BPWG Report 1

Members:

- Breakpoint Working Group (BP WG) **Folder 5**
- Dr. Eliopoulos and Dr. Lewis, Co-Chairholders
- Dr. Bush – Recording Secretary

- Members present: Karen Bush, Marcelo Galas, Jim Lewis, Amy Mathers, David Nicolau, Michael Satlin, Simone Shurland, Lauri Thrupp, , Barb Zimmer
- Matthew Wikler (non-voting technical advisor)
- Members absent: George Eliopoulos, Robin Patel, Kerry Snow, Advisor, Hui Wang

Meropenem-Vaborbactam

- BPWG folder – File set 7 for supporting materials
- Sponsor slides presented at BPWG not available in the agenda book

Mechanism of Action of Vaborbactam: Unique Mechanism

•Vaborbactam is novel, non-hydrolysable inhibitor of class A and class C beta-lactamases that is based on a cyclic boronic acid pharmacophore

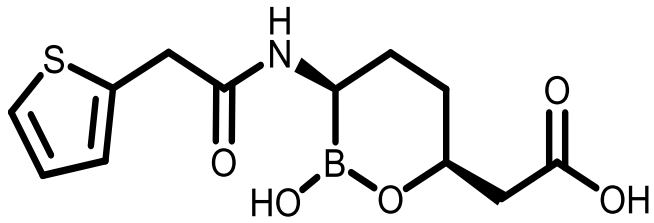
- Inhibition is based on formation of a covalent bond between the boronate moiety of vaborbactam and the catalytic serine residue of beta-lactamases

•Inhibition of KPC by vaborbactam has unique characteristics compared to its inhibition of other beta-lactamases

- Nearly irreversible inhibition of KPC due to very slow off-rate of dissociation of the enzyme-inhibitor complex

•The distinctive binding mode of vaborbactam to the KPC enzyme differentiates vaborbactam from other BLIs including avibactam

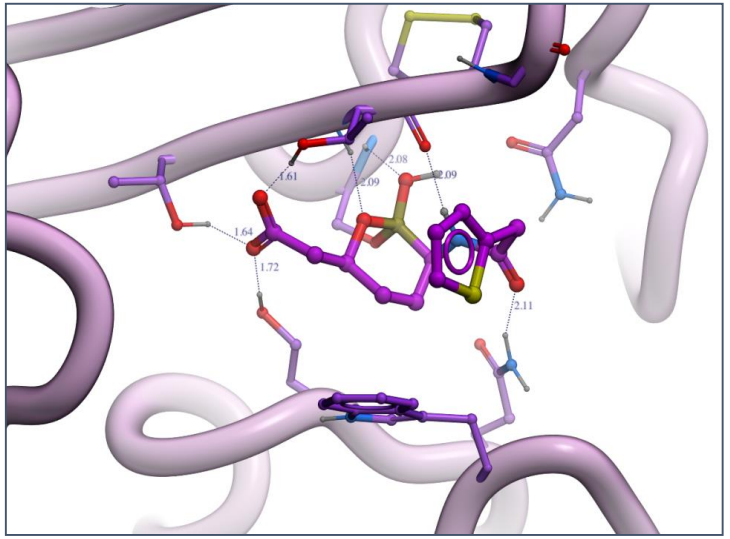
- The ability of vaborbactam to inhibit KPC even in the presence of KPC mutations shown to reduce the potency of KPC inhibition by avibactam



Vaborbactam

Hecker et. al. J Med Chem 2015;58:3682-3692

KPC with vaborbactam, 1.2 A



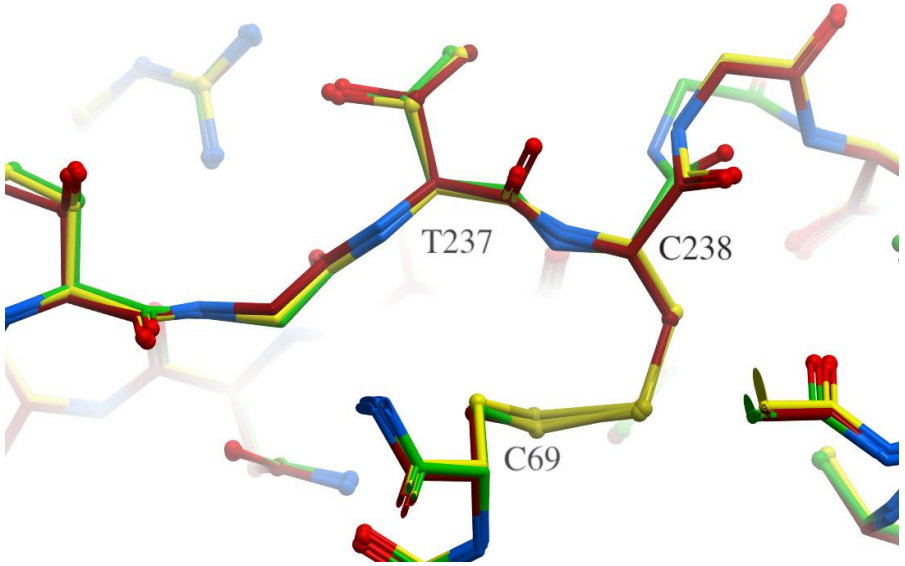
Kinetics of KPC inhibition by Vaborbactam

Nearly irreversible inhibition of KPC due to very slow off-rate of dissociation of the enzyme-inhibitor complex

	Inactivation efficiency k2/K, ($M^{-1}s^{-1}$)	k_{off}, min^{-1} (37ºC)	Residence time (min)	K_d (µM)
Vaborbactam	7.3×10^3	0.0010	**992**	0.0023
Avibactam	13.2×10^3	0.013	77	0.017

BD, Table 4, page 15

Comparison of backbone conformational changes in the vicinity of the active site of KPC-2 upon binding of vaborbactam (brown carbon atoms) and avibactam (green carbon atoms). Apo-enzyme structures shown with yellow carbon atoms.



- Active site of KPC-2 is “pre-adjusted” to vaborbactam binding:
  - ✓ no backbone movement is seen around oxyanion hole in our KPC-2-vaborbactam structure
  - ✓ avibactam binding does result in backbone shifts
  - ✓ This observation may explain particular potency of vaborbactam against KPC

Activity of Meropenem-Vaborbactam against Key Enterobacteriaceae Pathogens Collected in 2016 Worldwide Surveillance

Study	No. tested		MIC Range	50%	90%	%S[a] (4 mg/L)	%S[b] (8 mg/L)
All Enterobacteriaceae	12,084	MER	≤0.015 - >32	0.03	0.06	97 (97.8)	(98.2)
		MER+VAB	**≤0.015 - >32**	**0.03**	**0.06**	**99.2**	**99.3**
Escherichia coli	5,122	MER	≤0.015 - >32	≤0.015	0.03	99.8 (99.9)	(99.9)
		MER+VAB	**≤0.015 - >32**	**≤0.015**	**0.03**	**99.9**	**99.9**
Klebsiella pneumoniae	2,705	MER	≤0.015 - >32	0.03	2	89.5 (91.6)	(93.1)
		MER+VAB	**≤0.015 - >32**	**0.03**	**0.06**	**97.3**	**97.5**
Enterobacter cloacae species complex	1,086	MER	≤0.015 - >32	0.03	0.125	97.2 (98.3)	(98.6)
		MER+VAB	**≤0.015 - >32**	**0.03**	**0.03**	**98.9**	**99**
Serratia marcescens	552	MER	≤0.015 - >32	0.06	0.06	99.3 (99.5)	(99.6)
		MER+VAB	**≤0.015 - 1**	**0.06**	**0.06**	**100**	**100**
Citrobacter spp.	479	MER	≤0.015 - 4	≤0.015	0.06	99 (99)	(99.8)
		MER+VAB	**≤0.015 - 4**	**0.03**	**0.03**	**100**	**100**
Morganella morganii	254	MER	≤0.015 - 1	0.06	0.125	100 (100)	(100)
		MER+VAB	**≤0.015 - 0.25**	**0.06**	**0.06**	**100**	**100**

[a]Percent Susceptible using FDA Approved Breakpoints and Sponsor proposal using 3 categories
[b]Percent Susceptible using Proposed 2-category breakpoints

New data; 2015 data in BD, Table 7, page 19

Activity of Meropenem-Vaborbactam against CRE and KPC-producing CRE Collected in 2016 Worldwide and US Surveillance

Study	No. tested		MIC Range	50%	90%	%S[a]	%S[b]
CRE Enterobacteriaceae Worldwide	342	MER	0..25 - >32	32	>32	1.8 (21.3)	(37.1)
		MER+VAB	**≤0.015 - >32**	**1**	**>32**	**72.2**	**74.6**
CRE Enterobacteriaceae US	61	MER	1 - >32	16	>32	1.6 (30)	(50)
		MER+VAB	**≤0.015 - 4**	**0.03**	**1**	**100**	**100**
KPC-producing Enterobacteriaceae, Worldwide	174	MER	1 - >32	32	>32	0.6 (13.8)	(29.9)
		MER+VAB	**≤0.015 - 8**	**0.06**	**1**	**98.9**	**99.4**
KPC-producing Enterobacteriaceae, US	54	MER	1 - >32	16	>32	1.9 (31.5)	(46.3)
		MER+VAB	**≤0.015 - 2**	**0.03**	**1**	**100**	**100**

New data; 2015 data in BD, Table 7, page 19

[a]Percent Susceptible using FDA Approved Breakpoints and Sponsor proposal using 3 categories

[b]Percent Susceptible using Proposed 2-category breakpoints

Activity of Meropenem-Vaborbactam and Comparators against *Pseudomonas aeruginosa* Collected in US Surveillance

Pathogen	No. tested	Year	Drug	MIC Range	50%	90%	%S[a] (4 mg/L)	%S[b] (8 mg/L)	%S[b] (CLSI)
P. aeruginosa	1,130	2017	MER	≤0.015 - >32	0.5	16	82.7	88.2	75.8
			MER+VAB	**≤0.015 - >32**	**0.5**	**16**	**82.4**	**88.2**	**-**
			CAZ	0.12 - >32	2	32	75.9	82.2	82.2
			CAZ+AVI	≤0.015 - >32	2	8	89.9	97.1	97.1
	4,735 *	2012-2016	CEF+TAZ	0.03 - >32	0.5	2	97.4	98.7	97.4

[a]Percent Susceptible using FDA Approved Breakpoints and Sponsor proposal using 3 categories
[b]Percent Susceptible using Proposed 2-category breakpoints
Sponsor is not proposing *P. aeruginosa* breakpoints to CLSI
*Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2012–2016) Enterobacteriaceae and Pseudomonas aeruginosa Isolates by US Census DivisGlobal Surveillance: ID Week 2017

Activity of Meropenem-Vaborbactam against Acinetobacter , Stenotrophomonas and Burkholderia Collected in 2017 US Surveillance

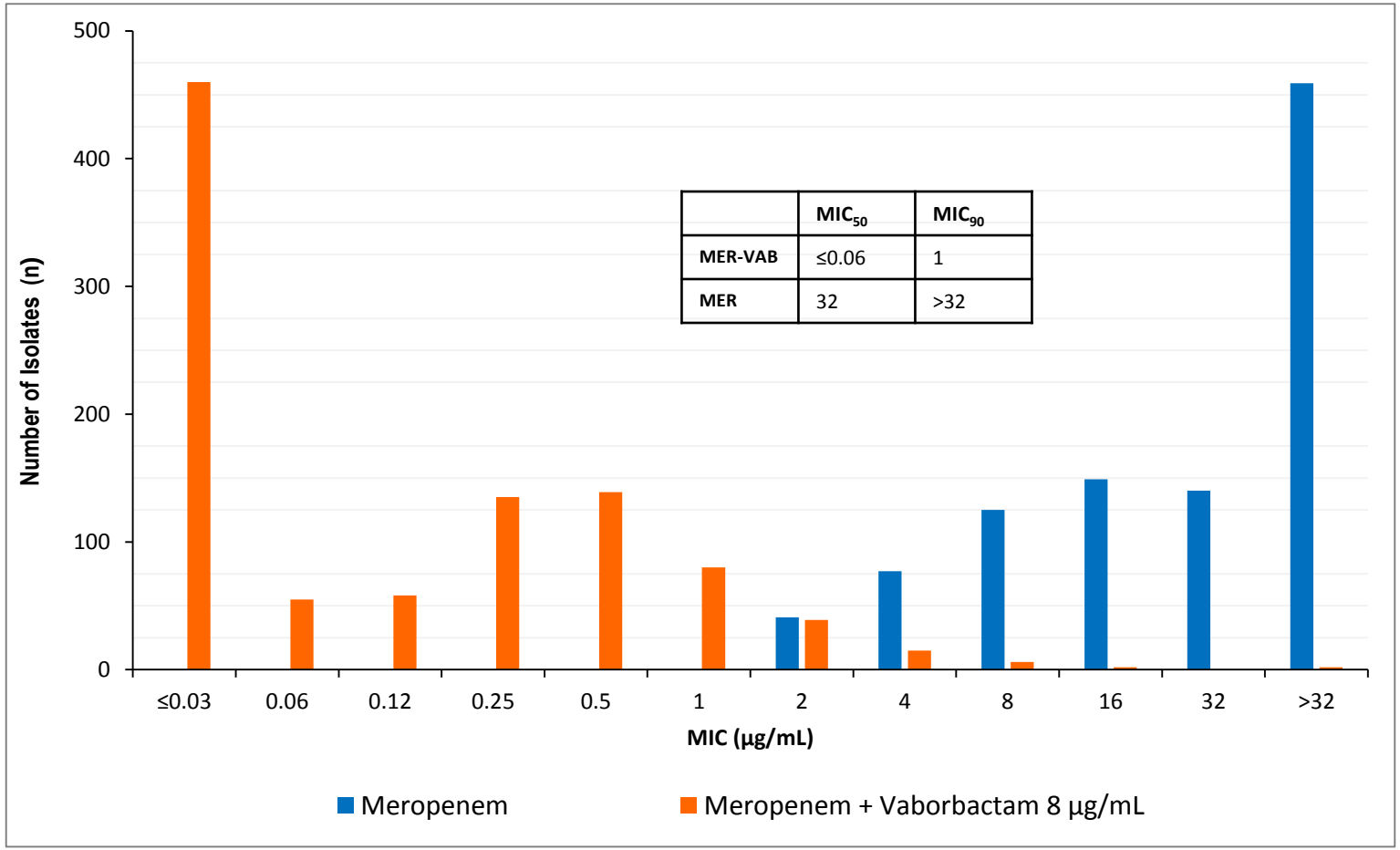
Study	No. tested		MIC Range	50%	90%	%S[a] (4 mg/L)	%S[b] (8 mg/L)
Acinetobacter baumannii calcoaceticus species **complex**	608	MER	0.12 - >32	>32	>32	31.2	32.7
		MER+VAB	**0.12- >32**	**>32**	**>32**	**31.1**	**32.1**
Stenotrophomonas maltophilia	196	MER	0.5 - >32	>32	>32	1.0	1.0
		MER+VAB	**0.12 - >32**	**>32**	**>32**	**1.0**	**2.0**
Burkholderia cepacia species complex	23	MER	0.12-8	2	4	100	100
		MER+VAB	**0.12-2**	**0.5**	**1**	**95.7**	**100**

[a]Percent Susceptible using FDA Approved Breakpoints and Sponsor proposal using 3 categories
[b]Percent Susceptible using Proposed 2-category breakpoints

New data; 2015 data in BD, Table 7, page 19

Meropenem-Vaborbactam has Potent Activity against KPC-producing Enterobacteriaceae

Activity in 991 KPC-producing *Enterobacteriaceae*



	MIC_{50}	MIC_{90}
MER-VAB	≤0.06	1
MER	32	>32

BD, Figure 3, page 22

Data from: Hackel et al., AAC 2017

Meropenem-Vaborbactam: Summary of Microbiology

- Vaborbactam inhibits Class A beta-lactamases, notably KPC, and thus restores the activity of meropenem against KPC-producing Enterobacteriaceae

- Vaborbactam does not have intrinsic antibacterial activity

- Vaborbactam does not potentiate the activity of meropenem against OXA-48- and MBL-containing strains

- The activity of meropenem-vaborbactam against *P. aeruginosa* and *Acinetobacter baumannii* is similar to that of meropenem alone.

- Vaborbactam does not decrease the activity of meropenem against meropenem susceptible organisms

- The in vitro potency of meropenem-vaborbactam is not reduced in the presence human serum, lung surfactant or urine.

- Reduced susceptibility to meropenem-vaborbactam in laboratory derived mutants and in clinical isolates is associated with the previously described meropenem resistance mechanisms such as inactivation of major porins, an increase in the copy number of the bla_{KPC} gene and an increased efflux. There is no a single mechanism that is responsible for M-V MICs at or above proposed breakpoints

- Isolates that are resistant to ceftazidime-avibactam due to mutations in bla_{KPC} are often susceptible to meropenem-vaborbactam

Bacterial Strains Used in Efficacy Studies

Strain	Beta-Lactamases	OmpK35	OmpK36	Meropenem MIC (µg/mL)		
				Alone	w/Vabor 4 µg/mL	w/Vabor 8 µg/mL
EC1007	KPC-3	ND	ND	8	≤0.06	≤0.06
ECL1058	KPC-3, SHV-11, TEM-1	FL	FL	8	0.125	0.125
ECL1061	KPC-3, Hyper AmpC Expression	FS aa#287	FL	16	0.125	0.125
ECL1079	KPC-3	stop aa#60	stop aa#77	>64	32*	8
KP1061	KPC-3, SHV-11, TEM-1	FS aa#42	FL	16	≤0.06	≤0.06
KP1074	KPC-3, SHV-11, TEM-1	FS aa#42	GD	>64	1	0.5
KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	FS aa#208	GD	32	0.5	0.25
KP1092	KPC-2, SHV-11, SHV-12, TEM-1	FS aa#42	IS at -45	>64	128	32
KP1093	KPC-3, SHV-11, TEM	FS aa#42	GD	>64	2	0.5
KP1094	KPC-2, TEM-1, LEN-17	stop aa#230	stop aa#92	>64	32	4
KP1096	KPC-2, TEM, SHV-11	L63V, E132K	IS at nt#126	>64	64	16
KP1099	KPC-2, SHV-11, SHV-12, CTX-M-14	FS aa#29	GD	>64	4	1
KP1100	KPC-3, TEM, SHV	FS aa#42	GD	>64	16	4
KP1194	KPC-2 TEM SHV	FS aa#42	IS at -45	>64	64	8
KP1223	KPC-2, SHV, TEM	FS aa#29	GD	>64	64	8
KP1244	KPC-3, SHV-11, SHV-12	FS aa#42	R191L, T333N	>64	64	16
KP1254	KPC-2, SHV, TEM, OXA-10	FS aa#42	IS and ΔompK36	>64	>64	64

BD, Table 16, page 30

- 17 KPC-producing strains of Enterobacteriaceae with meropenem-vaborbactam MICs ranging from 0.06 – 64 mg/L, including those with multiple beta-lactamases and various mutations in major carbapenem porins

Meropenem-Vaborbactam at human equivalent exposures produces bacterial killing against all strains with meropenem-vaborbactam (8 mg/L) MIC ≤16 mg/L

Change in Log CFU/Thigh Over 24 Hours in Neutropenic Mice Infected with Various KPC-producing Strains of Enterobacteriaceae When Treated with Exposures Equivalent to Meropenem 2 g and Vaborbactam 2 g Administered every 8 Hours by 3 Hour Infusion in Humans (MER, 300 mg/kg and VAB, 50 mg/kg, Q2)

Strain	Organism	Meropenem MIC (µg/mL)			Change in Log CFU/thigh	
		Alone	w/VAB	w/VAB	MER 300 mg/kg every 2 hrs	
			4 µg/mL	8 µg/mL	Alone	w/VAB
EC1007	*E. coli*	8	≤0.06	≤0.06	-0.04	**-1.24**
ECL1004	*E. cloacae*	16	≤0.125	ND	-0.31	**-1.82**
ECL1026	*E. cloacae*	8	≤0.125	ND	0.26	**-2.06**
ECL1055	*E. cloacae*	8	≤0.125	ND	-0.11	**-0.95**
ECL1079	*E. cloacae*	>256	64*	8	0.45	**-0.42**
KP1004	*K. pneumoniae*	16	≤0.06	≤0.06	-0.10	**-1.73**
KP1074	*K. pneumoniae*	128	1	0.5	1.01	**-1.21**
KP1093	*K. pneumoniae*	128	4	0.5	0.58	**-1.86**
KP1094	*K. pneumoniae*	>256	32*	4	0.10	**-2.37**
KP1096	*K. pneumoniae*	>256	64*	16	0.27	**-0.90**
KP1099	*K. pneumoniae*	128	4	1	1.75	**-1.25**
KP1100	*K. pneumoniae*	>64	8	4	2.44	**-0.82**
KP1223	*K. pneumoniae*	>256	64*	8	3.20	**-1.04**
KP1244	*K. pneumoniae*	256	64*	16	0.37	**-1.80**
KP1382	*K. pneumoniae*	256	128*	16	0.29	**-1.79**

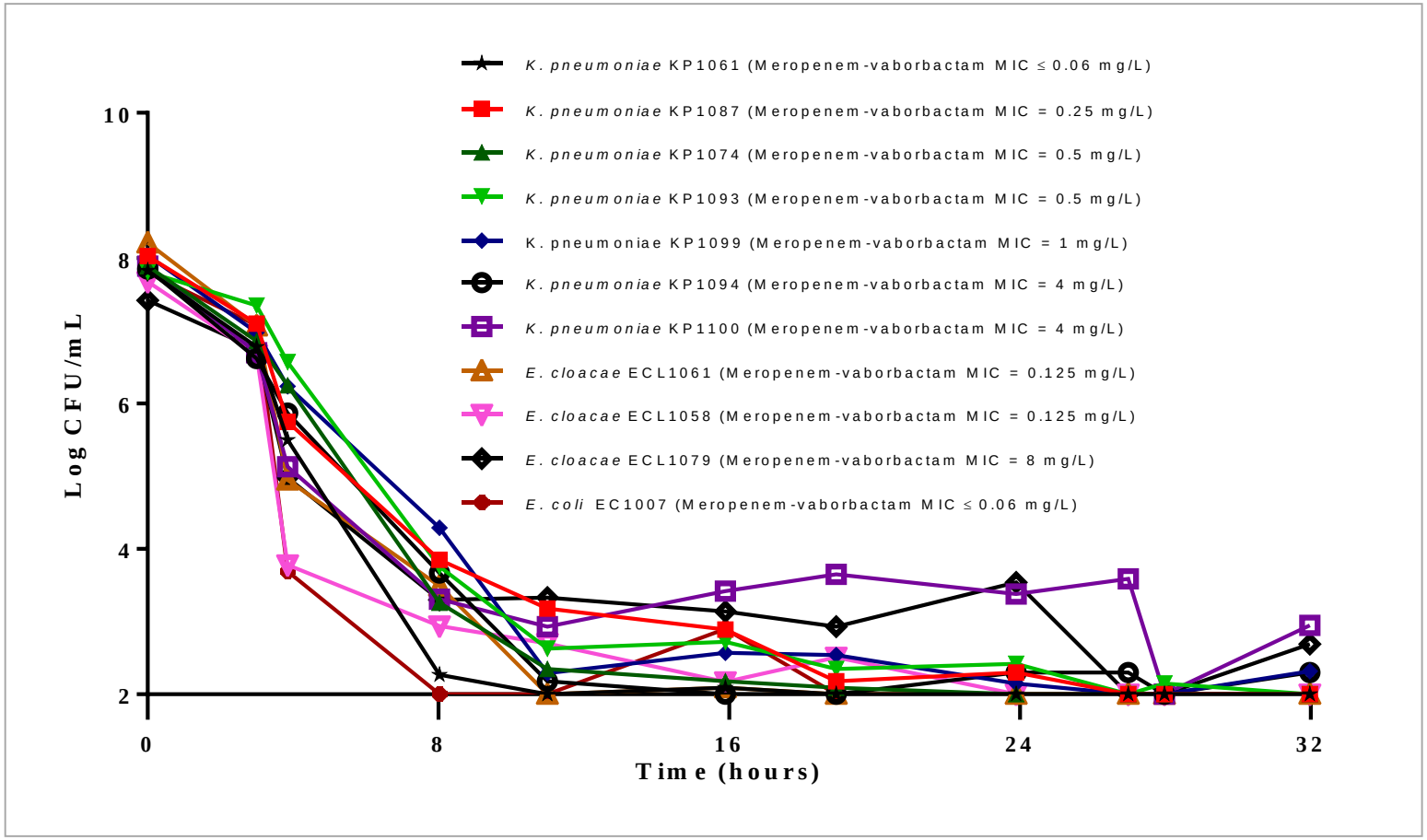
* Given used meropenem exposure no efficacy is expected against the strains with meropenem-vaborbactam MIC=32-64 mg/L

SD, Table 25, page 46

Meropenem MIC determined with vaborbactam at 8 mg/L are predictive of efficacy at human equivalent exposures

Meropenem-Vaborbactam at human equivalent exposures produces bacterial killing against all strains with meropenem-vaborbactam (8 mg/L) MIC ≤8 mg/L

Activity of simulated exposures similar to meropenem 2 g with vaborbactam 2 g based on Phase 1 data administered every 8 hours by 3 hour infusion against carbapenem-resistant, KPC-containing Enterobacteriaceae (Hollow-fiber PK-PD model)



Studies were performed using high inoculum to detect potential resistance development

BD, Figure 10, page 48

PK-PD in Non-clinical Models: The magnitude of PK-PD index

Vaborbactam PK-PD Parameter	Neutropenic mouse thigh infection model				Hollow Fiber Model			
	Goodness of Fit (R^2)	Magnitude Required for			Goodness of Fit (R^2)	Magnitude Required for		
		Stasis	1-log kill	2-log kill		Stasis	1-log kill	2-log kill
%Free > 4 mg/L	0.5	21	54	95	0	No relationship found		
%Free> 8 mg/L	0.48	12	35	62	0			
Free 24h AUC	0.5	50	267	720	0			
Free 24h AUCM-V MIC	0.70	9	38	220	0.81	12	18	25

- The PK-PD parameter that best describes the antibacterial activity of vaborbactam when administered in combination with meropenem exposures equivalent to 2 g meropenem every 8 hours by 3 hour infusion in humans is 24 h free vaborbactam AUC/meropenem-vaborbactam (at 8 mg/L) MIC ratio
- The magnitude of PK-PD index associated with 1 log reduction in mouse model was 38
- No resistance development in hollow-fiber model was observed at AUC/MIC ~36
- **24h free vaborbactam AUC:MV MIC ratio target of 38 was used for the subsequent probability of target attainment analysis**

BD, Tables 28 and 29, page 54-55

Summary of Vaborbactam Pharmacokinetics

- Dose proportional exposures and linear PK for doses of 250 – 2000 mg
- Matched PK with meropenem
- No effect of vaborbactam on meropenem PK (and vice-versa)
- Low protein binding ~ 33%
- Low potential for metabolic drug-drug interactions
  - No CYP450-dependent metabolism
  - No inhibition or induction of CYP450 enzymes
- Elimination mainly through renal excretion
  - Like meropenem, dose adjustment is required in patients with moderate and severe renal impairment

Meropenem-Vaborbactam Pharmacokinetics

Pharmacokinetic Parameters (Mean [SD] in Healthy Volunteers and Population Pharmacokinetic Parameters (Mean [SD]) of Meropenem and Vaborbactam Following Administration of VABOMERE 4 grams (meropenem 2 grams and vaborbactam 2 grams) by 3-hour Infusion in Patients

	Healthy Volunteers		Pooled Patients From Phase 3 Studies	
Parameter	**Meropenem**	**Vaborbactam**	**Meropenem**	**Vaborbactam**
C_{max} (µg/mL)	46.0 (5.7)	50.7 (8.4)	62.5 (45.9)	75.0 (41.0)
AUC_{0-24}, Day 1 (µg•h/mL)	426 (84)	504 (96.6)	683 (506)	866 (465)
AUC_{0-24}, steady-state (µg•h/mL)	414 (83.1)	588 (110.1)	668 (447.6)	909 (794)
CL (L/h)	14.6 (2.7)	12.3 (2.2)	10.3 (6.7)	7.62 (4.44)
t1/2, β (h)	1.50 (1.0)	1.99 (0.8)	2.06 (1.19)	3.22 (5.76)

BD, Table 23, page 43

Meropenem-Vaborbactam Completed Phase 3 Studies

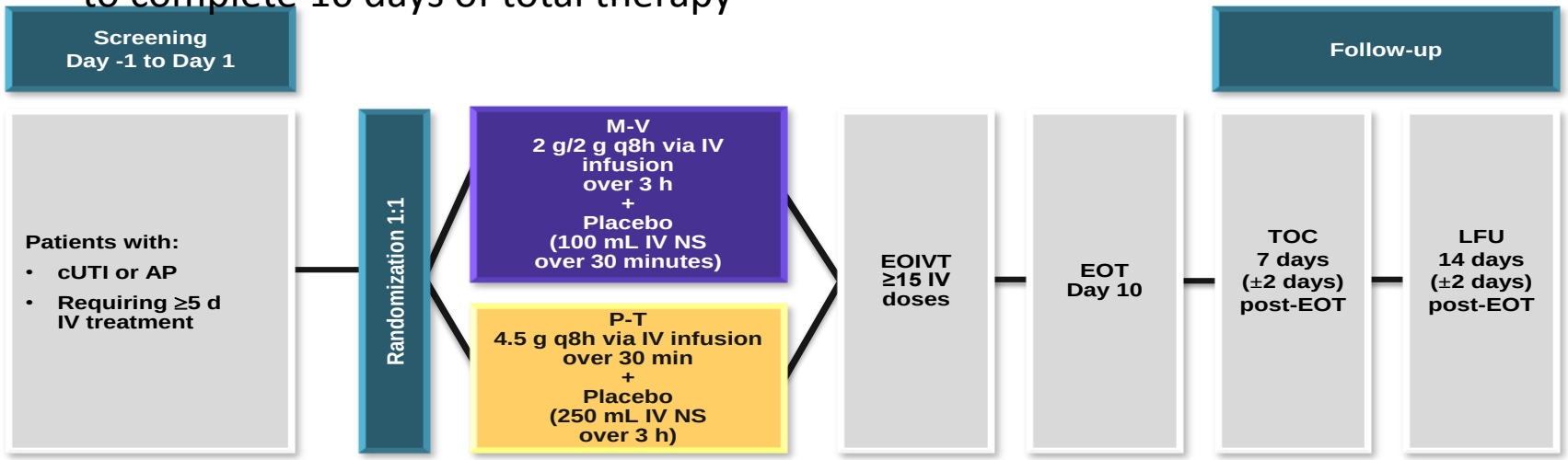
TANGO
Targeting Antibiotic Non-susceptible Gram-negative Organisms

	TANGO I	TANGO II
Features	*Site/Indication Focus* (Where CRE Frequently Found)	*Pathogen-Focused: CRE Infections*
Role in Development	Adequate and well-controlled trial to support regulatory registration per guidance	Translation of nonclinical data Efficacy & safety of **monotherapy** in target patients vs. standard of care (BAT)
Sites of Infection	Complicated UTI and AP	cUTI/AP, cIAI, HABP, VABP, bacteremia
Design	Randomized 1:1 Double-blind	Randomized 2:1 Open-label
No. of Patients	550	75
Comparator	Piperacillin-Tazobactam	"Best available therapy" (aminoglycoside, tigecycline, polymyxin, carbapenem alone or in combination); or ceftazidime-avibactam as monotherapy
Status	*NI shown; statistical difference favoring meropenem-vaborbactam*	*Was ongoing during review of NDA; Study stopped after interim analysis showed advantage for meropenem-vaborbactam.*

Status: FDA approved for cUTIs and pyelonephritis on August 29, 2017

TANGO I Study Design

- Phase 3, multinational, randomized, double-blind
- FDA primary endpoint: proportion of subjects in the m-MITT Population who achieve overall success (clinical cure or improvement and eradication of baseline pathogen to < 10^4 CFU/ml) at the EOIVT visit
- EMA-proportion of subjects in the co-primary m-MITT and ME Populations who achieve a microbiologic outcome of Eradication (eradication of baseline pathogen to < 10^3 CFU/ml) at the TOC visit
- Noninferiority if the lower limit of the two-sided 95% CI is > -15%
- If non-inferiority is demonstrated, an assessment for statistical superiority will be performed
- After at least 15 doses of IV therapy, may switch to oral levofloxacin 500 mg daily to complete 10 days of total therapy



*** Dose adjustments required for subjects with renal insufficiency**

TANGO 1 Primary Outcome

Primary Endpoints	Meropenem-Vaborbactam N = 192	Piperacillin/ Tazobactam N = 182	Difference (95% CI)
FDA Primary Endpoint			
Overall Success at EOIVT mMITT Population	188/192 (98.4%)	171/182 (94.0%)	**4.5 (0.7, 9.1)**
EMA Primary Endpoints			
Microbial Eradication at TOC mMITT Population	128/192 (66.7%)	105/182 (57.7%)	**9.0 (-0.9, 18.7)**
Microbial Eradication at TOC ME Population	118/178 (66.3%)	102/169 (60.4%)	**5.9 (-4.2, 16.0)**

BD, Table 33, page 63

All key efficacy endpoints met non-inferiority margin

Pathogen-specific Clinical Cure Rates at TOC

Baseline pathogen	M-V (N=192) n/N' (%)	P/T (N=182) n/N' (%)	Difference (%)	95% CI
m-MITT				
Enterobacter cloacae species complex	9/ 10 (90.0)	3/ 5 (60.0)	30	
Escherichia coli	89/125 (71.2)	68/117 (58.1)	13.1	(1.0, 24.9)
Klebsiella pneumoniae	19/ 30 (63.3)	14/ 28 (50.0)	13.3	(-12.2, 37.3)
ME				
Enterobacter cloacae species complex	9/ 10 (90.0)	3/5 (60.0)	30	
Escherichia coli	82/117 (70.1)	67/106 (63.2)	6.9	(-5.5, 19.2)
Klebsiella pneumoniae	18/ 28 (64.3)	13/ 27 (48.1)	16.1	(-10.2, 40.4)

BD, Table 34, page 65

reference

TANGO I : Outcomes by MIC for Meropenem-Vaborbactam

Cure and Eradication Rates in Patients with Enterobacteriaceae by Baseline MIC (m-MITT Population)

	Microbial Eradication* n/N' (%) FDA or EMA criteria		Clinical Cure	
M-V MIC (mg/L)	EOIVT	TOC	EOIVT	TOC
≤0.06	154/157 (98.1)	110/157 (70.1)	146/149 (98.0)	135/149 (90.6)
0.125	11/12 (91.7)	7/12 (58.3)	12/12 (100)	10/ 12 (83.3)
0.25	2/2 (100.0)	1/2 (100.0)	2/2 (100)	2/ 2 (100.0)
0.5	1/1 (100.0)	1/1 (100.0)	1/1 (100)	1/ 1 (100.0)
32	1/1 (100.0)	1/1 (100.0)	1/1 (100)	1/ 1 (100.0)

* pathogen level

Eradication Rates at TOC in Patients with Enterobacteriaceae by Baseline MIC (m-MITT Population)

M-V MIC (mg/L)	*E. coli*	*K. pneumonia*	*E. cloacae*
≤0.06	84/117 (71.8)	14/ 23 (60.9)	7/ 8 (87.5)
0.125	2/ 3 (66.7)	3/ 5 (60.0)	1/ 1 (100.0)
0.25	1/ 1 (100.0)		
0.5			
32		1/ 1 (100.0)	

* Only pathogens in > 5 patients at baseline are shown

BD, Table 36, page 68

5 isolates of *P. aeruginosa* had meropenem-vaborbactam MICs ranging from 0.25 to >64 mg/L. No microbiological failures were recorded at EOIVT or TOC.

No effect of meropenem-vaborbactam MIC on post-therapy outcomes

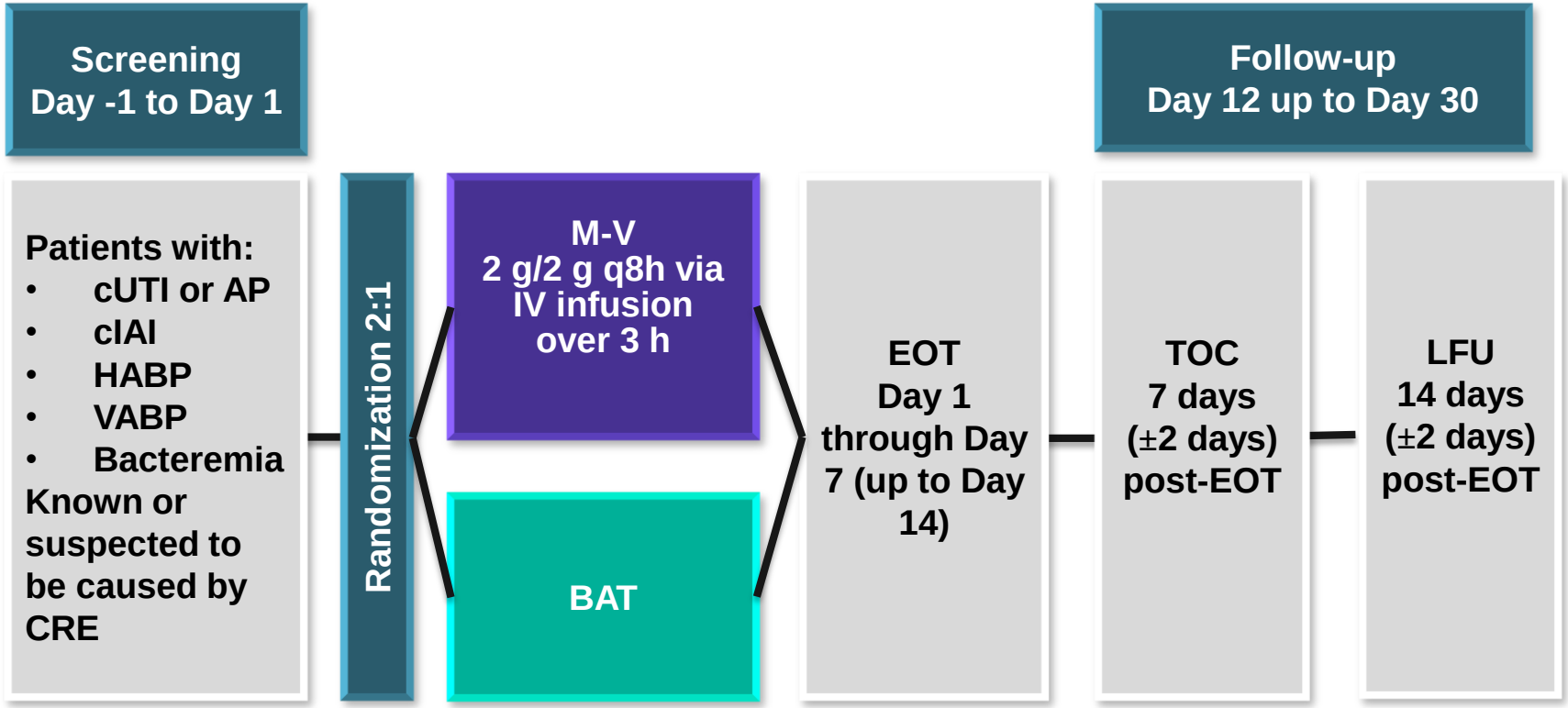
TANGO II Study Design: Summary

- Phase 3, multi-center, randomized, open-label study of adults with infections due to known or suspected CRE,
  - complicated urinary tract infection (cUTI),
  - acute pyelonephritis (AP),
  - hospital-acquired/ventilator-associated pneumonia
  - bacteremia
  - or complicated intra-abdominal infection (cIAI).
- Randomized 2:1 to monotherapy with M-V (2g/2g every 8h via 3-h infusion) or BAT for 7-14 days .
  - BAT (mono or combo): carbapenem, aminoglycoside, polymyxin, tigecycline, or ceftaz-avi (monotherapy only) at doses determined by the investigator.

TANGO II Study Design: Summary

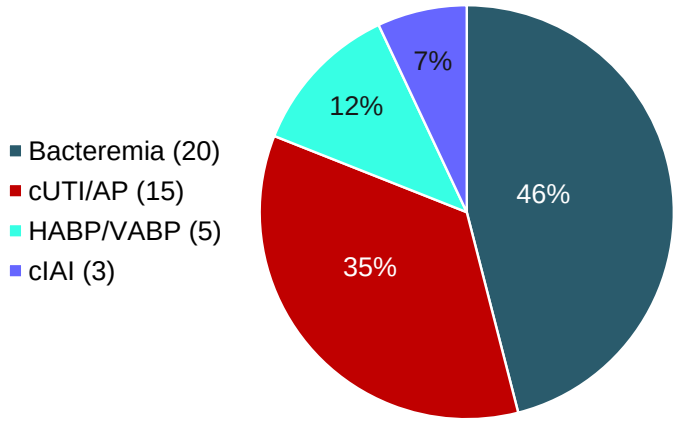
- Key inclusion criteria: known or suspected (evidence of CRE in culture or molecular testing within past 90 d) CRE pathogen, requirement of ≥7 days IV therapy, confirmed cUTI/AP, HABP/VABP, bacteremia, or cIAI.
- Clinical cure was defined as a complete resolution of signs/symptoms such that no further antimicrobial therapy was required.
- Clinical cure was assessed by the onsite blinded investigator (BI) and PI at two time points: end of treatment (EOT) and test of cure (TOC). In cases where the assessment by the BI and PI differed, clinical cure was adjudicated by the blinded independent adjudication committee.
- The study was not powered for formal inferential testing.

TANGO II Study Schema



TANGO II Baseline Characteristics

Distribution of Infection Types, mCRE-MITT (N=47)

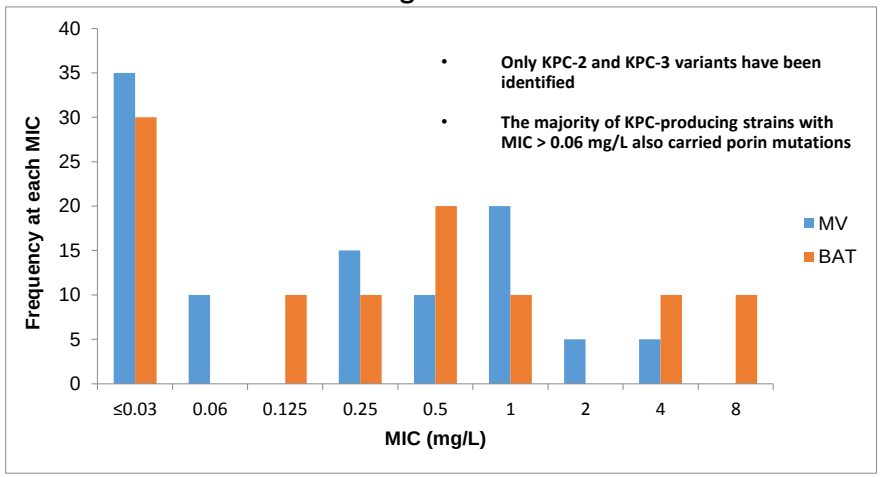


Baseline pathogens and molecular analysis, mCRE

M-V MIC (mg/L)	Meropenem-vaborbactam	BAT
Patients with CRE at baseline	32	15
Klebsiella pneumoniae	29[a]	12[b]
Escherichia coli	3	1[c]
Enterobacter cloacae	1	2
Serratia marcescens	1	1
Proteus mirabilis	-	2[c]
Molecular data available		
KPC	24	14
OXA-48	2	-
NDM-1	1	1[d]
Non-CP-CRE	2	-
Non CRE (lost plasmid?)	1	1

[a] Two different strains in one patient
[b] Two different strains in one patient
[c] *E. coli* strain and one of the *P. mirabilis* strains were isolated from the same patient that also carried *K. pneumoniae*
[d] The same patient also carried VIM-1 producing pathogen

In Vitro Activities of Meropenem-Vaborbactam against baseline KPC-Producing Enterobacteriaceae



- **The most common baseline pathogen was *K. pneumoniae* (86%).**
- **The most common molecular mechanism of carbapenem resistance was production of KPC carbapenemase (80%).**

BD, Figure 19, page 76

TANGO II Primary Efficacy Endpoints Across All Infection Types (mCRE-MITT)

	M-V (n = 32) n (%)	BAT (n = 15) n (%)	Absolute Difference[a] (95% CI)	P value
Patients with All Infection Types				
Clinical Cure at EOT	21 (65.6)	5 (33.3)	32.3 (3.3 to 61.3)	0.03
Clinical Cure at TOC	19 (59.4)	4 (26.7)	32.7 (4.6 to 60.8)	0.02
Microbiologic Cure[b] at EOT	21 (65.6)	6 (40.0)	25.6 (-4.1%–55.4)	0.09
Microbiologic Cure[b] at TOC	17 (53.1)	5 (33.3)	19.8 (-9.7%–49.3)	0.20
Day-28 Mortality	5 (15.6)	5 (33.3)	−17.7 (-44.7 to 9.3)	0.20
Sensitivity Analysis of Clinical Cure at TOC and All-Cause Mortality at Day 28 Across All Infection Types (mCRE-MITT) Excluding Prior Antibiotic Failure[c]				
	M-V (n=23) n (%)	**BAT (n=15) n (%)**	**Differencea (95% CI)**	**P value**
Patients with All Infection Types				
Clinical Cure at TOC	16 (69.6)	4 (26.7)	42.9 (13.7 to 72.1)	<0.01
Day-28 All-cause Mortality	1 (4.3)	5 (33.3)	-29.0 (-54.3 to -3.7)	0.02

[a] Data represent the difference in percentages for M-V and BAT (95% CI for that difference).
[b] Composite of either microbiologic eradication or presumed eradication at respective visit.
[c] Patients assessed as having prior antibiotic failure at randomization (meropenem-vaborbactam, 9; BAT, 0)

BD, Table 40, page 77

Improved outcomes with meropenem-vaborbactam compared to BAT

- Reduced mortality
- Higher clinical cure at EOT and TOC

TANGO II Outcomes by MIC

Cure Rates at the End of Treatment and at the Test of Cure in Patients (all infection types) by Baseline MIC (m-CRE-MITT Population, N=32)

Meropenem-vaborbactam MIC (µg/mL)	Cure rate, n/N (%) at EOT, n/N (%)	Cure rate, n/N (%) at TOC, n/N (%)	Comments
≤0.03	7/ 9 (77.8)	9/9 (100.0)	
0.06	1/ 2 (50.0)	1/ 2 (50.0)	Death in one subject due to cardiac arrest on D4
0.25	2/ 2 (100.0)	2/ 2 (100.0)	
0.5	2/ 3 (66.7)	2/ 3 (66.7)	Death in one subject on D3 of sepsis
1	2/ 5 (40.0)	0/ 3 (0.0)	Death in 2 subjects on D4 and D5 due to cardiac arrest or GI bleed
4	0/ 1 (0.0)	0/ 1 (0.0)	Death on D2 due to cardiac arrest
32	0/ 1 (0.0)	0/ 1 (0.0)	*K. pneumoniae* with OXA-48 at baseline
64	1/ 2 (50.0)	1/ 2 (50.0)	*K. pneumoniae* with OXA-48 at baseline (cure), with NDM-1 at baseline (failure)**

*Four of five patients that died failed previous antibiotic therapy

BD, Table 46, page 88

** Discontinued study drug on Day 4 and started on BAT due to discovery that the CRE was non-KPC producing, subject' s symptoms were improving at discontinuation

No obvious cutoff in meropenem-vaborbactam MIC that discriminated between clinical or microbiological successes and failures

TANGO II Results

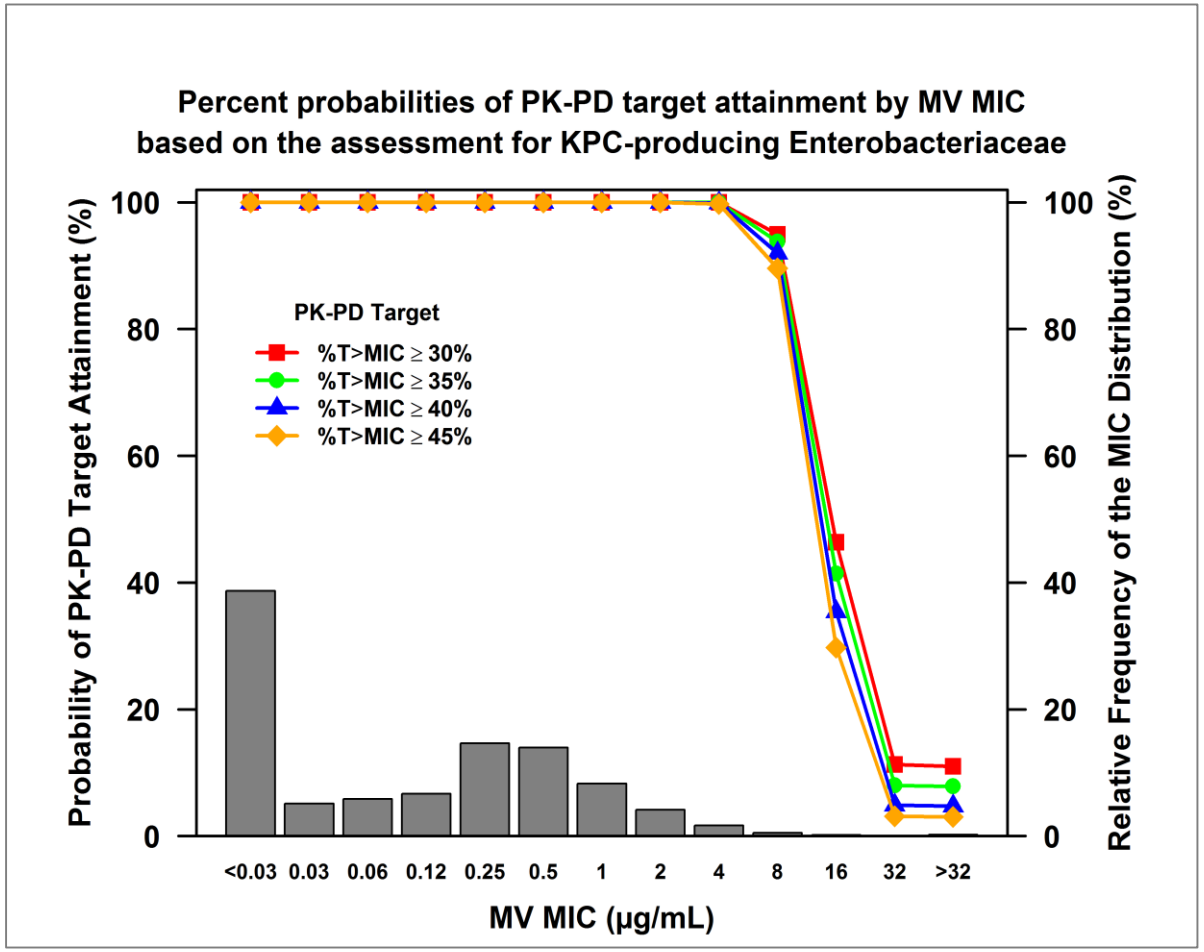
A Prospective, Randomized Comparative Trial
of Monotherapy with Vabomere™ vs. Best Available Therapy
in Suspected or Documented CRE Infection

TANGO
Targeting Antibiotic Non-susceptible Gram-negative Organisms

- Results - decreased mortality, increased clinical cure, and reduced nephrotoxicity with Vabomere (meropenem-vaborbactam) compared to BAT, including:
  - Day-28 all-cause mortality (ACM) was 17.9% for Vabomere and 33.3% for BAT; when prior antibiotic failures are excluded, Day-28 ACM was 5.3% for Vabomere and 33.3% for BAT (P=0.03)
  - Higher clinical cure at EOT (64.3% for Vabomere and 33.3% for BAT (p=0.04) and TOC 57.1% for Vabomere and 26.7% for BAT (p=0.04)
  - Benefits evident in important patient subgroups of HABP/VABP, bacteremia, renal impairment, and immunocompromised
  - Fewer treatment-related adverse events (Vabomere 24.4% vs. BAT 44.0%)
  - Decreased nephrotoxicity (serum creatinine increase ≥0.5 mg/dL) (Vabomere 11.1% vs. BAT 24.0%)
- no changes in susceptibility to meropenem-vaborbactam, but resistance to ceftazidime-avibactam observed in the few patients treated with this agent

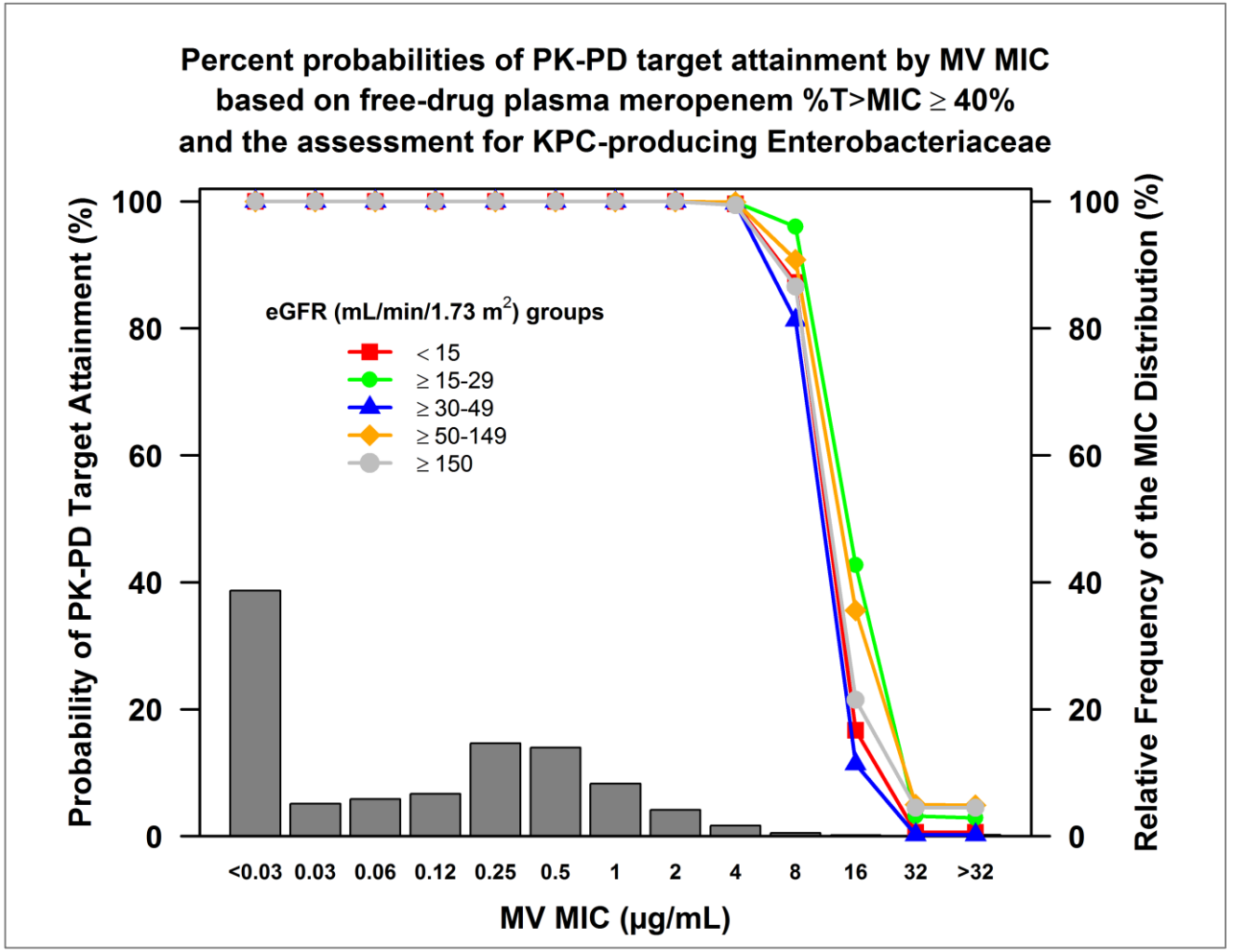
(Open Forum Infect. Dis. 2017;4(suppl.1):S534-40 (ID Week 2017 abstracts))

Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC among simulated patients with cUTI, overlaid upon the meropenem-vaborbactam MIC distribution for 1,331 KPC-producing Enterobacteriaceae isolates



BD, Figure 21, page 97

Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC among simulated patients by renal function group, overlaid upon the meropenem-vaborbactam MIC distribution for 1,331 KPC-producing Enterobacteriaceae isolates (meropenem %T>MIC target ≥ 40%)

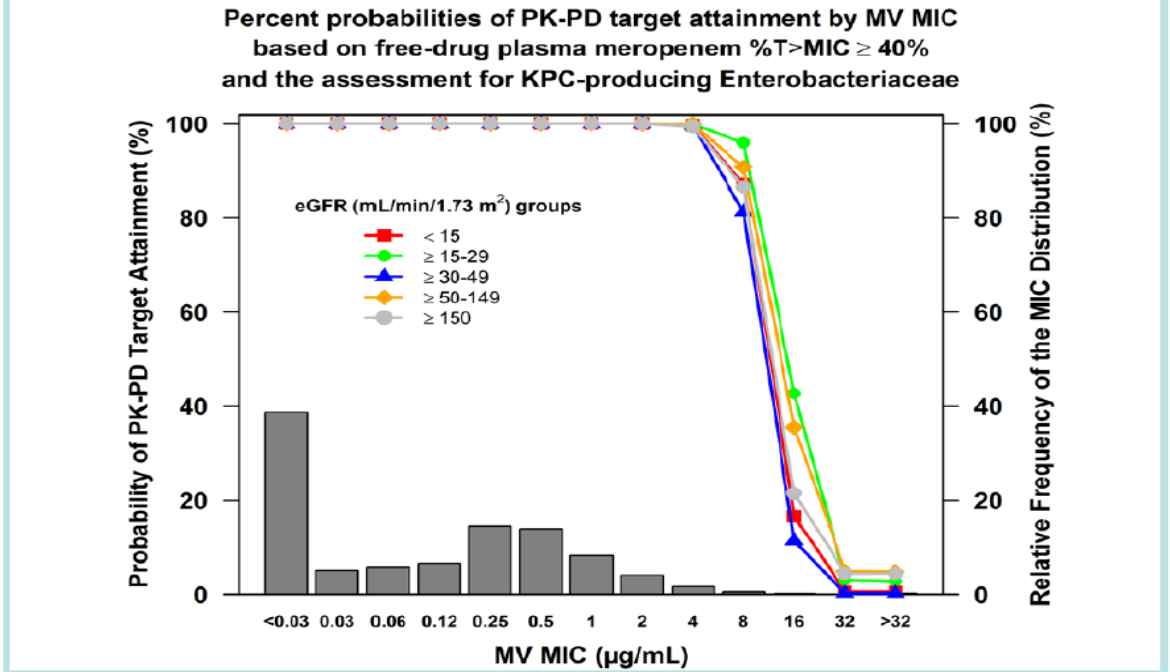


BD, Figure 22, page 98

4/27/18 Conference Call #4

- WG preferred FDA BPs with an MIC of 8 as I rather than S:
  - absence of any clinical data on outcomes with MICs of 8
  - the start of a PK-PD drop-off in probability of target attainment at an MIC of 8 (mid 80s)

Figure 22: Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for meropenem-vaborbactam dosing regimens based on the free-drug plasma meropenem %T>MIC target ≥ 40% and free-drug vaborbactam AUC:MIC ratio target ≥ 38 among simulated patients by renal function group, overlaid upon the meropenem-vaborbactam MIC distribution for 1,331 KPC-producing Enterobacteriaceae isolates



Rationale for FDA BPs

- This drug will be used primarily in sick patients with bacteremia and pneumonia
- OXA-48s can have an MIC of 8
- Intermediate category is preferred to accurately reflect uncertainties in efficacy depending on location and severity of infection and variations in precision of MIC testing
- Lack of strong evidence to go away from the FDA's recommendation
- 99% of KPC isolates have meropenem-vaborbactam MICs ≤4 (only 0.5% have an MIC of 8)
- WG voted 5/0 in favor of FDA BPs with dosage regimen of 4 g (2 g mero + 2 g vabor) every 8 h over 3 h
- Placement in Gp B Optional Primary Test &Report Selectively

Table 57: Susceptibility interpretive criteria for meropenem/vaborbactam approved by the FDA

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤4/8	8/8	≥16/8	≥17	14-16	≤13

S=Susceptible; I=Intermediate; R=Resistant

4/30/18 Conference Call #5

- Best option had minor errors (6.4%) for the ≥I+2 range slightly above the recommended threshold of <5%. A motion to pass the **≥18 (S) / 15-17 (I) / ≤ 14 (R)** breakpoints passed by a WG vote of 5/0.

Table 55: Summary of Error Rates Obtained for Meropenem-Vaborbactam (20/10-µg) Disks Versus Meropenem-Vaborbactam MIC At the Proposed Disk- and MIC Breakpoints against all Enterobacteriaceae Combined

BMD breakpoint	Disk breakpoint	Range	Number	Error rate			Error rate (%)		
				Very major	Major (%)	Minor (%)	Very major	Major	Minor
≤4(S)/8(I)/≥16 (R)	≥17 (S) / 14-16 (I) / ≤ 13 (R)	Total	934	0	3	39	0	0.32	4.18
		≥I+2	94	0	N/A	10	0	N/A	10.6
		I+1 to I-1	68	0	3	25	0	4.41	36.76
		≤I-2	772	N/A	0	4	N/A	0.00	0.52
≤4(S)/8(I)/≥16 (R)	≥16 (S) / 14-15 (I) / ≤ 13 (R)	Total	934	4	3	33	0.428	0.32	3.53
		≥I+2	94	1	N/A	9	1.06	N/A	9.57
		I+1 to I-1	68	3	3	24	4.41	4.41	35.29
		≤I-2	772	N/A	0	0	N/A	0	0
≤4(S)/8(I)/≥16 (R)	≥18 (S) / 15-17 (I) / ≤ 14 (R)	Total	934	0	3	42	0	0.32	4.50
		≥I+2	94	0	N/A	6	0	N/A	6.4
		I+1 to I-1	68	0	3	22	0	4.41	32.35
		≤I-2	772	N/A	0	14	N/A	0.00	1.81
≤8(S)/-/ ≥16 (R)	≥17 (S) / - / ≤ 16 (R)	Total	934	0	25	NA	0	2.68	NA
≤8(S)/-/ ≥16 (R)	≥16 (S) / - / ≤ 15 (R)	Total	934	4	11	NA	0.43	1.18	NA

Light green: FDA approved breakpoints; light blues: proposed breakpoints; numbers in red are those that are higher than CLSI acceptable discrepancy rate (CLSI M23-A3)

Summary

- The Ad hoc WG recommends the following meropenem-vaborbactam breakpoints for publication in M100 with the FDA approved dosage regimen of 4 g (2 g meropenem + 2 g vaborbactam) every 8 h over 3 h:

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤4/8	8/8	≥16/8	≥18	15-17	≤14

- The Ad hoc WG supports the sponsor's request for placement in Table 1A for *Enterobacteriaceae* in Group B, Optional Primary Test and Report Selectively (the same as ceftazidime-avibactam).

BPWG Meeting

- **A motion was made and seconded to accept this proposal.**
- Vote:
  - 6 Yes;
  - 0 No;
  - 3 Abstain.
  - Motion passed.

- [Note – no vote was taken on table placement.]

Ciprofloxacin and Levofloxacin Disk Diffusion Correlates

Romney Humphries, Keith Schaffer, Janet Hindler, Shelley Campeau

Dulini Gamage, Erika Matuschek

UCLA, Accelerate Diagnostics, EUCAST

1. Ciprofloxacin-levofloxacin disk correlates for breakpoints. (Folder 5, documents 6a-6b).

Background

- AST Subcommittee voted to accept revision to ciprofloxacin and levofloxacin MIC breakpoints for the Enterobacteriaceae and Pseudomonas aeruginosa in 2017/2018
  - Pending establishment of disk correlates
- Some data available in Jan 2017, did not meet M23 criteria for # of isolates for levofloxacin; not much data for isolates at 0.5 – 1.0 µg/mL
- New data presented in June 2017 – did not meet M23 criteria
  - Data set enriched with isolates with MICs of 0.5-1.0 µg/mL

Revised Breakpoints

Revised (projected for M100S 29)

Organism Group	Antimicrobial Agent	S	SDD	I	R
Enterobacteriaceae	Ciprofloxacin	≤0.25	–	0.5	≥1
	Levofloxacin	≤0.5	–	1	≥2
Pseudomonas aeruginosa	Ciprofloxacin	≤0.5	N/A	1	≥2
	Levofloxacin	≤1	N/A	2	≥4

Current (M100S 28)

Organism Group	Antimicrobial Agent	S	SDD	I	R
Enterobacteriaceae	Ciprofloxacin	≤1	–	2	≥4
	Levofloxacin	≤2	–	4	≥8
Pseudomonas aeruginosa	Ciprofloxacin	≤1	N/A	2	≥4
	Levofloxacin	≤2	N/A	4	≥8

Studies from which data was derived

1. UCLA (data presented June 2017)

- BMD panels made in-house, n=4 MICs per drug, per organism
  - 2 brands CA-MHB (BBL MHB II and Difco)
  - 2 stock solutions for ciprofloxacin and levofloxacin made & used
  - Ciprofloxacin range, 0.015 – 16 µg/mL
  - Levofloxacin range, 0.015 – 16 µg/mL
  - QC performed with *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922
  - MIC mode used for calculations
- 57 isolates selected based on ciprofloxacin MIC of 0.5 – 1.0 µg/mL (S by old BP, “I” or “R” by new BP)

Studies from which data was derived

2. Accelerate Diagnostics (new data)

- BMD panels made in-house, n=3 MICs per drug, per organism
  - 1 brands CA-MHB (Difco)
  - 1 stock solutions for ciprofloxacin and levofloxacin made & used
  - Ciprofloxacin range, 0.06 – 8 µg/mL
  - Levofloxacin range, 0.06 – 32 µg/mL
  - QC performed with *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922
  - MIC mode used for calculations
- Levofloxacin: 117 Enterobacteriaceae, 79 *P. aeruginosa*
- Ciprofloxacin: 85 Enterobacteriaceae, 55 *P. aeruginosa*

Studies from which data was derived

3. EUCAST data, courtesy of Erika
   - Ciprofloxacin MIC distribution: 0.03 – 4
   - Levofloxacin MIC distribution: 0.03 – 8

   Levofloxacin: 83 Enterobacteriaceae, 117 P. aeruginosa

   Ciprofloxacin: 261 Enterobacteriaceae, 158 P. aeruginosa

Data analysis

- MIC ranges truncated to consistent data set across all sources
  - Threw out values where lower end of range was high (0.12)
- Data analyzed as compared to EUCAST breakpoints (Enterobacteriaceae)
- Data analyzed by dBETs software (https://dbets.shinyapps.io/dBETS/)

Reminder, acceptable error rates, per M23:

MIC Range		Acceptable Discrepancy Rates		
1-Dilution Intermediate Range	2-Dilution Intermediate Range	Very Major	Major	Minor
$\geq I+2$	$\geq I_{High}+2$	< 2%	N/A	< 5%
$I+1$ to $I-1$	$I_{High}+1$ to $I_{Low}-1$	< 10%	< 10%	< 40%
$\leq I-2$	$\leq I_{Low}-2$	N/A	< 2%	< 5%

Isolates tested: ciprofloxacin / Enterobacteriaceae

Count of Organism	Column Labels								
Row Labels	0.03	0.06	0.12	0.25	0.5	1	2	4	Grand Total
Citrobacter freundii	1	1	1	1					4
Citrobacter koseri	2								2
Enterobacter aerogenes		1	1	1		1			4
Enterobacter cloacae-komplex			4		2	3	6	4	19
Escherichia coli	91	3	8	33	17	19	3	60	234
Klebsiella ascorbata							1		1
Klebsiella oxytoca			1		2	1	1	7	12
Klebsiella pneumoniae	38	9	5	10	11	15	7	19	114
Morganella morganii						1			1
Proteus mirabilis			2	1	4	5	3	6	21
R. ornithinolytica						1			1
Serratia marcescens		1	3		2				6
Grand Total	**132**	**15**	**25**	**46**	**38**	**46**	**21**	**96**	**419**

Ciprofloxacin and Enterobacteriaceae, dBETs breakpoint

	N	%
VME	0	0
ME	7	3.21100917
mE	60	14.3198091

Error Rate Bound Calculations				
	N	VME (%)	Major (%)	Minor (%)
I+≥2	117	0	n/a	2 (1.8)
I+/-1	130	0	6 (4.6)	55 (**42.3**)
I- ≤2	172	n/a	1 (0.6)	3 (1.7)

Note: only 4 mm range (is this ok?)

	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
0.03																						1	2	5	8	9	24	20	20	17	5	7	6	1	2	3	1	1	
0.06																							2		3	1	4	2	3										
0.12			1																		1	1	1	5	4	1	1				1	2		3	1			2	1
0.25	1		1										1			2	1		5	4	8	5	5	3	1	7	2												
0.5																2	3	7	6	10	3	2		1	1	2			1										
1														1	4	8	9	8	2	7	5	2																		
2			1				1	1				1	3	1	4	5	1	2		1																			
4			73	1		2	5	1	4	3	2	2	1			1					1																	

Isolates tested: Levofloxacin / Enterobacteriaceae

Count of Levo Mode MIC	Column Labels								
Row Labels	0.06	0.12	0.25	0.5	1	2	4	>=8	Grand Total
Enterobacter aerogenes	3				2				5
Enterobacter cloacae-komplex	5			4	1	2	5	5	22
Klebsiella oxytoca			2	4	1		3	2	12
Proteus mirabilis	2		2		8	3	1	1	17
R. ornithinolytica				1					1
Serratia marcescens		2		2					4
Escherichia coli	39		7	27	15	2	1	46	137
Klebsiella pneumoniae	5		2	19	10	5	3	14	58
Klebsiella ascorbata						1			1
Grand Total	**54**	**2**	**13**	**57**	**37**	**13**	**13**	**68**	**257**

Data: Levofloxacin & Enterobacteriaceae Using dBETs calculated breakpoints

Zone size (mm)

MIC, ug/mL	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
0.06																				4	1	2		5	8	7	5	3	8	7	1	2			1
0.12																						1	1												
0.25	1																		3	3	4		1			1									
0.5											1	1	1	3	10	10	13	8	2	3	2	2		1											
1	1		2			1						1	5	7	8	6	4		1	1														
2			1		3			1	1	2	3		1		1																			
4			2		2	2	2	1	1	1	1		1																					
>=8	60	1	4	1	1		1																											

	N	%
VME	0	0
ME	2	1.58730159
mE	34	12.8404669

Error Rate Bound Calculations				
	N	VME (%)	Major (%)	Minor (%)
I+≥2	81	0 (0)	n/a	1 (1.23)
I+/-1	107	0	1 (0.9)	33 (30.8)
I- ≤2	69	n/a	1 (1.5)	0 (0)

- 1 minor errors with “R” MIC
- 12 minor errors with “I” MIC and “S” disk

https://dbets.shinyapps.io/dBETS/

Summary: Enterobacteriaceae

Ciprofloxacin

EUCAST breakpoints (≥26/24-25/≤23)					dBETs Breakpoints (≥26/22-25/≤21)			
	N	VME	ME	mE	N	VME	ME	mE
I+>=2	117	0	n/a	0.9%	117	0	n/a	1.8%)
I +/- 1	130	0	11.5%	40.8%	130	0	2.6%	42.3%
I <=2	172	n/a	0.6%	1.7%	172	n/a	0.6%	1.7%

Levofloxacin

EUCAST breakpoints (≥23/19-22/≤18)					dBETs Breakpoints (≥21/17-20/≤16)			
	N	VME	ME	mE	N	VME	ME	mE
I+>=2	81	0	n/a	0	81	0	n/a	1.2%
I +/- 1	107	0	2.8%	45.8%	107	0	0.9	30.8%
I <=2	69	n/a	1.5%	0	69	n/a	1.5%	0

Red, out of M23 acceptance limit

Proposal: Enterobacteriaceae

Revised (projected for M100S 29)

		Disk (mm)			MIC (ug/mL)		
Organism Group	Antimicrobial Agent	S	I	R	S	I	R
Enterobacteriaceae	Ciprofloxacin	≥26	22-25	≤21	≤0.25	0.5	≥1
	Levofloxacin	≥21	17-20	≤16	≤0.5	1	≥2

Pseudomonas aeruginosa

- No “I” EUCAST breakpoint
- Evaluated Disk breakpoints using error-rate bound method (dBETs software as outlined in M23)

P. aeruginosa, Ciprofloxacin

	N	%		
VME	1	1.4		
ME	0	0		
mE	7	3.9		
Error rate bound calculations				
	N	VME (%)	Major (%)	Minor (%)
I+≥2	67	1 (1.5)	n/a	0
I+/-1	41	0	0	7 (17.0)
I- ≤2	69	n/a	0	0

Note: dBETs attempted breakpoint of <=21,

- M23 rules do not allow a 3 mm 'I' range
- Ciprofloxacin QC range: 25-33 mm (9mm) → min

Range for "I" is 5 mm

	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
0.125																							1	3	1	5	8	11	7	6	5	3			2
0.25																				1	1	2	1	1	4	3		2	2						
0.5																	1	1		2	6	2	8	2	3		1	2							
1											1						1		3	1															
2							1			1	2					1	2																		
4					2	1	1	1		1	1	1	1																						
>=8	51	1	3	1		1																			1										

Pseudomonas aeruginosa, levofloxacin

	N	%		
VME	0	0		
ME	0	0		
mE	11	5.7		
Error rate bound calculations				
	N	VME (%)	Major (%)	Minor (%)
I+≥2	111	0	n/a	0
I+/-1	85	0	0)	10 (11.7)
I- ≤2	166	n/a	0	1 (0.6)

* note, per M23 “I” zone can be as large
As QC range
QC range for P. aeruginosa ATCC 27583: 19-26mm

	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
0.125																								1					1	1			1	1	1
0.25																	1			1	5	7	8	4	7	2	1	1		1					
0.5															1		1	1	1	6	5	4	3		1						1				
1											1			1	3		2		3			1													
2	1							1		2	2	2	5	1	2	2																			
4	3		1		2	3	1	1	2	1	2																								
>=8	70		2	2	3	2																													

Proposal: Pseudomonas aeruginosa

		Disk (mm)			MIC (ug/mL)		
Organism Group	Antimicrobial Agent	S	I	R	S	I	R
P. aeruginosa	Ciprofloxacin	≥23	19-24	≤18	≤0.5	1	≥2
	Levofloxacin	≥22	15-21	≤14	≤1	2	≥4

		Zone diameter in mm		
		Susceptible	Intermediate	Resistant
Enterobacteriaceae	Ciprofloxacin	≥26	22-25	≤21
	Levofloxacin	≥21	17-20	≤16
Pseudomonas aeruginosa	Ciprofloxacin	≥23	19-24	≤18
	Levofloxacin	≥22	15-21	≤14

BPWG Vote: 8 Yes; 0 No; 1 Abstain.

Consultation to determine if reassessment of breakpoints for Piperacillin/tazobactam in Enterobacteriales is necessary

GERMAN ESPARZA
CLSI Expert Panel on Microbiology
Spring AST Subcommittee meeting St Diego 2018
gesparza@javeriana.edu.co

Rationale for this consultation (3):

3. Conflicting Data about Pip/tazo for ESBL therapy:

- Data so far , shows that Pip/tazo may be used safely for urinary and biliary tract infections caused by ESBL producing *E.coli*.
- There is scarce data about other species (*Klebsiella, Raoultella, Enterobacter, etc*)
- Increase in mortality have been reported for other infections like pneumonia.
- The efficacy of Pip/tazo seems to be related to MIC and the dose used.
- There is data about the use of prolonged infusions to improve the T>MIC for Pip/tazo in ESBL and not ESBL producing Enterobacteriales.

4. The current CLSI and EUCAST are different.

- There are some papers mentioning that EUCAST breakpoints could be more accurate to predict clinical efficacy with Pip/tazo for ESBL treatment.

Issues with data :

- Inconsistent criteria for ESBL production.
- Confounding by indication (ie, ill-appearing patients more likely to receive the more “aggressive” therapy, ie, carbapenems)
- Differences in outcomes definitions
- Classification issues for patients initially receiving empiric non-carbapenem ß-lactam therapy, then transitioned to carbapenem therapy
- Insufficient subgroups for analysis (eg, proportion of E.coli vs K.pneumoniae, proportion of $bla_{CTX\text{-}M}$ vs bla_{SHV})
- Insufficient data on dosing regimens
- Insufficient data on clinical outcomes with extended-infusion ß-lactam Therapy
- MIC not always provided for all species.

Based on : Tamma and Rodriguez Bano: CID 2017:64 (1 April)

The MERINO Trial: piperacillin-tazobactam versus meropenem for the definitive treatment of bloodstream infections caused by third-generation cephalosporin non-susceptible *Escherichia coli or Klebsiella spp*. : an international multi-centre openlabel non-inferiority randomised controlled trial

Methods: Authors enrolled adult patients from 32 sites in 9 countries with bloodstream infections caused by *E. coli or K.pneumoniae* non susceptible to 3 gen Cephalosporins but susceptible to Pip/tazo.

- The participants were randomized within 72 hours of Initial blood culture collection 1:1 to Pip/tazo (4.5g q6h) or meropenem (1g q8h) for a minimum of 4 days.
- Treating clinicians were not blinded to treatment allocation.
- The primary outcome was all-cause mortality at 30 Days post-randomisation. Secondary outcomes included days to clinical and microbiological resolution, clinical and Microbiological success at day 4, relapsed BSI and secondary Infection with a piperacillin-tazobactam or meropenem resistant organism or *Clostridium difficile.*

- The hypothesis was that definitive therapy with piperacillin-tazobactam was non-inferior to meropenem, using a margin of 5% for the primary outcome.

28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

The MERINO Trial: piperacillin-tazobactam versus meropenem for the definitive treatment of bloodstream infections caused by third-generation cephalosporin non-susceptible *Escherichia coli or Klebsiella spp*. : an international multi-centre openlabel non-inferiority randomised controlled trial

Results: Between February 2014 and July 2017, 391 patients were enrolled, from 1,646 screened.
Of these 379 were randomized appropriately, received at least one dose of study drug and were included in the modified intention to treat (mITT) population (Pip/tazo 188, meropenem=191). One patient was lost to follow-up. The majority of patients were enrolled in Singapore (40.6%), Australia (22.4%) and Turkey (12.1%).
BSIs were most frequently healthcare-associated (56.4%), of urinary tract origin (60.9%) and caused by *E. coli* (86.5%).

A total of 23/187 (12.3%) patients randomized to Pip/tazo met the primary outcome of mortality at 30 days, compared with 7/191 (3.7%) randomized to meropenem (risk difference 8.6%, 95% CI 3.4% to 14.5%; RR 3.4, 95% CI 1.5 to 7.6; p=0.002). Effects were consistent in an analysis of the per-protocol population.
There were no significant differences in subsequent infection with carbapenem resistant gram-negative organisms or *C. difficile* between treatment arms

Conclusions: The use of Pip/tazo as definitive therapy for BSI caused by *E. coli or K.pneumoniae* with non-susceptibility to 3 gen cephalosporins **was inferior to meropenem** and should be **avoided** in this context

Proposal for Breakpoint Working Group

- Establish the azithromycin breakpoint for *N. gonorrhoeae* consistent with ECV
  - S <= 1
- Proposed comment to be added to the table:
  - This breakpoint presumes that azithromycin (1 gm single dose) is used in an approved regimen that includes an additional antimicrobial agent (i.e. ceftriaxone 250mg IM single dose)
- Delete ECV
- Addition of azithromycin to table 1B, group A

US Treatment Recommendations

For Uncomplicated Gonorrhea (2015, MMWR)

- Ceftriaxone 250 mg IM + azithromycin 1 gm PO
- If ceftriaxone is not available or in case of allergies: Azithromycin + cefixime or + gentamicin or + gemifloxacin can also be used

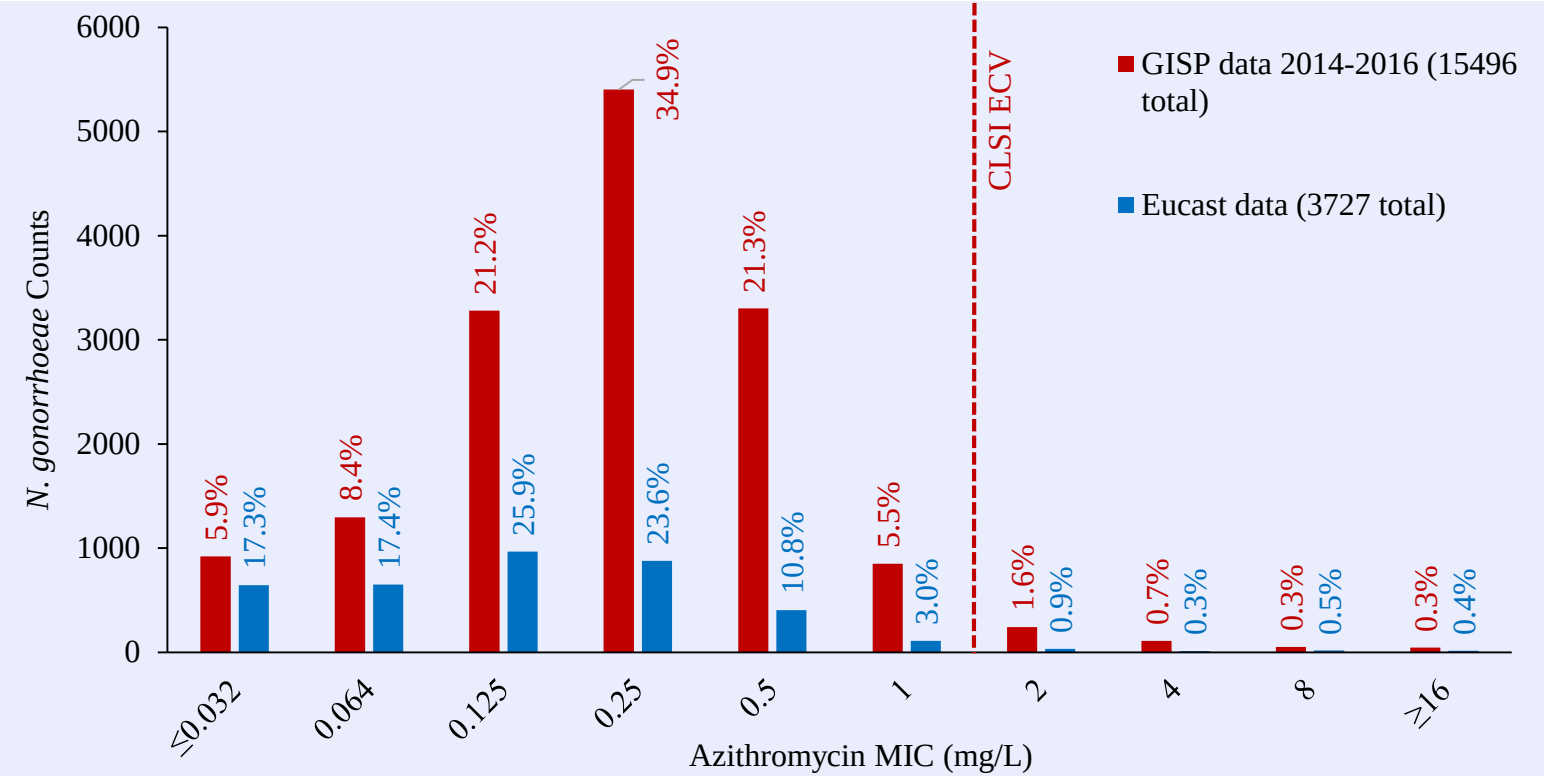
Source of Microbiological and Genetic Data

- MIC Distribution Surveillance Data from US GISP = Gonococcal Isolate Surveillance Program on > 15,000 isolates from 2014 - 2016
- They meet CLSI standards (AST by agar dilution, quality control, from multiple sites and laboratories, etc)
- Genetic Marker Analysis on a subset of GISP isolates (723 isolates, selection biased towards higher MICs)

Summary and Outline

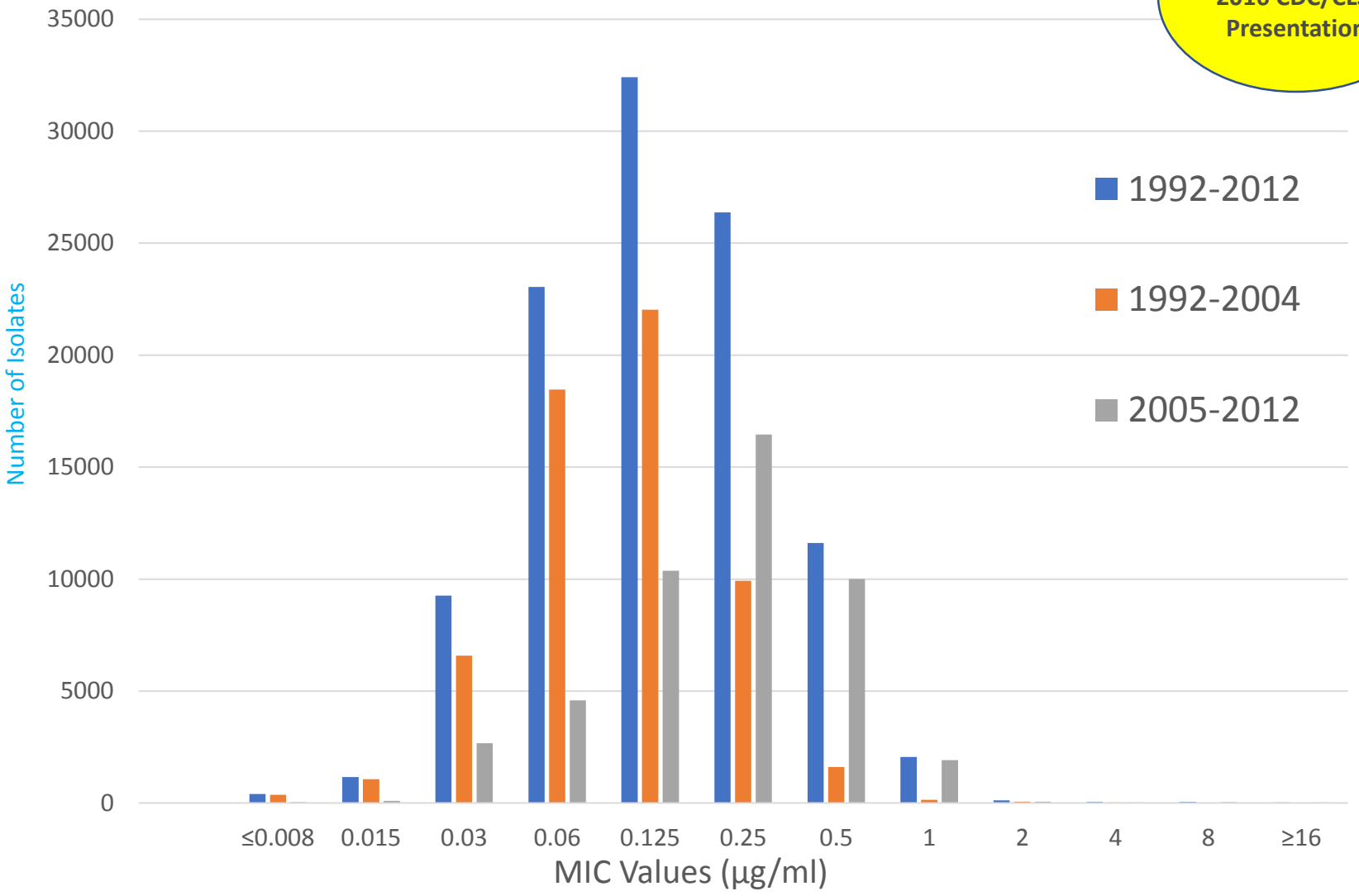
Antimicrobial Agent	CLSI Breakpoint	CLSI ECV	EUCAST Breakpoint	Action/ Proposal
Azithromycin	None published	≤1.0	S ≤0.25 R >0.5	Data review/ To set S≤1

GISP Azithromycin MIC Distribution, 2014 - 2016



N. gonorrhoeae Azithromycin MIC Distribution (1992-2012)

Slide from 2016 CDC/CLSI Presentation



ECV* Calculations

ECV obtained from GISP Azithromycin MIC data, 2014-2016								
Year	N	Mode	MIC_{50}	MIC_{99}	Method 1 ECV	Method 2 ECV	Method 3 ECV	Method 4 ECV
2014-2016	15,495	0.25	0.25	4	≤1	≤1	≤1	≤1

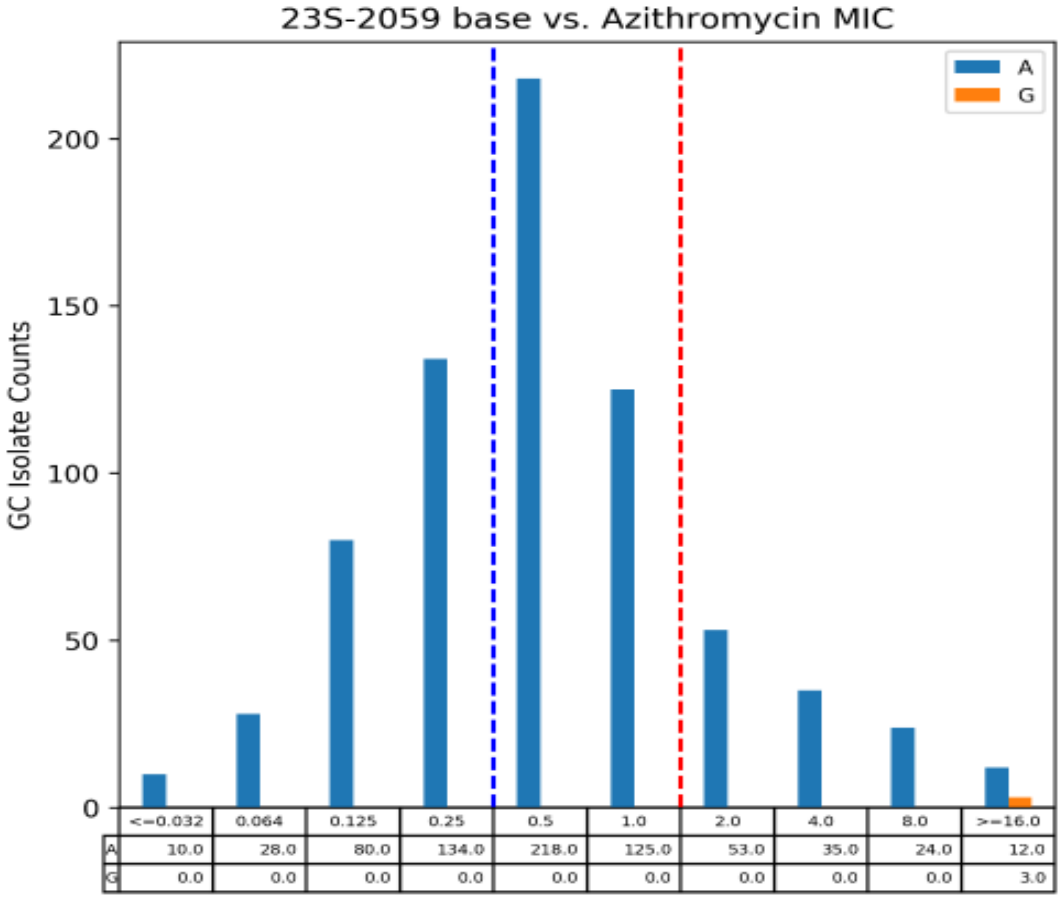
NO TREATMENT FAILURES

- 8.4% of the 15,495 GISP isolates (2014 – 2016) were at an MIC of 1 or above (~1,300 isolates)
- No treatment failures were reported to CDC
- Overall, 468,514 gonorrhea cases were reported to CDC in 2016
- National guidance is to contact CDC in case of suspected treatment failure
- CDC reported that 81% of patients with gonorrhea received the recommended regimen in 2016, based on data from SSuN (STD Surveillance Network; Weston et al, MMWR 2018)

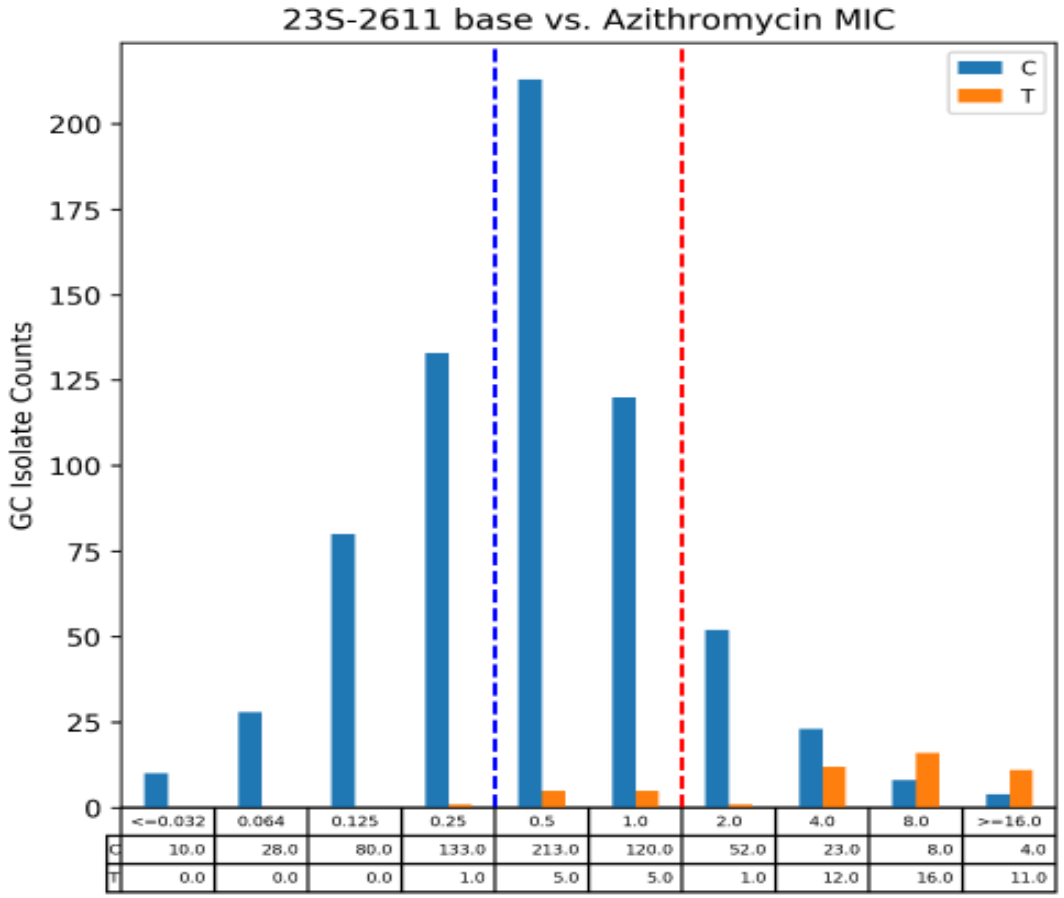
Genetic markers associated with treatment failure

Genetic marker	Mechanism of Action	Antimicrobial agent affected	Has the marker been associated with treatment failure? - Reference(s)	MICs of isolate(s) (ug/mL)	Dose of drug	Site of infection
23S rRNA C2611T	The 23S rRNA is a component of the large ribosomal subunit and is involved in protein translation.	Macrolides	Marita-Ishihara T et al, JAC, 2014	AZI 4	1X 2g Azithromycin-ER	Pharyngeal and vaginal
23S rRNA A2059G	Same as above.	Macrolides	Gose SO et al, STD, 2015	AZI >2048	1X 2g Azithromycin	Urethral
mosaic mtrR	mtrR is a repressor of the mtrCDE efflux pump. Loss of this repressor leads to reduced susceptibility.	Macrolides	No clinical reports available.			

Azithromycin genetic markers



	<=0.032	0.064	0.125	0.25	0.5	1.0	2.0	4.0	8.0	>=16.0
A	10.0	28.0	80.0	134.0	218.0	125.0	53.0	35.0	24.0	12.0
G	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0



	<=0.032	0.064	0.125	0.25	0.5	1.0	2.0	4.0	8.0	>=16.0
C	10.0	28.0	80.0	133.0	213.0	120.0	52.0	23.0	8.0	4.0
T	0.0	0.0	0.0	1.0	5.0	5.0	1.0	12.0	16.0	11.0

***For both graphs, rRNA allele copy number is not displayed. This is important for the right graph, where isolates that have a T at position 2611 that are in the 0.25-2.0 MIC range all have 2 or less copies of the T containing allele.**

PROPOSAL

Setting of Azithromycin Susceptibility Breakpoint at ≤ 1

RATIONALE

1. Absence of a breakpoint causes problems:
    - Interpretation of MIC results cannot be reported clinically.
    - This causes labs to not offer the test. Ultimately, patient care is not as good as it could be if it were based on laboratory results.
    - FDA is hampered in its ability to approve novel tests and devices (e.g., etest for Azithromycin is not FDA approved for gonorrhea, although it provides comparable data to AST in CDC's evaluation)

RATIONALE: GC AZI S ≤ 1

2. Why ≤1?

- ECV supports it
- No treatment failures have occurred even though ~1,300 isolates were at or above MIC 1 in this data set; and even though >450,000 gonorrhea cases were reported to CDC in 2016
- Setting it lower may lead to over-diagnosis of non-susceptible gonorrhea
- A lower breakpoint could lead to unnecessary use of higher Azithromycin doses with more side effects and higher cost
- It would likely foster the use of more broad spectrum antibiotics (e.g., ertapenem) without any evidence of additional clinical benefit
- If set lower, surveillance numbers of non-susceptible cases would artificially appear to go up; leading to calls for treatment recommendation changes

Azithromycin Pharmacokinetics/ Pharmacodynamics

Was originally attractive for STD treatment because it is “acid-stable, orally absorbed, and has unique pharmacokinetics, producing low plasma levels but high levels in tissues and intracellularly, with an average terminal plasma half-life of 68 hours after single oral doses” (Handsfield, 1994, STDs)

Packet insert indicates Zithromax use for

- **Urethritis and cervicitis** due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.
- **Genital ulcer disease** in men due to *Haemophilus ducreyi* (chancroid).

Mostly from the Zithromax packet insert

In part from the Zithromax packet insert

Azithromycin Pharmacokinetics/ Pharmacodynamics

Pharmacokinetics (from packet insert)
Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were (in blood)
AUC_{0-72} = 4.3 (1.2) ugxh/mL
C_{max} = 0.5 (0.2) ug/mL
T_{max} = 2.2 (0.9) hours

Neisseria gonorrhoeae is a facultative intracellular bacteria and can survive in PMNs
From packet insert: Median azithromycin exposure (AUC_{0-288}) in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following either a 5-day or 3-day regimen was more than a 1000-fold and 800-fold greater than in serum, respectively.

From the Zithromax packet insert

Azithromycin Pharmacokinetics/ Pharmacodynamics

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

AZITHROMYCIN CONCENTRATIONS FOLLOWING
A 500 mg DOSE (TWO 250 mg CAPSULES) IN ADULTS[1]

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (µg/g or µg/mL)	CORRESPONDING PLASMA OR SERUM LEVEL (µg/mL)	TISSUE (FLUID) PLASMA (SERUM) RATIO
SKIN	72-96	0.4	0.012	35
LUNG	72-96	4.0	0.012	>100
SPUTUM*	2-4	1.0	0.64	2
SPUTUM**	10-12	2.9	0.1	30
TONSIL***	9-18	4.5	0.03	>100
TONSIL***	180	0.9	0.006	>100
CERVIX****	19	2.8	0.04	70

[1] Azithromycin tissue concentrations were originally determined using 250 mg capsules.

* Sample was obtained 2-4 hours after the first dose.
** Sample was obtained 10-12 hours after the first dose.
*** Dosing regimen of two doses of 250 mg each, separated by 12 hours.
**** Sample was obtained 19 hours after a single 500 mg dose.

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical importance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low

Azithromycin Pharmacokinetics/ Pharmacodynamics

***STDs*, 1994**

Multicenter Trial of Single-Dose Azithromycin vs. Ceftriaxone in the Treatment of Uncomplicated Gonorrhea

H. HUNTER HANDSFIELD, MD, Z.A. DALU, MD, DAVID H. MARTIN, MD, JOHN M. DOUGLAS, JR., MD, JAMES M. McCARTY, MD, DAVID SCHLOSSBERG, MD, AND THE AZITHROMYCIN GONORRHEA STUDY GROUP

TABLE 2. Eradication of *Neisseria gonorrhoeae* in Men and Women With Uncomplicated Gonorrhea Treated With Azithromycin or Ceftriaxone

Sex	Site of Infection	No. Cured/No Evaluable (%)	
		Azithromycin	Ceftriaxone
Male	Urethra	236/237 (99.6)	110/112 (98.2)
	Rectum	4/5 (80)	4/4 (100)
Female	Cervix or Urethra	134/137 (97.8)	61/63 (96.8)
	Rectum	22/22 (100)	13/13 (100)
Male and Female	Pharynx	19/19 (100)	15/15 (100)
Total*		370/374 (98.9)	171/175 (97.7)
95% CI, percent†		97.9–100	95.5–99.9

* Total patients; some patients were infected at ≥2 sites.
† 95% CI denotes 95% confidence interval.

2 g AZI;
by culture,
but methods
or MICs not
stated

Clinical Data Results

- 413 articles identified
  - Exclusion criteria
    - Azithromycin efficacy of multiple pathogens
    - No MIC data
  - Only one study with systematic data correlating MIC to clinical failure
  - As presented earlier, clinical trial data that led to FDA approval did not correlate MIC in failure

Yasuda M et al J Antimicrobial Chemotherapy 2014

- Prospective study, no comparator
- 189 Japanese men with urethritis (2009-2013)
- Treated with a single dose of azithromycin SR (extended release) 2 gm
- MIC performed on pre-treatment isolates
  - Method: agar dilution using CLSI standards

Yasuda M et al., J Antimicrobial Chemotherapy 2014

- Results
  - 130/189 had follow up with NAAT 7-21 days later
  - 122 were cleared

MIC to azithromycin (mg/L)	# eradicated	# persistent
0.03	3	0
0.06	4	0
0.125	7	0
0.25	43	0
0.5	31	1
1	7	5
2	0	1
4	0	1
Unknown (not cultured)	27	0
Total	122	8

Caveats of this study

- Distribution of MICs in this population are shifted one dilution higher than the distribution in the GISP isolates
- Possibility of culture media affecting MIC shift upward. Therefore, denominator for patients with persistence would be larger
- NAAT was used for follow up and unclear who was tested at 7 days
- Pharmacokinetics of azithromycin SR may be different than standard formulation, may be different in tissues

Proactive Test of Cure in Canada

- Routine test of cure at a high risk clinic in Ontario (using culture)
- Dual therapy with ceftriaxone and azithromycin
- No evidence of clinical failures with *N. gonorrhoeae* associated with azithromycin MICs of 1 or greater

Table 1B

GROUP A PRIMARY TEST AND REPORT	*Haemophilus influenzae*[d] and *Haemophilus parainfluenzae*	*Neisseria gonorrhoeae*[i]	*Streptococcus pneumoniae*[j]
	Ampicillin[d,f]	Ceftriaxone[†] Cefixime[†]	Erythromycin[a,c]
		Ciprofloxacin[†]	Penicillin[k] (oxacillin disk)
		Tetracycline[b,†]	
		Azithromycin	Trimethoprim-sulfamethoxazole

CDC recommended therapy:

- Ceftriaxone 250 mg IM + azithromycin 1 gm PO
- Azithromycin missing from Table 1B

The Proposal for the CLSI Breakpoint Working Group

- Establish the azithromycin breakpoint for *N. gonorrhoeae* consistent with ECV
  - S <= 1
- Proposed comment to be added to the table:
  - This breakpoint presumes that azithromycin (1 gm single dose) is used in an approved regimen that includes an additional antimicrobial agent (i.e. ceftriaxone 250mg IM single dose)
- Delete ECV
- Addition of azithromycin to table 1B, group A

BPWG Actions

Vote: 7 Yes; 1 No; 1 Abstain. Motion passed.

Polymyxin Susceptibility Issues…

James Lewis, PharmD

A colistin crisis in India

Despite some global progress in limiting the use of antimicrobials in animals, inappropriate colistin use is still widespread. Madlen Davies and Timothy R Walsh report.

In India, at least five animal pharmaceutical companies advertise products containing colistin as growth promoters or to be used metaphylactically"

"…57% of *Klebsiella pneumoniae* are thought to be resistant to carbapenems…"

Lancet Infect Dis 2018. http://dx.doi.org/10.1016/ S1473-3099(18)30072-0

CLINICAL AND LABORATORY STANDARDS INSTITUTE

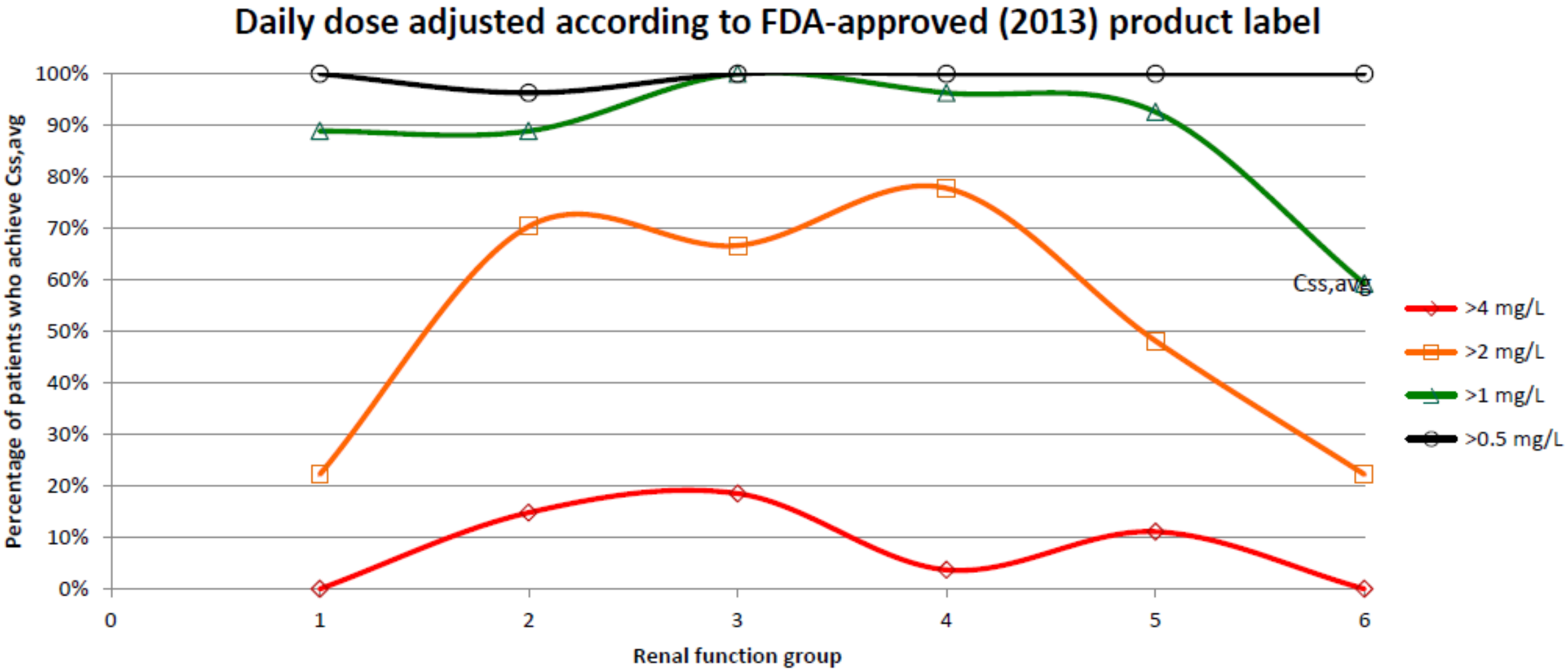
EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Epidemiological cutoff values for Enterobacteriaceae

- **Proposal 1:** The ECV/ECOFF for five species of Enterobacteriaceae, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. pneumoniae* and *R. ornitholytica*, should be set at 2 mg/L, until further acceptable MIC distributions are available to confirm whether the ECOFF for the two *Enterobacter* species should be lower.

ECOFFinder Results for Five Species of Enterobacteriaceae

Species (No. distributions)	ECOFF 95.0%	ECOFF 97.5%	ECOFF 99.0%	ECOFF 99.5%	ECOFF 99.9%
E. aerogenes (5)	1	1	1	1	2
E. cloacae (6)	1	1	1	1	2
E. coli (14)	1	1	1	2	2
K. pneumoniae (7)	1	1	1	2	2
R. ornitholytica (5)	1	1	2	2	2



The target attainment rate at each MIC is equivalent to the target attainment rate for Css,avg (*i.e.* for total colistin in plasma).

J Antimicrob Chemother
doi:10.1093/jac/dkx522

Journal of Antimicrobial Chemotherapy

Exploring colistin pharmacodynamics against *Klebsiella pneumoniae*: a need to revise current susceptibility breakpoints

Marilena Tsala[1], Sophia Vourli[1], Panagiota-Christina Georgiou[1], Spyros Pournaras[1,2], Athanasios Tsakris[2], George L. Daikos[3], Johan W. Mouton[4] and Joseph Meletiadis[1,4]*

- PK/PD target fAUC/MIC = 25
- PTAs built for most often used clinical regimens including loading
- fAUC/MIC target attainment of:
  - 100% at MIC of ≤0.5mg/L
  - 5-70% at MIC of 1mg/L
  - 0% at MIC of 2mg/L – currently considered by many “the breakpoint”

J Antimicrob Chemother 2018. doi:10.1093/jac/dkx522

Clinical Infectious Diseases

MAJOR ARTICLE

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

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

- 38 patients ceftaz-avi vs 99 colistin
- Colistin often used in combination
- 30 day after start of treatment mortality
  - Ceftaz-avi: 9%
  - Colistin 32%
  - 95% CI = 9-35%, P=.001

Clin Infect Dis 2018;66:163-71.

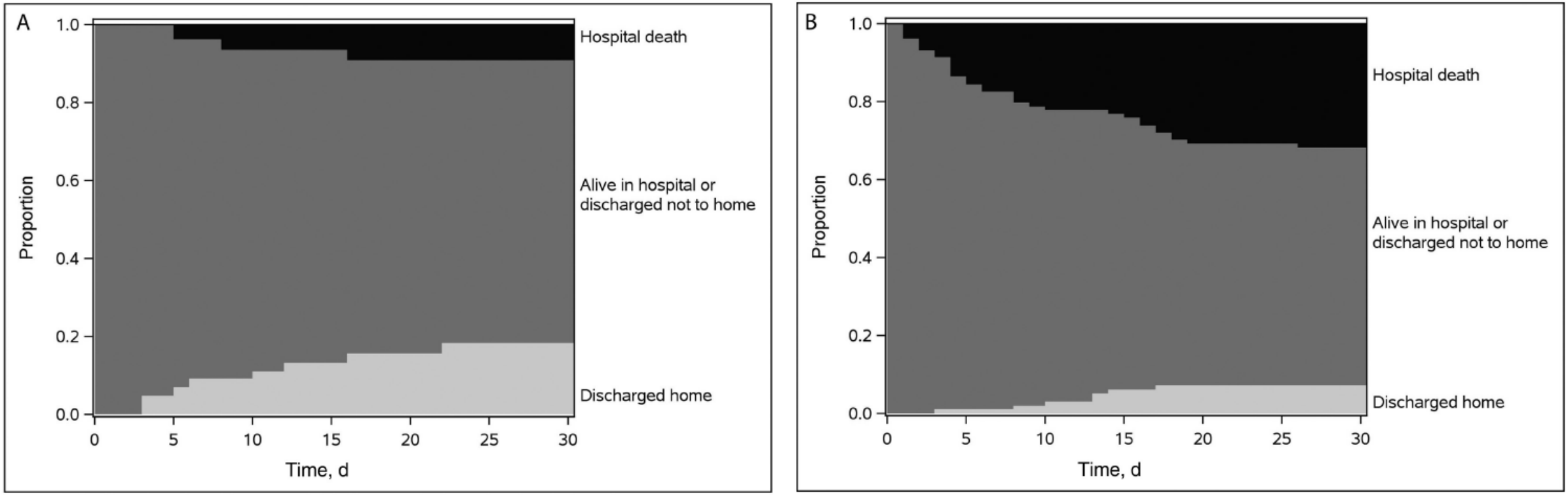


Figure 1. Inverse probability of treatment weighting (IPTW)–adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A,* Ceftazidime-avibactam group (n = 38). *B,* Colistin group (n = 99).

Clin Infect Dis 2018;66:163-71.

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

- Good dosing (9mu load followed by 4.5mu q12h)
- >70% failure in both monotherapy and combination arms

Clinical failure	Colistin	Colistin + Mero	95% CI for combo outcome	P
Acinetobacter baumannii	125 (83%), n=151	130 (81%), n=161	0·97 (0·87–1·09)	0·643
Enterobacteriaceae‡	23 (68%), n=34	18 (46%), n=39	0·78 (0·54–1·13)	0·185
Pseudomonas or others§	8 (62%), n=13	4 (50%), n=8	0·81 (0·36–1·84)	0·673

Lancet Infect Dis 2018;18:391

Evidence to improve the treatment of infections caused by carbapenem-resistant Gram-negative bacteria

- "The high patient mortality rate (44% at 28 days)… is sobering – considering that infection with bacteria susceptible to colistin was a criterion for inclusion and that colistin dosing was carefully controlled – but is not surprising."
- "…low Charlson and SOFA scores…"
- "…colistin, either as monotherapy or combined with a carbapenem, is not that effective."

Perez F & Bonomo R. *Lancet Infect Dis* 2018; epub 2/15/18

Plazomycin vs Colistin for CRE Bacteremia

- Resists most AG modifying enzymes – except methylases
- Active against the vast majority of U.S. CRE.
- No additional benefit for *P. aeruginosa* or *Acinetobacter* sp.

Figure 2. Mortality-Based Outcomes

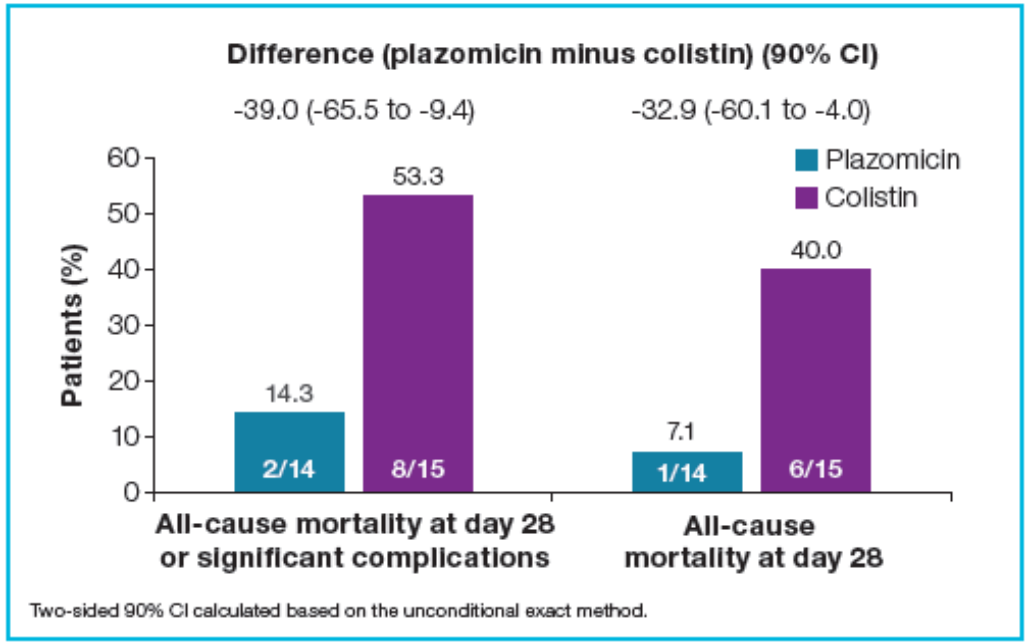
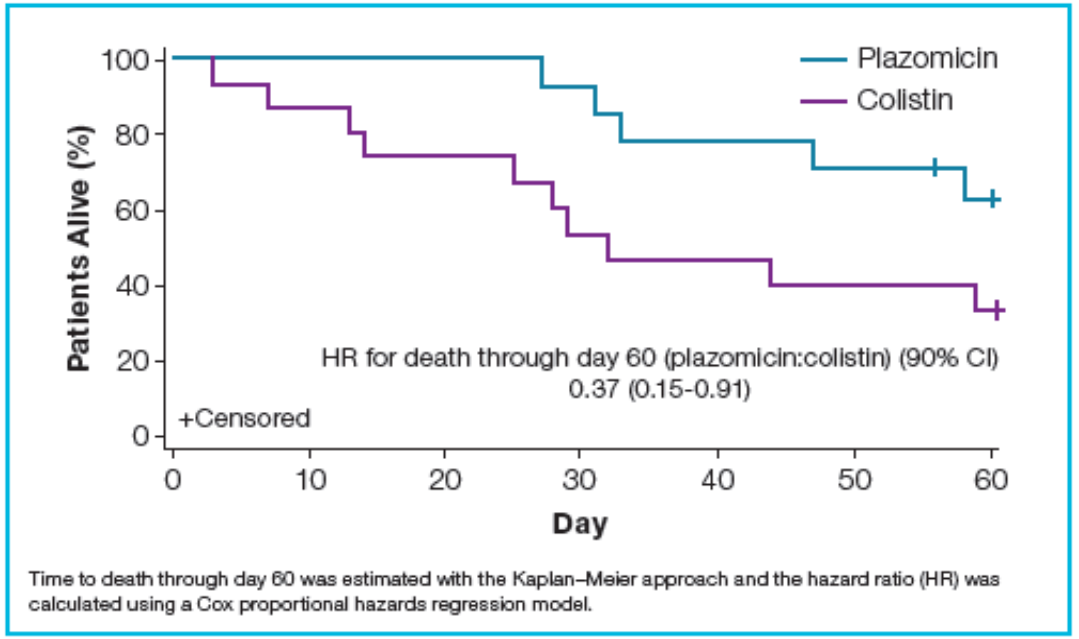
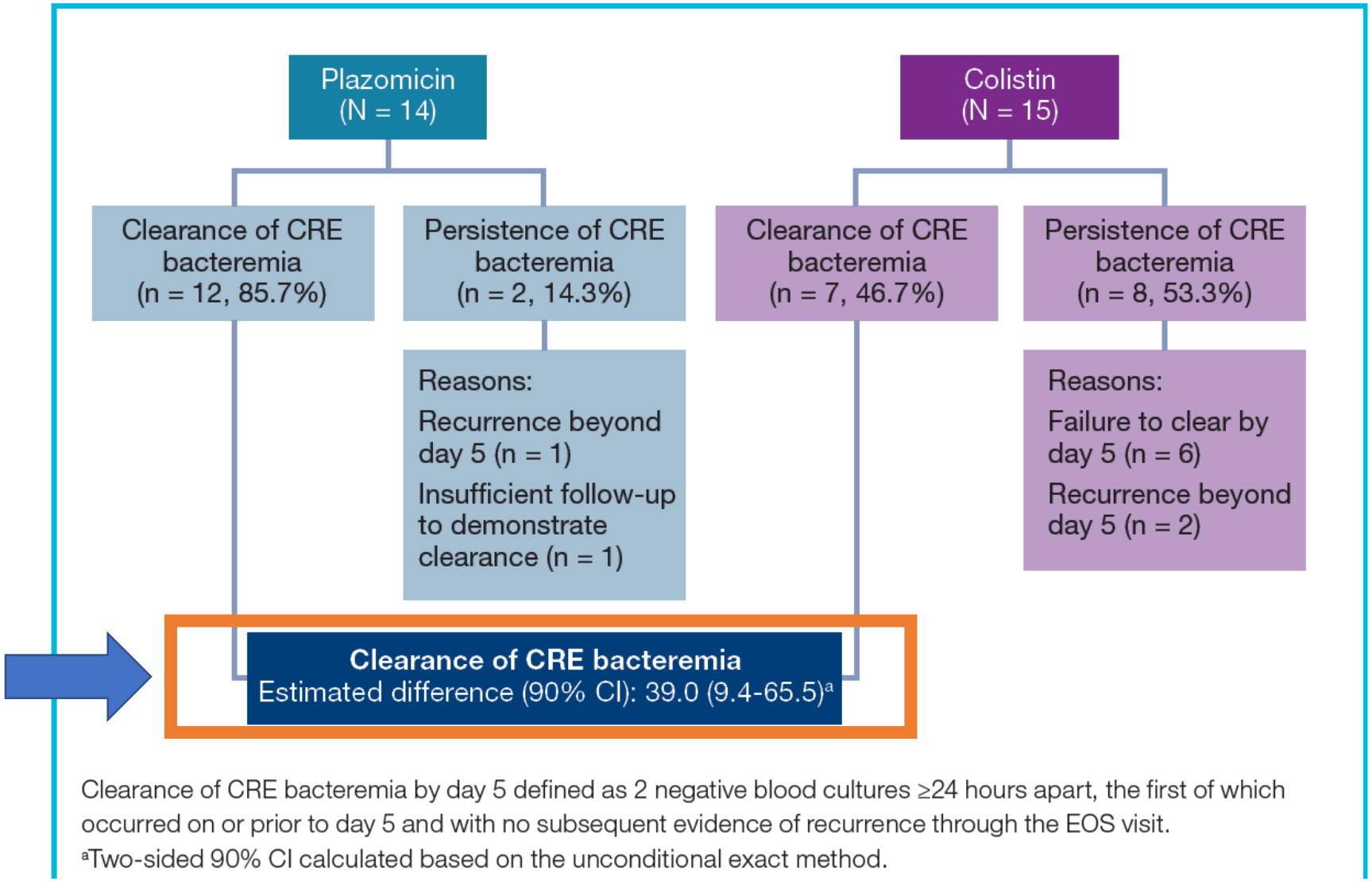


Figure 3. Survival Through Day 60



McKinnell JA, et al. IDWeek 2017. Poster 1853

Figure 4. Clearance of CRE Bacteremia by Day 5



Clearance of CRE bacteremia by day 5 defined as 2 negative blood cultures ≥24 hours apart, the first of which occurred on or prior to day 5 and with no subsequent evidence of recurrence through the EOS visit.
[a]Two-sided 90% CI calculated based on the unconditional exact method.

McKinnell JA, et al. IDWeek 2017. Poster 1853

Meropenem – Vaborbactam vs. Best Available Therapy: Tango 2

Polymyxin/Colistin as:	N (%)
Monotherapy	1 (6.7)
Dual Therapy	
Carbapenem + Polymyxin B/Colistin	1 (6.7)
Polymyxin/Colistin + Aminoglycoside	3 (20)
Triple Therapy	
Carbapenem + Polymyxin/Colistin + Tigecycline	1 (6.7)
≥4 Drugs	
Carbapenem + Polymyxin/Colistin + Tigecycline + Aminoglycoside	2 (13.3)
TOTAL	8/15

https://p.widencdn.net/hnb6zs/1862_Kaye_TANGO_2_All_Infection_Types - Accessed 4/18

Meropenem – Vaborbactam vs. Best Available Therapy: Tango 2

Patients with All Infection Types	Mero-Vabor N=19 N (%)	BAT N=15 N (%)	Absolute Difference (95% CI)
Clinical Cure at TOC	13 (68.4)	4 (26.7)	41.8 (11.1 to 72.4)
Day-28 All-cause Mortality	1 (5.3)	5 (33.3)	-28.1 (-54.0 to -2.2)

- "The study was discontinued 7/21/17 on the recommendation of the DSMB following their review of these data"

https://p.widencdn.net/hnb6zs/1862_Kaye_TANGO_2_All_Infection_Types - Accessed 4/18

RESTORE-IMI 1: A multicenter, randomized, double-blind, comparator-controlled trial comparing the efficacy and safety of imipenem/relebactam versus colistin plus imipenem in patients with imipenem-non-susceptible bacterial infections

Motsch J,[1] de Oliveira C,[2] Stus V,[3] Köksal I,[4] Lyulko A,[5] Boucher HW,[6] Kaye KS,[7] File TM,[8] Brown ML,[9] Khan I,[9] Du J,[9] Joeng H-K,[9] Tipping RW,[9] Aggrey A,[9] Young K,[9] Kartsonis NA,[9] Butterton JR,[9] Paschke A[9]

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28th ECCMID – Abstract 451

22 April, 2018

Efficacy

- 31 of 47 randomized and treated patients met mMITT criteria[a]
- mMITT baseline characteristics:
  - APACHE-II scores > 15: 29%
  - CrCL< 60 mL/min: 23%
  - ≥ 65 years old: 35%
- Baseline pathogens: *Pseudomonas aeruginosa* (77%), *Klebsiella* spp (16%), and other Enterobacteriaceae (6%)
- β-lactamases detected: AmpC (84% of all isolates), ESBLs (39%), KPC (16%), OXA-48 (3%)

Endpoint	IMI/REL (N=21)		COL + IMI (N=10)		Unadjusted difference	Adjusted difference	
	n	%	n	%	%	%	(90% CI)
Favorable overall response	**15**	**71.4%**	**7**	**70.0%**	**1.4%**	**-7.3%**	**(-27.5, 21.4)**
HABP/VABP	7/8	87.5%	2/3	66.7%	20.8		
cIAI	0/2	0.0%	0/2	0.0%	0.0		
cUTI	8/11	72.7%	5/5	100.0%	-27.3		
Favorable clinical response (Day 28)	15	71.4%	4	40.0%	31.4%	26.3%	(1.3, 51.5)
28-day all-cause mortality	2	9.5%	3	30.0%	-20.5%	-17.3%	(-46.4, 6.7)

[a]Modified intent-to-treat (mMITT) population: received ≥1 dose of study drug and had baseline pathogen that met inclusion criteria.