

Activity of Ceftazidime / NXL104 and Select Comparators against Geographically Diverse Clinical Isolates of *Pseudomonas aeruginosa*

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ABSTRACT

Background: NXL104, a new β -lactamase inhibitor with activity against class A and C enzymes including KPC carbapenemases, is currently being tested in human Phase II trials in combination with ceftazidime (CAZ). Utilization of β -lactamase inhibitors to enhance the activity of agents against *P. aeruginosa* is of interest due to increasing β -lactam resistance. In this study the activity of the CAZ/NXL104 combination was tested against a geographically diverse collection of *P. aeruginosa* clinical isolates.

Methods: A random selection of 300 *P. aeruginosa* clinical isolates collected across the U.S., Europe, and Asia from 2005 to 2008 was evaluated. Minimal inhibitory concentrations (MIC) for CAZ, CAZ/NXL104, and comparator β -lactams were determined by CLSI broth microdilution methods. NXL104 was held at a constant 4 μ g/mL.

Results: Overall, non-susceptibility rates were: 21% for CAZ, 20% for cefepime, 22% for imipenem and 15% for meropenem. Addition of NXL104 resulted in phenotypic reversion for the majority of isolates, with only 6% remaining non-susceptible to CAZ when combined with NXL104. MIC₅₀s and MIC₉₀s for CAZ alone were 2 μ g/mL and >32 μ g/mL, respectively. Combining CAZ with NXL104 at a fixed concentration of 4 μ g/mL reduced the MIC₉₀ by at least 4-fold against US, European, and Asian *P. aeruginosa* isolates. Geographically, no differences in MIC₅₀s and MIC₉₀s were apparent.

Conclusion: Combining the β -lactamase inhibitor NXL104 with CAZ enhances the activity profile seen with CAZ alone against these isolates, illustrating the potential of the combination against *P. aeruginosa*.

BACKGROUND

NXL104 is a new non- β -lactam inhibitor of β -lactamases that displays broad spectrum inhibition of both class A and class C enzymes; both are efficiently inactivated at low IC₅₀ values, with low turn-over numbers and long covalent intermediate half-lives (1). NXL104 has virtually no intrinsic antibacterial activity, but protects β -lactams from hydrolysis in a variety of class A and class C producing strains, including ESBL producers (2, 3). As infections caused by *P. aeruginosa* are particularly challenging from a therapeutic standpoint due to the high degree of resistance and multi-drug resistance associated with this organism, it is of interest to determine the activity profile of NXL104 tested in combination with CAZ against *P. aeruginosa* as part of the ongoing clinical development of this compound.

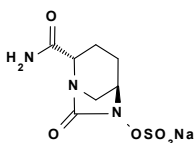
The study objective was to evaluate the *in vitro* activity of CAZ/NXL104 against recent *P. aeruginosa* clinical isolates collected across the United States, Europe, and Asia.

REFERENCES

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CHEMICAL STRUCTURE

FIGURE 1
Chemical structure of NXL104



METHODS

Compounds

The following antimicrobials were used: ceftazidime pentahydrate, cefepime, ciprofloxacin, colistin, imipenem, meropenem, piperacillin, ticarcillin and tobramycin.

The β -lactamase inhibitors tazobactam and NXL104 were used in combination at 4 μ g/mL fixed concentration.

Bacterial strains

A total of 300 *P. aeruginosa* clinical isolates were randomly selected from surveillance studies conducted during the period 2005-2008:

- 131 isolates (44%) from the United States
 - 137 isolates (46%) from Europe
 - 32 isolates (11%) from Asia (China, Hong kong, South Korea, Thailand, Indonesia, Taiwan, Philippines, Singapore, and Japan)
- ATCC control strains included *E. coli* ATCC25922, *E. coli* ATCC35218, and *P. aeruginosa* ATCC 27853.

Susceptibility testing

MIC determination was performed using CLSI methods for antimicrobial susceptibility testing with cation-adjusted Mueller-Hinton (MH) broth (4). MIC was defined as the lowest concentration which inhibited all visual growth. The *in vitro* interpretive break point criteria were applied for determination of susceptibility/resistance for marketed agents (5). All MIC test results were within CLSI recommended QC ranges for each comparator agent using the appropriate ATCC control strains (5).

RESULTS

TABLE 1
Antimicrobial susceptibility of Ceftazidime + NXL104 and comparators against *P. aeruginosa* by geographic region

Antimicrobial agent	Minimum Inhibitory Concentration (MIC μ g/mL) for <i>P. aeruginosa</i> isolates from																	
	US						EUROPE						ASIA					
	Range	MIC ₅₀	MIC ₉₀	%S	%I	%R	Range	MIC ₅₀	MIC ₉₀	%S	%I	%R	Range	MIC ₅₀	MIC ₉₀	%S	%I	%R
Ceftazidime	0.5 - >32	2	32	87	2	11	0.5 - >32	2	32	79	3	18	1 - >32	4	>32	50	3	47
Ceftazidime + NXL104 (4 μ g/mL)	\leq 0.25 - >32	1	4				\leq 0.25 - >32	2	8				1 - >32	2	8			
Cefepime	0.5 - >32	2	16	89	7	4	0.5 - >32	4	16	79	14	7	0.5 - >32	8	>32	50	19	31
Imipenem	\leq 0.25 - >32	1	16	80	7	13	\leq 0.25 - >32	1	16	80	5	15	0.5 - >32	1	16	63	6	31
Meropenem	\leq 0.12 - >32	0.25	4	90	5	5	\leq 0.12 - >32	0.5	16	85	2	13	\leq 0.12 - >32	1	32	62	13	25
Piperacillin	1 - >128	4	>128	87	-	13	\leq 0.5 - >128	8	>128	79	-	21	2 - >128	128	>128	47	-	57
Piperacillin + Tazobactam	\leq 0.5 - >128	4	128	89	-	11	\leq 0.5 - >128	4	>128	82	-	18	1 - >128	64	>128	53	-	47
Ticarcillin	\leq 1 - >128	16	128	86	-	14	\leq 1 - >128	32	>128	70	-	30	8 - >128	128	>128	41	-	59
Ciprofloxacin	\leq 0.12 - >4	\leq 0.12	>4	81	3	16	\leq 0.12 - >4	0.25	>4	71	3	26	\leq 0.12 - >4	0.5	>4	56	6	38
Colistin	\leq 0.12 - >4	1	2	92	4	4	0.25 - >4	1	2	93	2	5	0.5 - 4	1	2	97	3	0
Tobramycin	\leq 0.12 - >16	0.5	2	96	0	4	0.25 - >16	0.5	>16	82	1	17	0.5 - >16	1	>16	56	0	44

FIGURE 2
Scatterplot MICs of Ceftazidime/NXL104 vs Ceftazidime against *P. aeruginosa* for all the regions (Numbers on plot represent # isolates)

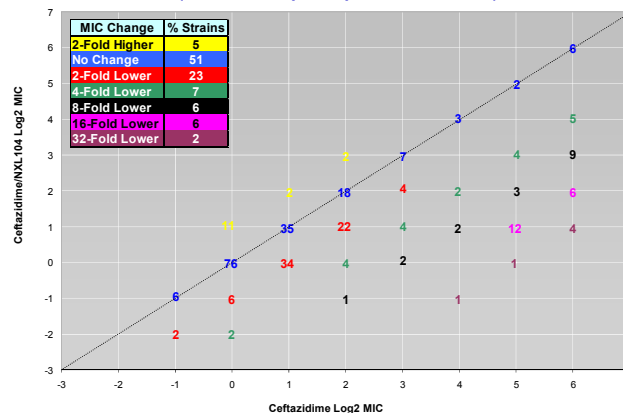
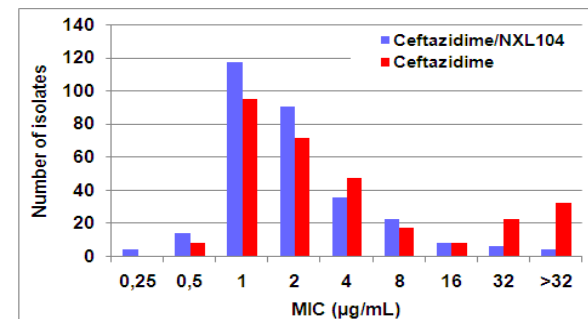


FIGURE 3
MIC distribution of *P. aeruginosa* clinical isolates (n = 300)



CONCLUSIONS

The *in vitro* profile of ceftazidime / NXL104 illustrates the potential of this β -lactam / β -lactamase inhibitor combination against *P. aeruginosa* isolates:

- Ceftazidime/NXL104 was more potent than all comparators except colistin based on MIC₉₀s (Table 1)
- When combined with NXL104, ceftazidime MIC₉₀s were reduced by at least 4-fold against US, European and Asian isolates (Table 1; Figure 3)
- 44% of global isolates showed improved ceftazidime MICs in the presence of NXL104 (Figure 2)