1401 ICAAC CC06_f 9/10/07 11:04 AM Page 1

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A Profile of Ceftobiprole (BPR) Activity Against Recent US Isolates of Enterobacteriaceae (EN) and *Pseudomonas aeruginosa* (PA) From Inpatients and ICU Patients

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Updated Abstract

Background: Ceftobiprole is an investigational cephalosporin with broad-spectrum activity against Gram-positive (eg, MRSA) and Gram-negative (GN) pathogens commonly encountered in hospitals. Because ceftobiprole will be used in this environment, this study evaluated its activity relative to other cephalosporins against key GN species isolated from inpatients (IP) and ICU patients (ICU).

Methods: From 2005–2007, isolates of EN (IP n=3520, ICU n=869; *E. coli, K. pneumoniae, P. mirabilis, E. cloacae, Citrobacter* spp., *S. marcescens*) and PA (IP n=733, ICU n=307) were collected across 9 US Census Bureau Regions, and were centrally tested by broth microdilution (CLSI; M7-A7; M100-S16) against ceftobiprole, cefepime (FEP), ceftriaxone (CRO), and ceftazidime (CAZ). Analysis was stratified by resistance (CAZ-susceptible [CAZ S] vs nonsusceptible [CAZ NS]) and patient location (IP vs ICU).

Results: Against EN, ceftobiprole MIC_{90}s for IP and ICU isolates were 0.25 and 4 µg/ml, respectively. This pattern was also observed for FEP (IP = 0.25 µg/ml, ICU = 1 µg/ml) and CRO (IP = 2 µg/ml, ICU = 64 µg/ml), though ceftobiprole and FEP MICs were impacted to a lesser extent than CRO MICs. The increase in cephalosporin MIC_{90}s among enteric ICU isolates relative to IP isolates correlated to an increased prevalence of CAZ NS enteric isolates (IP – 8%, ICU – 11%), as ceftobiprole and FEP MIC_{90}s for CAZ NS enterics were >32 mg/ml. ceftobiprole had similar activity against both ICU and IP PA (mode: 2 µg/ml IP and 4 µg/ml ICU, MIC_{50}: 4 µg/ml, MIC_{90}: 16 µg/ml) at levels comparable to that of FEP (mode: 4 µg/ml, MIC_{50}: 4 µg/ml, MIC_{90}: 16 µg/ml).

Conclusion: The profile of ceftobiprole and cefepime did vary with enteric isolate source, which is likely a reflection of resistance encountered in the IP vs ICU setting. This pattern was not as evident among PA. While ceftobiprole and cefepime activities were similar across populations, these findings demonstrate the importance of stratified analysis of surveillance data by patient location.

Introduction

Infections by pathogens with increased resistance to currently utilized therapeutics represent a significant challenge to modern medicine. Gram-positive cocci (most notably *Staphylococcus aureus*) and Gram-negative bacilli (primarily enterics and nonfermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* species) are frequently encountered pathogens in hospitals today and can be difficult to manage due to widespread antibiotic resistance. Ceftobiprole, a pyrrolidinone-3-ylidene-methyl cephalosporin, has broad-spectrum activity against the majority of clinically relevant Gram-negative and Gram-positive pathogens, including methicillin-resistant *S. aureus*. Due to this coverage, ceftobiprole has completed clinical trials for the treatment of pneumonia, including hospital-acquired pneumonia (HAP), and complicated skin and skin structure infections (cSSSI). In addition to *S. aureus,* Gram-negative enteric bacilli and *P. aeruginosa* are important pathogens in HAP and are also encountered among patients with cSSSI. To better understand the activity of ceftobiprole against Gram-negative pathogens likely to be encountered in patients suffering from HAP and cSSSI, this study examined the activity of ceftobiprole and comparator cephalosporins against Enterobacteriaceae and *P. aeruginosa* isolated from inpatients (IP) and patients in intensive care units (ICU).

Acknowledgment

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Methods

From 2005–2007, isolates of Enterobacteriaceae (IP n=3520, ICU n= 869; *Escherichia coli* [n=1375], *Klebsiella pneumoniae* [n=1130], *Proteus mirabilis* [n=484], *Enterobacter cloacae* [n=605], *Citrobacter* species [n=400], *Serratia marcescens* [n=395]) and *P. aeruginosa* (IP n=733, ICU n=307) were collected from 57 laboratories across 9 US Census Bureau Regions, and were centrally tested by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) guidelines (M7-A7; M100-S16) against ceftobiprole, cefepime, ceftriaxone, ceftazidime, piperacillin-tazobactam, and other relevant agents. MIC analysis was stratified by resistance (ceftazidime susceptible [CAZ S] versus nonsusceptible [CAZ NS]) and patient location (IP versus ICU).

Results

Enterobacteriaceae

- By MIC_{90}, ceftobiprole activity was 16-fold lower against ICU isolates (4 µg/ml) relative to IP isolates (0.25 µg/ml), although the MIC_{90}s between these 2 populations were similar (ICU: 0.06 µg/ml vs IP: 0.03 µg/ml) (**Table 1**). This pattern was also apparent for cefepime (MIC_{90}: ICU = 1 µg/ml, IP = 0.25 µg/ml) and ceftazidime (MIC_{90}: ICU = 32 µg/ml, IP = 2 µg/ml) (**Table 1**). However, little difference in ceftobiprole MIC distribution was apparent between the 2 populations (**Figure 1a**).
- The difference in activity based on patient location seen for ceftobiprole against Enterobacteriaceae overall correlated to an increased prevalence of ceftazidime NS isolates (ceftazidime MIC >16 µg/ml) among ICU patients (95/869, 11%) relative to inpatients (290/3520, 8%).
- This difference in the activity of ceftobiprole by patient location was no longer apparent by MIC_{50} or MIC_{90} after subdividing the Enterobacteriaceae based on ceftazidime susceptibility (**Table 1**).
- The distributions for ceftazidime-susceptible and ceftazidime-nonsusceptible Enterobacteriaceae appear similar for both ICU and IP populations (**Figure 1b** and **1c**) and reflect that higher ceftobiprole MICs are observed among ceftazidime-nonsusceptible isolates relative to ceftazidime-susceptible isolates (**Figure 1b** and **1c**).
- The cumulative susceptibility patterns of both ceftazidime-susceptible Enterobacteriaceae IP and ICU isolates to ceftobiprole most closely resemble the pattern observed with cefepime (**Figure 2a** and **2b**).
- Against ceftazidime-nonsusceptible Enterobacteriaceae, ceftobiprole appears slightly less active than cefepime based on the cumulative susceptibility of both IP and ICU isolates (**Figure 2c** and **2d**), though both are more active than ceftriaxone and ceftazidime.

P. aeruginosa

- Against *P. aeruginosa* overall, ceftobiprole had similar activity and MIC distributions against IP and ICU isolates (MIC_{50} = 4 µg/ml, MIC_{90} = 16 µg/ml) (**Table 2** and **Figure 3a**).
- Ceftobiprole activity against ceftazidime-susceptible *P. aeruginosa* isolates was not impacted by patient location (ICU: MIC_{50} = 2 µg/ml, MIC_{90} = 16 µg/ml; IP: MIC_{50} = 2 µg/ml, MIC_{90} = 8 µg/ml) (**Table 2**). MIC distributions for ceftobiprole against ceftazidime-susceptible isolates were similar for both IP and ICU populations (**Figure 3b**).
- Among both IP and ICU isolates, the level of activity of ceftobiprole resembled that of cefepime and ceftazidime as illustrated by the cumulative susceptibility of ceftazidime-susceptible *P. aeruginosa* isolates to ceftobiprole and comparator cephalosporins (**Figure 4a** and **4b**).
- Against ceftazidime-nonsusceptible *P. aeruginosa*, the MIC_{50} (8 µg/ml) and MIC_{90} (>32 µg/ml) for ceftobiprole was identical among IP and ICU populations but higher than that observed against ceftazidime-susceptible isolates (**Table 2**). Ceftobiprole MIC distributions were similar among ICU and IP populations (**Figure 3c**).
- The level of activity of ceftobiprole was slightly greater than that of cefepime against ceftazidime-nonsusceptible *P. aeruginosa* IP and ICU isolates by cumulative susceptibility analysis (**Figure 4c** and **4d**), while both cefepime and ceftobiprole were more active than ceftazidime and ceftriaxone.

Figure 1. Ceftobiprole MIC (µg/mL) distribution against Enterobacteriaceae by patient location.

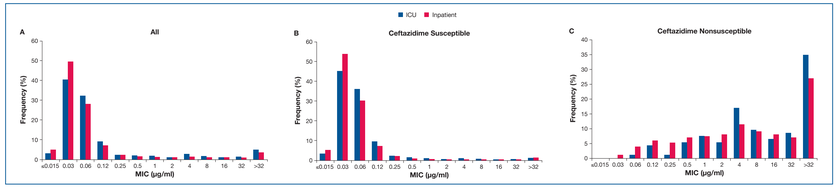


Table 1. *In-vitro* MIC (µg/ml) activity of ceftobiprole and comparators against Enterobacteriaceae

Organism	Phenotype*	Patient Location	Agent	MIC (µg/ml) Total n	Range	Mode	MIC_{50}	MIC_{90}	nS	(%S)	nI	(%I)	nR	(%R)
Enterobacteriaceae	All	ICU	Ceftobiprole	869	≤0.015->64	0.03	0.06	4	–b		–b		–b	
			Ceftriaxone		≤0.015->64	0.03	0.06	16	768	(88.4)	31	(3.6)	70	(8.1)
			Ceftazidime		≤0.03->128	0.12	0.12	32	774	(89.1)	6	(0.7)	89	(10.2)
			Cefepime		≤0.015->128	0.03	0.06	1	847	(97.5)	8	(0.9)	14	(1.6)
			Piperacillin/tazobactam		≤0.25->128	2	4	128	748	(86.1)	34	(3.9)	87	(10.0)
		Inpatient	Ceftobiprole	3520	≤0.015->64	0.03	0.03	0.25	–b		–b		–	
			Ceftriaxone		≤0.015->64	0.03	0.06	1	3233	(91.8)	95	(2.7)	192	(5.5)
			Ceftazidime		≤0.03->128	0.12	0.12	2	3230	(91.8)	39	(1.1)	251	(7.1)
			Cefepime		≤0.015->128	0.03	0.03	0.25	3457	(98.2)	16	(0.5)	47	(1.3)
			Piperacillin/tazobactam		≤0.25->128	4	2	16	3187	(90.5)	120	(3.4)	213	(6.1)
	CAZ S	ICU	Ceftobiprole	774	0.015->64	0.03	0.06	0.12	–b		–b		–b	
			Ceftriaxone		≤0.015->64	0.03	0.06	0.5	759	(98.1)	5	(0.6)	10	(1.3)
			Ceftazidime		≤0.03-8	0.12	0.12	0.5	774	(100.0)	0	(0.0)	0	(0.0)
			Cefepime		≤0.015-64	0.03	0.03	0.12	769	(99.4)	2	(0.3)	3	(0.4)
			Piperacillin/tazobactam		≤0.25->128	2	2	8	732	(94.6)	17	(2.2)	25	(3.2)
		Inpatient	Ceftobiprole	3230	≤0.015->64	0.03	0.03	0.12	–b		–b		–b	
			Ceftriaxone		≤0.015->64	0.03	0.06	0.25	3201	(99.1)	14	(0.4)	15	(0.5)
			Ceftazidime		≤0.03-8	0.12	0.12	0.5	3230	(100.0)	0	(0.0)	0	(0.0)
			Cefepime		≤0.015->128	0.03	0.03	0.12	3220	(99.7)	1	(0.0)	9	(0.3)
			Piperacillin/tazobactam		≤0.25->128	4	2	8	3116	(96.5)	51	(1.6)	63	(2.0)
	CAZ NS	ICU	Ceftobiprole	95	0.06->64	>32	8	>64	–b		–b		–b	
			Ceftriaxone		2->64	>64	64	>64	9	(9.5)	26	(27.4)	60	(63.2)
			Ceftazidime		16->128	>32	>32	>128	0	(0.0)	6	(6.3)	89	(93.7)
			Cefepime		0.06->128	2	2	32	78	(82.1)	6	(6.3)	11	(11.6)
			Piperacillin/tazobactam		2->128	>128	>128	>128	16	(16.8)	17	(17.9)	62	(65.3)
		Inpatient	Ceftobiprole	290	0.03->64	>32	8	>64	–b		–b		–b	
			Ceftriaxone		0.12->64	>64	64	>64	32	(11.0)	81	(27.9)	177	(61.0)
			Ceftazidime		16->128	>32	>32	128	0	(0.0)	39	(13.4)	251	(86.6)
			Cefepime		0.06->128	1	2	32	237	(81.7)	15	(5.2)	38	(13.1)
			Piperacillin/tazobactam		≤0.25->128	>128	128	>128	71	(24.5)	69	(23.8)	150	(51.7)

*CAZ S, ceftazidime susceptible; CAZ NS, ceftazidime nonsusceptible. bCeftobiprole CLSI interpretation of susceptible (S), intermediate (I), and/or resistant (R) not available.

Figure 2. Cumulative susceptibility of ceftobiprole and comparators against Enterobacteriaceae from the ICU and inpatients.

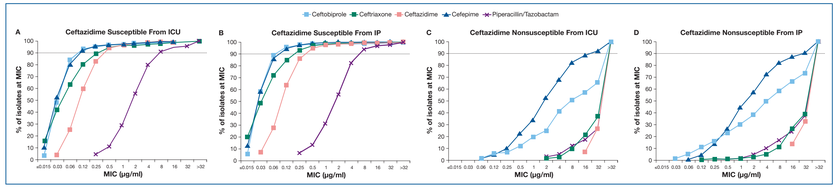


Table 2. *In-vitro* MIC (µg/ml) activity of ceftobiprole and comparators against *P. aeruginosa*

Organism	Phenotype*	Patient Location	Agent	MIC (µg/ml) Total n	Range	Mode	MIC_{50}	MIC_{90}	nS	(%S)	nI	(%I)	nR	(%R)
P. aeruginosa	All	ICU	Ceftobiprole	307	0.06->64	4	4	16	–b		–b		–b	
			Ceftriaxone		≤0.015->64	>64	64	>64	55	(17.9)	74	(24.1)	178	(58.0)
			Ceftazidime		0.06->128	2	2	>32	239	(77.9)	15	(4.9)	53	(17.3)
			Cefepime		0.06->128	2	4	16	241	(78.5)	39	(12.7)	27	(8.8)
			Piperacillin/tazobactam		0.5->128	4	16	>128	239	(77.9)	–c		68	(22.1)
		Inpatient	Ceftobiprole	733	≤0.015->64	2	4	16	–b		–b		–b	
			Ceftriaxone		≤0.015->64	>64	64	>64	141	(19.2)	195	(26.6)	397	(54.2)
			Ceftazidime		0.12->128	2	2	32	631	(86.1)	20	(2.7)	82	(11.2)
			Cefepime		0.25->128	2	4	16	636	(86.8)	61	(8.3)	36	(4.9)
			Piperacillin/tazobactam		≤0.25->128	4	8	>128	644	(87.9)	–c		89	(12.1)
	CAZ S	ICU	Ceftobiprole	239	0.06->64	1	2	16	–b		–b		–b	
			Ceftriaxone		≤0.015->64	>64	32	>64	55	(23.0)	74	(31.0)	110	(46.0)
			Ceftazidime		0.06->8	2	2	4	239	(100.0)	0	(0.0)	0	(0.0)
			Cefepime		0.06->64	2	2	8	226	(94.6)	11	(4.6)	2	(0.8)
			Piperacillin/tazobactam		0.5->128	4	8	32	226	(94.6)	–c		13	(5.4)
		Inpatient	Ceftobiprole	631	≤0.015->64	2	2	8	–b		–b		–b	
			Ceftriaxone		≤0.015->64	64	32	>64	141	(22.3)	194	(30.7)	296	(46.9)
			Ceftazidime		0.12->8	2	2	4	631	(100.0)	0	(0.0)	0	(0.0)
			Cefepime		0.25->32	2	2	8	609	(96.5)	19	(3.0)	3	(0.5)
			Piperacillin/tazobactam		≤0.25->128	4	8	32	616	(97.6)	–c		15	(2.4)
	CAZ NS	ICU	Ceftobiprole	68	0.25->64	8	8	>32	–b		–b		–b	
			Ceftriaxone		64->64	>64	>64	>64	0	(0.0)	0	(0.0)	68	(100.0)
			Ceftazidime		16->128	32	32	64	0	(0.0)	15	(22.1)	53	(77.9)
			Cefepime		1->128	16	16	>32	15	(22.1)	28	(41.2)	25	(36.8)
			Piperacillin/tazobactam		4->128	>128	>128	>128	13	(19.1)	–c		55	(80.9)
		Inpatient	Ceftobiprole	102	0.5->64	8	8	>32	–b		–b		–b	
			Ceftriaxone		32->64	>64	>64	>64	0	(0.0)	1	(1.0)	101	(99.0)
			Ceftazidime		16->128	32	32	64	0	(0.0)	20	(19.6)	82	(80.4)
			Cefepime		4->128	16	16	32	27	(26.5)	42	(41.2)	33	(32.4)
			Piperacillin/tazobactam		1->128	>128	>128	>128	28	(27.5)	–c		74	(72.5)

*CAZ S, ceftazidime susceptible; CAZ NS, ceftazidime nonsusceptible. bCeftobiprole CLSI interpretation of susceptible (S), intermediate (I), and/or resistant (R) not available. cPiperacillin/tazobactam CLSI interpretation of intermediate (I) for *P. aeruginosa* not applicable.

Figure 3. Ceftobiprole MIC (µg/mL) distribution against *P. aeruginosa* by patient location.

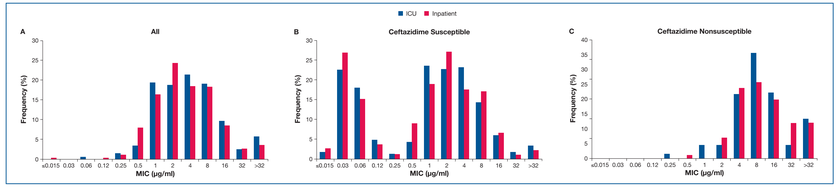
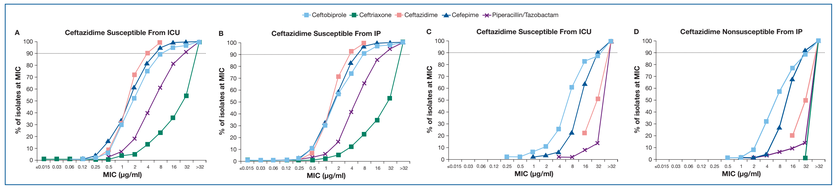


Figure 4. Cumulative susceptibility of ceftobiprole and comparators against *P. aeruginosa* from the ICU and inpatients.



Conclusions

- **Cephalosporin activity (ceftobiprole, ceftazidime, cefepime) against Enterobacteriaceae overall by MIC_{90} was impacted by patient location (MIC_{90} for cephalosporins was 4–16-fold higher among ICU population relative to IP population).**
- **This difference is likely due to the higher prevalence of ceftazidime-nonsusceptible isolates among the ICU population relative to the IP population.**
- **Against ceftazidime-susceptible and ceftazidime-nonsusceptible Enterobacteriaceae, the disparity in cephalosporin activity against IP and ICU populations by MIC_{50} and MIC_{90} was no longer apparent, and ceftobiprole maintained similar activity against both IP and ICU derived isolates.**
- **Ceftobiprole activity against ceftazidime-susceptible and ceftazidime-nonsusceptible Enterobacteriaceae was comparable to cefepime and superior to ceftazidime regardless of patient location.**
- **Ceftobiprole activity was similar among both IP and ICU populations of *P. aeruginosa* regardless of ceftazidime resistance phenotype.**
- **Against both IP and ICU isolates, ceftobiprole activity for ceftazidime-susceptible *P. aeruginosa* was comparable to cefepime and ceftazidime, while ceftobiprole was slightly more active than cefepime against ceftazidime-nonsusceptible IP and ICU isolates.**
- **The similar activity profiles observed for ceftobiprole against IP and ICU populations where the drug is ultimately targeted for use illustrated that patient location had no effect on ceftobiprole activity against Enterobacteriaceae and *P. aeruginosa*.**
- **Given the elevated resistance rates observed in an ICU population, further monitoring is warranted.**