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Antimicrobial Activity of Ceftazidime and Piperacillin-Tazobactam Tested in Combination with a Potentiator Molecule (SPR741) against *Enterobacteriaceae* Causing Urinary Tract Infections

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Introduction

- Complicated urinary tract infections (cUTIs) are commonly caused by gram-negative pathogens
  - The prevalence of cUTIs in the United States has been estimated at approximately 24 per 1,000 hospital discharges, with similar prevalence in Europe
- Antibiotic resistance is associated with significant adverse impact on clinical outcomes and increased consumption of healthcare resources, leading to higher costs
- Currently, UTIs caused by bacteria producing potent β-lactamases, especially due to CTX-M enzymes, are common in healthcare and community settings
  - In addition to extended-spectrum β-lactamases, production of carbapenemases, such as OXA-48 variants and NDM, has continued to spread and has become endemic in certain regions
- The emergence and spread of resistant pathogens challenge the clinical management of therapy, including the initial empirical therapy
- SPR741 is a novel polymyxin-B derivative with minimal intrinsic antibacterial activity and reduced nephrotoxicity
- This study assessed *in vitro* activity of ceftazidime or piperacillin-tazobactam in combination with SPR741 against pathogens causing complicated and uncomplicated UTIs

Materials and Methods

Organism collection

- A total of 424 bacterial clinical isolates selected from the SENTRY Antimicrobial Surveillance Program organism collection were included in this study
  - All isolates were collected from geographically diverse medical centres in the United States (US; 233; 55%) or Europe (191; 45%) during the 2016 surveillance year and were responsible for documented UTIs
- Species included *Escherichia coli* (160 isolates), *Klebsiella pneumoniae* (160 isolates), and *Enterobacter cloacae* species complex (104 isolates)

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) document
  - β-lactam agents were tested alone and in combination with SPR741 at a fixed concentration of 8 mg/L
- Quality control (QC) strains were tested before and concomitantly with clinical isolates, and bacterial inoculum density was monitored by counting the number of colony-forming units present in the inoculum material
  - QC strain collection followed the CLSI M100 (2018) guidelines and included *E. coli* ATCC 25922 and 35218; *Pseudomonas aeruginosa* ATCC 27853; and *Staphylococcus aureus* ATCC 29213
- Acceptable MIC ranges obtained for tested agents against ATCC QC strains were those published in the CLSI M100 (2018)

Table 1 MIC distribution of antimicrobial agents when tested against *Enterobacteriaceae* clinical isolates included in this study

Organism (no. of isolates)	Number of isolates and cumulative % 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	4	8	16	32	64	128	256	512	>[a]	
All isolates (424)																				
Ceftazidime					20 4.7	108 30.2	136 62.3	45 72.9	25 78.8	7 80.4	8 82.3	8 84.2	17 88.2	13 91.3					37 100.0	0.25	32
Ceftazidime-SPR741	12 2.8	6 4.2	8 6.1	61 20.5	150 55.9	118 83.7	18 88.0	10 90.3	12 93.2	8 95.0	3 95.8	6 97.2							12 100.0	0.06	0.5
Piperacillin-tazobactam							2 0.5	6 1.9	50 13.7	191 58.7	61 73.1	25 79.0	16 82.8	9 84.9	15 88.4	13 91.5	13 94.6	11 97.2	12 100.0	2	128
Piperacillin-tazobactam-SPR741				56 13.2	60 27.4	96 49.8	87 70.3	71 87.0	28 93.6	9 95.8	7 97.4	2 97.9	2 98.3	2 98.8	1 99.1				4 100.0	0.25	1
Escherichia coli (160)																				
Ceftazidime					9 5.6	47 35.0	69 78.1	10 84.4	4 86.9	2 88.1	6 91.9	1 92.5	7 96.9	3 98.8					2 100.0	0.25	4
Ceftazidime-SPR741	4 2.5	4 5.0	7 9.4	56 44.4	76 91.9	5 95.0	2 96.2	2 97.5	1 98.1	2 99.4	1 100.0									0.06	0.06
Piperacillin-tazobactam							2 1.2	4 3.8	30 22.5	86 76.2	17 86.9	2 88.1	2 89.4	2 90.6	2 91.9	3 93.8	4 96.2	5 99.4	1 100.0	2	32
Piperacillin-tazobactam-SPR741				32 20.0	41 45.6	53 78.8	21 91.9	11 98.8	1 99.4	1 100.0										0.12	0.25
Klebsiella pneumoniae (160)																				
Ceftazidime					10 6.2	57 41.9	38 65.6	18 76.9	10 83.1	5 86.2	1 86.9	5 90.0	5 93.1	4 95.6					7 100.0	0.25	8
Ceftazidime-SPR741				1 0.6	35 22.5	101 85.6	8 90.6	2 91.9	3 93.8	4 96.2	1 96.9	0 96.9							5 100.0	0.12	0.25
Piperacillin-tazobactam								1 0.6	10 6.9	67 48.8	33 69.4	15 78.8	9 84.4	4 86.9	5 90.0	1 90.6	2 91.9	4 94.4	9 100.0	4	64
Piperacillin-tazobactam-SPR741				3 1.9	5 5.0	16 15.0	61 53.1	49 83.8	13 91.9	4 94.4	4 96.9	1 97.5	0 97.5	1 98.1	0 98.1				3 100.0	0.25	1
Enterobacter cloacae (104)																				
Ceftazidime					1 1.0	4 4.8	29 32.7	17 49.0	11 59.6	0 59.6	1 60.6	2 62.5	5 67.3	6 73.1					28 100.0	1	>32
Ceftazidime-SPR741	8 7.7	2 9.6	1 10.6	4 14.4	39 51.9	12 63.5	8 71.2	6 76.9	8 84.6	2 86.5	1 87.5	6 93.3							7 100.0	0.06	8
Piperacillin-tazobactam								1 1.0	10 10.6	38 47.1	11 57.7	8 65.4	5 70.2	3 73.1	8 80.8	9 89.4	7 96.2	2 98.1	2 100.0	4	256
Piperacillin-tazobactam-SPR741				21 20.2	14 33.7	26 58.7	5 63.5	11 74.0	14 87.5	4 91.3	3 94.2	1 95.2	2 97.1	1 98.1	1 99.0				1 100.0	0.12	2

[a]">" represents results >32 mg/L for ceftazidime, >8/4 mg/L for ceftazidime-SPR741, >512/4 mg/L for piperacillin-tazobactam, and >4/4/4 mg/L for piperacillin-tazobactam-SPR741.

- MIC results obtained against clinical isolates were interpreted using the CLSI M100 (2018) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2018) documents, as available
- MIC interpretations for ceftazidime-SPR741 and piperacillin-tazobactam-SPR741 used the breakpoints available for the respective co-drugs, for comparison purposes

Results

- Adding SPR741 lowered the ceftazidime (MIC$_{50/90}$, 0.06/0.06 mg/L) and piperacillin-tazobactam (MIC$_{50/90}$, 0.12/0.25 mg/L) MIC$_{50}$ and MIC$_{90}$ results 4- to 64-fold and 16- to 128-fold, respectively, when compared with the associated co-drug tested alone against *E. coli*
- Meropenem (MIC$_{50/90}$, ≤0.015/0.03 mg/L) and ceftazidime-SPR741 (MIC$_{50/90}$, 0.06/0.06 mg/L) showed the lowest MIC$_{50}$ values against *E. coli*, which were 2- to 8-fold lower than ceftriaxone (MIC$_{50/90}$, ≤0.06/0.12 mg/L) and piperacillin-tazobactam-SPR741 (MIC$_{50/90}$, 0.12/0.25 mg/L)

Table 2 Activity of investigational combinations and comparator antimicrobial agents when tested against 160 *Escherichia coli* clinical isolates

Antimicrobial agent	MIC$_{50}$	MIC$_{90}$	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
Ceftazidime	0.25	4	91.9	0.6	7.5	86.9	5.0	8.1
Ceftazidime-SPR741	0.06	0.06	100.0	0.0	0.0	100.0	0.0	0.0
Piperacillin-tazobactam	2	32	89.4	2.5	8.1	88.1	1.2	10.6
Piperacillin-tazobactam-SPR741	0.12	0.25	100.0	0.0	0.0	100.0	0.0	0.0
Ceftriaxone	≤0.06	0.12	95.0	0.0	5.0	95.0	0.0	5.0
Cefepime	≤0.12	≤0.12	95.0	0.6 [b]	4.4	94.4	1.2	4.4
Meropenem	≤0.015	0.03	100.0	0.0	0.0	100.0	0.0	0.0
Levofloxacin	≤0.03	>4	81.2	1.9	16.9	81.2	0.0	18.8
Tetracycline	2	>16	73.1	0.0	26.9			
Trimethoprim-sulfamethoxazole	≤0.5	>4	71.9		28.1	71.9	1.2	26.9
Nitrofurantoin	16	32	98.1	0.6	1.2	98.8 [c]		1.2 [c]

[a] Criteria as published by CLSI (2018) and EUCAST (2018). MIC interpretations for ceftazidime-SPR741 and piperacillin-tazobactam-SPR741 used the breakpoints available for the respective co-drugs, for comparison purposes.
[b] Intermediate interpreted as susceptible-dose dependent.
[c] Using uncomplicated UTI only breakpoints.

- The ceftazidime and piperacillin-tazobactam MIC$_{90}$ values decreased 16- to 64-fold when adding SPR741 (MIC$_{50/90}$, 0.12/0.25 mg/L and MIC$_{50/90}$, 0.25/1 mg/L, respectively) against *K. pneumoniae*
- Ceftazidime-SPR741 (MIC$_{50/90}$, 0.12/0.25 mg/L), ceftriaxone (MIC$_{50/90}$, ≤0.06/0.25 mg/L), and cefepime (MIC$_{50/90}$, ≤0.12/0.5 mg/L) showed similar MIC$_{90}$ results against *K. pneumoniae*, while piperacillin-tazobactam-SPR741 (MIC$_{50/90}$, 0.25/1 mg/L) and meropenem (MIC$_{50/90}$, 0.03/0.03 mg/L) showed the highest susceptibility rates (97.5%–98.8%) against this species
- The piperacillin-tazobactam (MIC$_{50/90}$, 4/256 mg/L) MIC values were 32- to 128-fold higher against *E. cloacae* than piperacillin-tazobactam-SPR741 (MIC$_{50/90}$, 0.12/2 mg/L), which was similar in activity (95.2% susceptible) to meropenem (99.0% susceptible)
- Levofloxacin had moderate activities (81.2%–85.6% susceptible) against these 3 species, while nitrofurantoin (MIC$_{50/90}$, 16/32 mg/L; 98.8% susceptible) was active against *E. coli*

Table 3 Activity of investigational combinations and comparator antimicrobial agents when tested against 160 *Klebsiella pneumoniae* clinical isolates

Antimicrobial agent	MIC$_{50}$	MIC$_{90}$	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
Ceftazidime	0.25	8	86.9	3.1	10.0	83.1	3.8	13.1
Ceftazidime-SPR741	0.12	0.25	96.9	0.0	3.1	93.8	3.1	3.1
Piperacillin-tazobactam	4	64	84.4	5.6	10.0	78.8	5.6	15.6
Piperacillin-tazobactam-SPR741	0.25	1	97.5	0.6	1.9	97.5	0.0	2.5
Ceftriaxone	≤0.06	0.25	91.9	0.0	8.1	91.9	0.0	8.1
Cefepime	≤0.12	0.5	91.9	1.2 [b]	6.9	91.2	1.2	7.5
Meropenem	0.03	0.03	98.1	0.6	1.2	98.8	0.6	0.6
Levofloxacin	0.06	1	91.2	1.2	7.5	85.6	5.0	9.4
Tetracycline	1	>16	81.2	1.2	17.5			
Trimethoprim-sulfamethoxazole	≤0.5	>4	86.9		13.1	86.9	0.6	12.5
Nitrofurantoin	128	>128	13.1	20.0	66.9			

[a] Criteria as published by CLSI (2018) and EUCAST (2018). MIC interpretations for ceftazidime-SPR741 and piperacillin-tazobactam-SPR741 used the breakpoints available for the respective co-drugs, for comparison purposes.
[b] Intermediate interpreted as susceptible-dose dependent.

Table 4 Activity of investigational combinations and comparator antimicrobial agents when tested against 104 *Enterobacter cloacae* clinical isolates

Antimicrobial agent	MIC$_{50}$	MIC$_{90}$	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
Ceftazidime	1	>32	60.6	1.9	37.5	59.6	1.0	39.4
Ceftazidime-SPR741	0.06	8	87.5	5.8	6.7	84.6	2.9	12.5
Piperacillin-tazobactam	4	256	70.2	10.6	19.2	65.4	4.8	29.8
Piperacillin-tazobactam-SPR741	0.12	2	97.1	1.9	1.0	95.2	1.9	2.9
Ceftriaxone	0.5	>8	61.5	1.0	37.5	61.5	1.0	37.5
Cefepime	≤0.12	8	83.7	7.7 [b]	8.7	76.9	12.5	10.6
Meropenem	0.03	0.12	99.0	0.0	1.0	99.0	1.0	0.0
Levofloxacin	≤0.03	4	89.4	2.9	7.7	84.6	3.8	11.5
Tetracycline	2	>16	83.7	2.9	13.5			
Trimethoprim-sulfamethoxazole	≤0.5	>4	79.6		20.4	79.6	1.0	19.4
Nitrofurantoin	64	128	21.2	38.5	40.4			

[a] Criteria as published by CLSI (2018) and EUCAST (2018). MIC interpretations for ceftazidime-SPR741 and piperacillin-tazobactam-SPR741 used the breakpoints available for the respective co-drugs, for comparison purposes.
[b] Intermediate interpreted as susceptible-dose dependent.

Conclusions

- Overall, adding SPR741 at a fixed concentration of 8 mg/L potentiated the activity of ceftazidime and piperacillin-tazobactam when tested against main gram-negative organisms causing UTIs
- The *in vitro* activity of ceftazidime increased from 83.1%–91.9% susceptible when tested alone to 93.8%–100.0% susceptible when combined with SPR741 against *E. coli* and *K. pneumoniae*, respectively
- When tested against all species included here, piperacillin-tazobactam activity increased from 65.4%–89.4% susceptible when tested alone to 95.2%–100.0% susceptible when combined with SPR741
- These initial results provide important *in vitro* potency information and warrant further clinical and microbiologic development of these combinations
- The ability of SPR741 to extend the potency of these standard-of-care agents against gram-negative UTI pathogens suggests that the combinations have potential as empiric therapy and, consequently, to prevent delays in initiating appropriate therapy upon susceptibility results

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