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Antimicrobial Activity of Meropenem-WCK 4234 (WCK 5999) against Clinical Isolates of *Acinetobacter* spp. Collected Worldwide and Stratified by Infection Type

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Abstract

Background: WCK 5999 consists of WCK 4234 (WCK), a novel carbapenemase inhibitor with enhanced activity against class D carbapenemases (OXA type)-expressing organisms, combined with meropenem (MEM). The *in vitro* activity of WCK 5999 (MEM-WCK; fixed 8 µg/mL of WCK 4234) was evaluated against *Acinetobacter* spp. (ASP) isolates collected during 2013 (China) and 2015 (worldwide) and stratified by infection type.

Methods: A total of 639 isolates were from the United States (172), Europe (221), Asia-Pacific (188), and Latin America (58). MIC values for MEM-WCK and comparators were determined by reference broth microdilution methodology. Isolates were stratified by infection type and breakpoint interpretative criteria for comparators followed CLSI guidelines.

Results: MEM-WCK was very active against ASP isolates ($MIC_{50/90}$, 2/8 µg/mL; 66.2% and 83.9% inhibited at ≤2 and ≤4 µg/mL, respectively). The addition of WCK to MEM significantly increased the percentage of ASP isolates with MIC values ≤4 µg/mL (based on 2g TID MEM dose) from 39.0% (MEM alone) to 83.9% (MEM-WCK). Colistin (COL; $MIC_{50/90}$, ≤0.5/1 µg/mL; 94.8% susceptible [S]) was very active against this collection of ASP. Among other comparator agents, amikacin (AMK; $MIC_{50/90}$, >32/>32 µg/mL; 44.4%S) was the most active compound, followed by gentamicin ($MIC_{50/90}$, >8/>8 µg/mL; 39.7%S), imipenem ($MIC_{50/90}$, >8/>8 µg/mL; 39.5%S), MEM ($MIC_{50/90}$, 32/>32 µg/mL; 37.2%S), ampicillin-sulbactam (Amp-Sulb; $MIC_{50/90}$, 32/>32 µg/mL; 36.1%S), levofloxacin (LEV; $MIC_{50/90}$, >4/>4 µg/mL; 31.8%S), and ceftazidime (CAZ; $MIC_{50/90}$, >32/>32 µg/mL; 30.6%S). S rates varied among infection types for all agents (Table), and isolates from pneumonia were generally less susceptible compared to those from other infection types.

Conclusions: MEM-WCK (WCK 5999) was very active against ASP isolates and demonstrated enhanced activity over MEM alone. Resistance rates were very high for all comparators, except COL. These data support the continued development of this promising antibacterial combination.

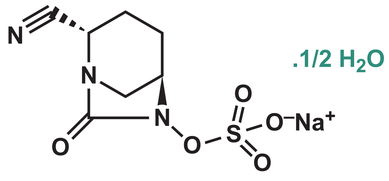
Infection type (no.)[a]	MEM-WCK (% at ≤4 µg/mL)	% susceptible (CLSI)				
		MEM	CAZ	Amp-Sulb	AMK	LEV
Pneumonia (348)	81.0	31.3	25.7	31.0	39.1	26.5
Skin/soft tissue (121)	88.4	37.2	29.2	36.7	41.7	32.5
Bloodstream (115)	83.5	42.6	33.0	38.3	47.8	36.5
Urinary tract (36)	88.9	52.8	47.2	55.6	66.7	41.7

[a] Does not include 19 isolates from other infections

Introduction

- WCK 5999 represents a new carbapenem/β-lactamase inhibitor combination in clinical development comprising meropenem (MEM) and the novel broader-spectrum β-lactamase inhibitor, WCK 4234 (Figure 1), with enhanced activity against class D carbapenemases
- We evaluated the *in vitro* antibacterial activity of WCK 5999 (meropenem-WCK 4234; MEM-WCK) against a collection of 639 contemporary isolates of *Acinetobacter* spp. collected worldwide

Figure 1 Compound structure of WCK 4234



Materials and Methods

Susceptibility testing

- Minimal inhibitory concentration (MIC) values were determined for the meropenem-WCK 4234 combination (WCK 4234 at fixed concentration of 8 µg/mL) and comparator agents using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method (M07-A10)
- Quality control (QC) reference strains were tested daily and the inoculum density monitored by colony counts. QC ranges and interpretive criteria for comparator compounds were as published in CLSI M100-S27 and EUCAST v7.0 (2017) documents
- The tested QC reference strains included *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *K. pneumoniae* ATCC BAA-1705, and *Pseudomonas aeruginosa* ATCC 27853

Organism collection

- *Acinetobacter* spp. (639) isolates were selected for testing from the 2015 SENTRY worldwide surveillance program.
- These isolates were collected during 2015 (except for China, which were collected in 2013) from 103 medical institutions worldwide, including Europe (EU; 31 medical centers), United States (US; 44), Latin America (LA; 8), the Asia-Pacific (APAC) region (excluding China, 10), and China (10)
- All isolates were obtained from documented infections and only 1 isolate per patient-infection episode was included in the surveillance collection
- Species identifications were confirmed by matrix-assisted laser desorption-time of flight mass spectrometry (MALDI-TOF MS), using the Bruker Daltonics MALDI Biotyper (Billerica, MA, USA)

Figure 2. MIC distributions for WCK 5999 (meropenem-WCK 4234; MEM-WCK) and meropenem when tested against *Acinetobacter* spp.

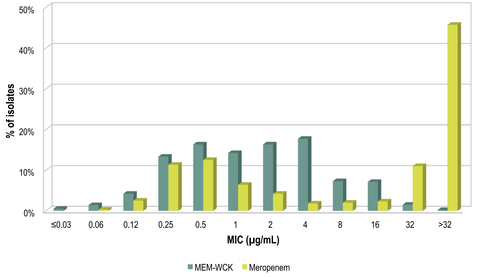
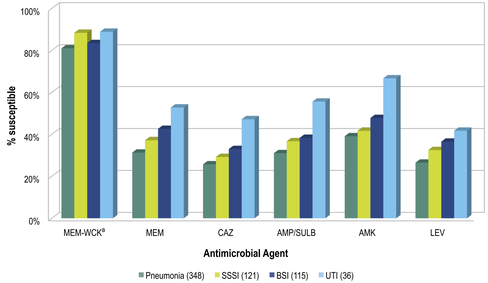


Figure 3. Antimicrobial activity of WCK 5999 (meropenem-WCK 4234; MEM-WCK) and comparator agents tested against clinical isolates of *Acinetobacter* spp. stratified by type of infection



[a] Inhibited at ≤4/8 µg/mL
Abbreviations: MEM-WCK, meropenem-WCK 4234 (WCK 5999); MEM, meropenem; CAZ, ceftazidime; AMP-SULB, ampicillin-sulbactam; AMK, amikacin; LEV, levofloxacin

Results

- Meropenem-WCK 4234 was very active against *Acinetobacter* spp. isolates with $MIC_{50/90}$ values of 2/8 µg/mL and 66.2% and 83.9% inhibited at ≤2 and ≤4 µg/mL, respectively (Table 1 and Figure 2)
- Adding WCK 4324 to meropenem significantly increased the percentage of *Acinetobacter* spp. isolates with MIC values ≤4 µg/mL (based on meropenem dose of 2g TID) from 39.0% (meropenem alone) to 83.9% (meropenem-WCK 4234; Table 1 and Figure 2)
- Colistin ($MIC_{50/90}$, ≤0.5/1 µg/mL; 94.8% susceptible) was the most active comparator agent tested against this collection of *Acinetobacter* spp., followed by amikacin ($MIC_{50/90}$, >32/>32 µg/mL; 44.4% susceptible), gentamicin ($MIC_{50/90}$, >8/>8 µg/mL; 39.7% susceptible), imipenem ($MIC_{50/90}$, >8/>8 µg/mL; 39.5% susceptible), meropenem ($MIC_{50/90}$, 32/>32 µg/mL; 37.2% susceptible), ampicillin-sulbactam ($MIC_{50/90}$, 32/>32 µg/mL; 36.1% susceptible), levofloxacin ($MIC_{50/90}$, >4/>4 µg/mL; 31.8% susceptible), and ceftazidime ($MIC_{50/90}$, >32/>32 µg/mL; 30.6% susceptible; Table 1)
- Susceptibility rates varied among infection types for all agents, and isolates from pneumonia were generally less susceptible compared to those from other infection types (Figure 3)

Table 1 Activity of meropenem-WCK4234 fixed 8 µg/mL and comparator antimicrobial agents when tested against 639 isolates of *Acinetobacter* spp.

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
Meropenem-WCK4234	2	8	—	—	—	—	—	—
Meropenem	32	>32	37.2	1.7	61.0	37.2	3.8	59.0
Imipenem	>8	>8	39.5	2.1	58.5	39.5	3.3	57.2
Piperacillin-tazobactam	>64	>64	28.5	6.2	65.3	—	—	—
Ampicillin-sulbactam	32	>32	36.1	12.3	51.6	—	—	—
Ceftazidime	>32	>32	30.6	3.9	65.4	—	—	—
Cefepime	64	>64	29.6	5.9	64.5	—	—	—
Aztreonam	>16	>16	—	—	—	—	—	—
Levofloxacin	>4	>4	31.8	6.2	62.1	30.8	0.9	68.2
Gentamicin	>8	>8	39.7	3.3	57.0	39.7	—	60.3
Amikacin	>32	>32	44.4	3.9	51.7	41.5	2.8	55.6
Colistin	≤0.5	1	94.8	—	5.2	94.8	—	5.2

[a] Criteria as published by CLSI [2017] and EUCAST [2017]
Organisms include: *Acinetobacter baumannii-calcoaceticus* species complex (593), *A. berezinae* (2), *A. guillouiae* (3), *A. haemolyticus* (7), *A. johnsonii* (6), *A. junii* (3), *A. lwoffii* (8), *A. pittii* (2), *A. radioresistens* (2), *A. soli* (1), *A. towneri* (1), *A. ursingii* (6), unspeciated *Acinetobacter* (5)

Conclusions

- Meropenem-WCK 4234 (WCK 5999) was very active against *Acinetobacter* spp. isolates and demonstrated enhanced activity over meropenem alone
- Resistance rates were very high for all comparators, except colistin
- These data support the continued development of meropenem-WCK 4234 (WCK 5999) to treat *Acinetobacter* spp. infections

Acknowledgements

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https://www.jmilabs.com/data/posters/ASMMicrobe17-WCK5999-acinetobacter.pdf