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Poster

In Vitro Activity of Tebipenem and Comparators against Enterobacterales Collected from Patients with Bloodstream Infections as Part of the Global STEWARD Surveillance Program

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ABSTRACT

Background: Bloodstream infections (BSI) are a significant cause of morbidity and mortality. *Enterobacterales* (ENT) are frequently implicated in BSI with an increase in organisms producing extended-spectrum β-lactamase (ESBL). This challenges a possible transition to current oral agents due to co-resistance. Carbapenems are active against ESBL-ENT and tebipenem (TBP) is a new oral carbapenem in clinical development. The aim of the study was to assess resistance (R) among BSI isolates and activity of TBP and comparators against ENT collected in a 2019 surveillance study.

Methods: 2612 ENT from BSI were centrally tested by reference broth microdilution. Isolates were from medical centers in the US, Europe (EU), Latin America (LA) and Asia Pacific (AP). MIC results were interpreted according to CLSI, including ESBL assignment. CRE were sequenced to identify carbapenemase genes.

Results: Among the ENT, non-susceptibility (NS) rates to ceftazidime, levofloxacin were 20.4 and 27.0%, respectively, and R to trimethoprim-sulfamethoxazole was 31.1%. NS rates for ertapenem (ETP) and MER were 4.9 and 2.7%, respectively. MIC_{90}s for TBP, ETP and MER were 0.12, 0.12 and 0.06 µg/mL, respectively. The MIC_{90} for TBP was 0.06 µg/mL for ENT from the US and 0.12 µg/mL for isolates from EU, LA and AP. *Escherichia coli* (EC) was the most prevalent (52% of ENT isolates) and the MIC_{90} for TBP ranged from 0.015 µg/mL for isolates in the US/EU to 0.03 µg/mL for isolates in LA/AP. ESBL-EC ranged from 15.7% in US to 34.3% in LA. TBP was active against ESBL-EC with an MIC_{90} of 0.03 µg/mL. *Klebsiella pneumoniae* (KP) accounted for 22.7% of BSI caused by ENT and TBP MIC_{90} ranged from 0.06 µg/mL for KP in US to >8 µg/mL in EU, LA and AP. MER-R KP ranged from 2.4% in US to 14.9% in LA. KPC-2, -3 and NDM were the most prevalent carbapenemases. TBP MIC_{90} values for MER-S ESBL KP in EU, LA and AP were ≤0.12 µg/mL.

Conclusions: TBP activity was similar to ETP and MER against ENT responsible for BSI. R to oral agents was compromised by ESBL co-resistance. TBP was among the most active agents against EC isolates and ESBL phenotypes. Among KP, TBP was more active against isolates from US

INTRODUCTION

Enterobacterales are a predominant cause of bloodstream infections (BSI) with *Escherichia coli* being the most prevalent pathogen. BSIs are a significant cause of morbidity and mortality and are among the most frequently observed hospital-acquired infections (HAIs). The increase in extended-spectrum-β-lactamase (ESBL)-producing Enterobacterales further complicates any transition to currently available oral step-down agents due to co-resistance to other classes including the fluoroquinolones and trimethoprim-sulfamethoxazole. Although the carbapenems have remained effective against ESBL and AmpC β-lactamase-producing Enterobacterales none are orally bioavailable. Tebipenem (TBP) is an oral carbapenem in clinical development that has a similar spectrum of activity to the intravenous carbapenems. The objective of the current study was to assess the prevalence of resistance phenotypes among BSI isolates and the activity of TBP against Enterobacterales collected in the global STEWARD surveillance program during 2019.

METHODS

A total of 2612 Enterobacterales non-duplicate clinically significant isolates from bloodstream infections were collected from medical centers in Europe (19 countries), Latin America (6 countries), Asia Pacific (8 countries), and the United States during 2019. All isolates were shipped to a central laboratory (JMI Laboratories, North Liberty, IA) for identification confirmation. Susceptibility testing was performed using the CLSI broth microdilution reference method and the results were interpreted using CLSI 2020 breakpoints, except in the case of tebipenem where tentative interpretive criteria were used (susceptible ≤0.12 µg/mL, intermediate = 0.25 µg/mL and resistant ≥0.5 µg/mL). ESBL phenotypes were assigned using MIC screening criteria for *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Proteus mirabilis*, as those isolates an MIC value ≥2 µg/mL for ceftriaxone, ceftazidime and/or aztreonam. Meropenem non-susceptible Enterobacterales were screened for the presence of carbapenemases by whole genome sequencing.

RESULTS

Table 1: Activity of tebipenem and comparators against global Enterobacterales (N = 2612) collected from patients with bloodstream infections in 2019

Agent	MIC (µg/mL)			CLSI[a]		
	Range	50%	90%	S	I	R
Tebipenem	≤0.004 - >8	0.015	0.12	94.5	1.7	3.8
Meropenem	≤0.015 - >32	0.03	0.06	97.2	0.3	2.4
Ertapenem	≤0.008 - >2	≤0.008	0.12	95.1	1	3.9
Ceftazidime	0.03 - >32	0.25	>32	79.6	1.8	18.6
Ceftriaxone	≤0.06 - >8	≤0.06	>8	75.9	0.7	23.5
Amoxicillin-clavulanate	0.5 - >32	8	>32	62.4	14.1	23.5
Piperacillin-tazobactam	0.12 - >128	2	32	88.2	3.9	7.9
Levofloxacin	≤0.015 - >32	0.06	16	73.1	3.3	23.7
Amikacin	0.5 - >32	2	8	97.6	0.7	1.7
Gentamicin	≤0.12 - >16	0.5	>16	86	0.7	13.3
TMP-SMX	≤0.12 - >16	≤0.12	>16	68.9	-	31.1

[a]Tebipenem: No CLSI/FDA breakpoints currently available. Results interpreted using tentative criteria: S ≤ 0.12 µg/mL, I = 0.25 µg/mL and R ≥ 0.5 µg/mL.

Figure 1: Species distribution of Enterobacterales from bloodstream infections (N = 2612)

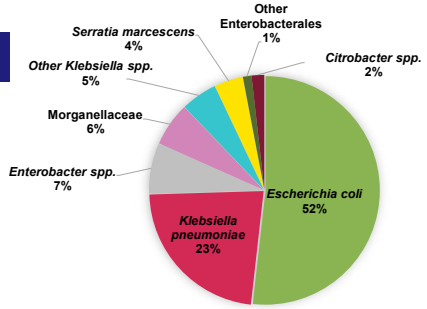


Figure 2: Prevalence of ESBL phenotypes among bloodstream isolates of *E. coli* and *K. pneumoniae* by region

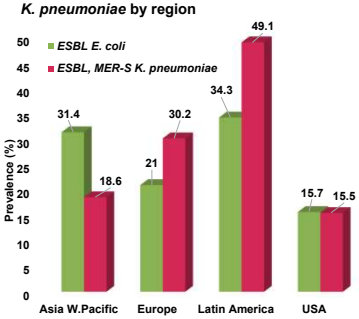


Table 2: Activity of tebipenem, ertapenem and meropenem against Enterobacterales from bloodstream infections by geographic region

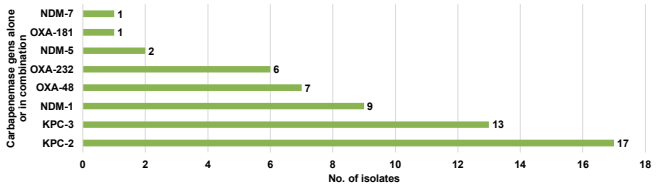
Antimicrobial Agent	Continent	N	MIC (µg/mL)			CLSI[a]		
			Range	MIC_{50}	MIC_{90}	S	I	R
Tebipenem	Asia-W. Pacific	327	≤0.004 - >8	0.015	0.12	94.2	1.5	4.3
	Europe	1,016	≤0.004 - >8	0.015	0.12	93.8	1.9	4.3
	Latin America	290	0.008 - >8	0.015	0.12	90.7	1.4	7.9
	United States	979	≤0.004 - >8	0.015	0.06	96.5	1.8	1.7
Ertapenem	Asia-W. Pacific	327	≤0.008 - >2	≤0.008	0.25	93.6	1.8	4.6
	Europe	1,015	≤0.008 - >2	≤0.008	0.12	94.8	0.8	4.4
	Latin America	290	≤0.008 - >2	0.015	0.5	90.7	1.7	7.6
	United States	979	≤0.008 - >2	≤0.008	0.06	97.2	0.7	2
Meropenem	Asia-W. Pacific	327	≤0.015 - >32	0.03	0.06	96.3	0.3	3.4
	Europe	1,016	≤0.015 - >32	0.03	0.06	96.9	0.5	2.6
	Latin America	290	≤0.015 - >32	0.03	0.12	93.8	0	6.2
	United States	979	≤0.015 - >32	0.03	0.06	98.9	0.3	0.8

[a]Tebipenem: No CLSI/FDA breakpoints currently available. Results interpreted using tentative criteria: S ≤ 0.12 µg/mL, I = 0.25 µg/mL and R ≥ 0.5 µg/mL.

Table 3: Activity of tebipenem against *E. coli* and *K. pneumoniae* from bloodstream infections

Organism	Phenotype	Continent	N	Tebipenem MIC (µg/mL)		
				Range	MIC_{50}	MIC_{90}
E. coli	All	Global	1353	≤0.004 - >8	0.015	0.015
		Asia-W. Pacific	172	≤0.004 - >8	0.015	0.03
		Europe	576	≤0.004 - 8	0.015	0.015
		Latin America	102	0.008 - 0.06	0.015	0.03
		United States	503	≤0.004 - 2	0.015	0.015
	ESBL	Global	289	≤0.004 - >8	0.015	0.03
		Asia-W. Pacific	54	0.008 - >8	0.015	0.06
		Europe	121	0.008 - 8	0.015	0.03
		Latin America	35	0.008 - 0.06	0.015	0.03
		United States	79	≤0.004 - 2	0.015	0.03
K. pneumoniae	All	Global	594	0.008 - >8	0.03	1
		Asia-W. Pacific	86	0.015 - >8	0.03	>8
		Europe	195	0.015 - >8	0.03	>8
		Latin America	114	0.008 - >8	0.03	>8
		United States	199	0.008- >8	0.015	0.06
	MER-S	Global	535	0.008 - 2	0.03	0.06
		Asia-W. Pacific	76	0.015 - 2	0.015	0.06
		Europe	169	0.015 - 1	0.03	0.12
		Latin America	97	0.008 - 2	0.03	0.03
		United States	193	0.008 - 1	0.015	0.03
	ESBL, MER-S	Global	162	0.015 - 2	0.03	0.25
		Asia-W. Pacific	16	0.015 - 2	0.03	0.25
		Europe	59	0.015 - 1	0.03	0.5
		Latin America	56	0.015 - 2	0.03	0.12
		United States	31	0.015 - 1	0.03	0.12
	MER-NS	Global	59	1 - >8	>8	>8
		Asia-W. Pacific	10	4 - >8	>8	>8
		Europe	26	1 - >8	>8	>8
		Latin America	17	2 - >8	>8	>8
		United States	6	1 - >8	4	NA

Figure 3: Carbapenemase genes identified among meropenem-NS *K. pneumoniae* from BSI



CONCLUSIONS

- ***E. coli* and *K. pneumoniae* were the most prevalent BSI pathogens accounting for 52% and 23%, respectively, of the isolates collected and tested (Figure 1)**
- **Among all Enterobacterales resistance rates ≥ 18-20% were observed for the cephalosporins, amoxicillin-clavulanate, levofloxacin and TMP-SMX (Table 1). Carbapenem (meropenem)-resistant rates ranged from 0.8% in the US to 6.2% for isolates from Latin America (Table 2)**
- **TBP exhibited similar activity to ertapenem and meropenem against all Enterobacterales from BSI with ≥94% of all isolates being susceptible regardless of geographic origin (Tables 1 and 2)**
- **Among *E. coli* and *K. pneumoniae* the prevalence of ESBL phenotypes ranged from 15% for both organisms in the US to 49% among *K. pneumoniae* isolates from Latin America (Figure 2).**
- **TBP was among most active against *E. coli* including ESBL phenotypes regardless of geographic origin.**
- **Among *K. pneumoniae* TBP was most active against isolates from the US (MIC_{90} = 0.06 µg/mL) where prevalence of CRE was lower than in Europe, Latin America and Asia Pacific (MIC_{90} >8 µg/mL). Among the meropenem-NS *K. pneumoniae*, KPC-2 and -3 were the most prevent carbapenemases (Figure 3).**

ACKNOWLEDGEMENT

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