Database (eICU-CRD)**
- Contains **200,859 ICU stays** across **208 U.S. hospitals**
- **Data period:** 2014–2015

Study Population

- Patients **admitted to ICU** and **Diagnosed with Sepsis** during their hospital stay

Intervention

- Patients who **received antibiotics within <3 hours** after ICU admission

Comparator

- Patients who **received antibiotics ≥3 hours** after ICU admission

OBJECTIVE

Primary Aim:
To **evaluate the causal impact of early antibiotic administration** on patient outcomes in sepsis management.

Guideline Basis:
Based on the **2021 Surviving Sepsis Campaign (SSC)** recommendations.

Outcomes:

- **Length of hospital stay**
- **Length of ICU stay**
- **Hospital mortality rate**
- **ICU mortality rate**

METHOD

- Used **Double Machine Learning (DML)** to estimate causal effects while minimizing confounding bias.
- Applied **cross-fit partialling out** to improve robustness and accuracy.
- A **Lasso regression model** served as the machine learning component, for variable selection and regularization.
- Performed **cross-validation** across multiple folds to estimate treatment and outcome residuals.
- Repeated **cross-fitting 10 times** and averaged results for reliability.

RESULTS

Confounding Factors

Demographics
- Age, gender, ethnicity, discharge year

Clinical & Hospital Factors
- ICU type and infection site
- Hospital ID (dummy control)

Severity of Illness Measures
- Acute Physiology Score (APS), APACHE IV
- Glasgow Coma Scale (GCS)

Elixhauser Comorbidity Index
- ICD-9 based, computed using *R package comorbidity v1.0.5*

Physiological Variables (First 24 Hours)
- Vital signs: HR, RR, Temp, Mean BP
- Labs: WBC, Na, pH, Hct, Creatinine, Albumin, PaO_2, $PaCO_2$, BUN, Glucose, Bilirubin, FiO_2
- Total urine output

Treatment & Intervention Controls
- Intubation, ventilation, dialysis
- Fluid resuscitation
- Vasopressor use
- Ventilation & oxygenation

Table 1. Summary Statistics – Outcome Variables and Time to First Antibacterial Therapy Administration

	< 3 hours (n= 7,891)	>= 3 hours (n=2,176)	P value
Hospital mortality, n (%)	1,095 (14.1%)	355 (16.7%)	0.002
ICU mortality, n (%)	690 (8.7%)	226 (10.4%)	0.019
Length of hospital stay, days	6.4 [4.0–10.8]	7.6 [4.4–13.2]	< 0.001
Length of ICU stay, days	2.6 [1.5–4.8]	3.1 [1.8–6.3]	< 0.001
Time to first antibacterial therapy, hours	1.0 [0.5–1.6]	5.0 [3.7–9.3]	< 0.001

Notes: The P-values for the first two rows of the table were obtained through the mean comparison t-test, whereas the P-values for the last three rows of the table were based on the Wilcoxon rank-sum (Mann–Whitney) test. N (%), Median [IQR].

Table 2. Main Results – DML Model

Outcome variable	Coefficient	95% bootstrap confidence interval	P value
Hospital mortality	0.00	(-0.01, 0.02)	0.67
ICU mortality	0.01	(-0.00, 0.02)	0.14
Length of hospital stay	-1.73	(-2.33, -1.13)	0.00
Length of ICU stay	-0.67	(-0.98, -0.37)	0.00

Notes: Estimated coefficients of the early antibacterial therapy on patient outcomes using cross-fit partialing-out lasso linear model. The Number of folds for cross-fitting was 10 and we allowed for 10 resampling iterations. We used the default plugin option to select an optimal value of the lasso penalty parameter. 249 covariate variables were included in the model.

CONCLUSIONS

Context
- The **2021 Surviving Sepsis Guidelines** stress antibiotic administration within **3 hours** to prevent organ failure and improve outcomes.
- Our study examined whether this timing causally impacts survival and hospital stay.
- Few studies link **antibiotic timing** to **ICU/hospital stay length**, a key efficiency indicator.

Findings
- Utilized a novel causal inference method: **Double Machine Learning (DML)**.
- **Early therapy improved efficiency** (shorter stays, lower costs) but **did not significantly reduce mortality**.

Methodological Considerations
- **Quasi-experimental approaches** provide **valuable evidence** when randomization is **unfeasible or unethical**.
- Credible **DML estimates** rely on: **Unconfoundedness** and **Sufficient Covariate Overlap.**

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CONTACT INFORMATION