Activity of Tebipenem Against a Set of Recent Clinical Isolates from Urinary Tract and Upper Respiratory Tract Infections

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INTRODUCTION

Tebipenem (TBP), an oral carbapenem with antibacterial activity against the most common Gram-negative pathogens which cause urinary tract infections (UTIs), is currently under development for the treatment of complicated UTIs. This study was undertaken to determine the *in vitro* activity of tebipenem and comparator agents against clinical isolates from respiratory and urinary tract sources.

METHODS

Minimum inhibitory concentration (MIC) values of TBP and comparators azithromycin (AZM), amoxicillin with clavulanic acid (2:1) (AMC), ceftriaxone (CRO), ertapenem (ETP), levofloxacin (LVX), meropenem (MEM), trimethoprim sulfamethoxazole (1:19) (SXT), and penicillin (PEN) were determined at a central laboratory against less common urinary and respiratory pathogens using the broth microdilution CLSI reference method (CLSI M07 A11 and M100 S30). Clinical isolate identification was confirmed by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker Daltronics, Bremen, Germany) library version MBT Compass 4.1.90. (version 4.1.100). Clinical isolates were collected in 2015-2019 from a wide geographic distribution:

Study isolates from UTIs (n/% of total):

- *Staphylococcus aureus* (30/9.1%)
- *S. epidermidis* (30/9.1%)
- *S. saprophyticus* (30/9.1%)
- *Enterococcus faecalis* (30/9.1%)
- *Streptococcus agalactiae* (30/9.1%)

Study isolates from respiratory tract infections (n/% of total):

- *Haemophilus influenzae* (30/9.1%)
- *H. parainfluenzae* (30/9.1%)
- *Moraxella catarrhalis* (30/9.1%)
- *S. pneumoniae* (30/9.1%)

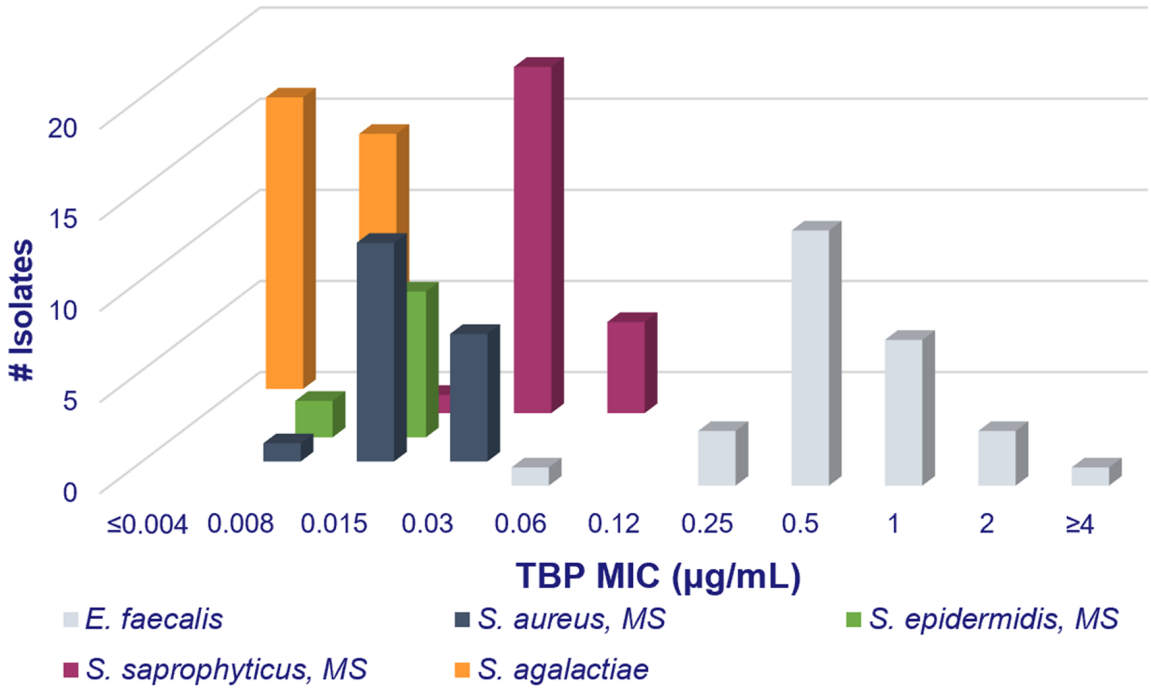
Quality control was monitored by testing CLSI QC isolates including *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 29213.

RESULTS

Table 1. Activity of Tebipenem and Comparator Antibiotics against Gram-positive Clinical Isolates from Urinary Tract Infections

***S. saprophyticus*, methicillin susceptible (25)**			
Tebipenem	0.25	0.25	≤0.06-0.25
Ertapenem	1	1	0.25-2
Meropenem	0.25	0.25	0.12-0.5
Amoxicillin-clavulanate	0.03	0.06	0.015-0.06
Ceftriaxone	16	16	1 - 16
Levofloxacin	0.5	0.5	0.25-1
Trimethoprim-sulfamethoxazole	≤0.25	4	≤0.25-8
***S. saprophyticus*, methicillin resistant (5)**			
Tebipenem	nc	nc	0.12-8
Ertapenem	nc	nc	0.25-> 4
Meropenem	nc	nc	0.12-2
Amoxicillin-clavulanate	nc	nc	0.015-0.25
Ceftriaxone	nc	nc	2-> 64
Levofloxacin	nc	nc	0.12-0.5
Trimethoprim-sulfamethoxazole	nc	nc	≤0.25-1
***S. agalactiae* (30)**			
Tebipenem	≤0.004	0.008	≤0.004 - 0.008
Ertapenem	0.03	0.06	0.008 - 0.06
Meropenem	0.06	0.06	≤0.004 - 0.06
Amoxicillin-clavulanate	≤0.06	≤0.06	≤0.06 - 4
Ceftriaxone	0.06	0.06	0.03 - 0.06
Levofloxacin	0.5	1	0.5 - > 8
Trimethoprim-sulfamethoxazole	≤0.25	≤0.25	≤0.25 - 8

Abbreviations: MIC, minimum inhibitory concentration; MIC_{50} and MIC_{90}, the concentration of antimicrobial agents required to inhibit 50% and 90% of test organisms, respectively; n, number of organisms; nc, not calculated.



- TBP activity against *E. faecalis* (MIC_{90}, 0.5 µg/mL) was equivalent to AMC (MIC_{90}, 0.5 µg/mL), at least 8-fold more active than ETP (MIC_{90}, >4 µg/mL) and MEM (MIC_{90}, 4 µg/mL).
- TBP activity against *Staphylococcus* spp. varied based on susceptibility to methicillin (oxacillin). For methicillin-susceptible *S. aureus (*MIC_{90}, 0.03 µg/mL) and PEN-susceptible *S. epidermidis*, (MIC range 0.008-0.015 µg/mL), TBP was the most active compound tested, and was at least 8-fold more active than ETP and MEM. For PEN-susceptible *S. saprophyticus*, the TBP MIC_{90} was 0.25 µg/mL, which was similar to AMC (MIC_{90}, 0.06 µg/mL) and MEM (MIC_{90}, 0.25 µg/mL). TBP was less active against methicillin-resistant organisms.
- TBP was the most active compound tested against *S. agalactiae* (MIC_{90}, 0.008 µg/mL), 8-fold lower than both ETP and MEM (MIC_{90} values of 0.06 µg/mL).
- Against *S. pneumoniae*, the TBP MIC_{90} was 0.12 µg/mL, at least 8-fold lower than any of the comparators.

RESULTS, CONTINUED

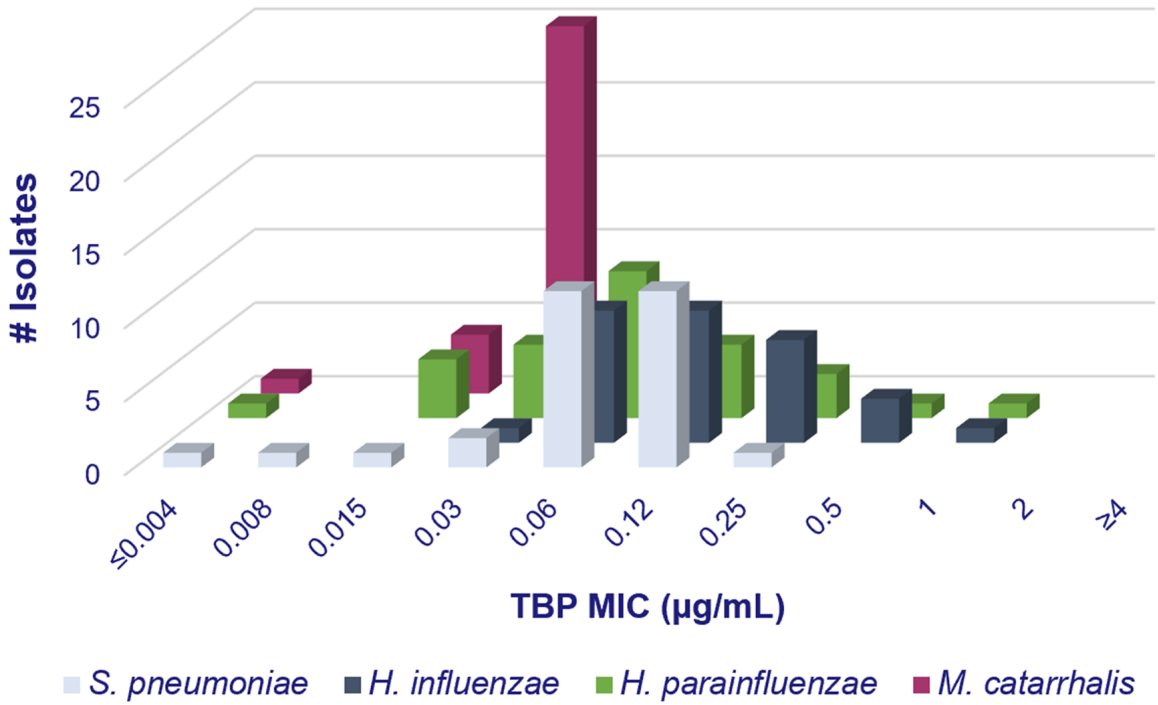
Table 2: Activity of Tebipenem and Comparator Antibiotics against Fastidious Clinical Isolates from Respiratory Tract Infections

Organism/organism group (n) Antimicrobial agent	MIC_{50}	MIC_{90} (µg/mL)	Range
***S. pneumoniae* (30)**			
Tebipenem	0.06	0.12	≤0.004 - 0.25
Ertapenem	0.5	1	0.03 - 4
Meropenem	0.5	1	0.015 - 2
Amoxicillin-clavulanate	1	4	≤0.06 - 4
Azithromycin	> 64	> 64	≤0.25 - > 64
Levofloxacin	0.5	1	0.12 - > 8
Penicillin	1	2	≤0.06 - 4
***H. influenzae* (30)**			
Tebipenem	0.12	0.5	0.03 - 1
Ertapenem	0.06	0.25	0.03 - 0.5
Meropenem	0.06	0.25	0.03 - 0.5
Amoxicillin-clavulanate	0.25	2	0.12 - 4
Azithromycin	1	2	0.5 - 8
Levofloxacin	0.015	0.015	0.008 - 0.03
Penicillin	1	> 16	≤0.06 - > 16
***H. parainfluenzae* (30)**			
Tebipenem	0.06	0.25	≤0.004 - 1
Ertapenem	0.03	0.06	≤0.004 - 0.12
Meropenem	0.06	0.12	≤0.004 - 0.25
Amoxicillin-clavulanate	0.25	0.5	≤0.06 - 1
Azithromycin	1	4	≤0.25 - 8
Levofloxacin	0.03	2	≤0.004 - 8
Penicillin	1	4	0.12 - > 16
***M. catarrhalis* (30)**			
Tebipenem	0.03	0.03	0.03 - 0.03
Ertapenem	0.008	0.015	0.008 - 0.015
Meropenem	≤0.004	0.008	≤0.004 - 0.008
Amoxicillin-clavulanate	0.12	0.12	0.12 - 0.12
Azithromycin	≤0.25	≤0.25	≤0.25 - ≤0.25
Levofloxacin	0.03	0.12	0.03 - 0.12
Penicillin	8	16	8 - 16

*H. influenzae 76.7% β-lactamase negative; 23.3% % β-lactamase positive

^H. parainfluenzae 90.0% β-lactamase negative; 10.0% % β-lactamase positive

Abbreviations: MIC, minimum inhibitory concentration; MIC50 and MIC90, the concentration of antimicrobial agents required to inhibit 50% and 90% of test organisms, respectively; n, number of organisms.



- TBP was active against *H. influenzae* with an MIC_{90} value of 0.5 µg/mL, while ETP and MEM MIC_{90} values were both 0.25 mg/mL. The TBP MIC_{90} against *H. parainfluenzae* was 0.25 µg/mL, in comparison to ETP and MEM where MIC_{90} values were 0.06 and 0.12 mg/mL, respectively.
- The TBP *M. catarrhalis* MIC_{90} value was 0.03 µg/mL, similar to ETP and MEM where MIC_{90} values were 0.015 and 0.008 mg/mL, respectively.

CONCLUSIONS

TBP was active against urinary pathogens, with MIC_{90} values ranging from 0.008-0.25 µg/mL for methicillin- (oxacillin) susceptible staphylococci, 0.008 µg/mL for *S. agalactiae*, and 0.5 µg/mL for *E. faecalis*. TBP also had activity against the respiratory pathogens *H. influenzae* (MIC_{90}, 0.5 µg/mL) *H. parainfluenzae* (MIC_{90}, 0.25 µg/mL), *M. catarrhalis* (MIC_{90}, 0.03 µg/mL), and *S. pneumoniae* (MIC_{90}, 0.12 µg/mL).

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ABSTRACT

Background: Tebipenem (TBP) is an orally bioavailable carbapenem with activity against bacterial pathogens known to cause urinary tract infections (UTIs) and upper respiratory tract infections (URTIs), including those resistant to commonly used oral therapeutics. In this study the in vitro activity of TBP was assessed vs. recent Gram positive and fastidious clinical isolates from UTI and URTI sources.

Methods: Minimum inhibitory concentration (MIC) values were determined using CLSI broth microdilution methodology. 330 isolates collected from global sources between 2015-2019 were tested. Isolates sourced from UTIs include (n): *Staphylococcus saprophyticus* (28 methicillin resistant; 2 methicillin susceptible), *S. epidermidis* (20 methicillin susceptible [MS]; 10 methicillin resistant [MR]), *Streptococcus agalactiae* (30), *S. aureus* (10 MR [MRSA]; 20 MS [MSSA]), and *Enterococcus faecalis* (30). Study isolates sourced from URIs include (n): *Haemophilus influenzae* (30) (76.7% β-lactamase neg.; 23.3% % β-lactamase pos.), *H. parainfluenzae* (30) (90.0% β-lactamase neg.; 10.0% % β-lactamase pos.), *Moraxella catarrhalis* (30), and *S. pneumoniae* (30; 96.7% were macrolide resistant). Comparator agents were azithromycin, amoxicillin-clavulanate, ceftriaxone, ertapenem (ETP), levofloxacin, meropenem (MEM), sulfamethoxazole-trimethoprim, and penicillin (PEN).

Results: TBP MIC90 vs. PEN-susceptible *S. saprophyticus* was 0.25 µg/mL, lower than ETP (MIC_{90}, 1 µg/mL) and similar to MEM (MIC_{90} 0.25 µg/mL). TBP was the most active agent tested vs. PEN-susceptible *S. epidermidis* (MIC_{90} 0.015 µg/mL), *S. agalactiae* (MIC_{90} 0.008 µg/mL) and *S. pneumoniae* (MIC_{90} 0.12 µg/mL) and was at least 8-fold more active than ETP and MEM as measured by MIC_{90}. TBP was active vs. MSSA with an MIC_{90} of 0.03 µg/mL, more active than ETP and MEM (MIC_{90}s 0.25 mg/mL). TBP was less active vs. MRSA (MIC_{90} 4 mg/mL), as were ETP and MEM (MIC_{90}s >4 mg/mL). TBP MIC_{90} was 0.5 µg/mL vs. *H. influenzae*, similar to ETP and MEM (MIC_{90}s 0.25 mg/mL). TBP MIC_{90} was 0.25 µg/mL for *H. parainfluenzae* while ETP MIC_{90} was 0.06 mg/mL and MEM MIC_{90} was 0.12 mg/mL. All carbapenems tested were highly active vs. *M. catarrhalis* with MIC_{90}s of 0.03 µg/mL (TBP), 0.015 mg/mL (ETP) and 0.008 mg/mL (MEM). TBP was less active vs. *E. faecalis* (MIC_{90}, 0.5 µg/mL) but was ≥ 8-fold more active than ETP (MIC_{90}, >4 µg/mL) and MEM (MIC_{90}, 4 µg/mL).

Conclusions: TBP provides good coverage against less common penicillin susceptible Gram positive UTI and common URTI bacterial pathogens.