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Antimicrobial Activity of Ceftaroline Tested against Drug-Resistant Subsets of *Streptococcus pneumoniae* from U.S. Medical Centers

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Streptococcus pneumoniae **isolates (6,958) were collected from patients at 163 U.S. medical centers during 2009 through 2012. Isolates were evaluated for multidrug resistance (MDR) to penicillin, ceftriaxone, erythromycin, tetracycline, trimethoprim-sulfamethoxazole, and levofloxacin. Ceftaroline was 16-fold more potent than ceftriaxone (MIC_{50}/MIC_{90}, ≤0.25/2 μg/ml) against all isolates. For MDR isolates (35.2% of tested strains), ceftaroline (MIC_{50}/MIC_{90}, 0.06/0.25 μg/ml; 100.0% susceptible) was the most active agent tested, being 8-fold more potent than ceftriaxone (MIC_{50}/MIC_{90}, 0.5/2 μg/ml) and 16-fold more potent than penicillin (MIC_{50}/MIC_{90}, 1/4 μg/ml).**

Ceftaroline fosamil is a parenteral prodrug which is rapidly hydrolyzed *in vivo* to release the active agent ceftaroline (1, 2). Ceftaroline displays broad-spectrum *in vitro* activity against *Staphylococcus aureus*, including methicillin-resistant strains (MRSA), *Streptococcus pneumoniae*, including multidrug-resistant (MDR) strains, and *Enterobacteriaceae* which do not produce extended-spectrum β-lactamases (ESBL) (3–13). Ceftaroline acts in the same manner as other β-lactams by inhibiting essential penicillin-binding proteins (PBPs); however, its affinity for altered PBPs (PBP2A in MRSA and PBP1A, -2B, and -2X in *S. pneumoniae*) allows it to be active against strains with elevated MICs to other β-lactams (14, 15).

The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) program monitors the activities of ceftaroline and comparator agents tested against pathogens causing either respiratory or skin and soft tissue infections (3, 6, 7, 16). The program is in its fifth year for the United States, providing longitudinal information on the antimicrobial activities of ceftaroline and comparator agents. In this report, we present an analysis of the activity of ceftaroline and comparators tested by reference methods against *S. pneumoniae* isolates collected during the 2009-2012 surveillance program, with an emphasis on the activity against resistant subsets (e.g., resistant to two or more antimicrobial classes).

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A total of 6,958 isolates were collected from patients in 163 U.S. medical centers. Respiratory tract pathogens were collected from patients with community-acquired and nosocomial respiratory tract infections (RTI). Isolates were submitted to the central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmatory identification and susceptibility testing. The majority of these isolates were from lower respiratory tract infections, with approximately 20% being from the upper respiratory tract (data not shown). Only isolates deemed clinically relevant by the submitting laboratory were included.

Broth microdilution tests were conducted at the central reference laboratory according to Clinical and Laboratory Standards Institute (CLSI) methods to determine susceptibility to ceftaroline and comparator antimicrobials (17). Validated MIC panels were manufactured by ThermoFisher Scientific (Cleveland, OH, USA). *S. pneumoniae* isolates were tested in cation-adjusted Mueller-Hinton broth supplemented with 2.5 to 5% lysed horse blood according to CLSI document M7-A09 (17). The quality control strain *S. pneumoniae* ATCC 49619 was tested concurrently with clinical isolates. Susceptibility determinations and quality control validation of results were based on CLSI guidelines (17, 18). The ceftaroline susceptibility breakpoint applied in this study was ≤0.5 μg/ml (CLSI and USA-FDA susceptibility breakpoint) (17–19).

Multidrug resistance (MDR) status was determined based on nonsusceptibility (NS) to the antimicrobial agents penicillin, ceftriaxone, levofloxacin, tetracycline, trimethoprim-sulfamethoxazole, and erythromycin. MDR isolates were defined as those that were NS to at least two of the above antimicrobial agents (MDR ≥ 2). Further analyses were done for *S. pneumoniae* isolates that tested as NS to at least three of the above (NS ≥ 3), four of the above (NS ≥ 4), and five of the above agents (NS ≥ 5).

The most frequently occurring NS phenotypic patterns are presented in Table 1. The most common pair of antimicrobials for which the NS phenotype was seen was erythromycin plus trimethoprim-sulfamethoxazole (1,866 occurrences) (Table 1). The most common combination of three antimicrobials for which the NS phenotype was seen was erythromycin plus tetracycline plus trimethoprim-sulfamethoxazole (1,401 occurrences), and that for four antimicrobials was penicillin plus erythromycin plus tetracycline plus trimethoprim-sulfamethoxazole (856 occurrences). The most common NS phenotype pattern for five antimicrobials was penicillin plus ceftriaxone plus erythromycin plus tetracycline plus trimethoprim-sulfamethoxazole (645 occurrences), and there were 13 occurrences of NS to all six antimicrobials evaluated.

Among the 6,958 *S. pneumoniae* isolates, 12.0% (831) were

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TABLE 1 Most frequently occurring non-drug-susceptible (NS) phenotype patterns

No. of drugs[a]	Most common pattern (no. of occurrences)[b]		
	First	Second	Third
Two	ERY + TMP/SMX (1,866)	ERY + TET (1,847)	TET + TMP/SMX (1,509)
Three	ERY + TET + TMP/SMX (1,401)	PEN + ERY + TMP/SMX (909)	PEN + ERY + TET (865)
Four	PEN + ERY + TET + TMP/SMX (856)	PEN + CRO + ERY + TMP/SMX (684)	CRO + ERY + TET + TMP/SMX (671)
Five	PEN + CRO + ERY + TET + TMP/SMX (645)	CRO + ERY + TET +TMP/SMX + LEV (14)	PEN + CRO + ERY + TET + LEV (13)
Six	PEN + CRO + ERY + TET + TMP/SMX + LEV (13)		

[a] Number of drugs to which isolates were nonsusceptible.
[b] Penicillin (PEN), ceftriaxone (CRO), levofloxacin (LEV), tetracycline (TET), trimethoprim-sulfamethoxazole (TMP/SMX), and erythromycin (ERY) were used to categorize multidrug resistance (six antimicrobial classes). Patterns are listed as most common (first), second most common, and third most common.

penicillin intermediate (Pen-I; MIC, 4 μg/ml) and 1.5% (106) were penicillin resistant (Pen-R; MIC, ≥8 μg/ml) (Table 2). A total of 10.8% (750) of all isolates were NS to ceftriaxone, with a MIC of ≥2 μg/ml (Table 2). For cefuroxime and amoxicillin/clavulanate, NS rates were 28.2 and 16.7%, respectively (Table 3). There was a high rate of resistance to erythromycin at 42.7%, and resistance to tetracycline, trimethoprim-sulfamethoxazole, and clindamycin ranged from 20.3 to 24.6% (Table 3). For the antimicrobials listed in Table 3, high rates of susceptibility were seen only for ceftaroline and levofloxacin (100.0 and 98.9%, respectively) (Table 3). Ceftaroline (MIC_{50}/MIC_{90}, ≤0.015/0.12 μg/ml) was 16-fold more potent than ceftriaxone (MIC_{50}/MIC_{90}, ≤0.25/2 μg/ml) and 64-fold more potent than cefuroxime (MIC_{50}/MIC_{90}, ≤2/8 μg/ml) (Table 3). A total of 66.0 and 100.0% of Pen-R isolates (MIC, ≥8 μg/ml) were inhibited by ceftaroline at ≤0.25 and ≤0.5 μg/ml, respectively (Table 2). Ceftaroline activity remained consistent through the study period, with a MIC_{50}/MIC_{90} for all *S. pneumoniae* isolates of ≤0.015/0.12 μg/ml, which varied only in 2009 (≤0.015/0.25 μg/ml) (data not shown). The percentage of *S. pneumoniae* isolates with the highest ceftaroline MICs, 0.5 μg/ml, ranged from 0.5 (2012) to 1.5% (2009). Limited variation in overall susceptibility occurred for other antimicrobials. Amoxicillin-clavulanate susceptibility by year ranged from 81.0 to 85.7%, erythromycin susceptibility ranged from 55.3 to 61.2%, clindamycin susceptibility ranged from 77.5 to 81.2%, and tetracycline susceptibility ranged from 73.8 to 75.7% (data not shown).

For MDR *S. pneumoniae* isolates (2,449 isolates), susceptibility to ceftaroline was 100.0%, whereas susceptibilities to penicillin (61.8%; MIC, ≤2 μg/ml [susceptibility breakpoint for parenteral nonmeningitis strains]), ceftriaxone (69.6%), and amoxicillin-clavulanate (58.0%) were markedly reduced (Table 3). Ceftaroline was the most active agent tested against MDR isolates, with a MIC_{50} and MIC_{90} of 0.06 and 0.25 μg/ml, respectively (Table 2). This was 8-fold more active than ceftriaxone (ceftriaxone MIC_{50}/MIC_{90}, 0.5/2 μg/ml) and 16-fold more potent than penicillin (penicillin MIC_{50}/MIC_{90}, 1/4 μg/ml) (Table 3). Only 16.5 and 61.8% of MDR isolates were inhibited at ≤0.06 and ≤2 μg/ml of penicillin, respectively, while 97.3 and 100.0% were inhibited at ≤0.25 and ≤0.5 μg/ml of ceftaroline, respectively (Table 2).

The subset of *S. pneumoniae* isolates that were NS to ≥3 drugs (1,509 strains) also exhibited 100.0% susceptibility to ceftaroline (Table 3). Susceptibility was further decreased for all other agents among the *S. pneumoniae* isolates that were NS to ≥3 drugs compared to the larger MDR group. For example, the proportion of strains susceptible to penicillin was 38.6% (MIC, ≤2 μg/ml [susceptibility breakpoint for parenteral nonmeningitis strains]), the proportion susceptible to ceftriaxone was 51.4%, and the proportion susceptible to amoxicillin-clavulanate was 35.3% (Table 3). Ceftaroline was the most active agent against *S. pneumoniae* isolates that were NS to ≥3 drugs, exhibiting a MIC_{50} and MIC_{90} of 0.12 and 0.25 μg/ml, respectively (Table 3), which were 8- and 16-fold more active than ceftriaxone (MIC_{50}/MIC_{90}, 1/2 μg/ml) and penicillin (MIC_{50}/MIC_{90}, 4/4 μg/ml), respectively (Table 3).

For *S. pneumoniae* isolates which were NS to ≥4 drugs (948 isolates) or ≥5 drugs (646 isolates), rates of susceptibility to ceftaroline remained at 100.0% (Table 3). Rates of susceptibility to the other antimicrobial agents, however were decreased as was noted previously for *S. pneumoniae* isolates when grouped as MDR or NS ≥3 (Table 3). Susceptibility in the NS ≥5 group was <10% for all agents except for ceftaroline (100.0%) and levofloxacin (97.8%) (Table 3).

In summary, ceftaroline demonstrated potent *in vitro* activity against a collection of contemporary *S. pneumoniae* isolates from U.S. medical centers, including isolates resistant to many commonly available antimicrobials, such as ceftriaxone. All *S. pneumoniae* isolates tested were susceptible to ceftaroline, but contin-

TABLE 2 Cumulative frequency of MIC distribution for ceftaroline tested against 6,958 *S. pneumoniae* isolates (United States, 2009 to 2012)

S. pneumoniae isolates (no.)[a]	No. (cumulative %) with a ceftaroline MIC (μg/ml) of:						MIC (μg/ml)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	50%	90%
Total (6,958)	4,224 (60.7)	591 (69.2)	612 (78.0)	992 (92.3)	473 (99.1)	66 (100.0)	≤0.015	0.12
Isolates with penicillin MIC of ≥8 μg/ml (106)			1 (0.9)	3 (3.8)	66 (66.0)	36 (100.0)	0.25	0.5
Isolates with penicillin MIC of 4 μg/ml (831)			6 (0.7)	407 (49.7)	390 (96.6)	28 (100.0)	0.25	0.25
Isolates with ceftriaxone MIC of ≥2 μg/ml (750)		2(0.3)	4 (0.8)	264 (36.0)	415 (91.3)	65 (100.0)	0.25	0.25
MDR isolates NS to ≥2 drugs (2,449)	548 (22.4)	274 (33.6)	431 (51.2)	661 (78.2)	469 (97.3)	66 (100.0)	0.06	0.25
Isolates NS to ≥3 drugs (1,509)	132 (8.7)	130 (17.4)	201 (30.7)	513 (64.7)	468 (95.7)	65 (100.0)	0.12	0.25
Isolates NS to ≥4 drugs (948)	6 (0.6)	3 (0.9)	17 (2.7)	397 (44.6)	461 (93.2)	64 (100.0)	0.25	0.25
Isolates NS to ≥5 drugs (646)			1 (0.2)	209 (32.5)	385 (92.1)	51 (100.0)	0.25	0.25

[a] MDR, multidrug resistant; NS, nonsusceptible (includes isolates that test as intermediate or resistant).

TABLE 3 *In vitro* activities of ceftaroline and comparator agents against *S. pneumoniae* (2009 to 2012)

Organism (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)		% S/% I/% R (CLSI)[a]
	50%	90%	
S. pneumoniae (6,958)			
Ceftaroline	≤0.015	0.12	100.0/—/—
Penicillin[b]	≤0.06	4	86.5/12.0/1.5
Penicillin[c]	≤0.06	4	57.3/22.0/20.7
Ceftriaxone	≤0.25	2	89.2/9.2/1.6
Cefuroxime	≤2	8	71.8/3.9/24.3
Amoxicillin-clavulanate	≤1	8	83.3/3.5/13.2
Erythromycin	≤0.25	>2	56.8/0.5/42.7
Clindamycin	≤0.25	>1	79.2/0.5/20.3
Tetracycline	≤2	>8	75.0/0.4/24.6
Trimethoprim-sulfamethoxazole	≤0.5	>2	65.9/9.5/24.6
Levofloxacin	1	1	98.9/0.1/1.0
Non-penicillin-susceptible (MIC, ≥8 μg/ml) isolates (106)			
Ceftaroline	0.25	0.5	100.0/—/—
Ceftriaxone	2	8	3.8/51.9/44.3
Cefuroxime	>8	>8	0.0/0.0/100.0
Amoxicillin-clavulanate	>8	>8	0.0/0.9/99.1
Erythromycin	>2	>2	0.0/0.0/100.0
Clindamycin	>1	>1	15.1/0.9/84.0
Tetracycline	>8	>8	10.4/0.0/89.6
Trimethoprim-sulfamethoxazole	>2	>2	0.0/0.9/99.1
Levofloxacin	1	1	99.1/0.0/0.9
Isolates NS to ≥2 drugs (2,449)			
Ceftaroline	0.06	0.25	100.0/—/—
Penicillin[b]	1	4	61.8/33.9/4.3
Penicillin[c]	1	4	16.5/35.8/44.7
Ceftriaxone	0.5	2	69.6/26.0/4.4
Cefuroxime	4	>8	37.9/7.9/54.2
Amoxicillin-clavulanate	≤1	8	58.0/4.7/37.3
Erythromycin	>2	>2	4.9/1.0/94.1
Clindamycin	>1	>1	43.2/0.5/56.3
Tetracycline	>8	>8	31.8/0.7/67.5
Trimethoprim-sulfamethoxazole	>2	>2	18.9/18.6/62.5
Levofloxacin	1	1	97.3/0.2/2.5
Isolates NS to ≥3 drugs (1,509)			
Ceftaroline	0.12	0.25	100.0/—/—
Penicillin[b]	4	4	38.6/54.4/7.0
Penicillin[c]	4	4	3.8/27.4/68.9
Ceftriaxone	1	2	51.4/41.6/7.0
Cefuroxime	8	>8	22.5/3.9/73.6
Amoxicillin-clavulanate	8	8	35.3/5.0/59.7
Erythromycin	>2	>2	0.8/0.5/98.7
Clindamycin	>1	>1	26.9/0.4/72.7
Tetracycline	>8	>8	12.2/0.4/87.4
Trimethoprim-sulfamethoxazole	>2	>2	1.7/17.3/81.0
Levofloxacin	1	1	96.1/0.4/3.6
Isolates NS to ≥4 drugs (948)			
Ceftaroline	0.25	0.25	100.0/—/—
Penicillin[b]	4	>4	4.9/84.0/11.1
Penicillin[c]	4	>4	0.4/1.7/97.9
Ceftriaxone	2	4	24.5/64.5/11.0
Cefuroxime	8	>8	1.4/0.3/98.3
Amoxicillin/clavulanate	8	>8	5.3/3.5/91.2
Erythromycin	>2	>2	0.3/0.1/99.6
Clindamycin	>1	>1	12.3/0.5/87.2
Tetracycline	>8	>8	6.5/0.4/93.1
Trimethoprim-sulfamethoxazole	>2	>2	0.4/1.7/97.9
Levofloxacin	1	1	96.3/0.3/3.4
Isolates NS to ≥5 drugs (646)			
Ceftaroline	0.25	0.25	100.0/—/—
Penicillin[b]	4	>4	0.2/85.1/14.7
Penicillin[c]	4	>4	0.0/0.0/100.0
Ceftriaxone	2	4	0.0/87.2/12.8
Cefuroxime	>8	>8	0.5/0.0/99.5
Amoxicillin-clavulanate	8	>8	1.1/2.2/96.7
Erythromycin	>2	>2	0.0/0.0/100.0
Clindamycin	>1	>1	8.5/0.3/91.2
Tetracycline	>8	>8	2.2/0.0/97.8
Trimethoprim-sulfamethoxazole	>2	>2	0.0/0.2/99.8
Levofloxacin	1	1	97.8/0.3/1.9

[a] Criteria published by the CLSI (18). S, susceptible; I, intermediate; R, resistant. —, no interpretive criteria defined for this category.
[b] Criteria published by the CLSI (18) for "penicillin parenteral non-meningitis" (S, ≤2 mg/liter; I, 4 mg/liter; R, ≥8 mg/liter).
[c] Criteria published by the CLSI (18) for "penicillin oral penicillin V" (S, ≤0.06 mg/liter; I, 0.12 to 1 mg/liter; R, ≥2 mg/liter).

ued surveillance is warranted to track the activity of ceftaroline and other important antimicrobial agents.

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