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Activity of Ceftaroline Against Recent (2009) and Multidrug-resistant *Streptococcus pneumoniae* Isolates from Europe and the United States

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Amended Abstract

Objective: To determine the activity of ceftaroline against recent (2009) *S. pneumoniae* (SPN) and multidrug-resistant (MDR) SPN isolated in Europe and the United States (USA). Antimicrobial resistance in SPN and MDR-SPN are increasing globally and rapidly in some countries, including the USA. Ceftaroline is a novel, parenteral, broad-spectrum cephalosporin exhibiting bactericidal activity against Gram-positive organisms including SPN and MDR-SPN and is currently under review for approval in the USA.

Methods: Susceptibility testing for ceftaroline and commonly used antimicrobials was performed by CLSI broth microdilution methods on a total of 987 isolates from the 2009 Ceftaroline Surveillance Program. MDR-SPN status was determined by resistance to 3 or more classes of antimicrobials.

Results: Ceftaroline MIC_{50}, MIC_{90}, and MIC range (all mg/L) against all isolates and resistance phenotypes are listed in the Table. Ceftaroline was very active against all isolates with an MIC range of ≤0.008-0.5 mg/L, and MIC_{50} and MIC_{90} of ≤0.008 and 0.12 mg/L, respectively. MIC_{50} and MIC_{90} were slightly higher in drug-resistant SPN and MDR-SPN than in non-MDR-SPN isolates. The highest ceftaroline MIC found was 0.5 mg/L. MIC_{90} was two-fold higher in USA isolates than in European isolates due to the higher prevalence of MDR-SPN in the USA (21.5% vs. 14.2% in Europe). Ceftaroline was very active against isolates resistant to the commonly used antimicrobials penicillin, ceftriaxone, erythromycin, levofloxacin, trimethoprim/sulfamethoxazole (TMP/SMX), and tetracycline.

Abstract Table

	n	MIC_{50}	MIC_{90}	Range
All isolates	987	≤0.008	0.12	≤0.008-0.5
All Europe	485	≤0.008	0.12	≤0.008-0.5
All USA	502	0.015	0.25	≤0.008-0.5
MDR-SPN	177	0.12	0.25	≤0.008-0.5
Penicillin ≥4 mg/L	109	0.25	0.25	0.06-0.5
Ceftriaxone ≥2 mg/L	105	0.25	0.25	0.06-0.5
Erythromycin ≥2 mg/L	344	0.12	0.25	≤0.008-0.5
Levofloxacin ≥4 mg/L	11	0.06	0.25	≤0.008-0.25
TMP/SMX ≥4 mg/L	218	0.12	0.25	≤0.008-0.5
Tetracycline ≥8 mg/L	242	0.12	0.25	≤0.008-0.5

Conclusions: Antimicrobial resistance in SPN and MDR-SPN continues to escalate each year, highlighting the need for new antimicrobials. This study demonstrated the potent in vitro activity of ceftaroline against recent (2009) SPN isolates, regardless of MDR status, resistance phenotype, or geographic location (Europe or USA). These data suggest a potentially important clinical role for ceftaroline in the treatment of infections caused by SPN, including those strains resistant to commonly used antibiotics.

Introduction

Ceftaroline fosamil (formerly PPI-0903 and TAK-599) is an N-phosphonoamino water-soluble prodrug cephalosporin possessing extended-spectrum antimicrobial activity. Its bioactive form, ceftaroline, is released in vivo upon hydrolysis of the phosphonate group. Ceftaroline has bactericidal activity against Gram-positive pathogens as well as many Gram-negative bacilli. As a result of its high affinity for penicillin-binding proteins (PBPs) 1a, 2a, 2b, and 2x, ceftaroline demonstrates potent in vitro activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae* (MDR-SPN).

Ceftaroline is currently under review for approval in the United States (USA). Encouraging results have been reported from phase III complicated skin and skin structure infection (cSSSI), as well as community-acquired bacterial pneumonia (CABP), clinical studies. In the CABP trials, ceftaroline was efficacious for the treatment of pneumonia caused by Gram-positive pathogens, including *S. pneumoniae* (SPN) as well as common Gram-negative species, including *Haemophilus influenzae*.

Antimicrobial resistance in SPN continues to increase globally and at a rapid pace in some countries, including the USA. The present study was conducted to evaluate the comparative in vitro antimicrobial activity and spectrum of ceftaroline and other commonly used agents against recent (2009) SPN and MDR-SPN isolated in Europe and the USA.

Materials and Methods

Bacterial Isolates

A total of 987 nonduplicate clinically significant SPN isolates were consecutively collected in 2009. A total of 485 isolates from 24 medical centers in 9 European countries, Turkey, and Israel, and 502 isolates from 32 medical centers in the USA, were tested. Criteria for MDR-SPN included resistance to 3 or more classes of antimicrobials represented by penicillin, erythromycin, trimethoprim/sulfamethoxazole (TMP-SMX), tetracycline, and levofloxacin.

Susceptibility Testing

Broth microdilution methods were performed according to the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) to determine the antimicrobial susceptibility of each organism. Validated MIC panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA) were used. All strains were tested in cation-adjusted Mueller-Hinton (MH) broth supplemented with 2-5% lysed horse blood. Susceptibility percentage rates were based on the CLSI M100-S20 and EUCAST (2010) breakpoints. Concurrent testing of ATCC quality control (QC) strain SPN ATCC 49619 was performed, with all QC results within established ranges.

Results

- Ceftaroline was very active against all isolates with an MIC range of ≤0.008-0.5 mg/L, and MIC_{50} and MIC_{90} of ≤0.008 and 0.12 mg/L, respectively (Table 1). Activity was slightly lower against isolates from the USA (MIC_{90}, 0.25 mg/L) when compared with Europe (MIC_{90}, 0.12 mg/L). Ceftaroline had the greatest activity of all agents tested (Table 2)
- MDR-SPN prevalence was higher in the USA (21.5%, 108/502 isolates) than in Europe (14.2%, 69/485 isolates). A ceftaroline MIC_{90} of 0.25 mg/L was observed for the 177 MDR-SPN isolates
- Resistance rates were generally higher in the USA compared with Europe (Table 2): penicillin (23.3% vs 15.3%, respectively), erythromycin (44.4% vs 25.4%), clindamycin (24.0% vs 17.9%), TMP/SMX (30.5% vs 13.4%), levofloxacin (1.2% vs 0.4%). All isolates were susceptible to both linezolid (MIC range, ≤1 mg/L to 2 mg/L) and vancomycin (MIC range, ≤1 mg/L)
- Against the 109 penicillin nonsusceptible isolates (MIC, ≥4 mg/L), ceftaroline (MIC_{50} and MIC_{90}, 0.25 mg/L) was 16-fold more active than ceftriaxone (MIC_{50} and MIC_{90}, 4 mg/L; 26.6% susceptible) and cefepime (MIC_{50} and MIC_{90}, 2 mg/L; 18.3% susceptible). Furthermore, these isolates showed high rates of resistance to erythromycin (92.7%), clindamycin (82.6%), and TMP/SMX (96.3%) (Table 2)
- Ceftaroline demonstrated excellent activity against isolates resistant to erythromycin (MIC_{50} and MIC_{90}, 0.12 and 0.25 mg/L), levofloxacin (MIC_{50} and MIC_{90}, 0.06 and 0.25 mg/L), TMP/SMX (MIC_{50} and MIC_{90}, 0.12 and 0.25 mg/L), and tetracycline (MIC_{50} and MIC_{90}, 0.12 and 0.25 mg/L; Table 1).

Table 1. Frequency of Occurrence for Ceftaroline MIC Values Tested Against *S. pneumoniae* Stratified by Geographical Region and Resistance Phenotype or Subgroup

	No. (cumulative %) of isolates inhibited at ceftaroline MIC (mg/L):								
Subgroup (no. tested)	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	MIC_{50}	MIC_{90}
All isolates (987)	536 (54.3)	114 (65.9)	59 (71.8)	66 (78.5)	114 (90.1)	88 (99.0)	10 (100.0)	≤0.008	0.12
All Europe (485)	299 (61.7)	56 (73.2)	26 (78.6)	17 (82.1)	66 (95.7)	21 (100.0)	-	≤0.008	0.12
All USA (502)	237 (47.2)	58 (58.8)	33 (65.3)	49 (75.1)	48 (84.7)	67 (98.0)	10 (100.0)	0.015	0.25
MDR-SPN (177)	4 (2.3)	5 (5.1)	4 (7.3)	7 (11.3)	69 (50.3)	81 (96.1)	7 (100.0)	0.12	0.25
Penicillin ≥4 mg/L (109)	-	-	-	1 (0.9)	24 (22.9)	74 (90.8)	10 (100.0)	0.25	0.25
Ceftriaxone ≥2 mg/L (105)	-	-	-	1 (1.0)	28 (27.6)	66 (90.5)	10 (100.0)	0.25	0.25
Erythromycin ≥2 mg/L (344)	47 (13.7)	29 (22.1)	34 (32.0)	51 (46.8)	95 (74.4)	81 (97.8)	7 (100.0)	0.12	0.25
Levofloxacin ≥4 mg/L (11)	1 (9.1)	2 (27.3)	2 (45.5)	1 (54.6)	3 (81.8)	2 (100.0)	-	0.06	0.25
TMP/SMX ≥4 mg/L (218)	18 (8.3)	11 (13.3)	13 (19.3)	22 (29.4)	60 (56.9)	84 (95.4)	10 (100.0)	0.12	0.25
Tetracycline ≥8 mg/L (242)	23 (9.5)	21 (18.2)	25 (28.5)	28 (40.1)	67 (67.8)	73 (97.9)	5 (100.0)	0.12	0.25

MDR-SPN = multidrug-resistant *S. pneumoniae*; TMP/SMX = trimethoprim/sulfamethoxazole.

Table 2. Antimicrobial Activity of Ceftaroline and Comparator Agents Tested Against *S. pneumoniae*

Population (n)/Antimicrobial	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
All isolates (987)					
Ceftaroline	≤0.008	0.12	≤0.008 – 0.5	-[b] / -	- / -
Penicillin[c]	≤0.03	4	≤0.03 – >4	89.0 / 0.9	- / -
Penicillin[d]	≤0.03	4	≤0.03 – >4	64.0 / 19.4	64.0 / 11.0
Ceftriaxone	≤0.25	2	≤0.25 – 8	89.4 / 1.4	79.2 / 1.4
Cefepime	≤0.12	2	≤0.12 – 4	88.9 / 0.8	88.9 / 0.8
Erythromycin	≤0.25	>2	≤0.25 – >2	64.6 / 35.1	64.6 / 35.1
Clindamycin	≤0.25	>2	≤0.25 – >2	78.5 / 21.0	79.0 / 21.0
Levofloxacin	1	1	≤0.5 – >4	98.9 / 0.8	98.9 / 1.1
TMP/SMX[e]	≤0.5	>2	≤0.5 – >2	70.0 / 22.1	74.8 / 22.1
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤1 – 1	100.0 / -	100.0 / 0.0
USA isolates (502)					
Ceftaroline	0.015	0.25	≤0.008 – 0.5	- / -	- / -
Penicillin[c]	≤0.03	4	≤0.03 – >4	82.1 / 1.6	- / -
Penicillin[d]	≤0.03	4	≤0.03 – >4	56.4 / 23.3	56.4 / 17.9
Ceftriaxone	≤0.25	2	≤0.25 – 8	86.1 / 2.4	75.7 / 2.4
Cefepime	≤0.12	2	≤0.12 – 4	85.1 / 1.2	85.1 / 1.2
Erythromycin	≤0.25	>2	≤0.25 – >2	55.4 / 44.4	55.4 / 44.4
Clindamycin	≤0.25	>2	≤0.25 – >2	75.6 / 24.0	76.0 / 24.0
Levofloxacin	1	1	≤0.5 – >4	98.8 / 1.2	98.8 / 1.2
TMP/SMX	≤0.5	>2	≤0.5 – >2	61.6 / 30.5	65.3 / 30.5
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤1 – 1	100.0 / -	100.0 / 0.0
European isolates (485)					
Ceftaroline	≤0.008	0.12	≤0.008 – 0.25	- / -	- / -
Penicillin[c]	≤0.03	2	≤0.03 – 8	96.1 / 0.2	- / -
Penicillin[d]	≤0.03	2	≤0.03 – 8	72.0 / 15.3	72.0 / 3.9
Ceftriaxone	≤0.25	1	≤0.25 – 4	92.8 / 0.4	82.9 / 0.4
Cefepime	≤0.12	1	≤0.12 – 4	92.8 / 0.4	92.8 / 0.4
Erythromycin	≤0.25	>2	≤0.25 – >2	74.2 / 25.4	74.2 / 25.4
Clindamycin	≤0.25	>2	≤0.25 – >2	81.4 / 17.9	82.1 / 17.9
Levofloxacin	1	1	≤0.5 – >4	99.0 / 0.4	99.0 / 1.0
TMP/SMX	≤0.5	>2	≤0.5 – >2	78.7 / 13.4	84.7 / 13.4
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Vancomycin	≤1	≤1	≤1	100.0 / -	100.0 / 0.0
Penicillin-susceptible (≤2 mg/L) (878)					
Ceftaroline	≤0.008	0.12	≤0.008 – 0.25	- / -	- / -
Penicillin[c]	≤0.03	1	≤0.03 – 2	100.0 / 0.0	- / -
Penicillin[d]	≤0.03	1	≤0.03 – 2	72.0 / 9.3	72.0 / 0.0
Ceftriaxone	≤0.25	1	≤0.25 – 4	97.2 / 0.2	89.0 / 0.2
Cefepime	≤0.12	1	≤0.12 – 4	97.6 / 0.2	97.6 / 0.2
Erythromycin	≤0.25	>2	≤0.25 – >2	71.8 / 27.9	71.8 / 27.9
Clindamycin	≤0.25	>2	≤0.25 – >2	86.2 / 13.3	86.7 / 13.3
Levofloxacin	1	1	≤0.5 – >4	99.0 / 0.7	99.0 / 1.0
TMP/SMX	≤0.5	>2	≤0.5 – >2	78.4 / 12.9	83.8 / 12.9
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤1 – 1	100.0 / -	100.0 / 0.0
Penicillin nonsusceptible (≥4 mg/L) (109)					
Ceftaroline	0.25	0.25	0.06 – 0.5	- / -	- / -
Penicillin[c]	4	4	4 – >4	0.0 / 8.3	- / -
Penicillin[d]	4	4	4 – >4	0.0 / 100.0	0.0 / 100.0
Ceftriaxone	2	4	≤0.25 – 8	26.6 / 11.0	0.9 / 11.0
Cefepime	2	2	1 – 4	18.3 / 5.5	18.3 / 5.5
Erythromycin	>2	>2	≤0.25 – >2	7.3 / 92.7	7.3 / 92.7
Clindamycin	>2	>2	≤0.25 – >2	16.5 / 82.6	17.4 / 82.6
Levofloxacin	1	1	1 – >4	98.2 / 1.8	98.2 / 1.8
TMP/SMX	>2	>2	≤0.5 – >2	1.8 / 96.3	2.8 / 96.3
Linezolid	0.5	1	0.5 – 1	100.0 / -	100.0 / 0.0
Vancomycin	≤1	≤1	≤1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2010] and EUCAST [2010], for staphylococci only. β-lactam susceptibility should be directed by the oxacillin test results
b. - = No breakpoint has been established by CLSI or EUCAST
c. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)' (Susceptible ≤2 mg/L)
d. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)' (Susceptible ≤0.06 mg/L)
e. TMP/SMX = Trimethoprim/sulphamethoxazole

Conclusions

- The prevalence of antimicrobial resistance among SPN, including MDR isolates, was high among the collection of respiratory isolates from both the USA and Europe (higher in the USA than in Europe). These elevated rates highlight the need for new antimicrobials for respiratory infections such as CABP
- Ceftaroline demonstrated potent high activity against recent pneumococcal isolates, regardless of MDR status, resistance phenotype, or geographic location (Europe or USA)
- These data suggest a potentially important clinical role for ceftaroline in the treatment of infections caused by *S. pneumoniae,* including those strains resistant to β-lactams and other commonly used antimicrobials

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