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A Comparison Of Ceftobiprole And Ceftazidime MICs by European Methods Against 121 Gram-positive And Gram-negative Organisms

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Abstract (Revised)

Background: Ceftobiprole is a new cephalosporin with a mechanism of PBP binding that includes inhibition of staphylococcal PBP2a, resulting in broad-spectrum activity against Gram-negative (GN) and Gram-positive (GP) pathogens, including MRSA. This 4-site study was undertaken to compare ceftobiprole and ceftazidime MIC methods with the CLSI broth microdilution method (BMD) against a selection of GP and GN strains. **Methods:** Each of the sites tested their MIC method (France (SFM), Sweden (SRGA), United Kingdom (BSAC), and Germany (DIN)) and the CLSI method against the same set of 125 strains (*S. aureus*, *S. epidermidis*, *E. faecalis*, *S. pneumoniae*, viridans strep., *S. pyogenes*, *S. agalactiae*, *E. coli*, *S. marcescens*, *P. mirabilis*, *C. freundii*, *E. aerogenes*, *K. pneumoniae*, *P. aeruginosa*, *H. influenzae).* Standard QC strains were also tested. **Results:** The geometric mean MICs of all strains for ceftobiprole and ceftazidime were within 1 dilution. In comparison to CLSI ceftobiprole MICs, the overall essential agreements % (EA) were: SFM 100, SRGA 91.9 and BSAC 77.4. EA based on same method comparison at the German site (CLSI/DIN) was 100. Ceftobiprole BSAC modal MICs are 1 dilution lower than CLSI, with the exception of *H. influenzae*, which are 1 dilution higher. The geometric geometric mean MICs (mg/L) for all strains tested were:

Testing Site/Method	n	Ceftobiprole	n	Ceftazidime
France/SFM	124	0.13	123	1.60
France/CLSI	124	0.15	112	1.59
Sweden/SRGA	123	0.16	113	2.35
Sweden/CLSI	123	0.18	113	1.77
UK/BSAC	123	0.13	111	1.86
UK/CLSI	123	0.23	113	1.86
Germany/DIN/CLSI #1	124	0.14	114	1.45
Germany/CLSI/DIN #2	124	0.15	114	1.40

Conclusions: Ceftobiprole MICs, by all European methods, correlated well with the CLSI BMD method with the same selected set of strains.

Introduction

- This study was performed to compare ceftobiprole MIC results for a selection of Gram-positive and Gram-negative isolates as determined by Société Français de Microbiologie (SFM), Swedish Reference Group for Antibiotics (SRGA), British Society for Antimicrobial Chemotherapy (BSAC) and Deutsches Institut für Normung (DIN) and Clinical and Laboratory Standards Institute (CLSI) methods.
- Each study site tested the same set of strains using their country MIC method and the CLSI MIC method.
- Overall, there was good correlation of ceftobiprole MICs by SFM, SRGA, BSAC agar dilution and CLSI/DIN broth microdilution methodologies.
- The geometric mean ceftobiprole and ceftazidime MICs of all strains were within one doubling dilution for all methods

Methods

Antimicrobial Agents
Ceftobiprole – 0.00025-8 µg/mL
Comparator Agent – Ceftazidime – 0.004-128 µg/mL

Testing Sites and Specific Method Tested
SFM – Claude-James Soussy, C.H.U. Henri Mondor, Créteil, France
SRGA- Gunnar Kahlmeter, Klinisk Mikrobiologi, Växjö, Sweden
BSAC – David Livermore, Central Public Health Laboratory, London, UK
DIN – Arne Rodloff, Universitat Leipzig, Leipzig, Germany

Microorganisms
The same set of 121 strains were tested by all sites and included: 24 Staphylococci, 10 E. faecalis, 34 Streptococci, 33 Enterobacteriaciae, 10 P. aeruginosa, and 10 H. influenzae

Methods

SFM MIC Method
Agar dilution using Mueller Hinton Agar (MHA) for staphylococci and gram negative bacilli. MHA + 5% defibrinated sheep blood (SB) for streptococci and Haemophilus Test Media agar (HTMA) for *H. influenzae*.

SRGA MIC Method
Agar dilutions using IsoSensitest (ISA) for staphylococci and gram negative bacilli and ISA + 5% defibrinated horse blood (HB) and 20 mg/L NAD for streptococci and *H. influenzae*.

BSAC MIC Method
Agar dilution using IsoSensitest Agar (ISA) for staphylococci and gram negative bacilli and ISA+ 5% defibrinated horse blood (dHB) for streptococci and ISA+5% whole horse blood + 20 mg/L NAD for *H. influenzae*.

DIN & CLSI MIC Method (All sites tested CLSI as common, comparative method)
Broth microdilution using Trek MIC panels (see Appendix 1 for plate format) with cation adjusted Mueller Hinton Broth (CAMHB) for staphylococci and gram negative bacilli and CAMHB + 5% Lysed Horse Blood (LHB) for streptococci and Haemophilus Test Media (HTM) for *H. influenzae*.

Results

- The geometric mean ceftobiprole MICs of all strains by all methods ranged from 0.13-0.23 µg/mL
- The geometric mean ceftazidime MICs of all strains by all methods ranged from 1.4-2.35 µg/mL.
- Overall essential agreement (within +/- 1 doubling dilution) compared to CLSI for ceftobiprole were: SFM - 100%, SRGA – 91.9%, BSAC – 77.4%, DIN – 100%.
- Overall essential agreement (within +/- 1 doubling dilution) compared to CLSI for ceftazidime were: SFM - 100%, SRGA – 81.3%, BSAC – 85.5%, DIN – 99.2%.
- With the exception of some *P. aeruginosa,* an *E. coli* and 2 outliers by CLSI from the UK site (1 Serratia marscens and 1 *H. influenzae*), there was excellent categorical agreement as all ceftobiprole MICs were susceptible by all methods. One *E. coli* strain tested non-susceptible by CLSI/DIN at the German site, susceptible by SFM and CLSI at the France site, and non-susceptible by CLSI and susceptible by SRGA and BSAC at the Swedish and UK sites.
- The number of major/very major errors in comparison to the CLSI MICs at each site among the 10 *P. aeruginosa* were DIN (0/0), SFM (3/1), SRGA (0/4) and BSAC (0/3).
- Ceftobiprole *in vitro* activity against all of the Gram positive strains (including MRSA) was signigicantly greater than ceftazidime. Ceftobiprole MICs against *Enterobacteriaciae* were 2.1 – 4.8 fold lower than ceftazidime. Ceftobiprole and ceftazidime MICs were similar for *P. aeruginosa* and *H. influenzae*.

Conclusions

- There was good reproducibility of ceftobiprole and ceftazidime MICs in this multi-national MIC method study.
- The geometric mean ceftobiprole and ceftazidime MICs of all strains were within one doubling dilution for all methods. Although there was lower correlation of ceftobiprole CLSI and BSAC MICs, the BSAC MICs were similar to the other country specific method MICs.
- The CLSI ceftobiprole MICs from the UK site were generally higher compared to the CLSI MICs from the other countries.
- Overall, there was good correlation of ceftobiprole MICs by SFM, SRGA, BSAC agar dilution and CLSI/DIN broth microdilution methodologies.

Figure 1: Geometric mean ceftobiprole MICs (µg/mL) by method of staphylococci and *E. faecalis*

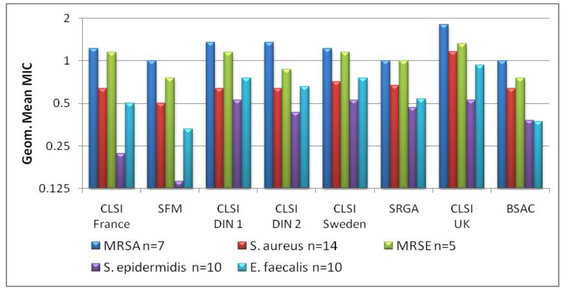

Figure 2: Geometric mean ceftobiprole MICs (µg/mL) by method of streptococci

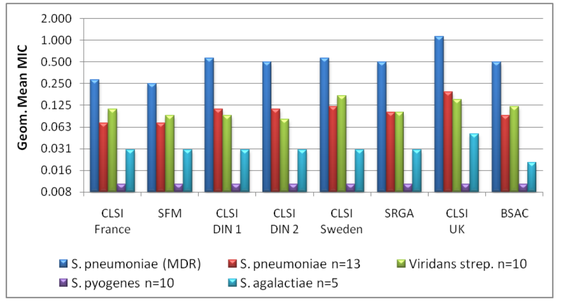

Figure 3: Geometric mean ceftobiprole MICs (µg/mL) by method of *Enterobacteriacieae* and *H. influenzae*

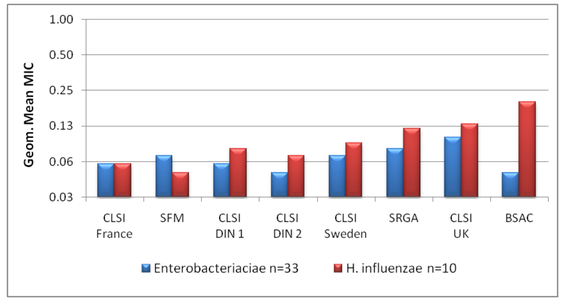

Figure 2: Geometric mean ceftobiprole MICs (µg/mL) by method of *Pseudomonas aeruginosa*

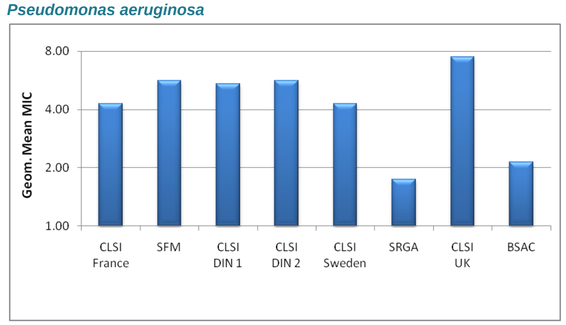

Table 1: Geometric mean ceftobiprole and ceftazidime MICs (µg/mL) by method and organism

Microorganisms	(n)	France		Germany		Sweden		United Kingdom	
		CLSI BMD	SFM Agar	CLSI/DIN BMD	CLSI/DIN BMD	CLSI BMD	SRGA Agar	CLSI BMD	BSAC Agar
Ceftobiprole									
MRSA	7	1.22	1	1.35	1.35	1.22	1	1.81	1
S. aureus (MRSA and MSSA)	14	0.64	0.5	0.64	0.64	0.71	0.67	1.16	0.64
MRSE	5	1.15	0.76	1.15	0.87	1.15	1	1.32	0.76
S. epidermidis (MRSE and MSSE)	10	0.22	0.14	0.53	0.43	0.53	0.47	0.53	0.38
E. faecalis	10	0.50	0.33	0.76	0.66	0.76	0.54	0.93[a]	0.37[a]
S. pneumoniae (MDR)	6	0.28	0.25	0.56	0.5	0.56	0.5	1.12	0.5
All *S. pneumoniae*	13	0.07	0.07	0.11	0.11	0.12	0.1	0.19	0.09
Viridans streptococci	10	0.11	0.09	0.09	0.08	0.17[a]	0.1[a]	0.15	0.12
S. pyogenes	10	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
S. agalactiae	5	0.03	0.03	0.03	0.03	0.03	0.03	0.05	0.02
Enterobacteriaciae	33	0.06	0.07	0.06	0.05	0.07[b]	0.08[b]	0.1	0.05
P. aeruginosa	10	4.29	5.66	5.44	5.66	4.29	1.74	7.46	2.14
H. influenzae	10	0.06[c]	0.05[c]	0.08[a]	0.07[a]	0.09	0.12	0.13	0.2
All Strains	125	0.15	0.13	0.15	0.14	0.18	0.16	0.23	0.13
Ceftazidime									
MRSA	7	141.32[a]	145.93[a]	115.93	128	115.93	172.28	115.93[a]	190.21[a]
S. aureus (MRSA and MSSA)	14	37.12	32	30.45	32	33.62	55.17	78.02	43.07
MRSE	5	36.76	36.76	48.5	55.72	42.22	55.72	42.22	27.86
S. epidermidis (MRSE and MSSE)	10	14.93	13	14.93	16	18.38	14.93	16	10.56
E. faecalis	10	207.94[a]	111.43[a]	194.01	194.01	207.94	222.86	219.45[a]	237.02[a]
S. pneumoniae (MDR)	6	4.46	5.62	8.98	8	11.31	17.96	11.31	16
All *S. pneumoniae*	13	1.23	1.45	1.62	1.62	2.1	3.41	1.99	2.61
Viridans streptococci	10	2.29	2.83	1.73	1.86	4[b]	5.44[b]	3.48	3.73
S. pyogenes	10	0.12	0.14	0.1	0.09	0.13	0.2	0.1	0.13
S. agalactiae	5	0.57	0.5	0.5	0.5	0.66	0.66	0.76	0.57
All *Enterobacteriaciae*	33	0.17	0.19	0.14	0.17	0.17[c]	0.28[c]	0.21	0.24
P. aeruginosa	10	5.28	4	5.28	4.29	6.5	3.03	8.57	3.48
H. influenzae	10	0.08[d]	0.14[d]	0.09[b]	0.1[b]	0.11	0.2	0.07	0.2
All Strains	125	1.59	1.6	1.4	1.45	1.77	2.35	1.86	1.86

[a] some offscale (>) MICs included as one doubling dilution above highest concentration tested
[b] 1 strain not tested, n=9
[c] 1 strain not tested, n=32
[d] 2strains not tested, n=8

Table 2: Dilution difference of ceftobiprole MICs (µg/mL) by method and organism

Microorganisms	SFM			SRGA					BSAC							CLSI/DIN		
	–1	0	+1	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3	–1	0	+1
S. aureus (MRSA)	2	5				2	5					1	4	2					7	
S. aureus (MSSA)	3	4					6	1				3	1	2	1			1	5	1
S. epidermidis (MRSE)	3	2				1	4					1	2	2				2	3	
S. epidermidis (MSSE)	3	2				1	4						1	4				1	4	
E. faecalis	6	4				5	5				1	1	7					2	8	
S. pneumoniae	1	5	1			3	4						7							1
S. pneumoniae (MDR)	1	5				1	5					3	1	2				1	5	
Viridans streptococci	4	5	1	1*	1	3	2	2				1	3	5	1			2	8	
S. pyogenes	1	7	2			2	6	2					5	5				1	9	
S. agalactiae	1	4				1	4					1	3	1					5	
E. coli	1	7	2	1*		1	6	2			1*		3	6				1	9	
S. marcescens	2	2					2	2			1*			3				3	1	
P. mirabilis		3	2			3	1	1				2	2	1				1	4	
C. freundii	2	2					1	2				1	2	1				1	3	
E. aerogenes	1	1	2				3	1					2	2				1	3	
K. pneumoniae	1	4	1			1		4	1			1	1	4				1	5	
P. aeruginosa	1	4	5		4	5	1				3*	3	1	3				2	7	1
H. influenzae	2	5	1		1	2	3	3		1*	1		1	1	4	3		1	8	
All Strains	35	71	17	2	6	31	62	20	1	1	7	18	46	44	6	3		21	100	3
Essential Agreement	100%					91.9%							75.0%					100%		

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