Evaluation of *In Vitro* Activity of Ceftaroline Tested against *Streptococcus pneumoniae* Isolates from United States Hospitals: Results from 7 Years of the AWARE Surveillance Program (2010–2016)

ID WEEK 2017

Poster #1239

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INTRODUCTION

- The epidemiology of *Streptococcus pneumoniae* in the US is constantly changing, requiring continuous monitoring of its antimicrobial resistance profile
- The superior activity of ceftaroline against *S. pneumoniae* isolates with elevated MICs to other β-lactams has been attributed to its affinity for altered penicillin binding protein targets (PBP-1A, -2B, and -2X) associated with β-lactam resistance
- Ceftaroline fosamil is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infection (ABSSSI) in adults and children 2 months of age and older, including ABSSSI caused by methicillin-resistant *Staphylococcus aureus* (MRSA)
- The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program has monitored ceftaroline activity against bacterial organisms in US medical centers since 2008
- The aim of this investigation is to describe the *in vitro* activity of ceftaroline and comparator agents against *S. pneumoniae*, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) isolates, collected from US medical centers participating in the AWARE Program from 2010 through 2016

MATERIALS AND METHODS

Bacterial isolates

- 8,768 *S. pneumoniae* isolates were collected from patients in 47 medical centers that participated in the AWARE Program during the entire investigation (2010–2016; 43 centers) or at least 6 of the 7 years (4 centers)
  - Only isolates deemed clinically relevant by the submitting laboratory were included (1 isolate per patient infection episode)
  - The isolates were from respiratory tract infections (81.0%), bloodstream infections (11.0%), and other infection types (8.0%)
  - Isolates were submitted to the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for identification, susceptibility testing, and molecular characterization, as needed

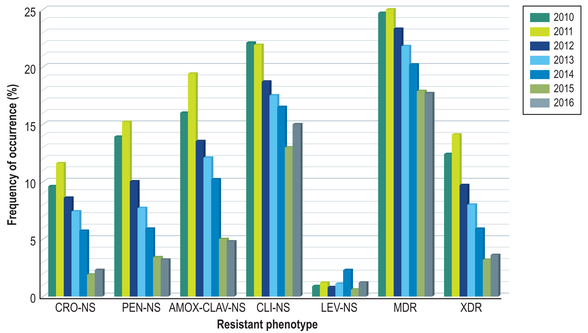
Antimicrobial susceptibility testing

- Broth microdilution tests were conducted at the central reference laboratory according to Clinical and Laboratory Standards Institute (CLSI) methods to determine the susceptibility to ceftaroline and comparator antimicrobial agents
  - Validated MIC panels were manufactured at JMI Laboratories (2015–2016) or by ThermoFisher Scientific (2010–2014) (Cleveland, Ohio, USA)
  - *S. pneumoniae* isolates were tested in cation-adjusted Mueller-Hinton broth supplemented with 2.5%–5% lysed horse blood according to CLSI document M07-A10
  - The quality control (QC) strain *S. pneumoniae* ATCC 49619 was tested concurrently with clinical isolates, and all results were within CLSI QC limits
  - The ceftaroline susceptibility breakpoint applied in this study was ≤0.5 mg/L as published by CLSI
- MDR status was determined based on nonsusceptibility (NS) to ≥3 classes of the following antimicrobial agents: penicillin (MIC, ≥4 mg/L), ceftriaxone (MIC, ≥2 mg/L), erythromycin (MIC, ≥0.5 mg/L), clindamycin (MIC, ≥0.5 mg/L), levofloxacin (MIC, ≥4 mg/L), tetracycline (MIC, ≥2 mg/L), and trimethoprim-sulfamethoxazole (TMP-SMX; MIC, ≥1 mg/L)
- XDR status was determined based on NS to ≥5 classes
- Further susceptibility analyses were performed for *S. pneumoniae* isolates that tested as NS to ceftriaxone, penicillin, amoxicillin-clavulanate, erythromycin, clindamycin, and levofloxacin

RESULTS

- Among the 8,768 *S. pneumoniae* isolates, MDR and XDR frequency decreased from 25.0% and 14.1% in 2011 to 17.7% and 3.6% in 2016, respectively (Figure 1)
- Susceptibility to penicillin, ceftriaxone, amoxicillin-clavulanic acid, clindamycin (Figure 1), trimethoprim-sulfamethoxazole (TMP-SMX), and tetracycline increased in the same period
- Ceftaroline was very active against the 8,768 *S. pneumoniae* ($MIC_{50/90}$, ≤0.015/0.12 mg/L) isolates: all but 1 isolate (>99.9% susceptible) were susceptible at the CLSI breakpoint of ≤0.5 mg/L (Table 1)
- The ceftaroline-NS isolate has been described previously and was MDR with an MIC value of 1 mg/L for ceftaroline, 8 mg/L for penicillin and ceftriaxone, 8 mg/L for erythromycin, >4 mg/L for TMP-SMX, >8 mg/L for amoxicillin-clavulanate, and 1 mg/L for meropenem
- Molecular characterization of the ceftaroline-NS isolate showed multiple substitutions in the penicillin binding proteins, mainly PBP2X, when compared with reference sequences and showed 31 amino acid alterations in MurM (Pfaller et al., 2017)
- For the antimicrobial agents listed in Table 1, high rates of susceptibility were seen with ceftaroline (>99.9%), ceftriaxone (93.1% susceptible at the non-meningitis breakpoint [≤1 mg/L]), penicillin (91.3%, susceptible at the parenteral non-meningitis breakpoint [≤2 mg/L]), levofloxacin (98.8%), linezolid (100.0%), tigecycline (99.9%), and vancomycin (100.0%)
- Ceftaroline retained activity against all drug-resistant (R) subsets, including 99.8% of ceftriaxone-NS isolates, 99.9% of penicillin-NS, and MDR isolates, and 100.0% of XDR isolates (Table 1)
  - Ceftaroline MIC values were slightly elevated for penicillin-R (MIC, ≥8 mg/L) isolates ($MIC_{50/90}$, 0.25/0.5 mg/L; 98.6% susceptible) (data not shown)
- Levofloxacin (96.9% and 95.8% susceptible), linezolid (100.0% and 100.0% susceptible), tigecycline (99.9% and 99.9% susceptible), and ceftaroline (99.9% and 100.0% susceptible) were the only agents with useful activity (>90% susceptible) against MDR and XDR isolates, respectively
- The activity of ceftaroline (99.9%–100.0%), levofloxacin (97.7%–99.4%), linezolid (100.0%), and tigecycline (99.5%–100.0%) was unchanged over the 7-year period (Table 2)
- The activity of all other comparators, except for erythromycin, showed steady improvement during the study (Table 2)

Figure 1. Yearly frequency of resistant phenotypes of *S. pneumoniae* in the AWARE Surveillance Program (2010–2016)



Abbreviations: CRO, ceftriaxone; NS, nonsusceptible; PEN, penicillin; AMOX-CLAV, amoxicillin-clavulanic acid; CLI, clindamycin; LEV, levofloxacin; MDR, multidrug-resistant; XDR, extensively drug-resistant.

CONCLUSIONS

- Ceftaroline was very active against *S. pneumoniae* from US medical centers, including MDR and XDR isolates and isolates NS to ceftriaxone and other antimicrobial agents commonly used to treat CABP
- The results of this investigation also indicate that antimicrobial susceptibility of *S. pneumoniae* improved in the 2010–2016 period in US medical centers participating in the AWARE program
- Ceftaroline has consistently retained potency against isolates obtained following its US clinical introduction
- Importantly, the *in vitro* data presented here confirm that the potency of ceftaroline against *S. pneumoniae* is higher than that exhibited by other β-lactams, including against isolate subsets exhibiting ceftriaxone-NS and MDR/XDR phenotypes

ACKNOWLEDGMENTS

The authors would like to thank all participants of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) program for providing bacterial isolates: Arkansas Children's Hospital (Little Rock, AR), Miller Children's Hospital (Long Beach, CA), University of Colorado Hospital (Aurora, CO), Sacred Heart Hospital (Pensacola, FL), Tampa General Hospital (Tampa, FL), Children's Healthcare of Atlanta (Atlanta, GA), Clinical Laboratories of Hawaii (Ewa Beach, HI), Iowa Methodist Medical Center (Des Moines, IA), Indiana University Health, Methodist Hospital (Indianapolis, IN), University of Louisville Hospital (Louisville, KY), University of Kentucky Hospital (Lexington, KY), VA Healthcare System of Boston (Boston, MA), Lahey Clinic (Burlington, MA), Henry Ford Health System (Detroit, MI), Children's Mercy Hospital (Kansas City, MO), Alegent-Creighton Laboratory (Omaha, NE), Robert Wood Johnson Medical School (New Brunswick, NJ), Columbia Presbyterian Medical Center (New York, NY), University of Rochester Medical Center (Rochester, NY), New York Presbyterian Hospital (New York, NY), Summa Health System (Akron, OH), University of Texas Medical School (Houston, TX), UTMB Health (Galveston, TX), University of Utah Medical Center (Salt Lake City, UT), University of Virginia Health System (Charlottesville, VA), Fletcher Allen Health Care (Burlington, VT), University of Washington Medical Center (Seattle, WA), Seattle Children's Hospital (Seattle, WA), and Children's Hospital of Wisconsin (Milwaukee, WI).

This study was supported by Allergan plc, Dublin, Ireland. Allergan was involved in the design and decision to present these results, and JMI Laboratories received compensation for services related to preparing the poster. Allergan had no involvement in the collection, analysis, and interpretation of data.

Table 1 Activity of ceftaroline and comparator antimicrobial agents when tested against *S. pneumoniae* isolates from US medical centers (2010–2016)

Antimicrobial agent (no. tested)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S[a]	%R[a]
All isolates (8,768)				
Ceftaroline	≤0.015	0.12	>99.9[b]	—
Ceftriaxone	≤0.06	1	93.1[c]	0.9
Penicillin	≤0.06	2	58.7[c]	16.3
			91.3[d]	0.8
Amoxicillin-clavulanate	≤1	4	88.1[b]	8.3
Meropenem	≤0.12	0.5	79.2	9.7
Clindamycin	≤0.25	>1	82.1	17.4
Erythromycin	≤0.12	>2	54.8	44.6
Levofloxacin	1	1	98.8	1.0
Linezolid	1	1	100.0	—
Tetracycline	≤0.5	>4	77.1	22.6
Tigecycline[e]	≤0.03	0.06	99.9[e]	—
TMP-SMX[f]	≤0.5	>4	77.1	22.6
Vancomycin	0.25	0.5	100.0	—
Ceftriaxone-nonsusceptible (MIC, ≥2 mg/L) (608)				
Ceftaroline	0.25	0.25	99.8[b]	—
Penicillin	4	>4	11.0[d]	11.5
Amoxicillin-clavulanate	>4	>4	6.6[b]	85.5
Meropenem	1	1	1.9	82.6
Clindamycin	>1	>1	17.3	82.6
Erythromycin	>2	>2	2.0	98.0
Tetracycline	>4	>4	12.0	87.8
TMP-SMX[f]	>4	>4	2.8	96.4
Penicillin-nonsusceptible (MIC, ≥4 mg/L) (766)				
Ceftaroline	0.12	0.25	99.9[b]	—
Ceftriaxone	2	2	29.4[b]	9.1
Amoxicillin-clavulanate	>4	>4	2.2[b]	89.8
Meropenem	1	1	0.4	86.0
Clindamycin	>1	>1	12.8	86.9
Erythromycin	>2	>2	0.8	99.2
Tetracycline	>4	>4	8.9	91.0
TMP-SMX[f]	>4	>4	0.0	100.0
Amoxicillin-clavulanate-nonsusceptible (MIC, ≥4 mg/L) (1,046)				
Ceftaroline	0.12	0.25	99.9[b]	—
Ceftriaxone	2	2	45.8[b]	6.7
Penicillin	4	4	0.4[c]	96.6
			28.5[d]	6.8
Meropenem	1	1	1.0	71.2
Clindamycin	>1	>1	27.9	71.5
Erythromycin	>2	>2	5.4	94.5
Tetracycline	>4	>4	23.7	76.1
TMP-SMX[f]	>4	>4	15.2	82.8
Erythromycin-nonsusceptible (MIC, ≥0.5 mg/L) (3,956)				
Ceftaroline	0.06	0.12	>99.9[b]	—
Ceftriaxone	0.25	2	84.9[b]	1.9
Penicillin	0.25	4	29.4[c]	32.3
			80.8[d]	1.8
Amoxicillin-clavulanate	≤1	>4	75.0[b]	18.2
Meropenem	≤0.12	1	59.6	21.1
Clindamycin	≤0.25	>1	60.6	38.3
Tetracycline	≤0.5	>4	52.0	47.6
TMP-SMX[f]	1	>4	45.7	37.4
Levofloxacin-nonsusceptible (MIC, ≥4 mg/L) (101)				
Ceftaroline	0.03	0.12	100.0[b]	—
Ceftriaxone	0.25	2	88.1[b]	2.0
Penicillin	0.25	4	37.6[c]	26.7
			89.1[d]	2.0
Amoxicillin-clavulanate	≤1	4	81.2[b]	9.9
Meropenem	≤0.12	1	72.3	10.6
Clindamycin	≤0.25	>1	58.4	39.6
Erythromycin	>2	>2	33.7	65.3
Tetracycline	>4	>4	46.5	53.5
TMP-SMX[f]	1	>4	49.5	38.6
MDR (1,907)				
Ceftaroline	0.12	0.25	99.9[b]	—
Ceftriaxone	1	2	69.0[b]	3.8
Penicillin	1	4	8.8[c]	49.5
			60.4[d]	3.7
Amoxicillin-clavulanate	2	>4	55.4[b]	37.3
Meropenem	0.5	1	46.8	39.0
Clindamycin	>1	>1	21.8	76.9
Erythromycin	>2	>2	0.1	99.6
Levofloxacin	1	1	96.9	2.8
Linezolid	0.5	1	100.0	—
Tetracycline	>4	>4	6.1	93.5
Tigecycline[e]	≤0.03	0.06	99.9	—
TMP-SMX[f]	4	>4	20.5	58.1
XDR (736)				
Ceftaroline	0.12	0.25	100.0[b]	—
Ceftriaxone	2	2	27.2[c]	8.3
Penicillin	4	4	0.1[c]	98.2
			5.6[d]	9.0
Amoxicillin-clavulanate	>4	>4	4.1[b]	87.8
Meropenem	1	1	1.6	84.6
Clindamycin	>1	>1	4.6	95.0
Erythromycin	>2	>2	0.0	100.0
Levofloxacin	1	1	95.8	3.8
Linezolid	0.5	1	100.0	—
Tetracycline	>4	>4	1.9	98.0
Tigecycline[e]	≤0.03	0.06	99.9	—
TMP-SMX[f]	>4	>4	0.3	98.8

[a] %S, % susceptible; %R, % resistant according to CLSI criteria
[b] Using non-meningitis breakpoints
[c] Using oral breakpoints
[d] Using parenteral, non-meningitis breakpoints
[e] Breakpoints from US FDA Package Insert
[f] TMP-SMX, trimethoprim-sulfamethoxazole

Table 2 Susceptibility of *S. pneumoniae* isolates over time to ceftaroline and comparators in the AWARE Program (2010–2016) [a,b]

	% susceptible (no. tested)							
Antibiotic	All years (8,768)	2010 (919)	2011 (1,755)	2012 (1,202)	2013 (1,333)	2014 (1,150)	2015 (1,237)	2016 (1,172)
Ceftaroline	>99.9	100.0	100.0	100.0	100.0	99.9	100.0	100.0
Ceftriaxone [c]	93.1	90.4	88.4	91.4	92.6	94.3	98.1	97.7
Penicillin [d]	91.3	86.1	84.8	90.0	92.3	94.1	96.6	96.8
Amox-clav	88.1	84.0	80.6	86.5	87.9	89.8	95.0	95.2
Meropenem	79.2	77.9	74.9	79.1	80.4	82.4	—	82.1
Clindamycin	82.1	77.9	78.1	81.3	82.5	83.5	87.0	85.0
Erythromycin	54.8	58.4	55.0	56.4	53.1	52.3	55.7	53.4
Levofloxacin	98.8	99.1	98.8	99.2	98.9	97.7	99.4	98.8
Linezolid	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Tetracycline	77.1	75.2	74.3	75.5	76.7	77.6	80.1	81.4
Tigecycline	99.9	100.0	99.9	100.0	99.9	100.0	99.8	99.5
TMP-SMX	68.1	65.9	64.4	66.1	67.0	69.5	73.5	71.3

[a] % susceptible according to CLSI criteria
[b] Abbreviations: Amox-clav, amoxicillin-clavulanic acid; TMP-SMX, trimethoprim-sulfamethoxazole
[c] Using non-meningitis breakpoints
[d] Using parenteral non-meningitis breakpoints

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