Advancing the Science of Stewardship

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Land Acknowledgement: The state of Texas, where Rice University is located, has been a meeting and trading location for Indigenous tribes including the Apache, Caddo, Comanche, Kiowa, and Wichita. Three federally recognized tribes and two state-recognized tribes currently reside in Texas. The land that Rice University occupies is the ancestral home of the Karankawa, Atakapa-Ishak, and Sana peoples. A painful history of settler colonialism, genocide, and forced migration and assimilation occurred here, and the descendants of these communities need to be recognized and included in the history of our community.

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Research

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Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection
The ACORN Randomized Clinical Trial

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Qian ET, Casey JD, Wright A, et al. Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection: The ACORN Randomized Clinical Trial. *JAMA.* 2023;330(16):1557–1567.

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QUESTION Does the choice between cefepime and piperacillin-tazobactam affect the risks of acute kidney injury or neurological dysfunction in adults hospitalized with acute infection?

CONCLUSION Among hospitalized adults, the risk of acute kidney injury did not differ between cefepime and piperacillin-tazobactam, but neurological dysfunction was more common with cefepime.

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POPULATION

1439 Men **1071** Women

Adults hospitalized with acute infection

Median age: **58** years

LOCATION

1
Medical center in Nashville, Tennessee

INTERVENTION

2634 Patients randomized
2511 Patients analyzed

1214
Cefepime
Administered as an intravenous push over 5 minutes

1297
Piperacillin-tazobactam
Administered as a bolus for the initial administration and then extended infusion over 4 hours for subsequent doses

PRIMARY OUTCOME

Highest stage of acute kidney injury or death by day 14 (measured on a 5-level ordinal scale; range: no acute kidney injury to death)

FINDINGS

Highest stage of acute kidney injury or death by day 14

Cefepime

Survived with stage 3 acute kidney injury	**7.0%** (85 of 1214 patients)
Died	**7.6%** (92 of 1214 patients)

Piperacillin-tazobactam

Survived with stage 3 acute kidney injury	**7.5%** (97 of 1297 patients)
Died	**6.0%** (78 of 1297 patients)

There was no significant between-group difference:
Odds ratio, 0.95 (95% CI, 0.80 to 1.13); $P = .56$

Qian ET, Casey JD, Wright A, et al; Vanderbilt Center for Learning Healthcare and the Pragmatic Critical Care Research Group. Cefepime vs piperacillin-tazobactam in adults hospitalized with acute infection: the ACORN randomized clinical trial. *JAMA*. Published online October 14, 2023. doi:10.1001/jama.2023.20583

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From: **Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection: The ACORN Randomized Clinical Trial**

JAMA. 2023;330(16):1557-1567. doi:10.1001/jama.2023.20583

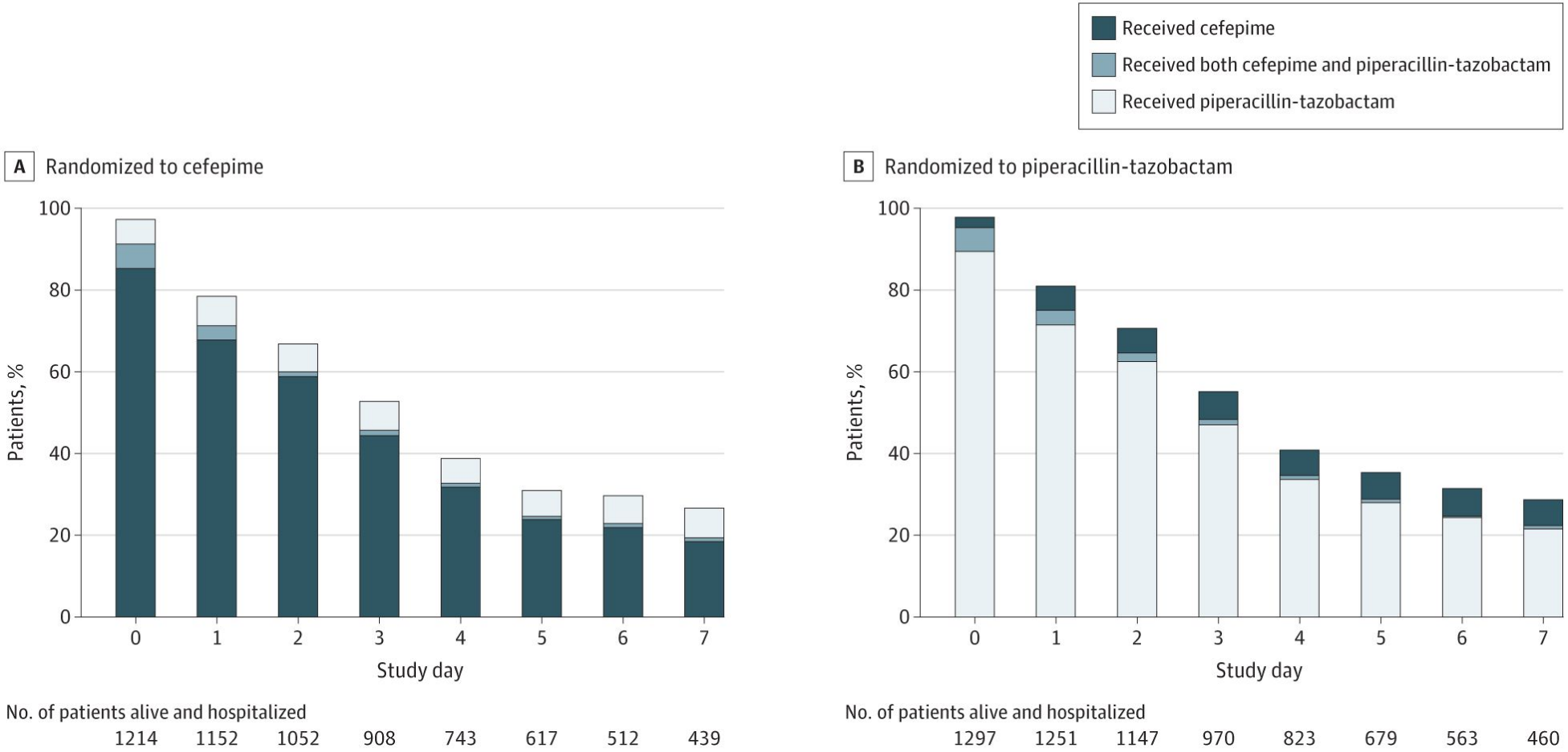

Table 2. Primary, Secondary, and Exploratory Outcomes

	Cefepime (n = 1214)	Piperacillin-tazobactam (n = 1297)	Between-group difference expressed as RD or OR (95% CI)[a]
Primary outcome			
Acute kidney injury or death by day 14, No. (%)			OR, 0.95 (0.80 to 1.13)
No stage (survived)	910 (75.0)	952 (73.4)	
Stage 1 (survived)	86 (7.1)	100 (7.7)	
Stage 2 (survived)	41 (3.4)	70 (5.4)	
Stage 3 (survived)	85 (7.0)	97 (7.5)	
Stage 4 (died)	92 (7.6)	78 (6.0)	
Secondary outcomes			
Major adverse kidney events at day 14, No. (%)[b]	124 (10.2)	114 (8.8)	RD, 1.4 (−1.0 to 3.8)
Death, No. (%)	92 (7.6)	78 (6.0)	RD, 1.6 (−0.5 to 3.6)
New kidney replacement therapy, No./total (%)	37/1136 (3.3)	28/1230 (2.3)	RD, 1.0 (−0.4 to 2.4)
Final creatinine level ≥2 times the baseline level, No./total (%)	15/1136 (1.3)	29/1230 (2.4)	RD, −1.0 (−2.2 to 0.1)
Delirium- and coma-free days within 14 d[c]			
Median (IQR)	14 (14 to 14)	14 (14 to 14)	OR, 0.79 (0.65 to 0.95)
Mean (SD)	11.9 (4.6)	12.2 (4.3)	
Delirium, No. (%)[d]	200 (16.5)	181 (14.0)	RD, 2.5 (−0.4 to 5.4)
Coma, No. (%)[d]	164 (13.5)	162 (12.5)	RD, 1.0 (−1.7 to 3.7)
Delirium or coma, No. (%)[d]	252 (20.8)	225 (17.3)	RD, 3.4 (0.3 to 6.6)
Exploratory outcomes			
Major adverse kidney events at day 28, No. (%)[b]	135 (11.1)	132 (10.2)	RD, 0.9 (−1.6 to 3.4)
Death, No. (%)	104 (8.6)	106 (8.2)	RD, 0.4 (−1.9 to 2.6)
New kidney replacement therapy, No./total (%)	44/1136 (3.9)	28/1230 (2.3)	RD, 1.6 (0.1 to 3.1)
Final creatinine level ≥2 times the baseline level, No./total (%)	14/1136 (1.2)	26/1230 (2.1)	RD, −0.9 (−2.0 to 0.2)
Delirium- and coma-free days within 28 d[c]			
Median (IQR)	28 (28 to 28)	28 (28 to 28)	OR, 0.80 (0.66 to 0.97)
Mean (SD)	24.4 (8.6)	24.8 (8.2)	
Kidney replacement therapy-free days within 28 d[c]			
Median (IQR)	28 (28 to 28)	28 (28 to 28)	OR, 0.78 (0.62 to 0.98)
Mean (SD)	24.4 (9.1)	25.0 (8.5)	
Vasopressor-free days within 28 d[c]			
Median (IQR)	28 (28 to 28)	28 (28 to 28)	OR, 0.96 (0.80 to 1.16)
Mean (SD)	24.8 (8.3)	25.1 (7.9)	
Ventilator-free days within 28 d[c]			
Median (IQR)	28 (28 to 28)	28 (28 to 28)	OR, 0.84 (0.68 to 1.03)
Mean (SD)	24.8 (8.4)	25.0 (8.2)	
Intensive care unit-free days within 28 d[c]			
Median (IQR)	28 (25 to 28)	28 (26 to 28)	OR, 0.92 (0.77 to 1.09)
Mean (SD)	23.9 (8.6)	24.2 (8.4)	
Hospital-free days within 28 d[c]			
Median (IQR)	22 (15 to 24)	22 (15 to 24)	OR, 0.99 (0.86 to 1.13)
Mean (SD)	18.1 (8.6)	18.3 (8.5)	
Allergic reaction to study antibiotic, No. (%)[e]	16 (1.3)	15 (1.2)	RD, 0.2 (−0.8 to 1.1)

[a] The absolute risk difference (RD) or odds ratio (OR). The ORs were generated

[c] An OR greater than 1.0 indicates a better outcome (eg, more days alive and

EDITORIAL

Acute Kidney Injury With Empirical Antibiotics for Sepsis

Steven Y. C. Tong, PhD; Balasubramanian Venkatesh, MD; Erin K. McCreary, PharmD

Sepsis describes life-threatening organ dysfunction due to a dysregulated host response to infection. It is a global health priority affecting 55 million people worldwide causing 11 million deaths annually.[1] Failure to initiate timely antibiotic therapy for sepsis can result in progression to septic shock, which is associated with a mortality rate of 30% to 40%.[2] Accordingly, sepsis is recognized as a time-critical medical emergency.

Related article page 1557

Current management focuses on "bundles"[3] of care incorporating early recognition, timely antibiotic administration, and fluid resuscitation. Two commonly prescribed antibiotics for empirical treatment of sepsis are the β-lactams piperacillin-tazobactam and cefepime. Both provide broad in vitro activity against gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa*. They are often used in combination with vancomycin to include activity against methicillin-resistant *Staphylococcus aureus*.

Both β-lactam antibiotics are associated with risk. The purported increased risk of acute kidney injury (AKI) from the combination of piperacillin-tazobactam plus vancomycin compared with other β-lactam agents has led to a cultural shift away from the empirical use of piperacillin-tazobactam serum concentrations. Because kidney dysfunction is common in patients with sepsis, some fear use of cefepime may precipitate delirium in an already tenuous population.

In this issue of *JAMA*, Qian and colleagues[11] provide needed randomized clinical trial evidence to guide empirical prescribing for patients presenting to the emergency department with suspected sepsis. In this single-center, pragmatic, open-label, randomized clinical trial, Qian and colleagues[11] sought to determine whether use of piperacillin-tazobactam or cefepime for empirical sepsis treatment affects the risks of AKI or neurological dysfunction. They enrolled 2511 patients almost exclusively in the emergency department (95%). At baseline, 54% of participants met sepsis criteria, 13% required vasopressors, and 8% required mechanical ventilation.

The primary outcome of highest stage of AKI or death by day 14 did not significantly differ between the cefepime group and the piperacillin-tazobactam group (OR, 0.95 [95% CI, 0.80-1.13], $P = .56$).[11] The primary outcome result was consistent across the adjusted and prespecified sensitivity analyses. There were no differences in the incidence of major adverse kidney events by day 14 between the groups. The day 14 mortality rates were similar (7.6% in the cefepime group vs 6.0% in the

Tong SYC, Venkatesh B, McCreary EK. Acute Kidney Injury With Empirical Antibiotics for Sepsis. *JAMA.* 2023;330(16):1531–1533.

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Research

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Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis

The BLING III Randomized Clinical Trial

Joel M. Dulhunty, MD, PhD; Stephen J. Brett, MD; Jan J. De Waele, MD, PhD;
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Sandra Peake, MD, PhD; Andrew Rhodes, MD, MD(Res); Jason A. Roberts, BPharm, PhD; Claire Roger, MD, PhD;
Charudatt Shirwadkar, MD; Therese Starr, RN; Colman Taylor, PhD; John A. Myburgh, MD, PhD;
Jeffrey Lipman, MD, DMed(Res); for the BLING III Study Investigators

Dulhunty JM, Brett SJ, De Waele JJ, et al. Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis: The BLING III Randomized Clinical Trial. *JAMA.* 2024;332(8):629-637.

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QUESTION Is there a difference in mortality between continuous and intermittent infusions of β-lactam antibiotics in critically ill patients with sepsis?

CONCLUSION In critically ill patients with sepsis, continuous vs intermittent β-lactam antibiotic infusions did not significantly reduce 90-day mortality in the primary analysis. A clinically important benefit with continuous infusions is possible.

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POPULATION

4608 Men
2423 Women

Critically ill adults aged ≥18 years treated for sepsis

Mean age: **59** years

LOCATION

104
ICUs worldwide

INTERVENTION

3498
Continuous infusion
Continuous infusion (over 24 hours) of either piperacillin-tazobactam or meropenem

3533
Intermittent infusion
Intermittent infusion (over 30 minutes) of either piperacillin-tazobactam or meropenem

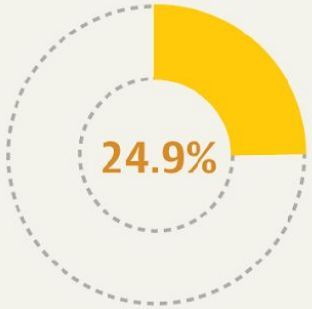
PRIMARY OUTCOME

All-cause mortality within 90 days after randomization

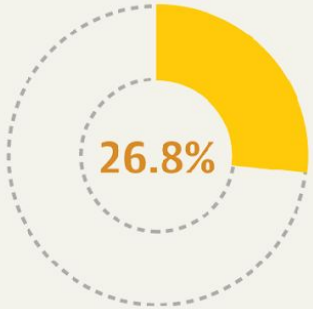
FINDINGS

All-cause mortality at day 90

Continuous infusion
864 of 3474 patients



Intermittent infusion
939 of 3507 patients



Absolute difference, **−1.9%** (95% CI, −4.9% to 1.1%)
Odds ratio, **0.91** (95% CI, 0.81 to 1.01); $P = .08$

Dulhunty JM, Brett SJ, De Waele JJ, et al; BLING III Study Investigators. Continuous vs intermittent β-lactam antibiotic infusions in critically ill patients with sepsis: the BLING III randomized clinical trial. *JAMA*. Published June 12, 2024. doi:10.1001/jama.2024.9779

Table 2. Reporting of Primary, Secondary, and Tertiary Outcomes

Outcome	Continuous infusion (n = 3498)[a]	Intermittent infusion (n = 3533)[a]	Absolute difference, % (95% CI)	Odds ratio or mean difference (95% CI)	*P* value[b]
Primary outcome					
All-cause mortality at day 90, No./total (%)	864/3474 (24.9)	939/3507 (26.8)	−1.9 (−4.9 to 1.1)	0.91 (0.81 to 1.01)	.08
Adjusted analysis			−2.2 (−5.5 to 1.1)	0.89 (0.79 to 0.99)	.04
Secondary outcomes					
Clinical cure at day 14, No./total (%)	1930/3467 (55.7)	1744/3491 (50.0)	5.7 (2.4 to 9.1)	1.26 (1.15 to 1.38)	<.001
New acquisition, colonization, or infection with an MRO or *C difficile*, No./total (%)[c]	253/3498 (7.2)	266/3533 (7.5)	−0.3 (−1.9 to 1.4)	0.96 (0.80 to 1.15)	.65
All-cause ICU mortality, No./total (%)	595/3474 (17.1)	645/3507 (18.4)	−1.3 (−4.0 to 1.4)	0.92 (0.81 to 1.04)	.35
All-cause hospital mortality, No./total (%)	808/3474 (23.3)	878/3507 (25.0)	−1.8 (−4.8 to 1.2)	0.91 (0.81 to 1.02)	.27
Tertiary outcomes					
Days alive and free of ICU up to day 90, mean (SD) [No.]	59.4 (33.9) [3481]	57.8 (34.2) [3516]	NA	1.5 (−0.1 to 3.0)	.18
Median (IQR)	78 (31 to 84)	76 (22 to 84)			
Days alive and free of hospital up to day 90, mean (SD) [No.]	42.4 (32.2) [3476]	40.6 (32.5) [3515]	NA	1.8 (0.3 to 3.3)	.08
Median (IQR)	52 (0 to 73)	48 (0 to 72)			
Days alive and free of mechanical ventilation up to day 90, mean (SD) [No.]	64.2 (34.5) [3486]	62.9 (34.8) [3520]	NA	1.2 (−0.4 to 2.8)	.28
Median (IQR)	84 (41 to 89)	83 (32 to 89)			
Days alive and free of KRT up to day 90, mean (SD) [No.]	71.2 (32.8) [3489]	70.2 (33.1) [3521]	NA	0.9 (−0.6 to 2.4)	.25
Median (IQR)	90 (70 to 90)	90 (54 to 90)			

Abbreviations: ICU, intensive care unit; KRT, kidney replacement therapy; MRO, multiresistant organism; NA, not applicable.

[a] Descriptive statistics and odds ratio or mean difference are reported for all participants with available data by group. The group denominator for each outcome is reported.

[b] *P* values for secondary and tertiary outcomes corrected with a Holm-Bonferroni adjustment.

[c] The number and percentage of new acquisition, colonization, or infection with an MRO, excluding *Clostridioides difficile*, was 6.1% (213/3498) in the continuous infusion group and 6.6% (232/3533) in the intermittent infusion group.

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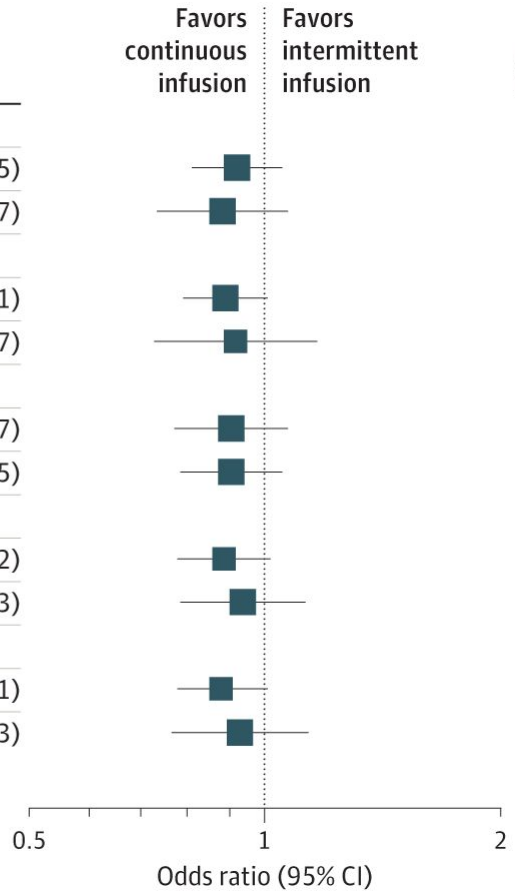
JAMA. Published online June 12, 2024. doi:10.1001/jama.2024.9779

	Group, No./total (%)				
	Continuous infusion	Intermittent infusion	Absolute difference, % (95% CI)[a]	Odds ratio (95% CI)[b]	*P* value for interaction
Pulmonary infection					
Yes	593/2178 (27.2)	647/2249 (28.8)	-1.7 (-5.2 to 1.9)	0.92 (0.81 to 1.05)	.73
No	271/1296 (20.9)	292/1258 (23.2)	-2.1 (-6.0 to 1.7)	0.88 (0.73 to 1.07)	
β-Lactam antibiotic					
Piperacillin-tazobactam	667/2749 (24.3)	722/2746 (26.3)	-2.2 (-5.3 to 1.0)	0.89 (0.79 to 1.01)	.83
Meropenem	183/696 (26.3)	203/714 (28.4)	-1.7 (-7.0 to 3.7)	0.92 (0.73 to 1.17)	
Age, y					
<65	348/1935 (18.0)	375/1938 (19.3)	-1.5 (-4.5 to 1.6)	0.91 (0.77 to 1.07)	.99
≥65	516/1539 (33.5)	564/1569 (35.9)	-2.2 (-6.5 to 2.0)	0.91 (0.78 to 1.05)	
Sex					
Male	563/2290 (24.6)	612/2279 (26.9)	-2.3 (-5.7 to 1.1)	0.89 (0.78 to 1.02)	.62
Female	301/1184 (25.4)	327/1228 (26.6)	-1.2 (-5.4 to 3.0)	0.94 (0.78 to 1.13)	
APACHE II score					
<25	543/2599 (20.9)	610/2661 (22.9)	-2.2 (-5.2 to 0.8)	0.88 (0.77 to 1.01)	.66
≥25	320/872 (36.7)	328/842 (39.0)	-1.7 (-7.1 to 3.7)	0.93 (0.76 to 1.13)	



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Research

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Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock
A Systematic Review and Meta-Analysis

Mohd H. Abdul-Aziz, BPharm, PhD; Naomi E. Hammond, RN, PhD; Stephen J. Brett, MD; Menino O. Cotta, BPharm, PhD; Jan J. De Waele, MD, PhD; Anthony Devaux, PhD; Gian Luca Di Tanna, PhD; Joel M. Dulhunty, MD, PhD; Hatem Elkady, MD; Lars Eriksson, BA; M. Shahnaz Hasan, MD; Ayesha Bibi Khan, MD; Jeffrey Lipman, MD, DMed; Xiaoqiu Liu, PhD; Giacomo Monti, MD; John Myburgh, MD, PhD; Emmanuel Novy, MD; Shahed Omar, MD; Dorrilyn Rajbhandari, RN; Claire Roger, MD, PhD; Fredrik Sjövall, MD, PhD; Irene Zaghi, MD; Alberto Zangrillo, MD; Anthony Delaney, MD, PhD; Jason A. Roberts, BPharm, PhD

Abdul-Aziz MH, Hammond NE, Brett SJ, et al. Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock: A Systematic Review and Meta-Analysis. *JAMA.* 2024;332(8):638-648.

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From: **Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock: A Systematic Review and Meta-Analysis**

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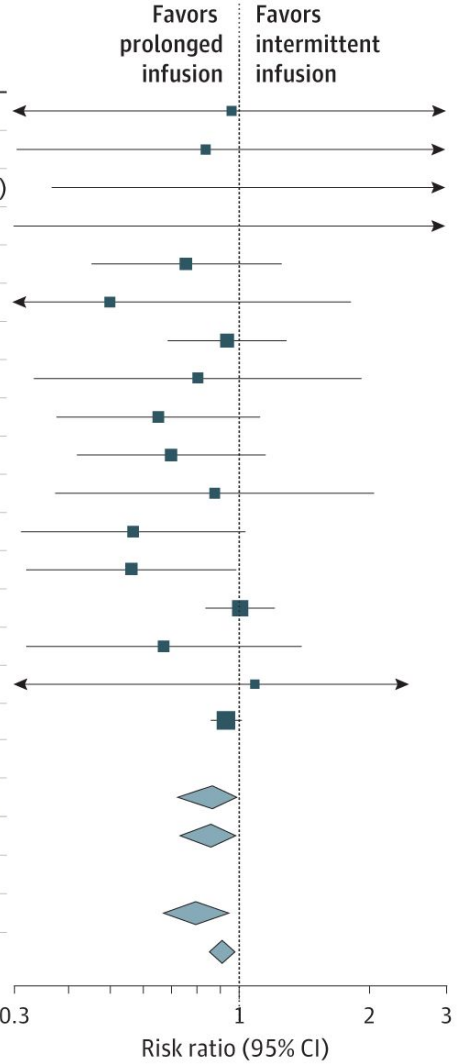
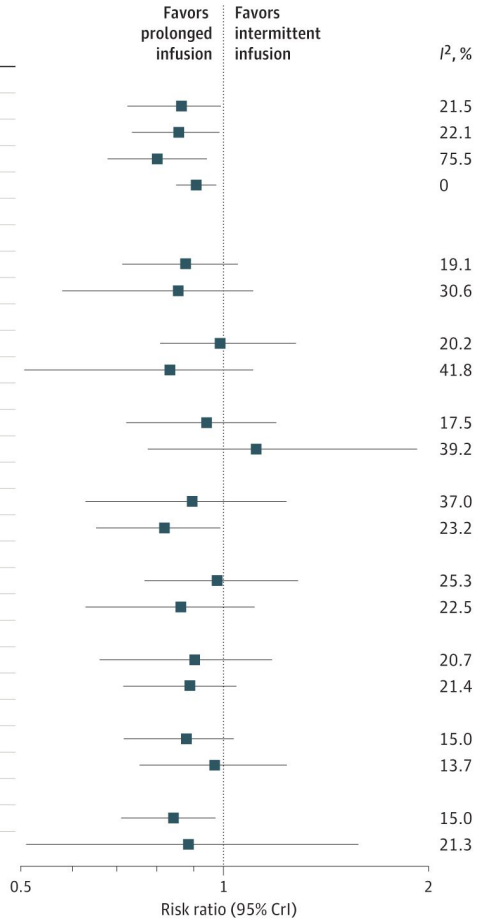
Study	Dead (prolonged)	Alive (prolonged)	Dead (intermittent)	Alive (intermittent)	Absolute difference (95% CI)	Risk ratio (95% CI)	Weight, %
Georges et al,[33] 2005	3	21	3	20	-0.01 (-0.02 to 0.01)	0.96 (0.21 to 4.27)	0.8
Rafati et al,[34] 2006	5	15	6	14	-0.05 (-0.09 to -0.01)	0.83 (0.30 to 2.29)	1.6
Roberts et al,[35] 2007	3	26	0	28	0.10 (0.09 to 0.11)	6.77 (0.37 to 125.32)	0.2
Roberts et al,[36] 2009	2	3	0	5	0.33 (0.23 to 0.44)	5.00 (0.30 to 83.69)	0.2
Chytra et al,[38] 2012	21	99	28	92	-0.06 (-0.06 to -0.05)	0.75 (0.45 to 1.24)	5.1
Dulhunty et al,[39] 2013	3	27	6	24	-0.10 (-0.12 to -0.08)	0.50 (0.14 to 1.82)	1.1
Dulhunty et al,[40] 2015	54	156	60	158	-0.02 (-0.02 to -0.01)	0.93 (0.68 to 1.28)	9.8
Jamal et al,[41] 2015	4	4	5	3	-0.12 (-0.24 to -0.01)	0.80 (0.33 to 1.92)	2.1
Jamal et al,[42] 2015	5	3	8	0	-0.33 (-0.40 to -0.27)	0.65 (0.38 to 1.12)	4.6
Abdul-Aziz et al,[43] 2016	18	52	26	44	-0.11 (-0.13 to -0.10)	0.69 (0.42 to 1.14)	5.2
Zhao et al,[44] 2017	7	18	8	17	-0.04 (-0.07 to -0.01)	0.88 (0.37 to 2.05)	2.2
Khan and Omar,[22] 2023	12	40	20	29	-0.18 (-0.19 to -0.16)	0.57 (0.31 to 1.03)	4.0
Mirjalili et al,[45] 2023	14	54	25	43	-0.16 (-0.17 to -0.15)	0.56 (0.32 to 0.98)	4.4
Monti et al,[14] 2023	127	176	127	177	0.00 (0.00 to 0.00)	1.00 (0.83 to 1.21)	17.6
Saad et al,[46] 2024	8	22	12	18	-0.13 (-0.16 to -0.10)	0.67 (0.32 to 1.39)	2.8
Álvarez-Moreno et al,[47] 2024	2	10	2	11	0.01 (-0.03 to 0.06)	1.08 (0.18 to 6.53)	0.6
Dulhunty et al,[15] 2024	864	2610	939	2568	-0.02 (-0.02 to -0.02)	0.93 (0.86 to 1.01)	37.4
Bayesian							
Vague priors[a]					-0.03 (-0.08 to 0.00)	0.86 (0.72 to 0.98)	
Semi-informative priors[a]					-0.04 (-0.10 to 0.01)	0.86 (0.73 to 0.98)	
Frequentist							
Sidik-Jonkman					-0.05 (-0.10 to 0.00)	0.80 (0.67 to 0.94)	
DerSimonian-Laird					-0.03 (-0.07 to 0.00)	0.91 (0.85 to 0.97)	



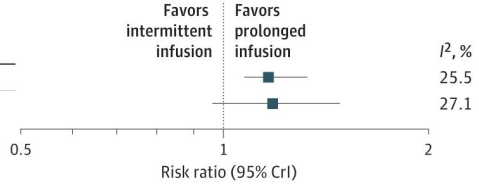
A Primary outcome, subgroup analysis of primary outcome, and secondary outcomes

Outcomes	No. of trials	No. of participants	Risk ratio (95% CrI)	I^2, %
Primary outcome: all-cause 90-d mortality				
Vague priors	17	9014	0.86 (0.72 to 0.98)	21.5
Semi-informative priors	17	9014	0.86 (0.73 to 0.98)	22.1
Hartung-Knapp-Sidik-Jonkman[a]	17	9014	0.80 (0.67 to 0.94)	75.5
DerSimonian-Laird[a]	17	9014	0.91 (0.85 to 0.97)	0
Subgroup analysis of the primary outcome				
Study β-lactam antibiotic				
Meropenem	10	2568	0.88 (0.71 to 1.04)	19.1
Piperacillin-tazobactam	7	6009	0.86 (0.58 to 1.10)	30.6
Microbiologic infection				
Culture-positive	8	4060	0.99 (0.80 to 1.27)	20.2
Culture-negative	7	4300	0.83 (0.51 to 1.10)	41.8
Gram infection				
Negative	7	2859	0.94 (0.72 to 1.19)	17.5
Positive	6	1597	1.11 (0.77 to 1.92)	39.2
Kidney replacement therapy				
Yes	4	802	0.90 (0.62 to 1.23)	37.0
No	13	7580	0.82 (0.65 to 0.98)	23.2
Infection				
Lung	8	5077	0.98 (0.76 to 1.28)	25.3
Other	7	3088	0.86 (0.62 to 1.11)	22.5
Sepsis vs septic shock				
Sepsis	7	2565	0.91 (0.65 to 1.17)	20.7
Shock	8	5782	0.89 (0.71 to 1.04)	21.4
Sex				
Male	10	5495	0.88 (0.71 to 1.03)	15.0
Female	10	2923	0.97 (0.75 to 1.23)	13.7
Secondary outcomes				
ICU mortality	15	8967	0.84 (0.70 to 0.97)	15.0
Adverse events	4	7761	0.89 (0.51 to 1.57)	21.3



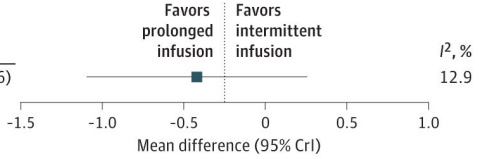
B Secondary outcomes

Outcomes	No. of trials	No. of participants	Risk ratio (95% CrI)	I^2, %
Clinical cure	12	8301	1.16 (1.07 to 1.31)	25.5
Microbiologic cure	4	352	1.18 (0.96 to 1.48)	27.1



C Secondary outcome

Outcome	No. of trials	No. of participants	Mean difference (95% CrI)	I^2, %
ICU length of stay	12	8935	-0.42 (-1.09 to 0.26)	12.9



EDITORIAL

Resolving the Dilemma on Continuous vs Intermittent β-Lactam Antibiotics in Sepsis

W. Joost Wiersinga, MD, PhD, MBA; Michiel A. van Agtmael, MD, PhD

The Surviving Sepsis Campaign guidelines recommend that adults with sepsis or septic shock should receive prolonged infusion of β-lactams (after an initial bolus) vs conventional intermittent infusion.[1] However, this is only a weak recommendation based on moderate quality of evidence. In this issue of *JAMA*, 2 major new contributions strengthen the evidence for this recommendation.[2,3]

Related articles

Up to 40% of patients treated with β-lactam antibiotics in the intensive care unit (ICU) may not achieve antibiotic concentrations above the minimum inhibitory concentration (MIC) during 50% to 100% of the dosing intervals.[4] In sepsis, many physiologic changes have pharmacokinetic-pharmacodynamic consequences, including increased cardiac output leading to increased drug clearance, and leaky capillaries necessitating intravenous volume resuscitation leading to an increased volume of distribution. Both of these changes will result in lower antimicrobial plasma concentrations.

paring 3498 patients receiving continuous infusions with 3533 patients receiving intermittent infusions (with loading dose) of β-lactam antibiotics (piperacillin-tazobactam or meropenem).[2] Nearly 30 000 patients were screened for eligibility, of whom 21 840 were excluded, with receipt of antibiotics for more than 24 hours being the primary reason for exclusion. Enrolled patients had a mean age of 59 years and were predominantly male, with no mention of comorbidities. The percentage of patients with septic shock was not specified, but approximately 70% received vasopressors within the 24 hours prior to randomization. The respiratory tract was the most common source of sepsis, followed by intra-abdominal infections, with *Escherichia* spp, *Klebsiella* spp, *Pseudomonas* spp, and methicillin-sensitive *Staphylococcus aureus* being the most prevalent causative pathogens.

All-cause mortality within 90 days after randomization, the primary outcome of the study, occurred in 24.9% of those receiving continuous infusion of β-lactam antibiotics and

Wiersinga WJ, van Agtmael MA. Resolving the Dilemma on Continuous vs Intermittent β-Lactam Antibiotics in Sepsis. *JAMA.* Published online June 12, 2024.

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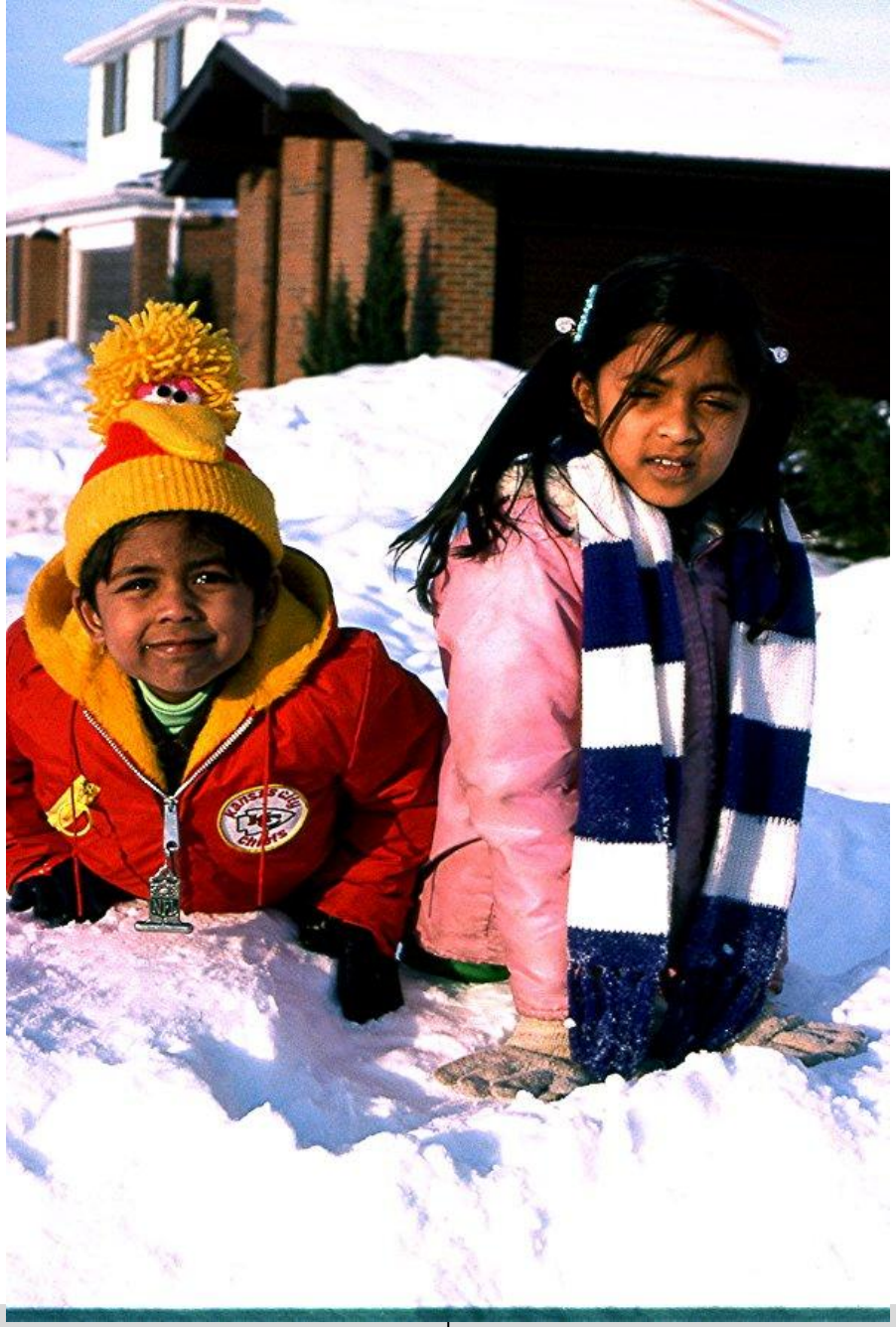

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Research

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Stewardship Prompts to Improve Antibiotic Selection for Pneumonia
The INSPIRE Randomized Clinical Trial

Shruti K. Gohil, MD, MPH; Edward Septimus, MD; Ken Kleinman, ScD; Neha Varma, MPH; Talisser R. Avery, MS; Lauren Helm, MPH; Risa Rahm, PharmD; William S. Cooper, PharmD; Mandelin Cooper, PharmD; Laura E. McLean, MEd; Naoise G. Nickolay, RPh; Robert A. Weinstein, MD; L. Hayley Burgess, PharmD; Micaela H. Coady, MS; Edward Rosen, BA; Selsebil Sijivo, MPH; Kenneth E. Sands, MD, MPH; Julia Moody, MS; Justin Vigeant, BA; Syma Rashid, MD; Rebecca F. Gilbert, BA; Kim N. Smith, MBA; Brandon Carver, BA; Russell E. Poland, PhD; Jason Hickok, MBA; S. G. Sturdevant, PhD; Michael S. Calderwood, MD, MPH; Anastasia Weiland, MD; David W. Kublak, PharmD; Sujan Reddy, MD, MSc; Melinda M. Neuhauser, PharmD, MPH; Arjun Srinivasan, MD; John A. Jernigan, MD, MS; Mary K. Hayden, MD; Abinav Gowda, BS; Katyuska Eibensteiner, BA; Robert Wolf, BS; Jonathan B. Perlin, MD, PhD; Richard Platt, MD, MSc; Susan S. Huang, MD, MPH

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA.* 2024;331(23):2007–2017.

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JAMA | Original Investigation

Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection
The INSPIRE Randomized Clinical Trial

Shruti K. Gohil, MD, MPH; Edward Septimus, MD; Ken Kleinman, ScD; Neha Varma, MPH; Talisser R. Avery, MS; Lauren Helm, MPH; Risa Rahm, PharmD; William S. Cooper, PharmD; Mandelin Cooper, PharmD; Laura E. McLean, MEd; Naoise G. Nickolay, RPh; Robert A. Weinstein, MD; L. Hayley Burgess, PharmD; Micaela H. Coady, MS; Edward Rosen, BA; Selsebil Sijivo, MPH; Kenneth E. Sands, MD, MPH; Julia Moody, MS; Justin Vigeant, BA; Syma Rashid, MD; Rebecca F. Gilbert, BA; Kim N. Smith, MBA; Brandon Carver, BA; Russell E. Poland, PhD; Jason Hickok, MBA; S. G. Sturdevant, PhD; Michael S. Calderwood, MD, MPH; Anastasiia Weiland, MD; David W. Kubiak, PharmD; Sujan Reddy, MD, MSc; Melinda M. Neuhauser, PharmD, MPH; Arjun Srinivasan, MD; John A. Jernigan, MD, MS; Mary K. Hayden, MD; Abinav Gowda, BS; Katyuska Eibensteiner, BA; Robert Wolf, BS; Jonathan B. Perlin, MD, PhD; Richard Platt, MD, MSc; Susan S. Huang, MD, MPH

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection: The INSPIRE Randomized Clinical Trial. *JAMA.* 2024;331(23):2018–2028.

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QUESTION Can computerized provider order entry (CPOE) prompts that provide patient-specific risk estimates for multidrug-resistant organisms (MDROs) reduce extended-spectrum antibiotic use in noncritically ill patients admitted with pneumonia?

CONCLUSION Empiric extended-spectrum antibiotic use was significantly lower among adults admitted with pneumonia in hospitals using education, feedback, and CPOE prompts recommending standard-spectrum antibiotics for patients at low risk of MDRO infection.

POPULATION

49 963 Women
46 232 Men

Adults hospitalized with pneumonia

Mean age: **68** years

LOCATION

59
Community hospitals in the US

INTERVENTION

59 Hospitals randomized

29

CPOE bundle

CPOE prompts recommending standard-spectrum antibiotics coupled with clinician education and feedback

30

Routine stewardship

Educational materials and quarterly coaching calls to maintain stewardship activities per national guidelines

PRIMARY OUTCOME

Extended-spectrum antibiotic days of therapy

FINDINGS

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Rate ratio of extended-spectrum antibiotic days of therapy

CPOE bundle	Routine stewardship
Rate ratio, **0.68** (95% CI, 0.64 to 0.72)	Rate ratio, **0.94** (95% CI, 0.89 to 1.00)

Overall difference-in-differences rate ratio, **0.72** (95% CI, 0.66 to 0.78); $P < .001$

The results showed a 28.4% (95% CI, 22.2% to 34.1%) reduction in empiric extended-spectrum days of therapy

Gohil SK, Septimus E, Kleinman K, et al. Stewardship prompts to improve antibiotic selection for pneumonia: the INSPIRE randomized clinical trial. *JAMA*. Published online April 19, 2024. doi:10.1001/jama.2024.6248

Table 2. Primary, Secondary, and Safety Outcomes in the INSPIRE Pneumonia Trial

Effectiveness outcomes	CPOE bundle			Routine stewardship			Overall rate ratio difference-in-differences (95% CI)	*P* value[c]
	Days of therapy (raw rate)[a]		Rate ratio (95% CI)[b]	Days of therapy (raw rate)[a]		Rate ratio (95% CI)[b]		
	Baseline	Intervention		Baseline	Intervention			
Primary outcome								
Extended-spectrum days of therapy	613.9 (46 993/76522)	428.5 (27 971/65 272)	0.68 (0.64-0.72)	633.0 (45 595/72 033)	615.2 (38 690/62 892)	0.94 (0.89-1.00)	0.72 (0.66-0.78)	<.001
Secondary outcomes								
Vancomycin days of therapy	235.4 (18 019/76 552)	161.4 (10 534/65 272)	0.68 (0.64-0.72)	241.4 (17 390/72 033)	219.1 (13 778/62 892)	0.89 (0.84-0.94)	0.77 (0.71-0.83)	<.001
Antipseudomonal days of therapy	342.4 (26 210/76 552)	240.1 (15 670/65 272)	0.67 (0.62-0.72)	356.7 (25 696/72 033)	360.7 (22 683/62 892)	0.98 (0.91-1.06)	0.68 (0.61-0.75)	<.001
	Days to event, mean (SD)[d]		**Hazard ratio (95% CI)[e]**	**Days to event, mean (SD)[d]**		**Hazard ratio (95% CI)[e]**	**Overall hazard ratio difference-in-differences (95% CI)**	***P* value[f]**
Safety outcomes[d]								
Length of stay	6.9 (6.4)	7.1 (6.9)	1.00 (0.96-1.03)	6.9 (5.8)	6.8 (5.9)	1.04 (1.00-1.07)	0.96 (0.91-1.01)	.13
Time to ICU transfer	6.6 (5.4)	7.1 (5.9)	1.06 (0.95-1.19)	6.7 (5.6)	6.5 (5.2)	1.02 (0.92-1.14)	1.04 (0.89-1.21)	.62
Time to antibiotic escalation	5.5 (4.2)	6.1 (5.9)	0.81 (0.73-0.91)	5.4 (3.9)	5.3 (3.8)	0.99 (0.88-1.12)	0.82 (0.69-0.97)	.02

Abbreviations: CPOE, computerized provider order entry; INSPIRE, Intelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection.

[a] Days of therapy rate calculated per patient per empiric day (first 3 days of hospitalization) expressed with multiplier 1000 empiric days.

[b] Rate ratios represent group-specific comparisons of intervention to baseline.

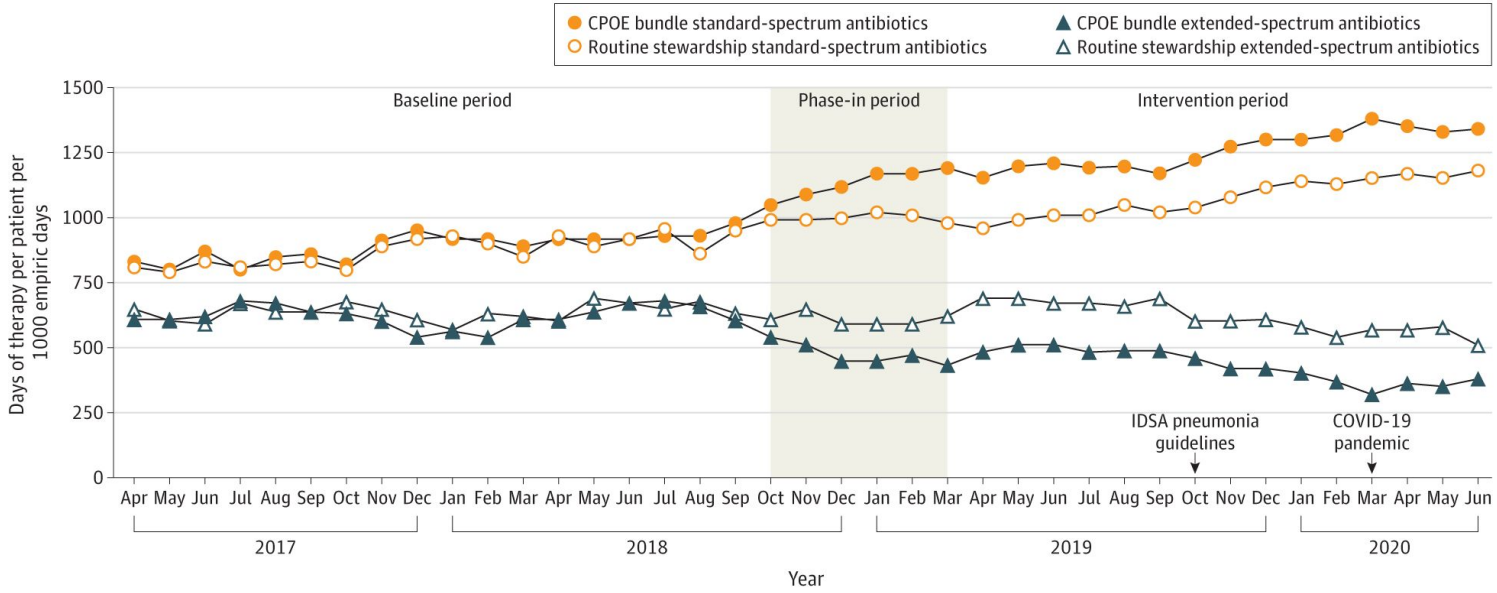
[c] Results are based on unadjusted generalized linear mixed-effects models that accounted for clustering within hospitals and period. *P* value assessed at 2-tailed significance set at $\alpha = .05$ for null hypothesis that the relative rate ratio in each group is not different for primary outcome; $\alpha = .025$ for secondary outcomes to account for multiple comparisons.

[d] Days to event is defined as mean days calculated within a single admission. Days to intensive care unit (ICU) transfer is the days from admission to date of first ICU transfer among those requiring transfer on hospital day 3 through discharge. Days to antibiotic escalation is the days from admission to date of first change in antibiotics from standard-spectrum to extended-spectrum among those who started standard-spectrum in the empiric period (first 3 days of hospitalization). Length of stay is calculated as days from admission to date of hospital discharge among those discharged alive.

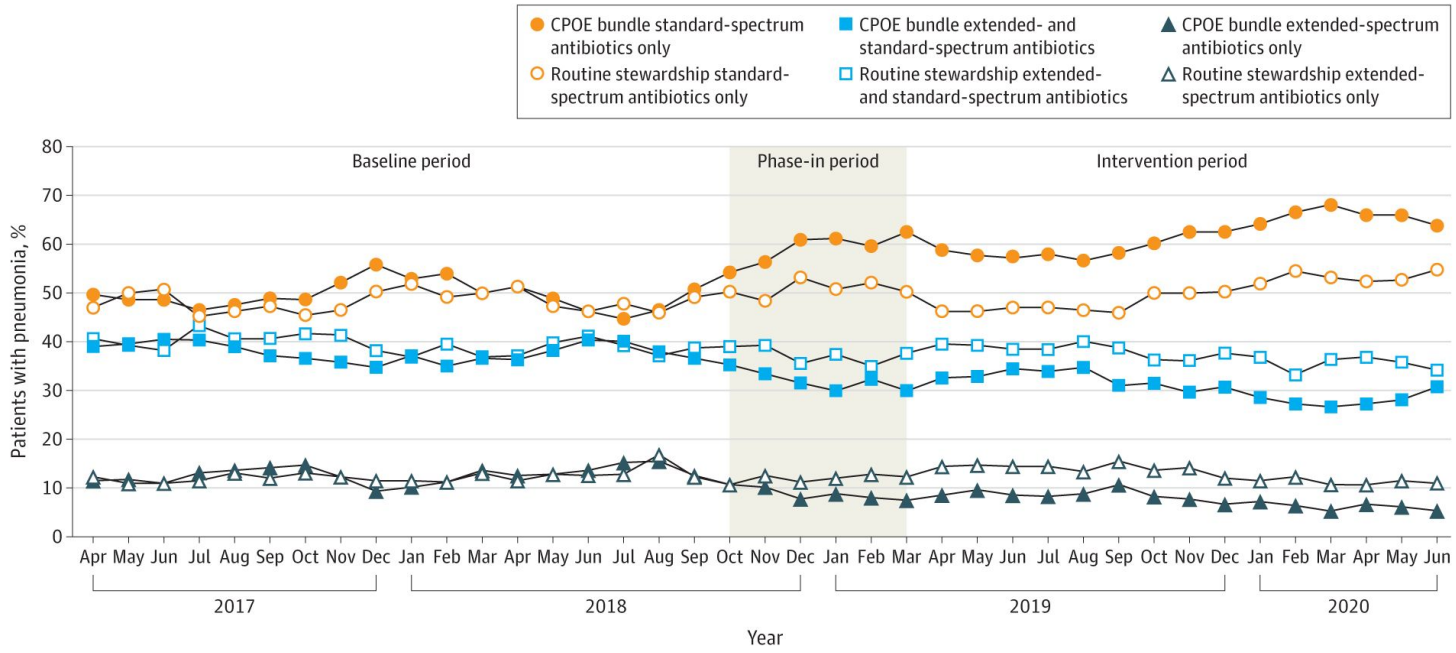
[e] Hazard ratios represent group-specific comparisons of intervention to baseline.

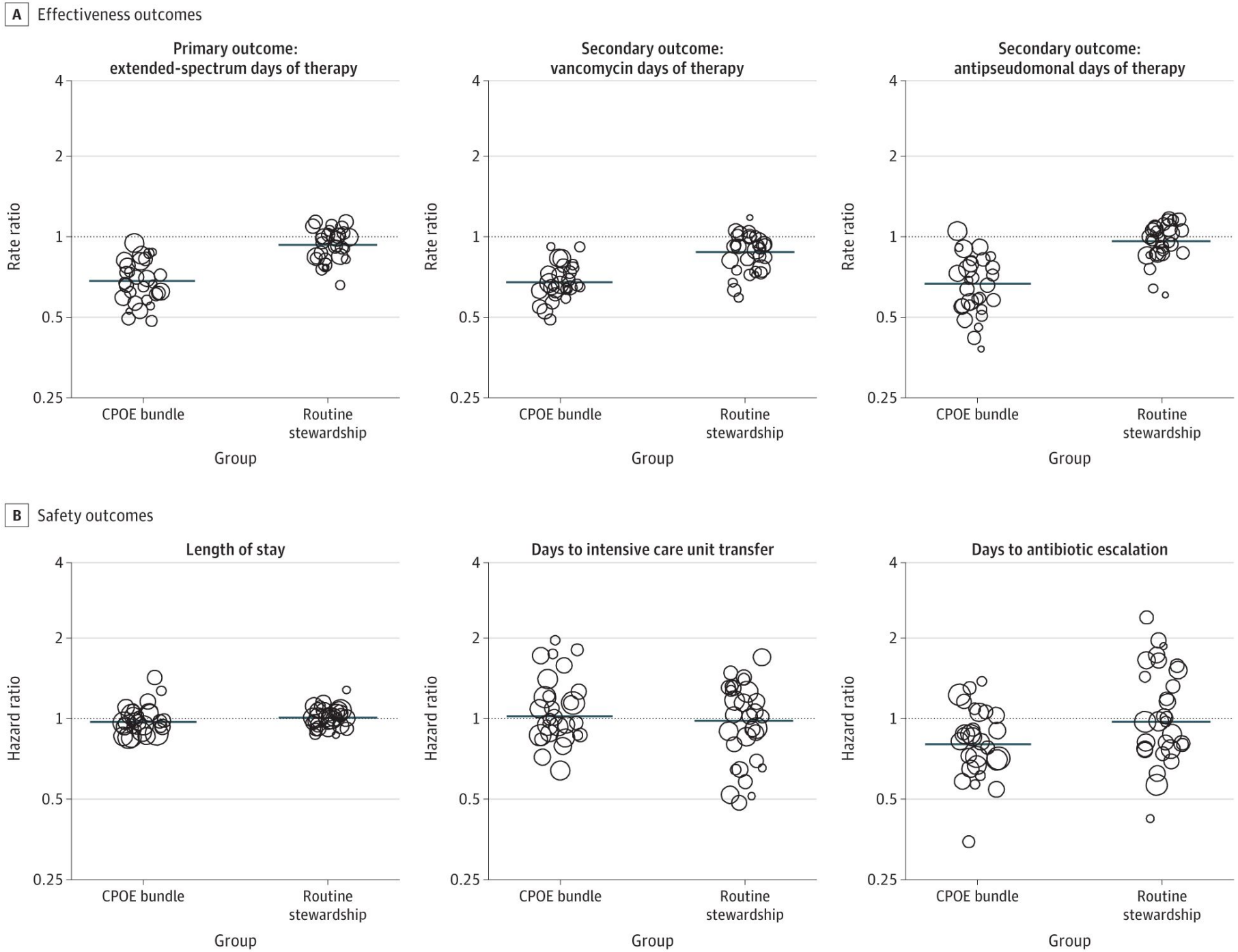
[f] Results are based on unadjusted proportional hazards models that accounted for clustering within hospitals and period. *P* value for the difference in hazard ratio between periods.

A Extended and standard-spectrum empiric days of therapy in patients with pneumonia



B Percentage of patients with pneumonia receiving extended- or standard-spectrum antibiotics only or a combination of both




A Effectiveness outcomes
Primary outcome: extended-spectrum days of therapy
Secondary outcome: vancomycin days of therapy
Secondary outcome: antipseudomonal days of therapy
Rate ratio
4
2
1
0.5
0.25
CPOE bundle
Routine stewardship
Group
B Safety outcomes
Length of stay
Days to intensive care unit transfer
Days to antibiotic escalation
Hazard ratio

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QUESTION Can computerized provider order entry (CPOE) prompts that present patient-specific multidrug-resistant organism (MDRO) risk estimates reduce empiric extended-spectrum antibiotics in patients admitted with urinary tract infection (UTI)?

CONCLUSION CPOE prompts plus feedback and education significantly reduced empiric extended-spectrum antibiotic use among noncritically ill adults with UTI without changing hospital length of stay or days to ICU transfers.

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POPULATION

88 249 Women
38 729 Men

Noncritically ill adults aged ≥18 years hospitalized with UTI

Mean age: **69.4** years

LOCATION

59
Hospitals in the US

INTERVENTION

59 Hospitals randomized

29

CPOE bundle

CPOE prompts recommending standard-spectrum antibiotics in low-risk patients with UTI coupled with clinician education and feedback

30

Routine stewardship

Educational materials and quarterly coaching calls to maintain stewardship activities per national guidelines

PRIMARY OUTCOME

Empiric extended-spectrum antibiotic days of therapy

FINDINGS

Rate ratio of extended-spectrum antibiotic days of therapy

CPOE bundle	Routine stewardship
Rate ratio, **0.84** (95% CI, 0.80 to 0.88)	Rate ratio, **1.02** (95% CI, 0.97 to 1.07)

Overall difference-in-differences rate ratio, 0.83 (95% CI, 0.77 to 0.89); $P < .001$

The results showed a 17.4% (95% CI, 11.2% to 23.2%) reduction in empiric extended-spectrum days of therapy

Gohil SK, Septimus E, Kleinman K, et al. Stewardship prompts to improve antibiotic selection for urinary tract infection: the INSPIRE randomized clinical trial. *JAMA*. Published online April 19, 2024. doi:10.1001/jama.2024.6259

Table 2. INSPIRE Urinary Tract Infection Trial Primary, Secondary, and Safety Outcomes in the As-Randomized Analysis

Effectiveness outcomes	CPOE bundle			Routine stewardship			Overall rate ratio difference-in-differences	*P* value[b]
	Days of therapy (raw rate)[a]		Rate ratio (95% CI)[c]	Days of therapy (raw rate)[a]		Rate ratio (95% CI)[c]		
	Baseline	Intervention		Baseline	Intervention			
Primary outcome								
Extended-spectrum days of therapy	392.2 (39 497/100 711)	326.0 (25 987/79 714)	0.84 (0.80-0.88)	431.1 (45 340/105 168)	446.0 (35 023/78 528)	1.02 (0.97-1.07)	0.83 (0.77-0.89)	<.001
Secondary outcomes								
Vancomycin days of therapy	123.1 (12 393/100 711)	101.2 (8071/79 714)	0.83 (0.78-0.87)	131.5 (13 829/105 168)	124.7 (9795/78 528)	0.93 (0.88-0.98)	0.89 (0.82-0.96)	.002
Antipseudomonal days of therapy	213.0 (21 449/100 711)	178.0 (14 186/79 714)	0.83 (0.77-0.88)	248.8 (26 167/105 168)	264.8 (20 792/78 528)	1.05 (0.98-1.12)	0.79 (0.72-0.87)	<.001
	Baseline, days to event, mean (SD)[d]	Intervention, days to event, mean (SD)[d]	Hazard ratio (95% CI)[e]	Baseline, days to event, mean (SD)[d]	Intervention, days to event, mean (SD)[d]	Hazard ratio (95% CI)[e]	Overall hazard ratio difference-in-differences	*P* value[f]
Safety outcomes								
Length of stay	6.3 (6.0)	6.5 (6.6)	0.99 (0.95-1.02)	6.4 (5.8)	6.3 (5.8)	1.02 (0.98-1.05)	0.96 (0.91-1.01)	.21
Days to ICU transfers	6.6 (5.4)	7.0 (5.8)	0.96 (0.87-1.06)	6.8 (6.7)	6.6 (5.7)	0.98 (0.89-1.08)	0.98 (0.85-1.12)	.77
Days to antibiotic escalations	5.0 (4.4)	5.4 (5.2)	1.04 (0.94-1.15)	5.1 (4.5)	5.0 (4.5)	1.01 (0.91-1.11)	1.03 (0.89-1.19)	.66

Abbreviations: CPOE, computerized provider order entry; ICU, intensive care unit; INSPIRE, Intelligent Stewardship Prompts to Improve Real-time Empiric antibiotic selection.

[a] Days of therapy rate calculated per patient per empiric day (first 3 days of hospitalization) expressed with multiplier 1000 empiric days.

[b] Results are based on unadjusted generalized linear mixed-effects models that accounted for clustering within hospitals and period. *P* value assessed at 2-tailed significance set at α = .05 for null hypothesis that the relative rate ratio in each group is not different for the primary outcome; α = .025 for secondary outcomes to account for multiple comparisons.

[c] Rate ratios represent group-specific comparisons of intervention to baseline.

[d] Days to event indicates mean days calculated within a single admission; days to ICU transfer, days from admission to date of first ICU transfer among those requiring transfer on hospital day 3 through discharge; and days to antibiotic escalation, days from admission to date of first change in antibiotics from standard-spectrum to extended-spectrum antibiotics among those who were started with standard-spectrum antibiotic in the empiric period (first 3 days of hospitalization). Length of stay was calculated as days from admission to date of hospital discharge among those discharged alive.

[e] Hazard ratios represent group-specific comparisons of intervention to baseline.

[f] Results are based on unadjusted proportional hazards models that accounted for clustering within hospitals and period. *P* value for the difference in hazard ratio between periods.

EDITORIAL

Harnessing the Electronic Health Record to Improve Empiric Antibiotic Prescribing

Anurag N. Malani, MD; Preeti N. Malani, MD, MSJ

Approximately half of hospitalized adults in the US receive antibiotics, with pneumonia and urinary tract infection (UTI) being the 2 most frequent indications.[1] Estimates suggest about 30% of all antibiotics prescribed in US hospitals are either unnecessary or suboptimal,[2] and extended-spectrum antibiotic use is common.[3] Unnecessary antibiotic use contributes to numerous harms, including drug-related adverse effects, increased risk of drug resistance, and higher costs.

Multimedia

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Antimicrobial stewardship aims to optimize antimicrobial use, minimize associated harms, and improve clinical outcomes, and over the past 2 decades, the field of stewardship has emerged and evolved. In 2014, the US Centers for Disease Control and Prevention introduced the Core Elements of Hospital Antibiotic Stewardship Programs to help hospitals with implementation.[2] Among these Core Elements are hospital leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, and education.

The CPOE algorithm was activated whenever extended-spectrum antibiotics were ordered for pneumonia or UTI in a location outside of an intensive care unit (ICU) within 72 hours of admission, including antibiotics ordered in the emergency department. In these instances, computerized prompts offered clinicians the option of seamlessly replacing orders for extended-spectrum antibiotics with guideline-recommended standard-spectrum antibiotics. The calculation of multidrug-resistant organisms risk was based on a sophisticated model that assessed more than 50 variables using the electronic health record (EHR) and included both hospital-specific (ie, local antibiogram) and patient-specific (ie, demographics, comorbidities, prior health care exposures, and history of multidrug-resistant organisms) factors.

The INSPIRE Pneumonia Trial included 96 451 patients (51 671 during the baseline period and 44 780 during the intervention period). Compared with routine stewardship, the hospitals assigned to the CPOE prompts reported a 28.4% reduction in empiric extended-spectrum days of therapy (rate ratio, 0.72 [95% CI, 0.66-0.78]; $P < .001$).[5] The INSPIRE UTI trial included 127 403 patients (71 991 during the baseline

Malani AN, Malani PN. Harnessing the Electronic Health Record to Improve Empiric Antibiotic Prescribing. *JAMA.* 2024;331(23):1993–1994.

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Antimicrobial Use Among Patients Receiving Palliative Care Consultation

American Journal of Hospice
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Erin Diviney Chun, MD,[1] Phillip E. Rodgers, MD,[2] Caroline A. Vitale, MD,[1,3,4] Curtis D. Collins, PharmD,[5] and Preeti N. Malani, MD, MSJ[1,3,4,6]

Abstract

Background: We sought to characterize antimicrobial use among patients receiving palliative care consultation. Methods: Retrospective review of patients seen by the Palliative Care Service at the University of Michigan Health System from January 2008 to May 2008. Results: Of 131 patients seen in consultation, 70 received antimicrobials. We identified 92 infections among these 70 patients; therapy for 54 (58.7%) was empiric. Empiric therapy was most commonly prescribed for respiratory infection and urinary tract infection. Piperacillin/tazobactam (P/T) was the most frequently used agent, with 26 patients receiving P/T (37.1%); 22 of 26 received this agent empirically (84.6%, $P = .005$). Vancomycin was prescribed to 23 patients (32.9%). Sixteen patients (22.9%) died in hospital; another 31 were enrolled in hospice care. Conclusions: Our results suggest significant use of empiric, broad-spectrum antimicrobial therapy among hospitalized patients near the end of life. We advocate for careful assessment of potential benefits and treatment burdens of antimicrobial therapy, especially when palliation is the goal.

Chun et al. Am J Hosp Palliat Care 2010

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DOI: 10.1177/1049909111432625
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Antimicrobial Use at the End of Life Among Hospitalized Patients With Advanced Cancer

Andrew J. Thompson, MD[1], Maria J. Silveira, MD, MA, MPH[2,3], Caroline A. Vitale, MD[4,5], and Preeti N. Malani, MD, MSJ[1,4,5]

Abstract

Background: We sought to evaluate antimicrobial use among patients with advanced cancer. Methods: Retrospective review of patients experiencing cancer-related death while hospitalized. Results: Among 145 patients, 126 (86.9%) received antimicrobials for a mean of 12.5 $\pm$ 12.9 days. 88 (69.8%) of 126 had clinical findings suggestive of infection. Sixty-one patients (48.4%) had positive cultures, the remaining were treated empirically. "Comfort care" was ultimately pursued in 99 (78.5%) of 126; 35 (35.4%) of 99 continued to receive antimicrobials after a transition to comfort care for an average of 1.6 $\pm$ 1.1 days. On average, antimicrobials were discontinued <1 day prior to death. Conclusion: Antimicrobial use was common among patients with advanced cancer. Even after transition to comfort care, more than one third of patients remained on antimicrobials. The risks and burdens of antimicrobials should be carefully examined when comfort is the stated goal.

Thompson et al. Am J Hosp Palliat Care 2012

Clinical Infectious Diseases Advance Access published April 13, 2016

Clinical Infectious Diseases

IDSA FEAT

Implemen Guidelines and the Sc

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School of Medicine, Winston-Salem
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Evidence-based guidelir
cluding long-term care
for Healthcare Epidemi
medicine, microbiology
recommendations addr

Keywords. antibiot

XXVII. Should Antimicrobial Stewardship Programs Implement Interventions to Reduce Antibiotic Therapy in Terminally Ill Patients?

Recommendation

28. In terminally ill patients, we suggest ASPs provide support to clinical care providers in decisions related to antibiotic treatment *(good practice recommendation)*.

Evidence Summary

End of life is defined as the final days or weeks of life in patients under hospice care where the primary goals are managing symptoms, improving comfort, and optimizing quality of life—not prolonging survival. In contrast, palliative care is more general and can be pursued along with curative therapies.

Antibiotic use, frequently with multiple antibiotics, is common in patients with terminal cancer. Therapy is often continued after transition to comfort care and discontinued less than 1 day prior to death [208]. Patients with advanced dementia also have high exposure to antibiotics, especially in the weeks prior

VIEWPOINT

Antimicrobials at the End of Life

An Opportunity to Improve Palliative Care and Infection Management

Manisha Juthani-Mehta, MD
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Patients in the final stage of an advanced illness often face challenging decisions about the direction of their overall medical care and treatment of specific complications that occur as the end of life approaches. Infections and febrile episodes are among the most common acute complications experienced by terminally ill patients.

Close to 90% of hospitalized patients with advanced cancer receive antimicrobials during the week prior to death,[1] and 42% of nursing home residents with advanced dementia are prescribed antimicrobials during the last 2 weeks of life.[2] Approximately one-quarter of hospice recipients, for whom the intended goal of care is comfort, receive antimicrobials during the final weeks of life.[3,4] Research suggests that antimicrobials are commonly prescribed to dying patients in the absence of adequate clinical symptoms to support a bacterial infection.[4,5] How decisions for suspected infections are made in these patients warrants increased scrutiny by clinicians, patients, and family members.

Risks and Benefits

Although antimicrobial use may be viewed as relatively less burdensome than other potentially life-prolonging interventions (eg, intubation, dialysis), risks of this therapy are not trivial, especially among frail patients minally ill patients. No randomized trials have been conducted examining these outcomes in this population. A systematic review[8] included 8 observational studies that had measured symptoms following antimicrobial therapy among patients receiving hospice and palliative care. None of these studies, which were published between 2002 and 2008, had comparison groups of untreated patients, and their methodological heterogeneity and contrasting findings further limited any conclusions about whether antimicrobials provide symptom relief for patients at the end of life.

A subsequent prospective study[9] reported greater comfort, albeit shorter survival, among patients with advanced dementia and suspected pneumonia who were not treated with antimicrobials compared with those who were treated. Another notable finding in this study was that the survival benefit associated with antimicrobial use (vs no treatment) was similar regardless of the route of administration, whereas the most aggressive treatment approaches (intravenous therapy or hospitalization) were associated with the greatest discomfort. To date, no rigorously conducted study has reported the survival outcomes of patients in the final stages of other terminal diseases who did and did not receive antimicrobials for suspected infections.

THAT THING YOU ARE WRITING IS AWESOME!

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