Antibiotic Choice On ReNal outcomes
The ACORN trial

Development and Results

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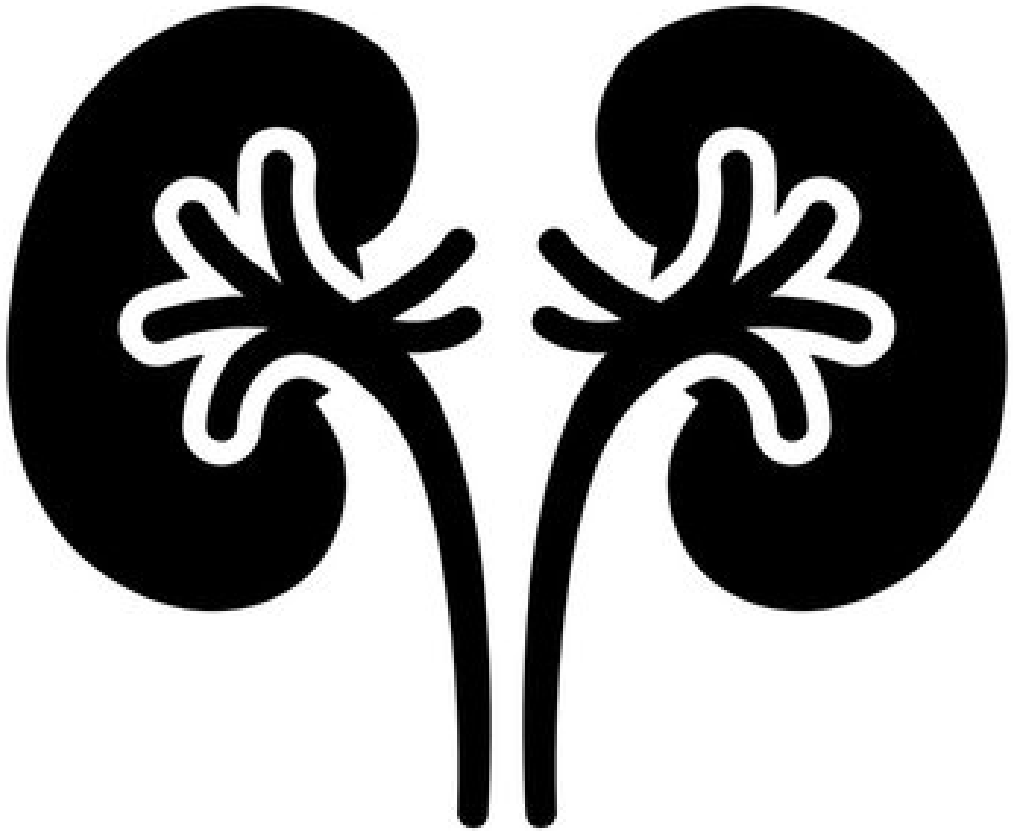
March 15,2024

Outline

- The Problem
- The Design
- The Results

The Problem

- Sepsis is a common cause of critical illness and death
- Commonly use vancomycin PLUS either piperacillin-tazobactam or cefepime
- Piperacillin-tazobactam and cefepime proposed to have unique risk/benefit profiles but comparative data are lacking



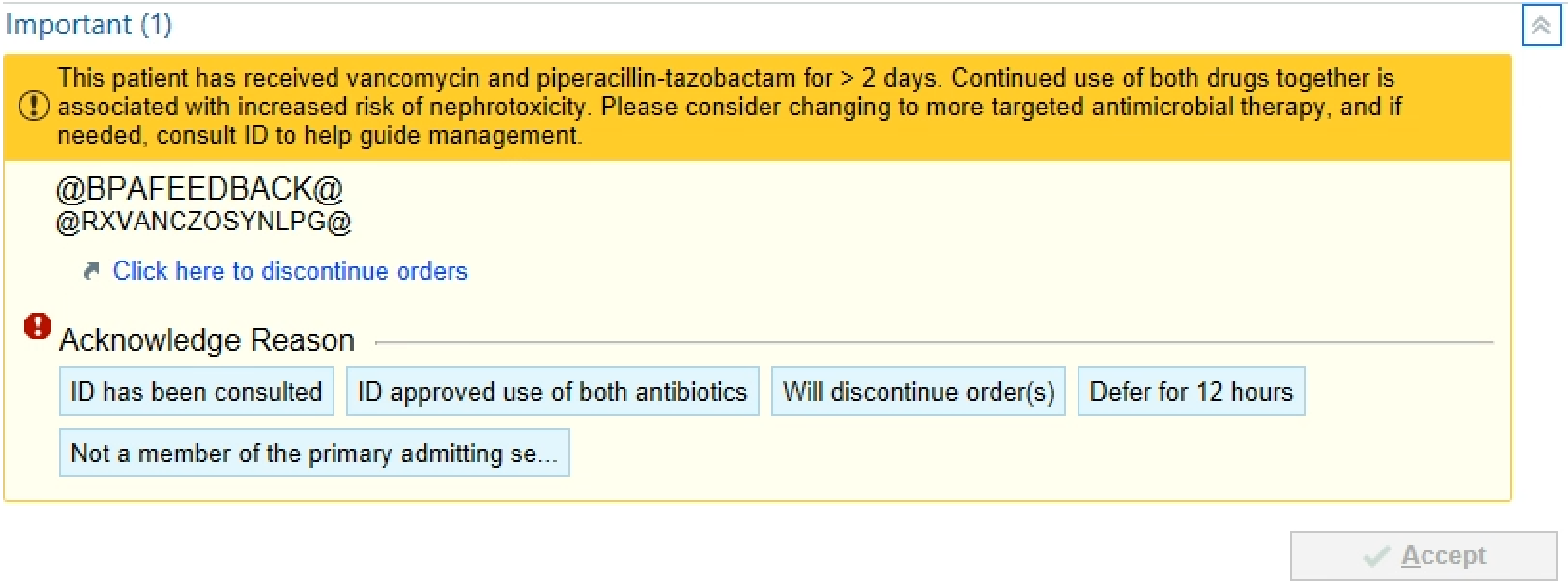
Acute Kidney Injury

- AKI associated with 6-8 fold increase in mortality in critically ill patients.
- Often multifactorial etiology

Association between concurrent vancomycin and piperacillin-tazobactam with creatinine elevations

- Retrospective, observational analysis are inconclusive but favor creatinine elevation

Acute Kidney Injury



Acute Kidney Injury?

Table 3 Rates of ≥ 50% increases of kidney function biomarkers at day two

	Cystatin C Cohort ($n = 192$)			Antibiotic Cohort ($n = 739$)		
	VN + CP	VN + PT	Rate ratio[a]	VN + CP	VN + PT	Rate ratio[a]
≥ 50% increase cystatin C, *n* (%)						
Crude	17 (14.2)	14 (19.4)	1.37 (0.72, 2.61)	–	–	–
IPTW			0.95 (0.44, 2.02)			–
≥ 50% increase creatinine, *n* (%)						
Crude	10 (8.3)	14 (19.4)	2.33 (1.09, 4.97)	43 (9.7)	54 (18.2)	1.87 (1.29, 2.71)
IPTW			1.86 (0.85, 4.09)			1.55 (1.02, 2.34)
≥ 50% increase BUN, *n* (%)						
Crude	27 (22.5)	19 (26.4)	1.17 (0.70, 1.95)	90 (20.4)	63 (21.2)	1.04 (0.78, 1.38)
IPTW			0.99 (0.57, 1.75)			0.88 (0.63, 1.23)

VN + PT vancomycin + piperacillin–tazobactam, *VN + CP* vancomycin + cefepime

[a] Rate ratio estimated from Poisson regression accounting for person-time at risk

Miano et al. *Intensive Care Medicine*. September 2022

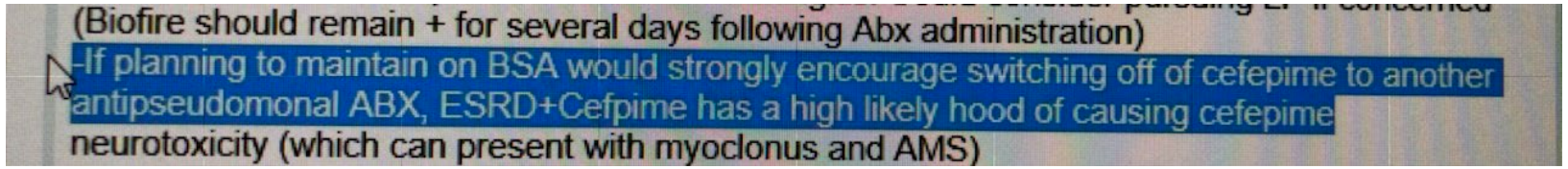
Delirium

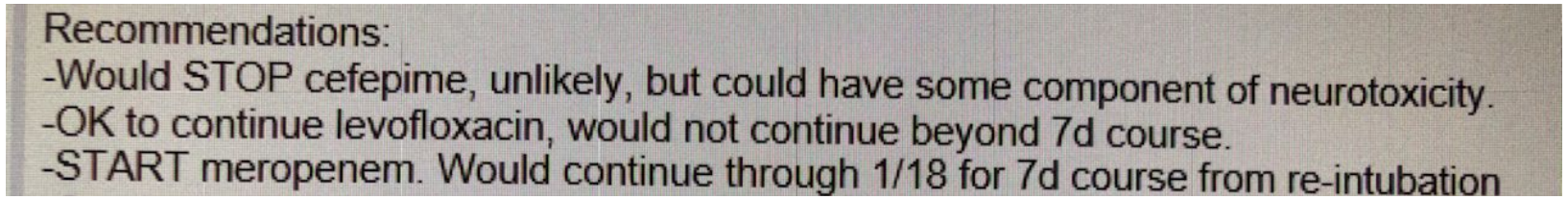
- Delirium common in critically ill patients and an independent predictor of poor outcomes including mortality

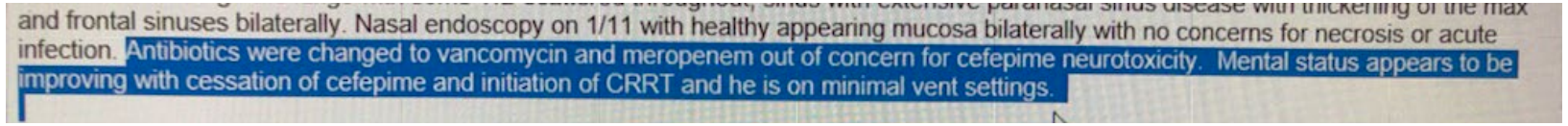
Cefepime Neurotoxicity

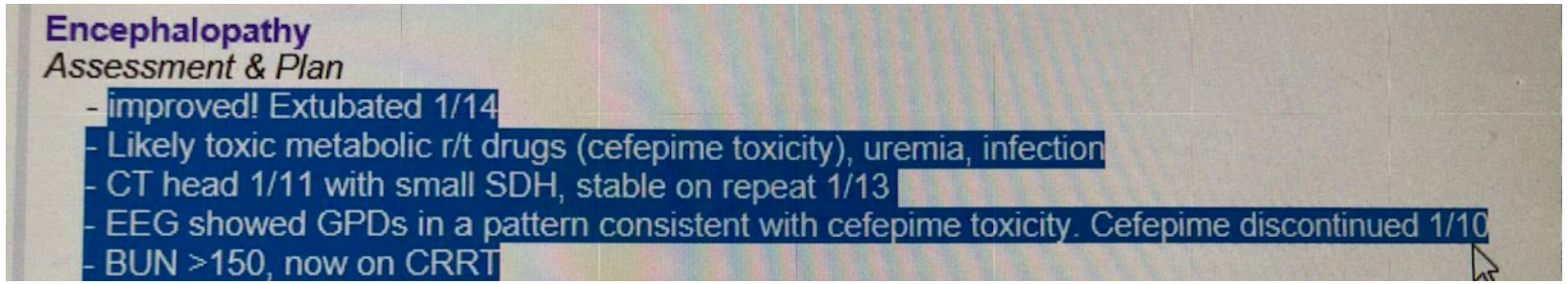
- Cefepime neurotoxicity is rare in the literature and difficult to define
- No gold standard test
- Spectrum of presentation (coma to agitation)

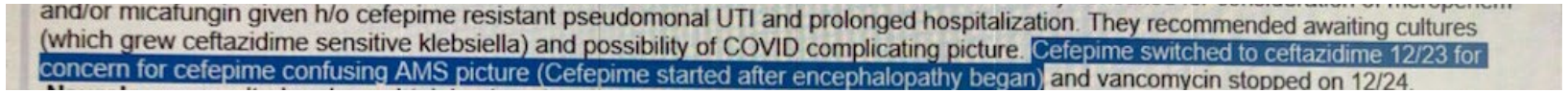
Delirium?


(Biofire should remain + for several days following Abx administration)
-If planning to maintain on BSA would strongly encourage switching off of cefepime to another antipseudomonal ABX, ESRD+Cefpime has a high likely hood of causing cefepime neurotoxicity (which can present with myoclonus and AMS)


Recommendations:
-Would STOP cefepime, unlikely, but could have some component of neurotoxicity.
-OK to continue levofloxacin, would not continue beyond 7d course.
-START meropenem. Would continue through 1/18 for 7d course from re-intubation


and frontal sinuses bilaterally. Nasal endoscopy on 1/11 with healthy appearing mucosa bilaterally with no concerns for necrosis or acute infection. Antibiotics were changed to vancomycin and meropenem out of concern for cefepime neurotoxicity. Mental status appears to be improving with cessation of cefepime and initiation of CRRT and he is on minimal vent settings.


Encephalopathy
Assessment & Plan
- improved! Extubated 1/14
- Likely toxic metabolic r/t drugs (cefepime toxicity), uremia, infection
- CT head 1/11 with small SDH, stable on repeat 1/13
- EEG showed GPDs in a pattern consistent with cefepime toxicity. Cefepime discontinued 1/10
- BUN >150, now on CRRT


and/or micafungin given h/o cefepime resistant pseudomonal UTI and prolonged hospitalization. They recommended awaiting cultures (which grew ceftazidime sensitive klebsiella) and possibility of COVID complicating picture. Cefepime switched to ceftazidime 12/23 for concern for cefepime confusing AMS picture (Cefepime started after encephalopathy began) and vancomycin stopped on 12/24.

Antibiotic Choice in Sepsis

Data comparing comparative effectiveness and toxicities is lacking

Aim: *Conduct a randomized trial to understand the effect of empiric antibiotic choice for patients in the ED and ICU.*

ACORN Trial

- 2,511-patient RCT
- Population:
  - Adults who are < 12 hours from hospital presentation in the ED or ICU who **receive at least one dose of empiric cefepime or piperacillin-tazobactam *(modified intention to treat)***
- Intervention:
  - Choice of empiric gram-negative antibiotic (cefepime or piperacillin-tazobactam)

Steps of a pragmatic clinical trial

1. Screening
2. Eligibility assessment
3. Informed consent
4. Randomization
5. Intervention Delivery
6. Compliance Monitoring
7. Safety Monitoring
8. Collection of study data

SCREENING

ACORN Study Enrollment

feedback: ☺ 😐 ☹

This patient is eligible for **ACORN**, a study of anti-pseudomonal cephalosporins (e.g., cefepime) vs anti-pseudomonal penicillins (e.g., piperacillin-tazobactam). If both cefepime (or ceftazidime) and piperacillin-tazobactam would be acceptable options for this patient, please click **"Remove" and "Open Order Set"**.

If any of the following reasons that the patient should not be enrolled in **ACORN** are present, please only click the Acknowledgement reason below to ensure **"Keep" and "Do Not Open"** are selected.

1. Patient is a prisoner
2. Patient is < 18 years of age
3. Allergy to cephalosporins or penicillins
4. Patient has received more than 1 dose of cefepime, ceftazidime, or piperacillin-tazobactam in last 7 days
5. Cefepime (or ceftazidime) is required for this patient (e.g., treatment of central nervous system infection)
6. Piperacillin-tazobactam is required for this patient (e.g., treatment of Bacteroides fragilis)

Remove the following orders?

Remove | Keep

cefepime (MAXIPIME) in D5W 50 mL IVPB
intravenous, Starting today at 1203

Apply the following?

Open Order Set | Do Not Open

ENROLL and RANDOMIZE in ACORN trial Preview

Acknowledge Reason

Prisoner | Age < 18 years | Allergy to PCN or cephalosporin | Received MORE than 1 dose PCN/cephalospo... | Cefepime required | Piperacillin-tazobactam required | Other (comment)

Accept

cefepime | New | Next

New Orders

cefepime (MAXIPIME) in D5W
50 mL IVPB
intravenous, Starting today at 1203

SCREENING

Inclusion/Exclusion Criteria

Inclusion

1. Age ≥ 18 years old
2. Located in a participating emergency department or medical intensive care unit
3. Less than 12 hours from presentation to study hospital
4. Treating clinician initiating an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin
5. (Also no allergies documented)

Exclusion

1. Known receipt of > 1 dose of an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin during the last 7 days
2. Current documented allergy to cephalosporins or penicillin
3. Known to be a prisoner
4. Treating clinicians feel that either an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin is required or contraindicated for the optimal treatment of the patient, including for more directed antibiotic therapy against known prior resistant infections or suspected sepsis with an associated central nervous system infection

SCREENING

Display

Display text: ACORN Study Enrollment

SmartLink: VUMC RSH CDS ACORN RECRUITMENT [103716]

Criteria

1. VUMC RSH CDS CL ACORN ORDERING ZOSYN OR CEFEPIME [6642]
2. VUMC RSH CDS CL ACORN PATIENT IN MICU OR ED [6643]
3. CL AGE >=18 YEARS [352]
4. VUMC RSH CDS CL ACORN <12 HOURS SINCE PRESENTATION [6644]
5. VUMC RSH CDS CL ACORN CEPHALOSPORIN OR PENICILLIN ALLERY [6646]
6. ACORN ENROLLED [7170]
7. ACORN FROM BPA [7225]

Logic: 1 AND 2 AND 3 AND 4 AND (NOT 5) AND (NOT 6) AND (NOT 7)

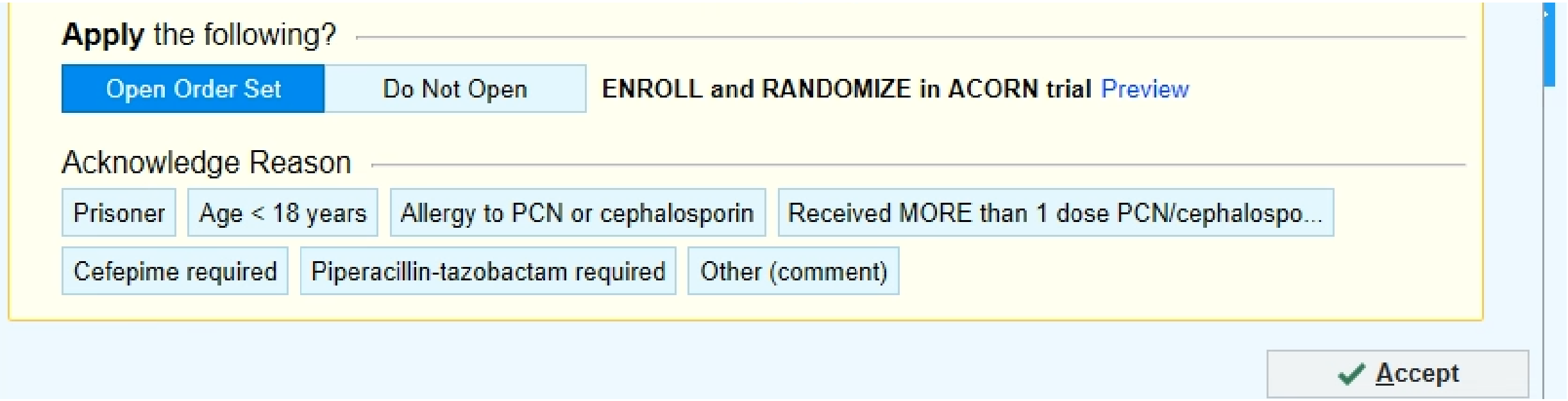
Triggers

Potential triggering actions:

- Enter order
- Select item in Order Set, SmartSet or Pathway

1. Located in a participating emergency department or medical intensive care unit
2. Age ≥ 18 years old
3. Less than 12 hours from presentation to study hospital
4. (No allergies documented)
5. Treating clinician initiating an order for an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin

ELIGIBILTY



1. Known to be a prisoner
2. Current documented allergy to cephalosporins or penicillin
3. Known receipt of > 1 dose of an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin during the last 7 days
4. Treating clinicians feel that either an anti-pseudomonal cephalosporin or anti-pseudomonal penicillin is required or contraindicated for the optimal treatment of the patient, including for more directed antibiotic therapy against known prior resistant infections or suspected sepsis with an associated central nervous system infection

Waiver of Informed Consent

- The research involves no more than minimal risk to subjects
  - Providers confirmed equipoise between the agents before enrollment
- The research could not be carried out practicably without the waiver or alteration
  - Antibiotic delay in sepsis associated with increased mortality
  - Unethical to delay antibiotics for traditional consent process

RANDOMIZATION

Triggers

Potential triggering actions:

- Enter order
- Select item in Order Set, SmartSet or Pathway

Remove Orders

Remove all triggering orders: Manually Selected

SmartSets, Order Sets, and Pathways

SmartSets, Order Sets, and Pathways	Status	Open As	Frequency
ACORN ORDERSET [6319]	Released	Order Set	Manually Selected

Triggers

Potential triggering actions:

- Enter order
- Select item in Order Set, SmartSet or Pathway

Extensions

Extension	Caption	Frequency
VUMC IP ACORN SAVE RANDOM NUMBER FOR ENCOUNTER [1129000055]		Once Automatically

INTERVENTION

Summary for SmartSet: ACORN ORDERSET [6319]

About

General Info

Display name:	ENROLL and RANDOMIZE in ACORN trial	Version number:	12
SmartSet type:	General	Version date:	5/30/2022
Merge priority:	0	Status:	Unreleased
Log access:	No		

Description: Order set for the ACORN trial

Configuration

ACORN Trial: Anti-pseudomonal cephalosporin

ACORN Trial: Anti-pseudomonal Cephalosporins (1333123) — Released on 2/4/2022

ACORN Trial: Anti-pseudomonal penicillin

ACORN Trial: Anti-pseudomonal Penicillin (1333124) — Released on 11/16/2021

Settings

When orders from this SmartSet are discontinued the system should:	Discontinue as individual orders
When orders from this SmartSet are released the system should:	Use System Definitions setting
In the Pended/Held form display:	Use default System Definitions setting
Apply offset at the time of release:	Use System Definitions setting
Prevent users from saving their own versions of this SmartSet:	No

Criteria

SmartSet restricted by security point:	No
Allow restriction by research study:	No

Restrictions

SB INPATIENT DECISION SUPPORT ONLY (1905)

Potential Triggering Actions

Decision Support Inpatient

INTERVENTION

General Info

Display name:	ACORN Trial: Anti-pseudomonal Cephalosporins		
Version number:	16	Version date:	2/4/2022
Status:	Released	Panel:	No
Used as building block:	No	Single response:	No
Prevent users from saving their own versions of this SmartGroup:	No	When orders from this SmartGroup are discontinued:	Group when used as a panel. Otherwise, use setting from containing SmartSet.

Description:

Cefepime Dosing

Creatinine Clearance	Dose
≥60 ml/min	2 gm iv q8h
59-30 ml/min	2 gm iv q12h
29-10 ml/min	2 gm iv q24h
<10 ml/min or anuric	1 gm iv q24h
CRRT	2 gm iv q12h
HD	1 gm iv q24h

SmartGroup Info

Hide unchecked items upon selection:	No
Show only checked items upon loading:	No
Require users to select an item from this SmartGroup:	Yes
Display SmartGroup in two columns:	No
Allow SmartGroup to be merged:	Yes

Criteria

Restrictions

ACORN ZERO (6980)

12h	1	1		piperacillin-tazoba (ZOSYN) 3.375 g in Dextrose (premix) 50 mL - Wed Feb 23, 2022 2109	Diclofenac Sodium, Meloxicam, Rosuvastatin	Feb 17, 2022 02:47:20 PM
15h	1	1	cefepime (MAXIPIME) injection 2,000 mg - Wed Feb 23, 2022 2316	piperacillin-tazoba (ZOSYN) 3.375 g in Dextrose (premix) 50 mL - Wed Feb 23, 2022 1535	Nickel	Jul 29, 2019 02:17:47 PM
15h	1	0	cefepime (MAXIPIME) injection 2,000 mg - Wed Feb 23, 2022 1831		No Known Allergies	
19h	1	0	cefepime (MAXIPIME) injection 2,000 mg - Wed Feb 23, 2022 1557		No Known Allergies	
2d 8h	1	1		piperacillin-tazoba (ZOSYN) 3.375 g in Dextrose (premix) 50 mL - Mon Feb 21, 2022 1854	Niacin	Feb 21, 2022 06:03:18 PM
2d 14h	1	0	cefepime (MAXIPIME) injection 2,000 mg - Mon Feb 21, 2022 2034		No Known Allergies	

SAFETY

ACORN Enrolled Patient

@BPAFEEDBACK@

This patient is in **ACORN** comparing anti-pseudomonal cephalosporins vs anti-pseudomonal penicillins for acutely ill adults. This patient has been assigned to receive an **@CERMSG(765857:29104;765856:29103,0,1,1)@**

As the treating team, you may manage the antibiotics per your usual clinical practice. If an **@CERMSG (765857:29104;765856:29103,0,1,1)@** remains an acceptable antibiotic choice for this patient click **"Remove" and "Open Order Set"**.

If an @CERMSG(765857:29104;765856:29103)@ is no longer an acceptable antibiotic choice, please click **"Keep" and "Do Not Open"**, and provide the reason below.

Open Order Set | Do Not Open | **CONTINUE in the ACORN Trial** Preview

Acknowledge Reason

Suspected Allergy (Comment) | Non-allergic Drug Reaction (Comment) | Alternate Superior (Comment)

Other (comment)

SAFETY

ACORN Study Reminder

feedback:

This patient is in **ACORN** comparing anti-pseudomonal cephalosporins vs anti-pseudomonal penicillins for acutely ill adults.
This patient has been assigned to receive an **anti-pseudomonal cephalosporins (e.g. cefepime)**

As the treating team, you may manage the antibiotics per your usual clinical practice. If an anti-pseudomonal cephalosporins (e.g. cefepime) remains an acceptable antibiotic choice for this patient please modify the existing order.

If an anti-pseudomonal cephalosporins (e.g. cefepime) is no longer an acceptable antibiotic choice, please provide the reason below.

Acknowledge Reason

De-escalation | Escalation | No Infection Suspected | Suspected Allergy (Comment) | Non Allergic Drug Reaction (Comment) | Other (Comment)

Accept | Cancel

Warning Name	Alert Date / Time	Override Reason	Override Captio	Action Taken	Alert Comments	User
VUMC RSH CDS BASE ACORN REORDER	02/24/22 1207	--		Remove ERX single order	--	QIAN, EDWARD T
ACORN DISCONTINUE REASON	02/24/22 1206	Patient already had therapy	No Infection Suspected	Acknowledge/Override Warning	--	QIAN, EDWARD T
VUMC RSH CDS BASE ACORN RECRUITMENT	02/24/22 1203	Acknowledged		Remove ERX single order	--	QIAN, EDWARD T

OUTCOMES

Outcomes

Primary Outcome:

- **AKI Ordinal Scale Between Enrollment and Day 14**
  - 0 = No AKI
  - 1 = *Creatinine* increase by 1.5-1.9 times baseline
    - OR Increase by >= 0.3 mg/dL
  - 2 = Creatinine increase by 2.0-2.9 times baseline
  - 3 = Creatinine increase by >= 3.0 times baseline
    - OR Increase by >= 4.0 mg/dL
    - OR New *Dialysis*
  - 4 = Death

Secondary Outcome:

- **Major Adverse Kidney Events within 14 days**
  - Composite of: *Death* or New *dialysis* within 14 days or stage 2 AKI on day 14
- **Days Alive and Free of Delirium and Coma to day 14**
  - Days where either *CAM-ICU* is positive or *RASS* -4 or -5

Original Investigation | Caring for the Critically Ill Patient

October 14, 2023

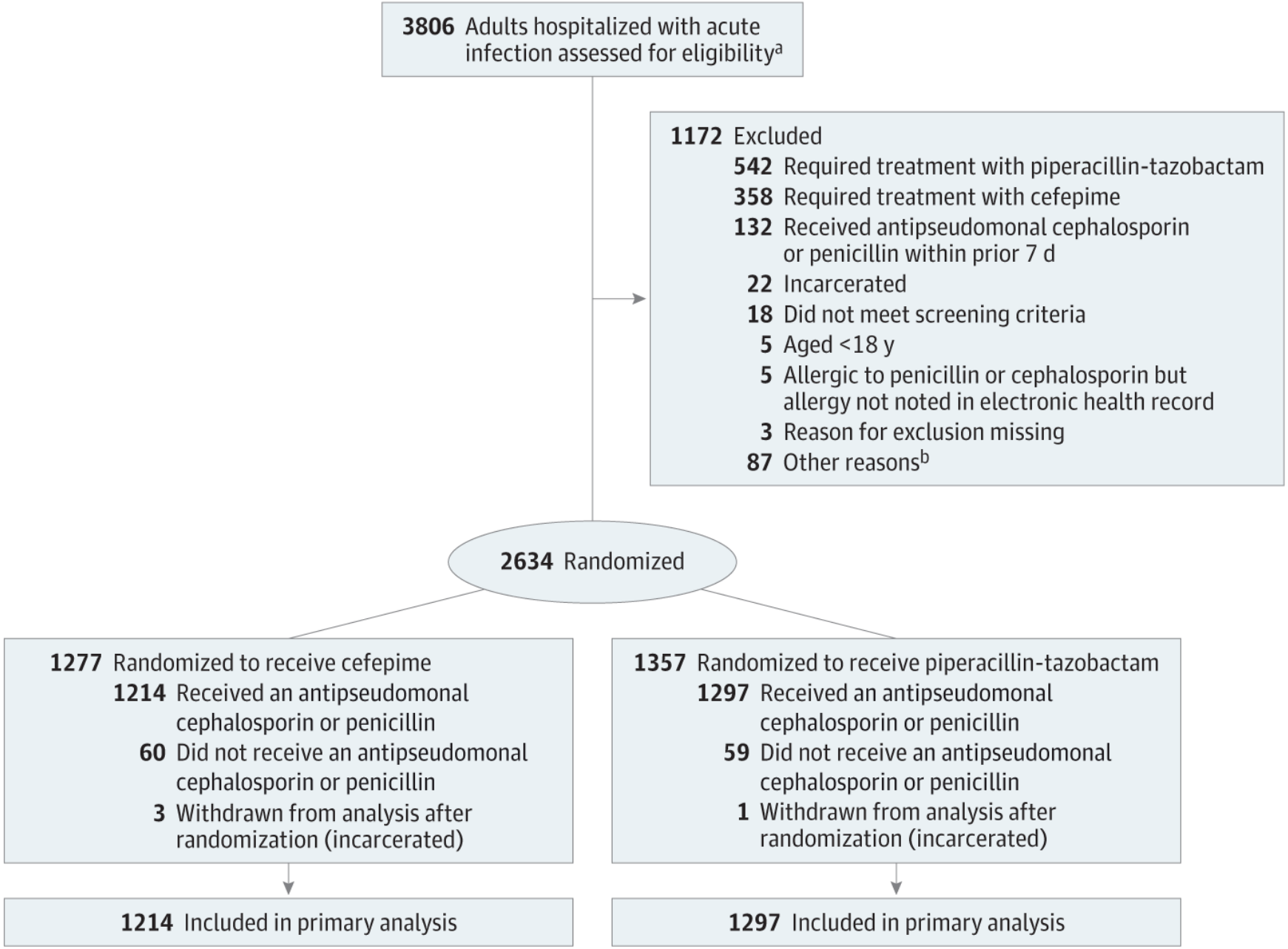
Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection

The ACORN Randomized Clinical Trial

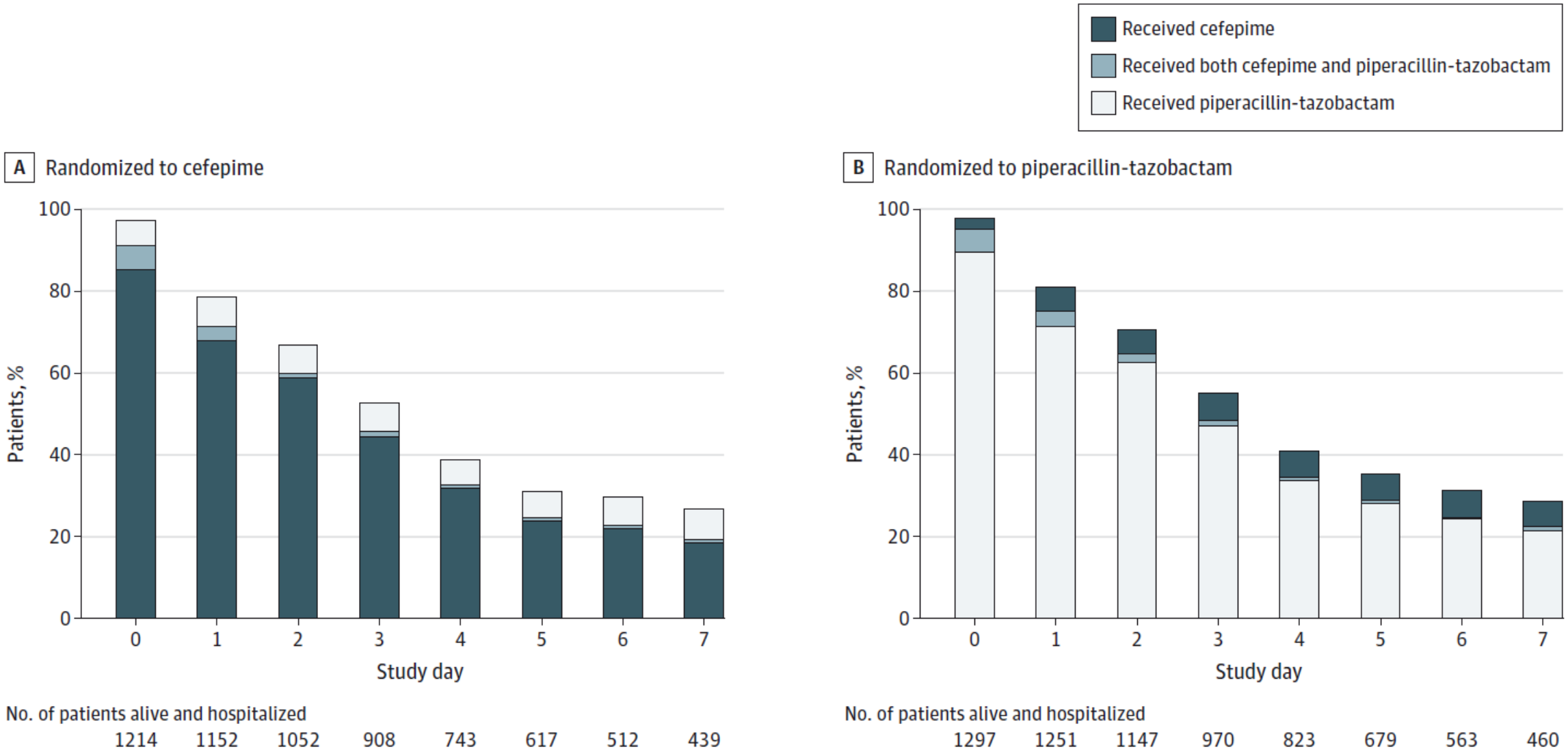
Edward T. Qian, MD, MSc[1]; Jonathan D. Casey, MD, MSc[1]; Adam Wright, PhD[2,3]; Li Wang, MS[4]; Matthew S. Shotwell, PhD[4]; Justin K. Siemann, PhD[5]; Mary Lynn Dear, PhD[5]; Joanna L. Stollings, PharmD[6]; Brad D. Lloyd, RRT-ACCS[7]; Tanya K. Marvi, MD[3]; Kevin P. Seitz, MD, MSc[1]; George E. Nelson, MD[8]; Patty W. Wright, MD[8]; Edward D. Siew, MD, MSc[9]; Bradley M. Dennis, MD[10]; Jesse O. Wrenn, MD, PhD[7]; Jonathan W. Andereck, MD, MBA[7]; Jin H. Han, MD, MSc[7,11]; Wesley H. Self, MD, MPH[5,7]; Matthew W. Semler, MD, MSc[1,5]; Todd W. Rice, MD, MSc[1,5]; for the Vanderbilt Center for Learning Healthcare and the Pragmatic Critical Care Research Group

» Author Affiliations

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


3806 Adults hospitalized with acute infection assessed for eligibility[a]
1172 Excluded
542 Required treatment with piperacillin-tazobactam
358 Required treatment with cefepime
132 Received antipseudomonal cephalosporin or penicillin within prior 7 d
22 Incarcerated
18 Did not meet screening criteria
5 Aged <18 y
5 Allergic to penicillin or cephalosporin but allergy not noted in electronic health record
3 Reason for exclusion missing
87 Other reasons[b]
2634 Randomized
1277 Randomized to receive cefepime
1214 Received an antipseudomonal cephalosporin or penicillin
60 Did not receive an antipseudomonal cephalosporin or penicillin
3 Withdrawn from analysis after randomization (incarcerated)
1357 Randomized to receive piperacillin-tazobactam
1297 Received an antipseudomonal cephalosporin or penicillin
59 Did not receive an antipseudomonal cephalosporin or penicillin
1 Withdrawn from analysis after randomization (incarcerated)
1214 Included in primary analysis
1297 Included in primary analysis

Antibiotic Receipt



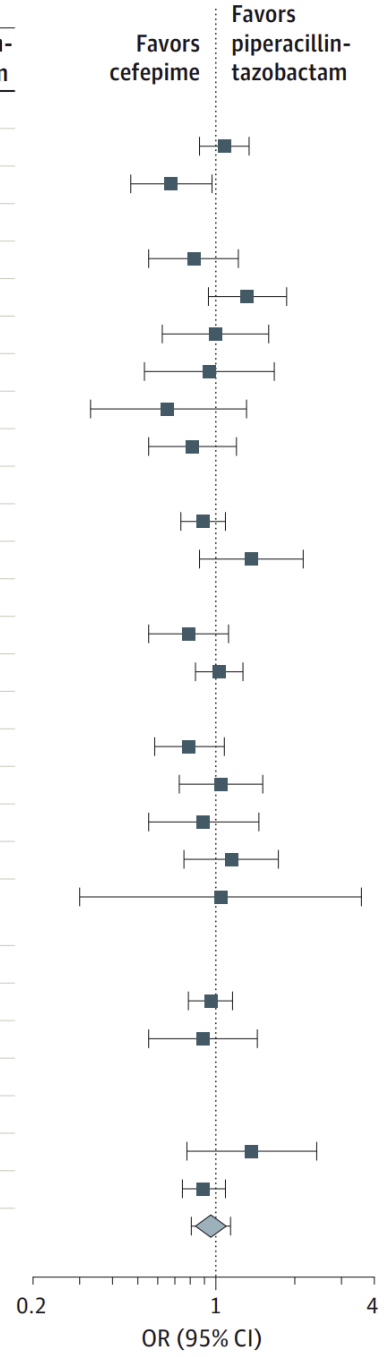
Patients may have received both cefepime and piperacillin-tazobactam on a study day when switching from one antibiotic to the other; 32 patients (1.3%) received both antibiotics on more than 1 consecutive study day.

Primary Outcome

Primary Outcome	Cefepime (n = 1214)	Piperacillin-Tazobactam (n = 1297)	Odds ratio (95% CI)
New or worsening AKI or death by day 14 – no. (%)			0.95 (0.80 to 1.13)
0 = No AKI	910 (75.0)	954 (73.6)	
1 = Stage 1 AKI	97 (8.0)	103 (7.9)	
2 = Stage 2 AKI	40 (3.3)	77 (5.9)	
3 = Stage 3 AKI	75 (6.2)	85 (6.6)	
4 = Death	92 (7.6)	78 (6.0)	

Effect Modification for Primary Outcome

Subgroup	No. of patients	Acute kidney injury ordinal scale, median (IQR)[a]	
		Cefepime	Piperacillin-tazobactam
Sepsis			
Yes	1362	0 (0-2)	0 (0-2)
No	1149	0	0
Source of infection			
Intra-abdominal	612	0	0
Lung	557	0 (0-2)	0 (0-1)
Skin and soft tissue	446	0	0
Urinary	244	0 (0-1)	0 (0-1)
Other	201	0	0
Unknown[d]	451	0 (0-1)	0 (0-2)
Vancomycin			
Yes	1939	0 (0-1)	0 (0-1)
No	572	0	0
Chronic kidney disease			
Yes	502	0 (0-1)	0 (0-2)
No	1965	0	0
Acute kidney injury[e]			
No	1275	0	0
Stage 1	542	0 (0-1)	0 (0-1)
Stage 2	257	0 (0-3)	0 (0-2)
Stage 3	292	3 (0-3)	3 (0-3)
Prior kidney replacement therapy	145	0	0
Admission type			
Medical	1966	0 (0-1)	0 (0-1)
Surgical	496	0	0
Post hoc subgroup			
Coma			
Yes	161	3 (0-4)	2 (0-4)
No	2350	0	0
Overall	2511	0 (0-1)	0 (0-1)



Secondary Outcomes

Secondary Outcomes	Cefepime (n = 1214)	Piperacillin-Tazobactam (n = 1297)	Absolute Difference or Odds ratio (95% CI)
Major adverse kidney events by day 14	124 (10.2)	114 (8.8)	1.4% (-1.0% to 3.8%)
Death	92 (7.6)	78 (6.0)	
New kidney replacement therapy	37 (3.3)	28 (2.3)	
Final creatinine level ≥ 2x baseline	15 (1.3)	29 (2.4)	
Delirium and Coma-free days by day 14			**0.79 (0.65 to 0.95)**
Median (IQR)	14.0 (14.0 to 14.0)	14.0 (14.0 to 14.0)	
Mean ± SD	11.9 ± 4.6	12.2 ± 4.3	

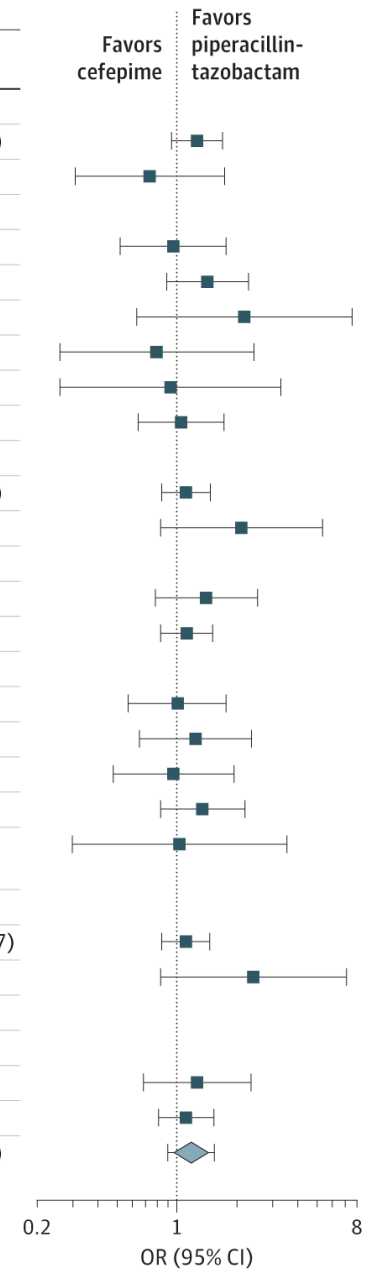
Median (IQR), Mean ± SD, or No. (%)

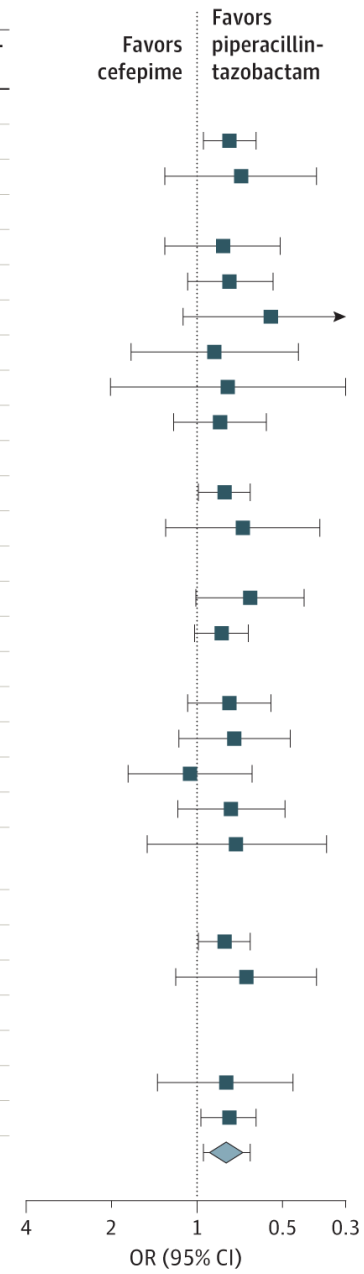
Effect Modification for Secondary Outcomes

MAKE14:
No difference overall or in any subgroup

Delirium and coma-free days:
Point estimate favors piperacillin-tazobactam over cefepime overall and in almost every subgroup.

Subgroup	Major adverse kidney events at 14 d, No./total (%)[b]		Delirium- and coma-free days, median (IQR)[c]	
	Cefepime	Piperacillin-tazobactam	Cefepime	Piperacillin-tazobactam
Sepsis				
Yes	115/658 (17.5)	101/704 (14.3)	14 (8-14)	14 (11-14)
No	9/556 (1.6)	13/593 (2.2)	14 (14-14)	14 (14-14)
Source of infection				
Intra-abdominal	23/319 (7.2)	22/293 (7.5)	14 (14-14)	14 (14-14)
Lung	44/257 (17.1)	38/300 (12.7)	14 (8-14)	14 (11-14)
Skin and soft tissue	7/201 (3.5)	4/245 (1.6)	14 (14-14)	14 (14-14)
Urinary	5/100 (5)	9/144 (6.2)	14 (14-14)	14 (14-14)
Other	5/104 (4.8)	5/97 (5.2)	14 (14-14)	14 (14-14)
Unknown[d]	40/233 (17.2)	36/218 (16.5)	14 (9-14)	14 (10-14)
Vancomycin				
Yes	111/942 (11.8)	107/997 (10.7)	14 (12-14)	14 (14-14)
No	13/272 (4.8)	7/300 (2.3)	14 (14-14)	14 (14-14)
Chronic kidney disease				
Yes	28/243 (11.5)	22/259 (8.5)	14 (14-14)	14 (14-14)
No	95/948 (10)	92/1017 (9)	14 (14-14)	14 (14-14)
Acute kidney injury[e]				
No	25/623 (4)	26/652 (4)	14 (14-14)	14 (14-14)
Stage 1	19/231 (8.2)	21/311 (6.8)	14 (14-14)	14 (14-14)
Stage 2	19/134 (14.2)	18/123 (14.6)	14 (9-14)	14 (10-14)
Stage 3	55/148 (37.2)	44/144 (30.6)	12 (0-14)	14 (2-14)
Prior kidney replacement therapy	6/78 (7.7)	5/67 (7.5)	14 (10-14)	14 (14-14)
Admission type				
Medical	111/948 (11.7)	109/1018 (10.7)	14 (13-14)	14 (14-14)
Surgical	11/240 (4.6)	5/256 (2)	14 (14-14)	14 (14-14)
Post hoc subgroup				
Coma				
Yes	42/84 (50)	34/77 (44.2)	0 (0-8)	2 (0-10)
No	82/1130 (7.3)	80/1220 (6.6)	14 (14-14)	14 (14-14)
Overall	124/1214 (10.2)	114/1297 (8.8)	14 (14-14)	14 (14-14)





Strengths and Limitations

Strengths

- Design
  - Randomized trial
  - Embedded in “real-world” care
- Large sample size
  - Adequate power among the 1939 patients receiving vancomycin at enrollment
- Early intervention: trial control antibiotic from first dose
  - Facilitated separation between groups
  - Minimized pre-trial contamination

Limitations

- Single center trial limits generalizability
- Unblinded
- Median duration of 3 days
  - Sensitivity analysis limited to patients who received >48, >72, and >96 hours were similar
- 1 in 5 patients received at least one dose of the non-assigned study drug
- Cefepime neurotoxicity spans a spectrum from coma to agitation

Trial Conclusions

Compared to cefepime, piperacillin-tazobactam does not increase the incidence of AKI.

Compared to piperacillin-tazobactam, cefepime may decrease the number of days alive and free of delirium and coma.

Thank you for listening!

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