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Activity of Ceftaroline/NXL104 Tested Against Contemporary (2009) Clinical Isolates of Staphylococci and Streptococci Collected From USA Medical Centers

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Amended Abstract

Background: Ceftaroline is a novel broad-spectrum cephalosporin with activity against Gram-positive (including MRSA and *S. pneumoniae* [SPN]) and Gram-negative organisms. NXL104 is a novel non-β-lactam β-lactamase inhibitor that inhibits Ambler class A, C, and D enzymes. We evaluated the spectrum of activity and potency of ceftaroline/NXL104 (CXL; fixed concentration of 4 μg/mL) against clinical staphylococcal and streptococcal isolates.

Methods: Isolates were consecutively collected from >50 USA medical centers in 2009. Susceptibility (S) testing for CXL and 16 comparators was performed by CLSI broth microdilution method (M07-A8, 2009) on a total of 6367 strains: 3329 *S. aureus* (SA; 47.8% oxacillin-resistant [R]; MRSA), 687 CoNS (73.8% oxacillin-R), 1225 SPN (20.3% penicillin-R [MIC, ≥2 μg/mL]), 921 β-haemolytic (BHS) and 205 viridans group streptococci (VGS).

Results: All MRSA strains were inhibited at ≤2 μg/mL of CXL. Against oxacillin-S SA, CXL inhibited 99.6% of strains at MIC ≤0.5 μg/mL and was 8- to 16-fold more active than ceftriaxone (CRO). CXL activity against CoNS was similar to that against SA. CXL was 8-fold more active than CRO against PEN-R SPN; the highest CXL MIC was only 0.5 μg/mL. BHS and VGS were highly CXL-S (see Table).

	MIC_{50}/MIC_{90} (μg/mL)				
Organism (no.)	**CXL[a]**	**Ceftriaxone**	**Levofloxacin**	**Linezolid**	**Vancomycin**
S. aureus					
Oxacillin-S (MSSA; 1739)	0.25/0.5	4/4	≤0.5/2	2/2	1/1
MRSA (1590)	1/1	>32/>32	>4/>4	2/2	1/1
CoNS (687)	0.25/0.5	8/32	4/>4	1/1	1/2
S. pneumoniae (1225)	≤0.03/0.25	≤0.25/2	1/1	-/-	≤1/≤1
PEN-R (MIC, ≥2 μg/mL; 249)	0.25/0.5	2/4	1/1	-/-	≤1/≤1
β-haemolytic strep. (921)	≤0.03/≤0.03	≤0.25/≤0.25	1/1	1/1	0.5/0.5
Viridans group strep. (205)	≤0.03/0.12	≤0.25/1	1/2	1/1	0.5/1

a. Concentrations reported in the table for ceftaroline/NXL104 (CXL) refer to the concentration of ceftaroline tested with fixed 4 μg/mL NXL104 concentration.

Conclusions: CXL was the most potent β-lactam agent tested against staphylococci and streptococci collected from USA hospitals. MRSA and PEN-R-SPN were particularly S to CXL. CXL represents a potential therapeutic option for infections caused by these organisms and has activity against Gram-negative pathogens.

Introduction

Ceftaroline, the active form of the prodrug ceftaroline fosamil, is a novel, broad-spectrum cephalosporin exhibiting bactericidal activity against Gram-positive organisms, including methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae*, as well as common Gram-negative pathogens.

Ceftaroline has been combined with NXL104, a new non-β-lactam inhibitor of β-lactamases currently in clinical development that displays a broad-spectrum inhibition profile against Ambler class A, C, and D enzymes. NXL104 has virtually no intrinsic antibacterial activity, but efficiently protects β-lactams from hydrolysis caused by a variety of strains producing class A and class C enzymes, including extended-spectrum β-lactamase and KPC enzymes.

In this study, we report the activity and potency of ceftaroline combined with NXL104 (CXL; fixed 4 μg/mL) against a large clinical sample of staphylococci and streptococci isolates collected from United States (USA) medical centers during 2009.

Methods

Bacterial isolates. A total of 6367 staphylococci (3329 *S. aureus* [47.8% MRSA] and 687 coagulase-negative staphylococci [CoNS; 73.8% oxacillin-resistant]) and streptococci isolates (1225 *S. pneumoniae* [20.3% penicillin-resistant; MIC ≥2 μg/mL]; 921 β-haemolytic streptococci and 205 viridans group streptococci) were consecutively collected from >50 USA medical centers. Only 1 isolate per patient from documented clinical infections were included in this prevalence design study. Species identification was confirmed by standard biochemical tests, the Vitek System (bioMerieux; Hazelwood, MO), or 16S rRNA sequencing, when necessary.

Antimicrobial susceptibility testing. All isolates were tested for antimicrobial susceptibility using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009). Cation-adjusted Mueller-Hinton broth was used for staphylococci and cation-adjusted Mueller-Hinton broth supplemented with 3% to 5% lysed horse blood was used for streptococci testing in validated panels. CXL was tested in a fixed 4 μg/mL concentration of NXL104. Categorical interpretations were those found in CLSI (M100-S20) and quality control (QC) was performed using *Escherichia coli* ATCC 25922, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619. All QC results were within specified ranges as published in CLSI documents.

Results

- CXL MIC distributions for staphylococci and streptococci are summarized in Table 1. All *S. aureus* isolates showed CXL MIC values ≤2 μg/mL ($MIC_{50,}$ 0.5 μg/mL and $MIC_{90,}$ 1 μg/mL)
- Against methicillin (oxacillin)-susceptible *S. aureus* (MSSA), CXL ($MIC_{50,}$ 0.25 μg/mL and $MIC_{90,}$ 0.5 μg/mL) was 8- to 16-fold more active than ceftriaxone (MIC_{50} and $MIC_{90,}$ 4 μg/mL) and cefepime ($MIC_{50,}$ 2 μg/mL and $MIC_{90,}$ 4 μg/mL; Table 2)
- CXL MIC results were generally 4-fold higher for MRSA (MIC range, 0.25-2 μg/mL; $MIC_{50/90,}$ 1 μg/mL) compared with MSSA (MIC range, ≤0.03-1 μg/mL, $MIC_{50/90,}$ 0.25/0.5 μg/mL). However, CXL activity was considerably greater than other cephalosporins tested and imipenem against MRSA strains (Table 2)
- CXL (MIC_{50} and $MIC_{90,}$ 1 μg/mL) was 2-fold more potent than linezolid (MIC_{50} and $MIC_{90,}$ 2 μg/mL) and showed the same potency as vancomycin (MIC_{50} and $MIC_{90,}$ 1 μg/mL) when tested against MRSA (Table 2)
- CXL was slightly more active against CoNS ($MIC_{50,}$ 0.25 μg/mL and $MIC_{90,}$ 0.5 μg/mL; Tables 1 and 2) when compared with *S. aureus* ($MIC_{50,}$ 0.5 μg/mL and $MIC_{90,}$ 1 μg/mL). All strains were inhibited by a CXL MIC of ≤2 μg/mL except for 1 strain that showed a CXL MIC of 4 μg/mL
- When tested against *S. pneumoniae* strains, CXL ($MIC_{50,}$ ≤0.03 μg/mL and $MIC_{90,}$ 0.25 μg/mL) was 8-fold more potent than ceftriaxone ($MIC_{50,}$ ≤0.25 μg/mL and $MIC_{90,}$ 2 μg/mL). As with other β-lactam agents, CXL MIC results varied according to the susceptibility to penicillin (Tables 1 and 2)
- CXL was highly active against both β-haemolytic streptococci (MIC_{50} and $MIC_{90,}$ ≤0.03 μg/mL) and viridans group streptococci ($MIC_{50,}$ ≤0.03 μg/mL and $MIC_{90,}$ 0.12 μg/mL). The highest CXL MIC observed was 0.06 μg/mL for β-haemolytic streptococci and 2 μg/mL for viridans group streptococci (99.0% inhibited at ≤0.5 μg/mL; Tables 1 and 2).

Table 1. Summary of Ceftaroline/NXL104 (CXL) Activity Against 6367 Staphylococci and Streptococci Strains From USA Medical Centers in 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**
Staphylococcus aureus (3329)	1 (0.03)	5 (0.2)	72 (2.3)	1353 (43.0)	1012 (73.4)	744 (95.7)	142 (100.0)	-
Oxacillin-susceptible (1739)	1 (0.1)	5 (0.4)	72 (4.5)	1333 (81.1)	321 (99.6)	7 (100.0)	-	-
Oxacillin-resistant (1590)	0 (0.0)	0 (0.0)	0 (0.0)	20 (1.3)	691 (44.7)	737 (91.1)	142 (100.0)	-
Coagulase-negative staphylococci (687)	19 (2.8)	76 (13.8)	91 (27.1)	221 (59.2)	231 (92.9)	41 (98.8)	7 (99.9)	1 (100.0)
Streptococcus pneumoniae (1225)	839 (68.5)	87 (75.6)	100 (83.8)	170 (97.6)	24 (99.6)	5 (100.0)	-	-
Penicillin-susceptible (728)	715 (98.2)	9 (99.5)	3 (99.9)	1 (100.0)	-	-	-	-
Penicillin-intermediate (248)	124 (50.0)	77 (81.1)	45 (99.2)	2 (100.0)	-	-	-	-
Penicillin-resistant (249)	0 (0.0)	1 (0.4)	52 (21.3)	167 (88.4)	24 (98.0)	5 (100.0)	-	-
Viridans group streptococci (205)	144 (70.2)	36 (87.8)	13 (94.2)	4 (96.1)	6 (99.0)	1 (99.5)	1 (100.0)	-
β-haemolytic streptococci (921)	903 (98.1)	18 (100.0)	-	-	-	-	-	-

Table 2. Activity of Ceftaroline/NXL104 (CXL) and Comparator Antimicrobial Agents When Tested Against Isolates Collected From Medical Centers Located in the United States in 2009

Organism/Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Staphylococcus aureus (3329)					
CXL	0.5	1	≤0.03 – 2	- / -	- / -
Ceftriaxone	8	>32	0.5 – >32	52.2 / 47.8	52.2 / 47.8
Cefepime	4	>16	≤0.12 - >16	52.2 / 47.8	52.2 / 47.8
Imipenem	≤0.12	4	≤0.12 - >8	52.2 / 47.8	52.2 / 47.8
Oxacillin	1	>2	≤0.25 – >2	52.2 / 47.8	52.2 / 47.8
Clindamycin	≤0.25	>2	≤0.25 – >2	79.9 / 19.7	79.3 / 20.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	58.8 / 40.4	58.8 / 40.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.6 / 1.4	98.6 / 1.4
Linezolid	2	2	≤0.06 – >8	99.8 / 0.2	99.8 / 0.2
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -	>99.9 / <0.1
Oxacillin-susceptible *S. aureus* (1739)					
CXL	0.25	0.5	≤0.03 – 1	- / -	- / -
Ceftriaxone	4	4	0.5 – 32	99.3 / 0.0	100.0 / 0.0
Cefepime	2	4	≤0.12 - 16	99.9 / 0.0	100.0 / 0.0
Imipenem	≤0.12	4	≤0.12 - >8	100.0 / 0.0	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	94.8 / 4.9	94.2 / 5.2
Levofloxacin	≤0.5	2	≤0.5 – >4	89.4 / 9.8	89.4 / 9.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.9 / 1.1	98.9 / 1.1
Linezolid	2	2	≤0.06 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Oxacillin-resistant *S. aureus* (1590)					
CXL	1	1	0.25 – 2	- / -	- / -
Ceftriaxone	>32	>32	2 – >32	0.0 / 100.0	0.0 / 100.0
Cefepime	16	>16	1 - >16	0.0 / 100.0	0.0 / 100.0
Imipenem	0.5	>8	≤0.12 - >8	0.0 / 100.0	0.0 / 100.0
Clindamycin	≤0.25	>2	≤0.25 – >2	63.6 / 35.9	63.0 / 36.4
Levofloxacin	>4	>4	≤0.5 – >4	25.3 / 73.9	25.3 / 73.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.3 / 1.7	98.3 / 1.7
Linezolid	2	2	0.5 – >8	99.7 / 0.3	99.7 / 0.3
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.5	0.5	≤0.06 – 2	99.9 / -	99.9 / 0.1
Coagulase-negative staphylococci (687)					
CXL	0.25	0.5	≤0.03 – 4	- / -	- / -
Ceftriaxone	8	32	≤0.25 – >32	26.2 / 73.8	26.2 / 73.8
Oxacillin	>2	>2	≤0.25 – >2	26.2 / 73.8	26.2 / 73.8
Cefepime	2	16	≤0.12 - >16	26.2 / 73.8	26.2 / 73.8
Imipenem	≤0.12	8	≤0.12 - >8	26.2 / 73.8	26.2 / 73.8
Clindamycin	≤0.25	>2	≤0.25 – >2	68.0 / 31.0	66.1 / 32.0
Levofloxacin	4	>4	≤0.5 – >4	46.1 / 52.1	46.1 / 52.1
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	59.6 / 40.4	59.6 / 40.4
Linezolid	1	1	0.12 – >8	98.7 / 1.3	98.7 / 1.3
Vancomycin	1	2	≤0.12 – 4	100.0 / 0.0	99.1 / 0.9
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
β-haemolytic streptococci (921)					
CXL	≤0.03	≤0.03	≤0.03 – 0.06	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Cefepime	≤0.12	≤0.12	≤0.12 - 1	99.8 / -	100.0 / 0.0
Imipenem	≤0.12	≤0.12	≤0.12 – 0.25	- / -	100.0 / 0.0
Penicillin	0.03	0.06	≤0.015 – 0.12	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	82.6 / 16.8	83.2 / 16.8
Levofloxacin	1	1	≤0.5 – >4	98.0 / 1.8	94.4 / 2.0
Linezolid	1	1	≤0.06 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Viridans group streptococci (205)					
CXL	≤0.03	0.12	≤0.03 – 2	- / -	- / -
Ceftriaxone	≤0.25	1	≤0.25 – >32	92.7 / 3.4	87.3 / 12.7
Cefepime	0.25	1	≤0.12 - 16	91.7 / 3.4	85.4 / 14.6
Imipenem	≤0.12	0.25	≤0.12 – 4	- / -	98.5 / 1.5
Penicillin	0.06	1	≤0.015 – 32	72.2 / 3.4	82.0 / 3.4
Clindamycin	≤0.25	>2	≤0.25 – >2	86.3 / 11.7	88.3 / 11.7
Levofloxacin	1	2	≤0.5 – >4	91.7 / 6.3	- / -
Linezolid	1	1	0.12 – 2	100.0 / -	- / -
Vancomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Daptomycin	0.5	1	≤0.06 – 2	99.0 / -	- / -
Streptococcus pneumoniae (1225)					
CXL	≤0.03	0.25	≤0.03 – 0.5	- / -	- / -
Penicillin[b]	≤0.03	4	≤0.03 – >4	84.0 / 2.8	- / -
Penicillin[c]	≤0.03	4	≤0.03 – >4	59.5 / 20.3	59.5 / 16.0
Amoxicillin/clavulanate	≤1	8	≤1 – 16	82.6 / 15.2	- / -
Ceftriaxone	≤0.25	2	≤0.25 – 8	87.3 / 2.4	78.9 / 2.4
Cefuroxime	≤1	8	≤1 – >8	73.8 / 23.3	73.8 / 26.2
Erythromycin	≤0.25	>2	≤0.25 – >2	61.4 / 38.0	61.4 / 38.0
Clindamycin	≤0.25	>2	≤0.25 – >2	79.0 / 20.6	79.4 / 20.6
Levofloxacin	1	1	≤0.5 – >4	99.3 / 0.7	99.3 / 0.7
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	65.7 / 26.8	70.4 / 26.8
Vancomycin	≤1	1	≤1 – 1	100.0 / -	100.0 / 0.0
Penicillin-susceptible (MIC, ≤0.06 μg/mL)					
S. pneumoniae (729)					
CXL	≤0.03	≤0.03	≤0.03 – 0.25	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0	100.0 / 0.0
Cefuroxime	≤1	≤1	≤1 – 2	99.7 / 0.0	99.7 / 0.3
Amoxicillin/clavulanate	≤1	≤1	≤1	100.0 / 0.0	- / -
Erythromycin	≤0.25	>2	≤0.25 – >2	87.1 / 11.9	87.1 / 11.9
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.3 / 2.3	97.7 / 2.3
Levofloxacin	1	1	≤0.5 – >4	97.9 / 0.1	98.9 / 0.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	90.9 / 4.3	94.5 / 4.3
Penicillin-intermediate (MIC, 0.12-1 μg/mL)					
S. pneumoniae (248)					
CXL	≤0.03	0.12	≤0.03 – 0.25	- / -	- / -
Ceftriaxone	≤0.25	0.5	≤0.25 – 2	99.6 / 0.0	93.5 / 0.0
Cefuroxime	≤1	4	≤1 – 8	73.2 / 15.7	73.2 / 26.8
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	- / -
Erythromycin	>2	>2	≤0.25 – >2	36.4 / 63.2	36.4 / 63.2
Clindamycin	≤0.25	>2	≤0.25 – >2	74.8 / 25.2	74.8 / 25.2
Levofloxacin	1	1	≤0.5 – >4	98.4 / 1.6	98.4 / 1.6
Trimethoprim/sulfamethoxazole	1	>2	≤0.5 – >2	46.6 / 30.8	58.7 / 30.8
Penicillin-resistant (MIC, ≥2 μg/mL)					
S. pneumoniae (249)					
CXL	0.25	0.5	0.06 – 0.5	- / -	- / -
Ceftriaxone	2	4	≤0.25 – 8	38.2 / 11.6	2.8 / 11.6
Cefuroxime	8	>8	≤1 – >8	0.8 / 97.6	0.8 / 99.2
Amoxicillin/clavulanate	8	16	≤1 – 16	14.5 / 74.7	- / -
Erythromycin	>2	>2	≤0.25 – >2	10.8 / 89.2	10.8 / 89.2
Clindamycin	>2	>2	≤0.25 – >2	29.7 / 69.5	30.5 / 69.5
Levofloxacin	1	1	≤0.5 – >4	98.4 / 1.6	98.4 / 1.6
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	10.8 / 88.8	11.2 / 88.8

a. Criteria as published by the CLSI [2010] and EUCAST [2009]; R = resistant and S = susceptible.
b. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)'.
c. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)'.

Conclusions

- Against the staphylococci and streptococci strains tested from USA medical centers in 2009, CXL was the most potent β-lactam agent tested
- CXL showed potent activity against both MRSA and penicillin-resistant *S. pneumoniae,* unlike other tested β-lactam agents
- Ceftaroline combined with a fixed concentration of 4 μg/mL of NXL104 represents a potential therapeutic option for the treatment of infections caused by staphylococci or streptococci while still possessing excellent Gram-negative activity.

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