Emerging Gram-negative Pathogens: Metallo-β-lactamase Producers

IDAC Spring Symposium 2022

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5/22/22

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Disclosures

- **Speaker's bureau: Abbvie Inc, Astellas Pharma, Melinta Therapeutics, Shionogi Inc.**
- **Scientific advisory board: Shionogi Inc.**
- **Research/grants: Daiichi Sankyo, Bristol-Myers Squibb, CDC, Melinta Therapeutics, Shionogi, Astellas Pharma, Paratek Pharmaceuticals, Merck & Co., Inc., Cystic Fibrosis Foundation**

Blood culture Order: 4039939803

Collected **5/1/2022 05:04** Status: **Edited Result - FINAL** Visible to patient: **Yes (not seen)**

Specimen Information: **Blood, Venous**

Growth in 1 of 2 bottles: Aerobic Bottle only

DETECTED:

Pseudomonas aeruginosa DNA. VIM beta-lactamase.

DNA NOT DETECTED for the following organisms:
Acinetobacter ssp
Citrobacter ssp
Enterobacter ssp
Proteus ssp
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca

Testing performed by Verigene nucleic acid method.

A. **Piperacillin-tazobactam**

B. **Ceftazidime-avibactam**

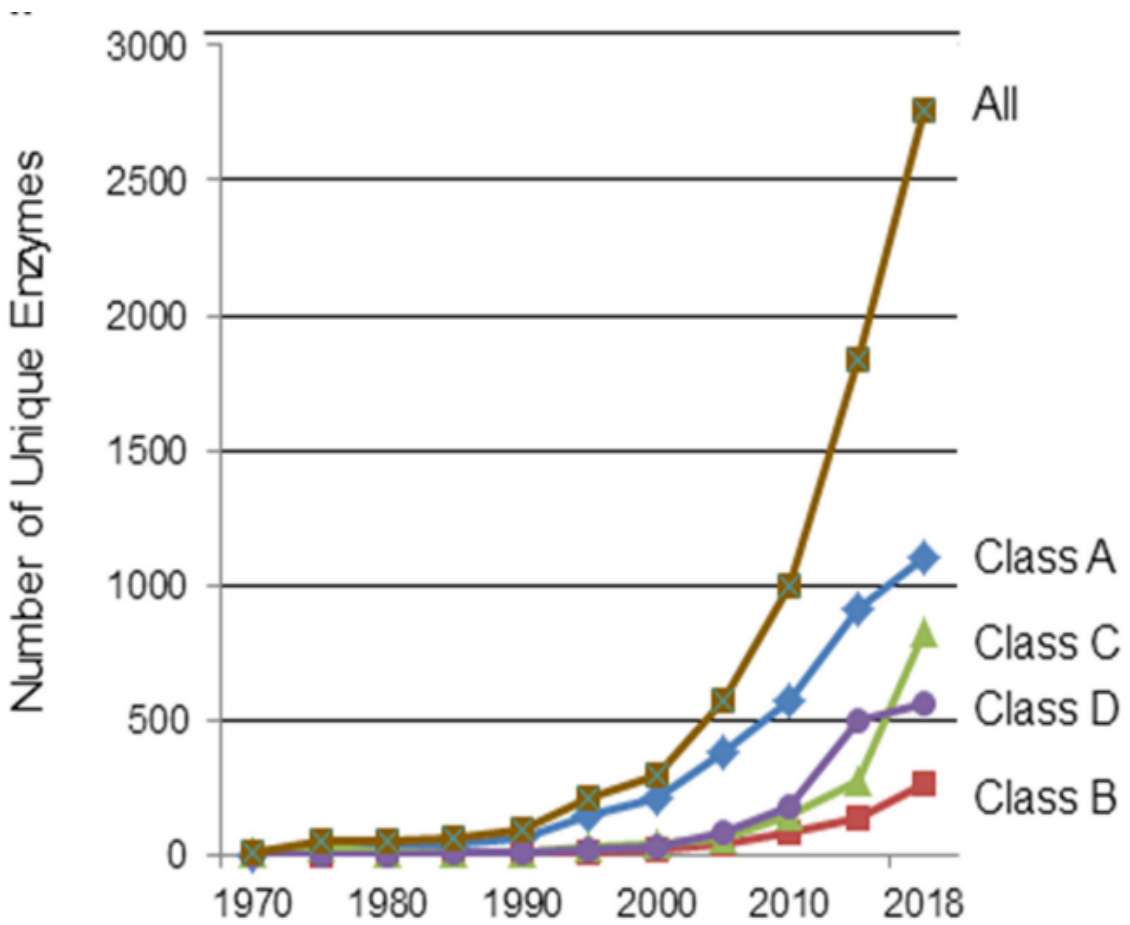
C. **ATM + CAZ-AVI**

D. **Cefiderocol**

	Pseudomonas aeruginosa			
	LAB SUSCEPTIBILITY METHOD (MIC)		ETEST SUSCEPTIBILITY METHOD	
$$ Amikacin	>32 ug/ml	Resistant		
$ Aztreonam	16 ug/ml	Intermediate		
$$ Cefepime	16 ug/ml	Intermediate		
$$ Ceftazidime	>16 ug/ml	Resistant		
Ceftazidime/Avibactam			>256 ug/ml	Resistant [1]
Ceftolozane/Tazobactam			>=16/4 ug/ml	Resistant [2]
$$$ Colistin			1 ug/ml	Susceptible
$ Gentamicin	>8 ug/ml	Resistant		
$$$ Imipenem	8 ug/ml	Resistant		
$$$ Levofloxacin	>4 ug/ml	Resistant		
$$$ Meropenem	>8 ug/ml	Resistant		
$$ Piperacillin + Tazobactam	16 ug/ml	Susceptible		
$ Tobramycin	>8 ug/ml	Resistant		

Epidemiology

- **Roughly 30-60% of Enterobacterales in U.S. will harbor one of the big 5 carbapenemase genes**
  - **KPC still responsible for >85% of carbapenemase-producing CRE (CP-CRE)**
  - **MBLs comprise 5-10%; 40-50% NDM, 30% VIM, 10-20% IMP**
- **2-4% of *P. aeruginosa* are CP-CRPA in U.S.**
  - **60-70% VIM, 10-20% IMP, <10% NDM**
- ***S. maltophilia* intrinsically co-harbors inducible L1 (MBL) and L2 (class A) β-lactamases**
  - **Now most common CR pathogen isolates from blood in U.S.**



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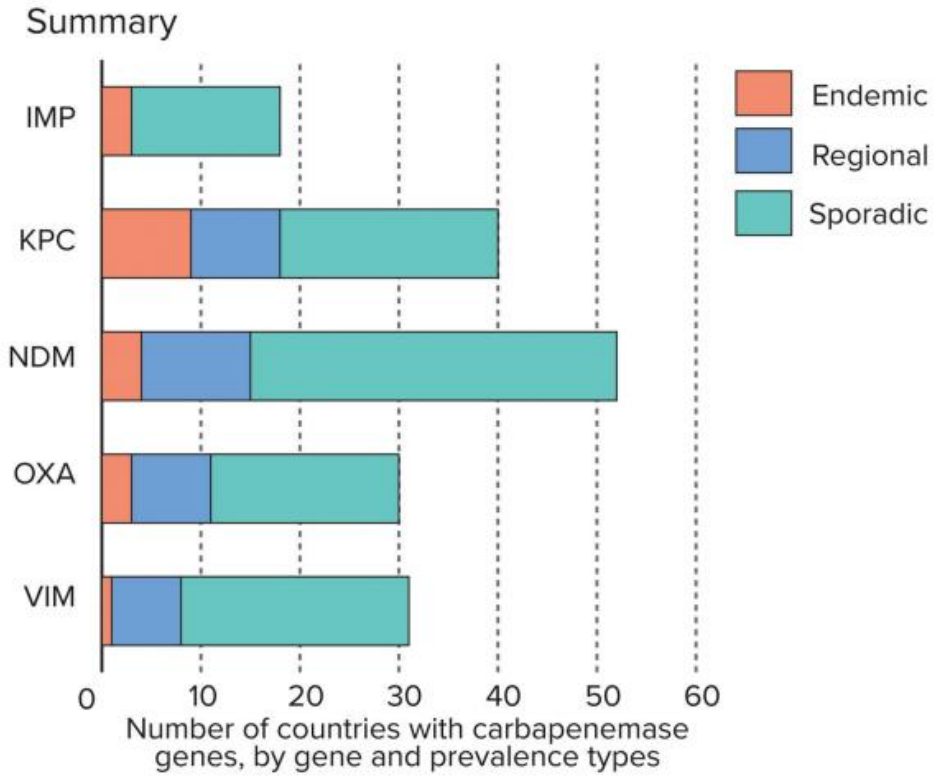
van Duin D, et al. Lancet Infect Dis **2020**; 20(6): 731-41. 1. Bush K, Bradford PA. Clinical microbiology reviews **2020**; 33(2): e00047-19. Bush K.. Antimicrob Agents Chemother **2018**; 62(10).Logan LK, Weinstein RA. J Infect Dis **2017**; 215(suppl_1): S28-s36.Woodworth KR,, et al.. MMWR Morb Mortal Wkly Rep 2018;67:396-401.

Epidemiology



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Epidemiology

- **Metallo-β-lactamase (MBL)-producing Gram negative pathogens including carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and *Stenotrophomonas maltophilia* are phenotypically best categorized as having difficult-to-treat resistance (DTR)**
  - **DTR: non-susceptibility to all reported carbapenems, all reported extended-spectrum cephalosporins, and all reported fluoroquinolones among *Escherichia coli, Klebsiella spp., Enterobacter spp., Pseudomonas aeruginosa, and Acinetobacter baumannii***
- **DTR phenotype delays time to effective therapy leading to increased mortality, longer length of stay, and necessitating the use of less effective, more toxic agents such as the aminoglycosides and polymyxins**
- **Although not traditionally considered DTR as its carbapenem resistance is intrinsic and chromosomally-mediated, *S. maltophilia* will be discussed alongside CRE and CRPA given emerging nature and similar challenges in detecting, testing, and treating**

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1. Magiorakos AP, et al.. *Clin Microbiol Infect*. 2012;18(3):268-281. **2.** Kadri SS, et al. *Clin Infect Dis*. 2018;67(12):1803-1814.

Epidemiology

TABLE 1 *In vitro* activities of antibiotics tested against *Enterobacterales* with bla_{NDM} collected in the United States from January 2017 to November 2018

Organism(s) (*n*) and drug[a]	MIC (μg/ml)			CLSI interpretive criteria		
	Range	MIC_{50}	MIC_{90}	% S[b]	% I[c]	% R[d]
All *Enterobacterales* (275)						
Doripenem	1 to >8	>8	>8	0.4	2.9	96.7
Imipenem	2 to >64	16	64	0.0	2.9	97.1
Meropenem	0.5 to >8	>8	>8	1.8	1.8	96.4
Cefepime[e]	8 to >32	>32	>32	0.0	0.7	99.3
Piperacillin-tazobactam	16/4 to >128/4	>128/4	>128/4	0.7	0.7	98.5
Aztreonam	≤2 to >64	>64	>64	18.2	1.8	80.0
Ceftazidime-avibactam	≤0.5/4 to >16/4	>16/4	>16/4	0.7	NA[f]	99.3
Imipenem-relebactam	2/4 to >64/4	8/4	32/4	0.0	2.5	97.5
Meropenem-vaborbactam	≤0.5/8 to >16/8	16/8	>16/8	10.2	17.1	72.7
Aztreonam-avibactam	≤0.03/4 to 32/4	0.25/4	4/4	NA	NA	NA
Cefepime-taniborbactam	0.12/4 to >64/4	2/4	32/4	NA	NA	NA
Cefepime-zidebactam	0.06/0.06 to >64/64	0.25/0.25	4/4	NA	NA	NA
Ciprofloxacin	≤0.25 to >8	>8	>8	5.8	2.5	91.6
Levofloxacin	≤0.12 to >8	>8	>8	9.8	4.4	85.8
Amikacin	≤1 to >64	16	>64	52.7	0.7	46.5
Gentamicin	≤0.25 to >16	>16	>16	32.0	1.8	66.2
Plazomicin	0.12 to >128	2	>128	52.7	1.5	45.8
Tobramycin	≤0.5 to >16	>16	>16	20.0	5.5	74.5
Eravacycline	0.12 to >4	0.5	2	66.2	NA	NA
Minocycline	≤4 to >16	8	>16	48.4	16.4	35.3
Omadacycline	0.5 to >32	4	32	59.6	18.9	21.5
Tetracycline	≤2 to >32	>32	>32	35.6	6.9	57.5
Tigecycline	≤0.5 to >4	≤0.5	4	86.5	8.4	5.1
Trimethoprim-sulfamethoxazole	≤0.5/8.5 to >8/152	>8/152	>8/152	20.7	NA	79.3
Chloramphenicol	≤2 to >16	>16	>16	24.0	22.2	53.8
Nitrofurantoin[g]	≤16 to >128	64	>128	35.3	16.4	48.4
Nitrofurantoin[h] (*n* = 144)	≤16 to >128	64	>128	45.1	12.5	42.4
Colistin	≤0.25 to >8	0.5	1	NA	NA	NA

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1. Lutgring JD,et al. Antimicrob Agents Chemother. 2020 Aug 20;64(9):e00499-20.1.Biedenbach DJ, et al. Antimicrob Agents Chemother **2015**; 59(7): 4239-48.

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

Table 3. Recommended Antibiotic Treatment Options for Carbapenem-Resistant Enterobacterales, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Metallo-β-lactamase (ie, NDM, VIM, IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (generally limited to intra-abdominal infections)

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Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Clin Infect Dis **2022**.

ATM + CAZ-AVI

Table 2 Aztreonam and Aztreonam-Avibactam Susceptibilities Among MBL-Producing Enterobacterales

MBL Enzyme	No. of Isolates	$MIC_{50/90}$ [mg/L]		Ref.
		ATM	ATM/AVI[a]	
MBL	267[b]	64/>128	0.12/1	44
	70[c]	64/>64	0.5/2	67
	161[d]	≥64/≥64	≤0.125/1	153
NDM	25[e]	>64/>64	0.25/1	66
VIM	26[e]	16/>64	0.12/1	66
IMP	17[e]	16/>64	0.12/1	66

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1. Lutgring JD,et al. Antimicrob Agents Chemother. 2020 Aug 20;64(9):e00499-20.2.Biedenbach DJ, et al. Antimicrob Agents Chemother **2015**; 59(7): 4239-48. 3.Mushtaq S, et al.. Antimicrob Agents Chemother **2020**; 64(12).

ATM + CAZ-AVI

TABLE 1 MIC distributions for 64 *Enterobacterales* isolates tested against ceftazidime-avibactam, aztreonam, and aztreonam-avibactam: AR Lab Network, March 2019 to December 2020

Isolate categories	Antimicrobial agent[a]	No. of isolates at each MIC (μg/ml) for each antimicrobial agent[b]													MIC_{50}[c]	MIC_{90}[c]
		≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64		
All (64)	CZA													64	>64/4	>64/4
	ATM			2		1		1		3	4	4	8	41	>64	>64
	AZA		7	7	11	13	7	1	9	7	2				0.5/4	8/4
Escherichia coli (28)	CZA													28	>64/4	>64/4
	ATM							1		3		2	3	19	>64	>64
	AZA		1	4		3	2	1	8	7	2				4/4	8/4
NDM (27)	CZA													27	>64/4	>64/4
	ATM							1		3		2	3	18	>64	>64
	AZA		1	4		3	2	1	8	6	2				4/4	8/4
NDM & OXA-48-like (1)	CZA													1		
	ATM													1		
	AZA									1						
Klebsiella pneumoniae (24)	CZA													24	>64/4	>64/4
	ATM					1						1	5	17	>64	>64
	AZA		3	2	8	8	2		1						0.25/4	1/4
NDM (17)	CZA													17	>64/4	>64/4
	ATM					1							4	12	>64	>64
	AZA		2	2	7	4	1		1						0.25/4	1/4
NDM & OXA-48-like (7)	CZA													7		
	ATM											1	1	5		
	AZA		1		1	4	1									
Enterobacter cloacae complex, NDM (10)	CZA													10	>64/4	>64/4
	ATM			2							2	1		5	32	>64
	AZA		2	1	3	1	3								0.25/4	1/4

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Bhatnagar A, et al. Antimicrob Agents Chemother. 2021 Jul 16;65(8):e0048621

ATM + CAZ-AVI

TABLE 1 MIC cumulative frequency distribution of aztreonam and aztreonam-avibactam tested against Gram-negative pathogens collected worldwide (2012 and 2013)

Organism (*n*) and drug	% frequency distribution by MIC (μg/ml)[a]: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
P. aeruginosa															
All (3,766)															
Aztreonam	0.1	0.1	0.1	0.2	1.0	2.3	3.1	5.8	29.4	58.5	78.0	**91.0**	95.9	97.9	100
Aztreonam-avibactam	0.1	0.1	0.2	0.5	1.6	3.3	4.0	7.4	35.4	73.6	86.2	**96.0**	99.2	99.6	100
MBL positive (118)															
Aztreonam	0.0	0.0	0.0	0.0	0.0	0.9	0.9	0.9	12.7	22.0	60.2	86.4	**91.5**	94.9	100
Aztreonam-avibactam	0.0	0.0	0.0	0.0	0.9	0.9	0.9	0.9	13.6	44.1	76.3	**91.5**	96.6	99.2	100

Isolate	β-Lactamase(s)	ATM	ATM-AVI[b]	CAZ-AVI
UIC1	IMP-14, OXA-10, OXA-488, VEB-9, PDC-2	>128, R	64, R	>128, R
UIC2	VIM-4, OXA-396, PDC-3	16, I	16, I	128, R
UIC3	VIM-2, OXA-488, PDC-2	64, R	64, R	64, R
UIC4	VIM-2, OXA-488, PDC-3	64, R	32, R	64, R
UIC5	VIM-2, PDC-8	16, I	32, R	128, R

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1. Lutgring JD,et al. Antimicrob Agents Chemother. 2020 Aug 20;64(9):e00499-20.1.Biedenbach DJ, et al. Antimicrob Agents Chemother **2015**; 59(7): 4239-48.

Susceptibility/Synergy Testing

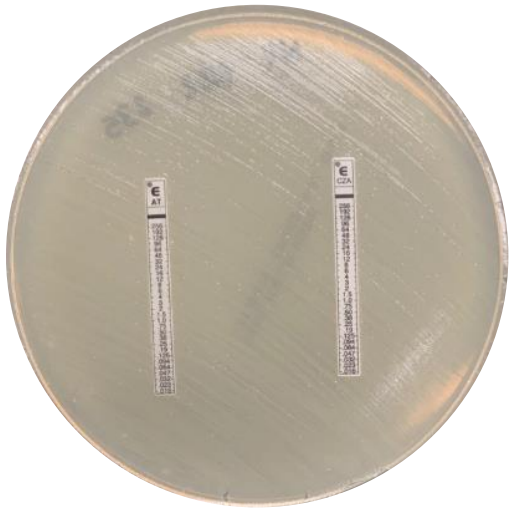

Table 1
MIC values and synergistic activity assessed via Etest MIC:MIC ratio method.

Organism	MIC (μg/mL)			Ceftazidime + Aztreonam		Ceftazidime + Ceftazidime-avibactam		Aztreonam + Ceftazidime-avibactam	
	Ceftazidime	Aztreonam	Ceftazidime-avibactam	∑FIC	Interpretation	∑FIC	Interpretation	∑FIC	Interpretation
E. coli NDM	>256	>256	>256/4	2	I	2	I	0.016	S
P. aeruginosa IMP	>256	32	>256/4	0.5	S	2	I	1.5	I
C. freundii VIM	>256	8	>256/4	0.5	S	2	I	0.031	S
E. cloacae KPC	>256	>256	2/4	0.125	S	0.011	S	0.009	S
K. pneumoniae KPC	>256	>256	2/4	0.125	S	0.039	S	0.011	S
A. baumannii OXA	>256	32	16/4	0.094	S	0.063	S	1	A
K. pneumoniae ATCC[a]	32	>256	2/4	0.25	S	0.078	S	0.0094	S

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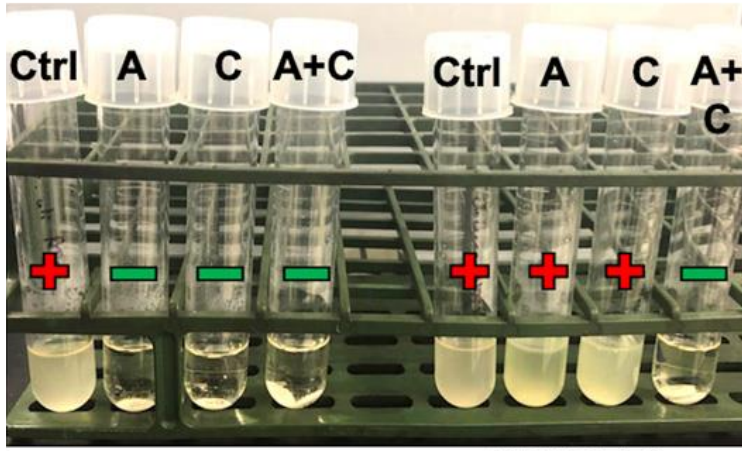
Wenzler E, Deraedt MF, Harrington AT, Danizger LH. Diagn Microbiol Infect Dis. 2017 Aug;88(4):352-354.

Susceptibility/Synergy Testing

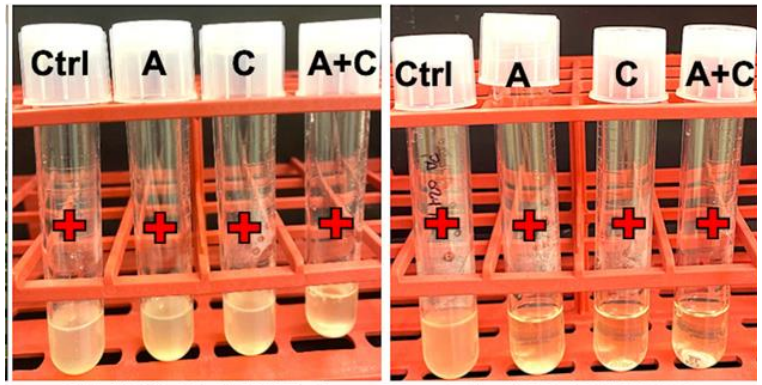
TABLE 4 Evaluation of overall qualitative and quantitative performance of combination testing methods compared to mBMD[a]

	Results by assay					
			Strip stacking		Strip crossing	
Parameter	Disk elution	Disk stacking	E-test	MTS	E-test	MTS
Sensitivity	100	42.67	87.5	100	95.83	100
Specificity	100	100	100	100	100	100
EA			38/45 (84)	38/45 (84)	42/45 (93)	42/45 (93)
CA	51/51 (100)	22/51 (43)	42/51 (82)	43/51 (84)	46/51 (90)	48/51 (94)
VME		0/7	0/7	0/7	0/7	0/7
ME		16/37 (43)	2/37 (5)	1/37 (3)	2/37 (5)	0/37
MI		13/51 (25)	7/51 (14)	7/51 (14)	3/51 (6)	3/51 (6)



ATCC *E. coli*

KP #2770
Synergy



PA #0246 NDM-1
NO synergy

PA #0249 VIM-2
NO synergy

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Khan A, et al. Antimicrob Agents Chemother **2021**; 65(11): e0084621.

ATM + CAZ-AVI

Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

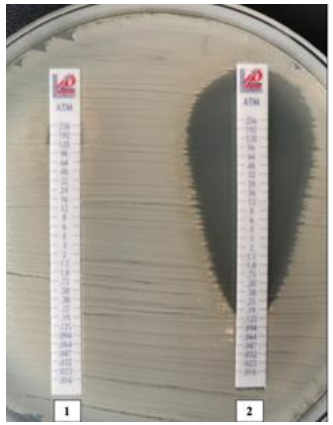
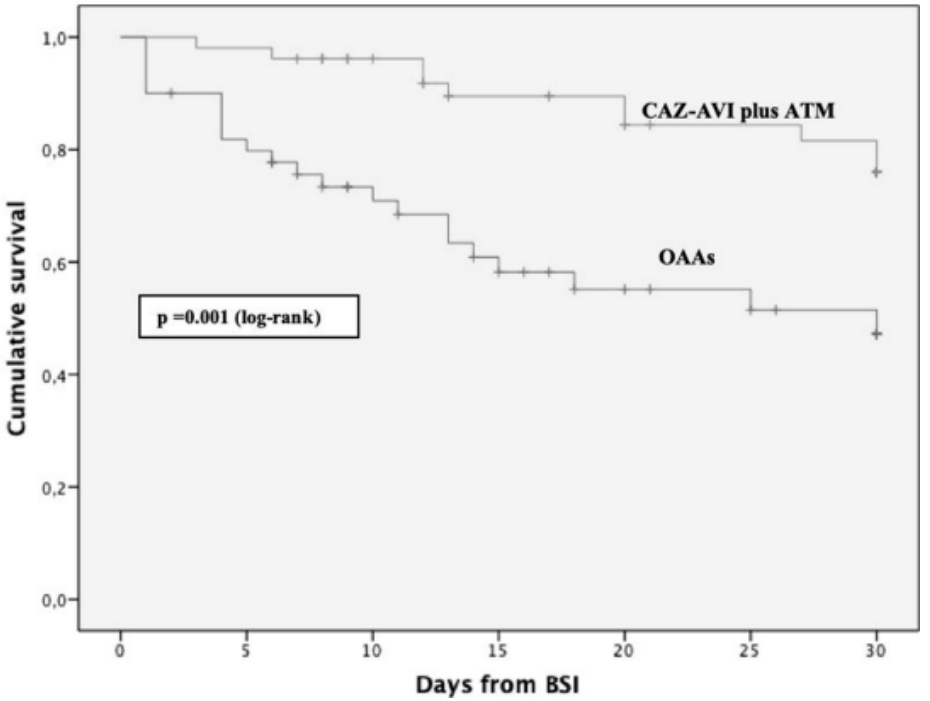


Table 2. Targeted Antibiotic Regimens Administered in 102 Bloodstream Infections Due to Metallo-β-Lactamase–Producing Enterobacterales

Antibiotic Regimen	No. (%) (N = 102)	Mortality, No. (%)
CAZ-AVI + ATM[a]	52 (51)	10/52 (19.2)
OAAs		
Colistin-containing regimens	27 (26.5)	16/27 (59.3)
Colistin + fosfomycin + tigecycline	7	6/7
Colistin + fosfomycin	7	5/7
Colistin + meropenem	5	3/5
Colistin + ATM ± piperacillin-tazobactam	4	1/4
Colistin + gentamicin	1	0/1
Colistin + cotrimoxazole	1	0/1
Colistin alone	2	1/2
Regimens not containing colistin	23 (22.5)	6/23 (26.1)
Tigecycline + aminoglycosides	8	2/8
Fosfomycin + aminoglycosides	5	0/5
Tigecycline + fosfomycin	2	2/2
Tigecycline + meropenem	1	0/1
ATM + aminoglycosides	4	1/4
ATM + fosfomycin	1	0/1
ATM alone	2	1/2

Table 4. Cox Regression Analysis of Factors Independently Associated With 30-Day Mortality

Factor	HR (95% CI)	*P* Value
Cardiovascular disease	6.62 (2.77–15.78)	< .001
Solid organ transplantation	3.52 (1.42–8.69)	.006
SOFA score (1-point increment)	1.21 (1.1–1.32)	< .001
CAZ-AVI + ATM (vs OAAs)	0.17 (.07–.41)	< .001



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Falcone M, et al. Clin Infect Dis **2021**; 72(11): 1871-8.

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

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Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Clin Infect Dis **2022**.

Cefiderocol

Table 3 Cefiderocol Susceptibilities Among MBL-Producing Enterobacterales

MBL Enzyme	No. of Isolates	%S ($MIC_{50/90}$ [mg/L] or Range MIC [mg/L])	Ref.
		CFDC	
MBL	64[a]	70 (N/A)	124
NDM	49[b] 12[c] 61[d]	89.8 (1/4) N/A (4/8) 72.1 (4/8)	154 155 77
VIM	12[b] 27[c] 47[d]	91.7 (≤0.12/0.25) 100 (1/4) 95.7 (0.5/4)	154 155 77
IMP	8[b] 15[d]	87.5 (≤0.125–16)[e] 100 (0.25/2)	154 77

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Cefiderocol

TABLE 3 MIC distributions of cefiderocol by resistance mechanism and species group

Mechanism	No. of isolates with MIC (μg/ml) of:													% susceptible at MIC (μg/ml) of:	
	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥128	2	4
Enterobacterales															
NDM				3	3	6	13	19	13	2	2			41.0	72.1
KPC	9	4	10	7	5	10	6	4	1					91.1	98.2
OXA-48 like	13	5	6	7	10	6	5	3	1					92.9	98.2
VIM	2	1	3	10	9	11	2	7	2					80.9	95.7
ESBL + porin loss			2		6	2	6	7	2		1			61.5	88.5
AmpC + porin loss		2	3	6	4	4	6							100	100
IMP	2	1		6	1		4	1						93.3	100
GES, IMI, or SME		3	3	3	3	2	5							100	100
Total	26	16	27	42	41	41	47	41	19	2	3			78.7	92.1
P. aeruginosa															
VIM	1	2	10	4	6	4	1			1			1	93.3	93.3
IMP		5	4	7	3	1			3	2				80.0	80.0
GES		4	2	5	5	1	1	2						90.0	100
PER		1		2	2	3	2	1	2	2				66.7	73.3
NDM						2	3	3	1	1			1	45.5	72.7
VEB					4	3	2		1					90.0	90.0
Total	1	12	16	18	20	14	9	6	7	6			2	81.1	86.5

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1. Lutgring JD,et al. Antimicrob Agents Chemother. 2020 Aug 20;64(9):e00499-20.2.Biedenbach DJ, et al. Antimicrob Agents Chemother **2015**; 59(7): 4239-48. 3.Mushtaq S, et al.. Antimicrob Agents Chemother **2020**; 64(12).4. Kazmierczak KM, et al. Int J Antimicrob Agents **2019**; 53(2): 177-84. **1.** Meredith A. Hackel et al. Antimicrob. Agents Chemother. 2018; doi:10.1128/AAC.01968-17 **2.** Simner PJ, Patel R. J Clin Microbiol. 2020 Jul 29:JCM.00951-20. **3.** Yamano Y. *Clin Infect Dis*. 2019;69(Suppl 7):S544-S551.

Susceptibility Testing

TABLE 4 Disk diffusion performance characteristics compared to broth microdilution[a]

Organism(s)	No. of isolates	% (no.) with agreement or error																				
		30-μg HardyDisks (FDA cleared)											30-μg MASTDISCS (RUO)									
		CLSI				FDA[b] (*n* = 73)				EUCAST			CLSI				FDA[b]				EUCAST		
		CA	mE	ME	VME	CA	mE	ME	VME	CA	ME	VME	CA	mE	ME	VME	CA	mE	ME	VME	CA	ME	VME
Carbapenem-resistant *Enterobacterales*	58	91 (53)	9 (5)	0	0	84 (49)	16 (9)	0	0	88 (51)	17 (7)	0	88 (51)	12 (7)		0	86 (50)	14 (8)	0	0	90 (52)	14 (6)	0
Carbapenemase-producing CRE	26	88 (23)	12 (3)	0	0	81 (21)	19 (5)	0	0	88 (23)	12 (3)	0	88 (23)	12 (3)	0	0	81 (21)	19 (5)	0	0	92 (24)	8 (2)	0
Non-carbapenemase-producing CRE	32	94 (30)	6 (2)	0	0	88 (28)	12 (4)	0	0	88 (28)	12 (4)	0	88 (28)	12 (4)	0	0	91 (29)	9 (3)	0	0	88 (28)	12 (4)	0
Citrobacter freundii complex	2	50 (1)	50 (1)	0	0	50 (1)	50 (1)	0	0	50 (1)	100 (1)	0	50 (1)	50 (1)	0	0	50 (1)	50 (1)	0	0	50 (1)	100 (1)	0
Enterobacter cloacae complex	15	93 (14)	7 (1)	0	0	80 (12)	20 (3)	0	0	87 (13)	25 (2)	0	87 (12)	13 (2)	0	0	87 (13)	13 (2)		0	93 (14)	7 (1)	0
Escherichia coli	15	100 (15)	0	0	0	100 (15)	0	0	0	80 (12)	20 (3)	0	100 (15)	0	0	0	100 (15)	0	0	0	87 (13)	13 (2)	0
Klebsiella aerogenes	2	100 (2)	0	0	0	100 (2)	0	0	0	100 (2)	0	0	100 (2)	0	0	0	100 (2)	0	0	0	100 (2)	0	0
Klebsiella oxytoca	6	83 (5)	17 (1)	0	0	83 (5)	17 (1)	0	0	83 (5)	17 (1)	0	100 (6)	0	0	0	83 (5)	17 (1)	0	0	83 (5)	17 (1)	0
Klebsiella pneumoniae	15	87 (13)	13 (2)	0	0	73 (11)	27 (4)	0	0	100 (15)	0	0	73 (11)	27 (4)	0	0	73 (11)	27 (4)	0	0	83 (14)	7 (1)	0
Serratia marcescens	3	100 (3)	0	0	0	100 (3)	0	0	0	100 (3)	0	0	100 (3)	0	0	0	100 (3)	0	0	0	100 (3)	0	0
Non-glucose-fermenting Gram-negative bacilli	39	85 (33)	8 (3)	12 (3)	0	36 (5)	64 (9)	0	0	79 (31)	15 (4)	31 (4)	85 (33)	15 (6)	0	0	50 (7)	43 (6)	0	25 (1)	90 (35)	8 (2)	15 (2)
Pseudomonas aeruginosa	14	93 (13)	7 (1)	0	0	36 (5)	64 (9)	0	0	79 (11)	14 (2)	25 (1)	86 (12)	14 (2)	0	0	50 (7)	43 (6)	0	25 (1)	86 (12)	10 (1)	25 (1)
Acinetobacter baumannii complex	14	64 (9)	14 (2)	25 (3)	0					64 (9)	20 (2)	33 (3)	71 (10)	29 (4)	0	0					86 (12)[c]	20 (1)[c]	11 (1)[c]
Stenotrophomonas maltophilia	11	100 (11)	0	0	0					100 (11)	0	0	100 (11)	0	0	0					100 (11)[c]	0	0
All isolates	97	89 (86)	8 (8)	3 (3)	0	75 (54)	25 (18)		0	85 (82)	17 (11)	12 (4)	87 (84)	13 (13)	0	0	79 (57)	19 (14)	0	20 (1)	90 (87)	13 (8)	12 (4)

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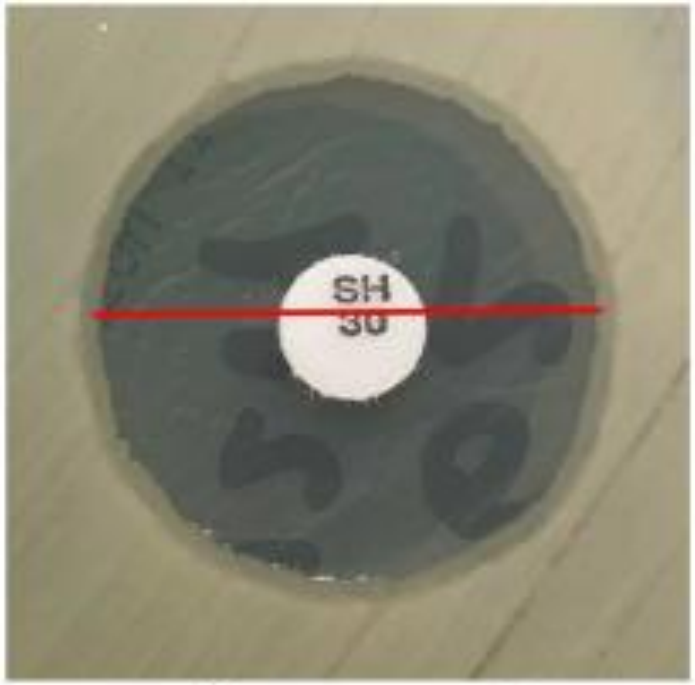
Morris CP, et al. J Clin Microbiol. 2020 Dec 17;59(1):e01649-20.

A



Zone diameter: 20 mm

B

Zone diameter: 12 mm

C

Zone diameter: 6 mm

D

Growth Control:

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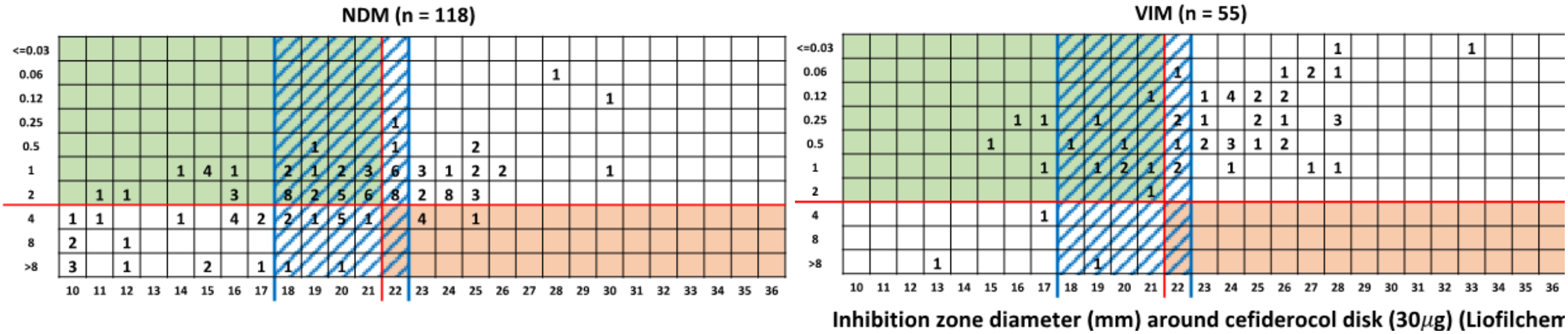
Morris CP, et al. J Clin Microbiol. 2020 Dec 17;59(1):e01649-20.

Susceptibility Testing



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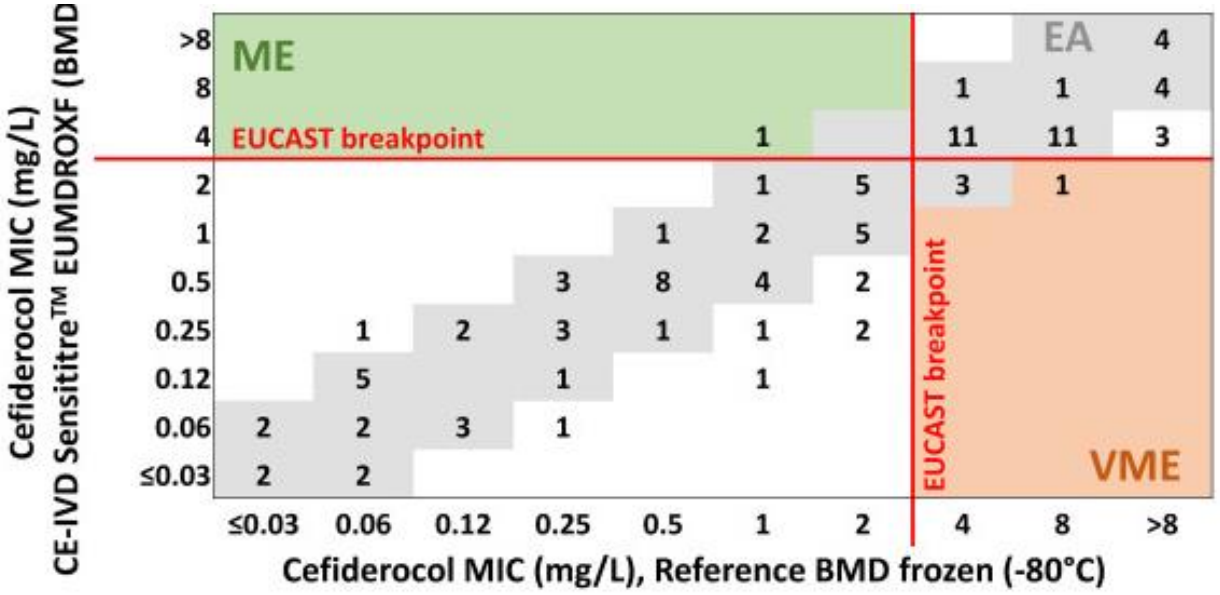
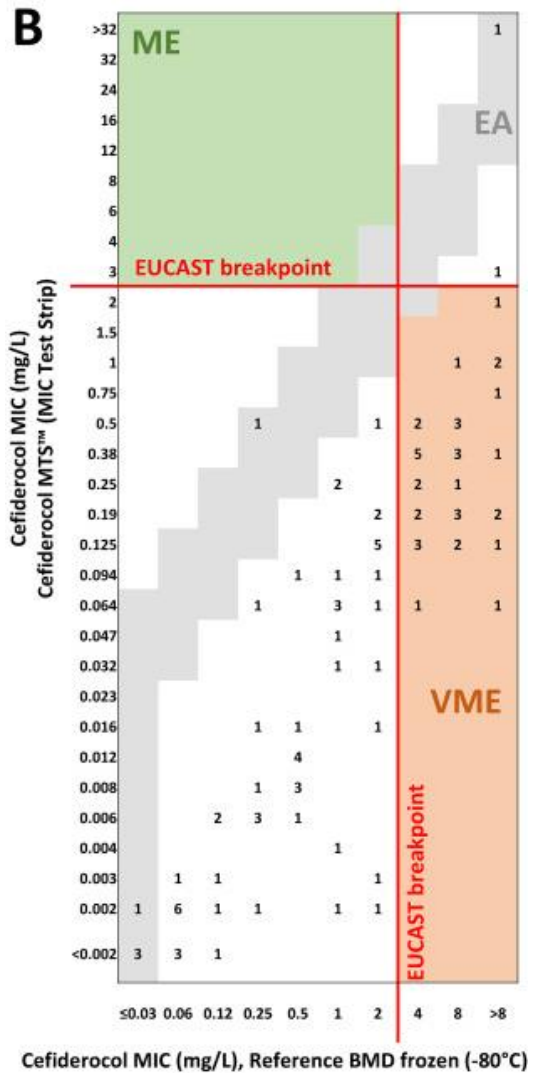
Bonnin RA, et al. Clin Microbiol Infect. 2022 May 6:S1198-743X(22)00221-X

Susceptibility Testing





- **Sensititre panel: 87% EA, 95% CA, 2.8% VME, 1.6% ME**
- **MTS strips: 6% EA, 63% CA, 95% VME, 0% ME**

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Bonnin RA, et al. Clin Microbiol Infect. 2022 May 6:S1198-743X(22)00221-X

Cefiderocol

- 18 patients treated with CFDC for MBL infections during an outbreak in Italy
  - 2 NDMs resistant to CFDC without prior exposure
- 10 ICU patients (most with COVID) treated with CFDC; 3 for NDM producing *K. pneumoniae* alone and with *S. maltophilia* and *A. baumannii*
- Overall clinical cure rate 71% (15/21)
- Overall ACM at 28-30 days 24% (5/21)
  - Comparable to outcomes observed with ATM + CAZ-AVI

Table 1. Description of 10 Intensive Care Unit Patients Treated With Cefiderocol

Age/ Sex	Underlying Diseases	Cause of ICU Admission	SOFA Score	APACHE II Score	Isolated Pathogen	CFDC MIC, µg/mL	Type of Infection	Initial Treatment Regimen	CFDC Dosage	CFDC Mono-therapy	CRRT	Clinical Outcome at 30 d	30-d Mortality
79/F	Hypertension	COVID-19	10	39	NDM-producing Kp *Stenotrophomonas maltophilia*	1/0.5	VAP	CAZ-AVI + ATM + FOS	2g q6h	Yes	No	Success	No
44/M	Hypertension Obesity	COVID-19	9	40	NDM-producing Kp	1	VAP	COL + FOS	2g q6h	Yes	No	Success	No
77/M	Hypertension	COVID-19	9	36	*A. baumannii* + NDM-producing Kp	0.12/ 2	VAP	COL + CAZ-AVI + ATM	1.5 g q8h	No[a]	Yes	Failure	Yes

Table 1. Clinical Characteristics and Outcomes of Patients With Infections Caused by Metallo-β-Lactamase–Producing Enterobacterales Who Received Cefiderocol

Characteristics and Outcomes	N = 18
Demographics	
Age, median (IQR), years	70 (57.5–75.5)
Male sex	11 (61.1%)
Type of infection	
Bloodstream infection	8 (44.4%)
Hospital-acquired pneumonia/Ventilator-associated pneumonia	5 (27.8%)
Complicated intraabdominal infection	3 (16.7%)
Complicated urinary tract infection	2 (11.1%)
Type of isolate	
VIM-producing	2 (11.1%)
NDM-producing	16 (88.9%)
Intensive care unit stay	12 (66.7%)
Sequential organ failure assessment score, median (IQR)	4 (3–6.5)
Polymicrobial infection[a]	3 (16.7%)
Cefiderocol monotherapy	5 (23.8%)
Cefiderocol combination therapy[b]	16 (76.2%)
Outcomes	
Clinical cure	13 (72.2%)
Eradication at end of treatment	14 (77.8%)
28-day all-cause mortality	4 (22.2%)

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1. Falcone M, Tiseo G.. Clin Infect Dis **2022**. 2. Timsit JF, Paul M, Shields RK, et al. Clin Infect Dis **2022**. 3. Paterson DL, et al. Infect Dis Ther **2022**; 11(2): 853-70. Falcone M, et al. Clin Infect Dis. 2021 Jun 1;72(11):2021-2024.

Cefiderocol

- Post-hoc analysis of 34 patients enrolled in the Phase 3 CREDIBLE-CR (N=23) and APEKS-NP (N=11) studies who were infected with an MBL
- 20 Enterobacterales and 14 non-fermenters
- 82% of CFDC MICs vs. NDM ≤4 mg/L
- Only death in CFDC arm of CREDIBLE-CR had *Enterobacter cloacae* with MIC 16 mg/L
- In CREDIBLE-CR 28 ACM was 6.3% for CFDC (1/16) vs. 57% for BAT (4/7)
- Overall 28 ACM was 12.5% (3/24) for CFDC and 50% (5/10) for comparator

	Clinical Cure at TOC, % (n/N)		Eradication at EOT, % (n/N)		ACM Day 28, % (n/N)	
CREDIBLE-CR	**Cefiderocol**	**BAT**	**Cefiderocol**	**BAT**	**Cefiderocol**	**BAT**
	N = 16	**N = 7[a]**	**N = 16**	**N = 7[a]**	**N = 16**	**N = 7[a]**
Overall	75.0 (12/16)	28.6 (2/7)	62.5 (10/16)	14.3 (1/7)	6.3 (1/16)	57.1 (4/7)
Types of infection[b]						
Pneumonia	83.3 (5/6)	33.3 (1/3)	33.3 (2/6)	0 (0/3)	16.7 (1/6)	33.3 (1/3)
Other[c]	70.0 (7/10)	25.0 (1/4)	80.0 (8/10)	25.0 (1/4)	0 (0/10)	75.0 (3/4)
MBL type[b]						
NDM	60.0 (6/10)	20.0 (1/5[a])	70.0 (7/10)	0 (0/5[a])	10.0 (1/10)	60.0 (3/5[a])
Non-NDM	100 (6/6)	33.3 (1/3[a])	50.0 (3/6)	33.3 (1/3[a])	0 (0/6)	33.3 (1/3[a])
Pathogen type[b]						
Enterobacterales	80.0 (8/10)	0 (0/4)	70.0 (7/10)	0 (0/4)	10.0 (1/10)	75.0 (3/4)
Non-fermenters[d]	66.7 (4/6)	66.7 (2/3)	50.0 (3/6)	33.3 (1/3)	0 (0/6)	33.3 (1/3)

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1. Falcone M, Tiseo G.. Clin Infect Dis **2022**. 2. Timsit JF, Paul M, Shields RK, et al. Clin Infect Dis **2022**. 3. Paterson DL, et al. Infect Dis Ther **2022**; 11(2): 853-70.

Cefiderocol

Table 5 Outcomes by resistance mechanisms/extended-spectrum beta-lactamase for Enterobacterales in CREDIBLE-CR (intention-to-treat population)

Resistance mechanism	Response, *n/N'* (%)	Cefiderocol (*N* = 25)	BAT (*N* = 13)
Metallo-beta-lactamase (NDM, VIM, IMP)	Eradication at EA	3/4 (75.0)	1/2 (50.0)
	Persistence at EA	1/4 (25.0)	0/2 (0)
	Clinical cure at TOC	3/4 (75.0)	0/2 (0)
	Day 14 ACM	0/4 (0)	0/2 (0)
	Day 28 ACM	0/4 (0)	1/2 (50.0)
Serine-beta-lactamase (KPC, OXA-48-like)	Eradication at EA	6/8 (75.0)	3/4 (75.0)
	Persistence at EA	0/8 (0)	0/4 (0)
	Clinical cure at TOC	4/8 (50.0)	2/4 (50.0)
	Day 14 ACM	1/8 (12.5)	0/4 (0)
	Day 28 ACM	1/8 (12.5)	2/4 (50.0)

1. Falcone M, Tiseo G.. Clin Infect Dis **2022**. 2. Timsit JF, Paul M, Shields RK, et al. Clin Infect Dis **2022**. 3. Paterson DL, et al. Infect Dis Ther **2022**; 11(2): 853-70.

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

Table 3. Recommended Antibiotic Treatment Options for Carbapenem-Resistant Enterobacterales, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Metallo-β-lactamase (ie, NDM, VIM, IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (generally limited to intra-abdominal infections)

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Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Clin Infect Dis **2022**.

Blood culture Order: 4039939803

Collected **5/1/2022 05:04** Status: **Edited Result - FINAL** Visible to patient: **Yes (not seen)**

Specimen Information: **Blood, Venous**

Growth in 1 of 2 bottles: Aerobic Bottle only

DETECTED:

Pseudomonas aeruginosa DNA. VIM beta-lactamase.

DNA NOT DETECTED for the following organisms:
Acinetobacter ssp
Citrobacter ssp
Enterobacter ssp
Proteus ssp
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca

Testing performed by Verigene nucleic acid method.

A. **Piperacillin-tazobactam**

B. **Ceftazidime-avibactam**

C. **ATM + CAZ-AVI**

D. **Cefiderocol**

	Pseudomonas aeruginosa			
	LAB SUSCEPTIBILITY METHOD (MIC)		ETEST SUSCEPTIBILITY METHOD	
$$ Amikacin	>32 ug/ml	Resistant		
$ Aztreonam	16 ug/ml	Intermediate		
$$ Cefepime	16 ug/ml	Intermediate		
$$ Ceftazidime	>16 ug/ml	Resistant		
Ceftazidime/Avibactam			>256 ug/ml	Resistant [1]
Ceftolozane/Tazobactam			>=16/4 ug/ml	Resistant [2]
$$$ Colistin			1 ug/ml	Susceptible
$ Gentamicin	>8 ug/ml	Resistant		
$$$ Imipenem	8 ug/ml	Resistant		
$$$ Levofloxacin	>4 ug/ml	Resistant		
$$$ Meropenem	>8 ug/ml	Resistant		
$$ Piperacillin + Tazobactam	16 ug/ml	Susceptible		
$ Tobramycin	>8 ug/ml	Resistant		

Genotype-phenotype

Table 1 Rapid Diagnostic Tests Relevant to MBL-Producing Enterobacterales

Test	Technology	Enterobacterales Detected?	Resistance Determinant Genes Detected[a]	Specimen Type	FDA Approved
Molecular Assays					
Verigene BC-GN	Multiplex PCR and Hybridization	Yes[b]	bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{CTX-M}, bla_{KPC}, bla_{OXA-48}, bla_{OXA-23}, bla_{OXA-40}, bla_{OXA-58}	Positive blood culture	Yes
Biofire BCID2 Panel	Multiplex PCR	Yes[c]	bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{KPC}, $bla_{OXA-48-like}$	Positive blood culture	Yes
GenMark Diagnostics ePlex BCID-GN	Multiplex PCR	Yes[d]	bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{CTX-M}, bla_{KPC}, bla_{OXA-23}, bla_{OXA-48}	Positive blood culture	Yes
Biofire FilmArray Pneumonia Panel	Multiplex PCR	Yes[e]	bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{KPC}, $bla_{OXA-48-like}$	BAL, sputum	Yes
Unyvero LRT Application[f]	Multiplex PCR	Yes[g]	bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{CTX-M}, bla_{KPC}, bla_{TEM}, bla_{OXA-48}, bla_{OXA-23}, bla_{OXA-24}, bla_{OXA-58}	Endotracheal aspirate, BAL	Yes

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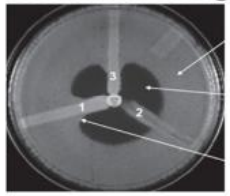
1. Lutgring JD,et al. Antimicrob Agents Chemother. 2020 Aug 20;64(9):e00499-20.1.Biedenbach DJ, et al. Antimicrob Agents Chemother **2015**; 59(7): 4239-48. Tan X, et al. Infect Drug Resist. 2021;14:125-142. Tamma PD, Simner PJ. Phenotypic Detection of Carbapenemase-Producing Organisms from Clinical Isolates. J Clin Microbiol **2018**; 56(11).

Genotype-phenotype

Modified Hodge Test

A.



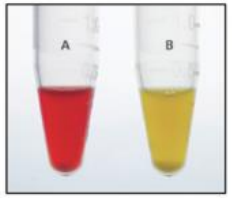
A lawn of carbapenem susceptible *E. coli* ATCC 25922

Zone of inhibition of *E. coli* ATCC 25922 by ertapenem

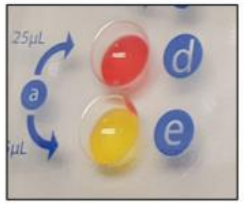
Indentation of *E. coli* ATCC 25922 growth (clover leaf appearance) around the streak line of the carbapenemase-producing *K. pneumoniae* ATCC BAA-1705.

Carba NP and variants

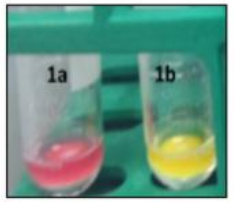
B.



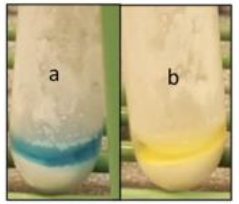
C.



D.



E.



Modified Carbapenem Inactivation Method (mCIM) & EDTA- mCIM (eCIM)

F.

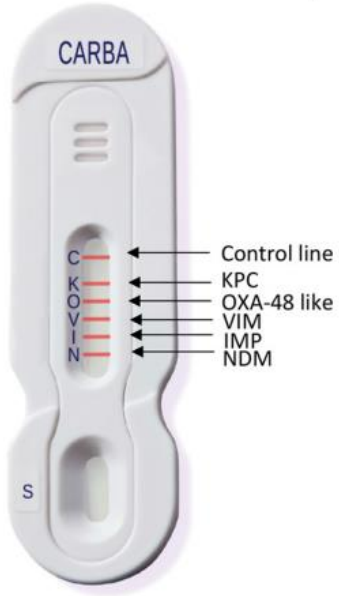
G.

H.

I.

Lateral Flow Immunoassay

J.



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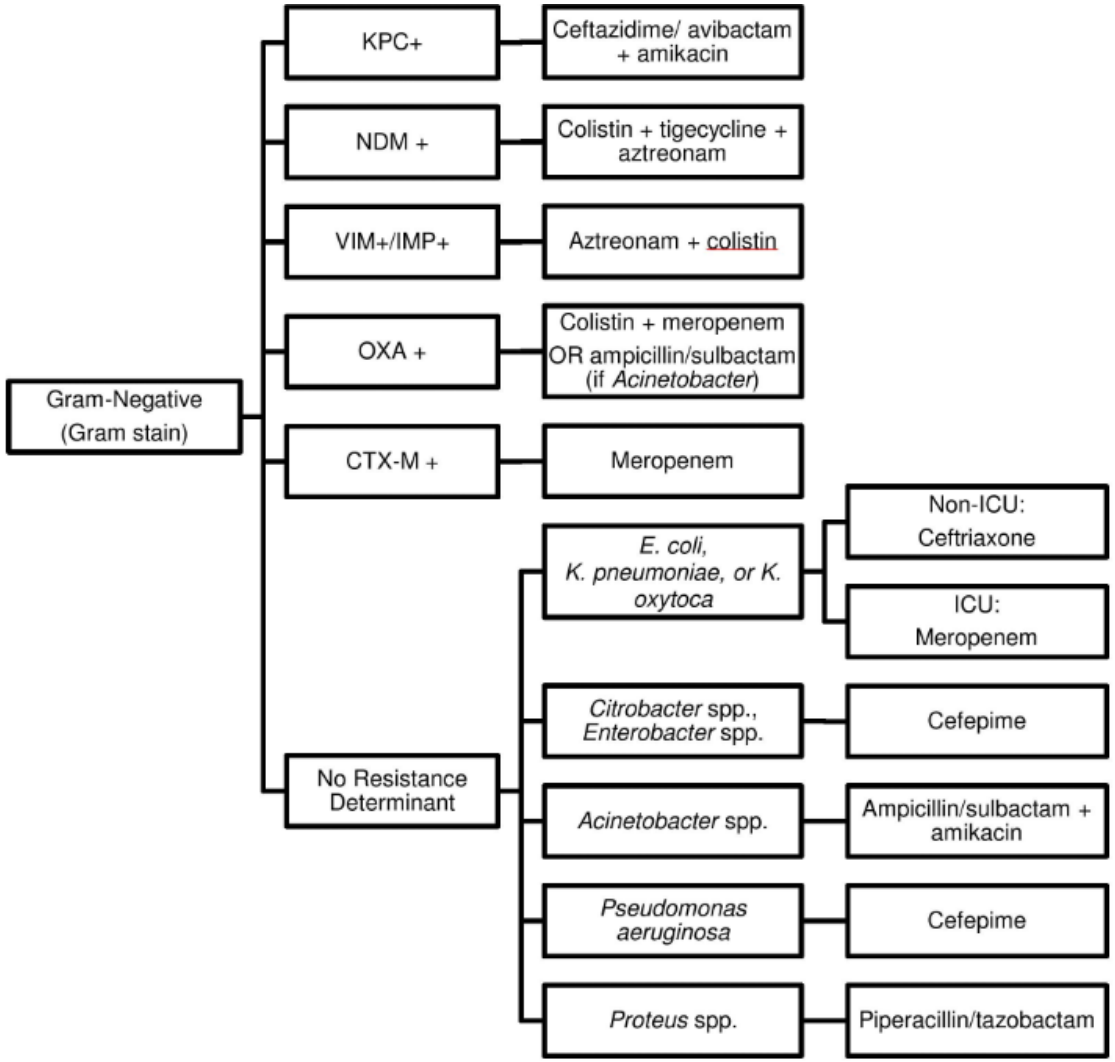
1. Lutgring JD,et al. Antimicrob Agents Chemother. 2020 Aug 20;64(9):e00499-20.1.Biedenbach DJ, et al. Antimicrob Agents Chemother **2015**; 59(7): 4239-48. Tan X, et al. Infect Drug Resist. 2021;14:125-142. Tamma PD, Simner PJ. Phenotypic Detection of Carbapenemase-Producing Organisms from Clinical Isolates. J Clin Microbiol **2018**; 56(11).

Genotype-phenotype

			%Susceptible Isolates							
Organism	Resistance Marker	*n*	SAM	CRO	FEP	CIP	GEN	MEM	TZP	T/S
K.pneumoniae	None	2629	82	98	99	89	98	99	94	87
	CTX-M	156	0	0	19	7	37	94	30	10
	KPC	64	0	0	13	8	64	8	0	37
	OXA	6	0	0	0	0	50	50	0	50
Proteus	None	501	98	97	99	57	93	100	100	70
	CTX-M	7	100	0	0	0	71	100	100	0
Pseudomonas	None	715	70	--	84	79	88	80	81	--
	VIM	6	0	--	0	0	0	0	0	--

Genotype-phenotype



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Claeys KC, et al. Open Forum Infect Dis 2018; 5(10): ofy233.

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

Severity of Infection	Preferred Treatment	Alternative Treatment
Mild	TMP-SMX, minocycline	Tigecycline, levofloxacin, cefiderocol
Moderate-severe	TMP-SMX + minocycline, ATM + CAZ-AVI	Two drug combination of TMP-SMX, minocycline, tigecycline, or cefiderocol

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Clin Infect Dis **2022**.

S. maltophilia

Antimicrobial	Susceptible	Intermediate	Resistant	Count	MIC_{50}	MIC_{90}	% Susceptible	% Resistant
TMP-SMX[b]	≤2/38	…	≥4/76	2095	≤0.5	1	95	5
Levofloxacin[b]	≤2	4	≥8	2099	1	>4	75	15
Minocycline[b]	≤4	8	≥16	1977	0.5	2	99	0.2
Ceftazidime[b]	≤8	16	≥32	2098	32	>32	26	64
T/C[c]	≤16/2	32/2 to 64/2	≥128/2	130	32	128	43[d]	57
Chloramphenicol[e]	≤8	16	≥32	66	4	16	80	NR
Cefiderocol[f]	≤4	8	≥16	217	0.06	0.25	100	0

	MIC (mg/liter)			
Agent(s)	50%	90%	Range	% susceptible
Aztreonam	≥256	≥256	8 to ≥256	2.1
Aztreonam-avibactam[b]	4	4	0.5 to 16	97.9
Aztreonam-clavulanate[c]	8	≥256	1 to ≥256	61.7
Aztreonam-clavulanate[d]	4	128	1 to ≥256	61.7
Aztreonam-relebactam[e]	8	16	1 to 128	72.3
Aztreonam-vaborbactam[f]	32	128	2 to ≥256	17.0
Aztreonam-vaborbactam[g]	64	≥256	2 to ≥256	6.4
Amoxicillin-clavulanate	≥256	≥256	16 to ≥256	
Ceftazidime-avibactam[h]	64	128	0.125 to ≥256	25.5
Imipenem-relebactam	≥64	≥64	0.5 to ≥64	
Levofloxacin	8	≥32	0.25 to ≥32	38.3
Meropenem-vaborbactam	≥64	≥64	0.25 to ≥64	
Trimethoprim-sulfamethoxazole[i]	8	≥16	0.03 to ≥16	44.7

	MIC (mg/liter)			Susceptibility[a] (%)		
Agent	50%	90%	Range	S	I	R
Cefiderocol	0.125	0.5	<0.03 to 1	100	0	0
Ceftazidime	64	>128	1 to >128	16.2	2.7	81.1
Levofloxacin	8	>16	0.25 to >16	35.1	13.5	51.4
Minocycline	2	4	0.125 to 8	97.3	2.7	0
Polymyxin B[b]	0.5	>8	0.03 to >8	0	75.7	24.3
TMP-SMZ[c]	8	>8	0.03 to >8	37.8	0	62.2

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Biagi M, Tan X, Wu T, et al. J Clin Microbiol **2020**; 58(2). 2. Biagi M, et al.. Antimicrob Agents Chemother **2020**; 64(9). **3.**Biagi M, et al.. Antimicrob Agents Chemother **2020**; 64(12).

Susceptibility Testing

TABLE 4 Disk diffusion performance characteristics compared to broth microdilution[a]

Organism(s)	No. of isolates	% (no.) with agreement or error																				
		30-μg HardyDisks (FDA cleared)											30-μg MASTDISCS (RUO)									
		CLSI				FDA[b] (*n* = 73)				EUCAST			CLSI				FDA[b]				EUCAST		
		CA	mE	ME	VME	CA	mE	ME	VME	CA	ME	VME	CA	mE	ME	VME	CA	mE	ME	VME	CA	ME	VME
Carbapenem-resistant *Enterobacterales*	58	91 (53)	9 (5)	0	0	84 (49)	16 (9)	0	0	88 (51)	17 (7)	0	88 (51)	12 (7)		0	86 (50)	14 (8)	0	0	90 (52)	14 (6)	0
Carbapenemase-producing CRE	26	88 (23)	12 (3)	0	0	81 (21)	19 (5)	0	0	88 (23)	12 (3)	0	88 (23)	12 (3)	0	0	81 (21)	19 (5)	0	0	92 (24)	8 (2)	0
Non-carbapenemase-producing CRE	32	94 (30)	6 (2)	0	0	88 (28)	12 (4)	0	0	88 (28)	12 (4)	0	88 (28)	12 (4)	0	0	91 (29)	9 (3)	0	0	88 (28)	12 (4)	0
Citrobacter freundii complex	2	50 (1)	50 (1)	0	0	50 (1)	50 (1)	0	0	50 (1)	100 (1)	0	50 (1)	50 (1)	0	0	50 (1)	50 (1)	0	0	50 (1)	100 (1)	0
Enterobacter cloacae complex	15	93 (14)	7 (1)	0	0	80 (12)	20 (3)	0	0	87 (13)	25 (2)	0	87 (12)	13 (2)	0	0	87 (13)	13 (2)		0	93 (14)	7 (1)	0
Escherichia coli	15	100 (15)	0	0	0	100 (15)	0	0	0	80 (12)	20 (3)	0	100 (15)	0	0	0	100 (15)	0	0	0	87 (13)	13 (2)	0
Klebsiella aerogenes	2	100 (2)	0	0	0	100 (2)	0	0	0	100 (2)	0	0	100 (2)	0	0	0	100 (2)	0	0	0	100 (2)	0	0
Klebsiella oxytoca	6	83 (5)	17 (1)	0	0	83 (5)	17 (1)	0	0	83 (5)	17 (1)	0	100 (6)	0	0	0	83 (5)	17 (1)	0	0	83 (5)	17 (1)	0
Klebsiella pneumoniae	15	87 (13)	13 (2)	0	0	73 (11)	27 (4)	0	0	100 (15)	0	0	73 (11)	27 (4)	0	0	73 (11)	27 (4)	0	0	83 (14)	7 (1)	0
Serratia marcescens	3	100 (3)	0	0	0	100 (3)	0	0	0	100 (3)	0	0	100 (3)	0	0	0	100 (3)	0	0	0	100 (3)	0	0
Non-glucose-fermenting Gram-negative bacilli	39	85 (33)	8 (3)	12 (3)	0	36 (5)	64 (9)	0	0	79 (31)	15 (4)	31 (4)	85 (33)	15 (6)	0	0	50 (7)	43 (6)	0	25 (1)	90 (35)	8 (2)	15 (2)
Pseudomonas aeruginosa	14	93 (13)	7 (1)	0	0	36 (5)	64 (9)	0	0	79 (11)	14 (2)	25 (1)	86 (12)	14 (2)	0	0	50 (7)	43 (6)	0	25 (1)	86 (12)	10 (1)	25 (1)
Acinetobacter baumannii complex	14	64 (9)	14 (2)	25 (3)	0					64 (9)	20 (2)	33 (3)	71 (10)	29 (4)	0	0					86 (12)[c]	20 (1)[c]	11 (1)[c]
Stenotrophomonas maltophilia	11	100 (11)	0	0	0					100 (11)	0	0	100 (11)	0	0	0					100 (11)[c]	0	0
All isolates	97	89 (86)	8 (8)	3 (3)	0	75 (54)	25 (18)		0	85 (82)	17 (11)	12 (4)	87 (84)	13 (13)	0	0	79 (57)	19 (14)	0	20 (1)	90 (87)	13 (8)	12 (4)

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Morris CP, et al. J Clin Microbiol. 2020 Dec 17;59(1):e01649-20.

Susceptibility Testing

TABLE 3 Overall performance of Etest and MTS compared to BMD for 109 *S. maltophilia* bloodstream isolates[a]

			No. (%) with indicated value							
			Etest				MTS			
Antimicrobial	Isolate group	*n*	CA	VME	ME	MI	CA	VME	ME	MI
SXT	Overall	109	107 (98)	1 (9)	0 (0)	0 (0)	107 (98)	1 (9)	0 (0)	109 (0.9)
	≥R + 1	9		0	NA	0		0	NA	0
	R + S	23		1 (4)	0	0		1 (4)	0	1 (4)
	≤S − 1	77		NA	0	0		NA	0	0
LEV	Overall	109	93 (85)	4 (9)	4 (7)	17 (16)	90 (83)	1 (5)	0 (0)	16 (15)
	≥R + 2	9		0	NA	0		0	NA	0
	I ± 1	40		0	1 (3)	15 (38)		1 (3)	0	14 (35)
	≤I − 2	60		NA	1 (2)	2 (3)		NA	0	2 (3)
MIN	Overall		101 (93)	0 (0)	0 (0)	0 (0)	108 (99)	0/0 (0)	0 (0)	0 (0)
	≥R + 2	0		0	NA	0		0	NA	0
	I ± 1	4		0	0	0		0	0	0
	≤I − 2	105		NA	0	8 (8)		NA	0	1 (1)

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Khan A, et al. Antimicrob Agents Chemother. 2021 Feb 8;65(5):e02631-20.

Treatment

Author (Publication Year)	Study Design, Period, Region	Treatment Arms, No. of Patients	Dosing and Duration	Patient Demographics	Diagnosis and Source of Infection	Mortality	Clinical Outcomes	Microbiologic Outcomes
Clinical studies comparing monotherapy to combination therapy								
Jacobson (2016) [68]	Retrospective, single-center; 2010–2014, USA	93 adults; 45 MIN, 48 MIN combination	MIN 200 mg/d	Adults, 53% ICU; APACHE II 15 ± 6.6	PNA (63%), BSI (15%)	30 d mortality: MIN 16.0% (15/94)	Clinical failure: MIN MT and CT, 18% (17/94). MIN MT, 9% (4/45) Failure related to APACHE II, or MIC = 4 mg/L (29.4%) vs MIC <4 mg/L (2.6%) (P = .004)	NR
Araoka (2017) [51]	Retrospective, single-center, 2012–2014, Japan	20 pts; 14 TMP-SMX + FQ, 6 TMP-SMX or FQ	NR	Adults; ages, 60.5–65 y; Pitt scores 1–2.5; neutropenia 43%–50%	BSI	30 d mortality: TMP-SMX + FQ, 50% (7/14); TMP-SMX alone, 33% (2/6)	NR	NR
Shah (2019) [69]	Retrospective, single-center, 2011–2017, USA	252 adult pts; 218 monotherapy, 38 combination (various)	NR	Age 62 y; MV 69.4%; ICU 76.2%; 54.4% polymicrobial pneumonia; median APACHE II score 16	PNA	30 d ACM: CT 39.5% (15/38); MT 22.9% (49/214); (P = .03) 30 d IRM: CT 15.8% (6/38); MT 8.9% (19/214); (P = .19)	7 d clinical response: CT 47.4%; MT 39.7% (P = .38) controlling for immune status, APACHE II score, and polymicrobial pneumonia	Emergence of resistance during or after treatment (n = 33 pts): CT 15.8% (6/38) MT 12.6% (27/214) 30 d infection recurrence: CT 10.5%; MT 7.9% Emergence of resistance during therapy (n = 54): CT 37.5% (3/8); MT 32.6% (15/46) Emergence of resistanc after therapy (n = 21): CT 75% (3/4); MT 70.6% (12/17)
Tokatly Latzer (2019) [70]	Retrospective, multicenter (4 sites), 2012–2017, Israel	61 pts; 22 TMP-SMX, 13 CIP, 6 CAZ, 11 TMP-SMX + CIP, 9 TMP-SMX + CIP + MIN, 7 none	TMP-SMX 20 mg/kg/d, MIN 8 mg/kg/d, CIP 30 mg/kg/d, CAZ 150 mg/kg/d (IV)	Pediatric; age 2.1 y; prior MV 72%; recent chemotherapy 27%	BSI	42% ACM; attributable mortality within 30 d, 25%; CIP + TMP-SMX + MIN (n = 9) resulted in longest survival (mean, 54 d [range, 44–65 d])	NR	NR
Guerci (2019) [71]	Retrospective, multicenter (25 ICUs), 2012–2017, France	282 pts; 82 TMP-SMX, 71 CIP, 68 T/C	NR Median duration of effective therapy, 11 d (7–15)	Adults; age 65 y, 81% VAP, 84% intubated; 100% ICU, IC <15%	100% nosocomial PNA; 81% VAP	In-hospital mortality 49.7%; attributable mortality 24.3%	Treatment failure 23.1%; combination therapy and DOT >7 d did not impact mortality	NR
Sierra-Hoffman (2020) [72]	Retrospective, multicenter registry (6 sites), 2015–2018; USA	29 pts; 9 MIN, 20 MIN combination	25 MIN 100 mg BID, 4 MIN 200 mg BID Median 9 d (IQR, 5–15)	Adults; age 57.6 y; MV 53.5%	PNA 71.4%; BSI 14.3%; skin 8.6%; UTI 5.7%	30.0% (in-hospital)	Clinical response: PNA + BSI, 79.3% (23/29)	27.6% (PNA + BSI); 1 emergence of R in MIN

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Kullar R, Wenzler E, Alexander J, Goldstein EJC. Open Forum Infect Dis. 2022 Mar 21;9(5):ofac095.

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

Severity of Infection	Preferred Treatment	Alternative Treatment
Mild	TMP-SMX, minocycline	Tigecycline, levofloxacin, cefiderocol
Moderate-severe	TMP-SMX + minocycline, ATM + CAZ-AVI	Two drug combination of TMP-SMX, minocycline, tigecycline, or cefiderocol

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Clin Infect Dis **2022**.

Pipeline

Table 3 | **Activity of β-lactamase inhibitors in combination (modified according to the WHO clinical pipeline report[3])**

β-lactamase inhibitor (synonym, chemical class)	Combination partner	Development phase	ESBL-E	CRE				CRAB	CRPA
			Class A (ESBL)	Class A (KPC)	Class D (OXA-48)	Class B (NDM)	PBP2		
Durlobactam (ETX2514; DBO)	Sulbactam	3	/	/	/	/	●	●	/
Enmetazobactam (AAI101; penicillanic acid sulfone)	Cefepime	3	●	?	○	○	-	○	○
Taniborbactam (VNRX-5133; boronate)	Cefepime	3	●	●	●	●	-	○	?
Avibactam (DBO)	Aztreonam	3	●	●	●	●	○	○	○
Zidebactam (DBO)	Cefepime	1	●	●	●	?	●	○	?
Nacubactam (DBO)	Meropenem	1	●	●	●	?	●	○	○
ETX0282 (DBO)	Cefpodoxime (oral application)	1	●	●	●	○	●	○	○
VNRX-7145 (boronate)	Ceftibuten (oral application)	1	●	●	●	○	-	○	○
ARX-1796 (DBO; oral avibactam prodrug)	To be determined (oral application)	1	?	?	?	○	○	○	○

Theuretzbacher U, Bush K, Harbarth S, et al.. Nat Rev Microbiol **2020**; 18(5): 286-98. 2. Meletiadis J,, et al.. Int J Antimicrob Agents **2021**; 58(5): 106440.

Cefepime-taniborbactam

TABLE 2 K_i values for taniborbactam with various β-lactamases

		K_i (μM)[a]		
β-Lactamase	Class	Taniborbactam	Avibactam	Vaborbactam
SHV-5	A	0.003 ± 0.0002	ND	ND
CTX-M-15	A	0.017 ± 0.002	0.011 ± 0.001	0.158 ± 0.006
KPC-2	A	0.004 ± 0.001	0.0056 ± 0.0007	0.022 ± 0.002
NDM-1	B	0.081 ± 0.003	>30	>30
VIM-2	B	0.019 ± 0.001	>30	>30
IMP-1	B	>30	>30	>30
P99 AmpC	C	0.002 ± 0.0003	0.013 ± 0.0003	0.053 ± 0.004
OXA-48	D	0.35 ± 0.007	0.26 ± 0.005	0.35 ± 0.007

Theuretzbacher U, Bush K, Harbarth S, et al.. Nat Rev Microbiol **2020**; 18(5): 286-98. 2. Meletiadis J,, et al.. Int J Antimicrob Agents **2021**; 58(5): 106440.

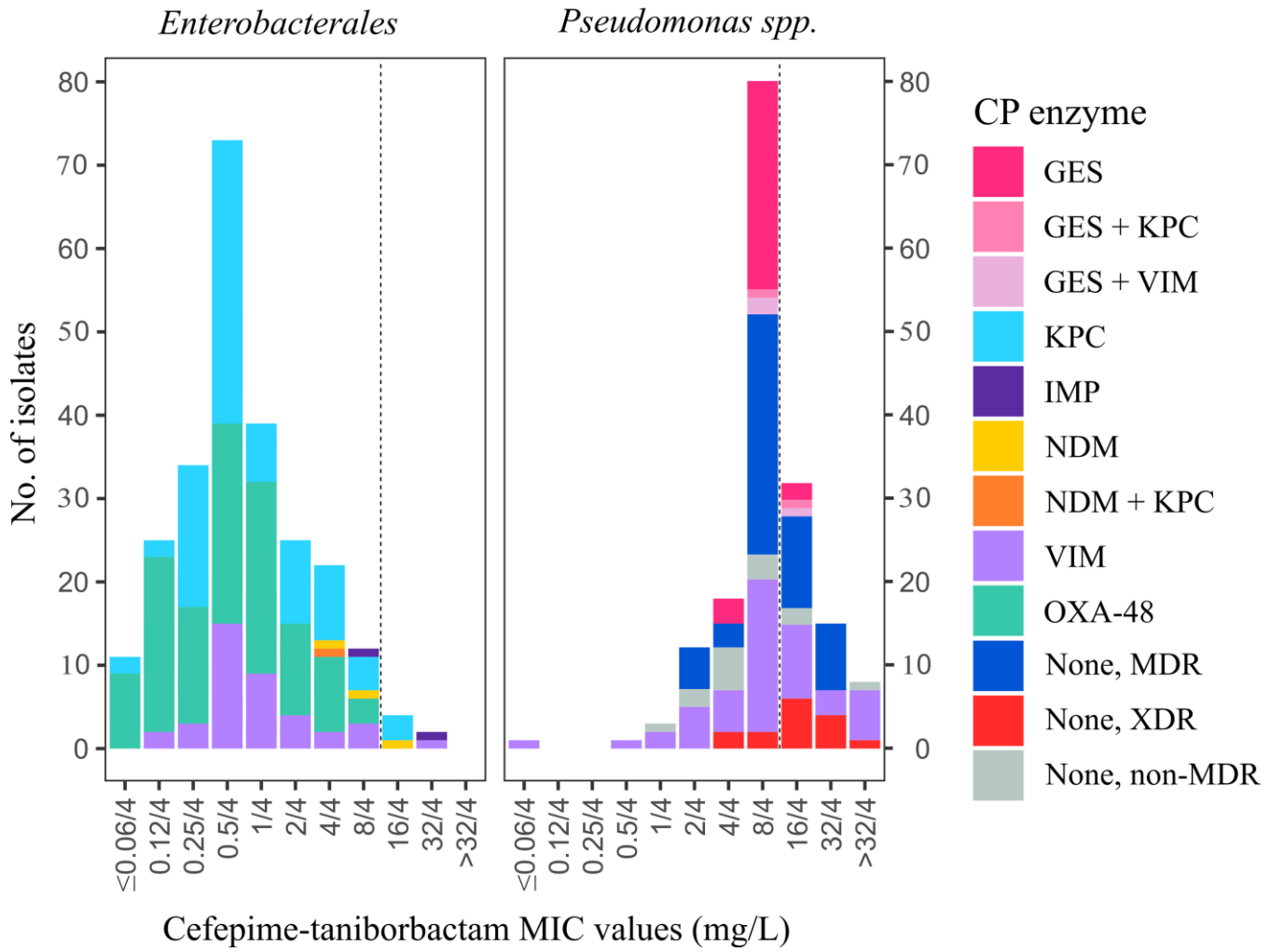
Cefepime-taniborbactam

TABLE 2 Activities of cefepime-taniborbactam and comparators in meropenem-resistant isolates according to EUCAST breakpoints by the carbapenemase group detected[a]

	FEP			FTB			CZA			CT			IMR			MEV		
	MIC (mg/L)			MIC (mg/L)			MIC (mg/L)			MIC (mg/L)			MIC (mg/L)			MIC (mg/L)		
Carbapenamase group	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S
Enterobacterales (*n* = 247)	32	>32	15.8	0.5/4	4/4	97.6	1/4	>32/4	80.6	>32/4	>32/4	11.7	1/4	8/4	71.7	1/8	16/8	89.1
MER-R (27.1% [67/247])	>32	>32	4.5	2/4	8/4	94.0	2/4	>32/4	73.1	>32/4	>32/4	3.0	2/4	>32/4	53.7	4/8	>32/8	62.7
KPC (35/67)	>32	>32	0	2/4	8/4	94.3	2/4	8/4	94.3	>32/4	>32/4	0	0.25/4	2/4	97.1	0.5/8	4/8	100
OXA-48 (15/67)	16	>32	20.0	4/4	8/4	100	1/4	2/4	93.3	>32/4	>32/4	13.3	32/4	>32/4	0	>32/8	>32/8	6.7
VIM, NDM, or IMP (16/67)	>32	>32	0	2/4	16/4	87.5	>32/4	>32/4	12.5	>32/4	>32/4	0	8/4	>32/4	12.5	16/8	>32/8	31.2
Pseudomonas spp. (*n* = 170)	32	>32	20.0	8/4	32/4	67.6	8/4	>32/4	61.2	8/4	>32/4	34.7	16/4	>32/4	37.1	32/8	>32/8	32.9
MER-R (71.8% [122/170])	32	>32	10.7	8/4	32/4	63.9	8/4	>32/4	51.6	8/4	>32/4	17.2	32/4	>32/4	16.4	>32/8	>32/8	8.2
GES (30/122)[b]	>32	>32	0	8/4	8/4	93.3	4/4	8/4	96.7	8/4	8/4	0	32/4	32/4	0	>32/8	>32/8	0
VIM (49/122)[c]	>32	>32	13.0	8/4	>32/4	61.2	>32/4	>32/4	14.3	>32/4	>32/4	0	>32/4	>32/4	0	>32/8	>32/8	4.1
Non-carbapenemase (43/122)	32	>32	16.3	16/4	32/4	46.5	8/4	>32/4	62.8	8/4	>32/4	48.8	4/4	32/4	46.5	16/8	>32/8	18.6

Lomovskaya O, et al.. Antimicrob Agents Chemother **2021**; 65(6). 2. Hernández-García M, et al.. Antimicrob Agents Chemother **2022**; 66(3): e0216121.

Cefepime-taniborbactam



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Lomovskaya O, et al.. Antimicrob Agents Chemother **2021**; 65(6). 2. Hernández-García M, et al.. Antimicrob Agents Chemother **2022**; 66(3): e0216121.

Cefepime-taniborbactam

Table 1
MIC distribution, MIC_{50}, MIC_{90} and susceptibility rates for *Klebsiella pneumoniae* strains (N=100), as obtained from susceptibility testing with broth microdilution ISO 20776 method.

Antimicrobial Agent	MIC distribution of *Klebsiella pneumoniae* isolates														MIC_{50}	MIC_{90}	S	I	R
	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512					
Aztreonam			11	1				2		4	2	79			128	128	13%	0%	87%
Cefepime			1				1		4	16	44	15	7	12	64	512	1%	1%	98%
Cefepime-taniborbactam 4 mg/L			8	16	20	17	17	6	5	5	1	2			2	16	N/A	N/A	N/A
Ceftazidime-avibactam 4 mg/L					2	1	1	1				95			128	128	5%	0%	95%
Ceftolozane-tazobactam 4 mg/L						1					2	97			128	128	1%	0%	99%
Gentamicin*			1	20	13	1	3	9	3	9	41				16	64	35%	0%	65%
Levofloxacin				2	1	1	1	8	54	19	12				16	64	4%	1%	95%
Meropenem					1	2	2	7	12	42	33				32	64	4%	9%	87%
Meropenem-taniborbactam 4 mg/L			15	16	1	5	2	4	2	1	3				0.12	4	N/A	N/A	N/A
Meropenem-vaborbactam 8 mg/L			2		2		1	8	9	31	30	16			32	128	14%	0%	86%
Piperacillin-tazobactam 4 mg/L								1	1			1	97		256	256	1%	1%	98%
Tigecycline				6	30	29	21	12	2						2	8	6%	0%	94%

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Theuretzbacher U, Bush K, Harbarth S, et al.. Nat Rev Microbiol **2020**; 18(5): 286-98. 2. Meletiadis J,, et al.. Int J Antimicrob Agents **2021**; 58(5): 106440.

Cefepime-taniborbactam

Table 2
MIC distribution, MIC_{50}, MIC_{90} and susceptibility rates for *Pseudomonas aeruginosa* strains (N=100), as obtained from susceptibility testing with broth microdilution ISO 20776 method.

Antimicrobial Agent	MIC distribution of *Pseudomonas aeruginosa* isolates														MIC_{50}	MIC_{90}	S	I	R
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512					
Amikacin					2	1	4	6	14	20	34	13	6		64	128	27%	0%	73%
Aztreonam							4	37	33	16	6	4			16	32	0%	74%	26%
Cefepime								10	23	30	29	5	2	1	32	64	0%	10%	90%
Cefepime-tazobactam 8 mg/L								7	34	36	19	4			32	64	N/A	N/A	N/A
Cefepime-taniborbactam 4 mg/L					1	9	4	32	42	9	3				16	32	N/A	N/A	N/A
Ceftazidime-avibactam 4 mg/L					2	3	3	12	28	30	12	10			32	64	20%	0%	80%
Ceftolozane-tazobactam 4 mg/L				1	2	1	1		2	4	7	82			128	128	5%	0%	95%
Ciprofloxacin			5	2	4			2	24	59					32	32	0%	11%	89%
Imipenem						2	1		5	12	17	63			128	128	0%	3%	97%
Meropenem							3	5	19	22	51				32	64	0%	8%	92%
Meropenem-vaborbactam 8 mg/L					1		3	5	14	14	31	32			64	128	9%	0%	91%
Piperacillin-tazobactam 4 mg/L							1		4			73	22		128	256	0%	5%	95%

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Theuretzbacher U, Bush K, Harbarth S, et al.. Nat Rev Microbiol **2020**; 18(5): 286-98. 2. Meletiadis J,, et al.. Int J Antimicrob Agents **2021**; 58(5): 106440.

Summary

- **Prevalence of MBL-producing Gram negative pathogens continues to increase in the U.S. and globally**
- **High mortality due to delays in recognition, detection, time to effective antimicrobial therapy, and the very limited number of treatment options**
- **ATM + CAZ-AVI should be first line for MBL producing Enterobacterales**
- **Cefiderocol should be first line for MBL producing *P. aeruginosa***
- ***S. maltophilia??***

Emerging Gram-negative Pathogens: Metallo-β-lactamase Producers

IDAC Spring Symposium 2022

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