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Change lives.



Children's Hospital Association
2024 Sepsis Webcast Series

The Impact of Fluid Bolus Volume and Antibiotic Timeliness on Pediatric Sepsis Outcomes

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Work **collaboratively to spread best practices** in the early recognition and rapid treatment of pediatric sepsis, ensuring outstanding care, and **minimizing sepsis attributable morbidity and mortality.**

Objectives

1. Evaluate the impact of **fluid bolus volume** on outcomes for pediatric sepsis patients.
2. Describe the impact of **antibiotic timeliness** on mortality for pediatric sepsis patients.

Our Speakers



Matt Eisenberg, MD, MPH
*Director of Critical Care, Division of
Emergency Medicine*
Boston Children's Hospital

Annals of Emergency Medicine *An International Journal*

Association Between the First-Hour Intravenous Fluid Volume and Mortality in Pediatric Septic Shock

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*Pediatric Emergency Medicine
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JAMA Network | **Open**

Delays to Antibiotics in the Emergency Department and Risk of Mortality in Children With Sepsis

[Roni D. Lane, MD](#); [Troy Richardson, PhD](#); [Halden F. Scott, MD, MSCS](#); [Raina M. Paul, MD](#); [Fran Balamuth, MD, PhD](#); [Matthew A. Eisenberg, MD, MPH](#); [Ruth Riggs](#); [W. Charles Huskins, MD, MSc](#); [Christopher M. Horvat, MD, MHA](#); [Grant E. Keeney, MD, MS](#); [Leslie A. Hueschen, MD](#); [Justin M. Lockwood, MD, MSCS](#); [Vishal Gunnala, MD](#); [Bryan P. McKee, MD](#); [Nikhil Patankar, MD, MBA](#); [Venessa Lynn Pinto, MBBS](#); [Amanda M. Sebring, MD](#); [Matthew P. Sharron, MD](#); [Jennifer Treseler, MSN, RN, CPN, CPHQ](#); [Jennifer J. Wilkes, MD, MSCE](#); [Jennifer K. Workman, MD, MS](#)

Challenge sepsis.
Change lives.



First hour IVF in septic shock – what is the right amount?

Matthew Eisenberg, MD MPH
Boston Children's Hospital
November 13, 2024



Disclosure

- No financial disclosures
- No conflict of interest

Learning Objectives

- To briefly review existing evidence on association between volume of IV fluid given during resuscitation and sepsis outcomes
- To highlight an IPSO investigator-initiated study on this question

Volume of Fluids: What do Guidelines suggest?

- Society of Critical Care Medicine (US): 20 ml/kg boluses up to 60 ml/kg
- European Resuscitation Council: 10-20 ml/kg bolus, no target volume
- Surviving Sepsis Campaign (international): 10-20 ml/kg bolus, goal 40-60 ml/kg in healthcare systems with available intensive care

Why so much variation?

- Data on the question is sparse and often contradictory
- Mostly small retrospective studies
- A few smaller RCT's
- 1 large RCT with questionable generalizability

Give lots of fluid! Carcillo, *JAMA*, 1991

- Retrospective review of 34 children with septic shock and pulmonary artery catheter placed
- Stratified by amount of IVF obtained in first hour (and first 6 hours)
- Median age = 13.5 months

Give lots of fluid! Carcillo, *JAMA*, 1991

Table 2.—Fluid Administration

	1 h (mean ± SD)	6 h (mean ± SD)
Group 1 (n = 14; <20 mL/kg in 1 h)	11 ± 6*	71 ± 29†
Group 2 (n = 11; 20-40 mL/kg in 1 h)	32 ± 5*	108 ± 54
Group 3 (n = 9; >40 mL/kg in 1 h)	69 ± 19*	117 ± 29
All patients (n = 34)	33 ± 26	95 ± 42
Survivors (n = 18)	42 ± 28‡	97 ± 49
Nonsurvivors (n = 16)	23 ± 18	94 ± 37

* $P < .05$, comparing the mean volume administered at 1 hour in each group to the other groups.

† $P < .05$, comparing the mean volume administered at 6 hours in group 1 to group 2 or group 3.

‡ $P < .05$, mean volume administered in first hour in survivors compared with nonsurvivors.

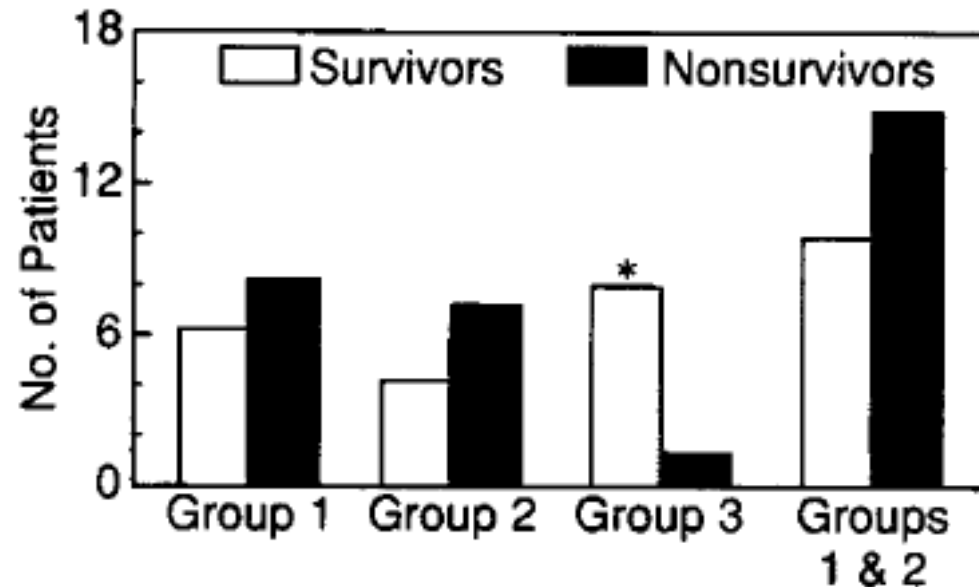


Fig 1.—The distribution of survivors and nonsurvivors within fluid resuscitation groups (see text for definition of groups). The asterisk indicates a significant difference in survival between group 3 and groups 1 and 2 individually and combined.

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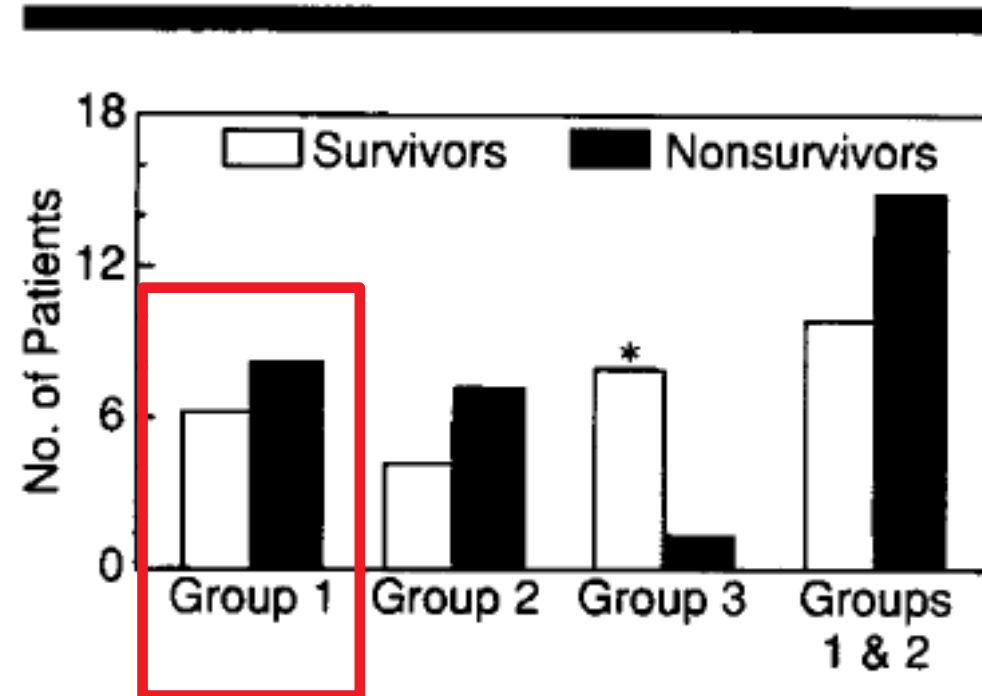


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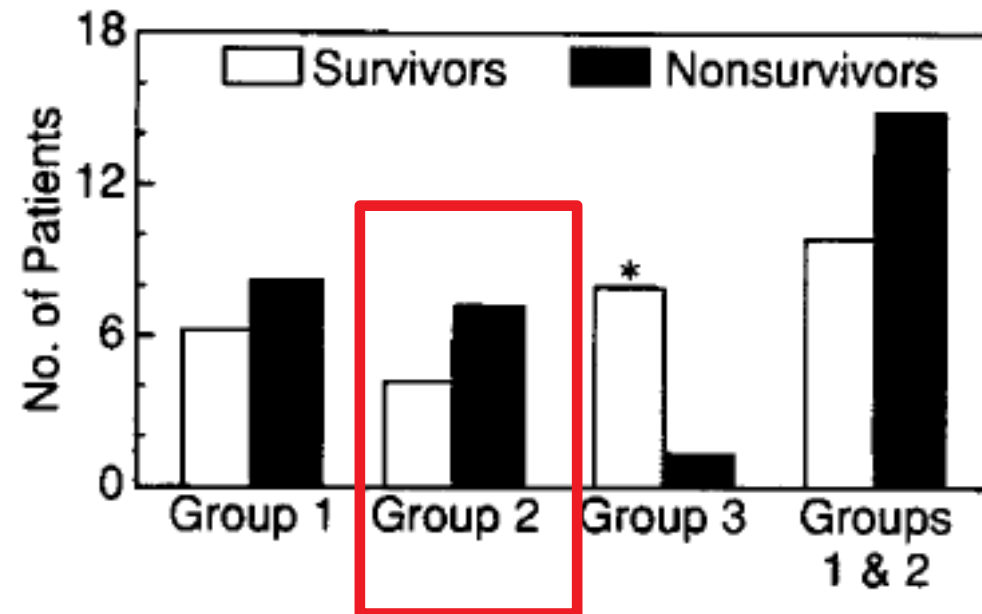


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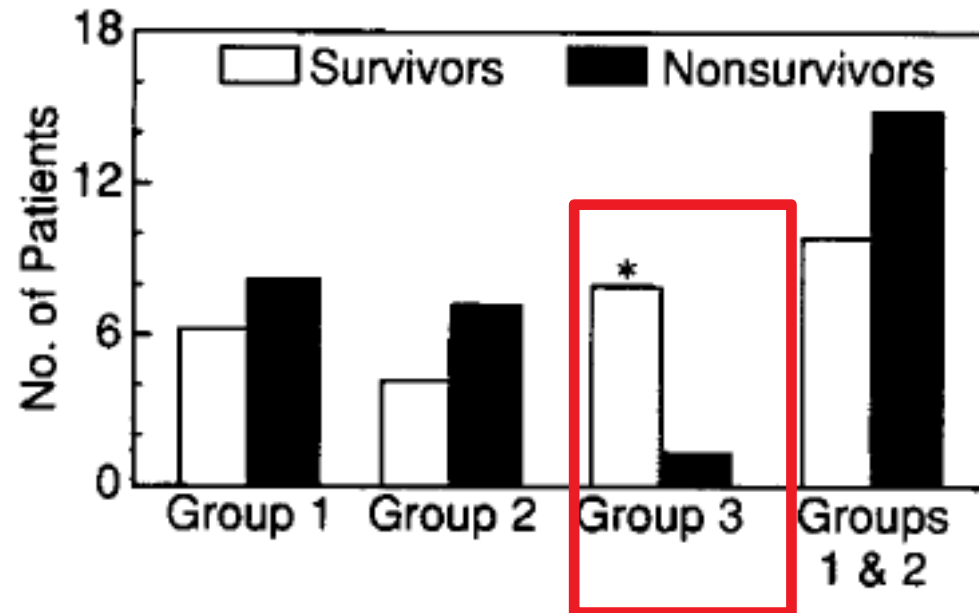


Fig 1.—The distribution of survivors and nonsurvivors within fluid resuscitation groups (see text for definition of groups). The asterisk indicates a significant difference in survival between group 3 and groups 1 and 2 individually and combined.

Give lots of fluid! Olivera, *PEC*, 2008

- Retrospective review of adherence to PALS guidelines
- 90 pediatric patients with septic shock
- Both first-hour volume and time to 40 ml/kg associated with mortality

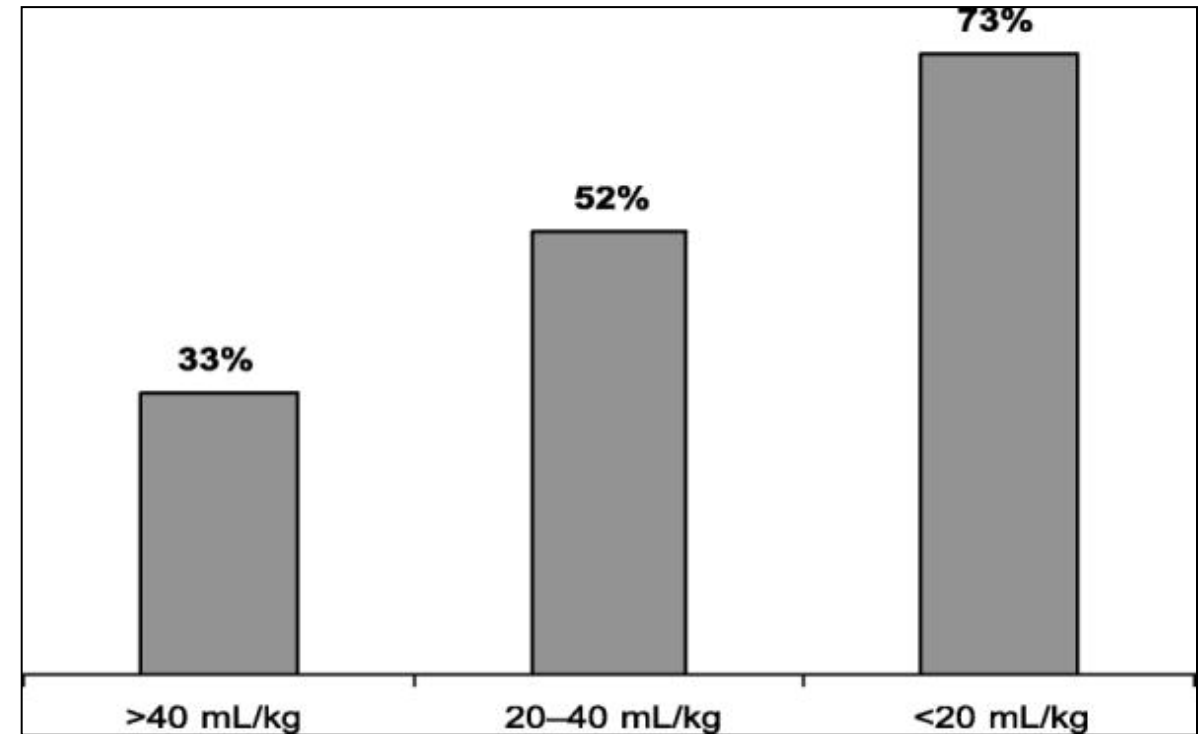


FIGURE 1. Patients with septic shock-mortality versus first-hour resuscitation volume.

Give Lots of fluid! Summary

- Dramatic effect size but...
- Small studies
- Not randomized

Don't give too much fluid! Maitland, *NEJM*, 2011

- 3141 children with “severe febrile illness and impaired perfusion” in several sites in Africa
- Randomized to receive
 - 20-40 ml/kg boluses of 5% Albumin
 - 20-40 ml/kg boluses of 0.9% saline
 - No bolus
- All given appropriate antimicrobial treatment
- 57% had malaria

Don't give too much fluid! Maitland, *NEJM*, 2011

Table 2. Death and Other Adverse Event End Points at 48 Hours and 4 Weeks.

End Point	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Saline Bolus vs. No Bolus		Albumin Bolus vs. No Bolus		Albumin Bolus vs. Saline Bolus		Albumin and Saline Boluses vs. No Bolus	
				Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
no. (%)											
48 Hours											
Death — no. (%)	111 (10.6)	110 (10.5)	76 (7.3)	1.44 (1.09–1.90)	0.01	1.45 (1.10–1.92)	0.008	1.00 (0.78–1.29)	0.96	1.45 (1.13–1.86)	0.003
Pulmonary edema — no. (%)	14 (1.3)	6 (0.6)	6 (0.6)								
Increased intracranial pressure — no. (%)	16 (1.5)	18 (1.7)	11 (1.1)								
Severe hypotension — no. (%)*	1 (0.1)	2 (0.2)	3 (0.3)								
Allergic reaction — no. (%)	3 (0.3)	4 (0.4)	2 (0.2)								
Pulmonary edema, increased intracranial pressure, or both — no. (%)†	27 (2.6)	23 (2.2)	17 (1.6)	1.34 (0.72–2.51)	0.34	1.57 (0.87–2.88)	0.10	1.17 (0.68–2.03)	0.49	1.46 (0.85–2.53)	0.17
4 Weeks											
Death — no. (%)	128 (12.2)	126 (12.0)	91 (8.7)	1.38 (1.07–1.78)	0.01	1.40 (1.08–1.80)	0.01	1.01 (0.80–1.28)	0.91	1.39 (1.11–1.74)	0.004
Neurologic sequelae — no./total no. (%)‡	22/990 (2.2)	19/996 (1.9)	20/997 (2.0)	0.95 (0.51–1.77)	0.87	1.10 (0.61–2.01)	0.74	1.16 (0.63–2.14)	0.62	1.03 (0.61–1.75)	0.92
Neurologic sequelae or death — no./total no. (%)‡	150/990 (15.2)	145/996 (14.6)	111/997 (11.1)	1.31 (1.04–1.65)	0.02	1.36 (1.08–1.71)	0.008	1.04 (0.84–1.28)	0.71	1.33 (1.09–1.64)	0.005

Don't give too much fluid! Santhanam, *PEC*, 2008

- Randomized 147 children >1 mo with septic shock to either:
 - 40 ml/kg over 15 mins followed by dopamine
 - 20 ml/kg boluses up to 60 ml/kg over 1 hour followed by dopamine
- No difference in mortality, rapidity of shock resolution, complications between groups
- More hepatomegaly in 40 ml/kg group

Don't give so much fluid! Summary

- Higher quality design (RCT's)
- Several small studies
- 1 large study – generalizable?

IPSO Study: Association between first hour intravenous fluid volume and mortality in pediatric septic shock

- Matthew Eisenberg, MD MPH
 - Halden F. Scott, MD, MSCS
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 - Lori Rutman, MD MPH
 - Amanda Sebring, MD
 - Zebulon Timmons, MD
 - IPSO Collaborative Investigators
- CHA Staff: Mary Headley, Jayne Stuart**

Study Objectives

- Evaluate the association between volume of bolus fluid delivered in the first hour after ED arrival and sepsis-attributable mortality in children presenting to the ED with hypotensive septic shock
- Secondary objective: evaluate the association between volume of bolus fluid delivered in the first hour after ED arrival and sepsis-attributable mortality in children presenting to the ED with sepsis identified in the first hour after ED arrival regardless of blood pressure

Methods: Study Design

- Retrospective cohort study using propensity matching
- Improving Pediatric Sepsis Outcomes (IPSO) Database
- Primary predictor: ≥ 30 ml/kg IV bolus fluid in first hour after ED arrival

Methods: Outcomes

- Primary outcome: 30-day sepsis-attributable mortality
 - Locally defined, guidance provided by IPSO
- Secondary outcomes:
 - 3-day sepsis-attributable mortality
 - ICU admission/ICU-free days
 - Mechanical ventilation/ventilator-free days
 - Vasoactive infusion/vasoactive-free days
 - Hospital LOS

Methods: Population

- ED patients <18 years
- Met IPSO sepsis criteria
- First bolus within 60 minutes of ED arrival
- Admitted to hospital
- Primary analysis: hypotension within 1 hour of ED arrival
- Secondary analysis: suspected sepsis within 1 hour of ED arrival
- Exclusions: transfers, no weight reported, non-sepsis death, first bolus <12 ml/kg

Methods: Propensity Matching

- Why propensity match?
 - Confounding by indication
- 1:1 match based on:
 - Age, positive blood culture, time to antibiotic, lactic acid
 - PMH: malignancy, asplenia, stem cell transplant, indwelling central line, solid organ transplant, severe cerebral palsy/intellectual disability, technology dependent, chronically ventilated
- Balance assessment: point estimates and absolute standardized differences

Results

- 60,839 sepsis cases at 57 hospitals
- 1,982 with hypotensive septic shock in first hour
 - Prior to matching: ≥ 30 ml/kg group younger, higher lactate, shorter time to antibiotics
- 1,204 included in propensity-match
 - Excellent matching
- Volumes received:
 - 1 hour: 40 ml/kg in high volume group vs. 20 ml/kg in low volume group
 - 6 hour: 58 ml/kg in high volume group vs. 40 ml/kg in low volume group

Results: Hypotensive septic shock

Propensity-matched variables	≥ 30 ml/kg (N = 602)	<30 ml/kg (N = 602)	Absolute standard difference
Age, median (IQR), years	6.7 (2.0,11.6)	6.7 (1.9,11.9)	0.00
Any High Risk Conditions, No. (%)	255 (42.4)	265 (44.0)	0.03
Positive Blood Culture, No. (%)	89 (14.8)	103 (17.1)	0.07
Lactate, median (IQR), mmol/L	2.9 (1.7,5.0)	2.6 (1.6,5.0)	0.02
Arrival to antibiotic time, median (IQR), minutes	29.0 (13.9,50.0)	31.0 (16.0,53.0)	0.01
Time to hypotension, median (IQR), minutes	16.0 (7.0,33.0)	16.0 (7.0,35.0)	0.08

Absolute standard difference < 0.1 for all other matched variables

Outcomes: Hypotensive septic shock

	≥ 30 ml/kg (N = 602)	<30 ml/kg (N = 602)	Odds Ratio (95% CI)
30-Day SA mortality, No. (%)	26 (4.3)	25 (4.2)	1.04 (0.59, 1.83)
3-Day SA mortality, No. (%)	19 (3.2)	18 (3.0)	1.06 (0.55, 2.05)
ICU admission, No. (%)	477 (80.2)	402 (67.8)	1.92 (1.48, 2.51)
ICU-free days, median (IQR)	25.0 (18.0,27.0)	25.0 (18.0,28.0)	n/a
Mechanical ventilation, No. (%)	272 (57.6)	215 (52.1)	1.25 (0.96, 1.63)
Ventilator-free days, median (IQR)	25.0 (16.0,27.0)	25.0 (18.0,28.0)	n/a
Hospital LOS, days, median (IQR)	8.0 (4.0,16.0)	6.0 (4.0,14.0)	n/a
Vasoactive Infusion, No. (%)	264 (45.6)	174 (30.0)	1.96 (1.54, 2.49)
Vasoactive-free days, median (IQR)	28.0 (26.0,29.0)	28.0 (26.0,29.0)	n/a

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Vasoactive-free days, median (IQR)	28.0 (26.0,29.0)	28.0 (26.0,29.0)	n/a

Results: Suspected sepsis

- 9,703 with suspected sepsis within 1 hour of ED arrival
- Prior to matching: ≥ 30 ml/kg group younger, less frequent high risk PMH, shorter time to antibiotics, higher lactate, more hypotension
- 2,988 in propensity-match
 - Excellent matching

Results: Sepsis within 1 hour

- **30-day sepsis-attributable mortality:**
 - 3% in ≥ 30 ml/kg vs. 2% in < 30 ml/kg
 - OR 1.52 (95% CI 0.95, 2.44)
- No difference in 3-day sepsis-attributable mortality
 - 1.8% in ≥ 30 ml/kg vs. 1.3% in < 30 ml/kg, OR 1.36 (95% CI 0.76, 2.46)
- ≥ 30 ml/kg group:
 - More ICU admission (74.4% vs. 66%)
 - More vasoactive medication (29.9% vs. 20.9%)
 - More mechanical ventilation (48.3% vs. 41.7%)

Limitations

- Unmeasured confounders
 - Was the ≥ 30 ml/kg group sicker?
- Dichotomized exposure at 30 ml/kg
 - Post hoc analysis at 40 ml/kg and 60 ml/kg → same results
- Site variability: hypotension, sepsis-attributable deaths
- Fluid-sensitive patients indirectly identified
- Only assessed first-hour fluid volume

Study Conclusions

- Receiving ≥ 30 mL/kg of bolus IV fluids in the first hour after ED arrival was not associated with mortality compared to receiving < 30 mL/kg among children with hypotensive septic shock or children with suspected sepsis within one hour of ED arrival
- All patients in this study received timely antibiotics and a first fluid bolus!
- When all care is timely, delivery of a specific volume of fluid resuscitation in the first hour was not associated with mortality

Take-Home Points

- Precise volume of fluid that should be given in first hour of sepsis care is not clear
- Thoughtful approach tailored to the patient
- Timely initiation of fluids (as well as antibiotics) is still crucial

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Questions/Comments?

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Methods: IPSO Sepsis

Stand-alone diagnostic criteria		
Severe sepsis, septic shock ICD10 codes (R65.20, R65.21)		
Severe sepsis order set		
Positive huddle (bedside diagnosis, locally defined) of sepsis		
Treatment criteria	Culture criterion	Additional criterion (any one of the following)
Intravenous antibiotic and 2 boluses OR (bolus and vasoactive agent)	Blood culture	Sepsis screen + (locally defined)
		ICU admission
		Lactate measured
		Vasoactive administered
		Other sepsis ICD10 codes
		Infectious disease order set (locally defined, included order sets such as pneumonia or fever/neutropenia order sets)
<i>within 6 hours of each other</i>	<i>within 72 hours of treatment</i>	<i>within 24 hours of treatment</i>

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Moving the Needle for Antibiotic Timing in Pediatric Sepsis?

CHA Webinar

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Salt Lake City, Utah

11.13.2024



Disclosures

- No relevant conflicts of interest or financial disclosures
- I am the site-PI for two NIH funded international studies and *do not* receive any direct funds

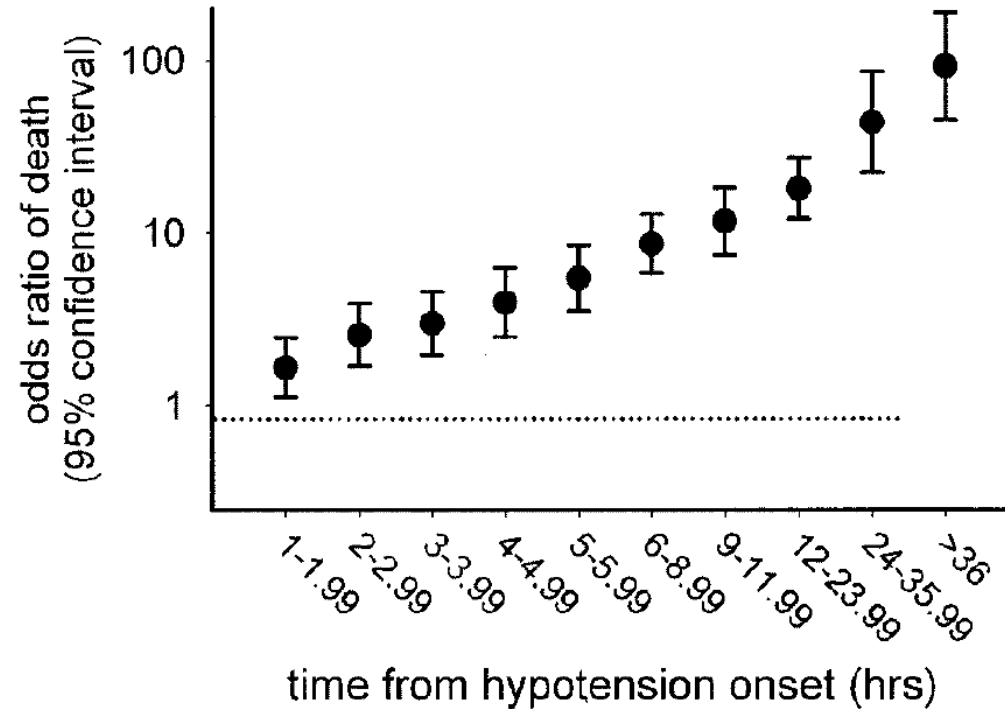
Background- *historic* adult data

Duration of antimicrobial survival in t

Kumar, Anand MD; Robe
Satendra MD; Suppes, F
Kumar, Aseem PhD; Che

[Author Information](#) ⌵

Critical Care Medicine 3

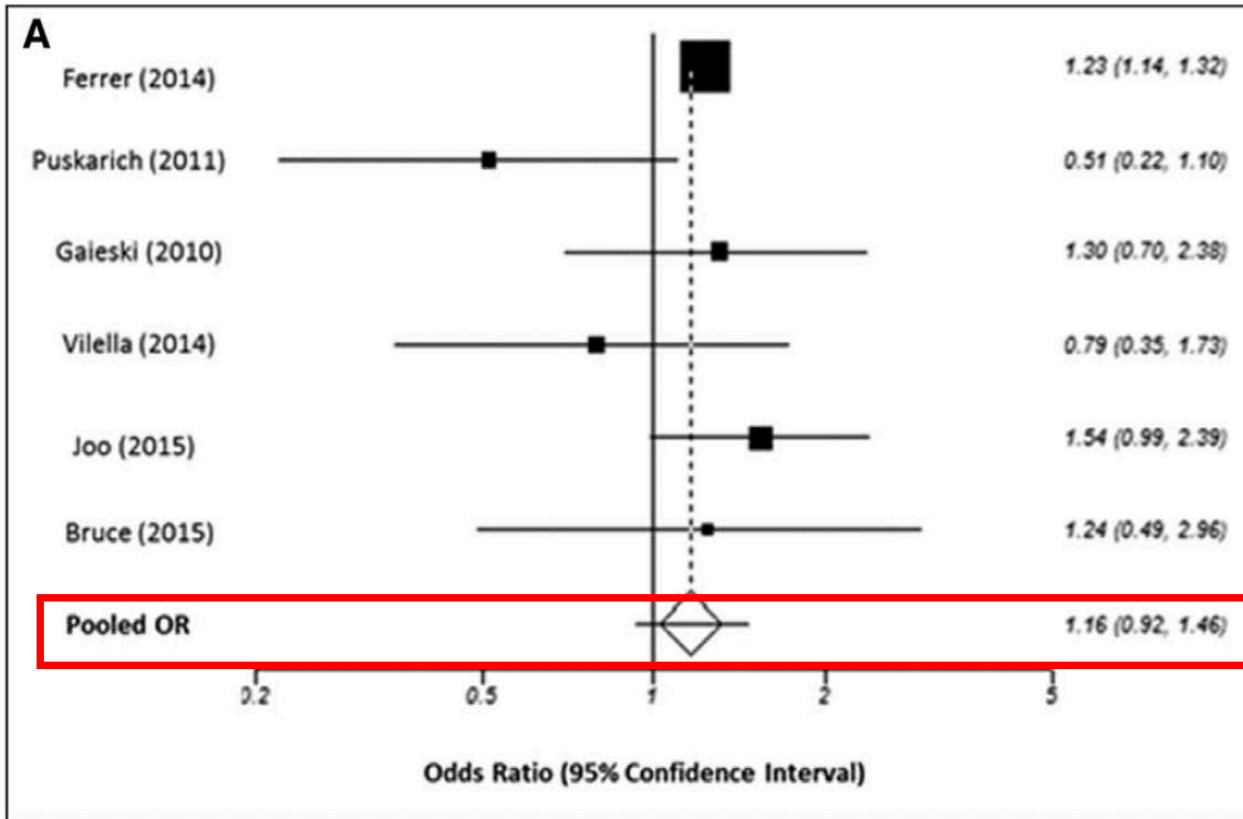


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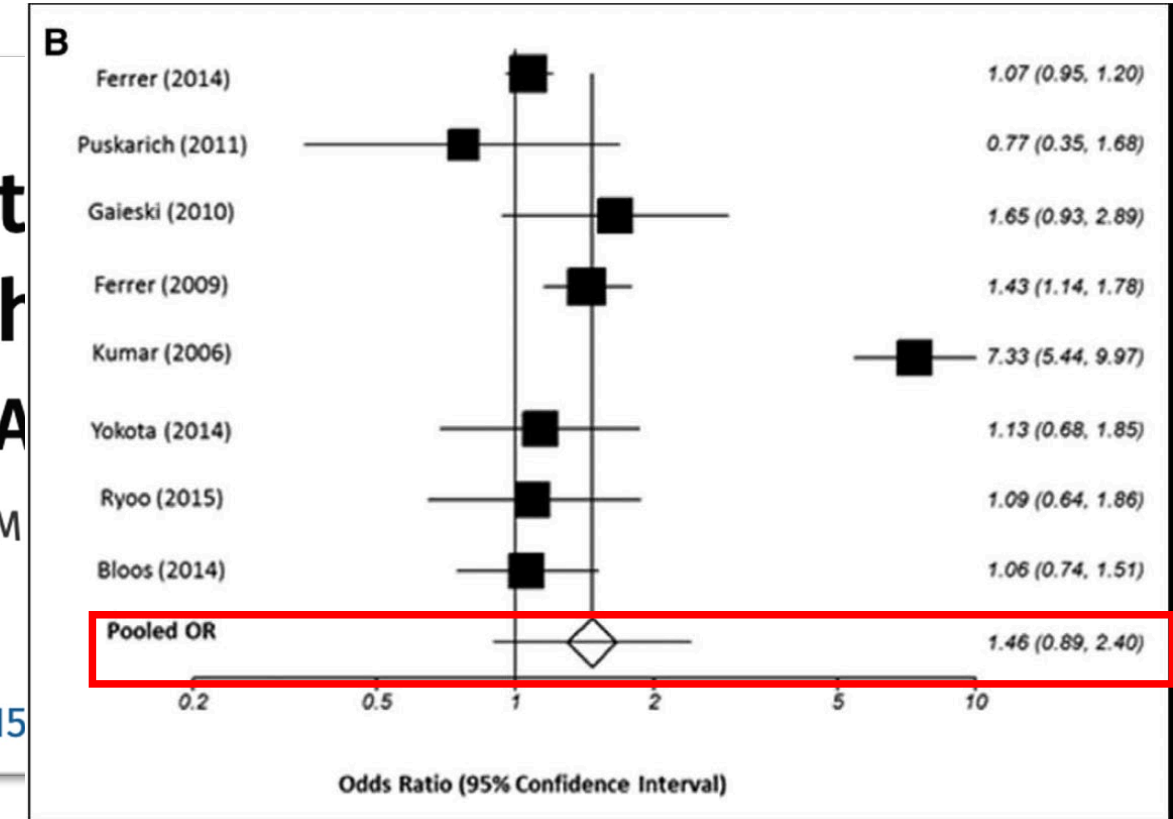
Joseph E. MD; Sharma,
o MD; Gurka, David MD;

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Background- adult data

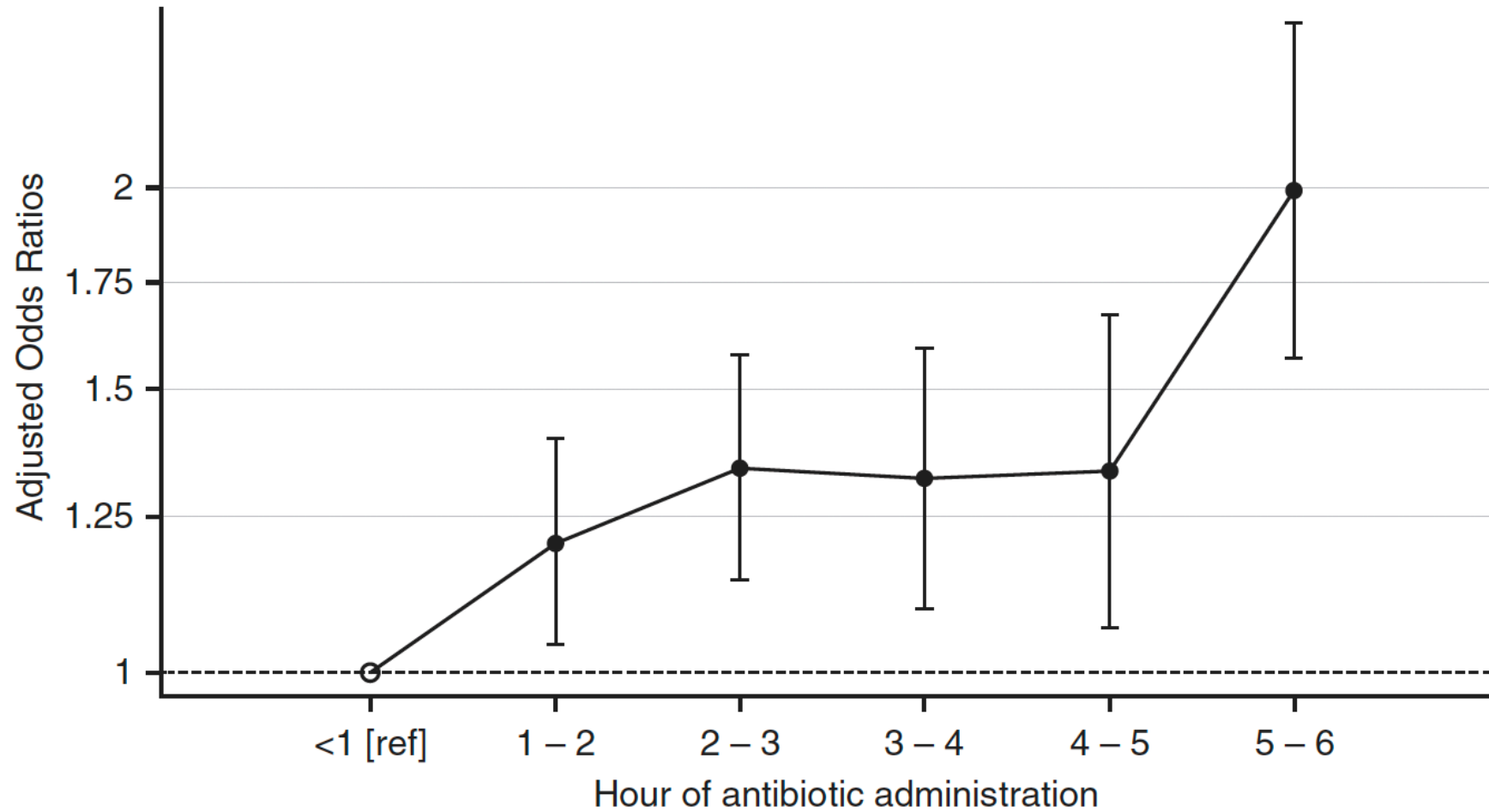


16,178 patients, pooled odds ratios for mortality and time to antibiotics > 3 hours from triage time



11,017 patients, pooled odds ratios for mortality and time to antibiotics > 1 hour from severe sepsis/shock recognition

Background- adult data



What about peds?





PEDIATRIC CRITICAL CARE

Delayed Antimicrobial Therapy Increases Mortality and Organ Dysfunction Duration in Pediatric Sepsis*

Weiss, Scott L. MD; Fitzgerald, Julie C. MD, PhD; Balamuth, Fran MD, PhD; Alpern, Elizabeth R. MD, MSCE; Lavelle, Jane MD; Chilutti, Marianne MS; Grundmeier, Robert MD; Nadkarni, Vinay M. MD, MS; Thomas, Neal J. MD, MSc

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Critical Care Medicine 42(11):p 2409-2417, November 2014. | DOI: 10.1097/CCM.0000000000000509

Num of Patients	24	31	23	52
Mortality	8.3%	6.5%	4.3%	21.2%

Figure 3. Crude In-Hospital Mortality and Predicted Risk of In-Hospital Death After the Time of Sepsis Protocol Initiation

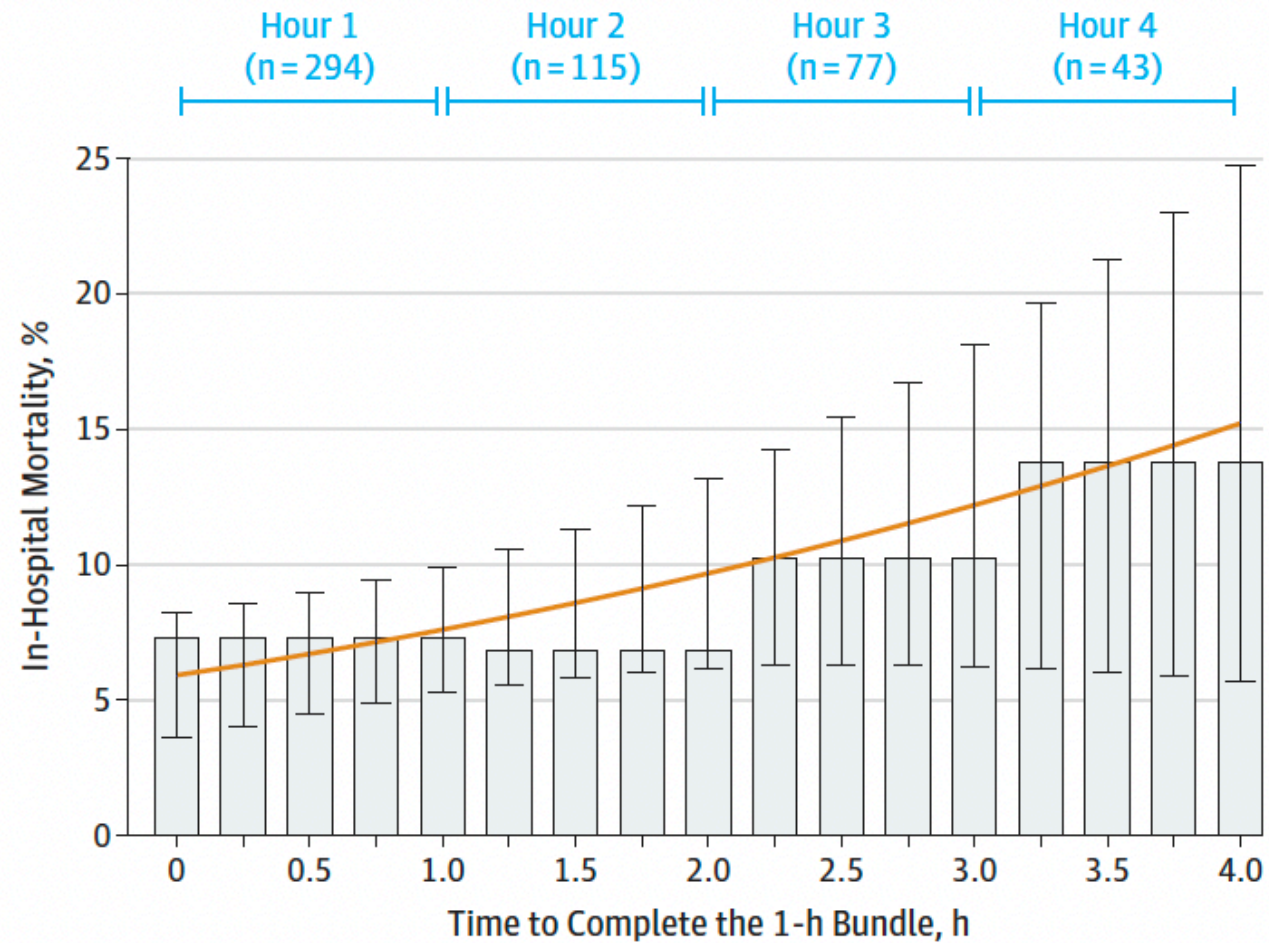
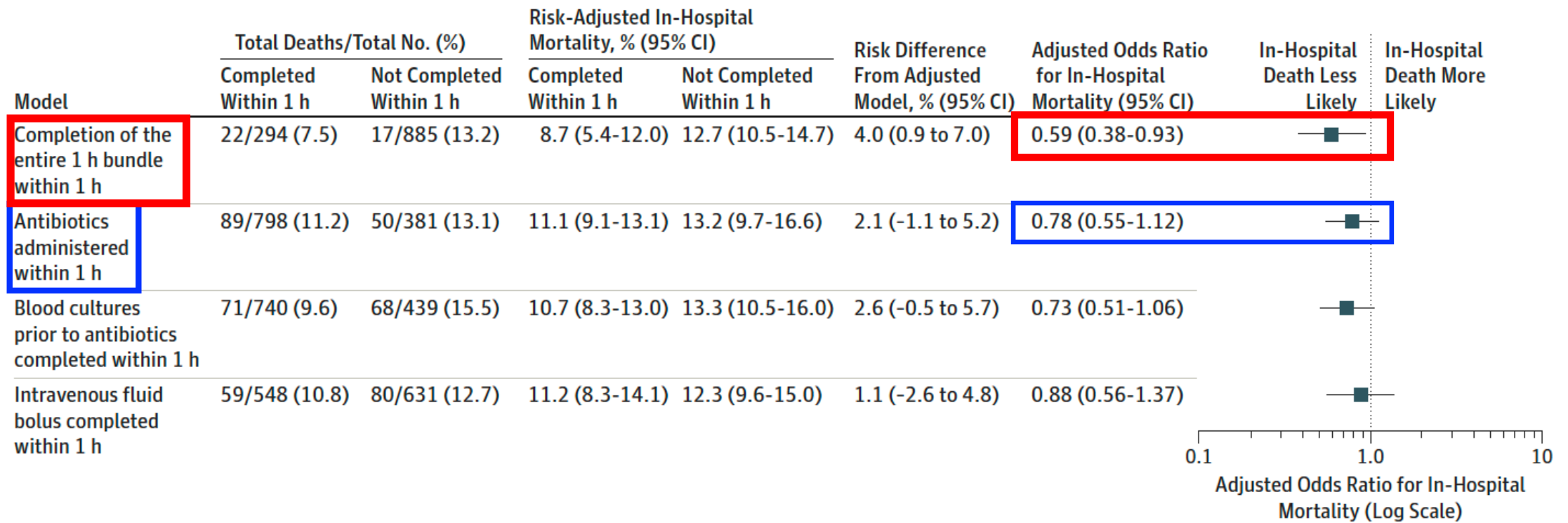


Figure 2. Risk-Adjusted Odds Ratios of In-Hospital Death in the Primary Models



Background

- Increased odds of mortality: antibiotics > 3 hours (Weiss, 2014)
- No association between mortality and antibiotics in < 1 hour (Evans, 2018)

Background

- Increased odds of mortality: antibiotics > 3 hours (Weiss, 2014)
- No association between mortality and antibiotics in < 1 hour (Evans, 2018)
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- Increased odds of mortality: antibiotics > 1 hour (Sankar, 2021)
- No association between mortality and antibiotics in < 1 hour (Evans, 2018)
- Pediatric Surviving Sepsis Campaign- antibiotics within 1 hour for septic shock; 3 hours for sepsis-associated organ dysfunction (Weiss, 2020)

Background

- Increased odds of mortality: antibiotics > 3 hours (Weiss, 2014)
- Increased odds of mortality: antibiotics > 1 hour (Sankar, 2021)
- No association between mortality and antibiotics in < 1 hour (Evans, 2018)
- Pediatric Surviving Sepsis Campaign- antibiotics within 1 hour for septic shock; 3 hours for sepsis-associated organ dysfunction (Weiss, 2020)
- Strict time requirement concerns (CID 2018, Schlapbach 2019)

Weiss et al., Crit Care Med. 2014 Nov;42(11):2409-17

Sankar et al., J Pediatr. 2021;233:183-90

Evans, et al. JAMA. 2018;320(4):358-367

Weiss et al., Pediatr Crit Care Med. 2020 Feb;21(2):e52-e106

Clinical Infectious Diseases. 2018;66(10):1631-5

Schlapbach, et al. JAMA Pediatr. 2019;173(5):409-410

Antibiotic timing study objective

To evaluate the association between time of antibiotic administration and sepsis-attributable (SA) mortality in children presenting to the emergency department (ED) with sepsis recognition within 1 hour of arrival.

Study Design

- Retrospective cohort study
- IPSO database
- Primary exposure: minutes from ED arrival to antibiotic administration
- Main outcome: 3-day sepsis attributable mortality

Study Population

- ED patients 29 days to <18 years old
- January 1, 2017 through December 31, 2021
- Admitted to the hospital
- First antibiotic administered within 7 hours of ED arrival
- Sepsis recognized within 1 hour of ED arrival (functional time zero-FTZ)
- Excluded: transfers, missing antibiotic administration time

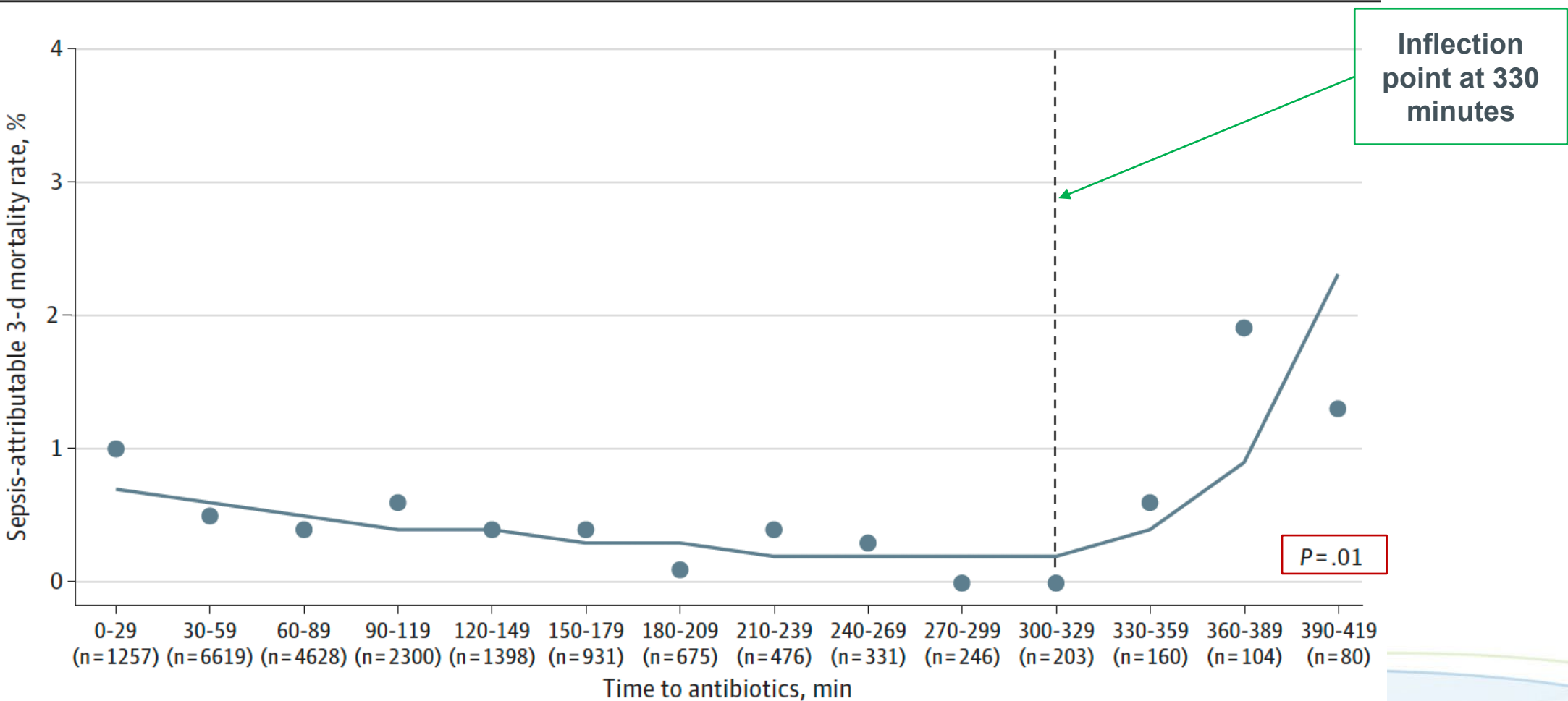
Challenge sepsis.
Change lives.



Results

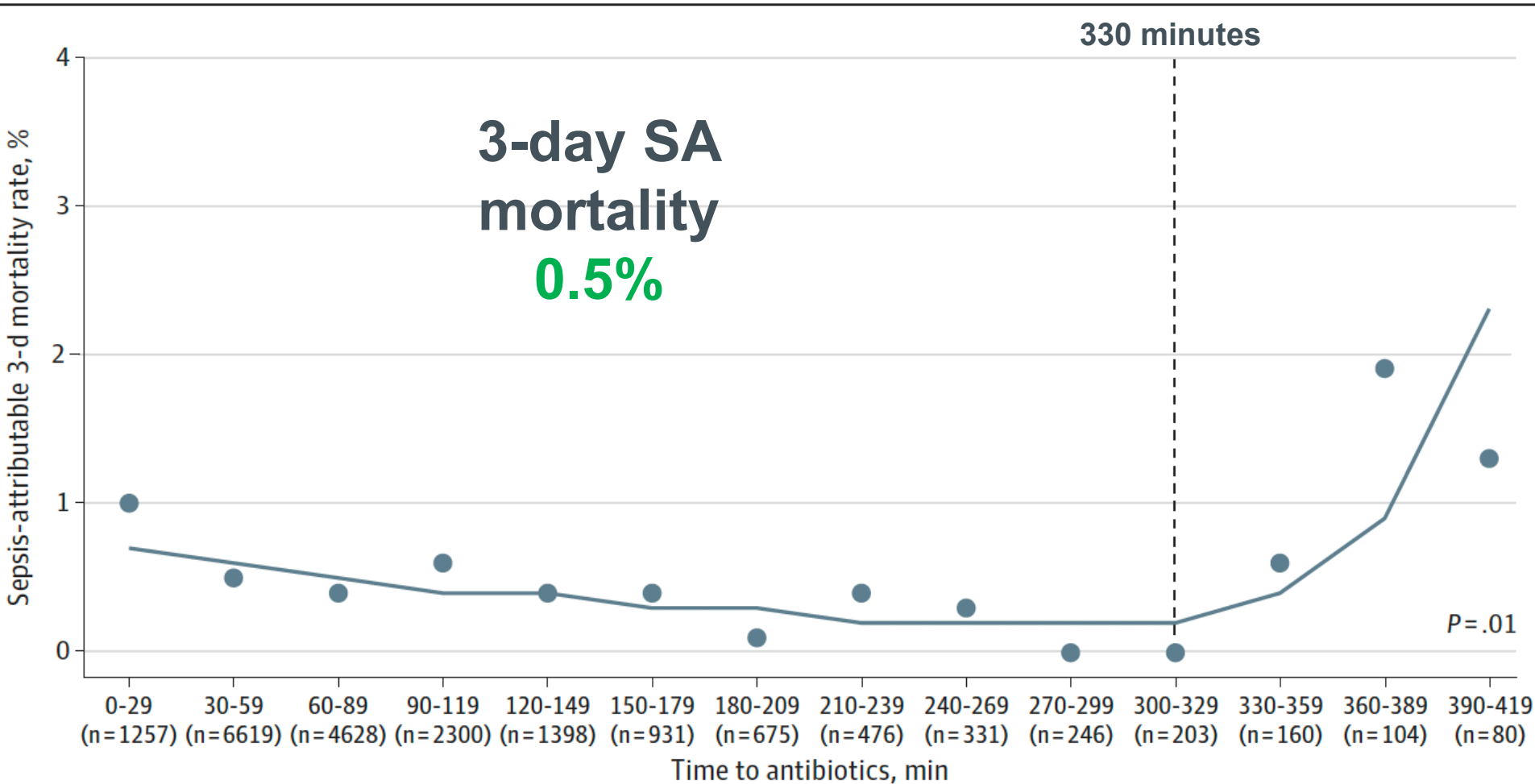
Piecewise Logistic Regression

Figure 1. Time to Antibiotics and 3-Day Sepsis-Attributable Mortality Among Children With Sepsis



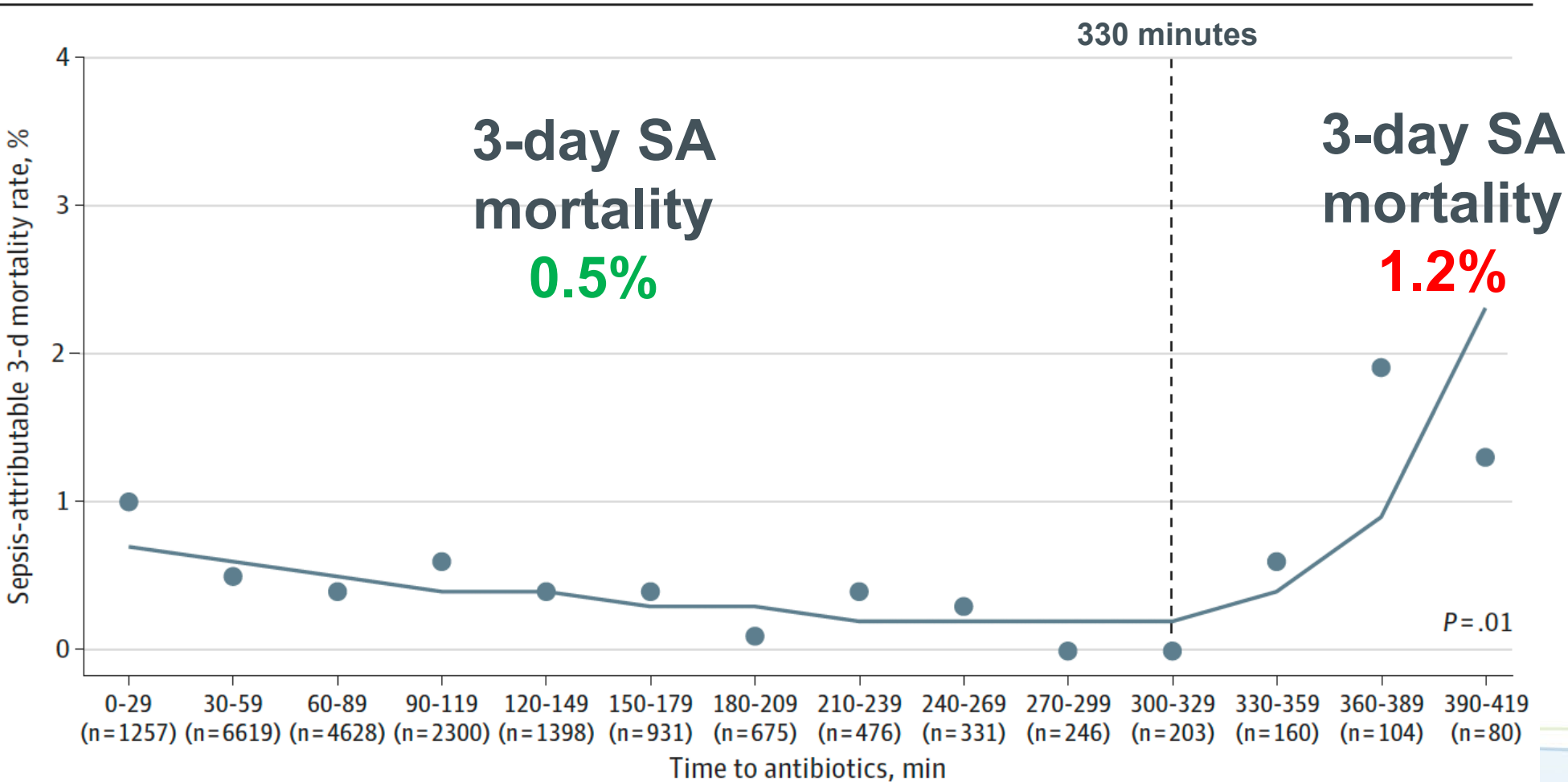
Piecewise Logistic Regression

Figure 1. Time to Antibiotics and 3-Day Sepsis-Attributable Mortality Among Children With Sepsis



Piecewise Logistic Regression

Figure 1. Time to Antibiotics and 3-Day Sepsis-Attributable Mortality Among Children With Sepsis



Select Baseline Characteristics

	Total (n=19,515)	Antibiotic 0- 329 min (n=19,164)	Antibiotic 330-419 min (n=351)	p-value
Age, median (IQR)	6 (2,12)	6 (2,12)	7 (2,13)	0.828
Any high-risk condition, n (%)	11,121 (57)	10,978 (57)	143 (41)	<0.001
Positive blood culture, n (%)	2,230 (12)	2,200 (12)	30 (10)	0.138
Lactic acid > 4 mmol/L, n (%)	1,371 (7.0)	1,353 (7)	18 (5)	<0.001
Minutes to 1st antibiotic, median (IQR)	69 (47,116)	68 (46,111)	364 (347,387)	<0.001
Minutes to FTZ from ED arrival, median (IQR)	13 (8,23)	13 (8,23)	16 (11,28)	<0.001
Minutes to 1st fluid bolus (>5 ml/kg), median (IQR)	45 (31,69)	45 (30,68)	93 (56,156)	<0.001
IPSO sepsis population, n (%)				<0.001
IPSO Suspected Sepsis	12,676 (65)	12,412 (65)	264 (75)	
IPSO Critical Sepsis	6,839 (35)	6,752 (35)	87 (25)	

Select Baseline Characteristics

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Multivariable Analysis of 3-day Sepsis Attributable Mortality

3-day SA Mortality Odds Ratio (95% CI)

Antibiotic timing (Reference: 0-329 min)

330-419 min

3.57 (1.04,12.27)

Positive blood culture (Reference: no)

2.43 (1.47,4.00)

Not reported

0.46 (0.12,1.82)

Chronic ventilator dependent (Reference: no)

2.06 (1.11,3.81)

Not reported

1.93 (0.85,4.37)

Lactic acid value (Reference: < 4 mmol/L)

≥ 4 mmol/L

9.40 (5.37,16.46)

Not reported

3.12 (1.72,5.65)

Multivariable Analysis of 3-day Sepsis Attributable Mortality

3-day SA Mortality Odds Ratio (95% CI)

Antibiotic timing (Reference: 0-329 min)

330-419 min

3.57 (1.04,12.27)

Technology dependent (Reference: no)

2.77 (1.65,4.65)

IPSO Sepsis cohort (Reference: suspected sepsis)

Critical sepsis

5.35 (3.11,9.21)

FTZ Source (Reference: screen)

Huddle

2.76 (1.29,5.92)

Order set

2.36 (1.38,4.06)

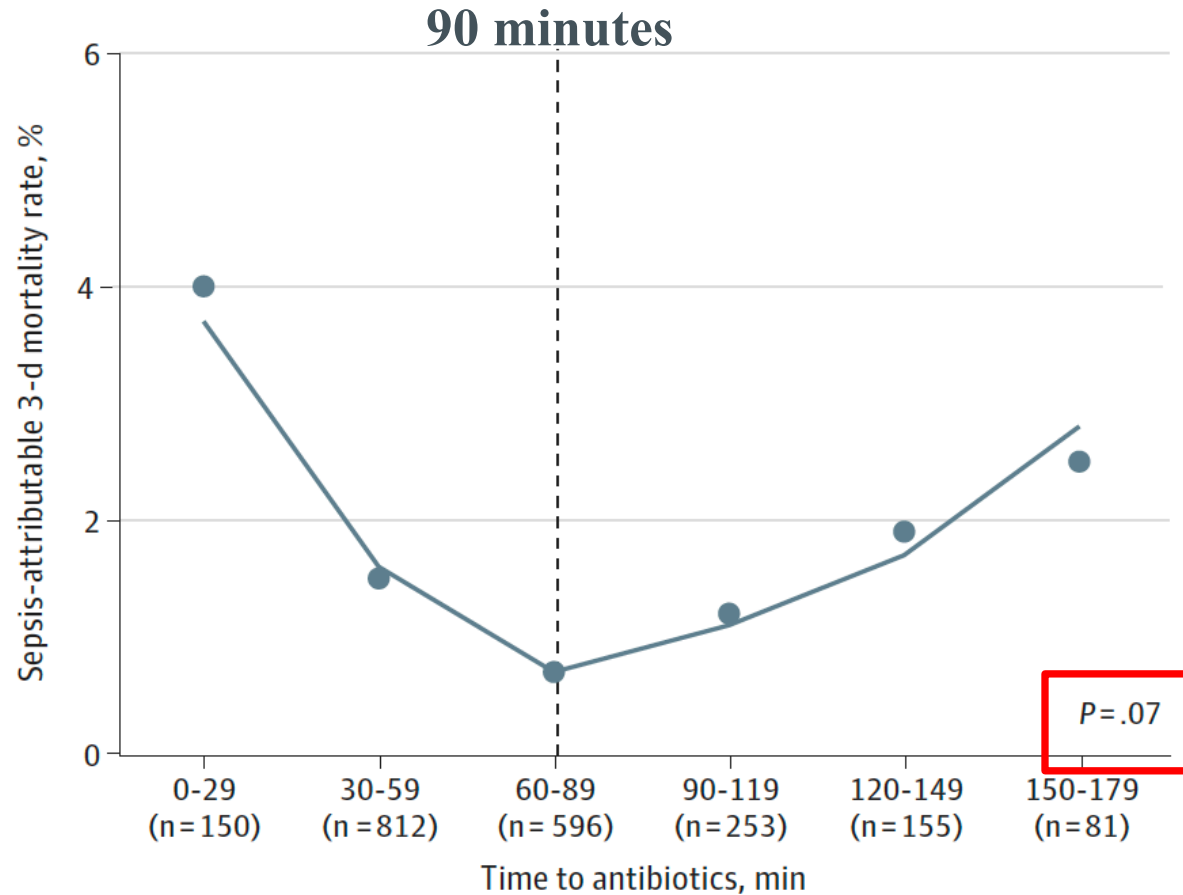
Received 1st fluid bolus (>5 mL/kg) >1 hour from ED arrival (Reference: no)

0.65 (0.37,1.12)



Piecewise Logistic Regression-bacteremia

Figure 2. Time to Antibiotics and 3-Day Sepsis-Attributable Mortality Among Children With Bacteremia and Sepsis



Select Baseline Characteristics of Children with Sepsis and Bacteremia

	Total (n=2,230)	Antibiotic 0-89 min (n=1,565)	Antibiotic ≥ 90 min (n=665)
Age, median (IQR)	6 (2,12)	6 (2,12)	7 (1,13)
Any high risk condition, n (%)	1,364 (61)	1,081 (65)	346 (52)
Lactic acid > 4 mmol/L, n (%)	220 (10)	168 (11)	52 (8)
Minutes to 1st antibiotic, median (IQR)	65 (46,99)	53 (40,68)	133 (107,184)
Minutes to FTZ from ED arrival, median (IQR)	13 (8,21)	12 (7,19)	16 (9,27)
Minutes to 1st fluid bolus (>5 ml/kg), median (IQR)	43 (29,66)	38 (27,54)	65 (38,98)
IPSO sepsis population, n (%)			
IPSO Sepsis	1,263 (57)	850 (54)	413 (62)
IPSO Critical Sepsis	967 (43)	715 (46)	252 (38)

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Unadjusted Outcomes Among Children with Sepsis and Bacteremia

	Total (n=2,230)	Antibiotic 0-89 min (n=1,565)	Antibiotic ≥ 90 min (n=665)	p-value
3-day SA mortality, n (%)	30 (1.4)	22 (1.4)	8 (1.2)	0.70
30-day SA mortality, n (%)	45 (2.0)	32 (2.1)	13 (2.0)	0.89
ICU admission, n (%)	1,067 (48)	745 (48)	322 (48)	0.45
Not reported	62 (3)	48 (3)	14 (2)	
ICU-free days, median (IQR)	26 (20, 28)	26 (19,28)	26 (21,28)	0.41
Mechanical ventilation, n (%)	385 (17)	280 (18)	105 (16)	0.19
Not reported	485 (22)	326 (21)	159 (24)	

Unadjusted Outcomes, cont.

	Total (n=2,230)	Antibiotic 0-89 min (n=1,565)	Antibiotic ≥ 90 min (n=665)	p-value
Ventilator-free days, median (IQR)	24 (16,27)	24 (15,27)	25 (18,27)	0.50
Vasoactive infusion, n (%)	425 (19)	312 (20)	113 (17)	0.04
Not reported	96 (4)	75 (5)	21 (3)	
Vasoactive infusion-free days, median (IQR)	28 (25,29)	28 (25,29)	28 (25,29)	0.73
Sepsis days, median (IQR)	9 (5,15)	9 (5,15)	8 (5,14)	0.01
CVL placement, n (%)	284 (13)	193 (12)	91 (14)	0.26
Not reported	902 (40)	650 (41)	252 (38)	

Limitations

- Low mortality rate
- Few patients received antibiotics very late
- No severity of illness score
- Site variability with sepsis attributable deaths
- Unknown/unreported variables

Conclusions

- Long delays in antibiotic administration are associated with mortality
 - Ideal timing remains undefined
 - A truly prospective RCT is unlikely
 - Observational well-controlled datasets are important
- Results do not change 2020 SSC international guidelines and recommendations
- Identifying children with bacteremia and sepsis may be a future area of investigation

Study Team



- Roni D. Lane, MD
- Jennifer K. Workman, MD, MSCI
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- Grant E. Keeney, MD, MS
- Christopher Horvat, MD, MHA
- Vishal Gunnala, MD

CHA Staff: Mary Headley, Jayne Stuart

Challenge sepsis.
Change lives.



Thank you!

Questions/Comments?

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16011 College Blvd. | Suite 250 | Lenexa, KS 66219 | 913-262-1436

www.childrenshospitals.org

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Challenge sepsis.
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Additional PRN Slides

Background- historic sentinel adult data

ORIGINAL RESEARCH |

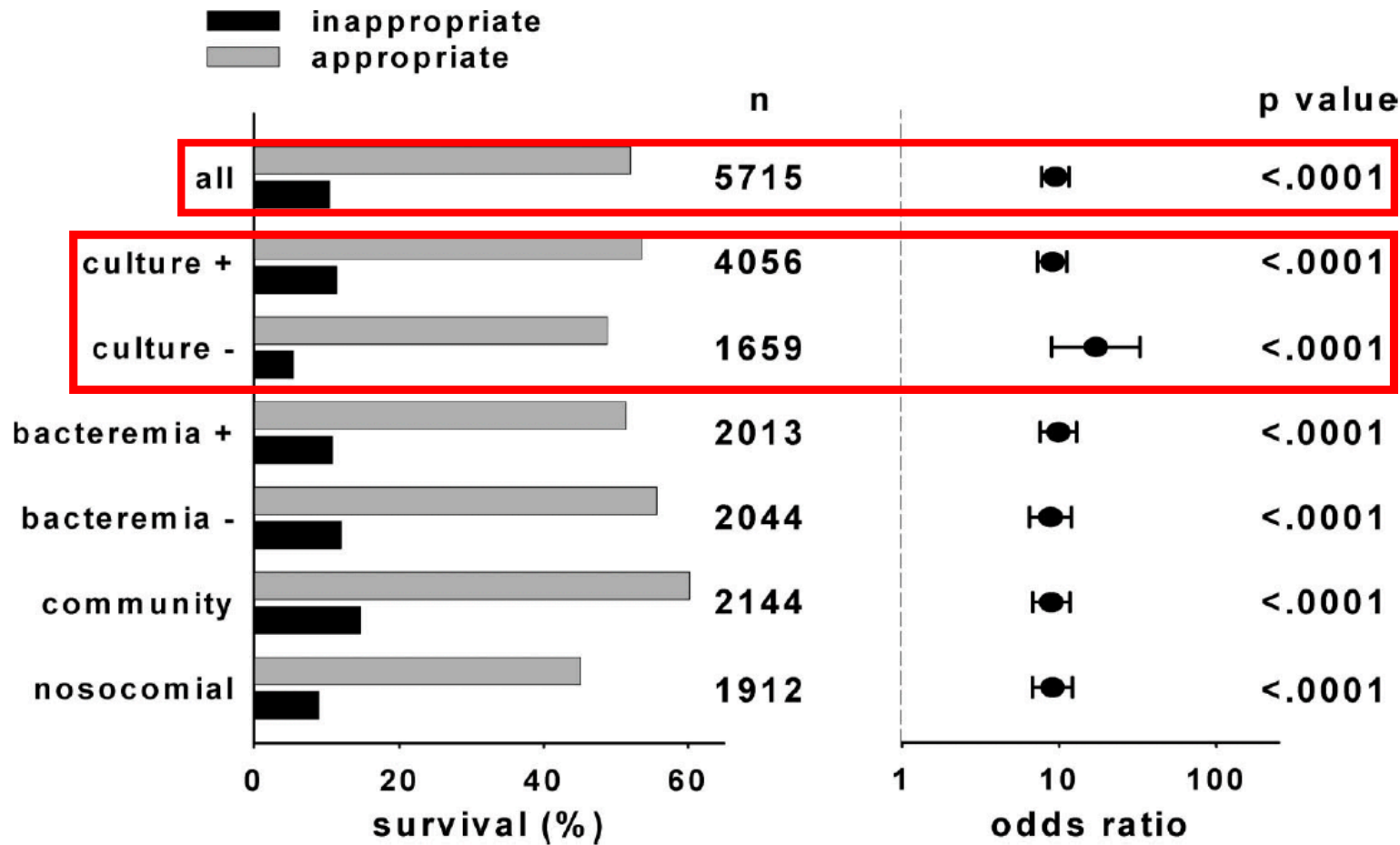
Initiation of
of Survival in

Anand Kumar, MD

Joseph E. Parrillo, MD

Cheryl Peters, RN^a

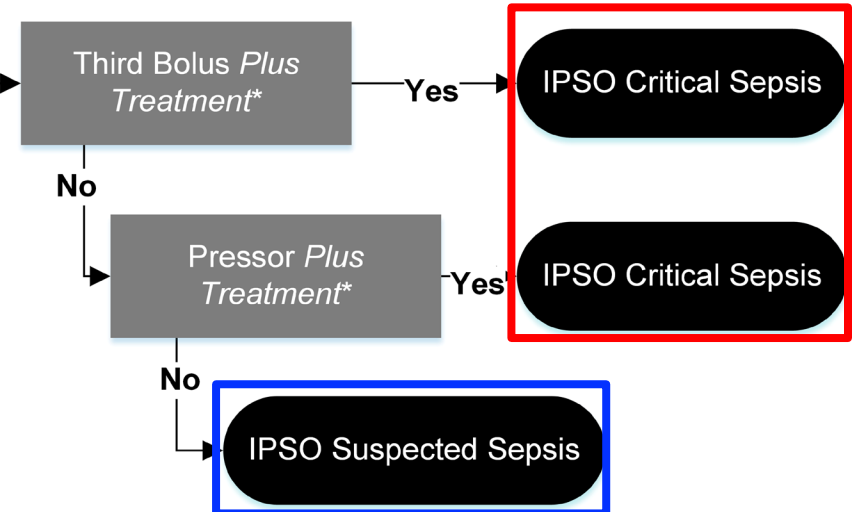
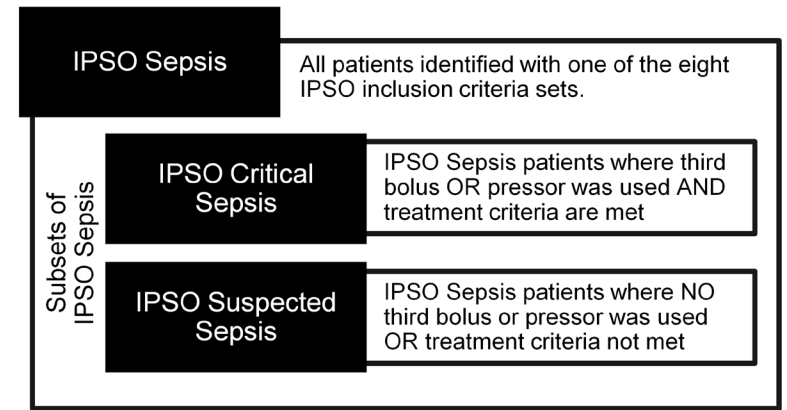
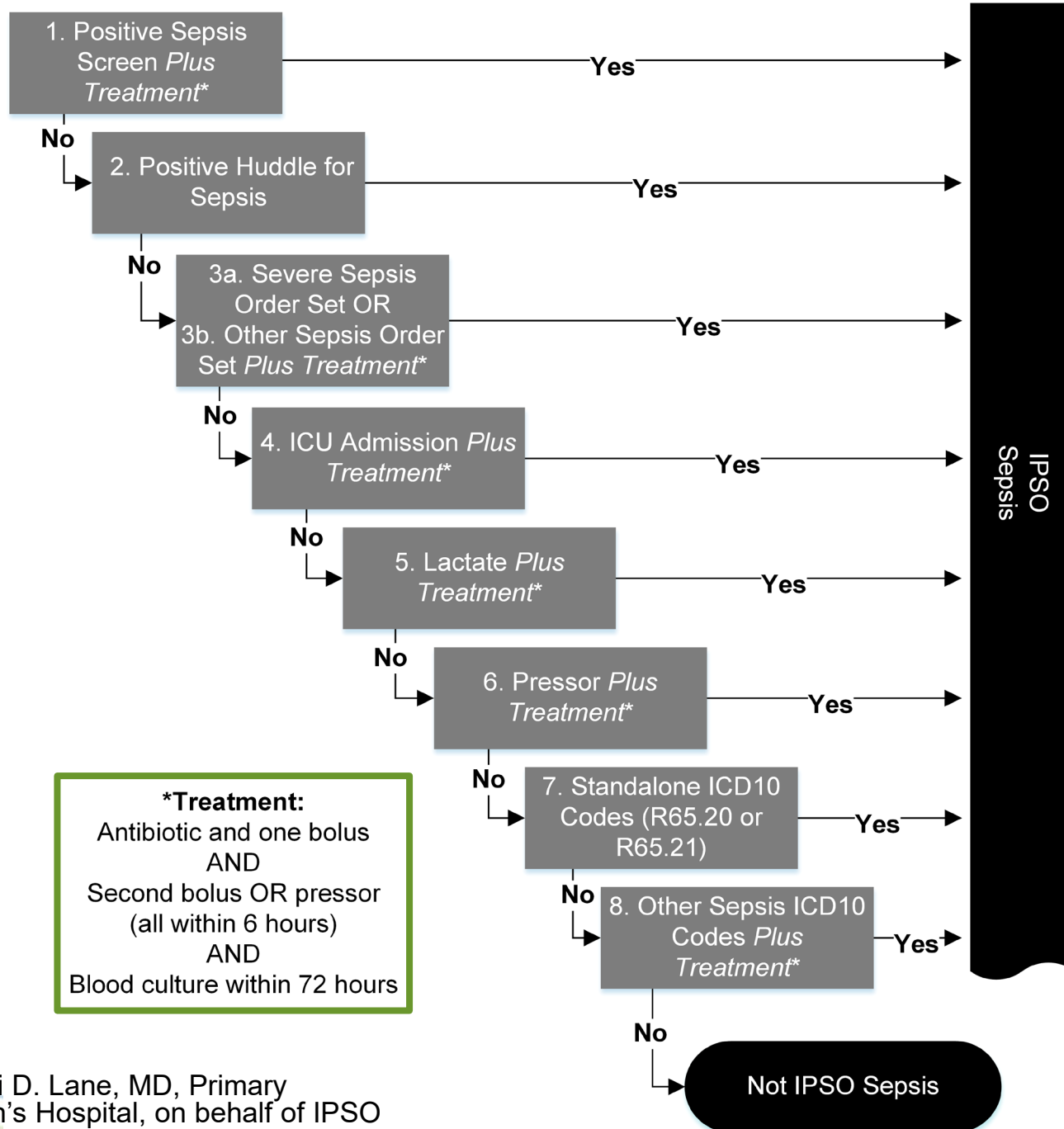
the Cooperative Anti



d Reduction

MD^h

FIGURE 2. Impact of antimicrobial appropriateness on survival in major epidemiologic subgroups. See the legend of Figure 1 for abbreviations not used in the text.



Statistical Analysis

- Piecewise logistic regression to find an inflection point after which 3-day SA mortality increased
- Univariable and multivariable analyses to assess for associations with 3-day SA mortality

Unreported Variables

	Total (n=19,515)	Antibiotic 0-329 min (n=19,164)	Antibiotic 330-419 min (n=351)	p-value
Ventilator dependence, n (%)				0.075
No	15,292 (78.4)	15,006 (78.3)	286 (81.5)	
Yes	1,604 (8.2)	1,584 (8.3)	20 (5.7)	
Not reported	2,619 (13.4)	2,574 (13.4)	45 (12.8)	
Lactic acid category, n (%)				<0.001
≤ 4 mmol/L	11,087 (56.8)	10,970 (57.2)	117 (33.3)	
> 4 mmol/L	1,371 (7.0)	1,353 (7.1)	18 (5.1)	
Not reported	7,057 (36.2)	6,841 (35.7)	216 (61.5)	
Positive blood culture, n (%)				0.138
No	15,874 (81.3)	15,591 (81.4)	283 (80.6)	
Yes	2,230 (11.4)	2,200 (11.5)	30 (8.5)	
Not reported	1,411 (7.2)	1,373 (7.2)	38 (10.8)	

Unadjusted Outcomes

	Total (n=19,515)	Antibiotic 0-329 min (n=19,164)	Antibiotic 330 min- 7 hrs (n=351)	p-value
3-day SA mortality, n (%)	97 (0.5)	93 (0.5)	4 (1.2)	0.079
30-day SA mortality, n (%)	170 (0.9)	163 (0.9)	7 (2.0)	0.020
ICU admission, n (%)	8,255 (44)	8,111 (44)	144 (43)	0.697
Not reported	657 (3)	643 (3)	14 (4)	
ICU-free days, median (IQR)	26 (22, 28)	26 (22,28)	26 (22,28)	0.103
Mechanical ventilation, n (%)	2,948 (20)	2,899 (20)	49 (18)	0.551
Not reported	4,565 (23)	4,482 (23)	83 (24)	

Unadjusted Outcomes, cont.

	Total (n=19,515)	Antibiotic 0-329 min (n=19,164)	Antibiotic 330 min-7 hrs (n=351)	p-value
Ventilator-free days, median (IQR)	26 (20,28)	26 (20,28)	24 (0,28)	0.176
Vasoactive infusion, n (%)	2,189 (12)	2,144 (12)	45 (14)	0.301
Not reported	988 (5)	967 (5)	21 (6)	
Vasoactive infusion-free days, median (IQR)	28 (26,29)	28 (26,29)	28 (25,29)	0.096
Sepsis days, median (IQR)	5 (3,9)	5 (3,9)	5 (3,8)	0.668
CVL placement, n (%)	1,676 (13)	1,630 (13)	46 (19)	0.009
Not reported	6,584 (34)	6,482 (34)	102 (29)	

Multivariable Analysis of 30-day Sepsis Attributable Mortality

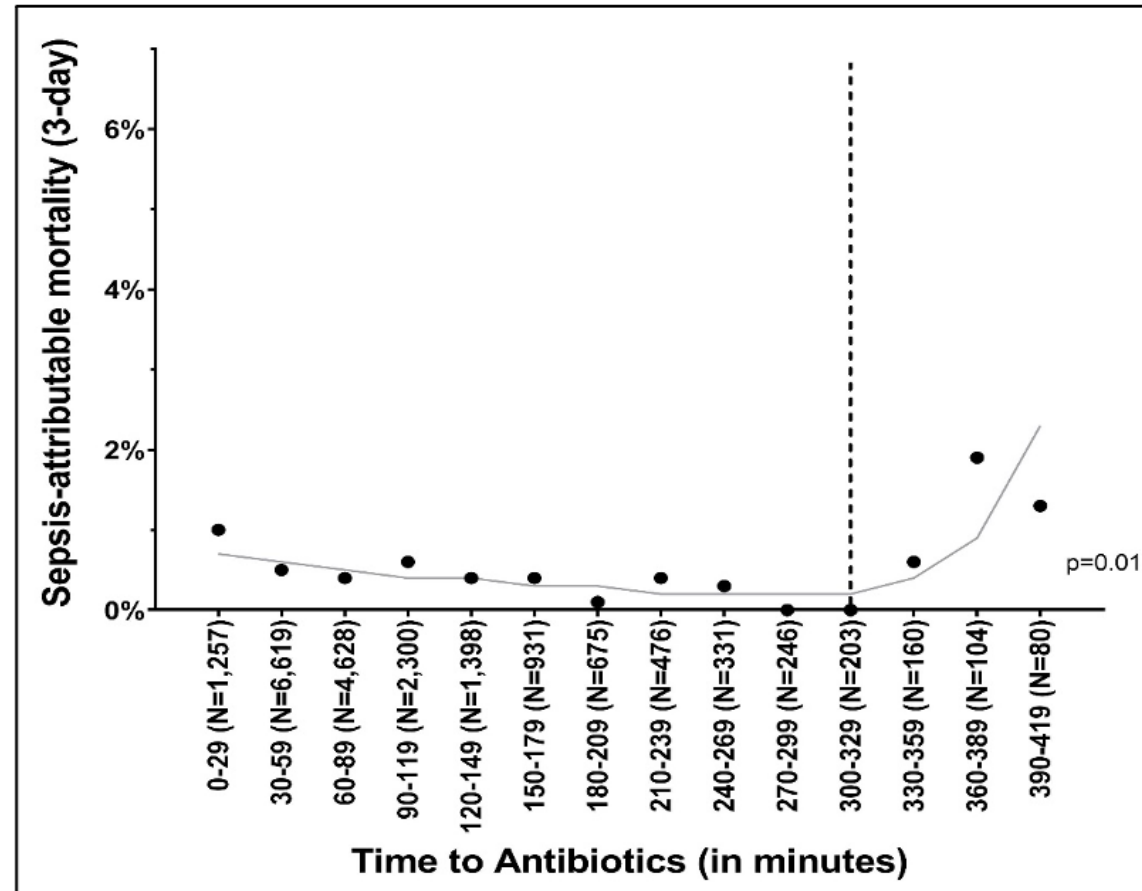
	30-day SA mortality Odds Ratio (95% CI)
Antibiotic timing (Reference: 0-329 min)	
330 min-7 hours	3.56 (1.56,8.16)
Intellectual disability	1.72 (1.12,2.62)
Positive blood culture	2.18 (1.49,3.17)
Lactic acid value (Reference: < 4 mmol/L)	
≥ 4 mmol/L	4.95 (3.34,7.32)
IPSO Sepsis cohort (Reference: Suspected sepsis)	
Critical sepsis	6.23 (4.24,9.16)
FTZ Source (Reference: screen)	
Huddle	2.53 (1.40,4.59)
Order set	2.32 (1.55,3.47)
Age	Not significant
Solid organ transplant	Not significant

Co-variables not retained in the model: other high risk conditions, time to first fluid bolus.

Exploratory Analysis of 0-29 and 30-329 Minutes to Antibiotics

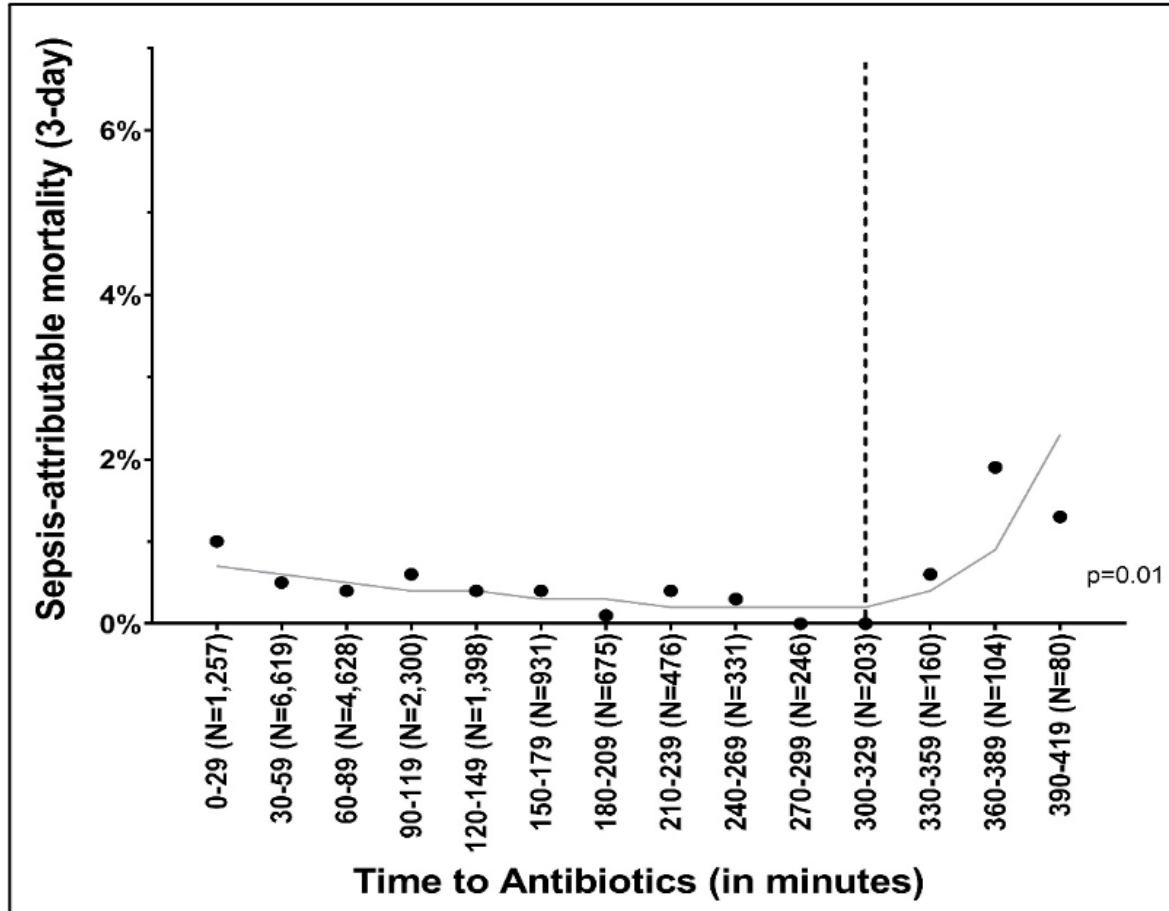
	Antibiotic 0-29 min (n=1,265)	Antibiotic 30-329 min (n=17,889)	p-value
Age, median (IQR)	7 (3,13)	6 (2,12)	0.003
High risk condition, n (%)			
Malignancy	278 (22)	3,360 (19)	0.005
Technology dependent	269 (21)	4,777 (27)	<0.001
Intellectual disability	155 (12)	3,324 (19)	<0.001
Positive blood culture, n (%)	150 (13)	2,050 (12)	0.394
Lactic acid > 4 mmol/L, n (%)	140 (11)	1,213 (7)	<0.001
Minutes to 1st antibiotic, median (IQR)	25 (21,27)	72 (50,116)	<0.001
Minutes to FTZ from ED arrival, median (IQR)	8 (5,14)	14 (8,24)	<0.001

Piecewise Logistic Regression, part 2



Pre Interruption Slope/Odds Ratio (95% CI):		
	OR (95% CI)	p-value
Unadj	0.849 (0.734, 0.982)	0.031
Adj	0.848 (0.732, 0.983)	0.032

Piecewise Logistic Regression, part 3



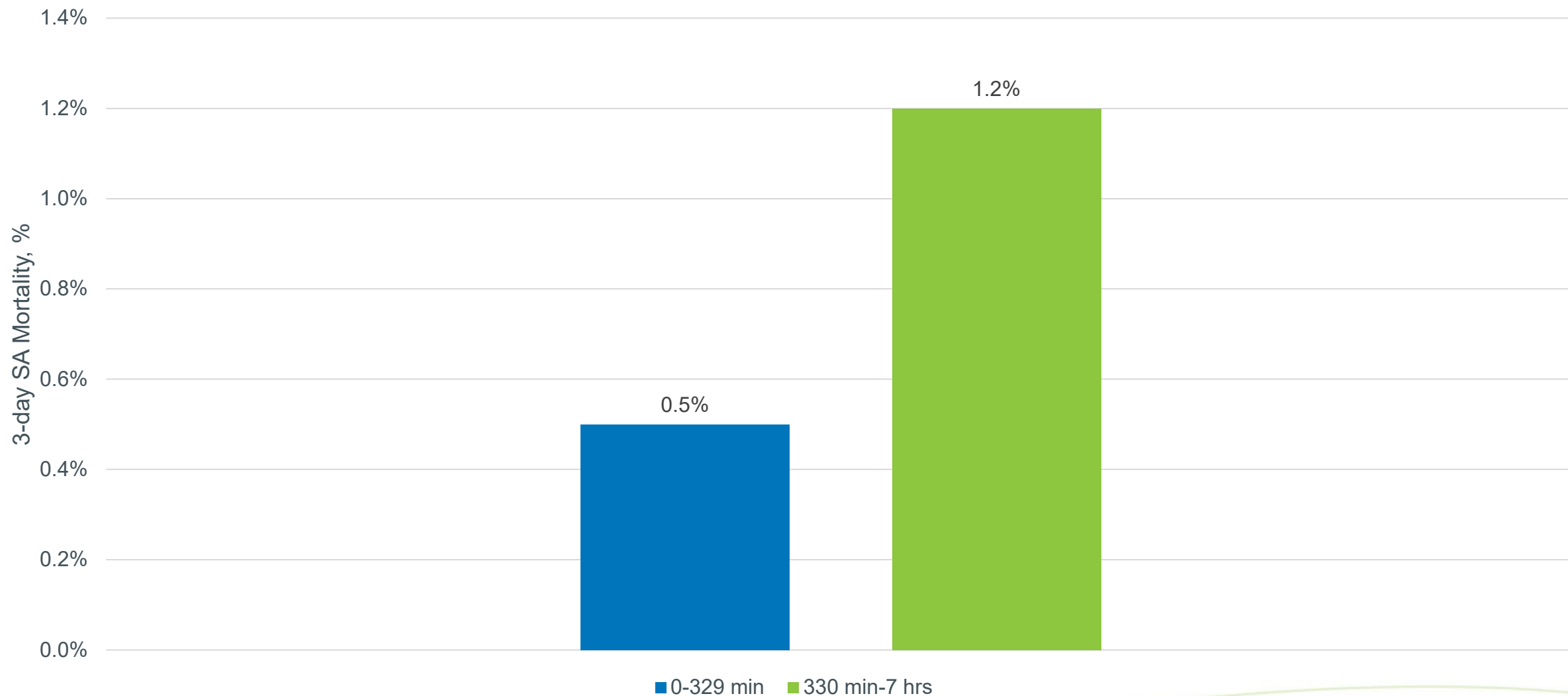
Pre Interruption Slope/Odds Ratio (95% CI):

	OR (95% CI)	p-value
Unadj	0.849 (0.734, 0.982)	0.031
Adj	0.848 (0.732, 0.983)	0.032

Pre Interruption First 30 minutes vs rest (unadj)

	OR (95% CI)	p-value
Step down after 30 min	0.337 (0.180, 0.629)	0.003
Slope (30 min - 330 min)	0.913 (0.786, 1.059)	0.195

3-day SA Mortality and Antibiotic Timing



IMPROVING PEDIATRIC SEPSIS OUTCOMES



- CHA 57 hospital QI collaborative
- Decrease pediatric sepsis mortality and reduce hospital-onset sepsis through standardized bundle care
- Intervention-based definitions of sepsis, suspected sepsis and critical sepsis

Challenge sepsis. Change lives.



Discussion

Children's Hospital Association

600 13th St., NW | Suite 500 | Washington, DC 20005 | 202-753-5500

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Reminder

Please complete the brief survey **by November 22.**
This must be completed to receive CE credit!

Continuing the Conversation

CHA Sepsis Community of Practice



Virtual events



Anytime discussion board



Tools & resources



Open to all CHA member hospital participants

Next Webinar:

Optimizing Antibiotic Administration for Sepsis: A Multidisciplinary Effort



Antimicrobial Stewardship
Advocate Children's Hospital



Antibiotic timeliness
*Monroe Carell Children's at
Vanderbilt*

Tuesday, January 21, 1pm ET
12p CT | 11a MT | 10a PT

Challenge sepsis. Change lives.



Thank you!

For additional questions, contact:
quality.programs@childrenshospitals.org

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