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Activity of ceftaroline and comparators against pathogens isolated from skin and soft tissue infections in Latin America – results of AWARE surveillance 2012



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ABSTRACT

As part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance program in 2012 the *in vitro* activity of ceftaroline and relevant comparator antimicrobials was evaluated in six Latin American countries (Argentina, Brazil, Chile, Colombia, Mexico and Venezuela) against pathogens isolated from patients with hospital associated skin and soft tissue infections (SSTIs). The study documented that ceftaroline was highly active (MIC₉₀ 0.25 mg/L/% susceptible 100%) against methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MIC₉₀ 2 mg/L/% susceptible 83.3%) and β-hemolytic streptococci (MIC₉₀ 0.008–0.015 mg/L/% susceptible 100%). The activity of ceftaroline against selected species of *Enterobacteriaceae* was dependent upon the presence or absence of extended-spectrum β-lactamases (ESBLs). Against ESBL screen-negative *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* the MIC₉₀ and percent susceptible for ceftaroline were (0.5 mg/L/94.1%), (0.5 mg/L/99.0%) and (0.5 mg/L/91.5%), respectively. Ceftaroline demonstrated potent activity against a recent collection of pathogens associated with SSTI in six Latin American countries in 2012.

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Introduction

Skin and soft tissue infections (SSTIs) cover a broad range of infectious processes including wounds, abscesses, skin structure, cellulitis, erysipelas, furuncles, burns, carbuncles, impetigo, and a variety of animal bite infections.¹ The

successful management of both community-associated and hospital associated SSTI involves accurate diagnosis, source control, laboratory microbiological support, and as needed appropriate antimicrobial regimens either empirical or directed post culture and susceptibility testing.^{1–3}

Irrespective of anatomical site, the bacterial etiology of SSTI most frequently involves two species of Gram-positive cocci

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namely *Staphylococcus aureus* and β -hemolytic streptococci as well as various members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa*, and rarely anaerobes.⁴⁻⁶

Surgical drainage/debridement as well as antimicrobial therapy remains the mainstay of appropriate SSTI management. However, increasing global antimicrobial resistance in both Gram-positive and Gram-negative pathogens including those associated with SSTI has complicated both empirical and directed antimicrobial therapy.¹ Prevalence studies have shown that over 50% of SSTI are caused by *S. aureus* including methicillin-resistant *S. aureus* (MRSA) thus greatly reducing the inherent or preferred use of a β -lactam for potential *S. aureus* SSTI.^{7,8} The CDC considers MRSA a serious threat with over 80,000 severe MRSA infections per year and an unknown but much higher number of less severe infections including SSTI.⁹

Over the past 15 years antimicrobials with activity against MRSA including vancomycin, daptomycin, tigecycline, and linezolid have been available, but each of these has therapeutic limitations and may not on their own provide coverage of polymicrobial infections that include Gram-negative pathogens. In the face of increasing antimicrobial resistance the search for new antimicrobials with activity against a variety of pathogens has led to the development and marketing of ceftaroline fosamil, a new broad-spectrum parenteral cephalosporin. Ceftaroline, the active metabolite of ceftaroline fosamil, inhibits penicillin-binding protein 2a of MRSA and shows effective activity against MRSA as well as against other Gram-positive cocci, and several species of *Enterobacteriaceae* (excluding those that produce extended-spectrum β -lactamases [ESBLs] or inducible AmpC β -lactamases).^{10,11} Prior *in vitro* susceptibility studies provide support of ceftaroline activity against many Gram-positive and commonly isolated Gram-negative pathogens.¹²⁻¹⁹

The AWARE (Assessing Worldwide Antimicrobial Resistance Evaluation) global surveillance program was established to monitor the susceptibility of pathogens to ceftaroline as well as relevant comparator antimicrobials to pathogens associated with SSTI as well as lower respiratory tract infection pathogens and complicated urinary tract infections in many areas of the world including Latin America. This report summarizes the data from SSTI pathogens from the AWARE program in Latin America in 2012.

Material and methods

Bacterial isolates

A total of 1142 clinical isolates from patients with SSTI were collected from 17 medical centers in six Latin American countries in 2012: Argentina (three), Brazil (two), Chile (three), Columbia (two), Mexico (five), and Venezuela (two). All isolates were collected from patients presenting with SSTI. The AWARE surveillance program is not designed as a prevalence of infection study as each participating laboratory was asked to collect and submit a defined number of specific pathogens from SSTI (one isolate per patient infection episode). All isolates were submitted to International Health Management Associates Inc. (Schaumburg, IL, USA). Organism identification was

Table 1 – *In vitro* activity of ceftaroline against key Gram-positive pathogens in SSTI from Latin America, 2012.

Organism	Drug	MIC ₉₀	%Sus.
<i>Staphylococcus aureus</i> (n = 696)	Ceftaroline	1	90.7
	Oxacillin	>2	44.0
	Erythromycin	>4	47.3
	Clindamycin	>2	76.0
	Levofloxacin	>2	71.3
	Moxifloxacin	>2	71.6
	Minocycline	0.5	99.6
	Tigecycline	0.5	100
	Linezolid	2	100
	Daptomycin	1	100
<i>Staphylococcus aureus</i> (MRSA) (n = 390)	Ceftaroline	2	83.3
	Oxacillin	>2	0
	Erythromycin	>4	32.6
	Clindamycin	>2	57.7
	Levofloxacin	>2	51.0
	Moxifloxacin	>2	51.0
	Minocycline	0.5	99.5
	Tigecycline	0.5	100
	Linezolid	2	100
	Daptomycin	1	100
<i>Staphylococcus aureus</i> (MSSA) (n = 306)	Ceftaroline	0.25	100
	Oxacillin	1	100
	Erythromycin	>4	66.0
	Clindamycin	0.12	99.4
	Levofloxacin	0.25	97.4
	Moxifloxacin	0.12	98.0
	Minocycline	0.5	99.7
	Tigecycline	0.5	100
	Linezolid	2	100
	Daptomycin	1	100
<i>Streptococcus pyogenes</i> (n = 56)	Ceftaroline	0.008	100
	Penicillin	≤0.015	100
	Erythromycin	0.06	96.4
	Clindamycin	0.03	96.4
	Levofloxacin	0.5	100
	Tigecycline	0.06	100
	Linezolid	1	100
	Daptomycin	0.12	100
	Vancomycin	1	100
	<i>Streptococcus agalactiae</i> (n = 25)	Ceftaroline	0.015
Penicillin		0.12	100
Erythromycin		>1	88.0
Clindamycin		0.5	84.0
Levofloxacin		1	100
Tigecycline		0.06	100
Linezolid		1	100
Daptomycin		0.5	100
Vancomycin		1	100
<i>Streptococcus dysgalactiae</i> (n = 12)		Ceftaroline	0.008
	Penicillin	0.03	100
	Erythromycin	0.12	91.7
	Clindamycin	0.06	100
	Levofloxacin	0.5	100
	Tigecycline	0.25	100
	Linezolid	1	100
	Daptomycin	0.12	100
	Vancomycin	0.25	100

CLSI susceptibilities defined by CLSI document M100-S24 (2014), where applicable; tigecycline susceptibilities under CLSI defined by FDA (2013).

Table 2 – Frequency distribution of ceftaroline against *Staphylococcus aureus* and *Streptococcus pyogenes* in SSTI from Latin America, 2012.

Organism	Country	n	MIC (mg/L) (n/cumulative %)									
			≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
<i>S. aureus</i>	All countries	696					3	56	248	231	93	65
						0.4	8.5	44.1	77.3	90.7	100	
	Argentina	174					7	52	94	10	11	
							4	33.9	87.9	93.7	100	
	Brazil	20					4	10	4		2	
							20.0	70.0	90.0			100
	Chile	126					1	16	44	17	3	45
							0.8	13.5	48.4	61.9	64.3	100
Colombia	47						5	20	18	1	3	
							10.6	53.2	91.5	93.6	100	
Mexico	189					1	16	71	25	76		
						0.5	9.0	46.6	59.8	100		
Venezuela	140					1	8	51	73	3	4	
						0.7	6.4	42.9	95.0	97.1	100	
MRSA	All countries	390							8	224	93	65
									20.1	59.5	83.3	100
	Argentina	116							1	94	10	11
									0.9	81.9	90.5	100
	Brazil	6								4		2
										66.7		100
	Chile	63							1	14	3	45
									1.6	23.8	28.6	100
Colombia	24								2	18	1	3
									8.3	83.3	87.5	100
Mexico	100								2	22	76	
									2.0	24.0	100	
Venezuela	81								2	72	3	4
									2.5	91.4	95.1	100
MSSA	All countries	306					3	56	240	7		
						1.0	19.3	97.7	100			
	Argentina	58							7	51		
									12.1	100		
	Brazil	14							4	10		
									28.6	100		
	Chile	63					1	16	43	3		
							1.6	27.0	95.2	100		
Colombia	23							5	18			
								21.7	100			
Mexico	89					1	16	69	3			
						1.1	19.1	96.6	100			
Venezuela	59					1	8	49	1			
						1.7	15.3	98.3	100			
<i>S. pyogenes</i>	All countries	56	43	12					1			
			76.8	98.2					100			
	Argentina	14	9	4					1			
			64.3	92.9					100			
	Brazil	2	2									
			100									
	Chile	20	13	7								
			65.0	100								
Mexico	12	11	1									
		91.7	100									
Venezuela	8	8										
		100										

confirmed using a Bruker Biotyper MALDI-TOF instrument (Bruker Daltonics, Billerica, MA, USA).

Antimicrobial susceptibility testing

Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method recommended by the Clinical and Laboratory Standards Institute (CLSI)

performance standard.²⁰ Susceptibility was determined according to interpretive criteria set by the CLSI or FDA as appropriate.^{21,22} Breakpoints for ceftaroline have been recommended for *S. aureus* (≤1 mg/L, susceptible), streptococci, and *Enterobacteriaceae* (≤0.5 mg/L, susceptible) by the CLSI. All MIC panels were prepared at IHMA and frozen at –80 °C prior to usage. MICs were entered into a central database and only accepted if quality control values using appropriate

Table 3 – In vitro activity of ceftaroline against key Gram-negative pathogens in SSTI from Latin America, 2012.

Organism	Drug	MIC ₉₀	%Sus.
<i>Citrobacter freundii</i> (n = 14)	Ceftaroline	64	64.3
	Ceftazidime	64	71.4
	Cefepime	1	100
	Aztreonam	32	78.6
	Meropenem	0.06	100
	Amoxicillin-clavulanic acid	>16	7.1
	Piperacillin-tazobactam	64	85.7
	Levofloxacin	>4	78.6
	Amikacin	16	92.9
	Tigecycline	1	100
<i>Citrobacter</i> spp. (n = 20)	Ceftaroline	16	75.0
	Ceftazidime	32	80.0
	Cefepime	0.25	100
	Aztreonam	16	85.0
	Meropenem	0.06	100
	Amoxicillin-clavulanic acid	>16	35.0
	Piperacillin-tazobactam	16	90.0
	Levofloxacin	>4	85.0
	Amikacin	2	95.0
	Tigecycline	1	100
<i>Enterobacter aerogenes</i> (n = 12)	Ceftaroline	32	83.3
	Ceftazidime	32	83.3
	Cefepime	4	91.7
	Aztreonam	8	83.3
	Meropenem	0.12	100
	Amoxicillin-clavulanic acid	>16	0.0
	Piperacillin-tazobactam	64	83.3
	Levofloxacin	0.12	100
	Amikacin	8	91.7
	Tigecycline	1	100
<i>Enterobacter cloacae</i> (n = 24)	Ceftaroline	>128	54.2
	Ceftazidime	128	54.2
	Cefepime	>16	79.2
	Aztreonam	128	58.3
	Meropenem	0.25	100
	Amoxicillin-clavulanic acid	>16	16.7
	Piperacillin-tazobactam	>128	62.5
	Levofloxacin	>4	75.0
	Amikacin	8	95.8
	Tigecycline	2	95.8
<i>Escherichia coli</i> (n = 86)	Ceftaroline	>128	50.0
	Ceftazidime	64	61.6
	Cefepime	>16	66.3
	Aztreonam	128	59.3
	Meropenem	0.03	98.8
	Amoxicillin-clavulanic acid	16	54.7
	Piperacillin-tazobactam	64	83.7
	Levofloxacin	>4	43.0

Table 3 (Continued)

Organism	Drug	MIC ₉₀	%Sus.
<i>Klebsiella oxytoca</i> (n = 17)	Amikacin	16	97.7
	Tigecycline	1	100
	Ceftaroline	>128	76.5
	Ceftazidime	4	94.1
	Cefepime	>16	82.4
	Aztreonam	128	82.4
	Meropenem	0.06	100
	Amoxicillin-clavulanic acid	8	94.1
	Piperacillin-tazobactam	32	88.2
	Levofloxacin	1	100
<i>Klebsiella pneumoniae</i> (n = 58)	Amikacin	8	100
	Tigecycline	0.5	100
	Ceftaroline	>128	46.6
	Ceftazidime	128	46.6
	Cefepime	>16	60.3
	Aztreonam	>128	46.6
	Meropenem	2	84.5
	Amoxicillin-clavulanic acid	>16	51.7
	Piperacillin-tazobactam	>128	63.8
	Levofloxacin	>4	65.5
<i>Morganella morganii</i> (n = 14)	Amikacin	32	89.7
	Tigecycline	2	91.4
	Ceftaroline	64	50.0
	Ceftazidime	16	71.4
	Cefepime	1	100
	Aztreonam	2	100
	Meropenem	0.25	100
	Amoxicillin-clavulanic acid	>16	0.0
	Piperacillin-tazobactam	8	100
	Levofloxacin	>4	35.7
<i>Proteus mirabilis</i> (n = 32)	Amikacin	2	100
	Tigecycline	8	14.3
	Ceftaroline	>128	75.0
	Ceftazidime	1	100
	Cefepime	>16	84.4
	Aztreonam	2	90.6
	Meropenem	0.12	100
	Amoxicillin-clavulanic acid	16	81.3
	Piperacillin-tazobactam	2	100
	Levofloxacin	>4	56.3

CLSI susceptibilities defined by CLSI document M100-S24 (2014), where applicable; tigecycline susceptibilities under CLSI defined by FDA (2013).

American Type Culture Collection control strains were within acceptable ranges. ESBL phenotypic activity was determined by screening *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* with ceftazidime and aztreonam according to CLSI guidelines.²¹ ESBL screen-positive was defined as any *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*

Table 5 – Frequency distribution (n) and cumulative percent inhibited (%) at each MIC for ceftaroline against *Klebsiella pneumoniae* and phenotypes in SSTI from Latin America, 2012.

Country	Phenotype (n)	MIC (mg/L) (n/cumulative %)													
		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
All countries combined	All isolates (58)		14	6	5	2			1			1		6	23
			24.1	34.5	43.1	47.0			48.0			50.0		60.0	100
	ESBL screen-positive (31)								1			1		6	23
Argentina	All isolates (19)		3	1	2										13
			15.8	21.1	31.6										100
	ESBL screen-positive (13)														13
Brazil	All isolates (1)														1
															100
	ESBL screen-positive (1)														1
Chile	All isolates (9)		1	1										1	6
			11.1	22.2										33.0	100
	ESBL screen-positive (7)													1	6
Colombia	All isolates (2)														1
															100
	ESBL screen-positive (2)														1
Mexico	All isolates (20)		8	3	1	1								5	2
			40.0	55.0	60.0	65.0								90.0	100
	ESBL screen-positive (7)													5	2
Venezuela	All isolates (7)		2	1	2	1									1
			28.6	42.9	71.4	86									100
	ESBL screen-positive (1)														1
Venezuela	All isolates (7)		2	1	2	1									1
			33.3	50.0	83.3	100									100
	ESBL screen-negative (6)														100

isolate with either ceftazidime or aztreonam MIC values of >1 mg/L. All other *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* isolates were designated as ESBL screen-negative.

Results and discussion

In 2012 the 17 participating medical centers in Latin America contributed 1142 clinical isolates. The majority of isolates, both Gram-positive and Gram-negative, came from four main infection sources: wound (44%), abscess (26%), cellulitis (10%), and skin ulcers (9%). All other infection sites contributed ≤4% of isolates.

The susceptibility of various Gram-positive cocci to ceftaroline and relevant comparators is provided in Table 1. Against 696 *S. aureus* isolates (methicillin susceptible [MSSA] and MRSA isolates combined) the ceftaroline MIC₉₀ was 1 mg/L with 90.7% of all isolates susceptible. Only tigecycline and minocycline demonstrated lower MIC₉₀ values of 0.5 mg/L.

S. aureus isolates irrespective of methicillin phenotype were susceptible to daptomycin, linezolid, tigecycline, and vancomycin. 100% of MSSA were susceptible to ceftaroline with an MIC₉₀ of 0.25 mg/L and 83.3% of MRSA susceptible to ceftaroline with MIC₉₀ of 2 mg/L. No MRSA were identified with an MIC >2 mg/L (Table 1).

Variations in MIC₉₀ for ceftaroline against MRSA were relatively minor with ranges from 0.5 mg/L in isolates from Venezuela to 2 mg/L in isolates from Brazil, Chile, and Colombia. Ceftaroline MICs for MSSA isolates displayed minimal variation (0.06–0.5 mg/L) with MIC₉₀ of 0.25 mg/L irrespective of country (Table 2). All β-hemolytic streptococci (*Streptococcus agalactiae*, *Streptococcus dysgalactiae*, and *Streptococcus pyogenes*) were susceptible to ceftaroline with MIC₉₀ ranges of 0.008–0.015 mg/L (Table 1) with 55/56 *S. pyogenes* ceftaroline MIC₉₀ of ≤0.008 mg/L in all countries studied (Table 2). Isolates were 100 percent susceptible to most comparators with the exception of clindamycin and erythromycin where susceptibility ranged from 84.0 to 96.4%.

The activity of ceftaroline and comparators is shown in Table 3 for relevant Gram-negative bacilli where $n > 10$. MIC₉₀/% susceptible for ceftaroline by species were: *Citrobacter freundii* (64/64.3%), *Citrobacter* spp. (16/75%), *Enterobacter aerogenes* (32/83.3%), *Enterobacter cloacae* (>128/54.2%), *E. coli* (>128/50.0%), *K. oxytoca* (>128/76.5%), *K. pneumoniae* (>128/46.6%), *Morganella morganii* (64/50.0%), and *Proteus mirabilis* (>128/75%). For most Gram-negative bacilli examined tigecycline, piperacillin-tazobactam, amikacin, and meropenem displayed the highest percent susceptible ranging from 91 to 100% susceptible with the exception of *K. pneumoniae*. The MIC frequency distributions of ceftaroline against both ESBL screen-positive and ESBL screen-negative *E. coli*, *K. pneumoniae*, and *K. oxytoca* are shown in Tables 4-5. For all six Latin American countries combined the ceftaroline MIC₉₀ was >128 mg/L for all 86 *E. coli* with 50% of isolates susceptible at the CLSI breakpoint of 0.5 mg/L (Table 4). Ceftaroline was not active against ESBL screen-positive *E. coli* isolates with all isolates demonstrating MICs ≥ 8 mg/L. However for ESBL screen-negative isolates the MIC₉₀ was 0.5 mg/L with 95% of isolates susceptible. Two ESBL screen-negative *E. coli* isolates (one each from Argentina and Colombia) were resistant to ceftaroline with MICs of 2 mg/L. The MIC frequency distribution of ceftaroline against 58 *K. pneumoniae* from all Latin American countries is shown in Table 5. MIC₉₀ values were >128 mg/L with only 48% of isolates susceptible at the CLSI breakpoint of 0.5 mg/L. All 31 ESBL screen positive isolates were resistant to ceftaroline, whereas all ESBL screen-negative isolates were fully susceptible to ceftaroline. The MIC₉₀ of ceftaroline for all Latin American *K. oxytoca* isolates (17) was >128 mg/L with 76.5% susceptible at 0.5 mg/L (data not shown). Only three ESBL screen-positive isolates were identified from this region: Chile (one) and Venezuela (two) with MIC values of >128 mg/L. For the ESBL screen-negative isolates the MIC₉₀ was 0.5 mg/L with only one isolate from Argentina for which the ceftaroline MIC was 4 mg/L.

All MSSA and all isolates of β -hemolytic streptococci in this study of SSTI major pathogens in Latin America were susceptible to ceftaroline (Table 1). This analysis confirms prior reports from Europe,¹⁵ Latin America,^{12,13} and the United States¹⁴ that include MSSA isolates not only from SSTI but lower respiratory tract infections. Of the MRSA isolates collected from SSTI in Latin America 9.3% were identified as ceftaroline intermediate (MIC 2 mg/L) and none of MRSA isolates were ceftaroline resistant (MIC > 2 mg/L). The present study again demonstrated that whereas ceftaroline resistance in MRSA is uncommon geographical and regional variances can alter the overall susceptibility of MRSA to ceftaroline.^{12,19} Ceftaroline exhibited potent activity against ESBL screen-negative *E. coli*, *K. pneumoniae* and *K. oxytoca* in the present study as has been previously shown in several surveillance studies in various geographical areas.¹²⁻¹⁸ However ceftaroline had minimal *in vitro* activity against ESBL screen-positive *Enterobacteriaceae* SSTI isolates studied in this 2012 surveillance study in Latin America. All surveillance studies have limitations including isolate collection and data analysis. The AWARE surveillance study is not a prevalence of infection study nor a direct marker of phenotype prevalence as pathogen collection is dictated by rigorous study protocols. However, organism identification and susceptibility testing and interpretation are

rigorously followed with comprehensive quality control in place.

In conclusion ceftaroline has been shown in this study and in prior surveillance studies to exhibit potent activity against MSSA and as a β -lactam agent potent activity against MRSA as well as β -hemolytic streptococci and ESBL screen-negative *E. coli*, *K. pneumoniae*, and *K. oxytoca*. SSTI currently represents one of the most common community and hospital associated infections globally and the need for new antimicrobials with activity against the most common pathogens associated with SSTI will need to continue to evolve. Ceftaroline represents one such newer antimicrobial with documented *in vitro* activity against the critical SSTI pathogens tested in this study from Latin America.

Conflicts of interest

This study at IHMA was supported by AstraZeneca Pharmaceuticals LP, which also included compensation fees for services in relation to preparing the manuscript. DJH, DJB, and DFS are employees of International Health Management Associates, Inc. None of the IHMA authors have personal financial interests in the sponsor of this paper (AstraZeneca Pharmaceuticals). ER and JPI are employees of AstraZeneca.

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