Importance of Utilizing Local Carbapenem-Resistant *Enterobacteriaceae* (CRE) Surveillance Isolates to Determine Potential Efficacy of Novel Agents: Meropenem/Vaborbactam (M/V) Exhibits Robust Activity at a US Healthcare Center with a Predominance of Non-KPC-Producing CRE

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BACKGROUND

- CRE is a major global threat with numerous resistance mechanisms
- Vaborbactam exhibits potent activity against Ambler class A and class C β-lactamases, but clinically is particularly useful in combination with meropenem for the treatment of KPC-mediated CRE infections
- Large surveillance AST studies have demonstrated muted efficacy of M/V against non-KPC-producing *Enterobacteriaceae* (MIC_{50} and MIC_{90} ≥8 mg/L)
- The epidemiological distribution of KPC-mediated resistance is highly variable, even within similar geographical areas
- University of Wisconsin Hospitals and Clinics has on average 1 KPC isolate per year (incidence of ~0.3/100,000 patient days and 0.007% of all *Enterobacteriaceae* isolates per year). However, phenotypic CRE isolates are 15-20-fold higher
- Given the published *in vitro* data and relative rarity of KPC-mediated resistance, our hypothesis was M/V may have limited utility at our center

METHODS

- Retrospective review of clinical microbiology database at UW Hospital from 1/15-12/17 (36 months).
- CRE isolates from the same encounter were excluded.
- Broth microdilution AST results and susceptibility interpretation was performed according to CLSI standards at the time of clinical encounter. Additionally, molecular testing was performed for presence of KPC, NDM-1, and OXA-48-like plasmid carbapenemases.
- Each isolate underwent additional M/V AST by antibiotic gradient strip (GS) and disk diffusion (DD) per manufacturer instructions.
- Susceptibility interpretation was performed according to approved FDA breakpoints.

RESULTS

- 48 CRE isolates were identified
- Figure 1 and Figure 2 demonstrate the species distribution and source

Figure 1. Species Distribution of CRE Isolates From 1/2015-12/2017 at UW Hospital and Clinics

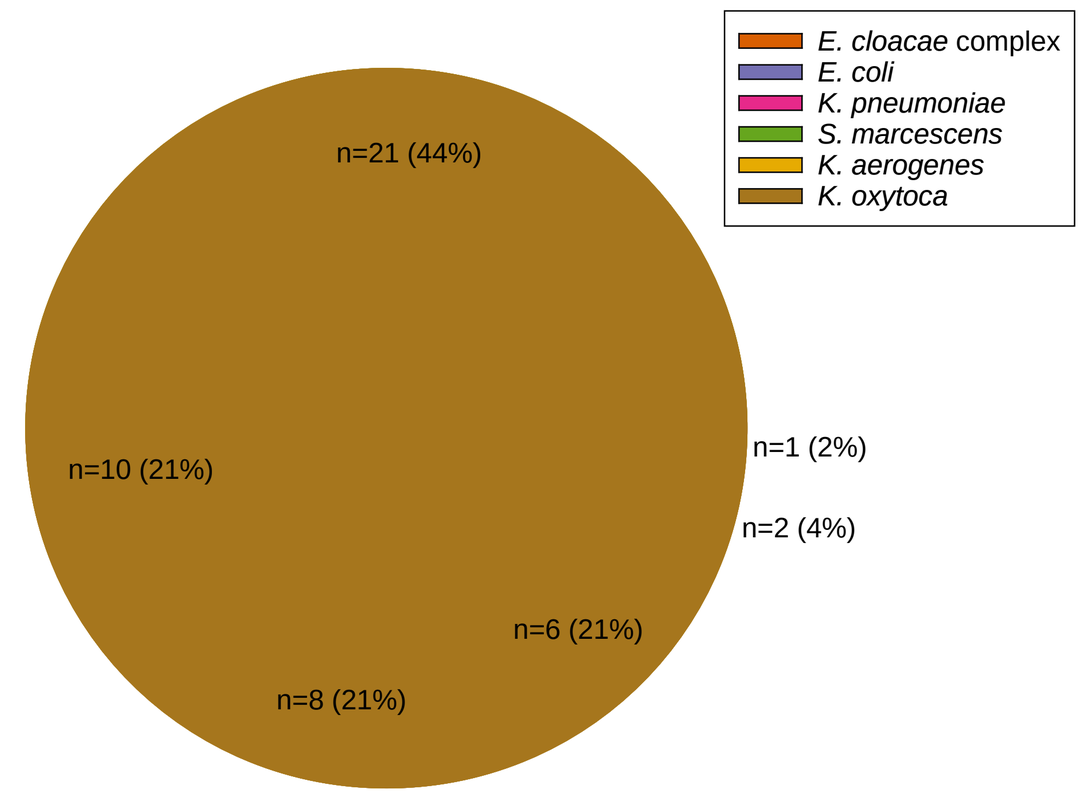
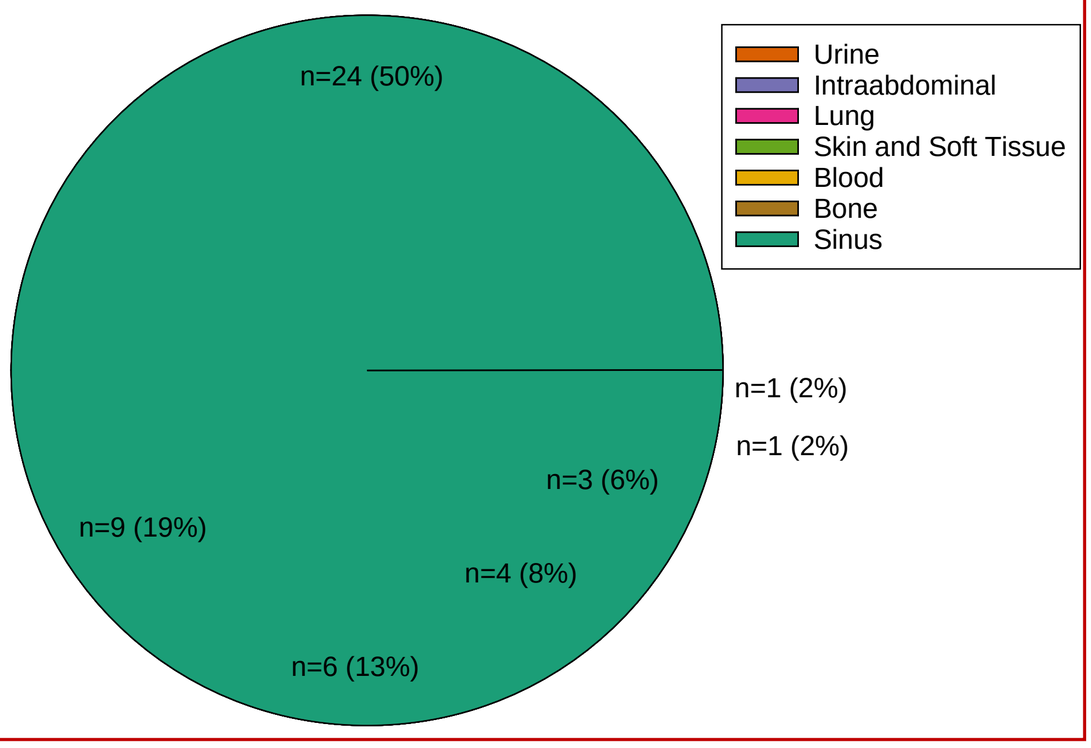


Figure 2. Source of Culture for CRE Isolates From 1/2015-12/2017 at UW Hospital and Clinics



- Two different phenotypic groups were observed amongst CRE isolates
  - Not-susceptible to ertapenem but susceptible to other carbapenems
  - Not-susceptible to all carbapenems
- 3 (6%) tested positive for KPC; there were no OXA-48-like or NDM-1
- M/V demonstrated potent in vitro activity against both groups

Table 1. CRE Phenotype

CRE Phenotype group	N (%)	M/V MIC_{50} (mg/L)	M/V MIC_{90} (mg/L)	N (%) susceptible to M/V[a]
Only Ertapenem Resistant	32 (67)	0.125	0.5	32 (100)
Ertapenem Resistant and Meropenem Nonsusceptible (see **Table 2**)	16 (33)	0.125	2	15 (94)

[a] Current U.S. FDA MIC interpretative breakpoints were used for meropenem-vaborbactam include susceptible ≤4 mg/L, intermediate 8 mg/L, resistant ≥16 mg/L.

- **In the latter group M/V significantly decreased the MIC in 13/16 (81%), led to an average 107-fold lower MIC, and yielded a susceptible MIC in 15/16 (94%) of isolates compared to meropenem**
- There were no discrepancies between antibiotic GS and DD result interpretation.

Table 2. M/V AST results for CRE Isolates Non-Susceptible to Meropenem

Organism	Meropenem MIC (mg/L)[a]	M/V GS MIC (mg/L)[b]	M/V DD Size (mm)[b]	Comment
Enterobacter cloacae complex	2	2	21	
Klebsiella oxytoca	4	0.032	29	
Klebsiella pneumoniae	>8	0.125	20	KPC
Serratia marcescens	>8	0.064	28	
Serratia marcescens	4	0.064	26	
Serratia marcescens	4	0.125	27	
Escherichia coli	8	8	14	
Serratia marcescens	>8	0.064	29	
Escherichia coli	>8	0.032	27	
Enterobacter aerogenes	4	4	17	
Klebsiella pneumoniae	8	0.064	23	KPC
Enterobacter cloacae complex	2	0.5	28	
Enterobacter cloacae complex	4	2	20	
Escherichia coli	4	0.064	30	
Klebsiella pneumoniae	>8	0.125	21	KPC
Escherichia coli	4	2	18	

[a] Current U.S. FDA MIC interpretative breakpoints for meropenem include susceptible ≤1 mg/L, intermediate 2 mg/L; resistant, ≥4 mg/L.
[b] Current U.S. FDA MIC interpretative breakpoints for meropenem-vaborbactam include susceptible ≤4 mg/L or ≥17 mm; intermediate 8 mg/L or 14-16 mm; resistant, ≥16 mg/L or ≤13 mm.

CONCLUSIONS

- M/V was quite potent against clinical CRE isolates at a tertiary-care center where KPC-mediated resistance is extremely rare.
- Against CRE non-susceptible to meropenem with a majority of non-KPC-producers, the M/V MIC_{50} was only 0.125 mg/L and MIC_{90} 2 mg/L. This is likely due to higher prevalence of other class A carbapenemases at our center (e.g. SME)
- This highlights the importance of evaluating novel β-lactam/β-lactamase inhibitors in the context of local epidemiology of circulating strains.
- This study can serve as a template for institutions to undertake similar evaluations for novel agents as they become available in order to best inform clinicians, guide antimicrobial stewardship efforts, and ensure patients have access to optimized therapies.

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