

Hellenic Sepsis Study Group
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ΕΛΛΗΝΙΚΟ ΙΝΣΤΙΤΟΥΤΟ ΜΕΛΕΤΗΣ ΤΗΣ ΣΗΨΗΣ
HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

MEROPENEM-VABORBACTAM



Εθνικόν και
Καποδιστριακόν
Πανεπιστήμιον
Αθηνών

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President-Elect: European Shock Society



CONFLICT OF INTEREST DISCLOSURE

- Honoraria (paid to the University of Athens) from bioMérieux, Greece, Biotest AG Germany, MSD Hellas, Pfizer Hellas
- Consultant for InflaRx GmbH, XBiotech Inc
- Independent educational grants (paid to the University of Athens) from AbbVie USA, AxisShield UK, Astellas Pharma Europe, Biotest AG Germany, BioMérieux France, InflaRx GmbH, the Medicines Company, ThermoFisher Brahms GmbH, XBiotech Inc
- Funding by the FrameWork 7 program HemoSpec (granted to the University of Athens) and by the Horizon 2020 ITN European Sepsis Academy

EPIDEMIOLOGY OF CARBAPENEMASES PUBLISHED SINCE 2014

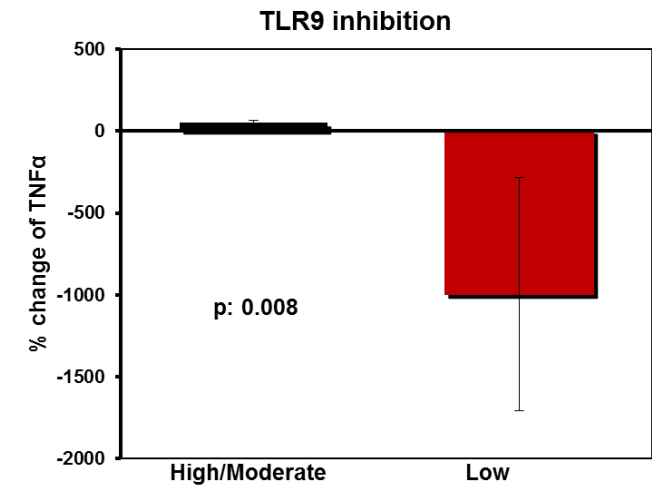
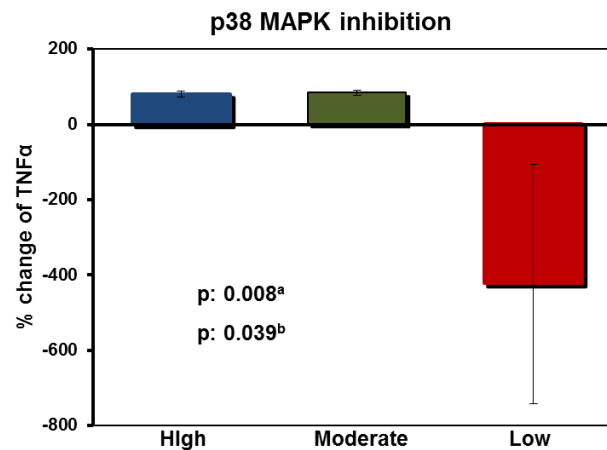
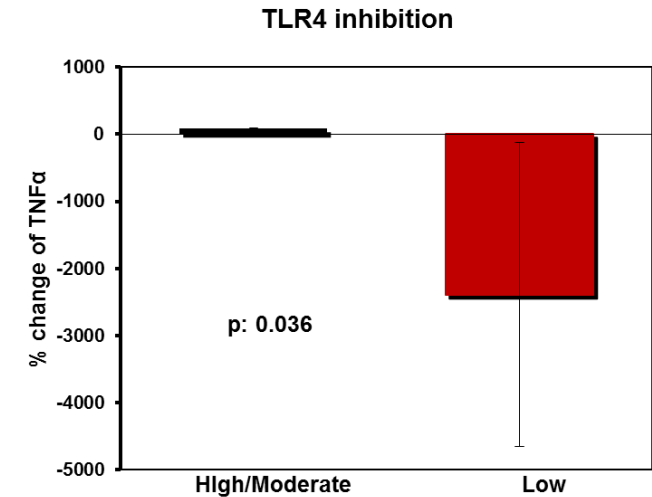
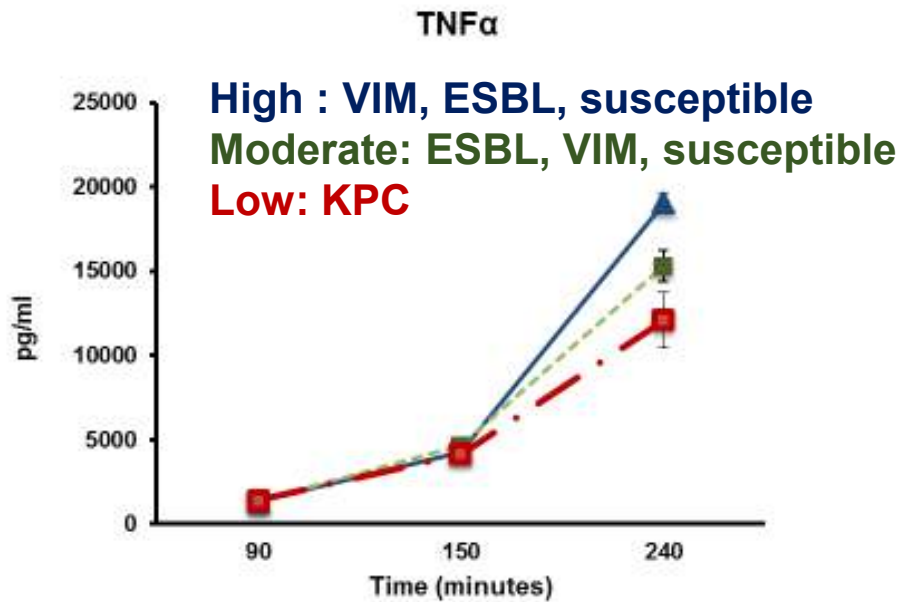
Ref.	Country	Year	species	N	Enzyme (%)
1	Serbia, Europe	2016-2017	<i>Enterobacter</i>	1,040	NDM (70.6)
2	Zhejiang, China	2017-2018	<i>K.pneumoniae</i>	29	KPC-2 (100)
3	England, Europe	2014-2016	<i>E.coli</i>	39	KPC-2 (58.3) OXA-48 (25.6)
4	Xiamen, China	2015-2017	<i>K.pneumoniae</i>	35	KPC-2 (80.9) NDM-1 (12.8)
5	Argentina, Latin America	2015-2017	<i>K.pneumoniae</i>	76	KPC-2 (98.7) KPC-3 (1.3)
6	Tunis, Africa	2014-2018	<i>K.pneumoniae</i>	197	OXA-48 (77.7) NDM (7.1)
7	15 cities, Greece	2014-2016	<i>K.pneumoniae</i>	384	KPC (66.5) NDM (13.7)
8	16 provinces, China	2015	<i>K.pneumoniae</i>	664	KPC (50.0) NDM (33.5)

1. Brkić S, et al. *Microb Drug Res* 2019; E-pub
2. Zhao Y, et al. *Front Public Health* 2019; 7: 229
3. Ellaby N, et al. *Euro Surveill* 2019; 24
4. Fang L, et al. *Pathog Dis* 2019; 77: pii: ftz034

5. Cejas D, et al. *J Glob Antimicrob Resist* 2019; 18: 238
6. Kollenda H, et al. *Eur J Microbiol Immunol* 2019; 9: 9
7. Galani I, et al. *Euro Surveill* 2018; 23
8. Zhang Y, et al. *Antimicrob Agents Chemother* 2018; 62: e01882

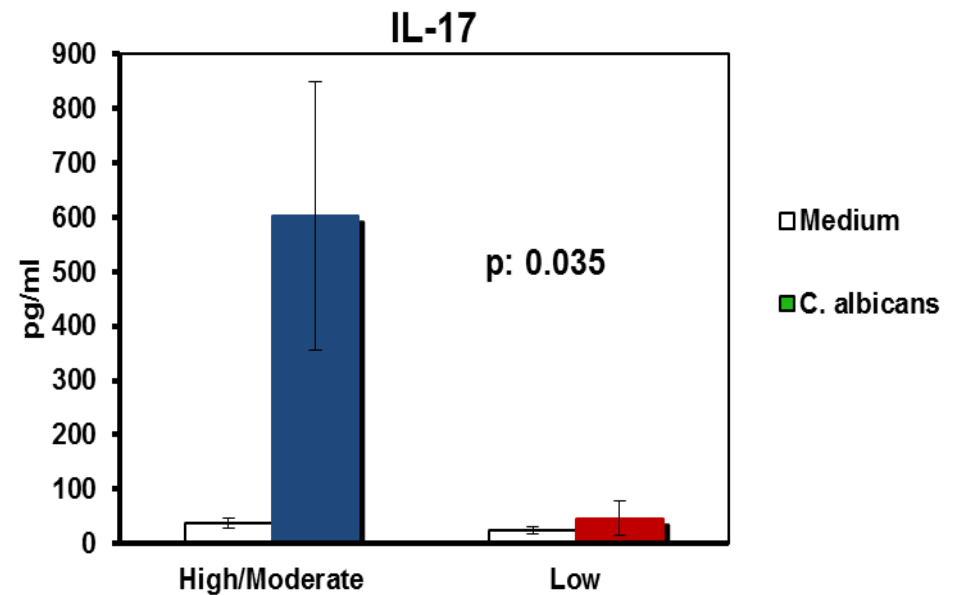
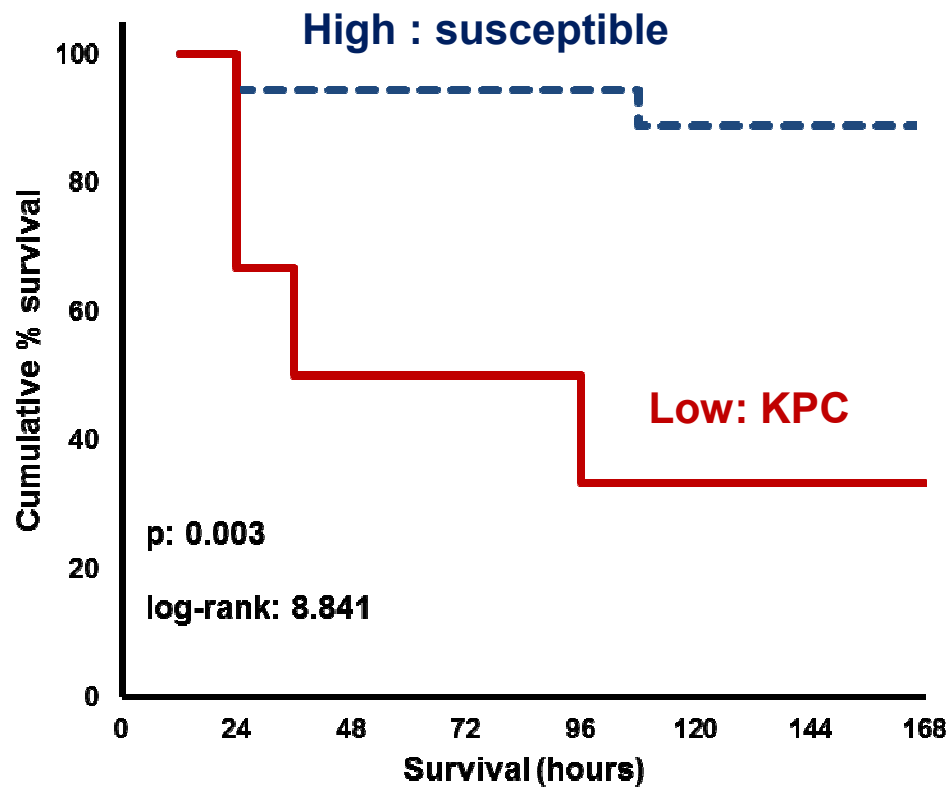
KPC-K.PNEUMONIAE & IMMUNE-SUPPRESSION (1)

(Pantelidou IM, et al. *Antimicrob Agents Chemother* 2015; 59: 7036)



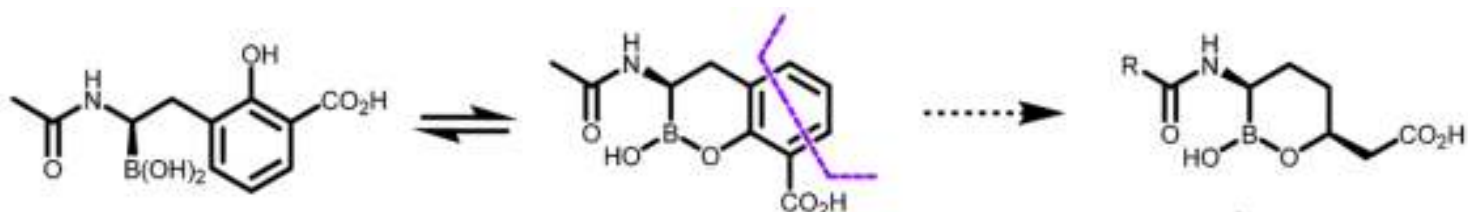
KPC-K.PNEUMONIAE & IMMUNE-SUPPRESSION (1)

(Pantelidou IM, et al. *Antimicrob Agents Chemother* 2015; 59: 7036)



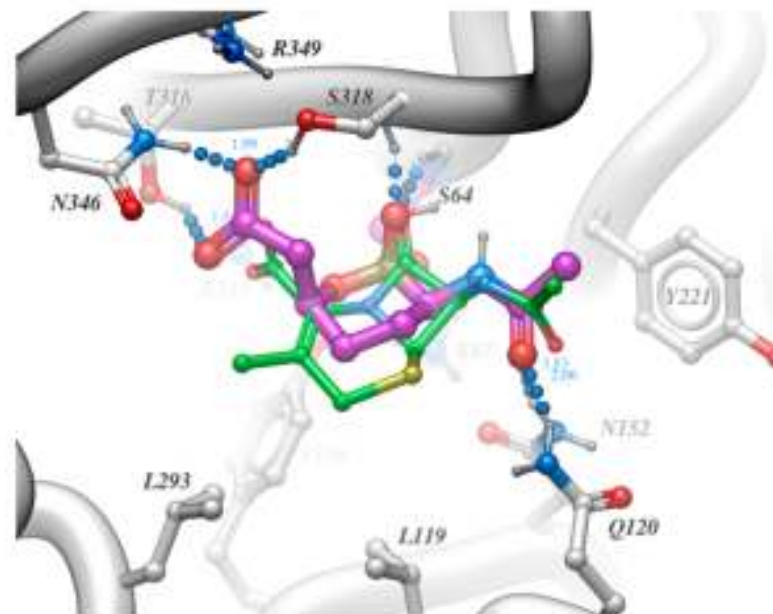
PRINCIPLES OF CHEMISTRY

(Hecker SJ, et al. *J Med Chem* 2015; 58: 3682)



Boronate

Vaborbactam



IN VITRO ACTIVITY AGAINST CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE* (CRE): WORLDWIDE COLLECTIONS (1)

Ref	Period	Species	N	Age nt	MIC50 (µg/ml)	MIC90 (µg/ml)	% inhibited
18	2007-2013	Total CRE	315	MV	≤0.06	1	67.6
				M	16	>64	2.2
		KPC-K.pneumoniae	208	MV	≤0.06	1	93.3
				M	16	>64	0.5
19	2014	Total CRE	265	MV	0.5	32	65.3
				M	16	>32	1.9
		KPC (+)	135	MV	0.12	0.5	96.3
				M	>32	>32	0.7
		OXA-48	25	MV	16	>32	8.0
				M	16	>32	4.0
		MBL(+)	41	MV	32	>32	14.6
				M	32	>32	14.6

REFERENCES

1. Castanheira M, et al *Antimicrob Agents Chemother* 2016; 60: 5454
2. Castanheira M, et al. *Antimicrob Agents Chemother* 2017; 61 : e00567

MV: meropenem-vaborbactam

M: meropenem

IN VITRO ACTIVITY AGAINST CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE* (CRE): WORLDWIDE COLLECTIONS (2)

Ref	Period	Species	N	Agent	MIC50 (µg/ml)	MIC90 (µg/ml)	% inhibited
1	2014-2015	KPC-CRE	991	MV	0.06	1	99.0
				M	32	>32	0
				CAZAVI	1	4	98.2
2	2015	Total CRE	330	MV	0.5	32	73.9
				M	16	>32	1.8
		KPC (+)	206	MV	0.25	1	99.5
				M	32	>32	1.9
		OXA-48	37	MV	16	32	24.3
				M	16	32	2.7
		MBL (+)	52	MV	32	>32	3.8
				M	32	>32	0

REFERENCES

1. Hackel MA, et al. *Antimicrob Agents Chemother* 2018; 62: e01904
2. Pfaller MA, et al. *Int J Antimicrob Agents* 2018; 52: 144

CAZAVI: ceftazidime-avibactam
 MV: meropenem-vaborbactam
 M: meropenem

CUMULATIVE PHARMACOKINETICS

Ref	N	Dose	C _{max} (µg/ml)
1	18	VAB 0.25g	4.81-5.03
	6	VAB 0.5 g	1.35
	6	VAB 0.75 g	1.24
	17	VAB 1g	1.43
	6	VAB 1.25g	1.32
	18	VAB 1.5g	1.65
	12	VAB 2g	1.66
2	30	MER 1g/VAB 0.25g	18.6/5.3
	9	MER 1g/VAB 1g	19.9/5.3
	13	MER 1g/VAB 1.5g	23.3/36.9
	14	MER 1g/VAB 2g	17.5/40.0
	14	MER 2g/VAB 2g	45.7/54.7
3	26	MER 2g/VAB 2g	58.2/59.0

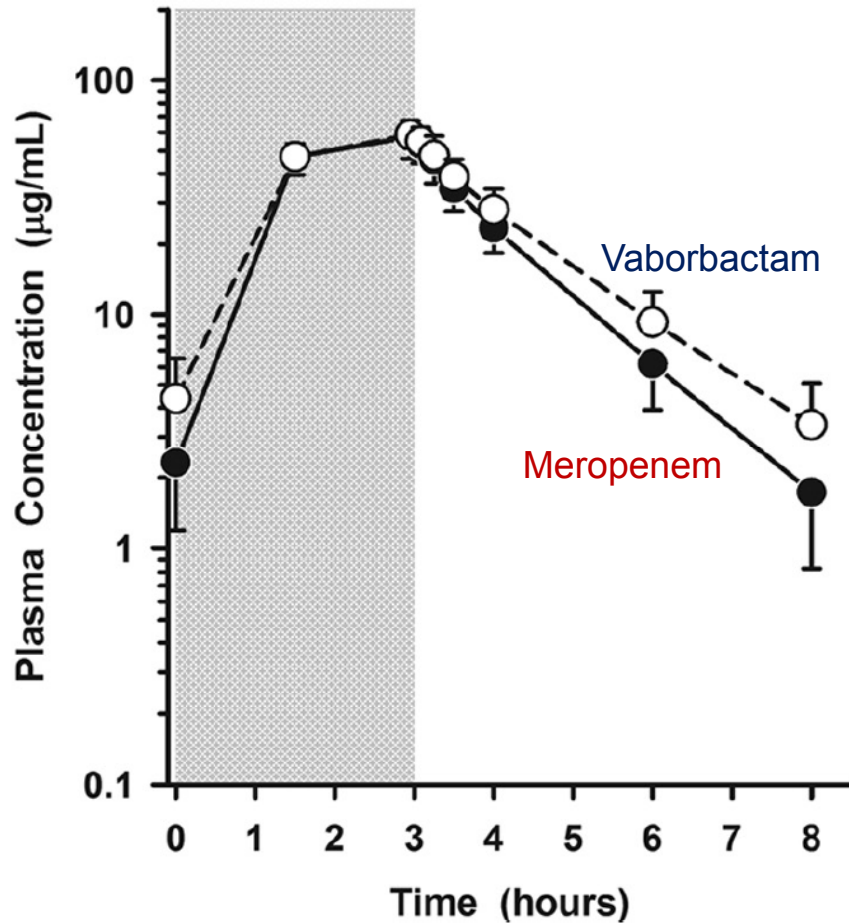
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1. Griffith DC, et al. *Antimicrob Agents Chemother* 2016; 60: 6326
2. Rubino CM, et al. *Antimicrob Agents Chemother* 2018; 62: e02228
3. Wenzler E, et al. *Antimicrob Agents Chemother* 2015; 59: 7323

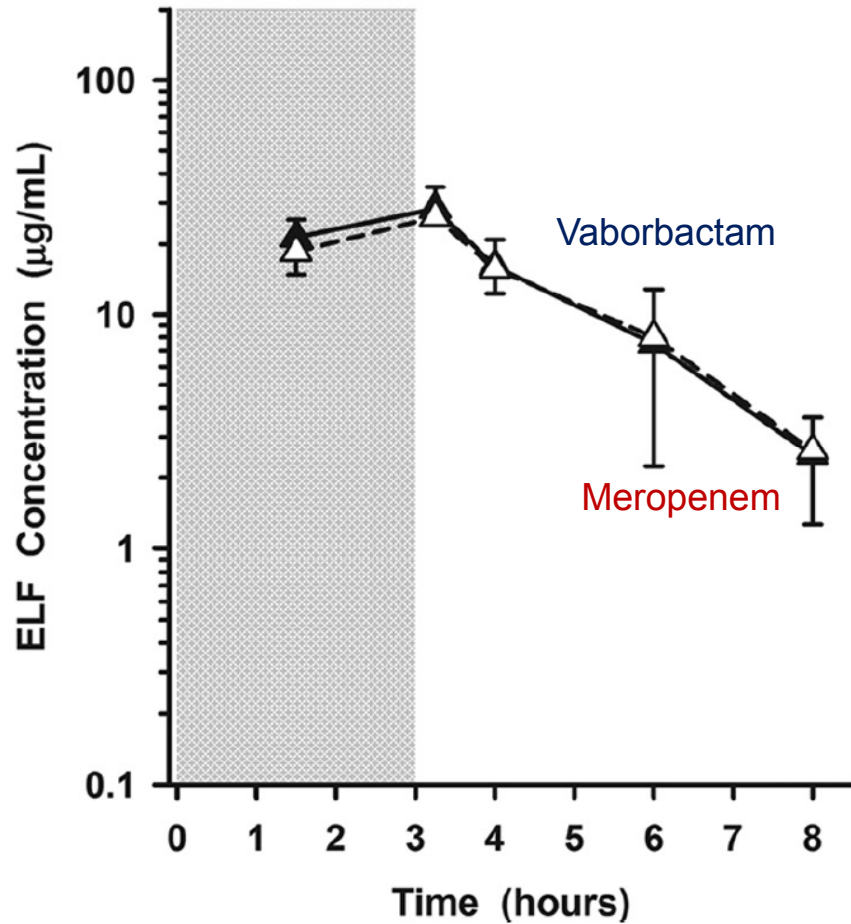
PLASMA AND EPITHELIAL LINING FLUID

(Wenzler E, et al. *Antimicrob Agents Chemother* 2015; 59: 7323)

Before 3rd 2g/2g dose

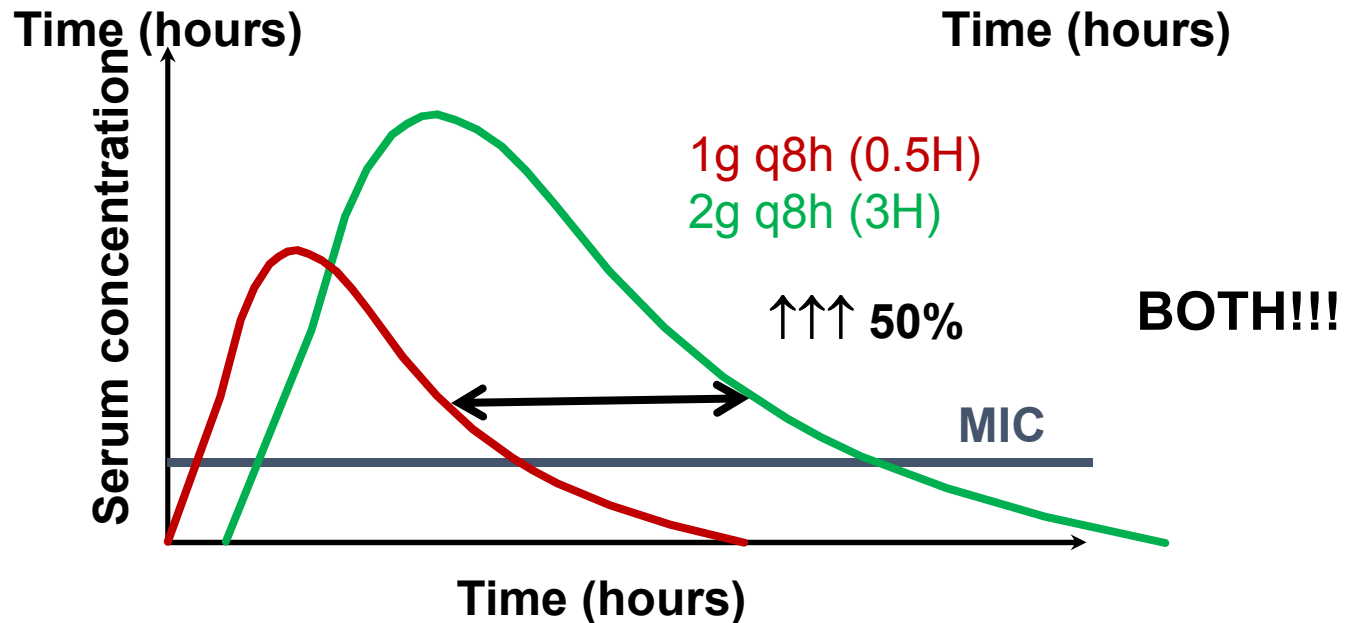
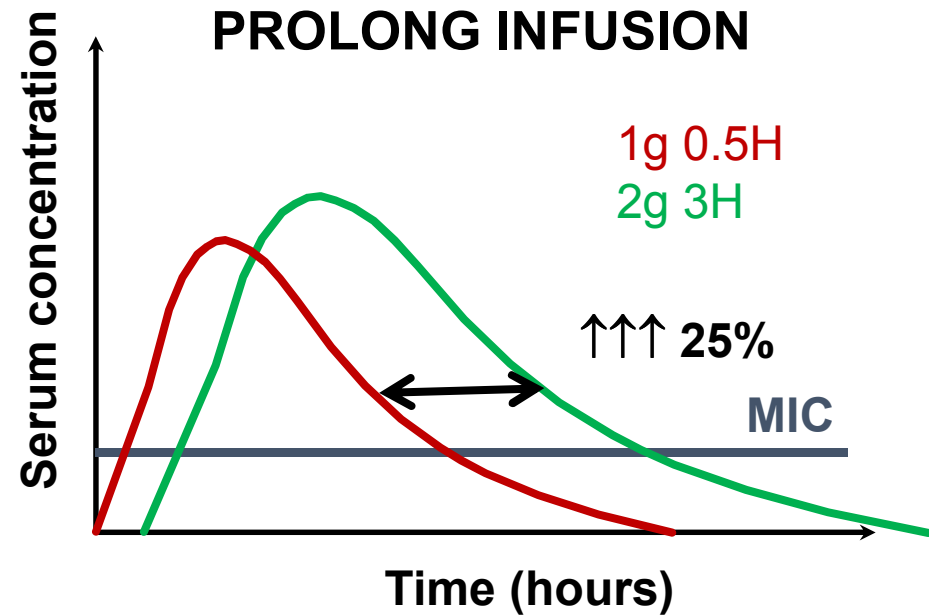
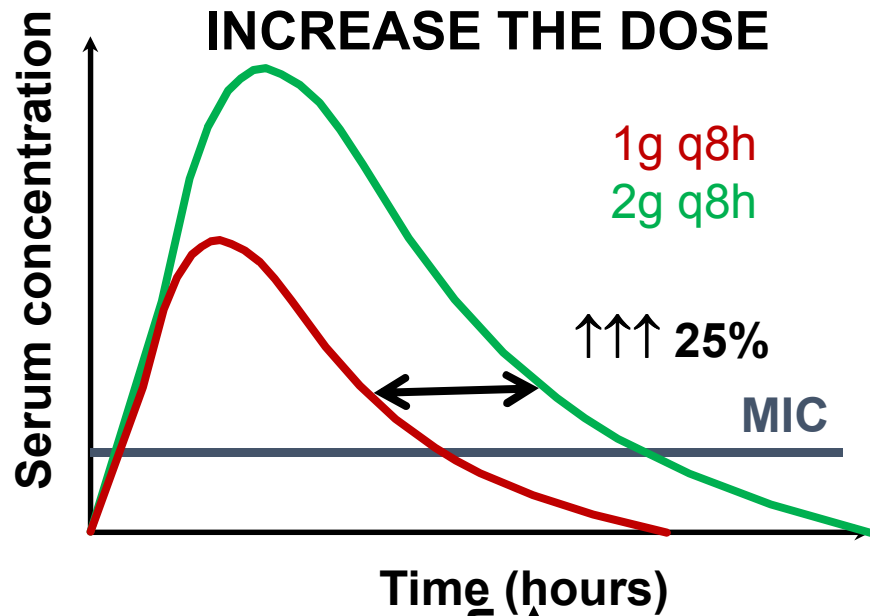


After 3rd 2g/2g dose



INCREASE T>MIC FOR MEROPENEM

(MacVane SH, et al. *Int J Antimicrob Agents* 2014; 43: 105)



NO COMPATIBILITY IN PARELLEL INFUSION

(Kidd JM, et al. *Clin Ther* 2018; 40: 261)

- Albumin
- Amiodarone
- Anidulafungin, caspofungin, isavuconazole
- Calcium chloride
- Ceftaroline, ciprofloxacin, daptomycin
- Diphenhydramine, dobutamine, midazolam, nicardipine, ondasetron , phenytoin

Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

The TANGO I Randomized Clinical Trial

Keith S. Kaye, MD, MPH; Tanaya Bhowmick, MD; Symeon Metallidis, MD; Susan C. Bleasdale, MD; Olexiy S. Sagan, MD; Viktor Stus, MD, PhD; Jose Vazquez, MD; Valerii Zaitsev, PhD; Mohamed Bidair, MD; Erik Chorvat, MD; Petru Octavian Dragoescu, MD; Elena Fedosiuk, MD; Juan P. Horcajada, MD, PhD; Claudia Murta, MD; Yaroslav Sarychev, MD; Ventsislav Stoev, MD; Elizabeth Morgan, BS; Karen Fusaro, BS; David Griffith, BS; Olga Lomovskaya, PhD; Elizabeth L. Alexander, MD; Jeffery Loutit, MBChB; Michael N. Dudley, PharmD; Evangelos J. Giamarellos-Bourboulis, MD, PhD

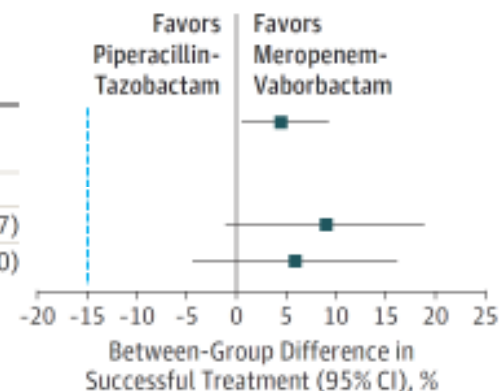
- Complicated urinary tract infections + acute pyelonephritis
- MV (2g/2g) q8h 3-hour iv infusion (n=272)
- Piperacillin/tazobactam (4g/0.5g) q8h 0.5-hour iv infusion (n=273)

TRIAL REGISTRATION [clinicaltrials.gov Identifier: NCT02166476](https://clinicaltrials.gov/ct2/show/study/NCT02166476)

JAMA. 2018;319(8):788-799. doi:10.1001/jama.2018.0438

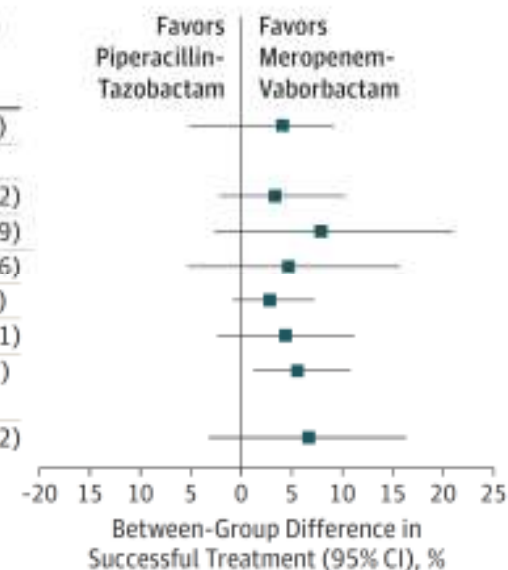
A Primary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis) ^{a,b}	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial eradication at test of cure			
Microbiologic MITT analysis ^b	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)



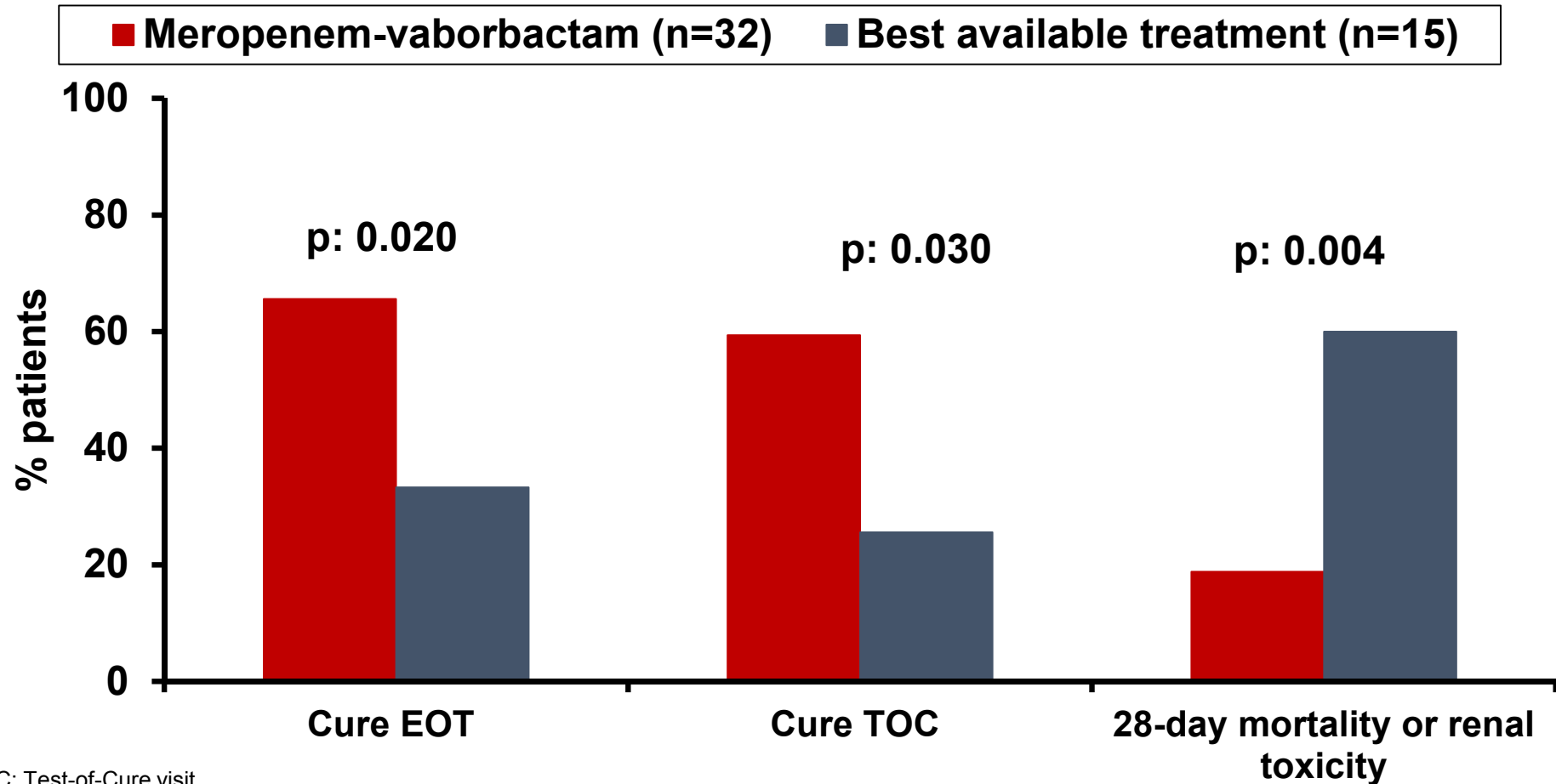
B Secondary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
Overall success at test of cure ^a	143/192 (74.5)	128/182 (70.3)	4.1 (-4.9 to 9.1)
Overall success at end of intravenous treatment ^a			
Acute pyelonephritis	117/120 (97.5)	95/101 (94.1)	3.4 (-2.0 to 10.2)
Complicated UTI, removable infection source ^c	35/35 (100)	35/38 (92.1)	7.9 (-2.5 to 20.9)
Complicated UTI, nonremovable infection source	37/37 (100)	41/43 (95.3)	4.7 (-5.1 to 15.6)
Clinical cure at end of intravenous treatment ^d	189/192 (98.4)	174/182 (95.6)	2.8 (-0.7 to 7.1)
Clinical cure at test of cure	174/192 (90.6)	157/182 (86.3)	4.4 (-2.2 to 11.1)
Microbial eradication at end of intravenous treatment (FDA criteria)	188/192 (97.9)	168/182 (92.3)	5.6 (1.4 to 10.7)
Microbial eradication at test of cure (FDA criteria)	132/192 (68.8)	113/182 (62.1)	6.7 (-3.0 to 16.2)



Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

Richard G. Wunderink · Evangelos J. Giamarellos-Bourboulis · Galia Bahar · Amy J. Mathers · Matteo Bassetti · Jose Vazquez · Oliver A. Cornely · Joseph Solomkin · Tanaya Bhownick · Jihad Bishara · George L. Daikos · Tim Felton · Maria Jose Lopez Purrut · Eun Jeong Kwak · Francesco Menichetti · Ilana Oren · Elizabeth L. Alexander · David Griffith · Olga Lomtovskaya · Jeffery Loutit · Shu Zhang · Michael N. Dudley · Keith S. Kaye



TOC: Test-of-Cure visit
LFU: Long-Follow-Up visit

DRUG APPROVALS

European Medicines Agency (December 2018)

- Acute pyelonephritis
- Complicated intra-abdominal infections
- Hospital-acquired pneumonia including ventilator-associated pneumonia
- Gram-negative infections when other treatments might not work

Food and Drug Administration (2017)

- Complicated urinary tract infections including acute pyelonephritis

Dosing	GFR (ml/min/1,73m ²)
2g/2g q8h	>50
1g/1g q8h	30-49
1g/1g q12h	15-29
0.5g/0.5g q12h	<15

SOME CRITICAL THOUGHTS...

	Meropenem- vaborbactam	Ceftazidime- avibactam	Colistin
CRE-KPC	↑↑↑	↑↑	↑
CRE-OXA-48	-	↑	↑
CRE-NDM/VIM	-	-	↑
Carbapenem NS <i>P.aeruginosa</i>	↑↑	-	↑↑↑
Carbapenem NS <i>A.baumannii</i>	↑↑	-	↑↑↑
cUTI and AP	↑↑↑ TANGO I	↑↑↑ RECAPTURE	No RCT
cIAI	Limited pts in TANGO II	↑↑↑ RECLAIM	No RCT
HAP/VAP	limited pts in TANGO II	↑↑↑ REPROVE	No RCT
CRE infections	↑↑↑ TANGO II	Indirect REPRISE	↑↑↑ AIDA

AP: acute pyelonephritis; cUTI: complicated urinary tract infection; HAP: hospital-acquired pneumonia;
VAP: ventilator-associated; RCT: randomized controlled trial

