

# Ceftazidime-avibactam Resistance in KPC

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**UPMC** LIFE  
CHANGING  
MEDICINE



# Ceftazidime-avibactam: *In vitro* spectrum

- FDA approved in 2015
  - cIAI, cUTI, HAP/VAP
- Avibactam is a diazabicyclooctane (DBO)  $\beta$ -lactamase inhibitor
  - Inhibits class A, C, and some D  $\beta$ -lactamases

Drug	KPC	MBL	OXA-48	AmpC + porin
Ceftazidime-				



# Ceftazidime–avibactam *in vitro* activity

Antimicrobial Activity of Ceftazidime-Avibactam Tested against Multidrug-Resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolates from U.S. Medical Centers, 2013 to 2016

Hello S. Sader, Marlana Castanheira, Dee Shortridge, Rodrigo E. Mendes, Robert K. Flamm  
JMI Laboratories, North Liberty, Iowa, USA

- Isolates from all 9 U.S. Census divisions collected from 2013–2016

Organism category and antimicrobial agent (no. of isolates tested)	MIC ( $\mu\text{g/ml}$ )		CLSI <sup>b</sup>		EUCAST	
	MIC <sub>50</sub>	MIC <sub>90</sub>	%S	%R	%S	%R
<i>Enterobacteriaceae</i>						
All isolates (36,380)						
Ceftazidime-avibactam	0.12	0.25	99.9	0.1*	99.9	0.1
Ceftriaxone	≤0.06	>8	85.3	13.6	85.3	13.6
Ceftazidime	0.25	8	88.8	9.9	86.2	11.2
Cefepime	≤0.12	2	91.2	6.7	89.8	7.7
Piperacillin-tazobactam	2	16	92.7	4.1	89.8	7.3
Meropenem	≤0.06	≤0.06	98.5	1.3	98.7	0.7
Levofloxacin	≤0.12	>4	82.6	15.6	78.7	18.8
Gentamicin	≤1	2	91.2	7.6	90.2	8.8
Amikacin	2	4	99.2	0.2	98.4	0.8
Tigecycline	0.25	1	98.0	0.1*	92.7	2.0
Colistin	≤0.5	>8			78.2	21.8
CRE (513) <sup>e</sup>						
Ceftazidime-avibactam	0.5	2	97.5	2.5*	97.5	2.5
Ceftriaxone	>8	>8	2.1	97.5	2.1	97.5
Ceftazidime	>32	>32	4.3	93.0	2.3	95.7
Cefepime	>16	>16	8.4	77.9	3.2	87.1
Piperacillin-tazobactam	>64	>64	3.1	91.2	2.7	96.9
Meropenem	>8	>8	2.7	89.7	10.3	52.4
Levofloxacin	>4	>4	23.4	72.9	15.0	81.3
Gentamicin	8	>8	49.5	33.9	44.4	50.5
Amikacin	8	32	68.2	7.0	51.5	31.8
Tigecycline	0.5	1	98.8	0.0*	90.3	1.2
Colistin	≤0.5	>8			79.1	20.9

# Baseline ceftazidime–avibactam resistance

## First Report of Ceftazidime-Avibactam Resistance in KPC-3-Expressing

### *Klebsiella pneumoniae* Isolate

Romney M. Humphris, Shangxin Yang, Peera Hemarajata, Kevin W. Ward, Janet A. Hindler, Shelley A. Miller, Aric Gregson

University of California, Los Angeles, Los Angeles, CA, USA

## Resistance to Ceftazidime-Avibactam Is Due to Transposition of KPC in a Porin-Deficient Strain of *Klebsiella pneumoniae* with Increased Efflux Activity

Kirk Nelson,\* Peera Hemarajata,\* Dongxu Sun,\* Debora Rubio-Aparicio,\* Ruslan Tsvtkovskii,\* Shangxin Yang,\* Robert Sebra,\* Andrew Kasarskis,\* Hoan Nguyen,\* Blake M. Hanson,\* Shana Leopold,\* George Weinstein,\* Oloa Lomovskaya,\* Romnev M. Humohries\*

## Clinical Infectious Diseases

### BRIEF REPORT

## High Rates of Nonsusceptibility to Ceftazidime-avibactam and Identification of New Delhi Metallo-β-lactamase Production in *Enterobacteriaceae* Bloodstream Infections at a Major Cancer Center

Samuel L. Aitken,<sup>1,4</sup> Jeffrey J. Tarrand,<sup>2</sup> Lalitagauri M. Deshpande,<sup>5</sup> Frank P. Tverdek,<sup>1</sup> Anne L. Jones,<sup>1</sup> Samuel A. Shelburne,<sup>3</sup> Randall A. Prince,<sup>1,3,4</sup> Micah M. Bhatti,<sup>2</sup> Kenneth V. I. Rolston,<sup>3</sup> Ronald N. Jones,<sup>5</sup> Mariana Castanheira,<sup>5</sup> and Roy F. Chemaly<sup>3</sup>

- ***K. pneumoniae* bloodstream isolate<sup>1</sup>**
  - Nonfunctional *ompK35*; T333N mutation in *ompK36*
  - Increased expression of *bla*<sub>KPC-3</sub> and *bla*<sub>SHV-12</sub> due to transposition of the TN4401 transposon into plasmid pIncX3 resulting in a higher copy number
  
- **64% (7/11) CRE bloodstream isolates were resistant to ceftazidime–avibactam<sup>2</sup>**
  - 6 harbored *bla*<sub>NDM</sub>
  - 1 isolate did not harbor a carbapenemase

# Ceftazidime-avibactam + aztreonam for MBL

Can Ceftazidime-Avibactam and Aztreonam Overcome  $\beta$ -Lactam Resistance Conferred by Metallo- $\beta$ -Lactamases in *Enterobacteriaceae*?

Steven Marshall,<sup>a</sup> Andrea M. Hujer,<sup>a,b</sup> Laura J. Rojas,<sup>a,b,c</sup> Kristina M. Papp-Wallace,<sup>a</sup> Romney M. Humphries,<sup>a</sup> Brad Spellberg,<sup>a</sup> Kristine M. Hujer,<sup>a,b</sup> Emma K. Marshall,<sup>a</sup> Susan D. Rudin,<sup>a,b</sup> Federico Perez,<sup>a,b</sup> Brigid M. Wilson,<sup>a</sup> Ronald B. Wasserman,<sup>a</sup> Linda Chikowski,<sup>a</sup> David L. Paterson,<sup>b</sup> Alejandro J. Vila,<sup>a</sup> David van Duin,<sup>a</sup> Barry N. Kreiswirth,<sup>a</sup> Henry F. Chambers,<sup>a</sup> Vance G. Fowler, Jr.,<sup>7b</sup> Michael R. Jacobs,<sup>a</sup> Mark E. Pulse,<sup>a</sup> William J. Weiss,<sup>a</sup> Robert A. Bonomo,<sup>a,b,c,p</sup>

Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio, USA<sup>a</sup>; Department of

- 21 Enterobacteriaceae with MBL
  - Addition of aztreonam lowered the ceftazidime-avibactam MIC for every isolate (81% became susceptible)
  - Time-kill and murine thigh model data are supportive

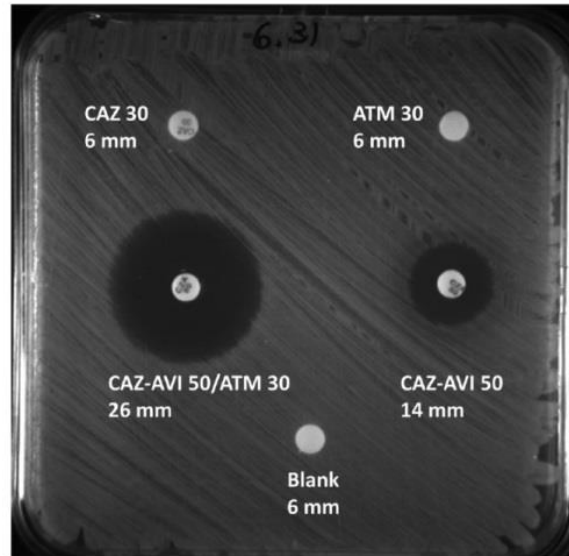
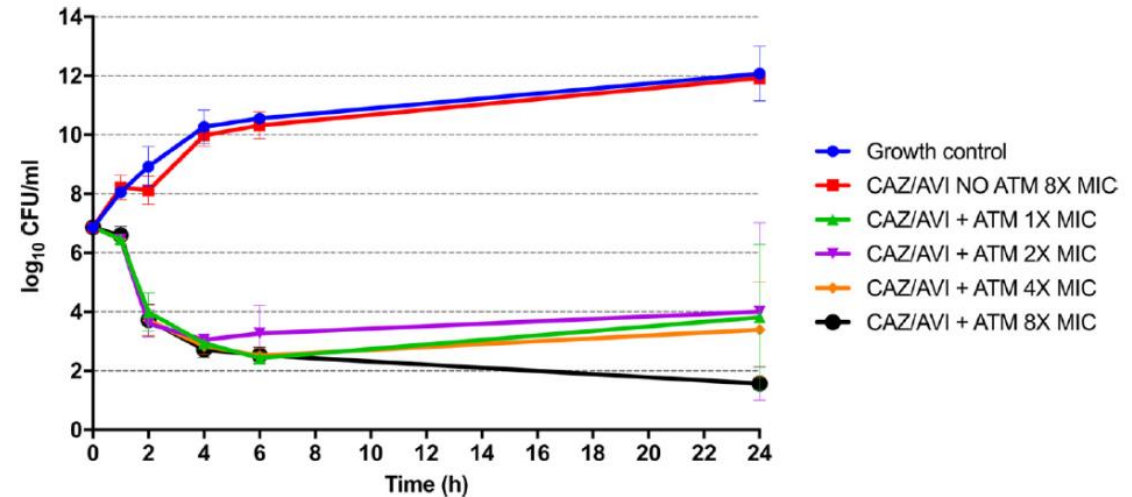


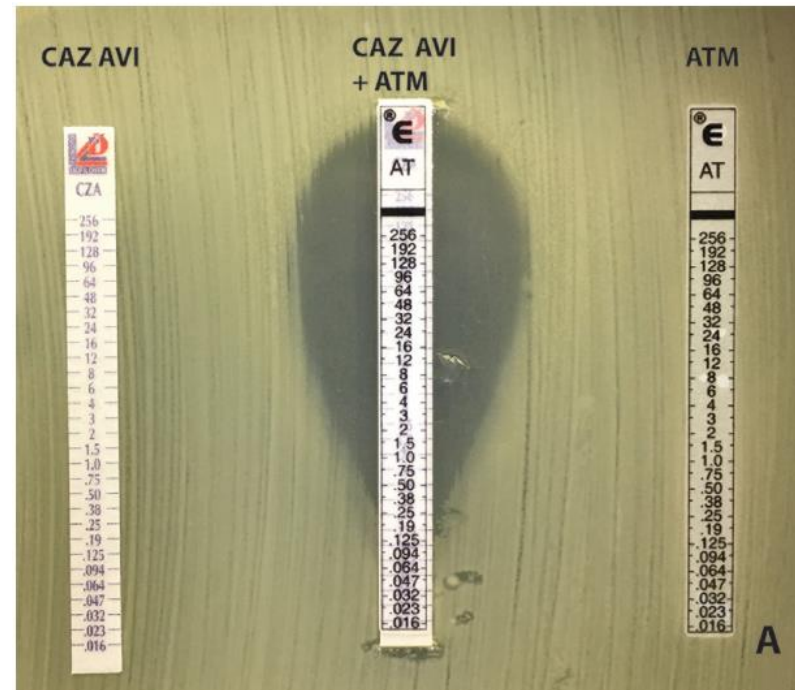
FIG 1 ATM placed directly on the CAZ-AVI disk to evaluate synergy. *E. cloacae* isolate 6.31 was used in this assay.



- 72 y/o woman with hip athroplasty infection
  - CR *E. cloacae* and ESBL *K. pneumoniae*
  - Treated successfully with combination

# Ceftazidime-avibactam + aztreonam for MBL

- 2 additional cases of successful therapy
  - 69 y/o male with persistent bacteremia
    - *K. pneumoniae* with OXA-48 and NDM-1
  - 55 y/o male with pneumonia and abscess
    - *P. aeruginosa* with NDM-1



Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome  $\beta$ -Lactam Resistance Conferred by Metallo- $\beta$ -Lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*

Benjamin Davido,<sup>a</sup> Lesly Fellous,<sup>b</sup> Christine Lawrence,<sup>c,d</sup> Virginie Maxime,<sup>e</sup> Martin Rottman,<sup>e,f</sup> Aurélien Dinh<sup>g</sup>

# #2. Ceftazidime–avibactam is better than salvage treatment of CRE

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

Ryan K. Shields,<sup>a,c</sup> M. Hong Nguyen,<sup>a,c</sup> Liang Chen,<sup>d</sup> Ellen G. Press,<sup>a</sup> Brian A. Potoski,<sup>a,c,e</sup> Rachel V. Marini,<sup>c</sup> Yohei Doi,<sup>a,c</sup> Barry N. Kreiswirth,<sup>d</sup> Cornelius J. Clancy<sup>a,b,f</sup>

## 109 patients with CR *K. pneumoniae* bacteremia were included:

**TABLE 1** Patient characteristics and clinical outcomes across treatment groups

Characteristic <sup>a</sup>	Treatment group <sup>b</sup>				P value
	C-A (n = 13)	CB+AG (n = 25)	CB+COL (n = 30)	Other <sup>c</sup> (n = 41)	
<b>Patient demographics</b>					
Male (n [%])	7 (54)	16 (64)	18 (60)	21 (51)	0.75
Age (median [range])	66 (32–91)	57 (32–87)	59 (26–84)	62 (25–90)	0.63
<b>Underlying disease</b>					
Diabetes (n [%])	4 (31)	8 (32)	8 (27)	15 (37)	0.85
Chronic liver disease (n [%])	0 (0)	9 (36)	9 (30)	13 (32)	0.11
Chronic respiratory disease (n [%])	5 (38)	5 (20)	8 (27)	8 (20)	0.51
Immunocompromised (n [%])	5 (38)	13 (52)	14 (47)	22 (54)	0.78
Solid-organ transplant recipient (n [%])	3 (23)	11 (44)	9 (30)	17 (41)	0.46
<b>Severity of illness</b>					
ICU at time of bacteremia (n [%])	6 (46)	13 (52)	12 (40)	25 (61)	0.36
RRT (n [%])	2 (15)	7 (28)	7 (23)	8 (20)	0.79
Pitt bacteremia score (median [range])	4 (1–6)	4 (0–9)	4 (0–9)	4 (0–9)	0.74
APACHE II score (median [range])	20 (16–33)	17 (8–38)	16 (7–36)	19 (4–34)	0.46
<b>Strain characteristic</b>					
Presence of KPC (n [%])	13 (100)	24 (96)	30 (100)	39 (95)	0.56
KPC-2	9	19	24	29	
KPC-3	4	5	6	10	
Primary bacteremia (n [%])	3 (23)	6 (24)	5 (17)	14 (34)	0.41
Secondary bacteremia (n [%])	10 (77)	19 (76)	25 (83)	27 (66)	0.41
Abdominal	2	12	16	20	
Respiratory	3	2	6	3	
Urinary tract	5	2	2	4	
Soft tissue	0	3	1	0	
<b>Treatment characteristic</b>					
≥2 active agents <sup>d</sup> (n [%])	5 (38) <sup>e</sup>	10 (40) <sup>f</sup>	9 (30)	8 (20)	0.28
Time to active treatment (median [IQR])	55.7 (25–67)	52.5 (28–64)	67.9 (30–133)	65.0 (35–95)	0.23
Duration of treatment (median days [range])	13 (5–23)	12 (3–28)	14 (3–96)	10 (3–47)	0.31

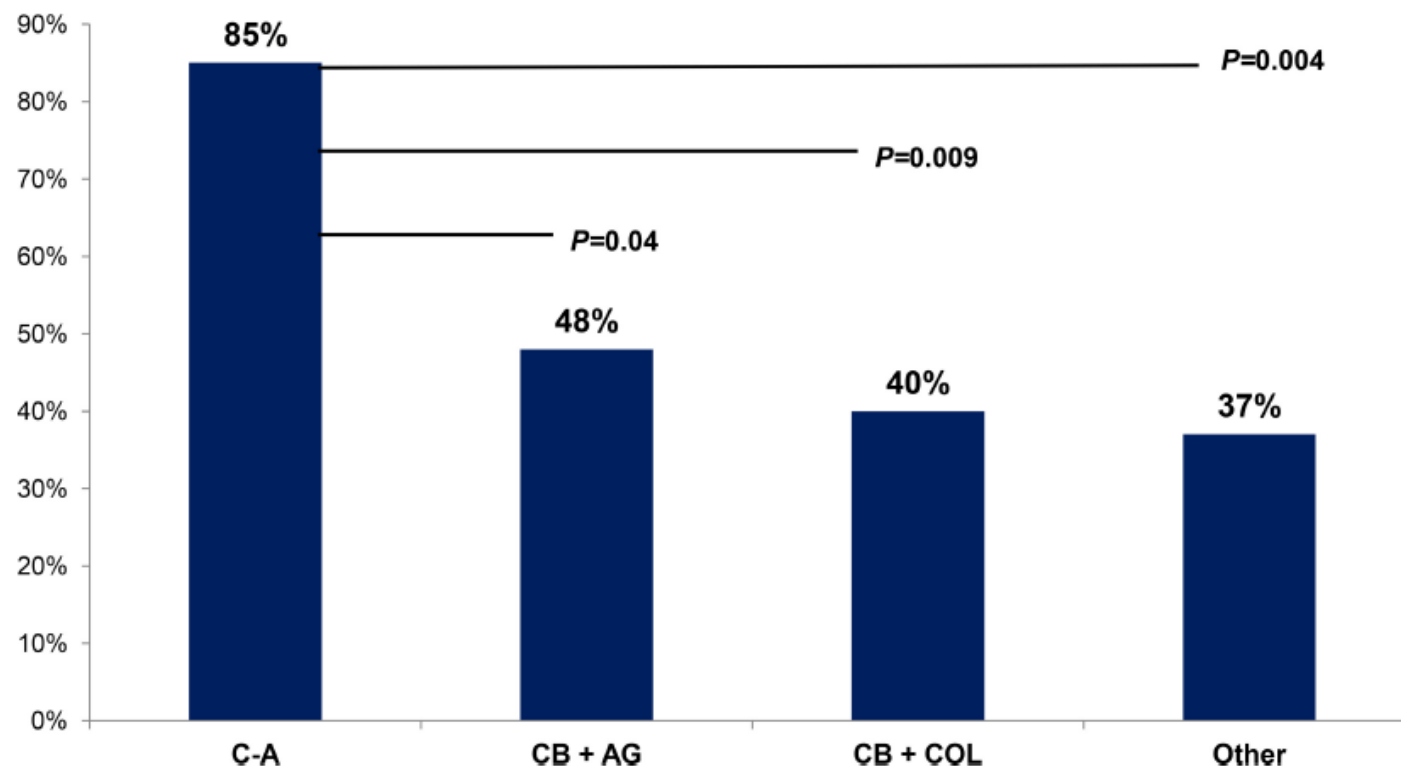


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Characteristic <sup>a</sup>	Treatment group <sup>b</sup>				P value
	C-A (n = 13)	CB+AG (n = 25)	CB+COL (n = 30)	Other <sup>c</sup> (n = 41)	
<b>Patient outcome</b>					
Clinical success (n [%])	11 (85)	12 (48)	12 (40)	15 (37)	0.02 <sup>g</sup>
30-Day survival (n [%])	12 (92)	17 (68)	21 (70)	28 (68)	0.37
90-Day survival (n [%])	12 (92)	14 (56)	19 (63)	20 (49)	0.04 <sup>h</sup>



- In multivariate analysis, treatment with ceftazidime-avibactam was independently associated with clinical success (aOR = 8.64, 95% CI: 1.61 – 46.39;  $P=0.01$ )

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*Clinical Infectious Diseases*

## MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

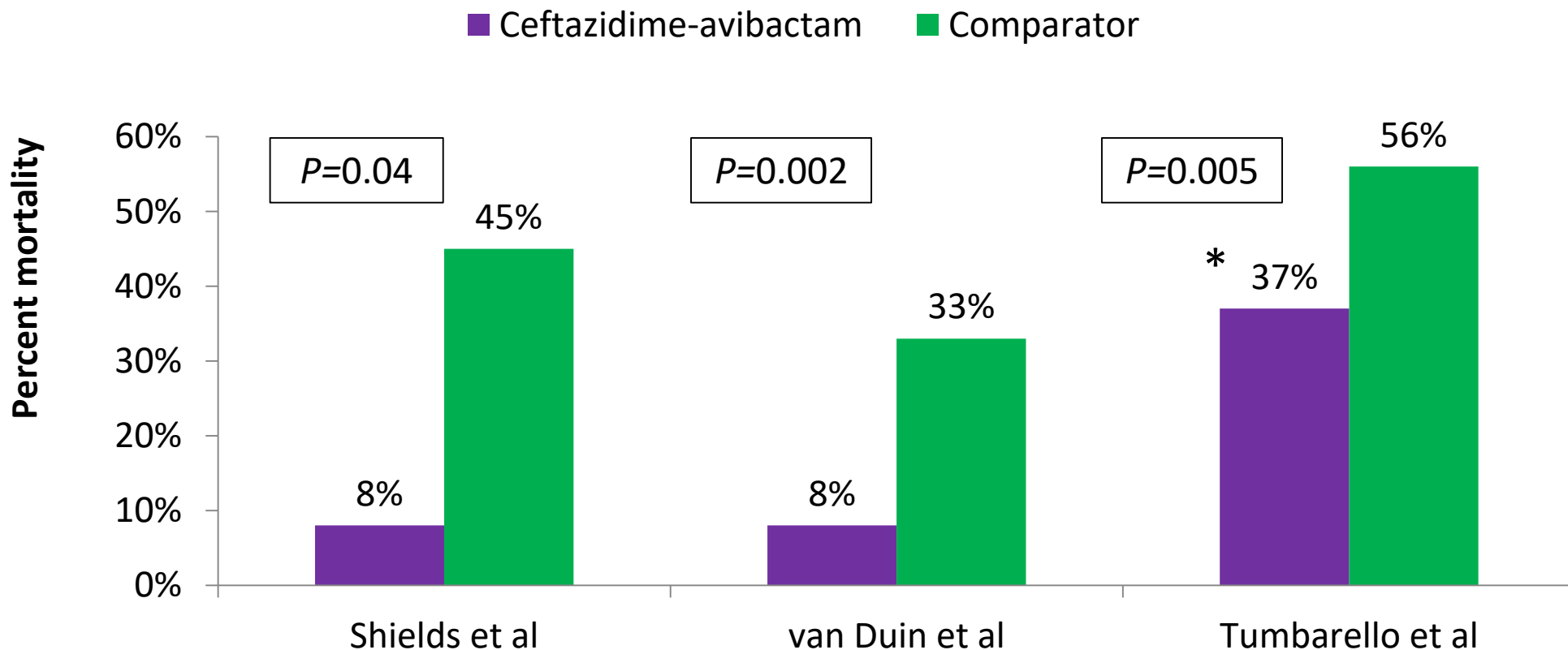
David van Duin, Judith J. Lok, Michelle Earley, Eric Cober, Sandra S. Richter, Federico Perez, Robert A. Salata, Robert C. Kalayjian, Richard R. Watkins, Yohei Doi, Keith S. Kaye, Vance G. Fowler Jr, David L. Paterson, Robert A. Bonomo, and Scott Evans for the Antibacterial Resistance Leadership Group

*Clinical Infectious Diseases*

## MAJOR ARTICLE

Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by KPC-producing *Klebsiella pneumoniae*

Mario Tumbarello, Enrico Maria Trearichi, Alberto Corona, Francesco Giuseppe De Rosa, Matteo Bassetti, Cristina Mussini, Francesco Menichetti, Claudio Viscoli, Caterina Compoli, Mario Venditti, Andrea De Gasperi, Alessandra Mularoni, Carlo Tascini, Giustino Parruti, Carlo Pallotto, Simona Sica, Ercole Concia, Rosario Cultrera, Gennaro De Pascale, Allesandro Capone, Spinello Antinori, Silvia Corcione, Elda Righi, Angela Raffaella Losito, Margherita Digaetano, Francesco Amadori, Daniele Roberto Giacobbe, Giancarlo Ceccarelli, Ernestina Mazza, Francesca Raffaelli, Teresa Spanu, Roberto Cauda, Pierluigi Viale



Data are almost exclusively against KPC-producing *K. pneumoniae*!

\* Used as salvage therapy

# Ceftazidime-avibactam: Summary

- Provides “broad-spectrum” CRE activity
  - KPC, OXA-48, NDM (+ aztreonam), and non-CP CRE (AmpC + porin)
  - Baseline (pre-exposure) resistance is rare in the U.S.
- Important addition to the CRE treatment armamentarium
  - Improved efficacy and safety compared to salvage treatment
- But....reports of resistance are increasing...!

Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections

Ryan K. Shields, M. Hong Nguyen, Liang Chen, Ellen G. Press, Barry N. Kreiswirth, Cornelius J. Clancy  
University of Pittsburgh, Pittsburgh, Pennsylvania, USA

*Clinical Infectious Diseases*

## BRIEF REPORT

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant *Enterobacteriaceae* Infections

Ryan K. Shields,<sup>1,3,4,\*</sup> Brian A. Potoski,<sup>1,2,3,\*</sup> Ghady Haidar,<sup>1</sup> Binghua Hao,<sup>4</sup> Yohei Doi,<sup>1</sup> Liang Chen,<sup>5</sup> Ellen G. Press,<sup>1</sup> Barry N. Kreiswirth,<sup>6</sup> Cornelius J. Clancy,<sup>1,4,5</sup> and M. Hong Nguyen<sup>1,3,4</sup>

## Ceftazidime-avibactam as first-line treatment for CRE infections

- **77 consecutive patients treated for CRE infections:**
  - Median age: 62 years (19–91)
  - 26% (20/77) transplant recipients
  - Median SOFA: 5 (0–20)
- Infections included: HAP/VAP (n=33), BSI (n=20), UTI (n=8), cIAI (n=7), others (n=9)
- CRE pathogens included: *K. pneumoniae* (n=60), *E. coli* (n=9), *Enterobacter spp.* (n=6), other (n=2)
  - 100% susceptible to ceftazidime–avibactam at baseline; median MIC = 1 µg/mL
  - 93% *K. pneumoniae* harbored *bla*<sub>KPC</sub>
- 69% received ceftazidime–avibactam as monotherapy

# Real-world experience with ceftazidime–avibactam

**Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections**

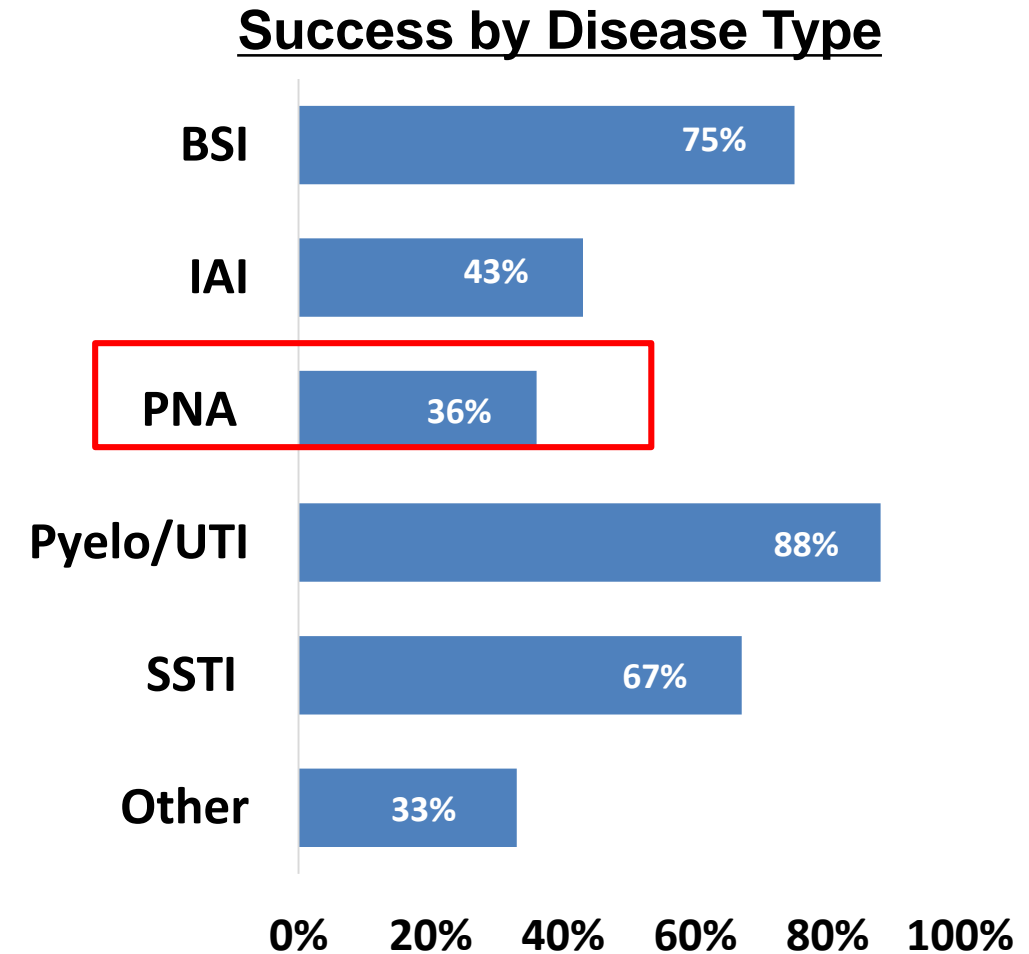
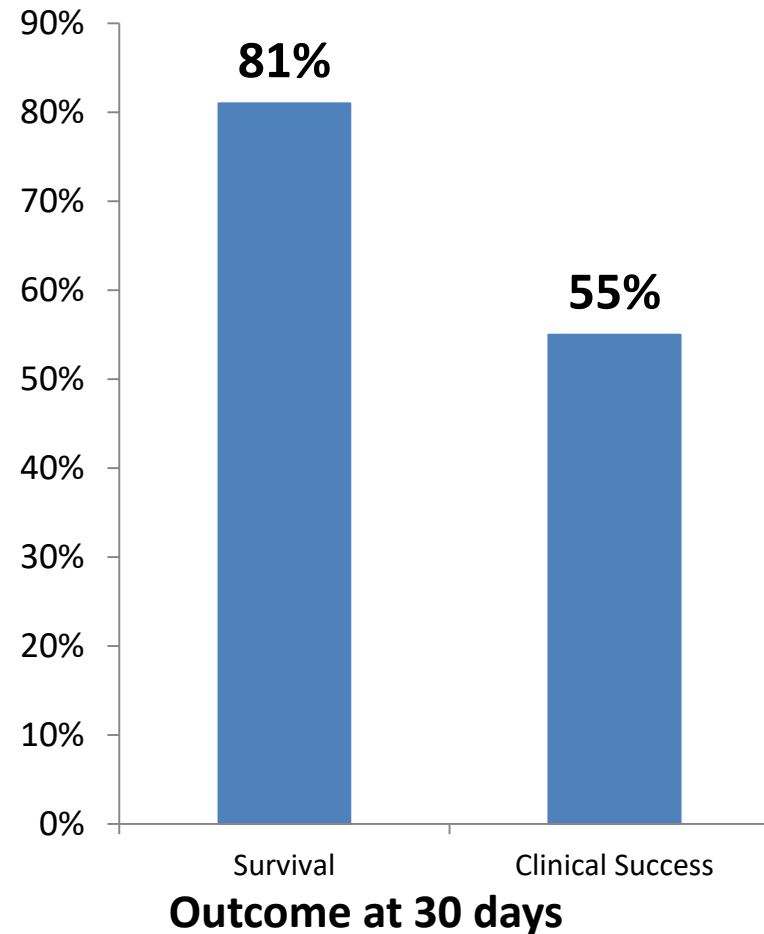
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University of Pittsburgh, Pittsburgh, Pennsylvania, USA

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**Pneumonia (aOR=3.09) and receipt of renal replacement therapy (aOR=4.78) were risk factors for clinical failure**

# Real-world experience with ceftazidime–avibactam

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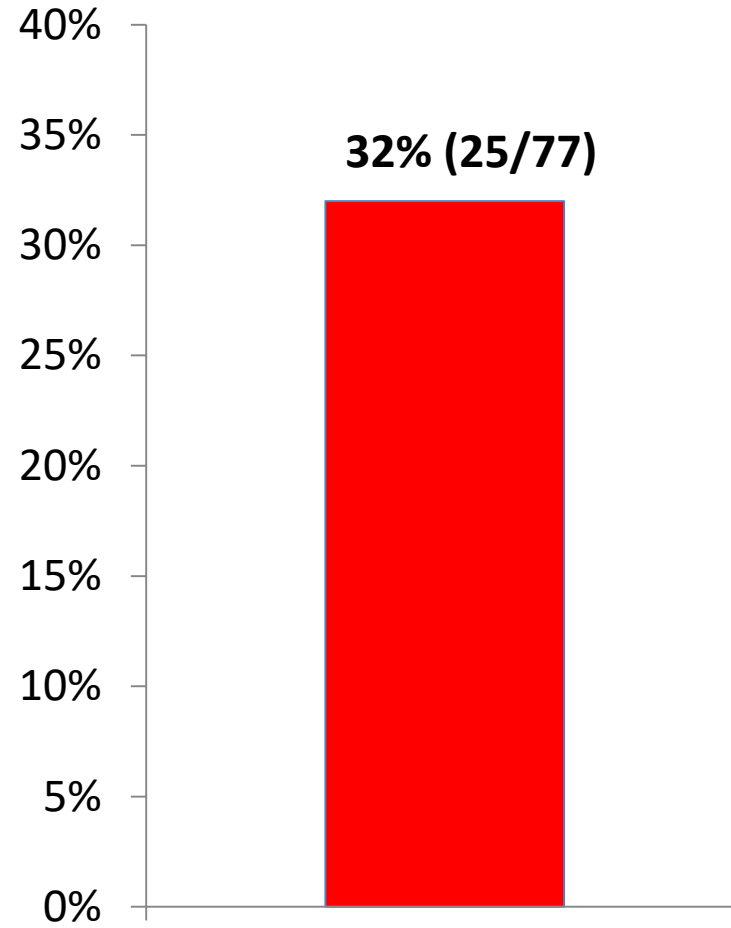
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### Clinical Infectious Diseases

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Outcome at 90 days

- Microbiologic failures
  - 3 *E. coli*
  - 22 *K. pneumoniae*
    - 8 KPC-2
    - 14 KPC-3
- 32% developed resistance
- Rates of ceftazidime-avibactam resistance
  - 10% overall
  - 14% of *K. pneumoniae*
  - 22% of KPC-3 *K. pneumoniae*

# Emergence of ceftazidime–avibactam resistance

## Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections

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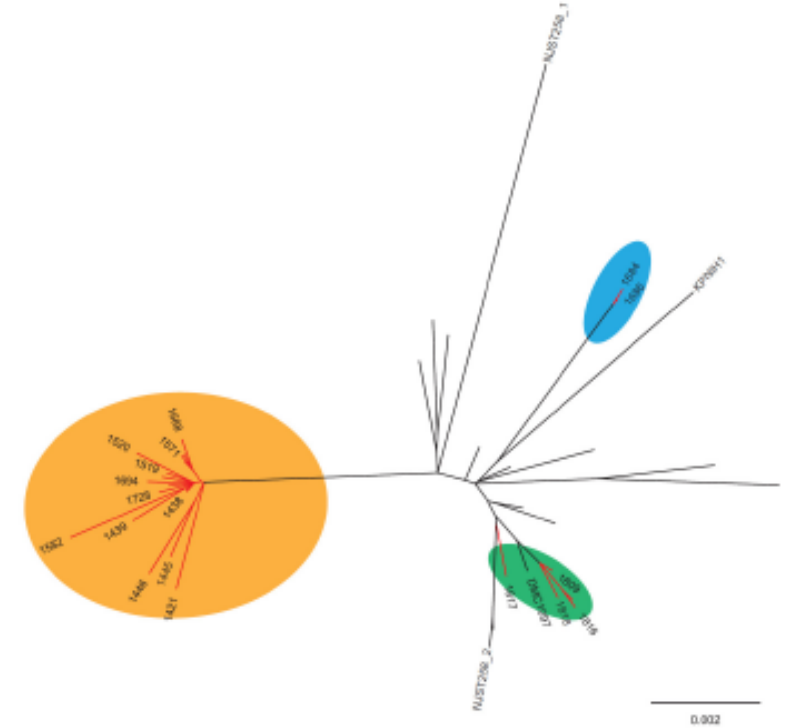
## Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *bla*<sub>KPC-3</sub> Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections

Ryan K. Shields,<sup>2,3</sup> Liang Chen,<sup>5</sup> Shaoli Cheng,<sup>2</sup> Kalyan D. Chavda,<sup>5</sup> Ellen G. Press,<sup>2</sup> Avin Snyder,<sup>2</sup> Ruchi Pandey,<sup>5</sup> Yohel Dol,<sup>2</sup> Barry N. Kreiswirth,<sup>5</sup> M. Hong Nguyen,<sup>2,3</sup> Cornelius J. Clancy<sup>2,3,4</sup>

## • Key features of ceftazidime–avibactam resistance in the clinic:

- Emerges in ~10% of patients following 7–19 days of ceftazidime–avibactam therapy
  - 22% of KPC-3 producing *K. pneumoniae* (compared to 0% with KPC-2)
- Receipt of renal replacement therapy is an independent risk factor for the emergence of ceftazidime-avibactam resistance (aOR=26.67; *P*=0.009)
- Identified among isolates clustered within a novel ST258 clade II sublineage
  - Due to *bla*<sub>KPC</sub> mutations

Figure 1. Phylogenetic comparison of ST258 *K. pneumoniae* isolates from our center and others in the United States



# Emergence of ceftazidime–avibactam resistance

Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *bla*<sub>KPC-3</sub> Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections

Ryan K. Shields,<sup>a,b</sup> Liang Chen,<sup>c</sup> Shaoji Cheng,<sup>a</sup> Kalyan D. Chavda,<sup>c</sup> Ellen G. Press,<sup>a</sup> Avin Snyder,<sup>a</sup> Ruchi Pandey,<sup>c</sup> Yohei Doi,<sup>a</sup> Barry N. Kreiswirth,<sup>c</sup> M. Hong Nguyen,<sup>a,b</sup> Cornelius J. Clancy<sup>a,b,d</sup>

Journal of Antimicrobial Chemotherapy

Activity of ceftazidime/avibactam against isogenic strains of *E. coli* containing KPC and SHV  $\beta$ -lactamases with single amino acid substitutions in the  $\Omega$ -loop

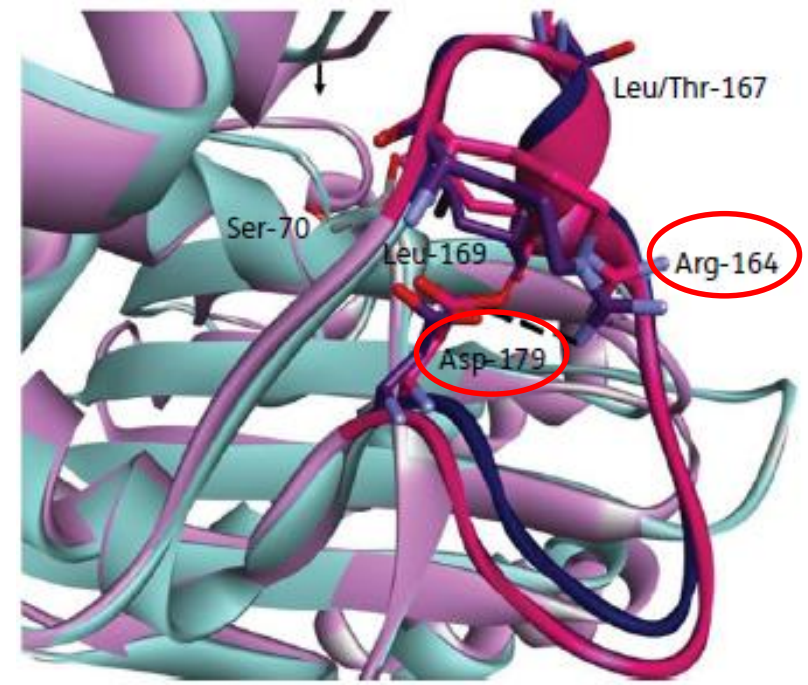
Marissa L. Winkler, Kristina M. Papp-Wallace, Roberta A. Bonomo  
Case Western Reserve University, Cleveland, Ohio, USA

*Klebsiella pneumoniae* Carbapenemase-2 (KPC-2), Substitutions at Ambler Position Asp179, and Resistance to Ceftazidime-Avibactam: Unique Antibiotic-Resistant Phenotypes Emerge from  $\beta$ -Lactamase Protein Engineering

Melissa D. Barnes,<sup>a,b</sup> Marisa L. Winkler,<sup>a,c</sup> Magdalena A. Taracila,<sup>a,b</sup> Malcolm G. Page,<sup>b</sup> Eric Desarbre,<sup>a</sup> Barry N. Kreiswirth,<sup>a</sup> Ryan K. Shields,<sup>a</sup> Minh-Hong Nguyen,<sup>a</sup> Cornelius Clancy,<sup>a</sup> Brad Spellberg,<sup>1,m</sup> Kristina M. Papp-Wallace,<sup>a,b,n,f</sup> Robert A. Bonomo<sup>a,b,c,d,e,f,g</sup>

- Resistance is predominantly due to mutations in KPC-3  $\Omega$ -loop
  - Validated through gene disruption, plasmid transfer, and *bla*<sub>KPC</sub> cloning into *E. coli*
- Mechanism identified among patients is consistent with:
  - Prior *in vitro* passage experiments
  - Biochemical characterization of isogenic *E. coli* and *K. pneumoniae*
- Substitutions result in:
  - Enhanced ceftazidime affinity
  - Preferential binding “traps” CAZ
  - Prevent binding of avibactam

	R164	167	L169					D179									
SHV-1	D	R	W	E	T	E	L	N	E	A	L	P	G	D	A	R	D
KPC-2	D	R	W	E	L	E	L	N	S	A	I	P	G	D	A	R	D
CTXM-15	D	R	T	E	P	T	L	N	T	A	I	P	G	D	P	R	D
TEM-1	D	R	W	E	P	E	L	N	E	A	I	P	N	D	E	R	D



Winkler ML, et al. *JAC* 2015;70:2279

# Emergence of ceftazidime–avibactam resistance

Mutations in *bla*<sub>KPC-3</sub> That Confer Ceftazidime-Avibactam Resistance Encode Novel KPC-3 Variants That Function as Extended-Spectrum β-Lactamases

Ghady Haidar,<sup>a</sup> Cornelius J. Clancy,<sup>b,c,d</sup> Ryan K. Shields,<sup>b,c</sup> Binghua Hao,<sup>c</sup> Shaoli Cheng,<sup>b</sup> M. Hong Nguyen<sup>a,b,c</sup>

Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections

Ryan K. Shields, M. Hong Nguyen, Liang Chen, Ellen G. Press, Barry N. Kreiswirth, Cornelius J. Clancy  
University of Pittsburgh, Pittsburgh, Pennsylvania, USA

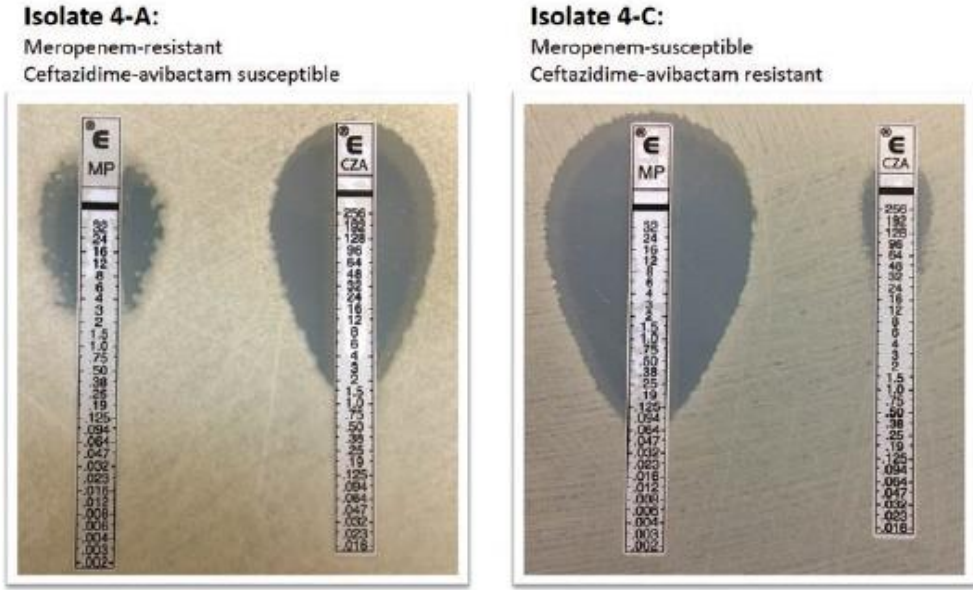
Open Forum Infectious Diseases

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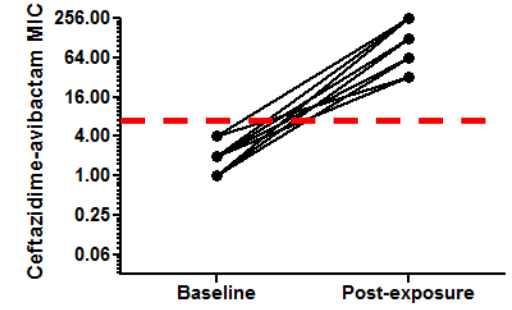
Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in *Klebsiella pneumoniae* Carbapenemase-Producing *K pneumoniae*: A Case Report and Review of Literature

Ryan K. Shields,<sup>1,2</sup> M. Hong Nguyen,<sup>1,2</sup> Ellen G. Press,<sup>1</sup> Liang Chen,<sup>3</sup> Barry N. Kreiswirth,<sup>3</sup> and Cornelius J. Clancy<sup>1,2,4</sup>

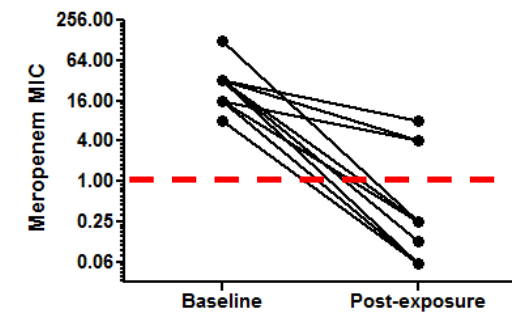
- Key features of ceftazidime–avibactam resistance in the clinic:
  - Associated with a reversion of carbapenem susceptibility
    - Carbapenem MICs are decreased 4–32 fold



Ceftazidime-avibactam MICs



Meropenem MICs



Are you testing ESBLs for CAZ-AVI susceptibility?

# Emergence of ceftazidime–avibactam resistance

Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *bla*<sub>KPC-3</sub> Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections

Ryan K. Shields,<sup>2,b</sup> Liang Chen,<sup>5</sup> Shaoji Cheng,<sup>2</sup> Kalyan D. Chavda,<sup>5</sup> Ellen G. Press,<sup>2</sup> Avin Snyder,<sup>2</sup> Ruchi Pandey,<sup>5</sup> Yohei Doi,<sup>2</sup> Barry N. Kreiswirth,<sup>5</sup> M. Hong Nguyen,<sup>2,b</sup> Cornelius J. Clancy<sup>2,b,d</sup>

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Ryan K. Shields, M. Hong Nguyen, Liang Chen, Ellen G. Press, Barry N. Kreiswirth, Cornelius J. Clancy  
University of Pittsburgh, Pittsburgh, Pennsylvania, USA

- Resistance phenotypes vary by *bla*<sub>KPC</sub> mutation

Cloned KPC variant*	MIC (µg/mL)	
	CAZ-AVI	MERO
pBC-SK alone	0.25	0.03
Wild-type KPC-2	1	16
Wild-type KPC-3	1	16
D179Y	>64	0.06
A177E, D179Y	>64	0.06
D179Y, T243M	>64	0.25
V240G	32	4
168 - 169 EL del	16	0.06
169 - 170 EL ins	8	1
A177E	4	16
T243A	2	2
169 – 170 EL ins; 278 - 281 SEAV ins	64	0.06

\* Cloned into *E. coli* TOP10

Introduction of *bla*<sub>KPC</sub> mutations results in:

- 2 to >64-fold increase in CAZ-AVI MICs
- 0 to 256-fold decrease in meropenem MICs

Meropenem MICs may still be elevated in the presence of *ompK36* porin mutations

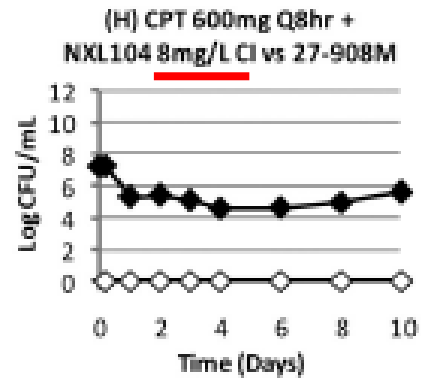
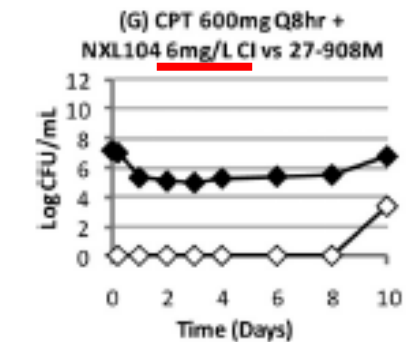
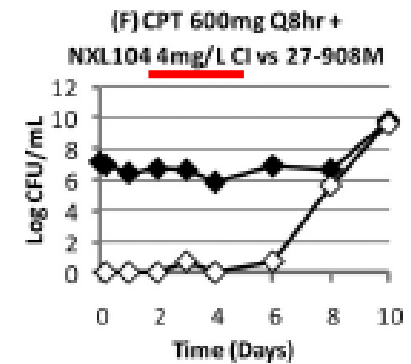
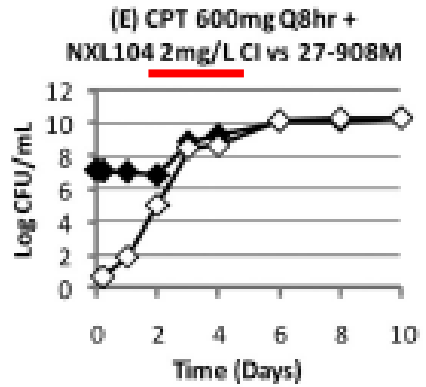
# Patient factors associated with CAZ-AVI resistance

- Resistance has emerged in 13 patients at UPMC
  - 11 with ST258 KPC-3 *K. pneumoniae*
  - 1 with ST258 KPC-2 *K. pneumoniae*
  - 1 with KPC-3 *E. coli*
- Treatment courses ranged from 7 – 52 days prior to the emergence of resistance
- 77% (10/13) had CRE HAP/VAP
- 62% (8/13) received renal replacement therapy

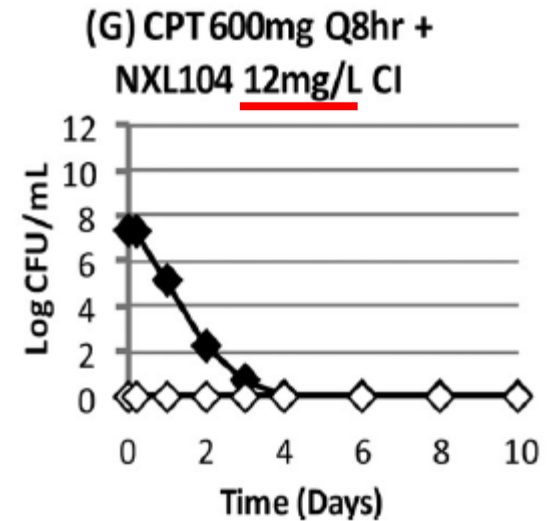
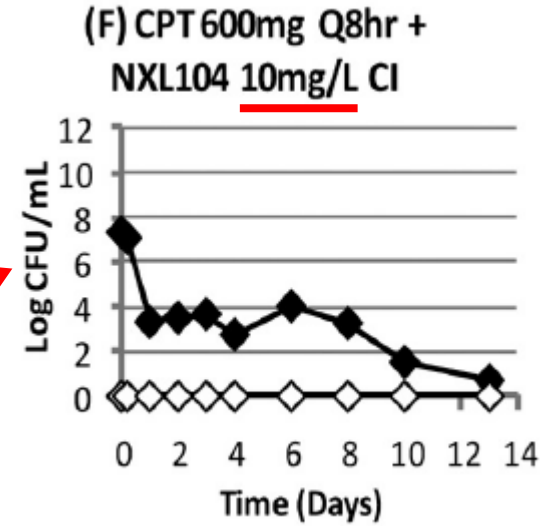


Are we giving enough drug?

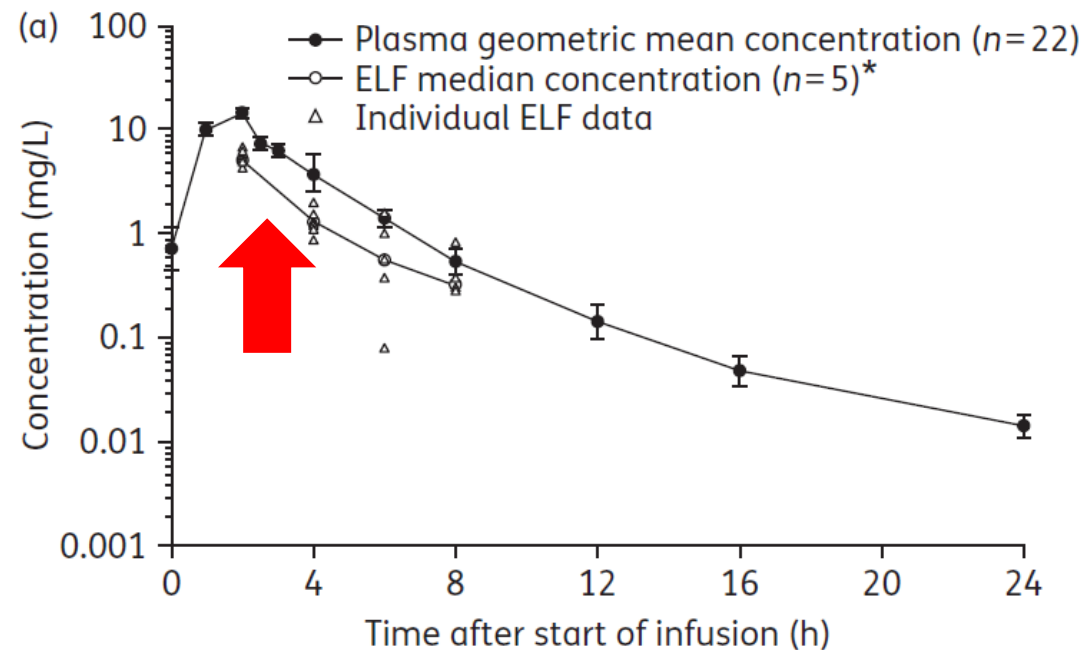
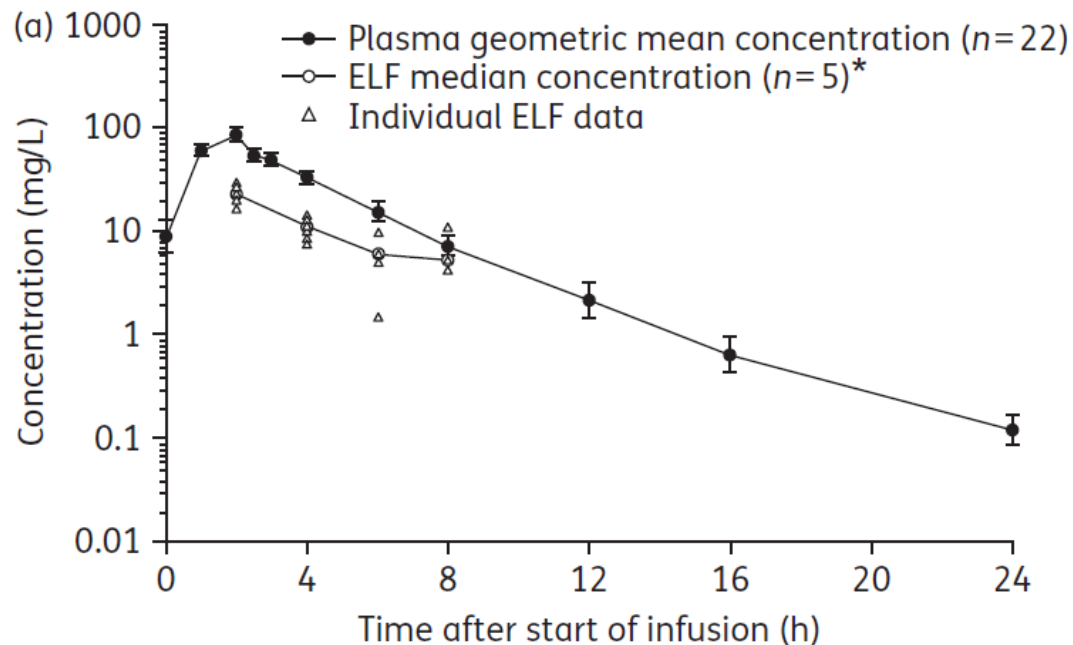
# Are we giving enough avibactam?



Need at least 8µg/mL to  
inhibit resistance  
amplification



# Do we achieve adequate exposures in patients?

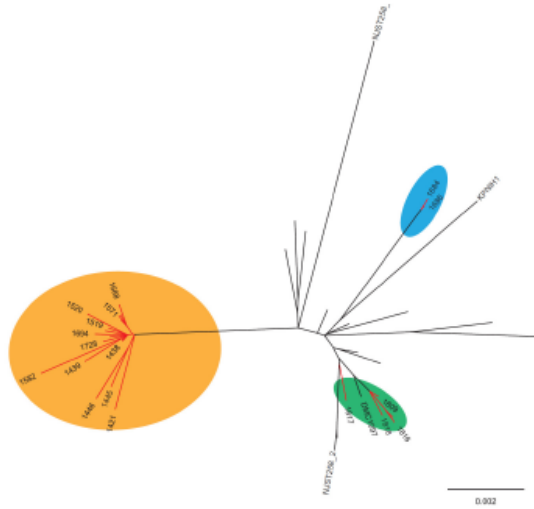


**Table 2.** Summary of key PK parameters of ceftazidime and avibactam (PK analysis set)

Parameter, cohort	AVI		CAZ	
	plasma	ELF, composite profile <sup>a</sup>	plasma	ELF, composite profile <sup>a</sup>
Geometric mean (CV, %) $C_{max}$ (mg/L)				
2000 mg of CAZ + 500 mg of AVI (n=22)	14.5 (9.7)	5.1	90.1 (13.3)	23.2
3000 mg of CAZ + 1000 mg of AVI (n=20)	28.5 (10.2)	7.9	140 (9.6)	32.7

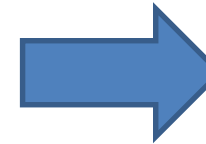
~30% of serum concentrations of ceftazidime-avibactam are detectable in epithelial lining fluid (ELF)

# ...or is this just a Pittsburgh thing?



Jason Gallagher  
@JGPharmD

As reported by @ryankshields CAZ-AVI resistance can lead to carbapenem susceptibility. This is a clinical isolate, so it doesn't just happen at @IDPittStop ! More on this issue here: [ncbi.nlm.nih.gov/pmc/articles/P...](https://ncbi.nlm.nih.gov/pmc/articles/P...)



Published  
(and unpublished)  
reports are  
increasing!

Culture & Susceptibility			
KLEBSIELLA PNEUMONIAE SSP PNEUMONIAE			
Antibiotic	Sensitivity	Susceptibility	Unit
Amikacin	Sensitive	=8	mcg/mL
Amoxicillin + Clavulanate	Resistant	>16	mcg/mL
Ampicillin + Sulbactam	Resistant	>16	mcg/mL
Aztreonam	Resistant	>16	mcg/mL
Cefazolin	Resistant	>32	mcg/mL
Cefepime	Resistant	>16	mcg/mL
Ceftazidime	Resistant	>16	mcg/mL
Ceftriaxone	Resistant	>32	mcg/mL
Ciprofloxacin	Resistant	>2	mcg/mL
Ertapenem	Sensitive	=0.25	mcg/mL
Extended B-Lactamase	Resistant		mcg/mL
Gentamicin	Sensitive	=2	mcg/mL
Levofloxacin	Resistant	>4	mcg/mL
Meropenem	Sensitive	=0.125	mcg/mL
Piperacillin + Tazobactam	Resistant	>64	mcg/mL
Tetracycline	Sensitive	=2	mcg/mL
Tobramycin	Intermediate	=8	mcg/mL
Trimethoprim + Sulfamethoxazole	Resistant	>2	mcg/mL

3:42 PM · 6/4/19 · TweetDeck

# Other reports of CAZ-AVI resistance

Author (Year)	Patient characteristics	CRE infection types	CRE pathogen (carbapenemase)	CAZ-AVI dose (days)	Concomitant therapy (days)	Renal replacement therapy	CAZ-AVI MIC (µg/mL)		KPC Variant <sup>a</sup>
							Baseline	Posttreatment	
<b>Giddins (2018)</b>	Late 40s with pancreatitis	BSI, cIAI, HAP/VAP	ST307 <i>K. pneumoniae</i> (KPC-2)	2.5 g IV q 8 h (12)	Tigecycline (12)	CRRT	3	>256	D179Y
<b>Gaibani (2018)</b>	Liver transplant recipient	BSI, HAP/VAP	ST1519 <i>K. pneumoniae</i> (KPC-3)	Not given (17)	Gentamicin (17)	None	8	>256	D179Y
<b>Both (2017)</b>	Mid 50s with inflammatory bowel disease	BSI, VAP/VAP	ST383 <i>K. pneumoniae</i> (OXA-48, CTX-M)	2.5 g IV q 8 h (54)	Meropenem (54)	None	1	8 – 32	Mutations in <i>bla</i> <sub>CTX-M</sub> 1) P170S, R277P 2) P170S, T264I
<b>Athans (2018)</b>	24 y/o liver transplant recipient	BSI, cIAI, HAP/VAP	ST258 <i>K. pneumoniae</i> (KPC-2)	2.5 g IV q 8 h (33)	Tigecycline (6)	None	2 – 4	128 - >256	D179Y
<b>Castanheira (2018)</b>	44 y/o kidney transplant recipient	BSI, cIAI	<i>C. freundii</i> (KPC-2)	2.5 g IV q 12 h (12)	Tigecycline (12), Amikacin (8)	CRRT	4	64	D179Y
<b>Raisanen (2019)</b>	Pt following MVA	BSI	ST39 <i>K. pneumoniae</i> (KPC-2)	Not reported (33)	Tigecycline (14), Fosfomycin (19)	Not reported	1	>16	15 AA ins at 259
<b>Hemarajata (2019)</b>	Late 40s male with ESLD	BSI, HAP/VAP	ST258 <i>K. pneumoniae</i> (KPC-2)	0.94g IV q24h (10)	Gentamicin (10)	CRRT	0.5	16	L169P
<b>Venditti (2019)</b>	Not reported	BSI	ST512 <i>K. pneumoniae</i> (KPC-3)	Not reported (19)	Colistin (19)	Not reported	2	32	L169P

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Athans (2018)	24 y/o liver transplant recipient	BSI, cIAI, HAP/VAP	ST258 K. pneumoniae (KPC-2)	2.5 g IV q 8 h (33)	Various KPC K. pneumoniae STs have been implicated			128 - >256	D179Y
Castanheira (2018)	44 y/o kidney transplant recipient	BSI, cIAI	C. freundii (KPC-2)	2.5 g IV q 12h (12)				Tigecycline (12), Amikacin (8)	CRRT
Raisanen (2019)	Pt following MVA	BSI	<u>ST39</u> K. pneumoniae (KPC-2)	Not reported (33)	Tigecycline (14), Fosfomycin (19)	Not reported	1	>16	15 AA ins at 259
Hemarajata (2019)	Late 40s male with ESLD	BSI, HAP/VAP	ST258 K. pneumoniae (KPC-2)	0.94g IV q24h (10)	Gentamicin (10)	CRRT	0.5	16	L169P
Venditti (2019)	Not reported	BSI	<u>ST512</u> K. pneumoniae (KPC-3)	Not reported (19)	Colistin (19)	Not reported	2	32	L169P

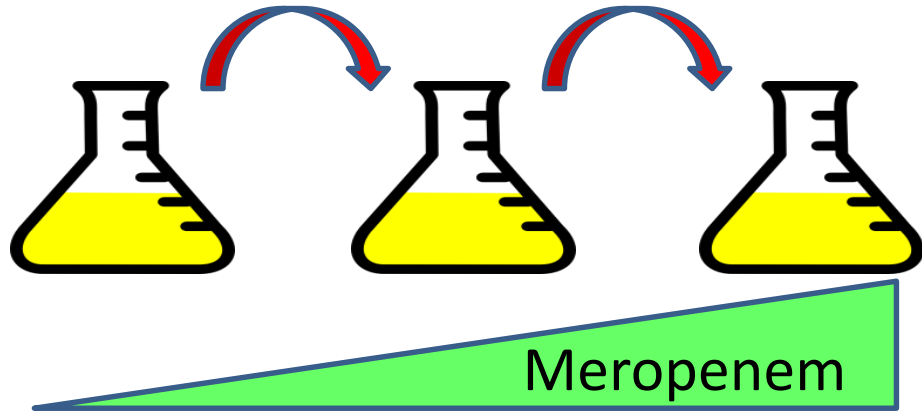
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							Baseline	Posttreatment	
<b>Giddins (2018)</b>	Late 40s with pancreatitis	BSI, cIAI, HAP/VAP	ST307 <i>K. pneumoniae</i> (KPC-2)	2.5 g IV q 8 h (12)	Tigecycline (12)	CRRT	3	>256	D179Y
<b>Gaibani (2018)</b>	Liver transplant recipient	BSI, HAP/VAP	ST1519 <i>K. pneumoniae</i> (KPC-3)	Not given (17)	Gentamicin (17)	None	8	>256	D179Y
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<b>Athans (2018)</b>	24 y/o liver transplant recipient	BSI, cIAI, HAP/VAP	<b>HAP/VAP and RRT remain common factors</b>			None	2 – 4	128 - >256	D179Y
<b>Castanheira (2018)</b>	44 y/o kidney transplant recipient	BSI, cIAI	<i>C. freundii</i> (KPC-2)	2.5 g IV q 12 h (12)	Tigecycline (12), Amikacin (8)	CRRT	4	64	D179Y
<b>Raisanen (2019)</b>	Pt following MVA	BSI	ST39 <i>K. pneumoniae</i> (KPC-2)	Not reported (33)	Tigecycline (14), Fosfomycin (19)	Not reported	1	>16	15 AA ins at 259
<b>Hemarajata (2019)</b>	Late 40s male with ESLD	BSI, HAP/VAP	ST258 <i>K. pneumoniae</i> (KPC-2)	0.94g IV q24h (10)	Gentamicin (10)	CRRT	0.5	16	L169P
<b>Venditti (2019)</b>	Not reported	BSI	ST512 <i>K. pneumoniae</i> (KPC-3)	Not reported (19)	Colistin (19)	Not reported	2	32	L169P

# Summarizing ceftazidime-avibactam resistance

- Emergence of resistance and KPC mutations are concerning
  - Potential byproduct of prolonged survival
  - Occurs in ~10% of patients after courses ranging from 7 – 52 days
  - Pneumonia and renal replacement therapy are common factors
  - May be identified as an ESBL by your micro lab
  - Reports are increasing with frequency!
- Strategies to treat or suppress resistance are unknown
  - What is the biological impact of restored carbapenem susceptibility?

# Is meropenem resistance restored with re-exposure?



Serial passage daily for 42 days +  
**MEROPENEM 0.25x MIC**  
 (3 colonies/isolate)

Clinical isolate	<i>bla</i> <sub>KPC</sub> genotype	Meropenem MIC (µg/mL)							
		Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	FINAL
Pt 4 – A	KPC-3	16							
Pt 1 – C	D179Y, T243M	0.5							
Pt 2 – B	V240G	8							
Pt 3 – C	D179Y	0.25							
Pt 4 - B	A177E, D179Y	0.25							

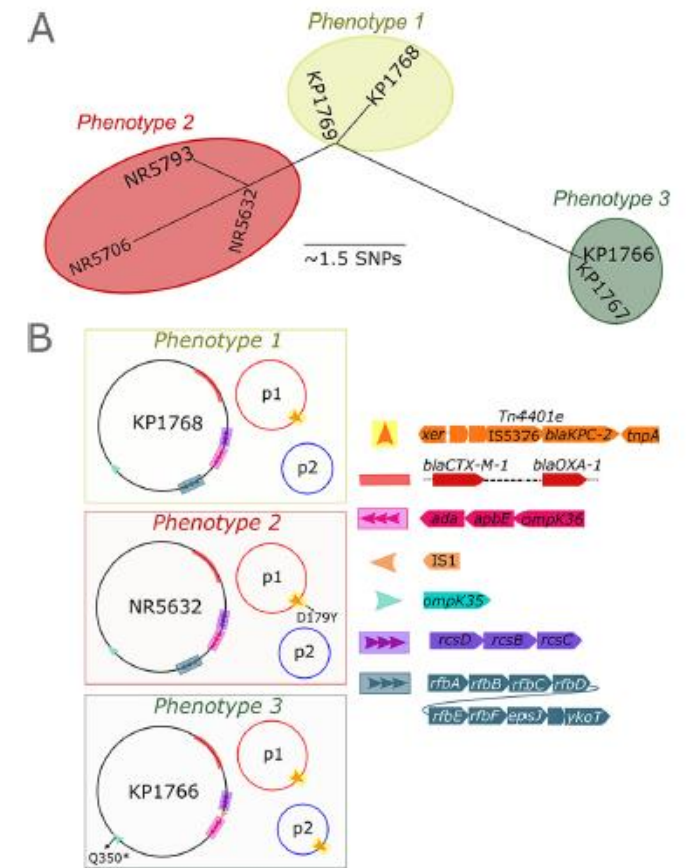
Meropenem MICs increased significantly for all *bla*<sub>KPC-3</sub> genotypes; 50% harbored *ompK36* mutations

# Carbapenem treatment for ceftazidime–avibactam resistance

## Successive Emergence of Ceftazidime-Avibactam Resistance through Distinct Genomic Adaptations in *bla*<sub>KPC-2</sub>-Harboring *Klebsiella pneumoniae* Sequence Type 307 Isolates

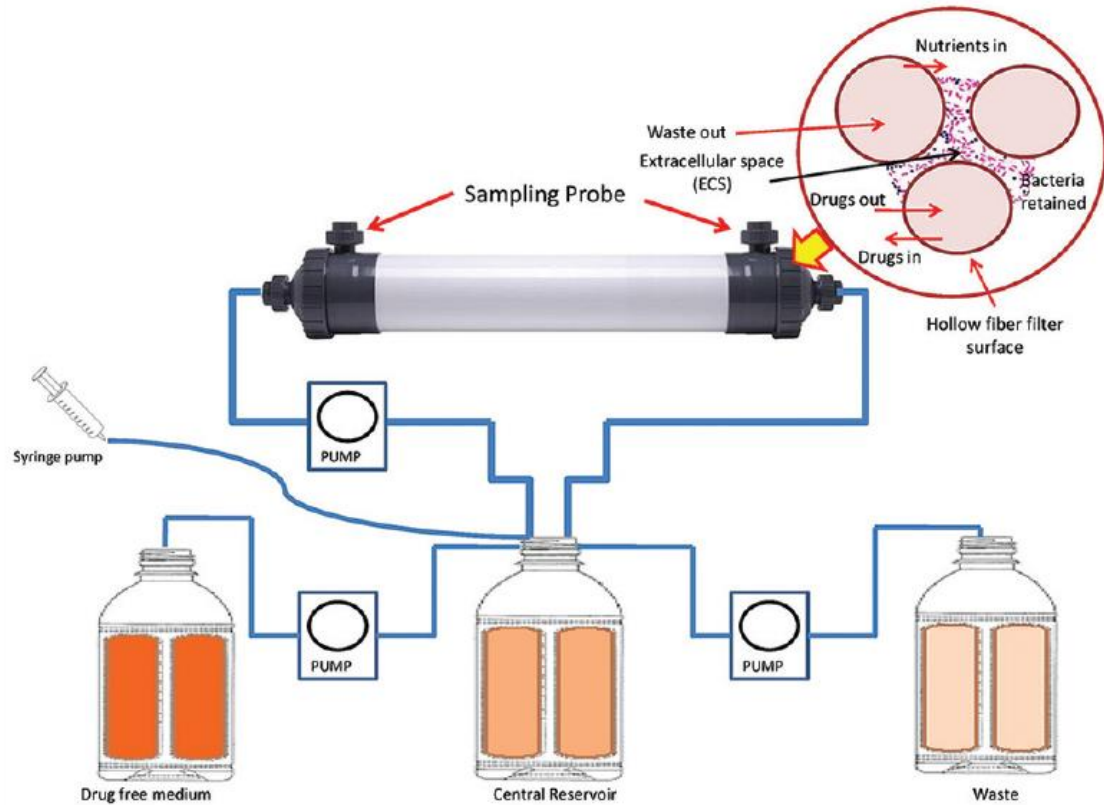
Marla J. Giddins, Nenad Macesic, Medini K. Annavajhala, Stephania Stump, Sabrina Khan, Thomas H. McConville, Monica Mehta, Angela Gomez-Simmonds, Anne-Catrin Uhlemann  
Columbia University Medical Center, New York, New York, USA

- Ceftazidime–avibactam treatment was initiated in a patient with cIAI due to carbapenem resistant *K. pneumoniae* (Phenotype 1)
- Resistance emerged after 12 days of therapy (Phenotype 2)
  - Ceftazidime-avibactam MIC = >256; Meropenem MIC = 2 µg/ml
  - ST307, KPC-2 *K. pneumoniae* with D179Y mutation in Ω-loop
- Patient was retreated with meropenem + polymyxin B
  - CR *K. pneumoniae* re-emerged in blood cultures (Phenotype 3)



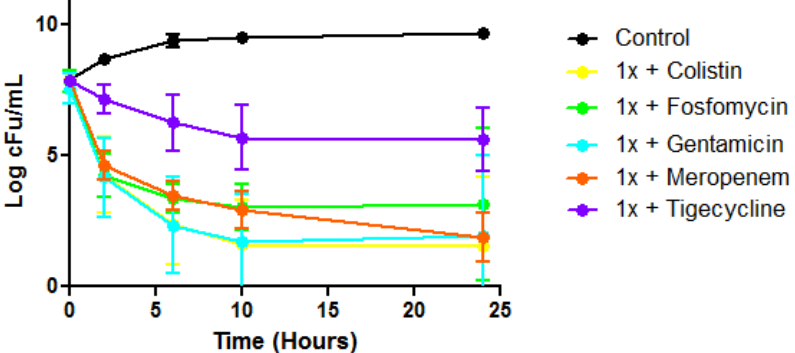
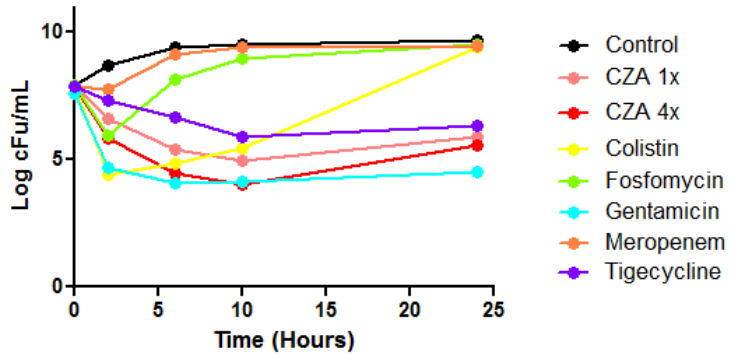
**FIG 1** Schematic representation of genomic adaptations during evolution of CAZ-AVI resistance in *K. pneumoniae* ST307. (A) Neighbor-joining phylogenetic tree illustrating that all three phenotypes had closely related core chromosomes. Phenotype 2 and 3 isolates arose independently from the phenotype 1 isolate. (B) Phenotype 2 isolates (CAZ-AVI resistant, MER susceptible) acquired a D179Y mutation in KPC-2. Phenotype 3 isolates harbored wild-type *bla*<sub>KPC-2</sub> in plasmid 1 as well as a second copy that was translocated as part of the Tn4401e cassette to the smaller plasmid. Additional adaptations included deletion of the *rfb* gene locus (green) and an insertion of *IS1* between the *rcs* locus and *ompK36* at position -48 bp.

# Can you combine ceftazidime-avibactam and meropenem to suppress resistance?

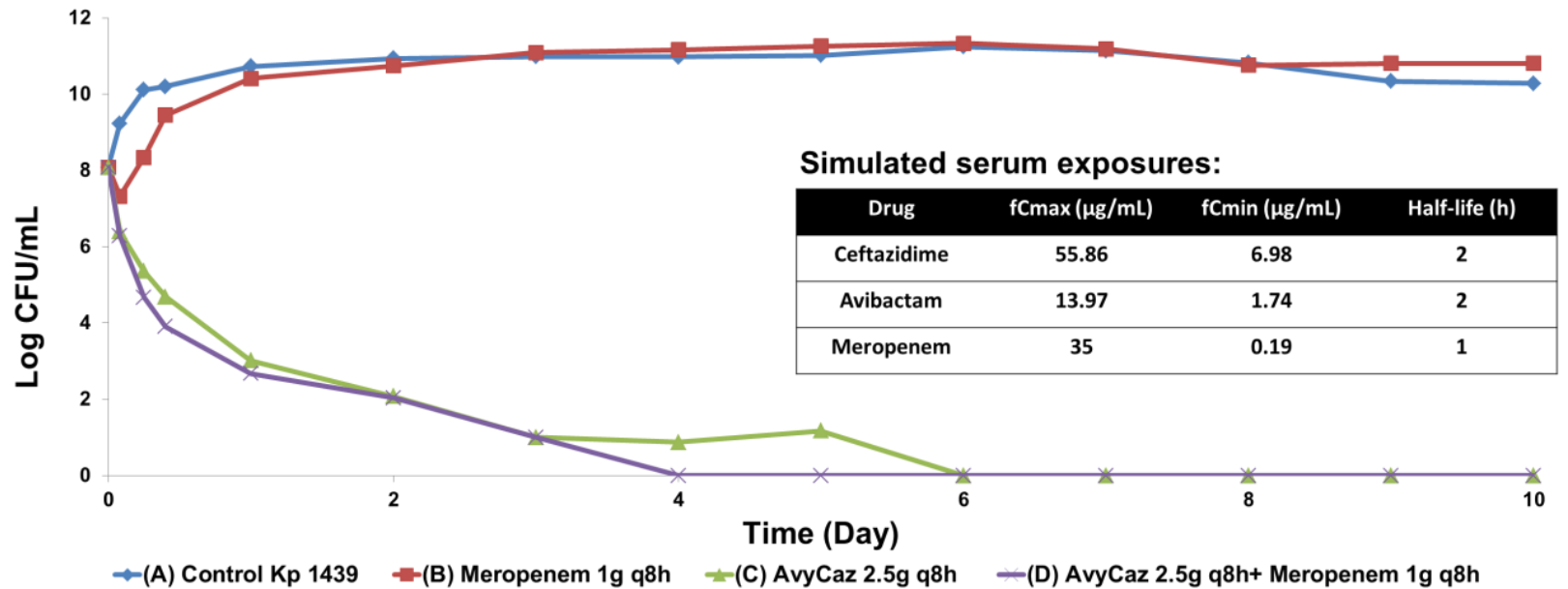


# Antibiotic combination studies

- Combination regimens that suppress the emergence of ceftazidime-avibactam resistance



Humanized serum exposures of ceftazidime-avibactam against a baseline KPC-3 *K. pneumoniae* isolate



Simulated serum exposures:

Drug	fCmax (µg/mL)	fCmin (µg/mL)	Half-life (h)
Ceftazidime	55.86	6.98	2
Avibactam	13.97	1.74	2
Meropenem	35	0.19	1

# Antibiotic combination studies

- Importance of site-specific PK exposures

AMERICAN SOCIETY FOR MICROBIOLOGY Antimicrobial Agents and Chemotherapy®

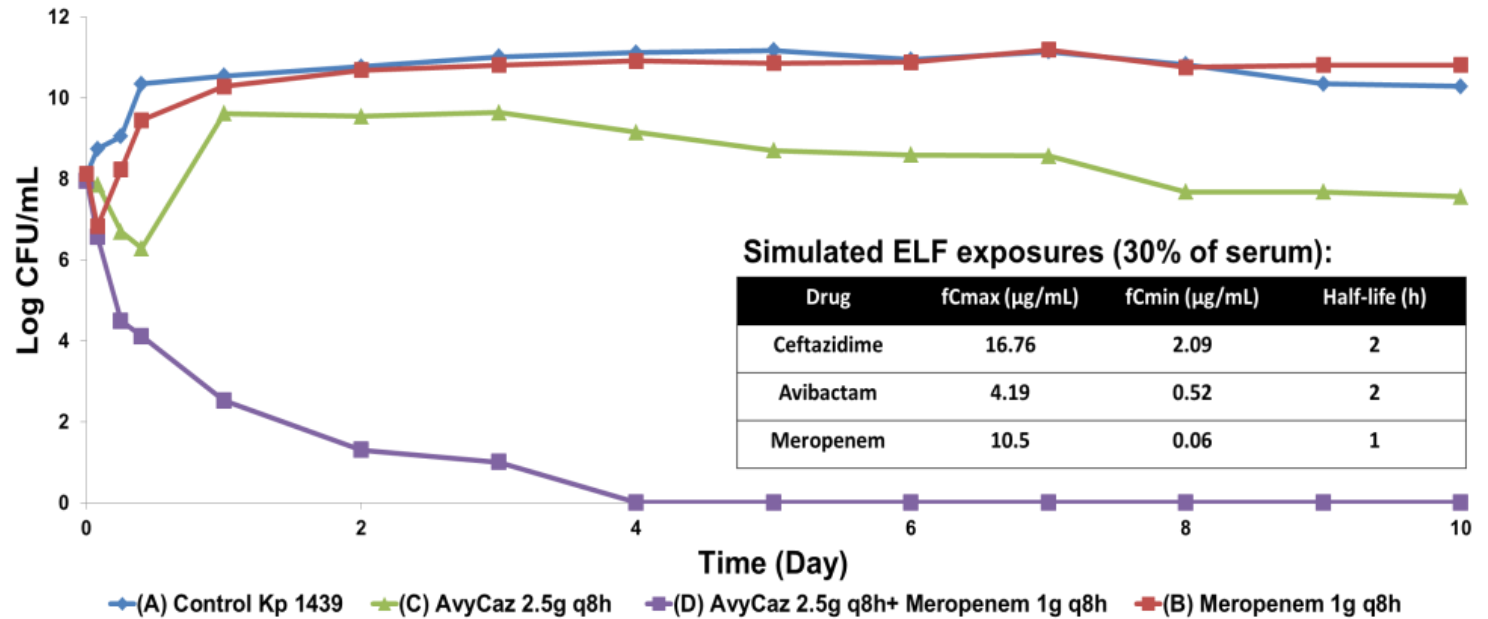
CLINICAL THERAPEUTICS



Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections

Ryan K. Shields,<sup>a,b</sup> M. Hong Nguyen,<sup>a,b</sup> Liang Chen,<sup>c</sup> Ellen G. Press,<sup>a</sup> Barry N. Kreiswirth,<sup>c</sup> Cornelius J. Clancy<sup>a,b,d</sup>

## Humanized ELF exposures of ceftazidime-avibactam against a baseline KPC-3 *K. pneumoniae* isolate

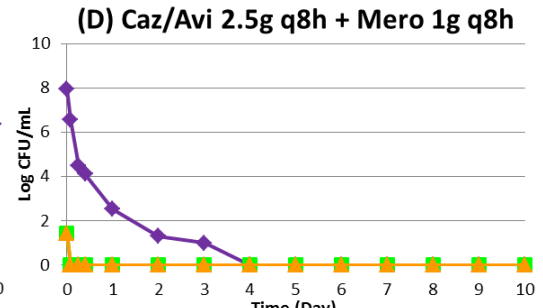
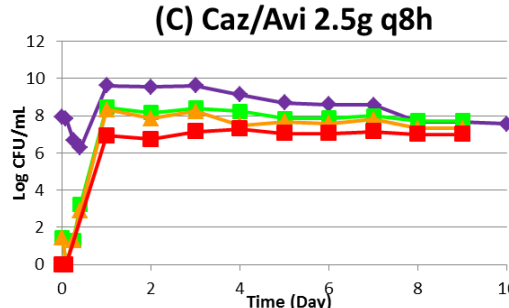
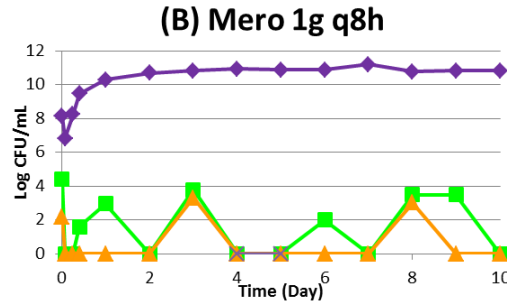
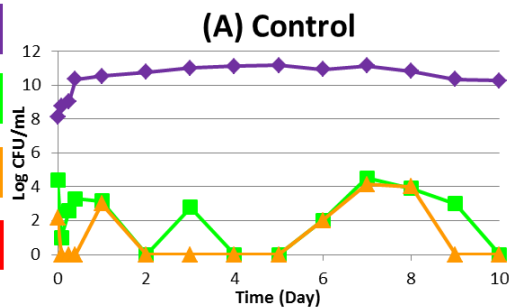


Total population

R population at 3x MIC

R population at 5x MIC

R population at 10x MIC



# What about new BL/BLIs?

Effects of KPC Variant and Porin Genotype on the *In vitro* Activity of Meropenem-vaborbactam against Carbapenem-Resistant *Enterobacteriaceae*

William R Wilson, Ellen G. Kline, Chelsea E. Jones, Kristin T. Morder, Roberta T. Mettus, Yohei Doi, M. Hong Nguyen, Cornelius J. Clancy, Ryan K. Shields  
University of Pittsburgh, Pittsburgh, Pennsylvania, USA

- Resistance phenotypes vary by *bla*<sub>KPC</sub> mutation

Cloned KPC variant*	MIC (µg/mL)	
	CAZ-AVI	MERO
pBC-SK alone	0.25	0.03
Wild-type KPC-2	1	16
Wild-type KPC-3	1	16
D179Y	>64	0.06
A177E, D179Y	>64	0.06
D179Y, T243M	>64	0.25
V240G	32	4
168 - 169 EL del	16	0.06
169 - 170 EL ins	8	1
A177E	4	16
T243A	2	2
169 – 170 EL ins; 278 - 281 SEAV ins	64	0.06

\* Cloned into *E. coli* TOP10



# What about new BL/BLIs?

Meropenem-Vaborbactam as Salvage Therapy for Ceftazidime-Avibactam-Resistant *Klebsiella pneumoniae* Bacteremia and Abscess in a Liver Transplant Recipient

Vasilios Athans,\* Elizabeth A. Neuner,\* Habiba Hassouna,\* Sandra S. Richter,\* George Keller,\* Mariana Castanheira,\* Kyle D. Britzandine\*

- Liver transplant recipient with recurrent *K. pneumoniae* bacteremia
- Ceftazidime-avibactam MIC from 4 → 128µg/mL
  - Due to *bla*<sub>KPC-2</sub> mutation (D179Y)
- Initially treated with polymyxin B, gentamicin, and tigecycline
  - Patient developed acute kidney injury
  - Recurrent *K. pneumoniae* abscess
- Treated with meropenem-vaborbactam\* for 25 days w/ successful re-transplantation
- Follow-up cultures were negative

# Comparing the newest BL/BLI combinations



	Ceftazidime-avibactam <sup>2-4</sup>	Meropenem-vaborbactam <sup>5,6</sup>	Imipenem-relebactam <sup>5</sup>
CRE	✓	✓	✓

1. CDC Antimicrobial Resistance Threats Report 2013. Available at: <https://www.cdc.gov/drugresistance/threat-report-2013/index.html>. [Accessed March 2018]; 2. Bush K. Int J Antimicrob Agents 2015;46:483–93; 3. Zavicefta SPC; 4. Lagacé-Wiens P, et al. Core Evid. 2014;9:1; 5. Wright H, et al. Clin Microbiol Infect 2017;23(10):704; 6. Lomovskaya O, et al. Antimicrob Agents Chemother 2017;61:e01443-17.

# Ceftazidime-avibactam for OXA-48

## Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae

Adrian Sousa<sup>1,2</sup>, María Teresa Pérez-Rodríguez<sup>1,2\*</sup>, Adriana Soto<sup>1</sup>, Lorena Rodríguez<sup>1</sup>, Antonio Pérez-Landeiro<sup>3</sup>, Lucía Martínez-Lamas<sup>4</sup>, Andrés Nodar<sup>1,2</sup> and Manuel Crespo<sup>1,2</sup>

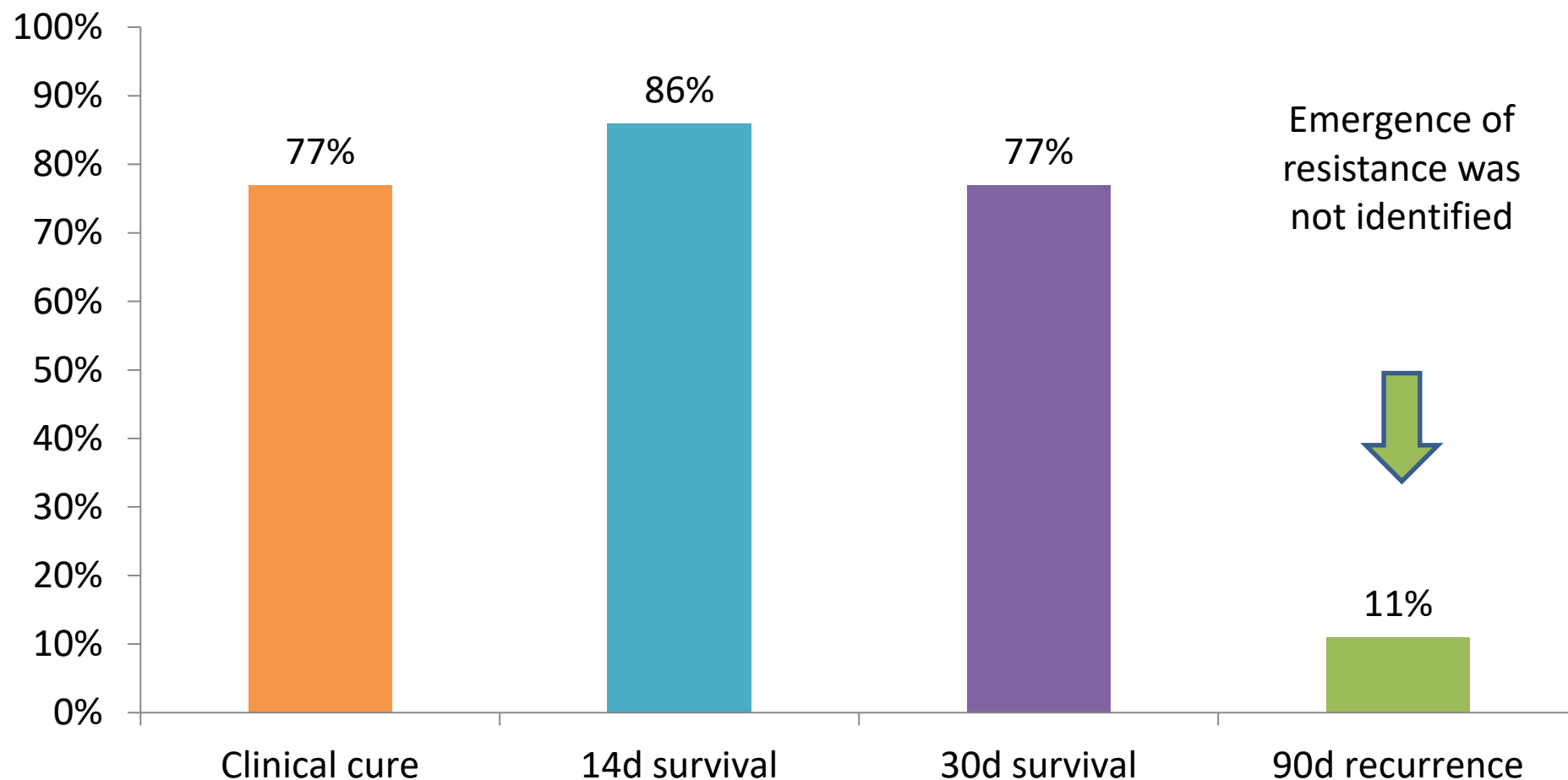
- **57 consecutive patients treated for OXA-48 producing CRE infections:**
  - Median age: 64 years (range: 26 – 86)
  - 54% with sepsis/septic shock
  - Median APACHE II score 24 (IQR: 8 – 45)
- Source of infection: Intra-abdominal (n=16), pneumonia (n=15), urinary (n=14), primary bacteremia (n=6), others (n=6)
  - 26 total cases with bacteremia
- CRE pathogens included: *K. pneumoniae* (n=54), *E. coli* (n=2), *Enterobacter spp.* (n=1)
  - 100% susceptible to ceftazidime–avibactam at baseline
- 81% received ceftazidime–avibactam as monotherapy

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Outcomes of 57 patients with OXA-48 infections treated with ceftazidime-avibactam



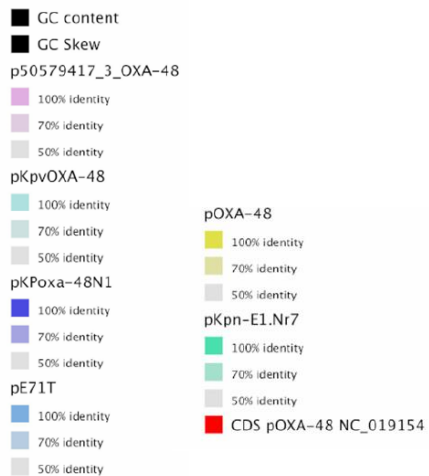
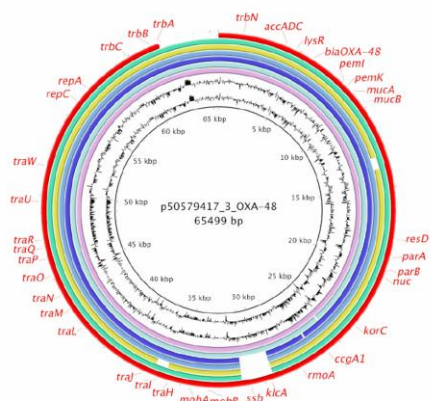


## OXA-48-Mediated Ceftazidime-Avibactam Resistance Is Associated with Evolutionary Trade-Offs

Christopher Fröhlich,<sup>a</sup> Vidar Sørum,<sup>b</sup> Ane Molden Thomassen,<sup>a</sup> Pål Jarle Johnsen,<sup>b</sup> Hanna-Kirsti S. Leiros,<sup>a</sup> Ørjan Samuelsen<sup>b,c</sup>

Clinical *E. coli* carrying OXA-48 on IncL plasmid

- Plasmid transferred to *E. coli* TOP10 → mutant selection



**TABLE 2** MIC after mutant selection of *E. coli* MG1655 (MP100) expressing OXA-48 (MP101) toward CAZ (MP102) and CAZ-AVI (MP103)<sup>a</sup>

Strain	MIC (mg/liter) <sup>b</sup>	
	CAZ	CAZ-AVI
MP100	0.25	0.12
MP101	0.25	0.12
MP102	32	2
MP103	32	16

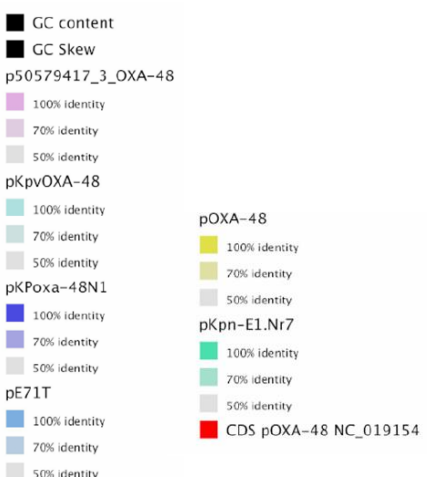
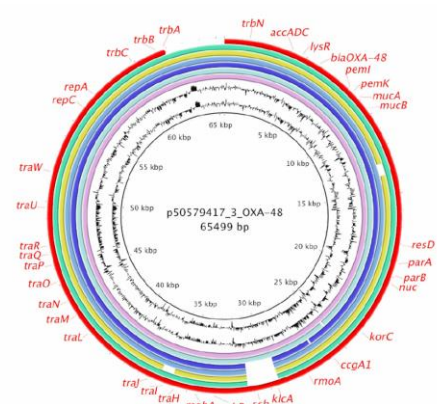
- Single (P68A) or double (P68A, Y211S) mutations were identified
  - Increase MICs to CAZ (32-fold) and CAZ-AVI (4-fold) in *E. coli* TOP10 background (decreased carbapenem MICs)
  - Results in increased CAZ hydrolysis and changes to active site
  - Also, a reduced AVI inhibitory effect



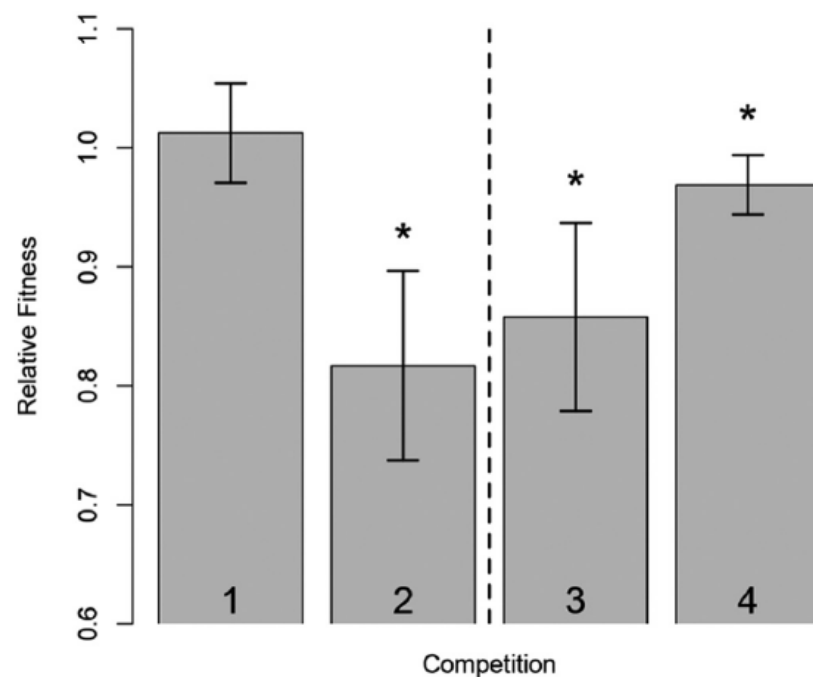
# Ceftazidime-avibactam for OXA-48

## OXA-48-Mediated Ceftazidime-Avibactam Resistance Is Associated with Evolutionary Trade-Offs

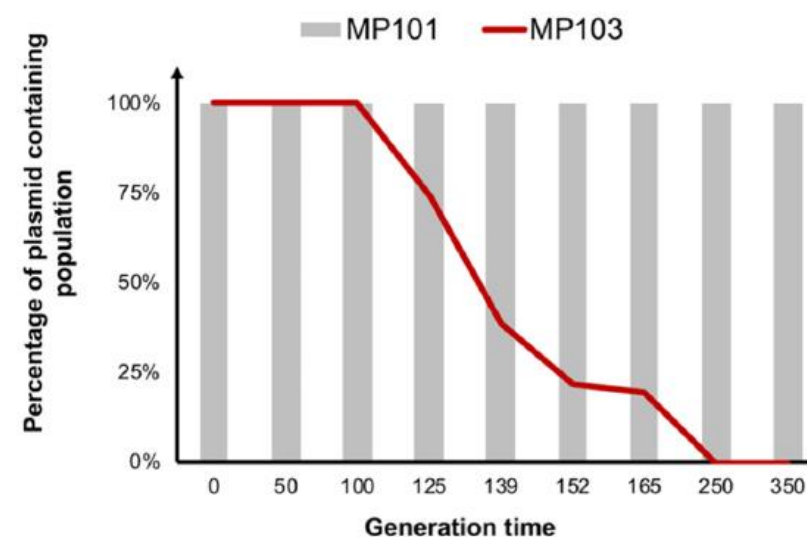
Christopher Fröhlich,<sup>a</sup> Vidar Sørum,<sup>b</sup> Ane Molden Thomassen,<sup>a</sup> Pål Jarle Johnsen,<sup>b</sup> Hanna-Kirsti S. Leiros,<sup>a</sup> Ørjan Samuelsen<sup>b,c</sup>



Competition experiments showed decreased fitness of OXA-48 variants



Adapted plasmid (MP103) was purged out of the population without additional selection



# Summary of ceftazidime–avibactam resistance

- **Baseline ceftazidime–avibactam resistance is:**<sup>1</sup>
  - Intrinsic among metallo- $\beta$ -lactamase producing CRE
  - Less commonly due to porin mutations and KPC expression
- **Acquired ceftazidime–avibactam resistance is:**<sup>1–4</sup>
  - Possible following treatment courses of 7–52 days
  - More common among patients requiring renal replacement therapy
  - Due to mutations in the KPC  $\Omega$ -loop (KPC-3 > KPC-2)
  - Associated with a reversion of carbapenem susceptibility
    - Identify ESBL phenotypes among patients treated with ceftazidime–avibactam
  - May be less common among OXA-48 producing CRE
- **Ongoing surveillance is needed to identify and characterize resistant isolates**
- **We need to identify strategies to overcome and suppress the emergence of ceftazidime–avibactam resistance**

# Ceftazidime-avibactam Resistance in KPC

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