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Efficacy of Human-Simulated Exposures Meropenem/Vaborbactam (MVB) and Meropenem (MEM) against OXA-48 β-lactamase-producing *Enterobacterales* in the Neutropenic Murine Thigh Infection Model

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ABSTRACT

Background: The introduction of the novel β-lactamase inhibitors, including avibactam and vaborbactam, has revolutionized treatment of carbapenemase-producing *Enterobacterales*. However, challenges remain with organisms harboring OXA-48 and its variants. OXA-48 exhibits variable hydrolytic activity toward carbapenems, with imipenem and meropenem MICs, though increased, often reporting within the 'susceptible' or 'intermediate' ranges defined by CLSI and EUCAST. Although vaborbactam does not enhance MEM activity against OXA-48, approximately a third of OXA-48-producing *Enterobacterales* will test susceptible to MVB due to its higher breakpoint compared with MEM. Clinical implications of this discordance warrant investigation.

Methods: 26 isolates harboring OXA-48 (n=24) and KPC (n=2) were evaluated in the neutropenic murine thigh model. Human-simulated regimens of MVB (simulating doses of 4 g IV q 8 hours over 3 hour) and MEM (2 g IV q 8 hours over 3 hours) were administered. Mice received MVB, MEM, or normal saline as sham control for 24 hours. Efficacy was assessed on the resulting overall mean $\log_{10}$ CFU/thigh as well as the achievement of 1 $\log_{10}$ reduction as an established surrogate marker predictive of success for serious infections.

Results: MVB and MEM MICs ranged from 1- 64 and 2 - >64 mg/L, respectively. Relative to 0 hour control, the mean bacterial growth (mean ± SD, CFU/thigh) at 24 hours in the untreated control mice was 2.69 ± 1.31 $\log_{10}$. As anticipated for KPCs, MVB resulted in a mean bacterial reduction > 1 $\log_{10}$ (-1.10 ± 0.26), whereas growth was observed on MEM (+1.45 ± 0.88). Considering all OXA-48 isolates, MVB resulted in variable bacterial densities ranging from -2.54 to +2.68 $\log_{10}$, similarly MEM resulted in -2.18 to +2.66 $\log_{10}$. Addition of vaborbactam did not enhance MEM activity against any isolate. For isolates with MVB MICs ≥ 16 (n=5), 8 (n=5, EUCAST breakpoint), 4 (n=9, CLSI breakpoint), and ≤ 2 (n=5) mg/L, 0%, 0%, 44%, and 60% of isolates treated with MVB or MEM achieved the target reduction of ≥ 1 $\log_{10}$ kill, respectively.

Conclusions: Over the range of the MIC distribution, MVB and MEM humanized exposures *in vivo* resulted in similar reductions and growth in bacterial density for OXA-48-producing *Enterobacterales*. Moreover, these data highlight the poor efficacy of MVB for OXA-48 defined as susceptible using the current EUCAST and CLSI susceptibility criterion. As a result of these observations, caution is warranted when treating *Enterobacterales* testing susceptible to MVB without the availability of the genotypic profile.

INTRODUCTION

- OXA-48-like harboring *Enterobacterales* represent a significant global threat.[1]
- Meropenem/vaborbactam offers potent activity against KPC-harboring *Enterobacterales*, however; vaborbactam lacks inhibitory activity against OXA-48 of which meropenem is a substrate resulting in a similar MIC distribution between meropenem/vaborbactam and meropenem alone.[2,3]
- Despite the lack of inhibitory activity by vaborbactam and the poor intrinsic activity of meropenem against OXA-48, susceptibility breakpoints for meropenem/vaborbactam are 2-fold higher than that of meropenem alone (CLSI: ≤4 mg/L versus ≤1 mg/L and EUCAST ≤8 mg/L versus ≤2 mg/L).[3]
- As high as 35% of OXA-48-like harboring *Enterobacterales* test at meropenem/vaborbactam MICs ≤ 8 mg/L.[2]
- The therapeutic implications of breakpoint discordance between meropenem/vaborbactam and meropenem against OXA-48 warrants investigation

OBJECTIVE

- To evaluate the *in vivo* activity of human-simulated exposures of meropenem/vaborbactam and meropenem against OXA-48-like harboring *Enterobacterales* in the neutropenic murine thigh infection model

MATERIALS & METHODS

Antibiotic Compounds

- Commercially available meropenem/vaborbactam and meropenem were utilized for *in vivo* experiments
- Supplemental meropenem was added to meropenem/vaborbactam and further diluted to final dosing concentration
- All antibiotics were administered as subcutaneous injections in 0.2 mL in normal saline (NS)

Bacterial Isolates

- 24 OXA-48-like harboring *Enterobacterales* with varying meropenem/vaborbactam were assessed *in vivo*
- 2 *Klebsiella pneumonia* isolates harboring KPCs were also evaluated as controls
- Broth microdilution MICs for meropenem/vaborbactam and meropenem were determined in triplicate per CLSI standards

Neutropenic Thigh Model

- Female CD-1 mice (mean weight 20-22 g) were used
- Neutropenia was induced with cyclophosphamide 150 mg/kg on day-4 and day-1
- Uranyl nitrate 5 mg/kg was given to produce predictable renal impairment to aid in humanizing drug exposures
- Mice were inoculated with ~10^7 CFUs as a 0.1 mL intramuscular injection 2 h before antibiotic dosing
- Euthanasia was performed via CO2 asphyxiation cervical dislocation
- The meropenem/vaborbactam human-simulated regimen (HSR) was administered as previously described.[4]
- The murine meropenem/vaborbactam regimen produced murine plasma concentrations with similar meropenem *f*T>MIC and vaborbactam *f*AUC to those seen in infected patients (**Table 1.**).

Table 1. Target human meropenem %*f*T>MIC exposure following administration of meropenem/vaborbactam 2g/2g IV every 8 hours as a 3 hour infusion and those achieved in mice administered the meropenem/vaborbactam HSR.

	%*f* T>MIC for a MIC (mg/L)							
Species	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**
Human[a]	100	100	100	86	63	37	0	0
Mouse (HSR)[a]	100	100	94	75	55	29	5	0

[a] Vaborbactam *f*AUC in humans 504 mg·h /L compared with 560 mg·h /L for the murine vaborbactam from the meropenem-vaborbactam HSR

In Vivo Efficacy Studies

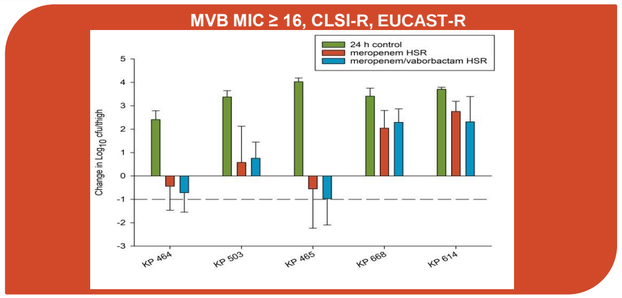
- For each isolate, 4 groups of 3 mice were utilized.
- Control groups were sacrificed at 0 h and 24 h
- Treatment groups received human-simulated regimens of meropenem/vaborbactam or meropenem
- Both thighs were aseptically harvested, homogenized in NS, and serially diluted before plating to measure bacterial burdens in lung tissue
- Efficacy was defined as $\log_{10}$ change in cfu/thigh at 24 h compared with 0 h controls
- Achievement of > 1 $\log_{10}$ reduction in bacterial burden as an established surrogate marker predictive of success for serious infections was assessed[5]

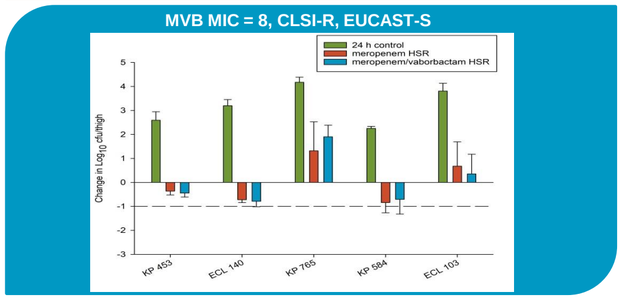
RESULTS

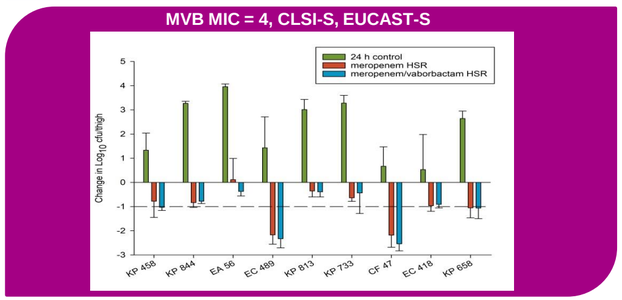
Table 2. Phenotypic and known genotypic profile of evaluated carbapenemase producing *Enterobacterales*.

Isolate #	MEM (mg/L)	MVB (mg/L)	β-lactamase genes
KP 732	>64	0.5	KPC-2, SHV-OSBL, TEM-OSBL
KP 329 B	64	≤0.06	KPC-2, SHV-11, SHV-5, OXA-9, TEM-1
KP 614	64	64	OXA-48, OXA-1, SHV-76, TEM-1, CTX-M-15
KP 668	32	32	OXA-48
KP 465	16	16	OXA-48
KP 503	16	16	OXA-48
KP 464	16	16	OXA-48
ECL 103	16	8	OXA-48
KP 584	8	8	OXA-48
KP 765	8	8	OXA-48(c), CTX-M-15, SHV-OSBL(b))
ECL 140	4	8	OXA-48, ACT-TYPE
KP 453	2-8^	8	OXA-48 + CTX-M-15
EA 56	4	4	OXA-48
KP 658	4	4	OXA-181,CTX-M-15, SHV-26
EC 418	4	4	OXA-48
CF 47	4	4	OXA-48, OXA-1
KP 844	2	4	OXA-181,CTX-M-15, SHV-26
KP 458	8	4	OXA-48
KP 733	4	4	OXA-48, SHV-12, TEM-1, CTX-M-15
KP 813	4	4	OXA-48, SHV-12, TEM-1, CTX-M-15
EC 489	4	4	OXA-48
KP 670	2	2	OXA-181,CTX-M-15, SHV-26
ECL 123	4	2	OXA-48, TEM-OSBL, CTX-M-15, ACT
CF 32	2	2	OXA-48
EC 486	2	2	OXA-48
KP 581	2	1	OXA-48

MEM = meropenem; MVB = meropenem/vaborbactam
^no mode







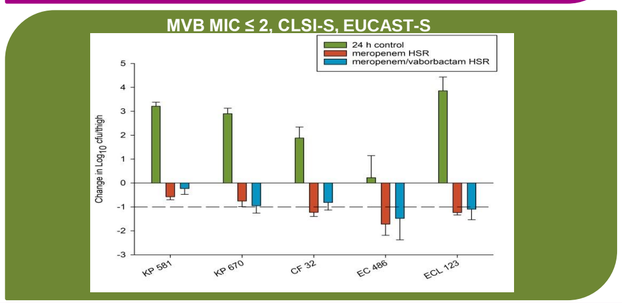


Figure 1. **Change in $\log_{10}$ CFU/thigh (mean ± SD) at 24 h in a neutropenic murine thigh infection model. All isolates were assessed after receiving a) 24-hr saline control, b) meropenem HSR, or c) meropenem/vaborbactam HSR.**

In Vivo Efficacy Studies

- As expected, meropenem/vaborbactam resulted in mean bacterial kill against KPC-harboring strains compared with growth for meropenem alone, mean±SD: -1.10 ± 0.26 vs. +2.69 ± 1.31, respectively.
- For isolates with meropenem/vaborbactam MICs ≥ 16 (n=5), 8 (n=5, EUCAST breakpoint), 4 (n=9, CLSI breakpoint), and ≤ 2 (n=5) mg/L, 0%, 0%, 44%, and 60% of isolates treated with MVB or MEM achieved the target reduction of ≥ 1 $\log_{10}$ kill, respectively.

CONCLUSIONS

- **Meropenem/vaborbactam and meropenem resulted in similar, albeit poor, efficacy against OXA-48 harboring strains despite receiving meropenem exposure >40%*f*T>MIC**
- **These data highlight the poor efficacy of meropenem/vaborbactam for OXA-48-harboring isolates despite their *in vitro* susceptibility as defined by current EUCAST and CLSI susceptibility criterion highlighting an important patient safety concern.**
- **Clinical use of meropenem/vaborbactam in OXA-48 endemic regions warrants caution when the absence of OXA-48 cannot be confirmed with genotypic testing or when meropenem/vaborbactam and meropenem MICs are similar**

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