ECCMID 2018
Poster #P1671

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)
- 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

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	95 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, >8/8 mg/L for ceftazidime-SPR741, >512/4 mg/L for piperacillin-tazobactam, and >64/4/8 mg/L for piperacillin-tazobactam-SPR741.

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$_{90}$ 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

Acknowledgements

This study was supported by Spero Therapeutics. JMI Laboratories received compensation fees for services in relation to preparing this presentation.

This presentation was supported by the Cooperative Agreement Number IDSEP160030 from ASPR/BARDA and by an award from Wellcome Trust, as administrated by CARB-X. The contents are solely the responsibility of the authors and do not necessarily represent the official views of CARB-X, the HHS Office of the Assistant Secretary for Preparedness and Response, the National Institutes of Health or Wellcome Trust.

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