Meropenem/vaborbactam

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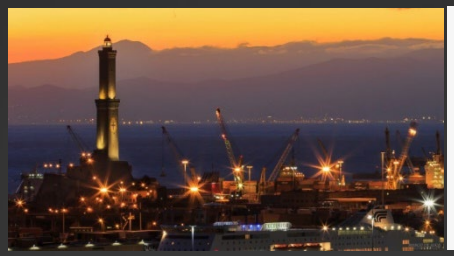

Disclosures (past 5 years)

- Research grants
  - Pfizer, MSD, Gilead
- Advisor/consultant/speaker bureau
  - Cidara, Gilead, Menarini, MSD, Pfizer, Shionogi

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Spectrum of activity of new antibiotics for difficult to treat (DTR) Gram-negative infections

	ESBL	CRE-KPC	CRE-OXA48	CRE-MBL	DTR *P. Aeruginosa*	DTR *Acinetobacter*
BL/BLI Combination						
• Ceftolozane/Tazobactam	🟢	🔴	🔴	🔴	1 🟢	🔴
• Ceftazidime-Avibactam	🟢	🟢	🟢	🔴	🟢	🔴
• Imipenem-Relebactam	🟢	🟢	2 🔴	🔴	3 🟢	🔴
• Meropenem-Vaborbactam	🟢	🟢	🔴	🔴	🔴	🔴
• Aztreonam-Avibactam	🟢	🟢	🟢	4 🟢	5 🔴	🔴
• Cefepime/Zidebactam	🟢	🟢	🟢	🟢	🟢	🟢
• Meropenem/Nacubactam	🟢	🟢	🟢	🔴	🔴	🔴
• Ceftaroline/Avibactam	🟢	🟢	🟢	🔴	🔴	🔴
Novel Cephalosporine						
• Cefiderocol	🟢	🟢	🟢	🟢	🟢	🟢
Novel Amynoglicoside						
• Plazomicin	🟢	🟢	6 🟢	7 🟢	8 🔴	8 🔴
Novel Tetracycline						
• Eravacyclin	🟢	🟢	🟢	🟢	🔴	🟢
• Murepavadin	🔴	🔴	🔴	🔴	🟢	🔴

🔴 No activity or intrinsic or acquired resistance. 🟢 Activity. Abbreviations: BL/BLI, β-lactam/β-lactamase Inhibitor CRE, carbapenem resistant Enterobacteriacae; ESBL, extended-spectrum beta-lactamase; MBLs, metallo-β-lactamases; OMPTA, outer membrane protein targeting antibiotics. 1. Decreased activity for carbapenemase- producing strains of CR *P. aeruginosa*; 2. Very weak activity; 3. Not have activity against MBL; 4. Reduced activity against certain NDM *Escherichia coli* isolates; 5. Activity comparable to aztreonam alone; 6. Activity against OXA-type CREs but increased resistance is observed; 7. Not active against many NDMs; 8. Activity toward *P. aeruginosa* and *A. baumannii* is overall comparable to existing aminoglycosides (tobramycin, amikacin, gentamicin).

Bassetti M et al. *Antibiotics* **2020**, 9, 632; doi:10.3390/antibiotics9090632

New BL-BLI combinations approved

	ESBL	AmpC	KPC	OXA	MBL
Ceftolozane-tazobactam	+	+/-	-	-	-
Ceftazidime-avibactam	+	+	+	+	-
Meropenem/vaborbactam	+	+	+	-	-
Imipenem-relebactam	+	+	+	-	-

Lagace-Wiens et al. Infect Drug Res 2014;9:13-25
Castanheira et al. AAC 2012;56:4779-85

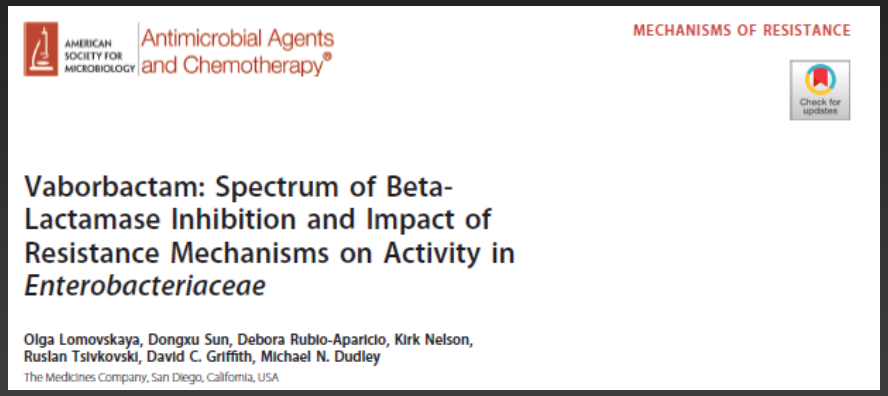
Livermore et al. AAC 2011; 55:390-4
Hong et al. Infect Drug Res 2013;6:215-23

Livermore et al. JAC 2013;68:2286-90

Meropenem-vaborbactam

- Combination of **meropenem** and **vaborbactam**
  - Well-matched pharmacokinetics
  - Vaborbactam is a potent KPC inhibitor
  - Standard dosing = 4g IV q 8h over a 3 hour infusion
- FDA approved indications (approved in 2017)
  - cUTI
- EMA approved indications
  - cUTI/AP, cIAI, HAP/VAP
  - Bacterial infections due to Gram-negative organisms with limited treatment options

Vaborbactam as a β-lactamase inhibitor



Antimicrob Agents Chemother. 2017;61(11).

Strain	Beta-lactamase	Class
ECM6704	None	
ECM6701	KPC-2	A-CARB
ECM6702	KPC-3	A-CARB
ECM6706	SME-2	A-CARB
ECM6696	NMC-A	A-CARB
ECM6718	SHV-5	A-ESBL
ECM6698	SHV-12	A-ESBL
ECM6699	SHV-18	A-ESBL
ECM6713	TEM-10	A-ESBL
ECM6714	TEM-26	A-ESBL
ECM6695	CTX-M-3	A-ESBL
ECM6693	CTX-M-14	A-ESBL
ECM6694	CTX-M-15	A-ESBL
ECM6692	DHA-1	C
ECM6691	MIR-1	C
ECM6705	FOX-5	C
ECM6715	AmpC-ECL (P99-like)	C
ECM6700	CMY-2	C
ECM6697	OXA-2	D
ECM6712	OXA-10	D
ECM6716	OXA-48	D-CARB
ECM6703	NDM-1	B
ECM6711	VIM-1	B

MICs against CAZ, ATM, and MER w/ or w/o vaborbactam

Vaborbactam against engineered *E. coli*:

✓**Potent inhibitor of KPC (≥32-fold MIC ↓)**

✓Good inhibitor of CTX-M (8 to 32-fold MIC ↓)

✓Okay inhibitor of SHV and TEM (4 to 16-fold MIC ↓)

Meropenem is highly stable

⊗Does not inhibit MBL or OXA

Meropenem-vaborbactam and Cystic Fibrosis.

In this Study (2020) Caverly et al tested the in vitro activities of ceftazidime-avibactam, ceftolozane tazobactam, meropenem-vaborbactam, piperacillin-tazobactam, and 11 other antimicrobial agents against 420 Burkholderia, Achromobacter, Stenotrophomonas, and Pandoraea strains, 89% of which were cultured from respiratory specimens from persons with cystic fibrosis.

Caverly LJ et all. 2020. *In vitro* activities of β-lactam–β-lactamase inhibitor antimicrobial agents against cystic fibrosis respiratory pathogens. Antimicrob Agents Chemother 64:e01595-19.

- Meropenem-vaborbactam and piperacillin-tazobactam demonstrated the greatest activity among the -lactam–-lactamase inhibitor agents against Achromobacter spp with 67% and 22%, respectively, of strains being inhibited by </=4 µg/ml of these agents
- Whereas the activity of meropenem-vaborbactam was consistent across all Burkholderia spp. tested, ceftazidime-avibactam and ceftolozane-tazobactam were 4- to 16-fold less active against B. gladioli than against B. cepacia complex spp.
- the activity of meropenem-vaborbactam was comparable to that of meropenem against Burkholderia spp., while meropenem-vaborbactam showed greater potency than meropenem against Achromobacter spp.
- None of the Beta-lactam–Beta-lactamase inhibitor agents showed good activity against S. maltophilia or Pandoraea spp.

TABLE 1 Activities of β-lactam–β-lactamase inhibitor antimicrobial agents and comparators against bacterial strains

Species or group (no. of isolates)	Antimicrobial agent	MIC (µg/ml)			% Susceptible[a]
		Range	MIC_{50}	MIC_{90}	
Achromobacter (100)	Ceftazidime	1 to >32	8	32	71
	Ceftazidime-avibactam	1 to >32	8	32	78
	Ceftolozane-tazobactam	≤0.5 to >32	>32	>32	1
	Meropenem	≤0.5 to >32	1	>32	72
	Meropenem-vaborbactam	≤0.5 to 32	≤0.5	8	86
	Piperacillin-tazobactam	≤2 to >128	≤2	128	87
Burkholderia cepacia complex (150)	Ceftazidime	≤0.5 to >32	4	8	91
	Ceftazidime-avibactam	≤0.5 to >32	4	4	97
	Ceftolozane-tazobactam	≤0.5 to >32	1	8	89
	Meropenem	≤0.5 to >32	2	4	90
	Meropenem-vaborbactam	≤0.5 to >32	1	2	97
	Piperacillin-tazobactam	≤2 to >128	4	64	85
Burkholderia gladioli (50)	Ceftazidime	4 to >32	16	32	20
	Ceftazidime-avibactam	2 to >32	16	16	24
	Ceftolozane-tazobactam	2 to >32	16	32	12
	Meropenem	≤0.5 to 4	1	2	100
	Meropenem-vaborbactam	≤0.5 to 4	1	2	100
	Piperacillin-tazobactam	≤2 to 4	≤2	≤2	100
Stenotrophomonas maltophilia (100)	Ceftazidime	≤0.5 to >32	32	>32	34
	Ceftazidime-avibactam	≤0.5 to >32	16	>32	40
	Ceftolozane-tazobactam	≤0.5 to >32	32	>32	27
	Meropenem	≤0.5 to >32	>32	>32	11
	Meropenem-vaborbactam	≤0.5 to >32	>32	>32	12
	Piperacillin-tazobactam	≤2 to >128	128	>128	18
Pandoraea (20)	Ceftazidime	>32	>32	>32	0
	Ceftazidime-avibactam	>32	>32	>32	0
	Ceftolozane-tazobactam	>32	>32	>32	0
	Meropenem	32 to >32	>32	>32	0
	Meropenem-vaborbactam	32 to >32	>32	>32	0
	Piperacillin-tazobactam	8 to >128	64	>128	5

[a]Susceptibility based on CLSI breakpoints established for *Pseudomonas aeruginosa* as follows: ceftazidime, ≤8 µg/ml; ceftazidime-avibactam, ≤8 µg/ml; ceftolozane-tazobactam, ≤4 µg/ml; meropenem, ≤4 µg/ml; meropenem-vaborbactam, ≤4 µg/ml; piperacillin-tazobactam, ≤16 µg/ml.

Caverly LJ et all. 2020. *In vitro* activities of β-lactam–β-lactamase inhibitor antimicrobial agents against cystic fibrosis respiratory pathogens. Antimicrob Agents Chemother 64:e01595-19.

M/V activity and Pseudomonas MDR

Carvhalaes et al. (2020) was evaluated the Activity of Meropenem-Vaborbactam against Bacterial Isolates Causing Pneumonia in Patients in U.S. Hospitals during 2014 to 2018

Carvalhaes et al. 2020. Activity of meropenem-vaborbactam against bacterial isolates causing pneumonia in patients in U.S. hospitals during 2014 to 2018. Antimicrob Agents Chemother 64:e02177-19

P. aeruginosa isolates were recovered from 3,193 PHP, including 545 isolates responsible for causing VAP.

- The most active agents against *P. aeruginosa* isolates were Colistin (MIC50/90, 1/2 mg/liter; 99.7% susceptible), amikacin (MIC50/90, 4/16 mg/liter; 94.2% susceptible), and meropenem-vaborbactam (MIC50/90, 0.5/16 mg/liter)
- 89.5% of *P. aeruginosa* isolates were inhibited at the meropenem-vaborbactam susceptible breakpoint established by EUCAST (8 mg/liter) compared to 76.4% susceptible to meropenem alone(at 2 mg/liter).
- MDR and extensively drug-resistant (XDR) phenotypes (33, 34) were observed among 697 (21.8%) and 440 (13.8%) respective *P. aeruginosa* isolates, and meropenem-vaborbactam was the most active -lactam agent tested, inhibiting 59.0% and 48.6% of these highly resistant pathogens, respectively.
- Colistin was the only compound active against 90% of MDR (MIC50/90, 0.5/2 mg/liter; 99.1% susceptible) and XDR (MIC50/90, 0.5/1 mg/liter; 99.1% susceptible) subsets, followed by amikacin (MIC50/90, 8/32 mg/ liter; 80.8 to 76.8% susceptible).
- Similar susceptibility rates were observed between *P. aeruginosa* isolates recovered from patients with PHP and VAP

TABLE 1 Antimicrobial susceptibility of *Enterobacterales*, *P. aeruginosa* and resistant subsets collected in 2014–2018 from patients hospitalized with pneumonia and VAP

	PHP					VAP				
	MIC (mg/liter)			CLSI (%)[a]		MIC (mg/liter)			CLSI (%)[a]	
Antimicrobial agent	50%	90%	*N*	S	R	50%	90%	*N*	S	R
Enterobacterales			4,790					814		
Meropenem-vaborbactam	0.03	0.06		>99.9	<0.1	0.03	0.06		100.0	0.0
Meropenem	0.03	0.06		97.2	2.3	0.03	0.06		98.3	1.5
Imipenem	0.25	1		92.8	3.6	0.25	1		94.3	2.2
Cefepime	≤0.5	8		87.8[b]	9.2	≤0.5	2		92.4	5.5
Ceftazidime	0.25	32		82.8	15.6	0.25	32		85.3	13.4
Ceftriaxone	0.12	>8		77.7	20.6	0.12	>8		80.6	17.2
Piperacillin-tazobactam	2	64		87.3	7.1	2	64		87.0	7.5
Aztreonam	≤0.12	>16		82.3	16.4	≤0.12	>16		84.0	14.6
Amikacin	2	4		98.7	0.3	2	4		99.1	0.1
Gentamicin	≤1	2		91.3	7.5	≤1	≤1		95.3	3.6
Tigecycline[c]	0.25	1		96.6	0.3	0.25	1		97.1	0.2
Levofloxacin	≤0.12	>4		80.7	16.8	≤0.12	>4		84.3	12.8
Colistin[d]	≤0.5	>8		76.1	23.9	≤0.5	>8		77.8	22.2
CRE[e]			131					13		
Meropenem-vaborbactam	0.03	0.5		98.5	0.8	0.06	1		100.0	0.0
Meropenem	16	>32		3.8	85.5	4	32		0.0	92.3
Imipenem	>8	>8		0.0	98.5	8	>8		0.0	84.6
Cefepime	>16	>16		8.4[e]	77.9	16	>16		30.8	53.8
Ceftazidime	>32	>32		4.6	93.1	>32	>32		15.4	76.9
Ceftriaxone	>8	>8		2.3	96.9	>8	>8		0.0	92.3
Piperacillin-tazobactam	>64	>64		3.8	89.3	>64	>64		7.7	61.5
Aztreonam	>16	>16		1.5	96.9	>16	>16		7.7	84.6
Amikacin	8	32		73.3	6.1	2	32		84.6	7.7
Gentamicin	4	>8		52.7	26.7	≤1	>8		76.9	15.4
Tigecycline[c]	0.5	2		96.9	1.5	0.5	1		100.0	0.0
Levofloxacin	>4	>4		16.8	79.4	0.5	>4		53.8	38.5
Colistin[d]	≤0.5	>8		76.9	23.1	≤0.5	>8		84.6	15.4
Pseudomonas aeruginosa			3,193					545		
Meropenem-vaborbactam[d]	0.5	16		89.5	10.5	0.5	16		88.8	11.2
Meropenem	0.5	16		76.4	16.9	0.5	16		73.8	10.3
Imipenem	1	>8		74.5	21.4	1	>8		77.2	22.8
Cefepime	4	16		82.4	6.1	4	16		82.5	5.1
Ceftazidime	2	32		81.7	13.2	2	32		82.4	12.7
Piperacillin-tazobactam	4	>64		77.5	11.7	8	>64		74.3	11.9
Aztreonam	8	>16		66.5	21.9	8	>16		63.7	23.5
Amikacin	4	16		94.2	3.3	4	8		96.9	1.3
Gentamicin	2	>8		82.5	10.3	2	8		85.0	9.0
Levofloxacin	1	>4		62.0	26.7	0.5	>4		67.7	23.9
Colistin	1	2		99.7	0.3	1	2		99.8	0.2
MDR[f] *P. aeruginosa*			697					124		
Meropenem-vaborbactam[d]	8	32		59.0	41.0	8	32		59.7	40.3
Meropenem	8	32		22.1	63.1	8	32		21.0	38.7
Imipenem	8	>8		22.8	69.6	8	>8		23.4	70.2
Cefepime	16	>16		32.9	24.7	16	>16		34.7	20.2
Ceftazidime	16	>32		35.3	48.5	16	>32		46.8	41.9
Piperacillin-tazobactam	64	>64		23.0	43.6	64	>64		19.4	41.1
Aztreonam	>16	>16		16.8	66.7	>16	>16		15.3	67.7
Amikacin	8	>32		80.8	12.1	8	16		90.3	3.2
Gentamicin	8	>16		44.9	35.7	8	16		49.2	33.1
Levofloxacin	>4	>4		9.2	74.5	>4	>4		14.5	69.4
Colistin	0.5	2		99.1	0.9	1	2		100.0	0.0
XDR[g] *P. aeruginosa*			440					70		
Meropenem-vaborbactam[d]	16	32		48.6	51.4	16	32		47.1	52.9
Meropenem	16	32		10.0	76.6	16	32		10.0	72.9
Imipenem	>8	>8		13.2	79.5	8	>8		15.7	77.1
Cefepime	16	>16		18.2	34.1	16	>16		20.0	24.3

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Carvalhaes et al. 2020. Activity of meropenem-vaborbactam against bacterial isolates causing pneumonia in patients in U.S. hospitals during 2014 to 2018. Antimicrob Agents Chemother 64:e02177-19

Meropenem-vaborbactam: Summary of key points

- Vaborbactam is a very potent KPC inhibitor
  - Does not inhibit class B or D carbapenemases
- Meropenem-vaborbactam demonstrates high rates of *in vitro* activity against KPC-producing Enterobacteriaceae
  - Including KPC variants that confer resistance to ceftazidime-avibactam
- Mutations in *ompK36* porin gene increases MICs 2 to 8-fold
- Selection for resistance *in vitro* is suppressed at clinically-relevant exposures

Meropenem-vaborbactam: TANGO I

JAMA | Original Investigation

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

- Phase III, multicenter, double-blind, double-dummy RCT enrolling patients with cUTI and acute pyelonephritis

Patients with cUTI/AP requiring ≥ 5 days of IV antibiotics

- **Meropenem-vaborbactam 2g/2g over 3 hours**
- **Piperacillin-tazobactam 4g/0.5g over 30 minutes**

→ **End of IV treatment (after ≥15 doses)** → **End of IV treatment (after 10 days)** → **Test of cure visit (7 days post EOT)**

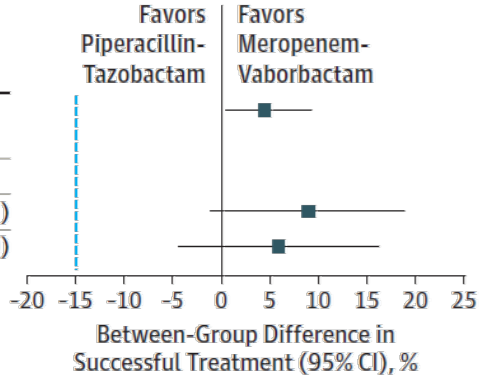
JAMA. 2018;319:788-799.

Meropenem-vaborbactam: TANGO I

- Phase III, multicenter, double-blind, double-dummy RCT enrolling patients with cUTI and acute pyelonephritis

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)



JAMA. 2018;319:788-799.

Meropenem-vaborbactam: TANGO II

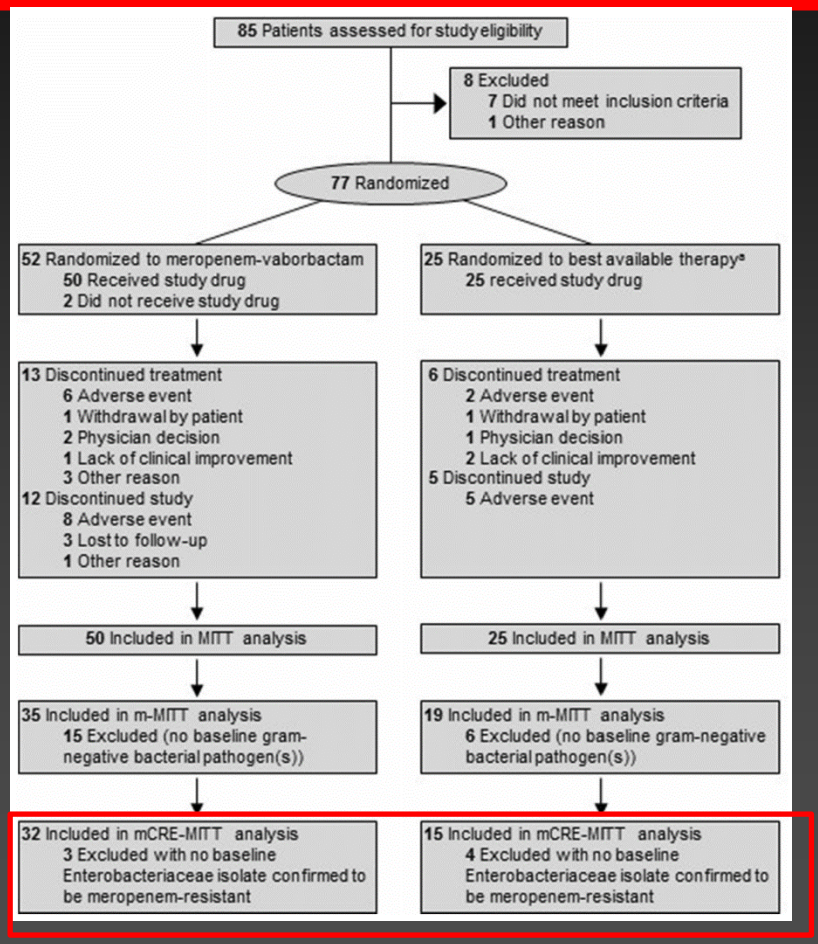
- Phase III, open-label randomized trial comparing the efficacy and safety of meropenem-vaborbactam* to best available therapy for patients with CRE infections

27 hospitals in 8 countries

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

Meropenem-vaborbactam: TANGO II

- Phase III, open-label randomized trial comparing the efficacy and safety of meropenem-vaborbactam* to best available therapy for patients with CRE infections



Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

Meropenem-vaborbactam: TANGO II

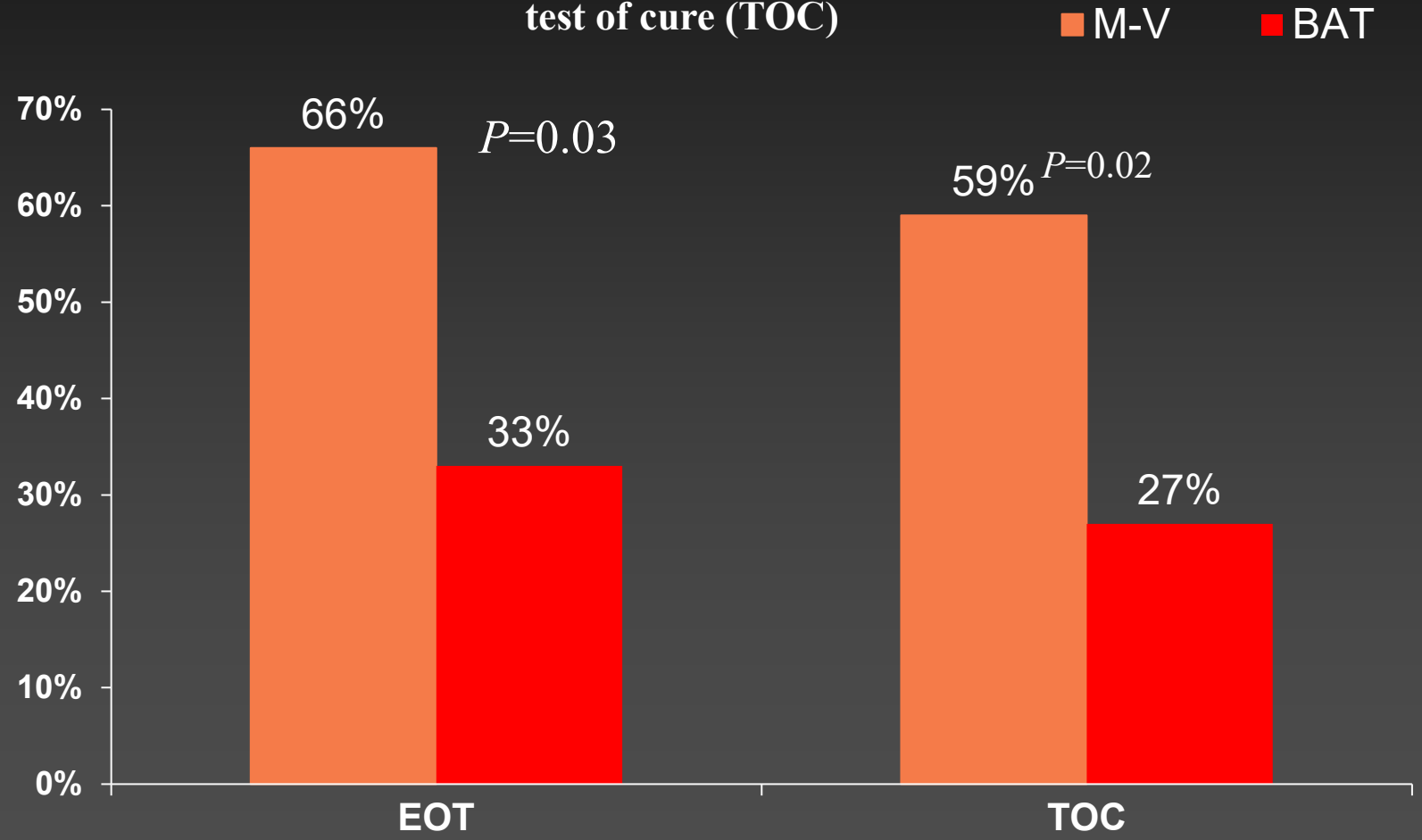
Baseline Characteristics	Meropenem/ vaborbactam N=32, n (%)	Best available therapy N=15, n (%)
Mean age (SD)	63.5 (14.1)	60.2 (13.0)
Charlson Score ≥5	25 (78.1)	12 (80.0)
Immunocompromised	11 (34.4)	8 (53.3)
SIRS	15 (46.9)	6 (40.0)
ICU admission	5 (15.6)	3 (20.0)
Prior Treatment Failure	**9 (28.1)**	**0/15 (0)**
Infection types • Bacteremia • cUTI/AP • HABP/VABP • cIAI	 14 (43.8) 12 (37.5) 4 (12.5) 2 (6.3)	 8 (53.3) 4 (26.7) 1 (6.7) 2 (13.3)
Pathogens • K. pneumoniae • E. coli • E. cloacae • Other	 29 (90.6) 3 (9.4) 1 (3.1) 1 (3.1)	 12 (80.0) 1 (6.7) 2 (13.3) 3 (20.0)

BAT Regimen	All (N=15*), n (%)
Monotherapy	**4 (26.7)**
Aminoglycoside	1 (6.7)
Carbapenem	1 (6.7)
Ceftazidime-Avibactam	1 (6.7)
Polymyxin B/Colistin	1 (6.7)
Dual Therapy	**7 (46.7)**
Carbapenem + Aminoglycoside	1 (6.7)
Carbapenem + PolymyxinB/Colistin	1 (6.7)
Carbapenem + Tigecycline	2 (13.3)
PolymyxinB/Colistin + Aminoglycoside	3 (20.0)
Triple Therapy	**1 (6.7)**
Carbapenem + Polymyxin/Colistin+Tigecycline	1 (6.7)
4 or More Drugs	**2 (13.3)**
Carbapenem+Colistin+Tigecycline+Aminoglycoside	2 (13.3)

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

Meropenem-vaborbactam: TANGO II

Meropenem-vaborbactam showed higher clinical cure rates at end of therapy (EOT) and test of cure (TOC)



Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

TANGO II
Day 28 All-Cause Mortality
All Infection Types (mCRE-MITT)

Endpoint/Statistics	MV N=32 n, (%)	Best Available Therapy N=15 n, (%)	Absolute Percent Difference (MV-BAT)	Relative Percent Difference [(MV-BAT)/BAT]
All-Cause Mortality Rate Day 28	5 (15.6)	5 (33.3)	-17.7	-53.2
Subjects Censored*	27 (84.4)	10 (66.7)		
Kaplan-Meier Estimate (95%CI)	15.6 (6.8 to 33.5)	33.3 (15.4 to 62.5)		

*Subjects whose survival status is unknown due to early termination or lost to follow up will be censored at the last day the subject was known to be alive.

Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1.

Efficacy and Safety of Meropenem–Vaborbactam Versus Best Available Therapy for the Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections in Patients Without Prior Antimicrobial Failure: A Post Hoc Analysis

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Received: March 6, 2019

Table 2 Efficacy results in patients without prior antimicrobial failure in the mCRE-MITT population

Efficacy endpoints (mCRE-MITT)	Meropenem–vaborbactam (*n* = 23)	Best available therapy (*n* = 15)	Absolute difference (95% CI)
Clinical cure at TOC	16 (69.6)	4 (26.7)	+ 42.9 (+ 13.7 to + 72.1)
Clinical cure at EOT	19 (82.6)	5 (33.3)	+ 49.3 (+ 20.8 to + 77.7)
Microbiologic cure[a] at EOT	19 (82.6)	6 (40.0)	+ 42.6 (+ 13.4 to + 71.8)
Microbiologic cure[a] at TOC	16 (69.6)	5 (33.3)	+ 36.2 (+ 5.9 to + 66.6)
Day 28 mortality	1 (4.3)	5 (33.3)	− 29.0 (− 54.3 to − 3.7)

CI confidence intervals, *EOT* end of therapy, *mCRE-MITT* microbiologic carbapenem-resistant *Enterobacteriaceae* modified intent-to-treat, *TOC* test of cure

[a] Microbiologic cure was defined as microbial eradication or presumed eradication

So how should meropenem-vaborbactam be used?

Potentially useful agent for **empiric** CRE treatment

Risk factors

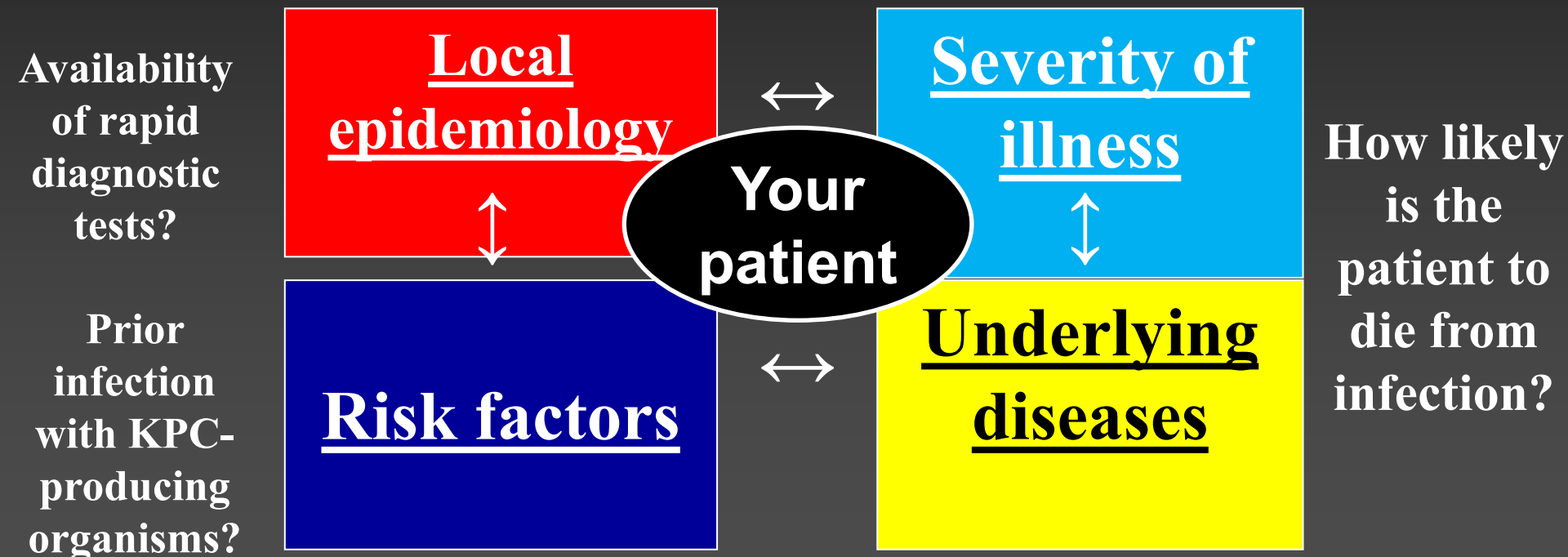
- **Previously known colonization**
- **Receipt of broad-spectrum antibiotics**
- **History of prolonged colonization**
- Invasive devices
- Immunosuppression
- Current or prior ICU admission
- Local outbreaks
- Travel to endemic areas

All very likely to be present, but prior colonization is the only specific risk factor!

Montravers and Bassetti. *Curr Opin Infect Dis* 2018;31:587

So how should meropenem-vaborbactam be used?

Potentially useful agent for **empiric** CRE treatment



Montravers and Bassetti. *Curr Opin Infect Dis* 2018;31:587

Examples of clinical experience of «old style vs new style treatment» in CRE infections

Study	Treament	Mortality
OLD		
Shields, 2017	Ceftazidime/avibactam (mono or combo)	8%
Wunderink RG, 2018	Meropenem/vaborbactam	15.6%
Motsch, 2019	Imipenem/relabactam*	9.5%
Bassetti, 2021	Cefiderocol	13.8%

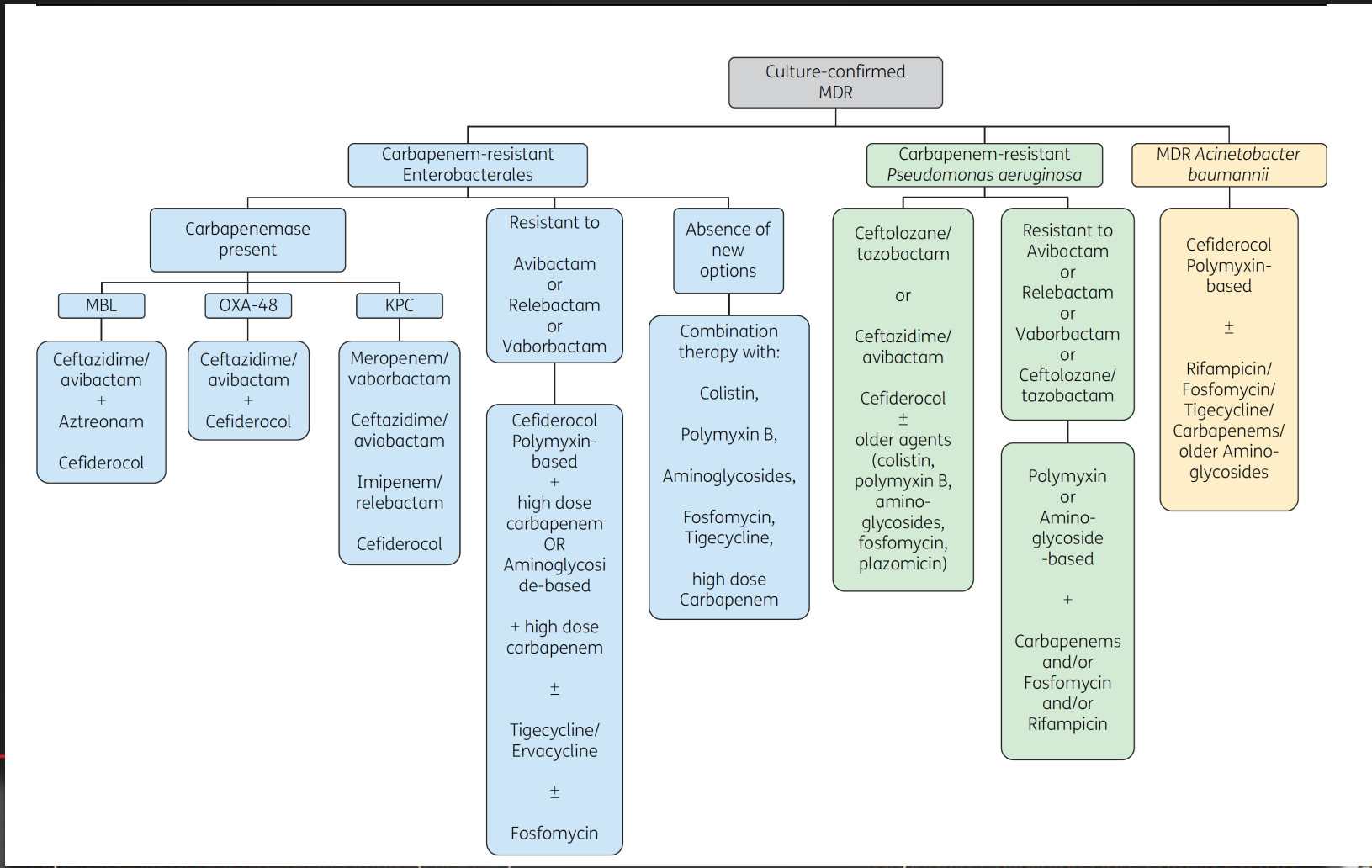
Recommendations are for non-colistin based regimens for MDR Gram-negatives: CRE Example

- 2020 IDSA "Resistance Guidance": Recommendations for Carbapenem-resistant Enterobacterales (CRE)

Source of Infection	Preferred Treatment	Alternative Treatment (first-line options not available or tolerated)
Infections outside of the urinary tract Resistant to ertapenem, meropenem, AND carbapenemase testing results are either not available or negative	Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)
KPC identified (Or carbapenemase positive but identity of carbapenemase unknown[3])	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)

Tamma PD, Aitken SL, Bonomo RA et al. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-negative Infections. Available at https://www.idsociety.org/practice-guideline/amr-guidance/ Published by IDSA, 8-Sep-2020, Last accessed November 2020

Suggested treatments for carbapenem-resistant Enterobacterales, multidrug-resistant Pseudomonas aeruginosa, and multidrug-resistant Acinetobacter baumannii



Genoa, Italy

Bassetti M, Garau X. . *J Antimicrob Chemother* 2021; **76** : iv23–iv37

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