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Antimicrobial Activity of Ceftaroline Tested Against Bacteria Collected from Patients with Community-Acquired Respiratory Tract Infections (CARTI) in the USA (2008-2011) RN JONES, RK FLAMM, PR RHOMBERG, HS SADER JMI Laboratories, North Liberty, Iowa, USA

Abstract

Background: Ceftaroline is a broad-spectrum cephalosporin with bactericidal activity against Gram-positive and -negative pathogens causing CARTI, including MRSA, multidrug-resistant S. pneumoniae and β -lactamase-producing H. influenzae. The prodrug, ceftaroline fosamil, is USA-FDA-approved for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections.

Methods: Isolates were consecutively collected in 72 USA medical centers from patients with CARTI from 2008-2011. Ceftaroline and comparator antimicrobials were evaluated by CLSI broth microdilution methods. 5873 strains were tested. including 3077 S. pneumoniae (23.1% penicillinresistant [MIC, ≥2 µg/mL]; 11.1% ceftriaxone-nonsusceptible), 1540 H. influenzae (28.1% β-lactamase-producers), 190 H. parainfluenzae, 451 *M. catarrhalis*, and 615 *S. aureus* (45.0%) MRSA).

Results: Against penicillin-resistant S. pneumoniae, ceftaroline (MIC_{50/90}, 0.12/0.25 µg/mL; highest MIC, 0.5 µg/mL) was 8- to 32-fold more active than ceftriaxone (MIC_{50/90}, $1/2 \mu g/mL$; 52.8% susceptible), cefepime (MIC_{50/90}, 2/2 µg/mL; 49.5% susceptible) and amoxicillin/ clavulanate (MIC_{50/90}, 8/8 µg/mL; 22.5% susceptible). Ceftaroline was also active against ceftriaxone-non-susceptible S. pneumoniae (MIC_{50/90}, 0.25/0.5 µg/mL). The highest ceftaroline MIC among *H. influenzae* was 0.5 µg/mL (1 isolate) and activity against *H. influenzae* was not adversely affected by β -lactamase production. *H. parainfluenzae* (MIC_{50/90}, ≤0.015/0.03 µg/mL) and *M. catarrhalis* (MIC_{50/90}, 0.06/0.12 µg/mL) were very ceftaroline-susceptible. Ceftaroline was highly active against MRSA (MIC_{50/90}, 0.5/1 µg/mL) and 16-fold more active than ceftriaxone (MIC_{50/90}, 4/4 μ g/mL) when tested against MSSA (MIC_{50/90}, 0.25/0.25 μg/mL).

Conclusion: Ceftaroline exhibited potent *in vitro* activity against pathogens collected from CARTI patients in USA centers, including multidrugresistant *S. pneumoniae* and MRSA. Ceftaroline fosamil appears to be a valuable agent for contemporary treatment of CARTI. Clinical studies of resistant pathogens are needed.

Introduction

Ceftaroline is a broad-spectrum cephalosporin with in vitro bactericidal activity against Gram-positive and common Gram-negative pathogens causing communityacquired respiratory tract infections (CARTI), including methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant (MDR) Streptococcus pneumoniae and β -lactamase-producing *Haemophilus influenzae*.

The prodrug, ceftaroline fosamil, is approved by the United States Food and Drug Administration (USA-FDA) for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI). As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program, a global ceftaroline surveillance study, we evaluated the activity of ceftaroline against bacterial isolates collected from patients with CARTI in the USA in 2008–2011.

Methods

<u>Organism collection</u>: Isolates were consecutively collected in 72 USA medical centers from patients with CARTI in the 2008-2011 time period. A total of 5,873 organisms were evaluated, including 3,077 S. pneumoniae (23.1% penicillin-resistant [MIC, ≥2 µg/mL] and 11.1% ceftriaxone-non-susceptible), 1,540 *H. influenzae* (28.1% β-lactamase-producers), 190 H. parainfluenzae, 451 M. catarrhalis, and 615 S. aureus (45.0% MRSA).

Susceptibility testing methods: Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) documents were performed to determine antimicrobial susceptibility of ceftaroline and numerous comparator antimicrobials used to treat CARTI. Validated MIC panels were manufactured by ThermoFisher Scientific[®] (formerly TREK Diagnostics[®]; Cleveland, Ohio, USA). S. aureus strains were tested in cation-adjusted Mueller-Hinton broth (CA-MHB), β-hemolytic streptococci were tested in CA-MHB supplemented with 2.5-5% lysed horse blood, and Haemophilus spp. strains were tested in Haemophilus test medium (HTM) according to CLSI document M7-A09 (2012).

QC strains included: S. aureus ATCC 29213, S. pneumoniae ATCC 49619 and H. influenzae 49247. Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S22) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012). USA-FDA interpretive criteria for ceftaroline susceptibility were used when available.

Results

											n pau				iedical centers (20	00-2011).			
 Ceftaroline was the most potent of all β-lactams The highest ceftaroline MIC value and a statement of all β-lactams 									Organism/antimicrobial		MIC (µ	g/mL)	- CLSI ^a	EUCAST ^a	Organism/antimicrobial	MIC (µ	ug/mL)	– CLSI ^a	EUCAST ^a
	•	•		H. influenz				•	agent (no. tested)	MIC ₅₀	MIC ₉₀	Range	%S / %R	%S / %R	agent (no. tested)	MIC ₅₀ MIC ₉₀	Range	%S / %R	%S / %R
tested against <i>S. pneun</i>		,	00/00			10 (,	Streptococcus pneumoniae	(3,077)					β-lactamase positive (433)				
≤0.015/0.12 µg/mL). Th	0			ceftaroline		0			Ceftarolineb	≤0.015	0.12	≤0.015 – 0.5	98.8 / - (100.0 / -) ^b	- / -	Ceftarolineb	≤0.015 0.03	≤0.015 – 0.5	99.1 / - (100.0 / -) ^b	- / -
MIC value observed wa	•		-	adversely			•		Ceftriaxone	≤0.25	2	≤0.25 – 8	88.9/1.8	76.4 / 1.8	Ceftriaxone	≤0.25 ≤0.25		100.0 / -	99.8 / 0.2
Tables 1 and 2), 98.8%	susceptik	ole by USA	A-FDA	(Tables 1 a	and 2). Mo	ost compai	rator ager	nts	Cefepime Penicillinº	≤0.5 ≤0.06	2 4	≤0.5 - 4 ≤0.06 – >4	88.2 / 1.0 85.2 / 1.3	88.2 / 1.0 - / -	Penicillin Amoxicillin/clavulanate	>4 >4 ≤1 2	0.25 – >4 ≤1 – 8	- / - 99.8 / 0.2	- / - 88.2 / 11.8
breakpoint criteria (≤0.2	25 µg/mL)	and 100.0	0%	exhibited g	good activ	ity (>98%	susceptib	ility)	Penicillin ^d	≤0.06		≤0.06 ->4	55.1 / 23.1	55.1 / 14.8	Cefuroxime	≤1 2	≤1 – 8	99.3 / 0.0	81.8 / 2.5
susceptible by CLSI (Ju	une 2012)	breakpoir	nt	against H.	influenza	e, except o	clarithrom	ycin	Amoxicillin/clavulanate Cefuroxime	≤1 ≤1	8 8	≤1 – >8 ≤1 – >8	81.9 / 14.2 70.9 / 25.2	- / - 69.6 / 29.1	Meropenem Clarithromycin	≤0.12 ≤0.12 8 16	≤0.12 – 0.25 ≤0.25 – >32	100.0 / - 6.4 / 3.9	100.0 / 0.0 1.4 / 0.5
criteria (≤0.5 µg/mL)	,	•		(MIC _{50/90} , 8	3/16 µa/m	L: 77.5% s	susceptibi	litv) and	Erythromycin	≤0.12	8<	≤0.12 – >8	57.2 / 42.4	57.2 / 42.4	Azithromycin	1 2	≤0.23 - >32 ≤0.03 - >4	98.6 / -	0.5 - 1.4
(····· ,				trimethopr				• 1	Clindamycin	≤0.25	>1	≤0.25 – >1	78.1/21.4	78.6/21.4	Levofloxacin	≤0.5 ≤0.5	≤0.5	100.0/-	100.0/0.0
• Against S. pneumoniae	with pen	cillin MIC	of ≥2	MIC _{50/90} , ≤			•		Levofloxacin Moxifloxacin	1 ≤0.5	1 ≤0.5	≤0.5 – >4 ≤0.5 – 4	98.9 / 1.0 99.1 / 0.6	98.9 / 1.1 98.9 / 1.1	Moxifloxacin Tetracycline	≤0.5 ≤0.5 ≤2 ≤2	≤0.5 – 1 ≤2 – >8	100.0 / - 96.1 / 3.2	99.8 / 0.2 96.1 / 3.9
µg/mL (penicillin-resista	ant by CLS	SI breakpo	pint for		0.0/ × 2 µg/	, 70.07	0 3030001	.iomry,	Tetracycline	≤2	>8	≤2 – >8	74.4 / 25.3	74.2 / 25.6	TMP/SMX ^e	≤0.5 >2	≤0.5−>2	77.6 / 21.0	77.6 / 21.9
oral penicillin), ceftarolir	ne (MIC ₅₀	/90, 0.12/0	.25	Table 2)					TMP/SMX ^e Penicillin-resistant (≥2 μg/n	≤0.5 nl·712)	>2	≤0.5 – >2	64.3 / 26.9	69.2 / 26.9	Haemophilus parainfluenza			- / -	
µg/mL) was 8- to 64-fold	v 50	,50,		Ceftaroline	e was verv	v active ad	ainst S. a	ureus	Ceftaroline ^b	0.12	0.25	0.03 – 0.5	94.9 / -	- / -	Ceftarolineb	≤0.015 0.03		, (99.0 / -) ^b	- / -
					•	•			Ceftriaxone	1	0.20	≤0.25 – 8	(100.0 / -) ^ь 52.8 / 7.3	, 4.9 / 7.3	Ceftriaxone Amoxicillin/clavulanate	≤0.06 ≤0.06 ≤1 ≤1	≤0.06 – 0.5 ≤1 – 4	100.0 / - 100.0 / 0.0	-/-
				overall (MIC _{50/90} , 0.25/1 µg/mL; 97.9%					Cefepime	2	2	≤0.25 - 8 ≤0.5 - 4	49.5 / 4.3	4.977.3	Cefuroxime	≤0.5 1	≤1 – 4 ≤0.5 – 16	99.5 / 0.5	- / -
susceptible), cefepime (MIC _{50/90} , 2/2 µg/mL;				susceptible by CLSI [June 2012] and USA-FDA breakpoint criteria). When tested against					Amoxicillin/clavulanate	8	8	≤1 – >8	22.5 / 61.1	- / -	Meropenem	≤0.12 ≤0.12		100.0/-	- / -
49.5% susceptible) and amoxicillin/clavulanate				-			•		Cefuroxime Erythromycin	8 >8	>8 >8	≤1 – >8 ≤0.12 – >8	0.7 / 97.6 11.2 / 88.5	0.6 / 99.3 11.2 / 88.5	Clarithromycin Azithromycin	8 16 1 2	≤0.25 - >32 ≤0.06 - >4	75.3 / 3.2 98.9 / -	- / - - / -
(MIC _{50/90} , 8/8 µg/mL; 22.5% susceptible;				oxacillin- (/ I		(,·	Clindamycin	>1	>1	≤0.25 – >1	37.4 / 62.2	37.8 / 62.2	Levofloxacin	≤0.5 ≤0.5	≤0.5 – >4	97.4 / -	- / -
Table 2) cefta					(MIC ₅₀ ar	nd MIC ₉₀ , (0.25 µg/m	L) was	Levofloxacin Moxifloxacin	1 ≤0.5	1 ≤0.5	≤0.5 – >4 ≤0.5 – 4	98.6 / 1.1 99.0 / 1.0	98.6 / 1.4 98.9 / 1.1	Moxifloxacin	≤0.5 ≤0.5	≤0.5 – >4 ≤0.25 – >8	93.2 / - 92.1 / 5.8	- / -
		1		16-fold mo	re active	than ceftria	axone (MI	C_{50} and	Tetracycline	≤0.5 >8	≤0.5 >8	≤0.5 – 4 ≤2 – >8	99.07 1.0 34.6/65.4	34.4 / 65.4	Tetracycline TMP/SMX ^e	≤0.5 >4	≤0.25 <i>- ></i> 6 ≤0.5 - >4	92.175.8 78.9/18.9	- / - - / -
Ceftaroline was also ver	5	0		MIC ₉₀ , 4 μ	a/mL) and	l four- to e	iaht-fold n	nore	TMP/SMX ^e	>2	>2	≤0.5−>2	20.9 / 76.0	22.8 / 76.0	Moraxella catarrhalis (451)			,	
S. pneumoniae strains v	with penic	cillin MIC o	of ≥8		• /		0		Penicillin-resistant (≥8 µg/n				55.0 / -	,	Ceftarolineb	0.06 0.12	≤0.015 – 0.5	- / - (- / -) ^b	- / -
μ g/mL (penicillin-resistant by CLSI breakpoint for μ g/mL (penicillin-resistant breakpoint for μ g/mL (penicil										0.25	0.5	0.25 – 0.5	(100.0 / -) ^b	-/-	Amoxicillin/clavulanate	≤1 ≤1	≤1	100.0 / 0.0	100.0 / 0.0
penicillin parenteral, nonmeningitis). Ceftaroline									Ceftriaxone Cefepime	4 2	8 4	1 – 8 2 – 4	2.5 / 42.1 0.0 / 32.4	0.0 / 42.1 0.0 / 32.4	Ceftriaxone Cefuroxime	≤0.25 0.5 ≤1 2	≤0.25 – 2 ≤1 – >8	100.0 / - 99.6 / 0.2	99.6 / 0.0 77.2 / 1.3
MIC values ranged from 0.25 to 0.5 µg/mL									Amoxicillin/clavulanate	8	>8	8 ->8	0.0 / 100.0	- / -	Meropenem	≤0.12 0.12	≤0.12 – 0.12	- / -	100.0 / 0.0
C C				Ceftaroline	MIC valu	les ranger	$1 \text{ from } 0.2^{\circ}$	5 to 2	Cefuroxime Erythromycin	>8 >16	>8 >16	8 – >8 ≤0.06 - >16	0.0 / 100.0 2.5 / 97.5	0.0 / 100.0 2.5 / 97.5	Levofloxacin Moxifloxacin	≤0.5 ≤0.5 ≤0.5 ≤0.5	≤0.5 – 1 ≤0.5	100.0 / - - / -	100.0 / 0.0 100.0 / 0.0
(MIC ₅₀ , 0.25 µg/mL) and 55.0% were inhibited at • Ceftaroline MIC values ranged from 0.25 to 2 ceftaroline MIC of ≤ 0.25 µg/mL. Ceftaroline was µg/mL (MIC _{50/90} , 0.5/1 µg/mL) when tested									Clindamycin	>1	>1	≤0.25 – >1	17.5 / 80.0	20.0 / 80.0	Tetracycline	≤2 ≤2	≤2 – 8	99.8 / 0.2	99.8 / 0.2
	10				00/00				Levofloxacin Moxifloxacin	1 <0.5	1 ≤0.5	≤0.5 - >4 ≤0.5 – >4	97.5 / 2.5 97.5 / 2.5	97.5 / 2.5 97.5 / 2.5	TMP/SMX ^e Staphylococcus aureus (61)	≤0.5 ≤0.5 5)	≤0.5 – >2	95.3 / 2.2	95.3 / 2.9
eight- and 32-fold more active than ceftriaxone against MRSA. Although ceftaroline MIC values								Tetracycline	>8	>8	≤2 ->8	12.5 / 87.5	12.5 / 87.5	Ceftaroline ^b	0.25 1	0.06 – 2	97.9/-	- / -	
(MIC ₅₀ , 4 µg/mL) and amoxicillin/clavulanate were slightly higher (two- to four-fold) among							0	TMP/SMX ^e Ceftriaxone-non-susceptibl	>2 le (341)	>2	2->4	0.0 / 97.5	0.0 / 97.5	Ceftriaxone	4 >8	1->8	(97.9 / 0.0) ^b 53.3 / 45.0	, 55.0 / 45.0	
(MIC ₅₀ , 8 µg/mL), respectively, against this group MRSA compared to MSSA, its activity was							las		0.25	0.5	≤0.008 – 0.5	89.7 / -	-/-	Oxacillin	0.5 >2	≤0.25 - >2	55.0 / 45.0	55.0 / 45.0	
of MDR organisms (Table 2). Furthermore, considerably greater than other cephalosporins							sporins	Ceftriaxone	2	8	2-8	(100.0 / -) ^ь 0.0 / 15.8	, 0.0 / 15.8	Erythromycin Clindamycin	>2 >2 ≤0.25 >2	≤0.25 – >2 ≤0.25 – >2	38.0 / 60.2 76.7 / 23.1	38.4 / 61.1 76.1 / 23.3	
ceftaroline was highly active against ceftriaxone- tested against MRSA. Furthermore, ceftaroline						aroline	Cefepime	2	2	≤0.5 - 4	13.8 / 8.7)	0.07 10.0	Levofloxacin	≤0.5 >4	≤0.5 – >4	58.2 / 41.0	58.2/41.0		
non-susceptible S. pneumoniae (MIC _{50/90} , was slightly more potent than linezolid (MIC _{50/90} ,						MIC _{EO/OO} .	Amoxicillin/clavulanate Cefuroxime	8 \8	>8 \8	≤1 – >8 ≤0.12 – >8	5.3 / 89.7 0.9 / 98.5	- / - 0.6 / 99.1	TMP/SMX ^e Tetracycline	≤0.5 ≤0.5 <2 <2	≤0.5 – >2 ≤2 – >8	98.7 / 1.3 95.1 / 4.6	98.7 / 1.1 94.5 / 5.4		
$0.25/0.5 \ \mu\text{g/mL}$; 89.7% susceptible by USA-FDA $1/2 \ \mu\text{g/mL}$) and vancomycin (MIC _{50/90} , 1/1 $\mu\text{g/mL}$)						00/00	Erythromycin	>8	>8	≤0.12 – >8	2.6 / 97.4	2.6 / 97.4	Tigecycline ^f	0.06 0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0		
breakpoint criteria ($\leq 0.25 \ \mu$ g/ml) and 100.0% when tested against MRSA (Table 2)						, i µ9/iii_/	Clindamycin Levofloxacin	>1 1	>1 1	≤0.25 – >1 ≤0.5 – >4	15.0 / 84.5 98.2 / 1.2	15.5 / 84.5 98.2 / 1.8	Linezolid Vancomycin	1 2	0.5 – >8 ≤0.12 – 2	99.8 / 0.2 100.0 / 0.0	99.8 / 0.2 100.0 / 0.0		
•	,			when teste	su agamst		d D C Z		Moxifloxacin	≤0.5	≤0.5	≤0.5 – 4	99.1 / 0.9	98.8 / 1.2	Daptomycin	0.25 0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
susceptible by CLSI (Ju	,	•	•	The overa	ll MRSA ra	ate was 45	5.0% and	MRSA	Tetracycline TMP/SMX ^e	>8 >2	>8 >2	≤2 – >8 ≤0.5 – >2	12.6 / 87.4 2.1 / 97.4	12.3 / 87.4 2.3 / 97.4	MSSA (338)			100.0/-	
criteria (≤0.5 µg/mL; Tat	bles 1 and	a 2)		strains exh					Haemophilus influenzae (1,5		~2	⊒0.5 - 22	2.17 57.4	2.57 57.4	Ceftarolineb	0.25 0.25	0.06 – 0.5	(100.0 / 0.0) ^b	- / -
• H. parainfluenzae (MIC	<0 0	15/0 03 14		erythromy	0				Ceftarolineb	≤0.015	0.03	≤0.015 – 0.5	99.7 / - (100.0 / -) ^b	- / -	Ceftriaxone Erythromycin	4 4 ≤0.25 >2	1 – 8 ≤0.25 – >2	96.2 / 0.0 64.8 / 32.8	100.0 / 0.0 65.4 / 33.7
	00/00			, , , , , , , , , , , , , , , , , , ,	,			0	Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	99.6 / 0.4	Clindamycin	≤0.25 ≤0.25	≤0.25−>2	93.2 / 6.5	92.6 / 6.8
and <i>M. catarrhalis</i> (MIC	00/00	•••	,	and EUCA	•		•		Amoxicillin/clavulanate Cefuroxime	≤1 <1	≤1 2	≤1 – 8 ≤1 – >8	99.9 / 0.1 99.3 / 0.1	91.1 / 8.9 78.9 / 3.8	Levofloxacin TMP/SMX ^e	≤0.5 1 ≤0.5 ≤0.5	≤0.5 – >4 ≤0.5 – >2	90.2 / 9.2 99.4 / 0.6	90.2 / 9.2 99.4 / 0.6
were also very suscepti	ible to cet	taroline (I	ables	clindamyci	n (43.3%)	and levof	Ioxacin (1	9.8%;	Meropenem	 ≤0.12	∠ ≤0.12	≤0.12 – 0.5	100.0 / -	100.0 / 0.0	Tetracycline	≤2 ≤2	≤2 – >8	97.6 / 1.8	99.4 / 0.0 97.6 / 2.4
1 and 2)				Table 2).						8	16	≤0.25 – >32	77.5/3.3	1.5 / 1.0	Tigecycline ^f	0.06 0.25	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
-									Azithromycin Levofloxacin	0.5	2 0.5	≤0.03 - >4 ≤0.5 – 0.5	98.8 / - 100.0 / -	0.4 / 1.2 100.0 / 0.0	Linezolid Vancomycin	1 2	0.5 – 2 ≤0.12 – 2	100.0 / 0.0 100.0 / 0.0	100.0 / 0.0 100.0 / 0.0
			l against o	organisms	collected f	rom natier	nts with re	spiratory	Moxifloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	99.9 / 0.1	Daptomycin	0.25 0.5	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Table 1 Summary of cefta	roline act	ivitv tester	agamor	organionio				opilatory	TMP/SMX ^e Tetracycline	≤0.5 ≤2	>2 ≤2	≤0.5 – >2 ≤2 – >8	76.6 / 21.0 98.6 / 1.2	76.6 / 22.8 98.2 / 1.4	MRSA (277)			95.3 / -	,
Table 1. Summary of cefta									β-lactamase negative (1,10						Ceftaroline ^b	0.5 1	0.25 – 2	(95.3 / 0.0) ^b	- / -
Table 1. Summary of cefta tract infections in USA hos			2			a/mi) of:				<0 01E	≤0.015	≤0.015 – 0.12	100.0 / -	- / -	Ceftriaxone	>8 >8	4 – >8	0.0 / 100.0	0.01.000
tract infections in USA hos	spitals (20	008-2011).		lative % inhibited at		č ,	4		Ceftaroline ^b	≥0.015			(100.0 / - ¹⁰		Ervthromvcin	>2 >2	≤0.25 – >2	5.4 / 93 5	0.0 / 100.0 5.4 / 94.6
tract infections in USA hose Organism/subset (no. tested)	spitals (20 ≤0.015	0 08-2011). 0.03	0.06	0.12	0.25	0.5	1	2	Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	(100.0 / -) ^b 100.0 / -	99.5 / 0.5	Erythromycin Clindamycin	≤0.25 >2	≤0.25 - >2 ≤0.25 - >2	5.4 / 93.5 56.7 / 43.3	5.4 / 94.6 56.0 / 43.3
tract infections in USA hose Organism/subset (no. tested) S. pneumoniae (3,077)	spitals (20 ≤0.015 53.5	008-2011). 0.03 66.7	0.06 76.1	0.12 91.2	0.25	0.5	1	2	Ceftriaxone Amoxicillin/clavulanate	≤0.25 ≤1	≤0.25 ≤1 2	≤1 – 8	100.0 / - 99.9 / 0.1	99.5 / 0.5 92.2 / 7.8	Clindamycin Levofloxacin	≤0.25 >2 >4 >4	≤0.25 – >2 ≤0.5 – >4	56.7 / 43.3 19.1 / 79.8	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8
tract infections in USA hose Organism/subset (no. tested) S. pneumoniae (3,077) Penicillin-resistant at ≥2 µg/mL (712)	spitals (20 ≤0.015 53.5 -	0 08-2011). 0.03	0.06 76.1 3.9	0.12	0.25 98.8 94.9	0.5 100.0 100.0	-	-	Ceftriaxone Amoxicillin/clavulanate Cefuroxime Meropenem	≤0.25 ≤1 ≤1		≤1 – 8 ≤1 – >8 ≤0.12 – 0.5	100.0 / - 99.9 / 0.1 99.3 / 0.1 100.0 / -	99.5 / 0.5 92.2 / 7.8 77.8 / 4.3 100.0 / 0.0	Clindamycin Levofloxacin TMP/SMX ^e Tetracycline	≤0.25 >2 >4 >4 ≤0.5 ≤0.5 ≤2 ≤2	≤0.25 - >2 ≤0.5 - >4 ≤0.5 - >2 ≤2 - >8	56.7 / 43.3 19.1 / 79.8 97.8 / 2.2 92.1 / 7.9	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8 97.8 / 1.8 90.6 / 9.0
tract infections in USA hose Organism/subset (no. tested) S. pneumoniae (3,077) Penicillin-resistant at ≥2 µg/mL (712) Penicillin-resistant at ≥8 µg/mL (40)	spitals (20 ≤0.015 53.5 - -	0.03 66.7 0.4 -	0.06 76.1 3.9 -	0.12 91.2 61.9 -	0.25 98.8 94.9 55.0	0.5 100.0 100.0 100.0	1 - - -	2	Ceftriaxone Amoxicillin/clavulanate Cefuroxime Meropenem Clarithromycin	≤0.25 ≤1 ≤1	≤1 2	≤1 – 8 ≤1 – >8 ≤0.12 – 0.5 ≤0.25 - >2	100.0/- 99.9/0.1 99.3/0.1 100.0/- 77.9/3.1	99.5 / 0.5 92.2 / 7.8 77.8 / 4.3 100.0 / 0.0 15 / 0.6	Clindamycin Levofloxacin TMP/SMX ^e Tetracycline Tigecycline ^f	≤0.25 >2 >4 >4 ≤0.5 ≤0.5	$\leq 0.25 - >2$ $\leq 0.5 - >4$ $\leq 0.5 - >2$ $\leq 2 - >8$ $\leq 0.03 - 0.5$	56.7 / 43.3 19.1 / 79.8 97.8 / 2.2 92.1 / 7.9 100.0 / -	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8 97.8 / 1.8 90.6 / 9.0 100.0 / 0.0
tract infections in USA hose Organism/subset (no. tested) S. pneumoniae (3,077) Penicillin-resistant at ≥2 µg/mL (712) Penicillin-resistant at ≥8 µg/mL (40) Ceftriaxone-non-susceptible (341)	spitals (20 ≤0.015 53.5 - - 0.3	0.03 66.7 0.4 - 0.3	0.06 76.1 3.9 - 0.6	0.12 91.2 61.9 - 29.9	0.25 98.8 94.9 55.0 89.7	0.5 100.0 100.0 100.0 100.0	-	-	Ceftriaxone Amoxicillin/clavulanate Cefuroxime Meropenem	≤0.25 ≤1 ≤0.12 8 1 0.5	≤1 2	≤1 - 8 ≤1 - >8 ≤0.12 - 0.5 ≤0.25 - >2 ≤0.03 - >4 ≤0.5 - 0.5	100.0 / - 99.9 / 0.1 99.3 / 0.1 100.0 / -	99.5 / 0.5 92.2 / 7.8 77.8 / 4.3 100.0 / 0.0 15 / 0.6 0.4 / 1.2 100.0 / 0.0	Clindamycin Levofloxacin TMP/SMX ^e Tetracycline	$\leq 0.25 > 2$ >4 >4 $\leq 0.5 \leq 0.5$ $\leq 2 \leq 2$ 0.06 0.25 1 2 1 1	$\leq 0.25 - >2 \\ \leq 0.5 - >4 \\ \leq 0.5 - >2 \\ \leq 2 - >8 \\ \leq 0.03 - 0.5 \\ 0.5 - >8 \\ 0.5 - 2$	56.7 / 43.3 19.1 / 79.8 97.8 / 2.2 92.1 / 7.9 100.0 / - 99.6 / 0.4 100.0 / 0.0	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8 97.8 / 1.8 90.6 / 9.0 100.0 / 0.0 99.6 / 0.4 100.0 / 0.0
tract infections in USA hose Organism/subset (no. tested) S. pneumoniae (3,077) Penicillin-resistant at ≥2 µg/mL (712) Penicillin-resistant at ≥8 µg/mL (40)	spitals (20 ≤0.015 53.5 - -	0.03 66.7 0.4 -	0.06 76.1 3.9 -	0.12 91.2 61.9 -	0.25 98.8 94.9 55.0	0.5 100.0 100.0 100.0	- - -	- - -	Ceftriaxone Amoxicillin/clavulanate Cefuroxime Meropenem Clarithromycin Azithromycin Levofloxacin Moxifloxacin	≤0.25 ≤1 ≤0.12 8 1 0.5 ≤0.5	≤1 2 ≤0.12 16 2 0.5 0.5	$\leq 1 - 8$ $\leq 1 - > 8$ $\leq 0.12 - 0.5$ $\leq 0.25 - > 2$ $\leq 0.03 - > 4$ $\leq 0.5 - 0.5$ $\leq 0.5 - 0.5$	100.0 / - 99.9 / 0.1 99.3 / 0.1 100.0 / - 77.9 / 3.1 98.8 / - 100.0 / - 100.0 / -	99.5 / 0.5 92.2 / 7.8 77.8 / 4.3 100.0 / 0.0 15 / 0.6 0.4 / 1.2 100.0 / 0.0 100.0 / 0.0	Clindamycin Levofloxacin TMP/SMX ^e Tetracycline Tigecycline ^f Linezolid	≤0.25 >2 >4 >4 ≤0.5 ≤0.5 ≤2 ≤2	$\leq 0.25 - >2 \\ \leq 0.5 - >4 \\ \leq 0.5 - >2 \\ \leq 2 - >8 \\ \leq 0.03 - 0.5 \\ 0.5 - >8 \end{cases}$	56.7 / 43.3 19.1 / 79.8 97.8 / 2.2 92.1 / 7.9 100.0 / - 99.6 / 0.4	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8 97.8 / 1.8 90.6 / 9.0 100.0 / 0.0 99.6 / 0.4
tract infections in USA hose Organism/subset (no. tested) S. pneumoniae (3,077) Penicillin-resistant at ≥2 μg/mL (712) Penicillin-resistant at ≥8 μg/mL (40) Ceftriaxone-non-susceptible (341) H. influenzae (1540)	spitals (20 ≤0.015 53.5 - - 0.3 88.5	0.03 66.7 0.4 - 0.3 96.7	0.06 76.1 3.9 - 0.6 99.1	0.12 91.2 61.9 - 29.9 99.7	0.25 98.8 94.9 55.0 89.7 99.9	0.5 100.0 100.0 100.0 100.0 100.0	- - -		Ceftriaxone Amoxicillin/clavulanate Cefuroxime Meropenem Clarithromycin Azithromycin Levofloxacin	≤0.25 ≤1 ≤0.12 8 1 0.5	≤1 2 ≤0.12 16 2 0.5	≤1 - 8 ≤1 - >8 ≤0.12 - 0.5 ≤0.25 - >2 ≤0.03 - >4 ≤0.5 - 0.5	100.0/- 99.9/0.1 99.3/0.1 100.0/- 77.9/3.1 98.8/- 100.0/-	99.5 / 0.5 92.2 / 7.8 77.8 / 4.3 100.0 / 0.0 15 / 0.6 0.4 / 1.2 100.0 / 0.0	Clindamycin Levofloxacin TMP/SMX ^e Tetracycline Tigecycline ^f Linezolid Vancomycin	$\leq 0.25 > 2$ >4 >4 $\leq 0.5 \leq 0.5$ $\leq 2 \leq 2$ 0.06 0.25 1 2 1 1	$\leq 0.25 - >2 \\ \leq 0.5 - >4 \\ \leq 0.5 - >2 \\ \leq 2 - >8 \\ \leq 0.03 - 0.5 \\ 0.5 - >8 \\ 0.5 - 2$	56.7 / 43.3 19.1 / 79.8 97.8 / 2.2 92.1 / 7.9 100.0 / - 99.6 / 0.4 100.0 / 0.0	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8 97.8 / 1.8 90.6 / 9.0 100.0 / 0.0 99.6 / 0.4 100.0 / 0.0
tract infections in USA hose Organism/subset (no. tested) S. pneumoniae (3,077) Penicillin-resistant at $\geq 2 \mu g/mL$ (712) Penicillin-resistant at $\geq 8 \mu g/mL$ (40) Ceftriaxone-non-susceptible (341) H. influenzae (1540) β -lactamase-positive (433)	spitals (20 ≤0.015 53.5 - 0.3 88.5 73.9	0.03 66.7 0.4 - 0.3 96.7 90.3	0.06 76.1 3.9 - 0.6 99.1 97.0	0.12 91.2 61.9 - 29.9 99.7 99.1	0.25 98.8 94.9 55.0 89.7 99.9 99.8	0.5 100.0 100.0 100.0 100.0 100.0 100.0	- - - -	- - - - -	Ceftriaxone Amoxicillin/clavulanate Cefuroxime Meropenem Clarithromycin Azithromycin Levofloxacin Moxifloxacin Tetracycline TMP/SMX ^e a. Criteria as published by	≤0.25 ≤1 ≤0.12 8 1 0.5 ≤0.5 ≤2 ≤0.5	≤1 2 ≤0.12 16 2 0.5 0.5 ≤2 >2 [2012] ar	$\leq 1 - 8$ $\leq 1 - > 8$ $\leq 0.12 - 0.5$ $\leq 0.25 - > 2$ $\leq 0.03 - > 4$ $\leq 0.5 - 0.5$ $\leq 0.5 - 0.5$ $\leq 2 - > 8$ $\leq 0.5 - > 2$ and EUCAST [20]	100.0/- 99.9/0.1 99.3/0.1 100.0/- 77.9/3.1 98.8/- 100.0/- 100.0/- 99.5/0.5 76.2/21.0	99.5 / 0.5 92.2 / 7.8 77.8 / 4.3 100.0 / 0.0 15 / 0.6 0.4 / 1.2 100.0 / 0.0 100.0 / 0.0 99.1 / 0.5 76.2 / 23.1	Clindamycin Levofloxacin TMP/SMX ^e Tetracycline Tigecycline ^f Linezolid Vancomycin Daptomycin	$\leq 0.25 > 2$ >4 >4 $\leq 0.5 \leq 0.5$ $\leq 2 \leq 2$ 0.06 0.25 1 2 1 1 0.25 0.5	$\leq 0.25 - >2$ $\leq 0.5 - >4$ $\leq 0.5 - >2$ $\leq 2 - >8$ $\leq 0.03 - 0.5$ 0.5 - 8 0.5 - 2 0.12 - 1	56.7 / 43.3 19.1 / 79.8 97.8 / 2.2 92.1 / 7.9 100.0 / - 99.6 / 0.4 100.0 / 0.0 100.0 / -	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8 97.8 / 1.8 90.6 / 9.0 100.0 / 0.0 99.6 / 0.4 100.0 / 0.0
tract infections in USA hoseOrganism/subset (no. tested)S. pneumoniae (3,077)Penicillin-resistant at $\geq 2 \ \mu g/mL$ (712)Penicillin-resistant at $\geq 8 \ \mu g/mL$ (40)Ceftriaxone-non-susceptible (341)H. influenzae (1540) β -lactamase-positive (433)H. parainfluenzae (190)	spitals (20) ≤0.015 53.5 - 0.3 88.5 73.9 83.7	0.03 66.7 0.4 - 0.3 96.7 90.3 92.6	0.06 76.1 3.9 - 0.6 99.1 97.0 94.7	0.12 91.2 61.9 - 29.9 99.7 99.1 96.8	0.25 98.8 94.9 55.0 89.7 99.9 99.8 97.9	0.5 100.0 100.0 100.0 100.0 100.0 100.0 99.0	- - - -	- - - - - 100.0	Ceftriaxone Amoxicillin/clavulanate Cefuroxime Meropenem Clarithromycin Azithromycin Levofloxacin Moxifloxacin Tetracycline TMP/SMX ^e a. Criteria as published by b. USA-FDA breakpoints v	≤0.25 ≤1 ≤0.12 8 1 0.5 ≤0.5 ≤2 ≤0.5 r the CLSI were applie	≤1 2 ≤0.12 16 2 0.5 0.5 ≤2 >2 [2012] ar ed when	$\leq 1 - 8$ $\leq 1 - > 8$ $\leq 0.12 - 0.5$ $\leq 0.25 - > 2$ $\leq 0.03 - > 4$ $\leq 0.5 - 0.5$ $\leq 0.5 - 0.5$ $\leq 2 - > 8$ $\leq 0.5 - > 2$ and EUCAST [20] available [Tefla	100.0 / - 99.9 / 0.1 99.3 / 0.1 100.0 / - 77.9 / 3.1 98.8 / - 100.0 / - 100.0 / - 99.5 / 0.5 76.2 / 21.0 12]. ro® Product Ins	99.5 / 0.5 92.2 / 7.8 77.8 / 4.3 100.0 / 0.0 15 / 0.6 0.4 / 1.2 100.0 / 0.0 100.0 / 0.0 99.1 / 0.5 76.2 / 23.1	Clindamycin Levofloxacin TMP/SMX ^e Tetracycline Tigecycline ^f Linezolid Vancomycin	$\leq 0.25 > 2$ >4 >4 $\leq 0.5 \leq 0.5$ $\leq 2 \leq 2$ 0.06 0.25 1 2 1 1 0.25 0.5	$\leq 0.25 - >2$ $\leq 0.5 - >4$ $\leq 0.5 - >2$ $\leq 2 - >8$ $\leq 0.03 - 0.5$ 0.5 - 8 0.5 - 2 0.12 - 1	56.7 / 43.3 19.1 / 79.8 97.8 / 2.2 92.1 / 7.9 100.0 / - 99.6 / 0.4 100.0 / 0.0 100.0 / -	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8 97.8 / 1.8 90.6 / 9.0 100.0 / 0.0 99.6 / 0.4 100.0 / 0.0
tract infections in USA hoseOrganism/subset (no. tested)S. pneumoniae (3,077)Penicillin-resistant at $\geq 2 \ \mu g/mL$ (712)Penicillin-resistant at $\geq 8 \ \mu g/mL$ (40)Ceftriaxone-non-susceptible (341)H. influenzae (1540) β -lactamase-positive (433)H. parainfluenzae (190)M. catarrhalis (451)	spitals (20) ≤0.015 53.5 - 0.3 88.5 73.9 83.7 15.1	0.03 66.7 0.4 - 0.3 96.7 90.3 92.6	0.06 76.1 3.9 - 0.6 99.1 97.0 94.7 74.9	0.12 91.2 61.9 - 29.9 99.7 99.1 96.8 96.9	0.25 98.8 94.9 55.0 89.7 99.9 99.8 97.9 99.3	0.5 100.0 100.0 100.0 100.0 100.0 99.0 100.0	- - - - 99.5 -	- - - - - 100.0 -	Ceftriaxone Amoxicillin/clavulanate Cefuroxime Meropenem Clarithromycin Azithromycin Levofloxacin Moxifloxacin Tetracycline TMP/SMX ^e a. Criteria as published by	≤ 0.25 ≤ 1 ≤ 0.12 8 1 0.5 ≤ 0.5 ≤ 2 ≤ 0.5 The CLSI were applied the CLSI the CLSI the CLSI	≤1 2 ≤0.12 16 2 0.5 0.5 ≤2 >2 [2012] ar ed when [2012] fo [2012] fo	$\leq 1 - 8$ $\leq 0.12 - 0.5$ $\leq 0.25 - >2$ $\leq 0.03 - >4$ $\leq 0.5 - 0.5$ $\leq 0.5 - 0.5$ $\leq 2 - >8$ $\leq 0.5 - >2$ available [Tefla or 'Penicillin pare or 'Penicillin (ora	100.0 / - 99.9 / 0.1 99.3 / 0.1 100.0 / - 77.9 / 3.1 98.8 / - 100.0 / - 99.5 / 0.5 76.2 / 21.0 12]. ro [®] Product Insenteral (non-me	99.5 / 0.5 92.2 / 7.8 77.8 / 4.3 100.0 / 0.0 15 / 0.6 0.4 / 1.2 100.0 / 0.0 100.0 / 0.0 99.1 / 0.5 76.2 / 23.1	Clindamycin Levofloxacin TMP/SMX ^e Tetracycline Tigecycline ^f Linezolid Vancomycin Daptomycin	$\leq 0.25 > 2$ >4 >4 $\leq 0.5 \leq 0.5$ $\leq 2 \leq 2$ 0.06 0.25 1 2 1 1 0.25 0.5	$\leq 0.25 - >2$ $\leq 0.5 - >4$ $\leq 0.5 - >2$ $\leq 2 - >8$ $\leq 0.03 - 0.5$ 0.5 - 8 0.5 - 2 0.12 - 1	56.7 / 43.3 19.1 / 79.8 97.8 / 2.2 92.1 / 7.9 100.0 / - 99.6 / 0.4 100.0 / 0.0 100.0 / -	5.4 / 94.6 56.0 / 43.3 19.1 / 79.8 97.8 / 1.8 90.6 / 9.0 100.0 / 0.0 99.6 / 0.4 100.0 / 0.0

Table 2. Activity of ceftaroline and comparator antimicrobial agents when tested against 5,873 bacterial isolates collected from patients with CARTI in USA medical centers (2008-2011).

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Conclusions

- Ceftaroline exhibited potent in vitro activity against pathogens collected from CARTI patients in USA centers as a part of the AWARE surveillance program in 2008-2011
- Ceftaroline was highly active in vitro against S. pneumoniae (MIC₉₀, 0.12 μ g/mL), including isolates with high-level penicillin resistance (pencillin MIC, $\geq 8 \mu g/mL$) and those non-susceptible to ceftriaxone (highest MIC, 0.5 µg/mL)
- Ceftaroline was also very active in vitro against S. aureus (MIC₉₀, 1 μ g/mL), including MRSA strains (highest MIC, 2 µg/mL)
- The results of this study confirm the potent in vitro activity of ceftaroline against resistant respiratory pathogens; additional clinical studies of ceftaroline fosamil in treating infections by resistant CABP pathogens are warranted.

References

- Clinical and Laboratory Standards Institute (2012). M07-A9. Methods for lilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition. Wayne, PA: CLSI.
- Clinical and Laboratory Standards Institute (2012). M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement. Wayne, PA: CLSI.
- European Committee on Antimicrobial Susceptibility Testing (2012). Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0, January 2012. Available at:
- http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2012. 4. Farrell DJ, Castanheira M, Mendes RE, Sader HS, Jones RN (2012). In vitro activity of ceftaroline against multidrug-resistant Staphylococcus aureus and Streptococcus pneumoniae: A review of published studies and the AWARE surveillance program (2008-2010). Clin Infect Dis 55 Suppl 3: S206-S214.
- 5. 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.
- 6. Jones RN, Farrell DJ, Mendes RE, Sader HS (2011). Comparative ceftaroline activity tested against pathogens associated with communityacquired pneumonia: Results from an international surveillance study. J Antimicrob Chemother 66 Suppl 3: iii69-iii80.
- Pfaller MA, Farrell DJ, Sader HS, Jones RN (2012). AWARE ceftaroline surveillance program (2008-2010): Trends in resistance patterns among Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis in the United States. Clin Infect Dis 55 Suppl 3: S187-S193.
- 8. Teflaro[®] Package Insert (2012). Available at http://www.frx.com/pi/Teflaro_pi.pdf. Accessed June 2012.
- 9. Tygacil[®] Package Insert (2011). Available at <u>www.tygacil.com</u>. Accessed June 2012.

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