Real world Outcomes of *Citrobacter freundii* *Klebsiella aerogenes* and *Enterobacter cloacae* bacteremia Treatment

(ROCKET)

29 August 2026
Three Rivers Antimicrobial Stewardship Symposium 2026
Sunish Shah, PharmD

Learning objective

- Identify treatment-emergent resistance rates among Enterobacterales at risk for clinically significant AmpC production

Disclosures

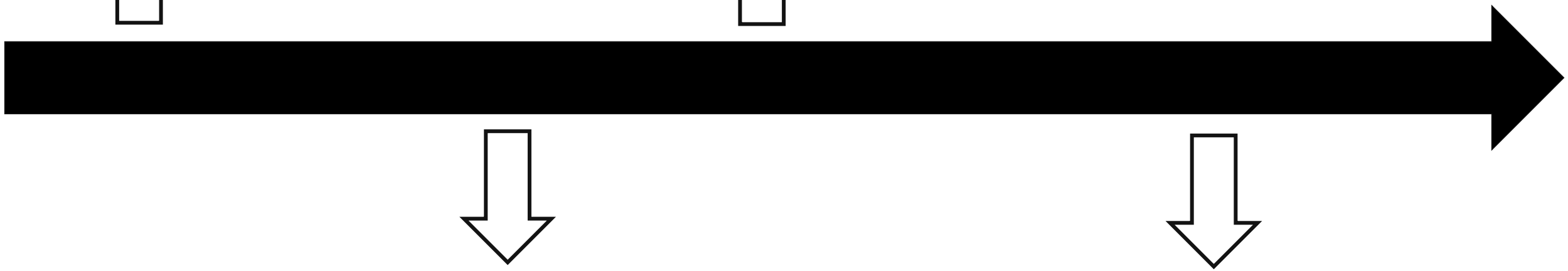
- This work was not directly supported by any funding agencies. This study was performed as part of our routine work.

The 1970s

1970
The Beatles end

1974
Rubik's Cube Invented

1977
Star Wars premiers



Role of a Cefoxitin-Inducible Beta-Lactamase in a Case of Breakthrough Bacteremia

DAVID G. BECKWITH[1]* AND JEFFREY A. JAHRE[2]

Departments of Pathology (Microbiology)[1] and Medicine (Infectious Diseases),[2] St. Luke's Hospital, Bethlehem, Pennsylvania 18015

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Development of resistance during therapy with cefamandole contributes to treatment failure. A simple cefoxitin disk test was recently described which detects a cefamandole-active inducible beta-lactamase not otherwise detectable with cefamandole as the inducer. A case of breakthrough *Enterobacter* bacteremia due to selection of a resistant subpopulation is reported in an immunocompromised patient. The use of this simple disk test in selected clinical cases is advocated.

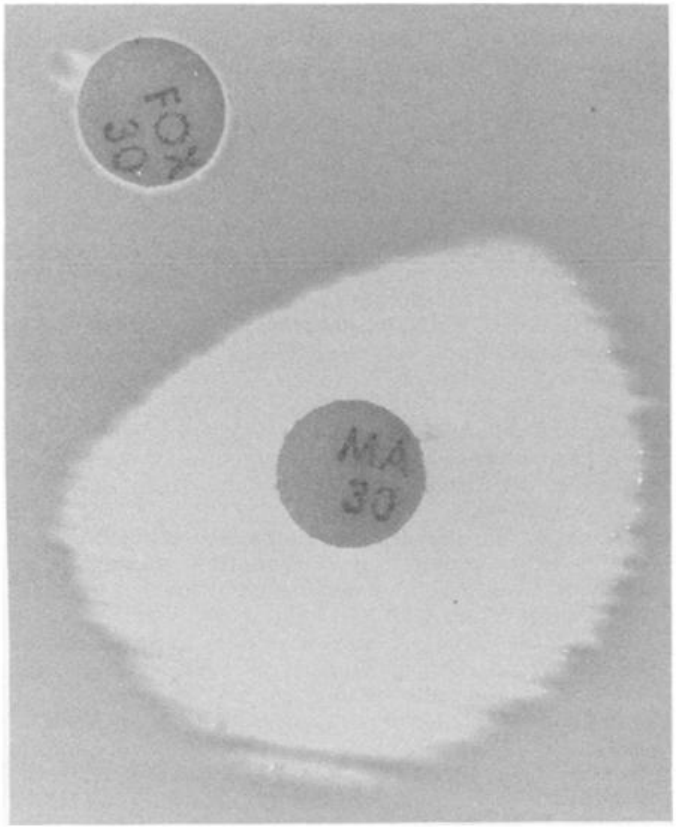

FIG. 1. *The cefoxitin disk test with E. aerogenes (BC494). Note the truncated zone of inhibition indicating an inducible beta-lactamase.*

Beckwith DG. J Clin Microbiol. 1980 Oct;12(4):517-20.

IDSA 2026 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Published July 30, 2026

Question 2.1: Which commonly identified Enterobacterales species should be considered at moderate risk for clinically significant inducible *ampC*?

Suggested approach: *Enterobacter cloacae* complex, *Klebsiella aerogenes*, and *Citrobacter freundii* are the most frequently encountered Enterobacterales at moderate risk for clinically significant inducible *ampC*. Although clinical experience is limited, in vitro data suggest *Hafnia alvei* exhibits similar inducible *ampC* potential and may be considered in the same risk category.

Question 2.5: What is the role of piperacillin-tazobactam for the treatment of infections caused by Enterobacterales at moderate risk of clinically significant AmpC production due to an inducible *ampC* gene?

Suggested approach: Piperacillin-tazobactam is not suggested for the treatment of invasive infections caused by Enterobacterales at moderate risk of clinically significant inducible AmpC production.

Tamma. Clin Infect Dis. 2026 Aug 8:ciag481.

Species-specific mutation rates for *ampC* derepression in Enterobacterales with chromosomally encoded inducible AmpC β-lactamase

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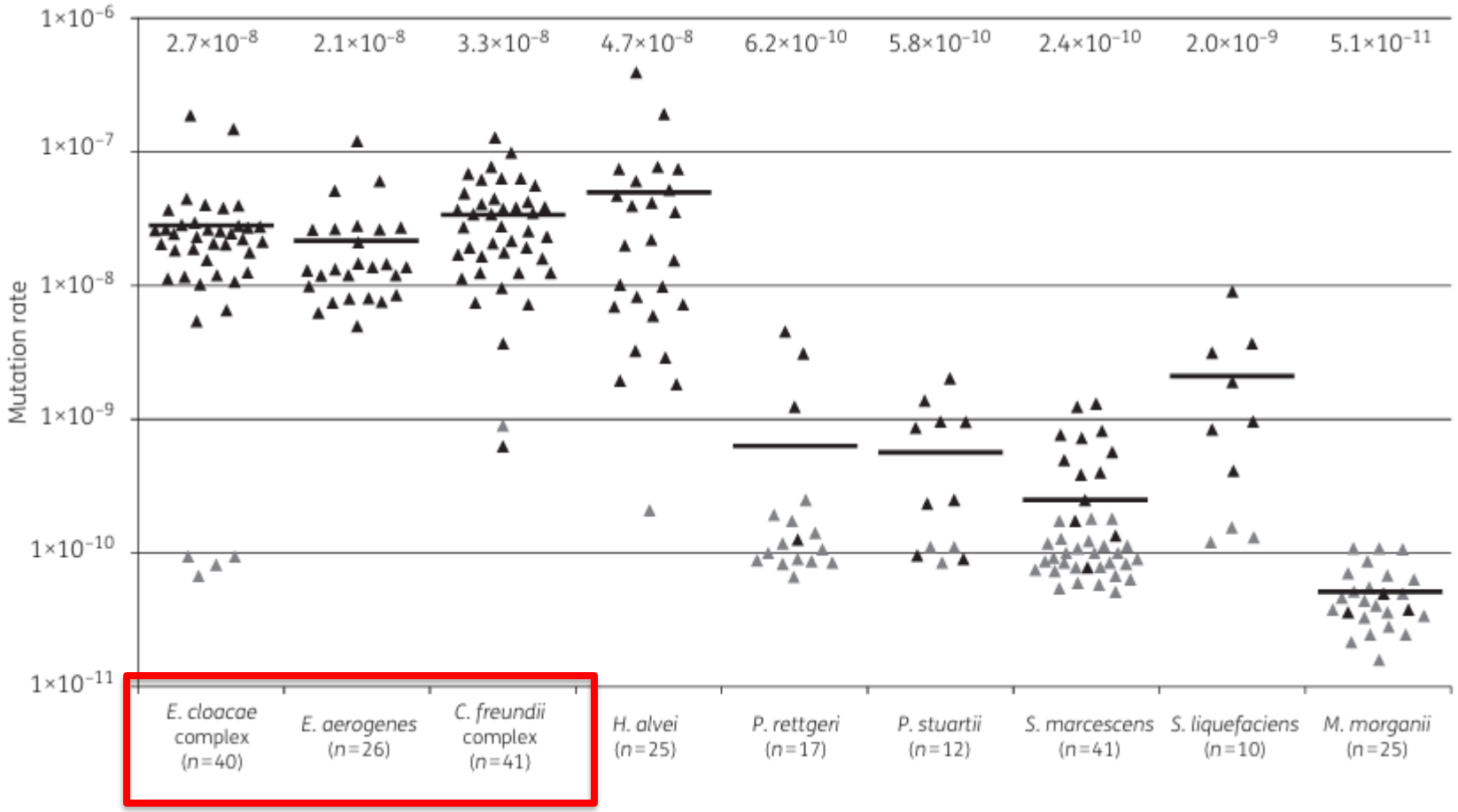


Kohlmann R. J Antimicrob Chemother. 2018 Jun 1;73(6):1530-1536.

Prior clinical studies

Open Forum Infectious Diseases
MAJOR ARTICLE

Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β-Lactamase–Producing *Enterobacter* spp, *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp, or *Serratia marcescens*: A Pilot Multicenter Randomized Controlled Trial (MERINO-2)

Adam G. Stewart,[1,2] David L. Paterson,[1,2] Barnaby Young,[3,4,5] David C. Lye,[3,4,5,6] Joshua S. Davis,[7,8] Kellie Schneider,[7] Mesut Yilmaz,[9] Rumeysa Dinleyici,[9] Naomi Runnegar,[10] Andrew Henderson,[1,10] Sophia Archuleta,[6,11] Shirin Kalimuddin,[12,13] Brian M. Forde,[1,14,15] Mark D. Chatfield,[1] Michelle J. Bauer,[1] Jeffrey Lipman,[1,16,17] Tiffany Harris-Brown,[1] and Patrick N. A. Harris[1,18]; for the MERINO Trial Investigators and the Australasian

- Only randomized Trial of AmpC β-lactamase–producing Enterobacterales (AmpC-E)
- Piperacillin/tazobactam (n=38) or meropenem (n=34)
- Microbiological failure in the piperacillin-tazobactam group compared to in the meropenem group (13% vs 0%)
  - Lack of source control
- Microbiological relapse was more common in the meropenem arm (9% vs 0%; P = .06)
- No difference in mortality or resistance rates

Clinical Infectious Diseases
BRIEF REPORT

Mutation Rate of AmpC β-Lactamase–Producing Enterobacterales and Treatment in Clinical Practice: A Word of Caution

Alexis Maillard,[1] Laurent Dortet,[2,3,4] Tristan Delory,[5] Matthieu Lafaurie,[6] and Alexandre Bleibtreu[1,7]; for the Treatment of AmpC-Producing Enterobacterales Study Group

- 575 patients with bloodstream infections or pneumonia due to wild-type AmpC-E
- Low risk and high risk AmpC-E
- Those treated with **piperacillin had a higher risk of AmpC-related** treatment failure (12% vs 4%; HR, 3.2 [95% CI, 1.4–7.4]) compared to cefepime/carbapenems

Stewart A. Open Forum Infect Dis. 2021 Aug 2;8(8):ofab387.

Maillard A. Clin Infect Dis. 2024 Jul 19;79(1):52-55.

Real world
Outcomes of
Citrobacter freundii
***Klebsiella aerogenes* and**
***Enterobacter cloacae* bacteremia**
Treatment

(ROCKET)

Methods

Design

- Multicenter, retrospective study of adult patients with bloodstream infections caused by *Enterobacter cloacae* complex*, Klebsiella aerogenes*, or *Citrobacter freundii*

- January 2017 and November 2025
  - Five hospitals; One central laboratory

Objectives

- To identify the appropriateness of piperacillin-tazobactam for the definitive treatment of high risk ampC-E

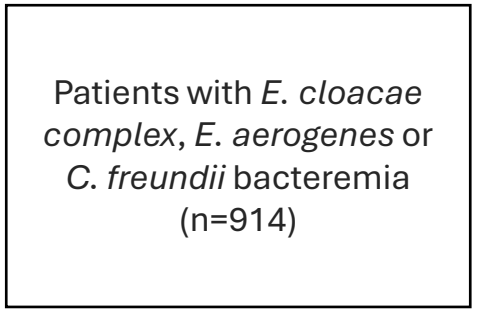
- To identify the rates of 90-day treatment emergent resistance

- To identify the significance of baseline ceftriaxone resistance

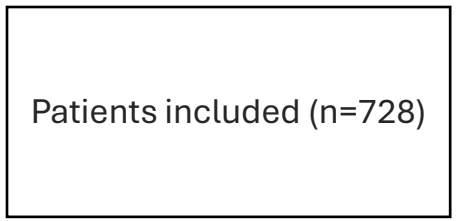
Definitions

- Empiric therapy → Gram-negative antimicrobial initiated within 24 hours of blood culture collection and administered for at least 2 days
- Definitive therapy → Definitive therapy was defined as the antibiotic selected by day 3 and administered for at least 48 hours
- Step down therapy → Initiation of an *in vitro* active antibiotic following definitive therapy
- Resistance
  - ≥4-fold increase in the minimum inhibitory concentration (MIC) or shift in susceptibility interpretation
  - Identified in the index organism recovered **within 90 days** of the index blood culture

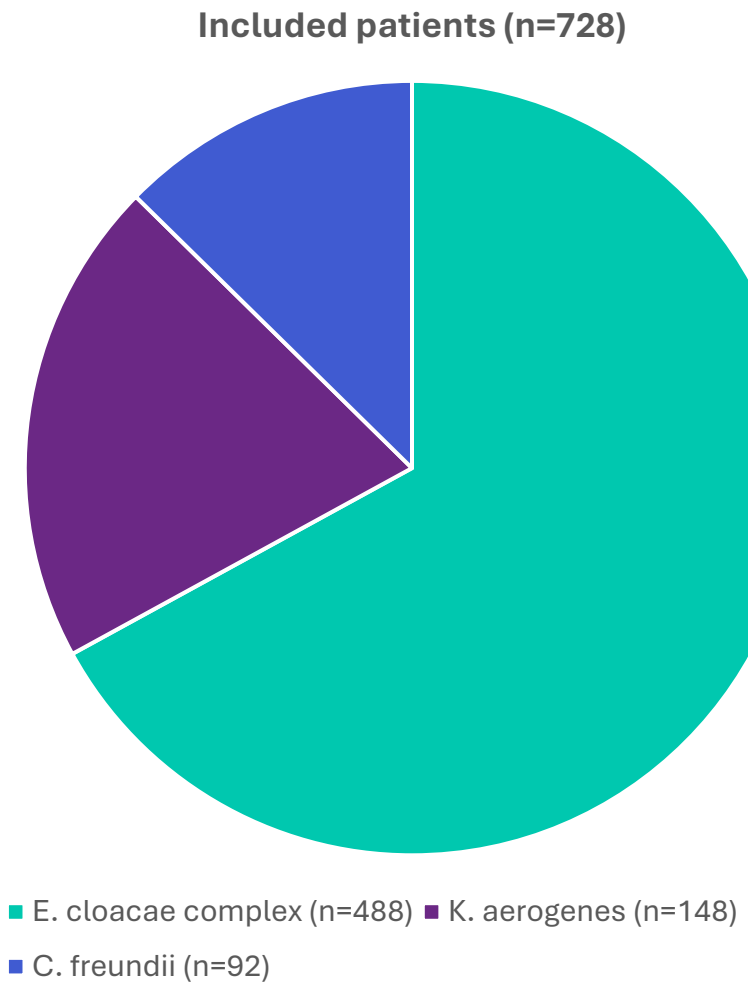
Inclusion and Exclusion



Reasons for exclusion	
Mortality or hospice within 48 hours of definitive treatment	66
Positive blood cultures at outside hospital	63
Concomitant non-lactose fermenter deemed resistant to empiric treatment	14
Carbapenemase production or treatment with novel agent	30
Not admitted	13

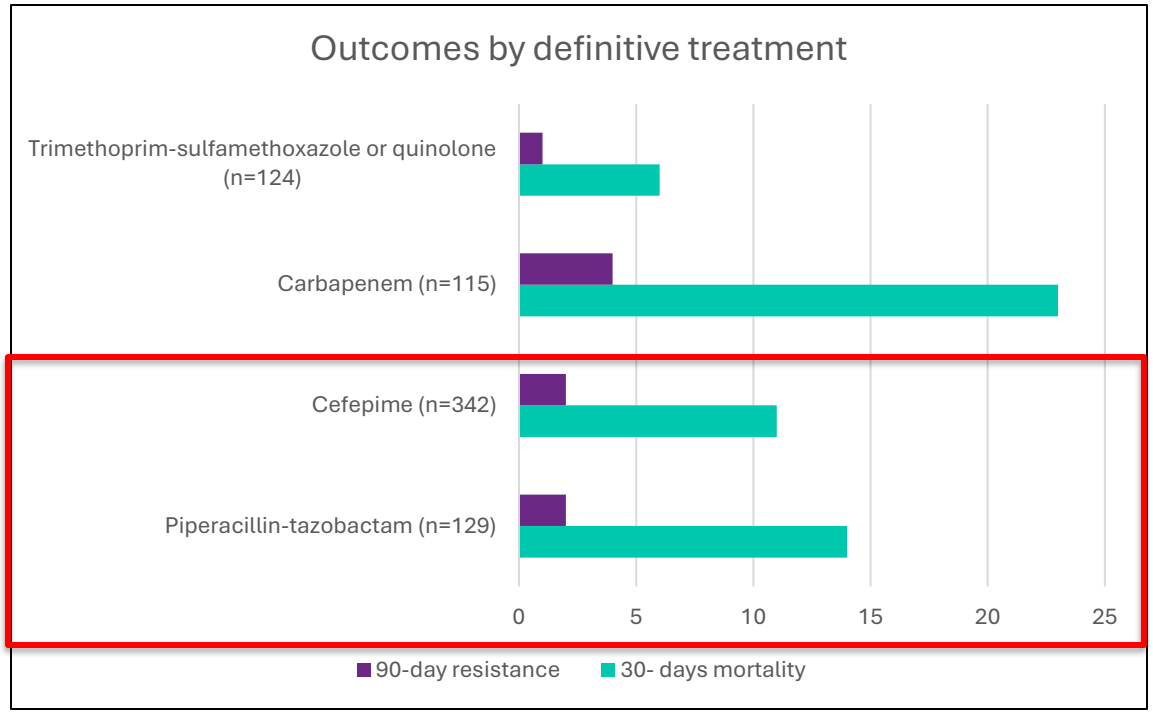


Epidemiology



	E. cloacae complex (n=488)	*K. aerogenes* (n=148)	*C. freundii* (n=92)	P-value
Baseline demographics and illness				
Age, median (IQR	66 (53-74)	68 (60-76)	67 (58-75)	**0.021**
Female, n (%)	212 (43)	21 (28)	43 (47)	**0.001**
Polymicrobic, n (%)	125 (26)	17 (12)	34 (37)	**<0.001**
Treatment information				
Empiric agent inactive, n (%)	46 (9)	11 (7)	2 (2)	**0.048**
Days of therapy, median (IQR)	14 (10-17)	13 (9-15)	14 (9-16)	**0.036**
Outcomes				
30-day mortality, n (%)	55 (11)	15 (10)	18 (20)	0.069

Definitive treatment



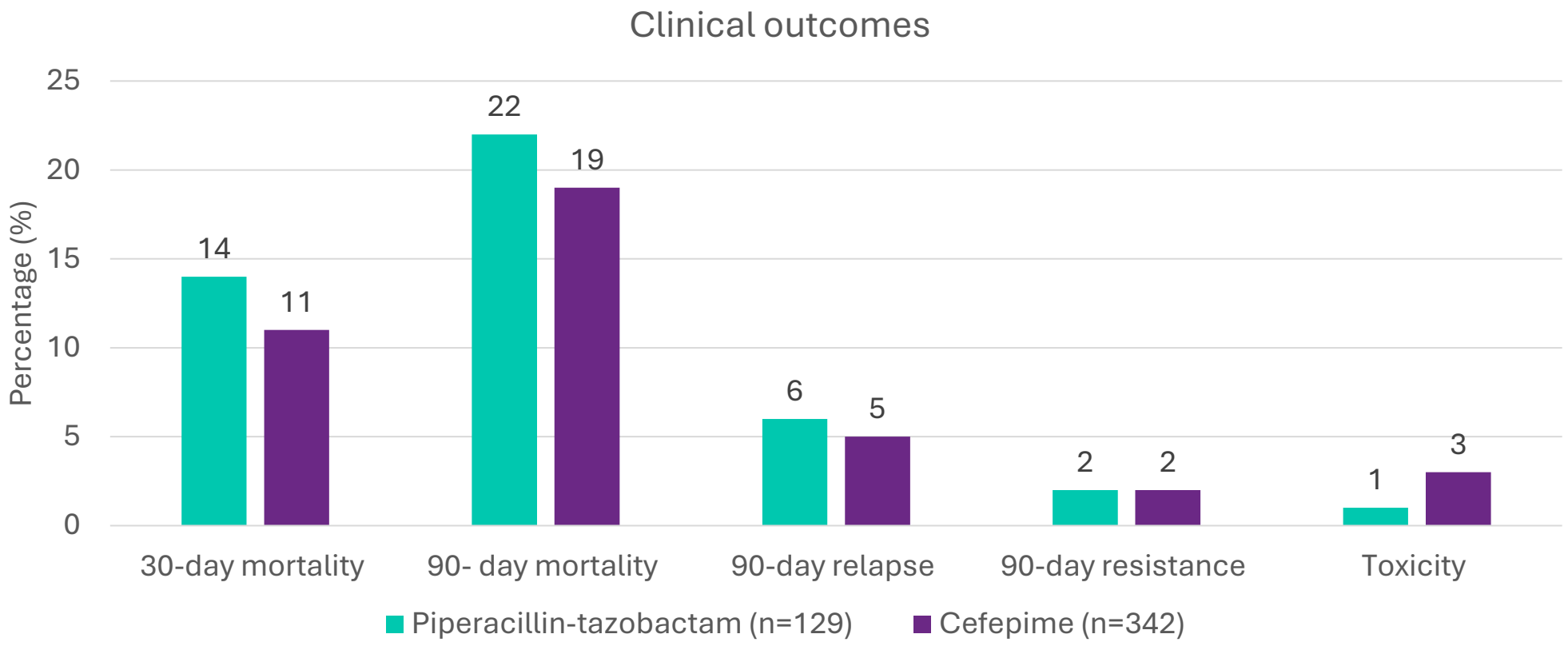
Carbapenem group

- Restricted to Infectious Diseases and stewardship program
- **Highest Pitt Bacteremia score**
  - Median (IQR) of 2 (0-3); P< 0.001
- **The longest time to active treatment**
  - Median (IQR) of 9.8 hours (2.5-26.2); P <0.001
- **Most likely to have ceftriaxone resistant isolates**
  - 60%; P< 0.001
- **Most likely to not receive source control**
  - 16%; P<0.001

Piperacillin-tazobactam versus cefepime

	TZP (n=129)	FEP (n=342)	P-value
Baseline demographics and illness			
Age, median (IQR	66 (54-75)	67 (53-74)	0.931
Female, n (%)	57 (44)	133 (39)	0.296
Immunocompromised, n (%)	48 (37)	122 (36)	0.757
CCI Score, median (IQR)	3 (2-6)	4 (2-6)	0.643
Pitt Bacteremia score, median (IQR)	2 (1-3)	1 (0-3)	**0.017**
Pathogen, n (%)			**< 0.001**
E. cloacae complex	74 (57)	236 (69)	
E. aerogenes	22 (17)	73 (21)	
C. freundii	33 (26)	33 (10)	
Polymicrobic, n (%)	41 (32)	82 (24)	0.085
Renal Replacement therapy, n (%)	8 (6)	29 (9)	0.413
Source control indicated but not received, n (%)	16 (12)	31 (9)	0.281
Complicated Bacteremia, n (%)	12 (9)	36 (11)	0.695
Time to source control, median (IQR)	N=62 0.5 (0-3)	N=146 1.6 (0-4.3)	**0.011**
Baseline ceftriaxone resistant, n (%)	N=113 23 (20)	N=290 88 (30)	**0.044**
Treatment information			
Rapid diagnostic, n (%)	4 (3)	50 (15)	**< 0.001**
Empiric agent inactive, n (%)	1 (1)	22 (6)	**0.008**
Empiric treatment, n (%)			**< 0.001**
Cefepime	4 (3)	207 (61)	
Piperacillin-tazobactam	114 (88)	92 (27)	
Carbapenem	5 (4)	18 (5)	
Other	6 (5)	25 (7)	
Total treatment days, median (IQR)	14 (11-17)	14 (9-17)	0.240
Definitive treatment days, median (IQR)	6 (5-9)	7 (4-12)	0.521
Transitioned/ step down antimicrobial, n (%)	87 (67)	186 (54)	**0.011**

Piperacillin-tazobactam versus cefepime



In a **propensity score model** adjusted for age, immunocompromised status, Charlson Comorbidity Index, Pitt Bacteremia Score, pathogen, renal replacement therapy, source control and source of Infection:

Piperacillin-tazobactam was **not associated** with an increased risk of **30-day mortality** (HR, 1.05 [95% CI, 0.57–1.92], P=0.882) or **90-day mortality** (HR, 0.98 [95% CI, 0.61–1.59], P=0.945) compared to cefepime

30-days mortality

30-day mortality
Rate of 12% (88/728)

	30-day mortality (n=88)	30-day survival (n=640)	P-value
Baseline demographics and illness			
Age, median (IQR	70 (60-76)	66 (55-74)	**0.007**
Immunocompromised, n (%)	43 (49)	209 (33)	**0.003**
CCI Score, median (IQR)	5 (4-7)	3 (2-5)	**< 0.001**
Pitt Bacteremia score, median (IQR)	3 (1-6)	1 (0-3)	**< 0.001**
Renal Replacement therapy, n (%)	19 (22)	46 (7)	**< 0.001**
Source control indicated but not received, n (%)	14 (16)	53 (8)	**0.021**
Source, n (%)			**<0.001**
Intrabdominal	30 (34)	183 (29)	
Line	9 (10)	112 (18)	
Multiple/unknown	16 (18)	87 (14)	
Osteomyelitis/ endocarditis	3 (3)	29 (5)	
Urinary tract infection	12 (14)	175 (27)	
Pneumonia	14 (16)	23 (4)	
Other	1 (1)	9 (1)	
Baseline ceftriaxone resistant, n (%)	N=80 35 (44)	N=559 179 (32)	**0.037**
Treatment information			
Empiric treatment, n (%)			**0.037**
Cefepime	33 (38)	254 (40)	
Piperacillin-tazobactam	29 (33)	251 (39)	
Carbapenem	17 (19)	70 (11)	
Fluroquinolone/TMP-SMX	6 (7)	15 (2)	
Other	3 (3.4)	50	

Impact and Factors Associated with baSeline cefTriaxone resistance on the

Real world Outcomes of *Citrobacter freundii* *Klebsiella aerogenes* and *Enterobacter cloacae* bacteremia Treatment

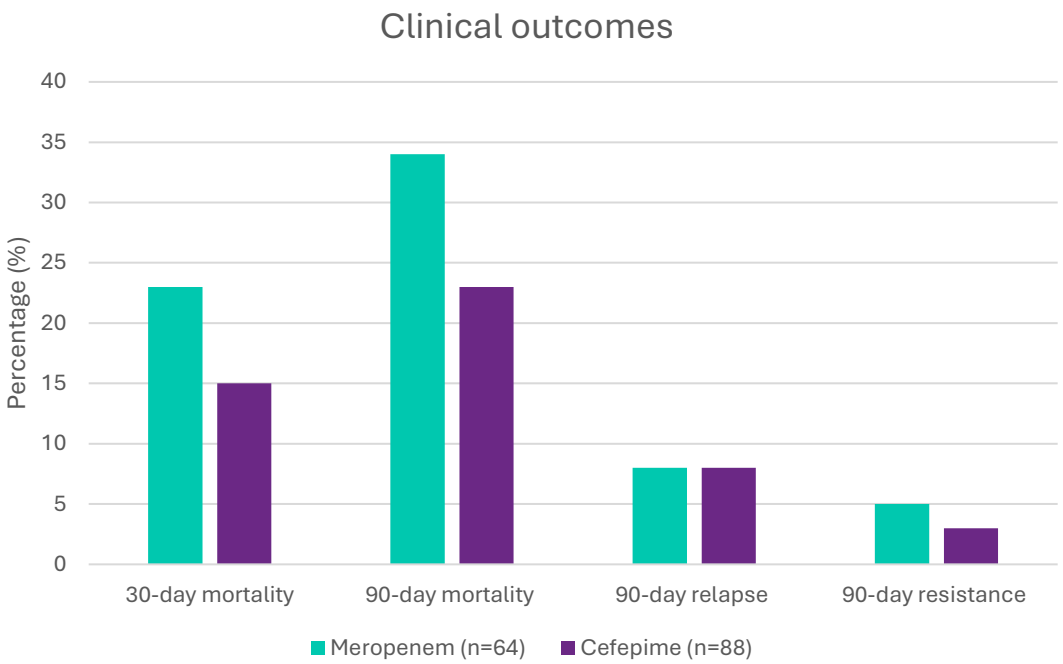
(FAST ROCKET)

Ceftriaxone susceptible versus non-susceptible

All CTX-M negative

	CRO R (n=214)	CRO S (n=425)	P-value
Baseline demographics and illness			
Pitt Bacteremia score, median (IQR)	2 (1-4)	1 (0-3)	**0.001**
Mechanical ventilation, n (%)	42 (20)	32 (8)	**< 0.001**
Vasopressors, n (%)	99 (47)	156 (37)	**0.019**
Admitted prior to 2020, n (%)	64 (30)	169 (40)	**0.015**
Nosocomial bacteremia, n (%)	102 (48)	111 (26)	**< 0.001**
90-day antimicrobial exposure			
Prior cefepime exposure, n (%)	48 (22)	64 (15)	**0.021**
Prior piperacillin-tazobactam exposure, n (%)	90 (42)	122 (29)	**< 0.001**
Prior third generation cephalosporin exposure, n (%)	67 (31)	42 (10)	**< 0.001**
Treatment information			
Rapid diagnostic, n (%)	30 (14)	47 (11)	0.278
hours to first active agent, median (IQR)	14 (2-33)	3 (1-15)	**< 0.001**
Empiric agent inactive, n (%)	53 (25)	4 (1)	**< 0.001**
Outcomes			
30-day mortality, n (%)	35 (16)	45 (11)	**0.037**
90-day mortality, n (%)	54 (25)	74 (17)	**0.019**
Relapse on days 5-90, n (%)	16 (8)	16 (4)	**0.042**
90-day resistance to empiric, definitive or transition treatment, n (%)	7 (3)	5 (1)	0.117
Post infection length of stay, median (IQR)	11 (6-20)	8 (5-14)	**< 0.001**

Meropenem versus cefepime: Ceftriaxone resistant subset



	MEM (n=64)	FEP (n=88)	P-value
Baseline demographics and illness			
Renal Replacement therapy, n (%)	13 (20)	6 (7)	**0.013**
Complicated Bacteremia, n (%)	17 (27)	10 (11)	**0.015**
Source control indicated but not received, n (%)	10 (16)	3 (3)	**0.016**
Treatment information			
Hours to first active agent, median (IQR)	21 (7-47)	14 (2-25)	**0.007**
Empiric agent inactive, n (%)	23 (36)	18 (21)	**0.034**
Empiric treatment			**< 0.001**
Cefepime	10 (16)	52 (59)	
Piperacillin-tazobactam	18 (28)	22 (25)	
Carbapenem	31 (48)	7 (8)	
Other	5 (8)	7 (8)	
Therapeutic drug monitoring, n (%)	1 (2)	10 (11)	**0.025**
Days of definitive therapy, median (IQR)	11 (6-14)	7 (5-13)	**0.034**

After propensity score weighting, **no statistically significant difference in 30-day mortality** (HR, 1.08; 95% CI, 0.49–2.39; P=0.848) or 90 day mortality (HR, 1.24; 95% CI, 0.65–2.37; P=0.507) was observed between patients who received definitive treatment with **meropenem or cefepime.**

Mechanism of meropenem resistance

Journal of Antimicrobial Chemotherapy

Clinical characteristics and outcomes of patients with bacteraemia caused by non-carbapenemase-producing, carbapenem-resistant *Enterobacterales*

Sunish Shah [1,2*], Lloyd G. Clarke[1], Ellen G. Kline [3], Rachel V. Marini[1,2], Kevin M. Squires[3] and Ryan K. Shields [1,3]

Patient information				Treatment		Baseline isolate (mg/L)			Follow-up isolate (mg/L)			Whole-genome sequencing		
Pt	Age	Sex	Pathogen	Definitive agent (DOT)	Stepdown (DOT)	MEM	CZA	MVB	MEM	CZA	MVB	β-Lactamases detected[a]	cgSNP[b]	Other gene mutations[c]
1	46	F	*E. cloacae complex*	MEM (16)	—	≤0.06	1	0.06	2	2	0.5	ACT-7	51	*ompC* (L357P)
2	61	M	*E. cloacae complex*	MEM (15)	—	0.25	≤0.25	0.03	16	128	16	ACT-15, LAP-2	170	*ompC* (del A401-L414), *mdtA* (L26W, A384E), *mdtC* (1 bp del), marA (T24I)

J Antimicrob Chemother. 2026 Aug 4;81(9):dkag267.

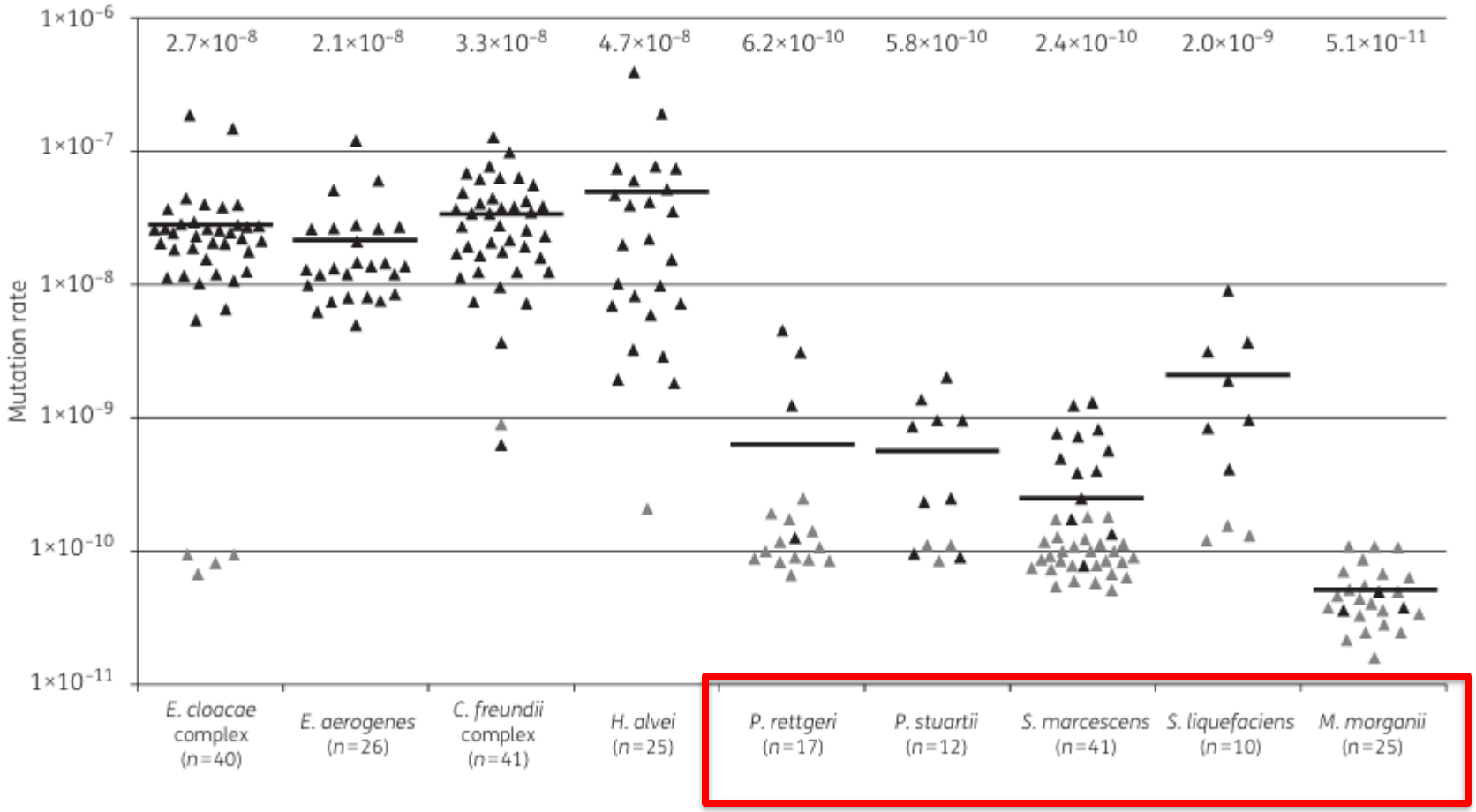
If the treatment emergent resistance rate of high risk ampC producing pathogens is low.....

What is the resistance rate of low risk ampC producing pathogens?

Species-specific mutation rates for *ampC* derepression in Enterobacterales with chromosomally encoded inducible AmpC β-lactamase

Rebekka Kohlmann*, Tobias Bähr and Sören G. Gatermann

Department of Medical Microbiology, Ruhr-Universität Bochum, Universitätsstraße 150, 44801 Bochum, Germany



Kohlmann R. J Antimicrob Chemother. 2018 Jun 1;73(6):1530-1536.

Low risk ampC producing pathogens

Design

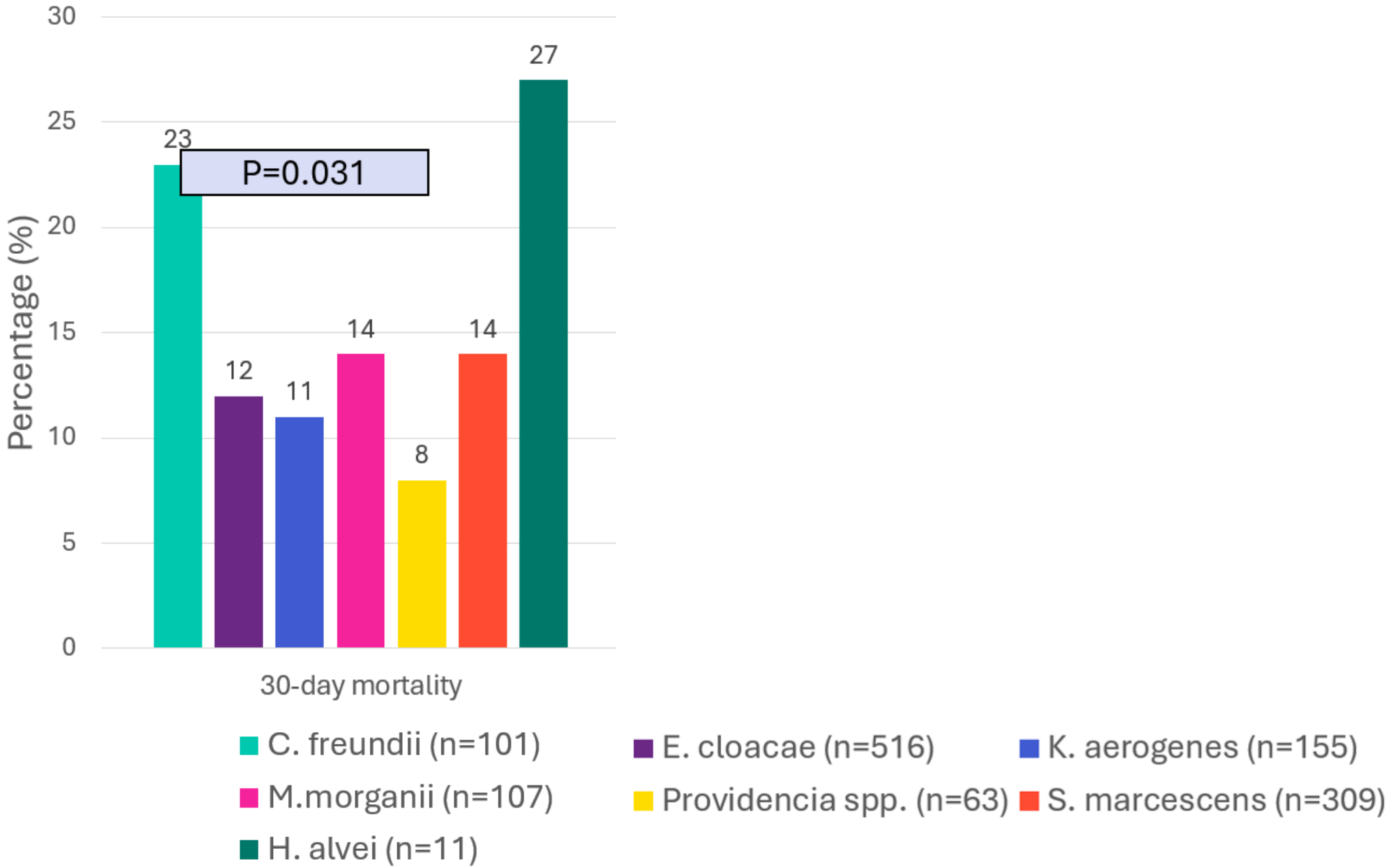
- Multicenter, retrospective study of adult patients with bloodstream infections caused by *Enterobacter cloacae* complex*, Klebsiella aerogenes*, *Citrobacter freundii,* ***Hafnia alvei, Providencia rettgeri, Providencia stuartii, Serratia marcescens, Serratia liquefasciens, Morganella morganii***

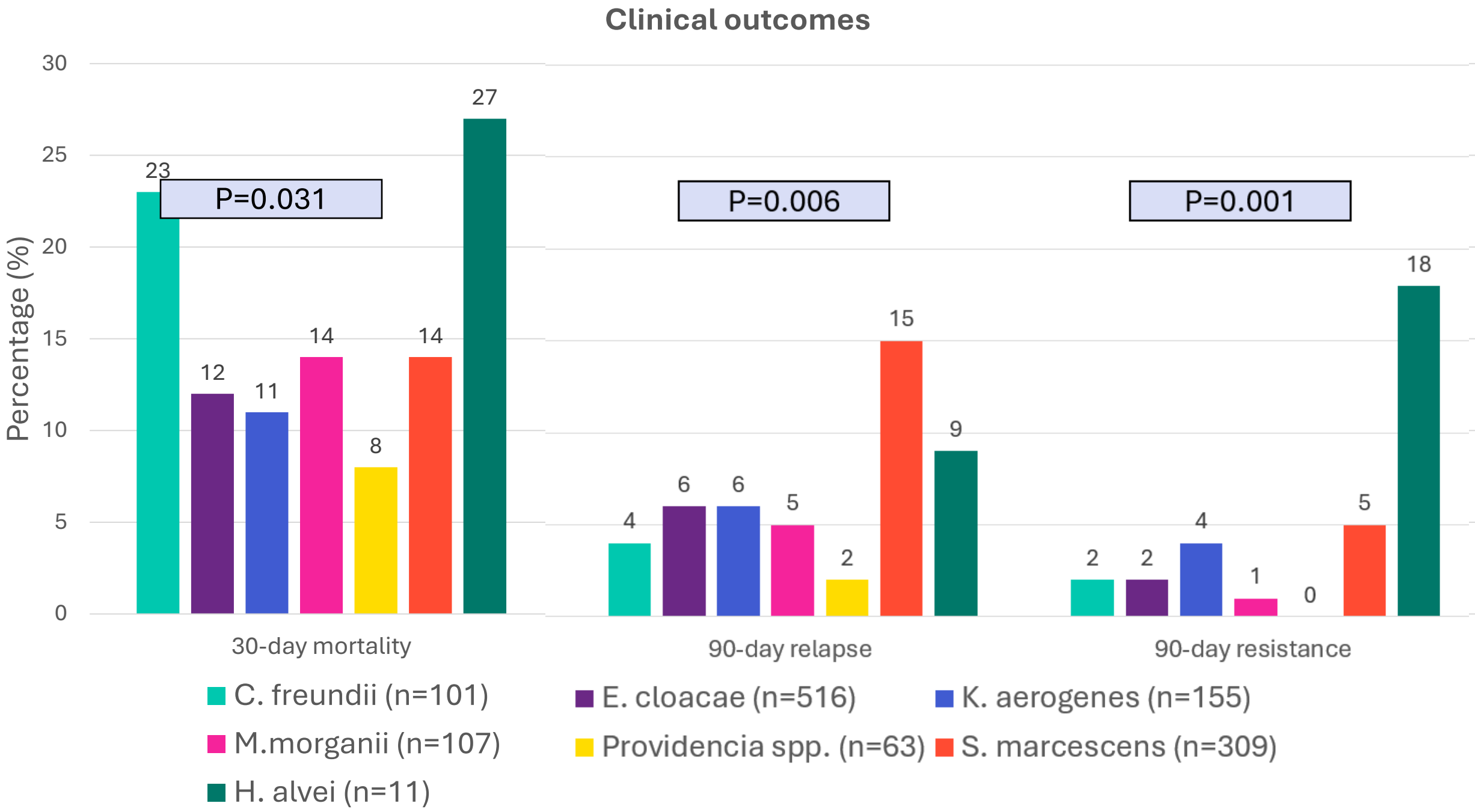
- January 2017 and **May 2026**
  - Five hospitals; One central laboratory

Low risk ampC producing pathogens

	Low risk (n=491)	High risk (n=783)	P-value
Baseline demographics and illness			
Age, median (IQR)	66 (55-75)	67 (55-74)	0.992
Female, n (%)	175 (36)	320 (41)	0.062
Immunocompromised, n (%)	132 (27)	275 (35)	**< 0.001**
CCI Score, median (IQR)	3 (2-5)	4 (2-6)	**< 0.001**
Pitt Bacteremia score, median (IQR)	1 (0-3)	1 (0-3)	0.129
Source control indicated but not received, n (%)	38 (8)	75 (10)	0.261
Definitive Treatment information			
Third generation cephalosporin, n (%)	60 (12)	18 (2)	**< 0.001**
TZP, median (IQR)	107 (22)	132 (17)	
FEP, n (%)	196 (40)	377 (48)	
Carbapenem, n (%)	51 (11)	124 (16)	
Outcomes			
90-day mortality, n (%)	109 (22)	165 (21)	0.634
90-day resistance to empiric, definitive or transition treatment, n (%)	17 (4)	18 (2)	0.216

Clinical outcomes




Clinical outcomes
Percentage (%)
30
25
20
15
10
5
0
P=0.031
P=0.006
P=0.001
23
12
11
14
8
14
27
4
6
6
5
2
15
9
2
2
4
1
0
5
18
30-day mortality
90-day relapse
90-day resistance
C. freundii (n=101)
E. cloacae (n=516)
K. aerogenes (n=155)
M.morganii (n=107)
Providencia spp. (n=63)
S. marcescens (n=309)
H. alvei (n=11)

Question

- Which of the following pathogens had the highest rate of treatment emergent resistance?

a. *Providencia* spp.
b. *Serratia marcescens*
c. *Morganella morganii*
d. *Serratia liquefasciens*

Conclusions

- Largest study to compare treatment outcomes of patients with bacteremia secondary to ampC producing pathogens

- Overall **low rates of treatment emergent resistance**
  - The highest 90-date resistance rate was observed with ***S. marcescens***

- Definitive treatment of piperacillin-tazobactam was not associated an increased risk of mortality or treatment emergent resistance
  - **Prior antimicrobial exposure** may drive resistance more than definitive treatment

- Baseline ceftriaxone resistance was associated with increased 30-day mortality, higher severity of illness, and a delayed time to active treatment
  - **Further data is warranted to define the optimal treatment** for ampC producing pathogens with baseline ceftriaxone resistance

Acknowledgement

Clinical data evaluation and design

- Jasanjeet Jawanda, MD
- Bonnie Falcione, PharmD
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- Matthew O'Donnell, MD
- Ryan Shields, PharmD, MS

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- Lingyi Peng, PhD

Special thanks

- Lloyd Clarke, BSc (Hons)
- Hannah Creager, PhD

Ongoing studies

- Nkechi Utomi-Obichie, PharmD
- Amy Huang, PharmD

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