

In vitro Activity of Ceftaroline Against Skin and Soft Tissue and Respiratory Pathogens Isolated from Latin America

D. Biedenbach¹, Meredith Hackel¹, J. Iaconis², D. Sahn¹
¹IHMA, Inc., Schaumburg, IL, USA
²AstraZeneca Pharmaceuticals, Waltham, MA, USA

IHMA, Inc.
 2122 Palmer Drive
 Schaumburg, IL 60173 USA
 Phone: +1.847.303.5003
 Fax: +1.847.303.5601
 www.ihmainc.com

Abstract

Background: Ceftaroline is a cephalosporin with *in vitro* activity against both gram-positive and gram-negative pathogens, including methicillin-resistant *S. aureus* (MRSA). This analysis was conducted to evaluate the activity of this compound against key bacterial groups collected from Latin America. **Methods:** ESBL-negative *Enterobacteriaceae*, *S. aureus* (MSSA and MRSA), and *S. pneumoniae* from skin and soft tissue and respiratory specimens were collected during 2012 – 2014 from across six countries. The identification of all organisms was confirmed centrally by MALDI-TOF and broth microdilution susceptibility testing and interpretation was performed according to CLSI M100 and M7 guidelines. **Results:** Ceftaroline activity was recorded based on % susceptibility (%S) and MIC₉₀ in the table provided. Against *S. aureus*, all MSSA were susceptible (MIC ≤ 1 mg/ml), only one MRSA isolate (from Venezuela) was resistant with a MIC of 4 mg/ml.; all other non-susceptible MRSA isolates were intermediate with a MIC of 2 mg/ml.

Table 1. In vitro Activity of Ceftaroline

	Argentina		Brazil		Chile		Colombia		Mexico		Venezuela	
	n	%SMIC ₉₀	n	%SMIC ₉₀	n	%SMIC ₉₀	n	%SMIC ₉₀	n	%SMIC ₉₀	n	%SMIC ₉₀
<i>S. aureus</i> , MRSA	474	93.0†	144	79.2	393	29.5	115	95.7	505	98.4†	418	90.4†
<i>S. aureus</i> , MSSA	773	100.0	150	100.0	313	100.0	263	100.0	338	100.0	281	100.0
<i>S. pneumoniae</i>	110	100.0	13	100.0	84	100.0	18	100.0	83	100.0	62	100.0
ESBL-negative <i>Enterobacteriaceae</i>	247	88.4	114	88.8	157	87.3	120	89.2	401	90.3	255	91.8

Conclusions: Based on these data generated with isolates collected from 2012 - 2014 ceftaroline continued to exhibit potent *in vitro* activity against the major bacterial species associated with skin and soft tissue infections and respiratory infections in Latin America. Nearly all non-susceptibility among MRSA to ceftaroline was due to isolates being intermediate with MICs of 2 mg/ml.

Introduction

Ceftaroline, the active metabolite of ceftaroline-foamil, is a cephalosporin developed for treating infections caused by *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), *S. pneumoniae*, β-hemolytic streptococci, and some gram-negative pathogens. This summarizes the *in vitro* activity of ceftaroline against clinically relevant isolates collected from skin and soft tissue infections (SSTI) and respiratory infections in 2012-2014 from Latin American countries.

Materials & Methods

- A total of 5,231 isolates were collected from patients with SSTI or respiratory infections in six countries in Latin America as part of the AWARE Surveillance Program during 2012-2014. Countries included (n): Argentina (1,104), Brazil (421), Chile (947), Colombia (416), Mexico (1,327) and Venezuela (1,016).
- Confirmation of isolate identification using MALDI-TOF mass spectroscopy (*S. pneumoniae* was identified by conventional methods) and antibiotic susceptibility testing was performed at a central laboratory (IHMA, Inc., Schaumburg, IL).
- Antimicrobial susceptibility testing was done by broth microdilution following CLSI guidelines [1]. CLSI interpretive guidelines were applied to define susceptibility [2].
- E. coli*, *K. pneumoniae*, and *K. oxytoca* were screened and confirmed for extended-spectrum β-lactamase (ESBL) activity according to CLSI guidelines [2].

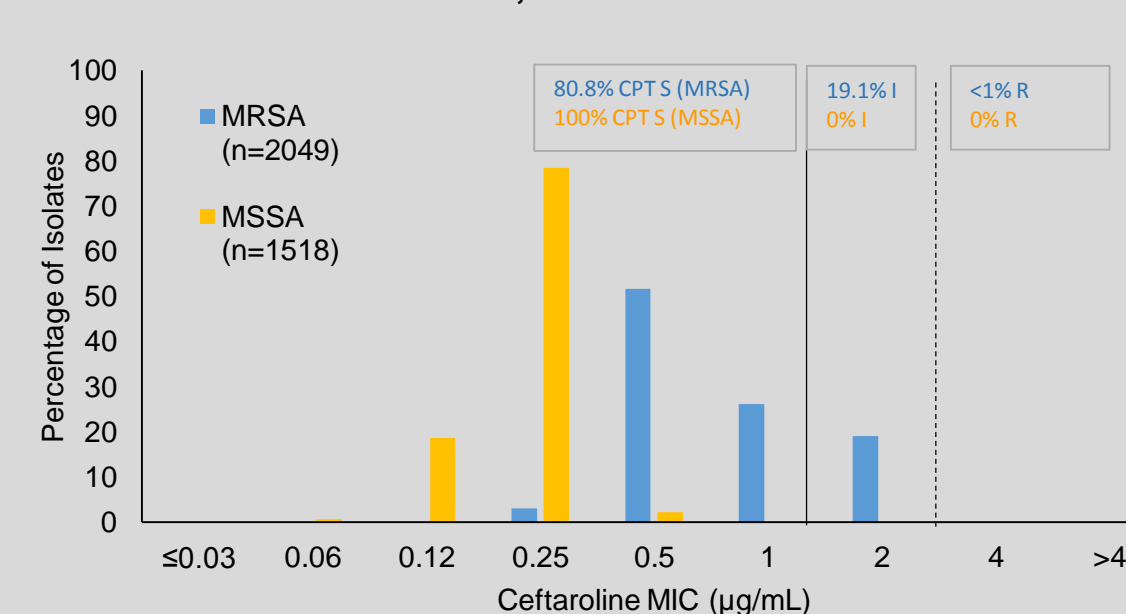
Results

Table 1. In Vitro Activity of Ceftaroline and Comparator Agents Tested Against Isolates from SSTI and Respiratory Infections in Latin America, 2012-2014.

Organism	Compound	Latin America				Argentina				Brazil				Chile				Colombia				Mexico				Venezuela			
		N	%S	MIC ₉₀	Range	N	%S	MIC ₉₀	Range	N	%S	MIC ₉₀	Range	N	%S	MIC ₉₀	Range	N	%S	MIC ₉₀	Range	N	%S	MIC ₉₀	Range	N	%S	MIC ₉₀	Range
<i>S. aureus</i> , MRSA	CPT	2049	80.8	2	0.25 - 4	474	93.0	1	0.25 - 2	144	79.2	2	0.25 - 2	393	29.5	2	0.25 - 2	115	95.7	1	0.25 - 2	505	98.4	1	0.25 - 2	418	90.4	1	0.25 - 4
	CLI	2049	50.8	>2	≤ 0.03 - >2	474	87.1	>2	≤ 0.03 - >2	144	35.4	>2	≤ 0.03 - >2	393	9.9	>2	≤ 0.03 - >2	115	89.6	2	0.06 - >2	505	14.1	>2	0.06 - >2	418	87.1	>2	≤ 0.03 - >2
	DAP	2049	99.8	1	≤ 0.06 - 2	474	100	1	0.25 - 1	144	100	1	0.5 - 1	393	99.8	1	≤ 0.06 - 2	115	100	1	0.12 - 1	505	99.4	1	0.12 - 2	418	100	1	0.12 - 1
	ERY	2049	32.5	>4	≤ 0.12 - >4	474	69.4	>4	≤ 0.12 - >4	144	15.3	>4	0.25 - >4	393	5.3	>4	≤ 0.12 - >4	115	76.5	>4	0.25 - >4	505	4.4	>4	0.25 - >4	418	44.0	>4	≤ 0.12 - >4
	GEN*	773	73.5	>32	≤ 2 - >32	164	80.5	32	≤ 2 - >32	62	69.4	>32	≤ 2 - >32	139	20.9	>32	≤ 2 - >32	39	97.4	≤ 2	≤ 2 - >32	215	93.0	≤ 2	≤ 2 - >32	154	81.8	>32	≤ 2 - >32
	LVX	2049	46.1	>2	0.03 - >2	474	83.5	>2	0.03 - >2	144	35.4	>2	0.06 - >2	393	4.1	>2	0.12 - >2	115	90.4	1	0.06 - >2	505	6.3	>2	0.06 - >2	418	82.5	>2	0.06 - >2
<i>S. aureus</i> , MSSA	LNZ	2049	100	2	≤ 0.5 - 4	474	100	2	≤ 0.5 - 4	144	100	2	≤ 0.5 - 4	393	100	2	≤ 0.5 - 4	115	100	2	1 - 4	505	100	2	≤ 0.5 - 4	418	100	2	≤ 0.5 - 4
	SXT*	773	99.0	≤ 1	≤ 1 - >4	164	99.39	≤ 1	≤ 1 - 4	62	95.2	≤ 1	≤ 1 - >4	139	100	≤ 1	≤ 1 - 2	39	100	≤ 1	≤ 1 - ≤ 1	215	98.6	≤ 1	≤ 1 - >4	154	99.4	≤ 1	≤ 1 - >4
	VAN	2049	100	2	≤ 0.25 - 2	474	100	2	≤ 0.25 - 2	144	100	2	0.5 - 2	393	100	1	≤ 0.25 - 2	115	100	2	0.5 - 2	505	100	2	≤ 0.25 - 2	418	100	2	0.5 - 2
	CPT	1518	100	0.25	0.06 - 0.5	273	100	0.25	0.06 - 0.5	150	100	0.25	0.06 - 0.5	313	100	0.25	0.06 - 0.5	163	100	0.25	0.06 - 0.5	338	100	0.25	0.06 - 0.5	281	100	0.25	0.06 - 0.5
	CLI	1518	96.9	0.12	≤ 0.03 - >2	273	99.3	0.12	≤ 0.03 - >2	150	96.0	0.12	≤ 0.03 - >2	313	98.1	0.12	≤ 0.03 - >2	163	96.3	0.12	≤ 0.03 - >2	338	93.5	0.25	≤ 0.03 - >2	281	98.2	0.12	≤ 0.03 - >2
	DAP	1518	99.9	1	≤ 0.06 - 2	273	100	1	0.25 - 1	150	99.3	1	0.25 - 2	313	100	1	0.25 - 1	163	100	1	0.12 - 1	338	100	1	≤ 0.06 - 1	281	100	1	0.12 - 1
<i>S. pneumoniae</i>	ERY	1518	74.1	>4	≤ 0.12 - >4	273	80.6	>4	≤ 0.12 - >4	150	59.3	>4	≤ 0.12 - >4	313	81.2	>4	≤ 0.12 - >4	163	73.0	>4	0.25 - >4	338	72.2	>4	≤ 0.12 - >4	281	70.8	>4	≤ 0.12 - >4
	GEN*	570	94.6	≤ 2	≤ 2 - >32	101	83.2	>32	≤ 2 - >32	61	96.7	≤ 2	≤ 2 - 16	112	99.1	≤ 2	≤ 2 - >32	76	98.7	≤ 2	≤ 2 - >32	116	94.8	≤ 2	≤ 2 - >32	104	96.2	≤ 2	≤ 2 - >32
	LVX	1518	96.4	0.5	≤ 0.015 - >2	273	97.1	0.5	≤ 0.015 - >2	150	98.0	0.25	0.06 - >2	313	96.8	0.5	0.06 - >2	163	97.6	0.5	0.12 - >2	338	95.0	0.5	≤ 0.015 - >2	281	95.4	0.5	0.06 - >2
	LNZ	1518	100	2	≤ 0.5 - 4	273	100	2	1 - 4	150	100	2	≤ 0.5 - 4	313	100	2	≤ 0.5 - 4	163	100	2	≤ 0.5 - 4	338	100	2	≤ 0.5 - 4	281	100	2	1 - 4
	SXT*	570	99.3	≤ 1	≤ 1 - >4	101	100	≤ 1	≤ 1 - ≤ 1	61	98.4	≤ 1	≤ 1 - >4	112	99.1	≤ 1	≤ 1 - >4	76	100	≤ 1	≤ 1 - ≤ 1	116	98.3	≤ 1	≤ 1 - >4	104	100	≤ 1	≤ 1 - ≤ 1
	VAN	1518	100	2	≤ 0.25 - 2	273	100	2	≤ 0.25 - 2	150	100	1	0.5 - 2	313	100	1	0.5 - 2	163	100	2	0.5 - 2	338	100	1	≤ 0.25 - 2	281	100	2	0.5 - 2
<i>Enterobacteriaceae</i> , ESBL Screen Negative	CPT	1294	88.9	1	≤ 0.015 - >128	247	85.4	2	0.03 - >128	114	86.8	1	0.03 - >128	157	87.3	1	≤ 0.015 - >128	120	89.2	1	≤ 0.015 - 16	401	90.3	0.5	≤ 0.015 - >128	255	91.8	0.5	≤ 0.015 - >128
	CAZ	1294	100	0.5	0.03 - 1	247	100	0.5	0.03 - 1	114	100	0.5	0.03 - 1	157	100	0.5	0.03 - 1	120	100	0.5	0.03 - 1	401	100	0.5	0.03 - 1	255	100	0.25	0.03 - 1
	CST*	527	73.6	>4	≤ 0.12 - >4	102	70.6	>4	≤ 0.12 - >4	51	72.6	>4	≤ 0.12 - >4	55	69.1	>4	0.25 - >4	44	75.0	>4	0.25 - >4	152	77.6	>4	0.25 - >4	123	73.2	>4	0.25 - >4
	LVX	1294	86.5	>4	≤ 0.03 - >4	247	87.5	4	≤ 0.03 - >4	114	86.8	>4	≤ 0.03 - >4	157	84.7	>4	≤ 0.03 - >4	120	93.3	1	≤ 0.03 - >4	401	85.3	>4	≤ 0.03 - >4	255	85.1	>4	≤ 0.03 - >4
	MEM	1294	99.9	0.12	0.008 - >8	247	100	0.12	0.015 - 0.12	114	98.3	0.12	0.015 - >8	157	100	0.12	0.015 - 0.25	120	100	0.12	0.015 - 0.25	401	100	0.06	0.015 - 1	255	100	0.12	0.008 - 0.25
	TZP	1294	97.5	4	≤ 0.25 - >128	247	95.6	4	≤ 0.25 - >128	114	98.3	4	≤ 0.25 - >128	157	99.4	4	≤ 0.25 - 64	120	98.3	4	≤ 0.25 - >128	401	97.5	4	≤ 0.25 - >128	255	97.3	8	≤ 0.25 - >128
	TGC	1294	90.7	2	0.06 - >8	247	89.9	4	0.06 - 4	114	93.9	2	0.06 - 8	157	83.4	4	0.06 - 8	120	95.0	2	0.06 - 4	401	89.3	4	0.06 - 8	255	94.9	2	0.06 - >8

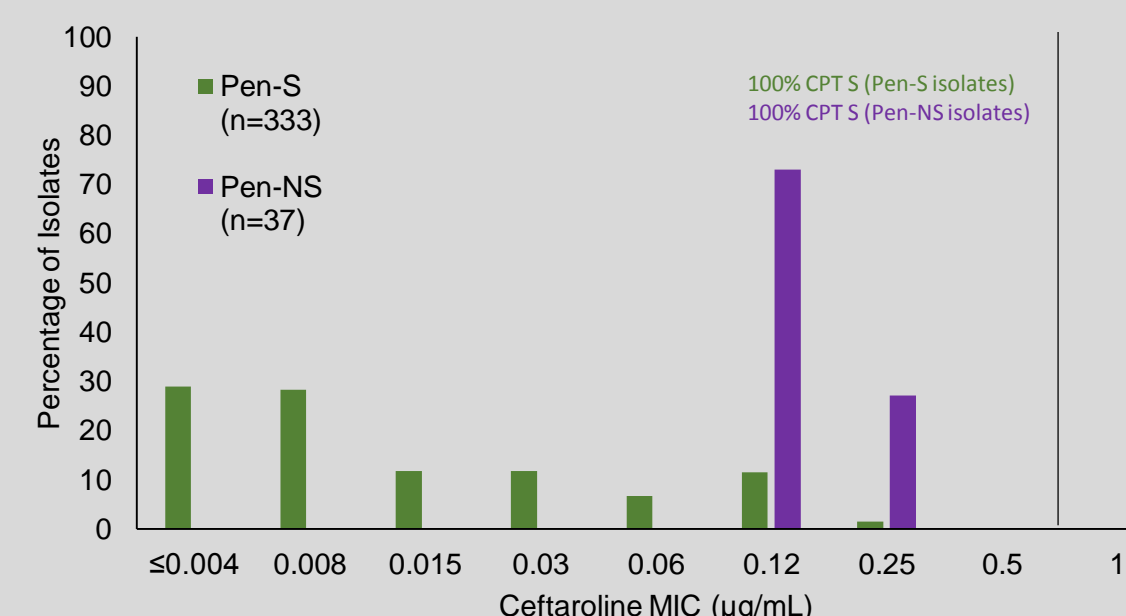
CPT, ceftaroline; CAZ, ceftazidime; CLI, clindamycin; DAP, daptomycin; ERY, erythromycin; CST, colistin; GEN, gentamicin; LVX, levofloxacin; LNZ, linezolid; MEM, meropenem; PEN, penicillin; TZP, piperacillin-tazobactam; SXT, trimethoprim-sulfamethoxazole; TGC, tigecycline; VAN, vancomycin; MIC₉₀, MIC₉₀, and Range in µg/mL; *GEN, SXT and CST tested in 2014 only

Figure 1. Ceftaroline MIC Distribution Against MRSA and MSSA from SSTI (n=2,579) and Respiratory Infections (n=988) Collected in Latin America, 2012-2014.



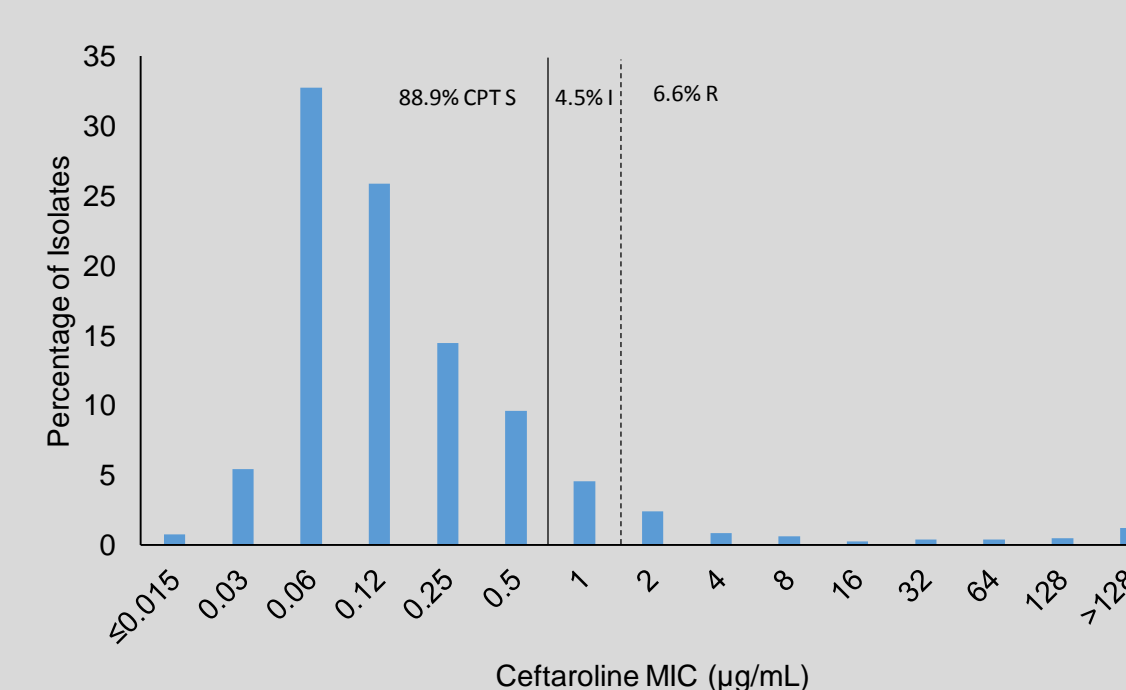
Solid black line represents the ceftaroline susceptible CLSI breakpoint; dashed line the resistant breakpoint; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; CPT S, susceptible to ceftaroline; CPT I, intermediate to ceftaroline; CPT R, resistant to ceftaroline

Figure 2. Ceftaroline MIC Distribution Against Penicillin-susceptible and Penicillin-resistant *S. pneumoniae* from SSTI (n=40) and Respiratory Infections (n=330) Collected in Latin America, 2012-2014.



Solid black line represents the ceftaroline susceptible CLSI breakpoint; Pen-S, susceptible to penicillin; Pen-NS, non-susceptible to penicillin; CPT-S, susceptible to ceftaroline

Figure 3. Ceftaroline MIC Distribution Against ESBL-negative *Enterobacteriaceae* from SSTI (n=798) and Respiratory Infections (n=496) Collected in Latin America, 2012-2014.



Solid black line represents the ceftaroline susceptible CLSI breakpoint; dashed line the resistant breakpoint; CPT S, susceptible to ceftaroline; I, intermediate to ceftaroline; R, resistant to ceftaroline

Results Summary

- The *in vitro* activity of ceftaroline and comparators against each organism group is provided in Table 1. Ceftaroline MIC distributions are provided in Figures 1 through 3.
- Overall, 80.8% of MRSA and 100% of MSSA from Latin America were susceptible to ceftaroline (MIC ≤1 µg/mL).
- The decreased percent susceptible of MRSA was due to a high number of intermediate (MIC=2 µg/mL) isolates from Chile (277/393; 70.5% I). Less than 1% of MRSA from Latin America were resistant to ceftaroline (MIC ≥4 µg/mL).
- 100% of *S. pneumoniae*, including penicillin-non-susceptible strains, were susceptible to ceftaroline (MIC ≤0.5 µg/mL).
- 88.9% of ESBL-negative *Enterobacteriaceae* were susceptible to ceftaroline (MIC ≤0.5 µg/mL).

Conclusions

- Ceftaroline was active against clinically relevant gram-positive SSTI and respiratory isolates collected in Latin America, with only one isolate (MRSA from Venezuela) resistant at the CLSI breakpoint.
- A lower percentage