Meropenem-Vaborbactam

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Consultant/Advisory Board/Speaker fees

- **Pfizer, MSD, Angelini, Thermo Fisher, Shionogi, BioTest, Nordic Pharma, InfectoPharma**
- **Gilead Sciences, GSK, Hikma, Advanz, Basilea**
- **Tillots, Menarini, Correvio**
- **Research grant**
  - Pfizer, MSD, Shionogi

Background

- **Epidemiology of MDR**
- **Carbapenemases: CPE & CRE**
- **KPC and the Lesson from Ceftazidime-avibactam**
  - Monotherapy Vs. Combination
  - Primary Vs. secondary resistance
  - Dosage in specific settings
    - ECMO, VAP, CVVH
  - Sparing regimens
- **Vaborbactam designed on KPC enzymes**

Meropenem-Vaborbactam Activity Vs. MDR Enterobacterales, Including Carbapenem-Resistant Isolates

Shortridge D et al. Microbiol Spectr. 2023 Feb 14

- **1,697 MDR Enterobacterales**
  - 31 U.S. medical centers in 2016 to 2020
  - CLSI methodology with broth dilution
  - Whole-genome sequencing done MIC >2 mg/L for imi or mero
- **222 CRE isolates (13.1%)**
  - KPC = 81.1% **99% sensitive ot mer/vab**
  - NDM (n = 7), VIM (n = 3)
  - OXA-48-like (n = 4) carbapenemases
  - 29 CRE isolates (13.1%) → **No detected carbapenemases**

Meropenem-Vaborbactam Activity Vs. MDR Enterobacterales, Including Carbapenem-Resistant Isolates

Shortridge D et al. Microbiol Spectr. 2023 Feb 14

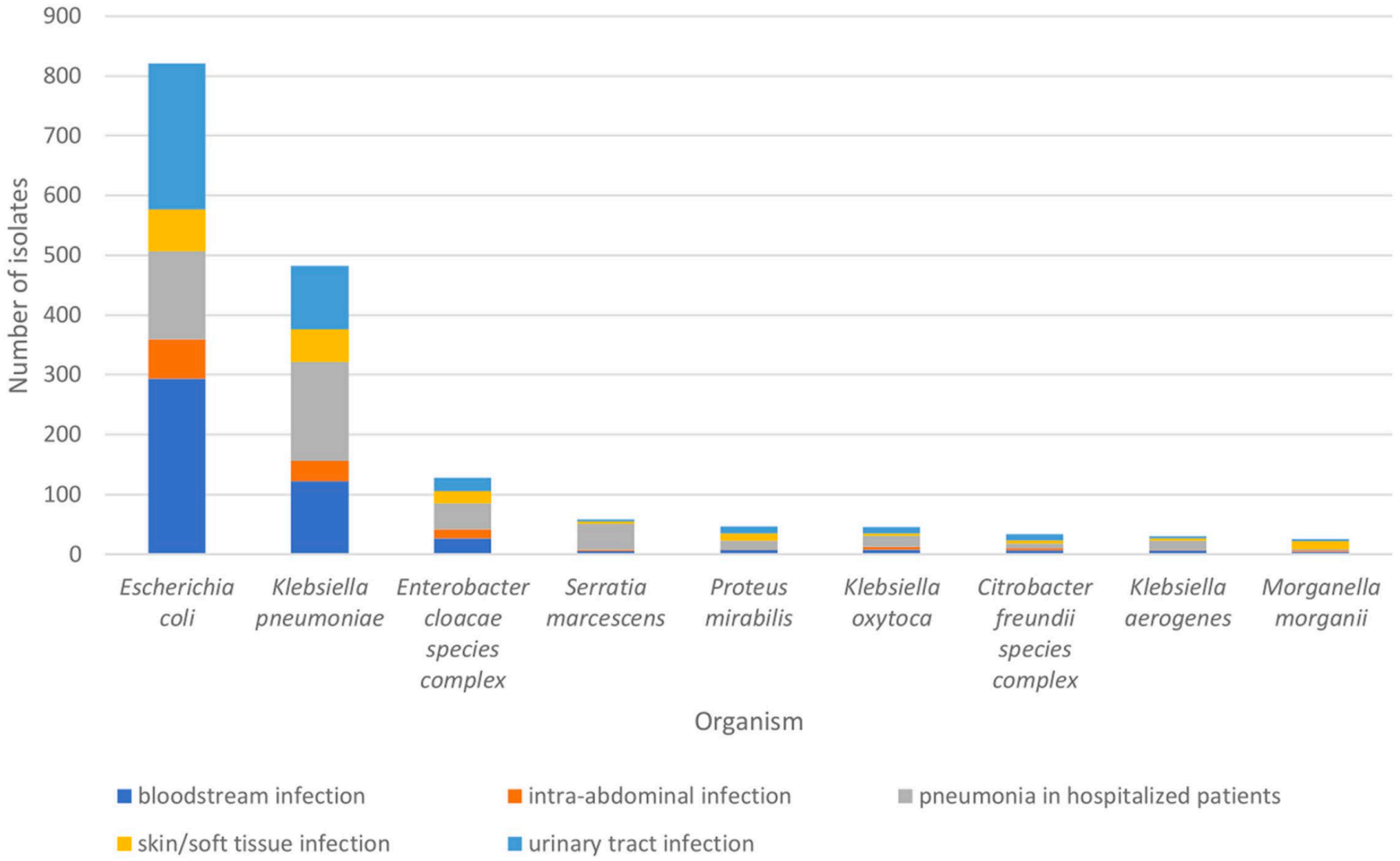

FIG 1 Species with >10 isolates, according to infection type.

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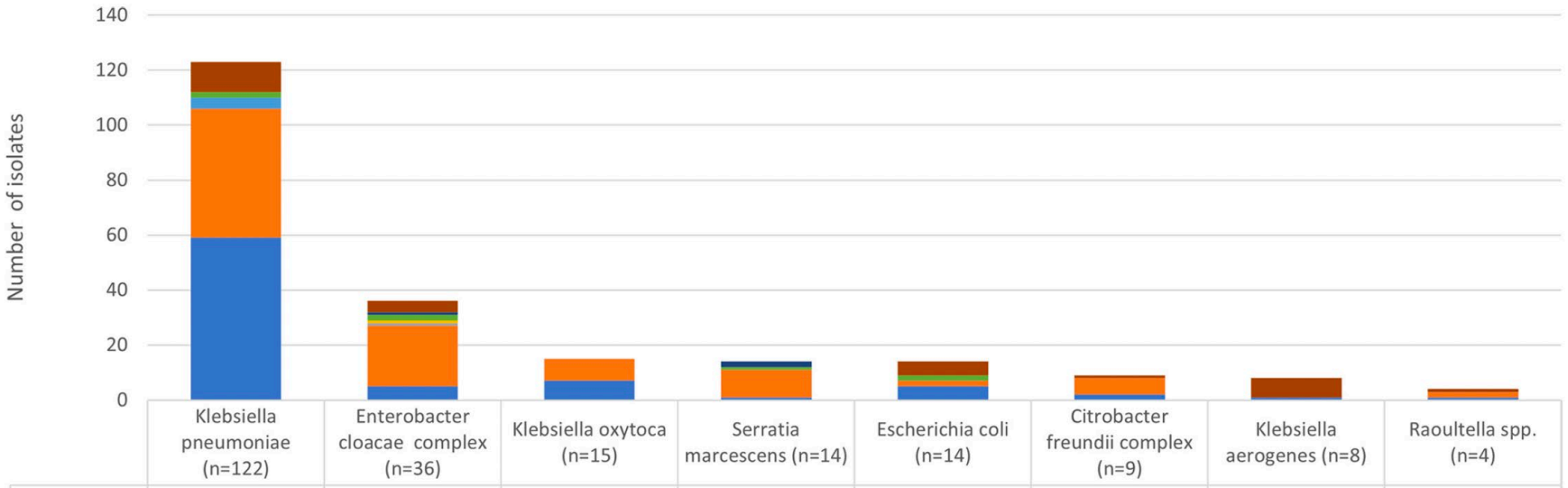


	Klebsiella pneumoniae (n=122)	Enterobacter cloacae complex (n=36)	Klebsiella oxytoca (n=15)	Serratia marcescens (n=14)	Escherichia coli (n=14)	Citrobacter freundii complex (n=9)	Klebsiella aerogenes (n=8)	Raoultella spp. (n=4)
NonCP	11	4			5	1	7	1
VIM-1		1		2				
NDM-1/5	2	2		1	2			
OXA-232/48	4							
KPC-6		1						
KPC-4		1						
KPC-3	47	22	8	10	2	6		2
KPC-2	59	5	7	1	5	2	1	1

FIG 2 CRE strains according to species (number of each organism is shown), carbapenemases produced, and nonCP CRE. One *K. pneumoniae* isolate had both OXA-232 and NDM-1. No other isolates contained more than one carbapenemase.

Efficacy of ceftazidime-avibactam, mer-vab & imi-rel Combinations Vs. CPE in Switzerland (2018-20)

Nordmann P et al. Eur J Clin Microbiol Infect Dis. 2023 Sep;42(9):1145-1152

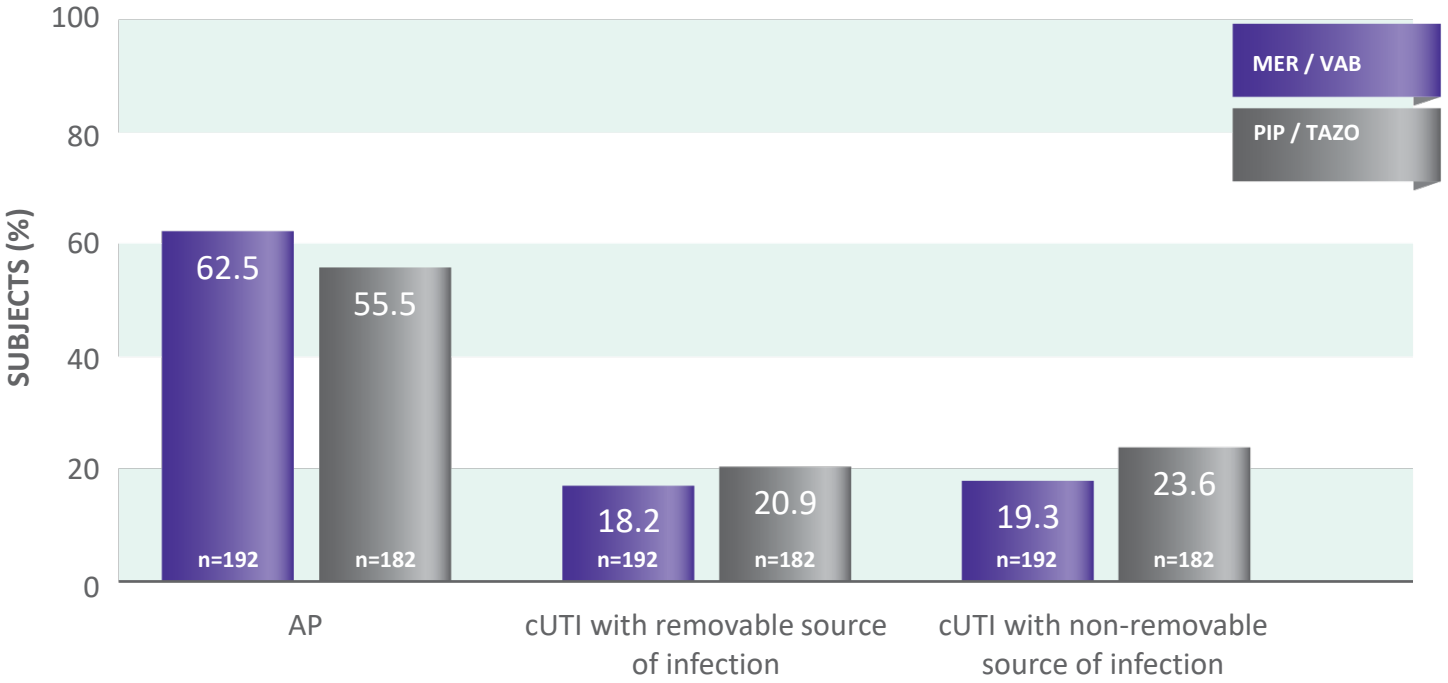
- **150 clinical isolates of CPE**
  - *Klebsiella pneumoniae* (n = 61, 40.3%) and *Escherichia coli* (n = 53, 35.3%)
- **Carbapenemases distribution:**
  - KPC-like 32%
  - OXA-48-like 32%
  - NDM-like 24%
  - **Combinations of carbapenemases 10%**
  - VIM-1 & IMI-1 producers n = 2/1, respectively
- **Strain sensitivities:**
  - Mer-vab: 77%
  - CAZ-AVI 63%
  - Imi-rel 62%

Vaborbactam (RPX7009)

Hecker SJ et al J Med Chem 2015

- **Specific design for KPC beta-lactamases**
  - No antibacterial activity alone MIC, 64 g/ml
    - Livermore DM et al JAC 20213
- **Cyclic boronic acid pharmacophore: first in class**
  - Inhibition of serine-lactamases of class A & C
  - KPC, IMI, SME, NMC-A, BKC-1, and FR-1 carbapenemases
  - No inhibition of mammalian serine proteases
- **Affinity of boronates for active sites of beta-lactamases**
  - Covalent complex between the catalytic serine side chain and the boronate moiety
  - Mimicking the tetrahedral transition state of acylation/deacylation reaction complex
- **Different structure from diazabicyclooctanes:**
  - Avibactam and relebactam

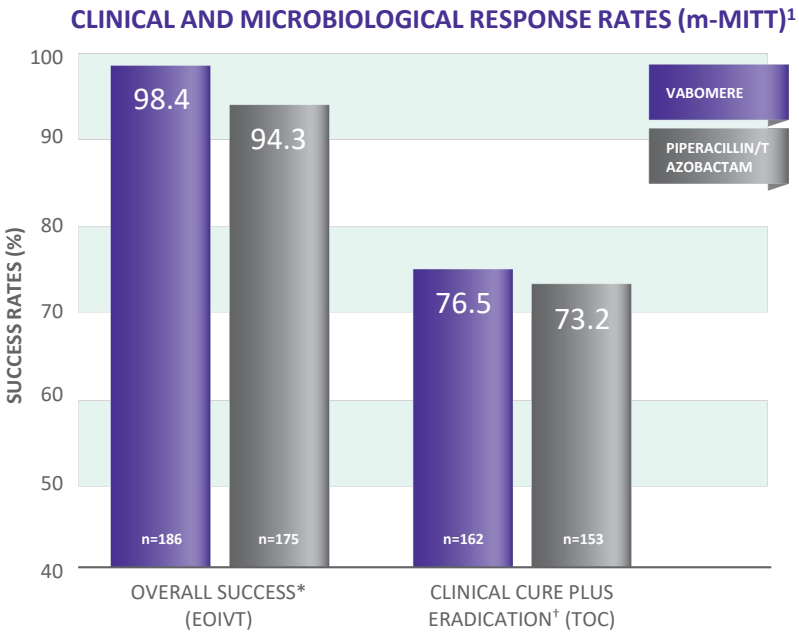
TANGO-I: Baseline Characteristics by Infection Type (m-MITT)



AP=acute pyelonephritis; m-MITT=microbiologic modified intent-to-treat population.

Kaye KS, et al. *JAMA*. 2018;319(8):788-799 (Supplementary Material).

MER / VAB Demonstrated an Overall Success Rate of 98.4% vs 94.3% with Piperacillin/Tazobactam[1]



PRIMARY ENDPOINT: Overall success at the EOIVT (composite of both a clinical outcome of cure or improvement and a microbiologic outcome of eradication) in the m-MITT population.[1,2] Clinical and microbiological response was also assessed at the TOC visit (approximately 7 days after completion of treatment) in the m-MITT population and required both a clinical outcome of cure and a microbiological outcome of eradication.

*EOIVT includes patients with organisms resistant to piperacillin/tazobactam at baseline.
†TOC visit excludes patients with organisms resistant to piperacillin/tazobactam at baseline in both arms.
EOIVT=end of IV treatment; TOC=test of cure visit.

1. VABOMERE [package insert]. Lincolnshire, IL: Melinta Therapeutics, Inc. 2. Data on file. Lincolnshire, IL: Melinta Therapeutics, Inc.; 2019.

Meropenem–Vaborbactam Vs. Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

Wunderink R et al *Infect Dis Ther (2018) 7:439–455*

- **Phase 3, open label, randomized controlled trial**
- **77 patients with confirmed/ suspected CRE infection**
  - Bacteremia, HAP/VAP, complicated intra-abdominal infection, complicated urinary tract infection/acute pyelonephritis
- **47 patients with confirmed CRE infection**
  - Primary analysis population
    - *Microbiologic-CREmodified intent-to-treat*, mCRE-MITT
- **Eligible patients were randomized 2:1**
  - **MER / VAB or BAT** mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or ceftazidime avibactam alone
  - **Efficacy endpoints:** clinical cure, Day-28 all-cause mortality, microbiologic cure, and overall success (clinical cure + microbiologic eradication)

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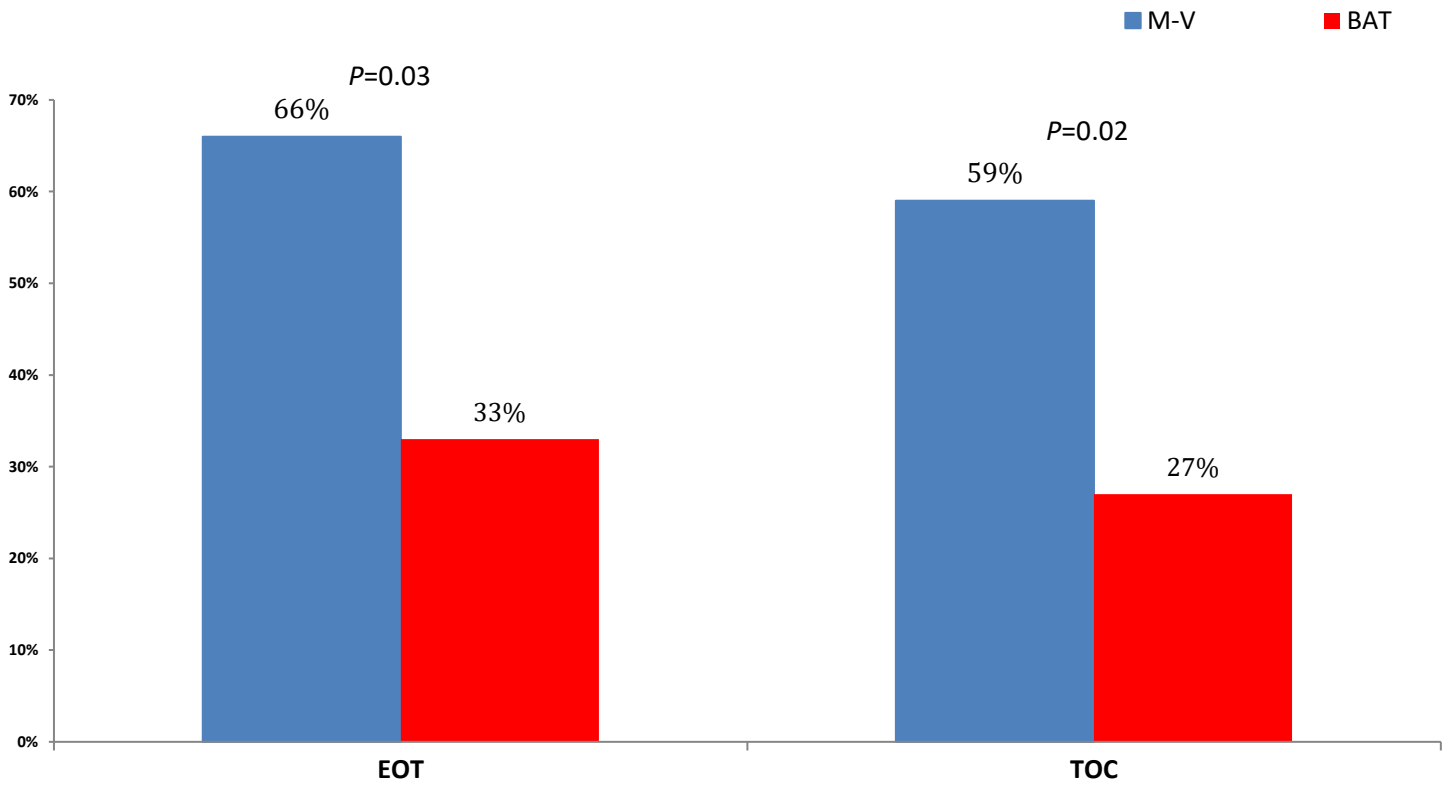
Higher clinical cure rates at end of therapy (EOT) and test of cure (TOC)



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

Wunderink R et al *Infect Dis Ther (2018) 7:439–455*

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)		

*

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

Matteo Bassetti · Daniele Roberto Giacobbe · Niki Patel · Glenn Tillotson · Jill Massey

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

Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections

Avoid R in vivo

- 131 patients; 105 w C/A VS 26 w M/V
- Overall, 53/105 (40.5%) had BSI.
- Most common sources of BSI: UTI (35.1%) in the C/A and the abdomen (37.5%) in the M/V.
- COMBO therapy: 61.0% pts in C/A VS 15.4% in M/V (p= 0.01).
- No differences in clinical cure and overall mortality.

	Ceftazidime-avibactam group (*n* = 105)	Meropenem-vaborbactam group (n = 26)	*P* value
No. of recurrences of CRE infection (%)	15 (14.3)	3 (11.5)	1.0
No. of increases in study drug MIC in mg/liter (%)	6 (40.0)	0	0.51
No. of emergences of study drug resistance (%)	3 (20.0)	0	1.0

Ackley R et al, AAC 2021

Real-Life Use of Meropenem/Vaborbactam in Turin Hospital City of Health & Science – 2022 -

94 patiens treated with mero/vabor:

- Year 2021: 36 pts
- Year 2022: 58 pts
- (Year 2023: 32 pts)

Among 58 pts (year 2022):

37.9% (22) pts targeted therapy, among them

45.5% (10) pts CAZ/AVI R

  - 27.2%(6) HAP/VAP, 9.1% (2) BSI + HAP/VAP, 22.7% (5) BSI, 4.5% (1) CVC-associated BSI, 9.1% (2) UTI, 18.2% (4) IAI
  - 36.4% (8) non-rectal carriers

- **67.2% (39): pre-emptive in rectal carriers**
- **20.7% (12): empirical for severe infections**

58 patients, 2022	N (%)
Pre-emptive in rectal carriers	39 (67.2)
Empirical therapy for critical conditions	12 (20.7)
Targeted therapy	22 (37.9)
Targeted therapy, type of infection HAP/VAP BSI + HAP/VAP BSI CVC-associated BSI UTI IAI	 6 (27.2) 2 (9.1) 5 (22.7) 1 (4.5) 2 (9.1) 4 (18.2)
Targeted therapy, microbiology CAZ/AVI resistant isolate	 10 (45.4)
Targeted therapy, rectal carriage	8 (36.4)

Corcione S, De Benedetto I, & De Rosa FG, *in preparation*

Effective Durations of Therapy for CRE Bloodstream Infections: A Multicenter Observational Study

Soto CL et al. Clin Infect Dis 2023 Aug 16

- **183 adults with CRE-BSI, 24 US hospitals**
  - **Short-courses of active therapy**
    - 7-10 days, median 9 days
  - **Prolonged courses of active therapy**
    - 14-21 days, median 14 days
- **Similar odds, propensity-score-weighted analysis**
  - **Recurrent bacteremia or death within 30 days**

Clinical Efficacy & Safety of Novel Antibiotics for cUTIs: Systematic Review & Meta-analysis of Randomized Controlled Trials

Hung KC et al Int J Antimicrob Agents 2023 Jul;62(1):106830

- **TOC, New drugs Vs. comparators**
- **Higher CCR in 11 RCTs, 3514 participants:**
  - 83.6% vs 80.3%, OR 1.37, 95% CI 1.08-1.74, P=0.01, I2=35%
- **Higher microbiological eradication rate, 4347 participants**
  - 77.7% vs 67.2%, OR 1.79, 95% CI 1.46-2.20, P<0.00001
- **No significant difference at TOC:**
  - CCR: OR 0.96, P=0.81, I2=4%
  - Risk of treatment-emergent AEs (OR 0.95, P=0.57, I2=51%
- **Results of TSA:**
  - Robust evidence regarding microbiological eradication rate & TEAEs
  - CCR at TOC and EOT remained inconclusive
- **→ Novel antibiotics may be more effective in cUTIs**

CCR: clinical cure rate; TOC: test of cure; AE: adverse event; TSA: trial sequential analysis

Meropenem-vaborbactam Restoration of First-line Drug Efficacy & Comparison of mer-vab-moxi Vs. BPaL MDR-TB Regimen

Singh S et al Int J Antimicrob Agents 2023 Sep 17

- **Resistance mutations to Rifa, INH & CEFs detected by WGS**
  - Mer-vab MIC of *M. tuberculosis* H37Rv / 16D = 2 mg/L & > 128 mg/L, respectively
  - Relebactam and vaborbactam improved potency and efficacy of mero in STKs
- **Mer-vab-moxi combination**
  - Most effective and outranking bedaquiline and pretomanid
- **Mer-vab-moxi & BPaL**
  - Highest K (log10 CFU/mL/day) in the hollow fiber model system of TB
  - 0.31 (95% CI 0.17-0.58) & 0.34 (95% CI 0.21-0.56)
- **Mer-vab-moxi-linezolid → antagonism**
- **→ Mer-vab may restore INH & Rifa efficacy Vs. MDR-TB**
- **→ Mer-vab-moxi as a potential new MDR-TB regimen**

CEFs: cephalosporins; WGS: whole genome sequencing; STKs: static kill studies; K: kill rate costant; BPaL: bedaquiline-pretonamid-linezolid

Conclusions

- **Pan-KPC agent: meropenem vaborbactam**
- **Treatment strategies:**
  - Targeted treatment: CRE
    - Pre-emptive or empiric strategies in patients colonized by CRE
  - Caz-avi sparing
- **"Differential" stewardship programs for the new BL/BLI**
  - Specific considerations for other drugs & MDR bacteria
- **Local Microbiology & CRE / CPE**