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In vitro Activity of Tebipenem against a Recent Collection of Fastidious Organisms Recovered from Respiratory Tract Infections

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Introduction

- Tebipenem is under development as an oral treatment option for complicated urinary tract infections and acute pyelonephritis.
- Tebipenem has completed a Phase 3 clinical trial evaluating its safety and efficacy for the treatment of complicated urinary tract infection and acute pyelonephritis.
- This study further evaluated the *in vitro* activity of tebipenem against various fastidious organisms recovered from community-acquired respiratory tract infections (CARTIs).

Materials and Methods

- The susceptibility of 2,476 fastidious organisms were tested, including:
  - *Haemophilus influenzae* (692 isolates, including fluoroquinolone-resistant, β-lactamase-positive, and β-lactamase-negative ampicillin-resistant [BLNAR])
  - *Haemophilus parainfluenzae* (29 isolates, including β-lactamase-positive and BLNAR)
  - *Moraxella catarrhalis* (490 isolates)
  - *Streptococcus pneumoniae* (1,264 isolates, including penicillin-resistant)
- Bacterial species were identified by JMI Laboratories using standard microbiology methods and matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).
- The isolates were collected in 2017–2019 (95% from 2019) as part of the SENTRY surveillance program and selected to be representative of these fastidious organisms commonly recovered from community-acquired respiratory tract infections with 37.6% from the United States, 44.0% from Europe, 13.7% from the Asia-Pacific region, and 4.7% from Latin America.
- The isolates were collected primarily from CARTIs (90.8%) and pneumonia in hospitalized patients (PIHPs, 9.2%).
  - Available patient demographic information does not allow enough granularity to identify patients with healthcare-associated infections.
- Isolates were tested in a central laboratory (JMI Labs) for antimicrobial susceptibility using the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) and M45 (2015) guidelines.
- QC organisms: *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *H. influenzae* ATCC 49247, *H. influenzae* ATCC 49766, and *S. pneumoniae* ATCC 49619 were tested concurrently with clinical isolates.
- JMI Laboratories produced frozen-form 96-well panels.
  - Cation-adjusted Mueller-Hinton broth (CA-MHB) was used as the testing medium.
  - CA-MHB was supplemented with 2.5–5% lysed horse blood for testing streptococci.
  - *Haemophilus* Test Medium broth was used for testing *Haemophilus* spp.
- The nitrocefin disk test (Remel, Lenexa, Kansas) was performed to determine β-lactamase production in *Haemophilus* spp. and *Moraxella catarrhalis*.
- All categorical interpretations used CLSI M100 (2021), CLSI M45 (2015), and EUCAST v11.0 (2021) breakpoint criteria, where published.

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Results

- Activity against *Haemophilus influenzae* isolates
  - Tebipenem and ertapenem had similar activity, with $MIC_{50/90}$ values of 0.12/0.5 mg/L and 0.06/0.25 mg/L, respectively, when tested against the overall collection of *H. influenzae* (Tables 1 and 2).
  - Similar MIC results for tebipenem were obtained against β-lactamase positive isolates ($MIC_{50/90}$, 0.12/0.5 mg/L) or fluoroquinolone non-susceptible isolates ($MIC_{50/90}$, 0.12/0.12 mg/L, Table 1).
  - Against 14 *H. influenzae* BLNAR isolates, tebipenem and ertapenem MIC results ranged from 0.25–1 mg/L (MIC_{50}, 1 mg/L) and 0.12–1 mg/L (MIC_{50}, 0.5 mg/L), respectively (Table 1 and data not shown).
  - Most comparator agents tested showed susceptibility rates ≥90.0% against *Haemophilus influenzae* isolates, except for trimethoprim-sulfamethoxazole, which was 62.9% susceptible.
- Activity against *Haemophilus parainfluenzae* isolates
  - Tebipenem and ertapenem had similar activity, with $MIC_{50/90}$ values of 0.06/1 mg/L and 0.06/0.25 mg/L, respectively, when tested against the overall collection of *H. parainfluenzae* (Table 3).
  - Against 5 *H. parainfluenzae* BLNAR isolates, tebipenem and ertapenem MIC results ranged from 0.03–1 mg/L (MIC_{50}, 1 mg/L) and 0.06–0.25 mg/L (MIC_{50}, 0.25 mg/L), respectively (Table 1 and data not shown).
  - Lower susceptibility rates were observed for trimethoprim-sulfamethoxazole (65.5%), levofloxacin (75.9%), cefepime (89.7%), and amoxicillin-clavulanic acid (89.7%).
  - Higher susceptibility rates were observed for ceftriaxone (100.0%) and azithromycin (96.6%, Table 3).
- Activity against *Moraxella catarrhalis* isolates
  - Tebipenem had an $MIC_{50/90}$ value of 0.03/0.03 mg/L (Table 1).
  - Tebipenem displayed similar activity to ertapenem ($MIC_{50/90}$, 0.008/0.015 mg/L) against *M. catarrhalis* isolates, which were very susceptible (≥94.5%S) to all antimicrobial agents tested (Table 4).
- Activity against *Streptococcus pneumoniae* isolates
  - In general, tebipenem displayed good activity against *S. pneumoniae* ($MIC_{50/90}$ of ≤0.004/0.12, 100.0% inhibited at ≤1 mg/L).
  - Tebipenem displayed 8-fold greater activity than ertapenem (MIC_{90}, 1 mg/L).
  - These isolates had lower susceptibility rates to azithromycin (60.9%S) and trimethoprim-sulfamethoxazole (70.2%S). Levofloxacin had the highest susceptibility rates observed (98.7%S; Table 5).
  - Higher MIC values (MIC_{50}, 0.12-0.25 mg/L) were observed for tebipenem in isolates with penicillin-intermediate and resistant phenotypes compared to the penicillin-susceptible group (MIC_{50}, <0.004 mg/L).

Conclusions

- Tebipenem displayed good activity against *H. influenzae* (MIC_{100}, 2 mg/L).
  - Production of TEM-like β-lactamase did not affect the activity of tebipenem.
  - Isolates supposedly possessing alterations at the penicillin-binding site (BLNAR) showed higher MIC results for both tebipenem and ertapenem when compared to the susceptible population.
- Tebipenem displayed good activity against *H. parainfluenzae* (MIC_{100}, 1 mg/L).
- For both *Haemophilus* species, tebipenem MIC_{50} values ≤0.12 mg/L were observed and tebipenem inhibited all BLNAR isolates at ≤1 mg/L.
- *M. catarrhalis* organisms were very susceptible to tebipenem and ertapenem (MIC_{100}, 0.03 mg/L).
- *S. pneumoniae* (MIC_{100}, 1 mg/L) organisms were very susceptible to tebipenem; its activity was 8-fold greater than ertapenem.
- *S. pneumoniae* isolates with an intermediate or resistant phenotype to penicillin had higher MIC values for tebipenem and ertapenem.
- These results demonstrate that tebipenem has an *in vitro* activity similar to or greater than its comparators, which supports further clinical development of tebipenem for CABP.

Table 1. Antimicrobial activity of tebipenem tested against the main organisms and organism groups

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:										MIC_{50}	MIC_{90}
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2		
Haemophilus influenzae (692)	0 0.0	8 1.2	21 4.2	71 14.5	184 41.0	200 69.9	117 86.8	72 97.3	17 99.7	2 100.0	0.12	0.5
β-lactamase-positive (162)	0 0.0	1 0.6	3 2.3	10 8.1	48 36.0	52 66.3	39 89.0	15 97.7	3 99.4	1 100.0	0.12	0.5
BLNAR (14)						0 0.0	2 14.3	4 42.9	8 100.0		1	1
Fluoroquinolone non-susceptible (18)		0 0.0	1 5.6	0 5.6	7 44.4	9 94.4	0 0.0	1 100.0			0.12	0.12
Haemophilus parainfluenzae (29)	0 0.0	3 10.3	3 20.7	4 34.5	8 62.1	3 72.4	2 79.3	2 86.2	4 100.0		0.06	1
β-lactamase-positive (5)		0 0.0	1 20.0	0 20.0	1 40.0	0 40.0	1 60.0	2 100.0			0.25	
BLNAR (5)			0 0.0	1 20.0	0 20.0	0 20.0	0 20.0	0 20.0	4 100.0		1	
Moraxella catarrhalis (490)	0 0.0	11 2.2	232 49.6	247 100.0							0.03	0.03
Streptococcus pneumoniae (1,264)	837 66.2	74 72.1	28 74.3	50 78.2	133 88.8	80 95.1	59 99.8	2 99.9	1 100.0		≤0.004	0.12
Penicillin-susceptible non-meningitis (<4 mg/L) (1,150)	814 70.8	74 77.2	28 79.7	50 84.0	128 95.1	41 98.7	13 99.8	1 99.9	1 100.0		≤0.004	0.06
Penicillin-intermediate non-meningitis (=4 mg/L) (68)				0 0.0	5 7.4	33 55.9	30 100.0				0.12	0.25
Penicillin-resistant non-meningitis (>4 mg/L) (22)					0 0.0	6 27.3	15 95.5	1 100.0			0.25	0.25

BLNAR, β-lactamase-negative ampicillin-resistant

Table 2. Antimicrobial activity of tebipenem and comparator agents tested against 692 *Haemophilus influenzae*

Antimicrobial agent	mg/L			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Tebipenem	0.12	0.5	0.008 to 2						
Ertapenem	0.06	0.25	0.008 to 1	99.7			99.7		0.3
Ceftriaxone	≤0.06	≤0.06	≤0.06 to 0.5	100.0			99.1		0.9
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.015 to >4	62.9	4.3	32.8	62.9	1.2	36.0
Amoxicillin-clavulanic acid	0.5	2	≤0.25 to >8	96.7		3.3			
Azithromycin	0.5	2	≤0.12 to >8	97.5			97.5 [b]		
Cefepime	0.06	0.25	≤0.015 to 2	100.0			94.5		5.5
Levofloxacin	0.015	0.03	0.008 to >2	97.7			95.5		4.5

[a] Criteria as published by CLSI (2021), EUCAST (2021), and FDA (2021)
[b] According to EUCAST, the percentage of wild type is based on the ECV.

Table 3. Antimicrobial activity of tebipenem and comparator agents tested against 29 *Haemophilus parainfluenzae*

Antimicrobial agent	mg/L			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Tebipenem	0.06	1	0.008 to 1						
Ertapenem	0.06	0.25	0.008 to 0.25	100.0			100.0		0.0
Ceftriaxone	≤0.06	0.25	≤0.06 to 0.5	100.0			86.2		13.8
Trimethoprim-sulfamethoxazole	0.06	32	≤0.03 to 32	65.5	3.4	31.0	65.5	3.4	31.0
Amoxicillin-clavulanic acid	0.5	8	≤0.25 to 8	89.7		10.3			
Azithromycin	1	2	≤0.12 to >8	96.6			96.6 [b]		
Cefepime	0.12	>2	≤0.015 to >2	89.7			72.4		27.6
Levofloxacin	0.03	>4	0.015 to >4	75.9			62.1		37.9

[a] Criteria as published by CLSI (2021), EUCAST (2021), and FDA (2021)
[b] According to EUCAST, the percentage of wild type is based on the ECV.

Table 4. Antimicrobial activity of tebipenem and comparator agents tested against 490 *Moraxella catarrhalis*

Antimicrobial agent	mg/L			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Tebipenem	0.03	0.03	0.008 to 0.03						
Ertapenem	0.008	0.015	≤0.004 to 0.03				100.0		0.0
Ceftriaxone	0.25	0.5	≤0.06 to 2	100.0			99.2	0.8	0.0
Trimethoprim-sulfamethoxazole	0.12	0.25	0.03 to 4	94.5	5.3	0.2	94.5	3.5	2.0
Amoxicillin-clavulanic acid	≤0.25	≤0.25	≤0.25 to 0.5	100.0		0.0			
Azithromycin	0.03	0.03	0.008 to 0.12	100.0			100.0	0.0	0.0
Cefepime	0.5	1	0.06 to >2				100.0		0.0
Levofloxacin	0.03	0.06	≤0.015 to 1	100.0			98.8		1.2

[a] Criteria as published by CLSI (2021), EUCAST (2021), and the US FDA (2021).

Table 5. Antimicrobial activity of tebipenem and comparator agents tested against 1,264 *Streptococcus pneumoniae*

Antimicrobial agent	mg/L			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Tebipenem	≤0.004	0.12	≤0.004 to 1						
Ertapenem	0.015	1	≤0.002 to 8	93.4	6.2	0.4	83.5		16.5
Ceftriaxone	≤0.06	1	≤0.06 to >8	86.3 [b] 95.6 [c]	9.3 3.2	4.4 1.2	86.3 [b] 86.3 [c]	12.5	13.7 1.2
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.015 to >4	70.2	10.4	19.5	76.1	4.4	19.5
Amoxicillin-clavulanic acid	≤0.25	2	≤0.25 to >4	91.8 [c]	3.5	4.7	77.5 [d]	5.9	16.6
Azithromycin	0.12	>4	≤0.03 to >4	60.9	0.5	38.6	59.8	1.1	39.1
Levofloxacin	1	1	0.25 to >4	98.7	0.1	1.2	[e]	98.7	1.3

[a] Criteria as published by CLSI (2021), EUCAST (2021), and the US FDA (2021).
[b] Using meningitis breakpoints.
[c] Using non-meningitis breakpoints.
[d] Using oral breakpoints.
[e] An arbitrary susceptible breakpoint of ≤0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure.

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