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Antimicrobial Spectrum and Potency of Ceftaroline Combined With NXL104 When Tested Against Enterobacteriaceae Collected From USA Hospitals

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Amended Abstract

Background: Ceftaroline (CPT), the active form of ceftaroline fosamil, is a broad-spectrum cephalosporin with activity against Gram-negative and -positive (including MRSA and multidrug-resistant [R] *S. pneumoniae*) organisms. NXL104 is a novel β-lactamase (BL) inhibitor that inhibits Ambler class A, C, and D enzymes (eg, ESBL, KPC, and AmpC). We evaluated the activity of CPT combined with NXL104 (CXL; fixed 4 μg/mL) against clinical Enterobacteriaceae (ENT) strains.

Methods: CXL and 13 comparators were tested for susceptibility (S) by CLSI broth microdilution methods against 3258 ENT, including ESBL-phenotype *E. coli* (124) and *Klebsiella spp.* (KSP; 130), AmpC derepressed *Enterobacter* spp. (ESP; 87) and carbapenem (CB)-non-S KSP (most KPC-producing; 40), among other R phenotypes. The strains were consecutively collected in 2009 from 51 medical centers located in the 9 USA Census Regions. CB-non-S strains were screened for BL genes by PCR.

Results: 99.7% of strains were inhibited at CXL MIC of ≤2 μg/mL (see Table). Highest CXL MIC was only 8 μg/mL (2 strains; 0.06%). Isolates with CXL MIC at >2 μg/mL were *S. marcescens* (8), indole-positive Proteae (2), KSP (2), and ESP (1). CXL was the most active compound tested against the ESBL-phenotype and CB-non-S KSP (98.5 and 95.4% inhibited at ≤2 μg/mL, respectively), followed by amikacin (76.2 and 51.2% S, respectively).

Abstract Table

	Cumulative % inhibited at CXL MIC (μg/mL) of:							
Organisms (no. tested)	**≤0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**
E. coli								
Non-ESBL-phenotype (1093)	91.4	98.9	100.0					
ESBL-phenotype (124)	56.5	85.5	96.0	99.2	100.0			
Klebsiella spp.								
Non-ESBL-phenotype (830)	61.3	88.4	96.8	99.3	100.0			
ESBL-phenotype (130)	19.2	46.2	67.7	85.4	93.9	98.5	99.2	100.0
Carbapenem-non-S (43)	18.6	25.6	39.5	65.1	83.7	95.3	97.7	100.0
Enterobacter spp.								
Ceftazidime-S/I (360)	29.2	71.7	93.3	99.2	100.0			
Ceftazidime-R (87)	6.9	20.7	40.2	70.1	94.3	98.9	100.0	

Conclusions: NXL104 can effectively lower CPT MIC values for ENT strains producing the most clinically significant BLs found in USA hospitals. CXL was highly active against ENT-producing KPC, various ESBL types, and AmpC (chromosomally derepressed or plasmid mediated). CXL represents a promising therapeutic option for treatment of infections caused by multidrug-R ENT.

Introduction

The production of β-lactamases is the most important contributing factor to β-lactam resistance among Gram-negative bacteria. These enzymes are widely spread among Enterobacteriaceae strains. Furthermore, the genes encoding β-lactamases are often carried by plasmids that also bear resistance genes to other antimicrobial classes, further narrowing the therapeutic options to treat infections caused by β-lactamase-producing organisms.

Ceftaroline, the active form of ceftaroline fosamil, is a novel broad-spectrum cephalosporin with potent activity against Gram-positive organisms (including methicillin-resistant *Staphylococcus aureus* [MRSA] and *Streptococcus pneumoniae*) and most Enterobacteriaceae species but, like all cephalosporins, has limited potency against extended-spectrum β-lactamase (ESBL)- and AmpC-hyperproducing strains. NXL104 is a new non-β-lactam inhibitor of β-lactamases currently in clinical development that displays a broad-spectrum inhibition profile against both class A and class C enzymes, and a variable level of activity against class D enzymes. NXL104 has very limited intrinsic antibacterial activity, but efficiently protects β-lactams from hydrolysis by a variety of strains producing class A and class C β-lactamases, including ESBL and KPC enzymes.

In this study, we report the activity of ceftaroline combined with NXL104 (CXL; fixed 4 μg/mL) against a collection of 3258 Enterobacteriaceae isolates, including ESBL- and KPC-producers, recovered from USA medical sites during 2009.

Methods

Bacterial isolates. A total of 3258 Enterobacteriaceae isolates collected from 51 medical centers located in the nine USA Census Regions were analyzed in the SENTRY Antimicrobial Surveillance Program. Only one isolate per patient from documented infections was included in this prevalence design study. Species identification was confirmed by standard biochemical tests, the Vitek System (bioMerieux; Hazelwood, Missouri, USA), or 16S rRNA sequencing, when necessary.

Antimicrobial susceptibility testing. All isolates were tested for antimicrobial susceptibility using the broth microdilution method (BMD) as described by the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009). Cation-adjusted Mueller-Hinton broth was used in validated BMD panels. CXL was tested at a fixed 4 μg/mL concentration of NXL104. Categorical interpretations were those found in CLSI; M100-S20-U and quality control (QC) were performed using *Escherichia coli* ATCC 25922, *S. aureus* ATCC 29213, and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within specified ranges as published in CLSI documents.

E. coli and *Klebsiella* spp. isolates for which ceftriaxone or ceftazidime or aztreonam MICs were ≥2 μg/mL were considered to be phenotypic-positive for ESBL production (CLSI, 2010).

Results

- CXL MIC distributions for Enterobacteriaceae strains are summarized in Table 1. All isolates showed CXL MIC values of ≤8 μg/mL and 99.7% of the strains were inhibited by 2 μg/mL
- *E. coli* strains were very susceptible to CXL (MIC_{50}, 0.06 μg/mL and MIC_{90}, 0.12 μg/mL), including 124 isolates with an ESBL-phenotype (MIC_{50}, 0.06 μg/mL and MIC_{90}, 0.25 μg/mL; Table 2)
- CXL activity against ESBL-producing *E. coli* was two-fold greater than that of imipenem (MIC_{50}, 0.25 μg/mL and MIC_{90}, 0.5 μg/mL; Table 2)
- CXL was the most active β-lactam tested against *Klebsiella* spp. (MIC_{50}, 0.06 μg/mL and MIC_{90}, 0.25 μg/mL), being more active than cefepime and imipenem (MIC_{50}, ≤0.12 and 0.25 μg/mL, MIC_{90}, 1 and 0.5 μg/mL, respectively; Table 2)
- CXL was very active against *Klebsiella* spp. displaying an ESBL-phenotype (MIC_{50}, 0.25 μg/mL and MIC_{90}, 1 μg/mL) and those showing decreased susceptibility to carbapenems, including 40 molecularly identified KPC-producers (MIC_{50}, 0.5 μg/mL and MIC_{90}, 2 μg/mL; Tables 1 and 2)
- The activity of CXL against ceftazidime-susceptible/intermediate *Enterobacter* spp. (MIC_{50}, 0.12 μg/mL and MIC_{90}, 0.25 μg/mL; Table 2) was comparable to that of cefepime (MIC_{50}, ≤0.12 μg/mL and MIC_{90}, 0.25 μg/mL)
- When tested against ceftazidime-resistant (possibly AmpC derepressed) *Enterobacter* spp. strains, CXL (MIC_{50}, 0.5 μg/mL and MIC_{90}, 1 μg/mL; Table 2) was at least four-fold more active than cefepime (MIC_{50}, 2 μg/mL and MIC_{90}, >16 μg/mL) and slightly more active than imipenem (MIC_{50}, 0.5 μg/mL and MIC_{90}, 4 μg/mL)
- CXL was very active against *Citrobacter* spp. (MIC_{50}, 0.12 μg/mL and MIC_{90}, 0.25 μg/mL; Table 2), *Proteus mirabilis* (MIC_{50}, 0.12 μg/mL and MIC_{90}, 0.25 μg/mL), and *Salmonella* spp. strains (MIC_{50} and MIC_{90}, 0.12 μg/mL)
- CXL was also active against *Serratia* ($MIC_{50/90}$, 0.5 and 2 μg/mL) and indole-positive *Proteae* ($MIC_{50/90}$, 0.06 and 2 μg/mL) species, but these two organism groups exhibited the highest CXL MIC_{90} values among the Enterobacteriaceae strains tested (2 μg/mL; Table 2).

Table 1. Summary of Ceftaroline/NXL104 Activity Against 3258 Enterobacteriaceae Strains From USA Medical Sites (2009)

	No. of organisms (cumulative %) inhibited at ceftaroline/NXL104 MIC (μg/mL) of:							
Organism (no. tested)	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**
Escherichia coli (all; 1217)	534 (43.9)	535 (87.8)	118 (97.5)	25 (99.6)	4 (99.9)	1 (100.0)	-	-	-
Non-ESBL phenotype (1093)	516 (47.2)	483 (91.4)	82 (98.9)	12 (100.0)	-	-	-	-	-
ESBL-phenotype (124)	18 (14.5)	52 (56.4)	36 (85.5)	13 (96.0)	4 (99.2)	1 (100.0)	-	-	-
Klebsiella spp. (all; 960)	90 (9.4)	444 (55.6)	260 (82.7)	97 (92.8)	44 (97.4)	17 (99.2)	6 (99.8)	1 (99.9)	1 (100.0)
Non-ESBL phenotype (830)	84 (10.1)	425 (61.3)	225 (88.4)	69 (96.7)	21 (99.3)	6 (100.0)	-	-	-
ESBL-phenotype (130)	6 (4.6)	19 (19.2)	36 (45.1)	28 (67.7)	23 (85.4)	11 (93.8)	6 (98.5)	1 (99.2)	1 (100.0)
Carbapenem-non-susceptible (43)	4 (9.3)	4 (18.6)	3 (25.6)	6 (39.5)	11 (65.1)	8 (83.7)	5 (95.3)	1 (97.7)	1 (100.0)
Enterobacter spp. (all; 447)	31 (6.9)	80 (24.8)	165 (61.7)	95 (83.0)	47 (93.5)	24 (98.9)	4 (99.8)	1 (100.0)	-
Ceftazidime-susceptible/intermediate (360)	30 (8.3)	75 (29.2)	153 (71.8)	78 (93.3)	21 (99.2)	3 (100.0)	-	-	-
Ceftazidime-resistant (87)[a]	1 (1.1)	5 (6.9)	12 (20.7)	17 (40.2)	26 (70.1)	21 (94.2)	2 (89.6)	3 (95.8)	2 (100.0)	-
Citrobacter spp. (82)	7 (8.5)	29 (43.9)	30 (80.5)	8 (90.2)	7 (98.8)	1 (100.0)	-	-	-	-
Proteus mirabilis (264)	7 (2.7)	82 (33.7)	133 (84.1)	35 (97.4)	7 (100.0)	-	-	-	-	-
Indole-positive Proteae (48)	11 (22.9)	16 (56.3)	7 (70.8)	6 (83.3)	1 (85.4)	2 (89.6)	3 (95.8)	2 (100.0)	-	-
Salmonella spp. (30)	2 (6.7)	3 (16.7)	22 (90.0)	3 (100.0)	-	-	-	-	-	-
Serratia spp. (210)	-	1 (0.5)	3 (1.9)	58 (29.5)	76 (65.7)	49 (89.1)	15 (96.2)	7 (99.5)	1 (100.0)

a. Highly likely to exhibit a stably derepressed AmpC enzyme.

Table 2. Activity of Ceftaroline/NXL104 and Comparator Antimicrobial Agents When Tested Against Isolates Collected From Medical Sites Located in the United States

Organism/ Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S / %R	EUCAST[a] %S / %R
Escherichia coli				
All strains (1217)				
Ceftaroline/NXL104	0.06	0.12	- / -	- / -
Ceftaroline	0.12	4	- / -	- / -
Ceftriaxone	≤0.25	0.5	91.2 / 8.5	91.2 / 8.5
Cefepime	≤0.12	0.5	95.7 / 3.6	92.8 / 4.3
Ceftazidime	0.25	1	93.6 / 5.4	91.3 / 5.4
Imipenem	≤0.12	0.25	99.7 / 0.0	99.9 / 0.0
Piperacillin/tazobactam	2	8	93.8 / 2.9	91.2 / 6.2
Levofloxacin	≤0.5	>4	68.6 / 30.6	68.6 / 31.4
Amikacin	2	4	99.4 / 0.0	98.4 / 0.6
Tigecycline[b]	0.12	0.25	100.0 / 0.0	99.8 / 0.0
Non-ESBL phenotype (1093)				
Ceftaroline/NXL104	0.06	0.06	- / -	- / -
Ceftaroline	0.12	0.5	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.12	≤0.12	99.9 / 0.0	99.5 / 0.1
Ceftazidime	0.12	0.5	100.0 / 0.0	100.0 / 0.0
Imipenem	≤0.12	0.25	99.8 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	96.2 / 2.3	95.2 / 3.8
Levofloxacin	≤0.5	>4	74.0 / 25.2	74.0 / 26.0
Amikacin	2	4	99.7 / 0.0	99.4 / 0.3
Tigecycline[b]	0.12	0.25	100.0 / 0.0	99.7 / 0.0
ESBL-phenotype (124)				
Ceftaroline/NXL104	0.06	0.25	- / -	- / -
Ceftaroline	>32	>32	- / -	- / -
Ceftriaxone	>32	>32	13.7 / 83.9	13.7 / 83.9
Cefepime	8	>16	58.9 / 35.5	33.9 / 41.1
Ceftazidime	16	>32	37.1 / 53.2	14.5 / 53.2
Imipenem	0.25	0.5	98.4 / 0.0	99.2 / 0.0
Piperacillin/tazobactam	8	64	72.6 / 8.1	56.5 / 27.4
Levofloxacin	>4	>4	21.0 / 79.0	21.0 / 79.0
Amikacin	4	8	96.8 / 0.0	90.3 / 3.2
Tigecycline[b]	0.25	0.25	100.0 / 0.0	100.0 / 0.0
Klebsiella spp.				
All strains (960)				
Ceftaroline/NXL104	0.06	0.25	- / -	- / -
Ceftaroline	0.12	32	- / -	- / -
Ceftriaxone	≤0.25	8	87.9 / 11.6	87.9 / 11.6
Cefepime	≤0.12	1	92.8 / 5.5	90.2 / 7.2
Ceftazidime	0.12	16	88.7 / 10.4	87.6 / 10.4
Imipenem	0.25	0.5	95.6 / 4.0	95.8 / 2.8
Piperacillin/tazobactam	4	32	88.8 / 8.6	83.1 / 11.3
Levofloxacin	≤0.5	>4	88.7 / 10.0	87.0 / 11.3
Amikacin	1	2	96.7 / 1.0	95.2 / 3.3
Tigecycline[b]	0.25	1	97.7 / 0.3	94.0 / 2.3
Non-ESBL phenotype[c] (830)				
Ceftaroline/NXL104	0.06	0.25	- / -	- / -
Ceftaroline	0.12	0.5	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.12	≤0.12	100.0 / 0.0	99.9 / 0.0
Ceftazidime	0.12	0.5	100.0 / 0.0	100.0 / 0.0
Imipenem	0.25	0.5	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	8	98.1 / 0.6	92.4 / 1.9
Levofloxacin	≤0.5	≤0.5	96.7 / 2.4	95.5 / 3.3
Amikacin	1	2	99.9 / 0.0	99.9 / 0.1
Tigecycline[b]	0.25	1	98.2 / 0.1	94.8 / 1.8
ESBL-phenotype[d] (130)				
Ceftaroline/NXL104	0.25	1	- / -	- / -
Ceftaroline	>32	>32	- / -	- / -
Ceftriaxone	>32	>32	10.8 / 85.4	10.8 / 85.4
Cefepime	16	>16	46.9 / 40.8	28.5 / 53.1
Ceftazidime	>32	>32	16.9 / 76.9	8.5 / 76.9
Imipenem	0.25	>8	67.7 / 29.2	69.2 / 20.8
Piperacillin/tazobactam	>64	>64	29.2 / 60.0	23.8 / 70.8
Levofloxacin	>4	>4	37.2 / 58.9	31.8 / 62.8
Amikacin	2	32	76.2 / 7.7	65.4 / 23.8
Tigecycline[b]	0.5	2	94.6 / 1.5	88.5 / 5.4
Carbapenem-non-susceptible[c] (43)				
Ceftaroline/NXL104	0.5	2	- / -	- / -
Ceftaroline	>32	>32	- / -	- / -
Ceftriaxone	>32	>32	0.0 / 100.0	0.0 / 100.0
Cefepime	>16	>16	11.6 / 65.1	0.0 / 88.4
Ceftazidime	>32	>32	0.0 / 97.7	0.0 / 97.7
Imipenem	>8	>8	2.3 / 88.4	7.0 / 62.8
Piperacillin/tazobactam	>64	>64	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>4	>4	9.3 / 90.7	7.0 / 90.7
Amikacin	16	>32	51.2 / 16.3	25.6 / 48.8
Tigecycline[b]	1	2	90.7 / 2.3	83.7 / 9.3
Enterobacter spp.				
All strains[e] (447)				
Ceftaroline/NXL104	0.12	0.5	- / -	- / -
Ceftaroline	0.25	>32	- / -	- / -
Ceftriaxone	≤0.25	>32	76.1 / 21.7	76.1 / 21.7
Cefepime	≤0.12	2	96.2 / 2.7	86.8 / 3.8
Ceftazidime	0.25	>32	79.6 / 19.5	75.8 / 19.5
Imipenem	0.5	2	89.5 / 1.6	98.0 / 0.7
Piperacillin/tazobactam	2	64	83.2 / 8.5	78.5 / 16.8
Levofloxacin	≤0.5	1	94.4 / 4.5	92.2 / 5.6
Amikacin	1	2	99.6 / 0.2	98.9 / 0.4
Tigecycline[b]	0.5	1	98.0 / 0.0	93.1 / 2.0
Ceftazidime-S/I[b] (360)				
Ceftaroline/NXL104	0.12	0.25	- / -	- / -
Ceftaroline	0.25	1	- / -	- / -
Ceftriaxone	≤0.25	0.5	94.4 / 2.8	94.4 / 2.8
Cefepime	≤0.12	0.25	99.7 / 0.3	99.7 / 0.3
Ceftazidime	0.25	1	98.9 / 0.0	94.2 / 0.0
Imipenem	0.5	1	90.6 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	98.3 / 0.0	95.0 / 1.7
Levofloxacin	≤0.5	≤0.5	98.1 / 1.1	97.2 / 1.9
Amikacin	1	2	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.25	0.5	98.6 / 0.0	96.4 / 1.4
Ceftazidime-resistant[f] (87)				
Ceftaroline/NXL104	0.5	1	- / -	- / -
Ceftaroline	>32	>32	- / -	- / -
Ceftriaxone	>32	>32	0.0 / 100.0	0.0 / 100.0
Cefepime	2	>16	81.6 / 12.6	33.3 / 18.4
Ceftazidime	>32	>32	0.0 / 100.0	0.0 / 100.0
Imipenem	0.5	4	85.1 / 8.0	89.7 / 3.4
Piperacillin/tazobactam	64	>64	20.7 / 43.7	10.3 / 79.3
Levofloxacin	≤0.5	>4	79.3 / 18.4	71.3 / 20.7
Amikacin	1	8	97.7 / 1.1	94.3 / 2.3
Tigecycline[b]	0.5	2	95.4 / 0.0	79.3 / 4.6
Citrobacter spp.[g] (82)				
Ceftaroline/NXL104	0.12	0.25	- / -	- / -
Ceftaroline	0.25	>32	- / -	- / -
Ceftriaxone	≤0.25	32	78.0 / 20.7	78.0 / 20.7
Cefepime	≤0.12	1	100.0 / 0.0	95.1 / 0.0
Ceftazidime	0.25	32	82.9 / 15.9	79.3 / 15.9
Imipenem	0.5	1	95.1 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	64	85.4 / 2.4	81.7 / 14.6
Levofloxacin	≤0.5	1	95.1 / 2.4	91.5 / 4.9
Amikacin	1	2	100.0 / 0.0	97.6 / 0.0
Tigecycline[b]	0.25	1	100.0 / 0.0	95.1 / 0.0
Proteus mirabilis (264)				
Ceftaroline/NXL104	0.12	0.25	- / -	- / -
Ceftaroline	0.12	0.5	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	98.5 / 0.8	98.5 / 0.8
Cefepime	≤0.12	≤0.12	100.0 / 0.0	99.6 / 0.0
Ceftazidime	0.06	0.12	99.2 / 0.0	99.2 / 0.0
Imipenem	1	2	54.2 / 0.4	92.4 / 0.0
Piperacillin/tazobactam	≤0.5	1	99.6 / 0.4	99.6 / 0.4
Levofloxacin	≤0.5	>4	75.4 / 19.7	70.1 / 24.6
Amikacin	4	8	100.0 / 0.0	98.1 / 0.0
Tigecycline[b]	2	4	82.6 / 1.1	45.5 / 17.4
Indole-positive *Proteus* spp.[k] (48)				
Ceftaroline/NXL104	0.06	2	- / -	- / -
Ceftaroline	0.12	>32	- / -	- / -
Ceftriaxone	≤0.25	2	85.4 / 8.3	85.4 / 8.3
Cefepime	≤0.12	0.25	100.0 / 0.0	97.9 / 0.0
Ceftazidime	0.12	8	89.6 / 6.3	81.3 / 6.3
Imipenem	2	4	22.9 / 0.0	72.9 / 0.0
Piperacillin/tazobactam	≤0.5	8	95.8 / 2.1	95.8 / 4.2
Levofloxacin	≤0.5	>4	68.8 / 25.0	66.7 / 31.3
Amikacin	2	4	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	1	4	87.5 / 4.2	72.9 / 12.5
Serratia spp.[l] (210)				
Ceftaroline/NXL104	0.5	2	- / -	- / -
Ceftaroline	1	8	- / -	- / -
Ceftriaxone	≤0.25	2	88.1 / 8.6	88.1 / 8.6
Cefepime	≤0.12	0.5	99.0 / 0.5	94.8 / 1.0
Ceftazidime	0.25	0.5	94.8 / 4.3	94.3 / 4.3
Imipenem	1	2	84.8 / 1.0	97.1 / 1.0
Piperacillin/tazobactam	2	4	97.6 / 1.4	95.2 / 2.4
Levofloxacin	≤0.5	1	95.7 / 2.9	90.5 / 4.3
Amikacin	2	4	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	1	2	95.2 / 1.0	83.3 / 4.8
Salmonella spp.[m] (30)				
Ceftaroline/NXL104	0.12	0.12	- / -	- / -
Ceftaroline	0.12	0.25	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Ceftazidime	0.25	0.25	100.0 / 0.0	100.0 / 0.0
Imipenem	0.5	0.5	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Amikacin	2	4	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.25	0.5	100.0 / 0.0	96.7 / 0.0

a. Criteria as published by the CLSI [2010] and EUCAST [2009].
b. US-FDA breakpoints were applied [Tygacil Product Insert, 2005].
c. Includes: *Klebsiella oxytoca* (138 strains), *Klebsiella oxytoca* (2 strains), *Klebsiella pneumoniae* (757 strains), and unspecified *Klebsiella* (63 strains).
d. Includes: *K. oxytoca* (122 strains), *K. ozaenae* (2 strains), *K. pneumoniae* (647 strains), and unspecified *Klebsiella* (59 strains).
e. Includes: *K. oxytoca* (16 strains), *K. pneumoniae* (110 strains), and unspecified *Klebsiella* (4 strains).
f. Includes: *K. oxytoca* (2 strains) and *K. pneumoniae* (41 strains).
g. Includes: *Enterobacter aerogenes* (98 strains), *Enterobacter asburiae* (9 strains), *Enterobacter cancerogenus* (1 strain), *Enterobacter cloacae* (323 strains), *Enterobacter gergoviae* (3 strains), *Enterobacter hormaechei* (1 strain), *Enterobacter intermedius* (1 strain), *Enterobacter sakazakii* (1 strain), and unspecified *Enterobacter* (10 strains).
h. S/I= susceptible/intermediate. Includes: *E. aerogenes* (83 strains), *E. asburiae* (9 strains), *E. cloacae* (252 strains), *E. gergoviae* (3 strains), *E. hormaechei* (1 strain), *E. intermedius* (1 strain), *E. sakazakii* (1 strain), and unspecified *Enterobacter* (10 strains).
i. Includes: *E. aerogenes* (15 strains), *E. cancerogenus* (1 strain), and *E. cloacae* (71 strains).
j. Includes: *Citrobacter amalonaticus* (5 strains), *Citrobacter braakii* (3 strains), *Citrobacter farmeri* (1 strain), *Citrobacter freundii* (44 strains), *Citrobacter koseri* (22 strains), *Citrobacter youngae* (4 strains), and unspecified *Citrobacter* (3 strains).
k. Includes: *Morganella morganii* (31 strains), *Proteus vulgaris* (5 strains), *Providencia rettgeri* (2 strains), *Providencia stuartii* (9 strains), and unspecified *Morganella* (1 strain).
l. Includes: *Serratia fonticola* (2 strains), *Serratia liquefaciens* (7 strains), *Serratia marcescens* (196 strains), and unspecified *Serratia* (5 strains).
m. Includes: *Salmonella enterica* (1 strain), *Salmonella enteritidis* (2 strains), *Salmonella paratyphi* (2 strains), *Salmonella schwarzer grund* (1 strain), *Salmonella typhi* (3 strains), Group B *Salmonella* (5 strains), Group C *Salmonella* (3 strains), Group D *Salmonella* (2 strains), and unspecified *Salmonella* (11 strains).

Conclusions

- CXL was very active against Enterobacteriaceae, including strains expressing broad-spectrum β-lactamase activity
- Overall, the activity of this β-lactam/inhibitor combination was comparable to that of the carbapenems. CXL was particularly active against Enterobacteriaceae strains with decreased susceptibility to carbapenems (MIC_{50}, 0.5 μg/mL and MIC_{90}, 2 μg/mL)
- The worldwide spread of β-lactamase-encoding genes among Enterobacteriaceae strains from nosocomial and community settings jeopardizes the use of β-lactam agents for the treatment of infections caused by these organisms. Our results demonstrated that CXL is a valuable option to treat infections caused by Enterobacteriaceae, including organisms producing/hyperexpressing AmpC cephalosporinases, ESBLs, and/or KPC β-lactamases.

References

1. Clinical and Laboratory Standards Institute (2009). *M07-A8. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eighth edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2010). *M100-S20-U. Performance standards for antimicrobial susceptibility testing: 20th informational supplement (June 2010 update).* Wayne, PA: CLSI.
3. Endimiani A, Choudhary Y, Bonomo RA (2009). In vitro activity of NXL104 in combination with beta-lactams against *Klebsiella pneumoniae* isolates producing KPC carbapenemases. *Antimicrob Agents Chemother* 53: 3599-3601.
4. Jacobs MR, Good CE, Windau AR, Bajaksouzian S, Biek D, Critchley IA, Sader HS, Jones RN (2010). Activity of ceftaroline against recent emerging serotypes of *Streptococcus pneumoniae* in the United States. *Antimicrob Agents Chemother* 54: 2716-2719.
5. Livermore DM, Mushtaq S, Warner M, Miossec C, Woodford N (2008). NXL104 combinations versus Enterobacteriaceae with CTX-M extended-spectrum beta-lactamases and carbapenemases. *J Antimicrob Chemother* 62: 1053-1056.
6. Mushtaq S, Warner M, Williams G, Critchley I, Livermore DM (2010). Activity of chequerboard combinations of ceftaroline and NXL104 versus beta-lactamase-producing Enterobacteriaceae. *J Antimicrob Chemother* 65: 1428-1432.
7. Pitout JD (2010). Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: Changing epidemiology and drug treatment choices. *Drugs* 70: 313-333.
8. Stachyra T, Levasseur P, Pechereau MC, Girard AM, Claudon M, Miossec C, Black MT (2009). *In vitro* activity of the β-lactamase inhibitor NXL104 against KPC-2 carbapenemase and Enterobacteriaceae expressing KPC carbapenemases. *J Antimicrob Chemother* 64: 326-329.
9. Zhanel GG, Sniezek G, Schweizer F, Zelenitsky S, Lagace-Wiens PR, Rubinstein E, Gin AS, Hoban DJ, Karlowsky JA (2009). Ceftaroline: A novel broad-spectrum cephalosporin with activity against meticillin-resistant *Staphylococcus aureus*. *Drugs* 69: 809-831.

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